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EDITORIAL

Future of processing and facilitating change and learning

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Abstract

The field of the sciences of the mind is evolving fast. With the diversification of knowledge and accumulation of data, often lacking integration and reproducibility, questions arise. The role of critical thinking and research is evident. As the science of the unconscious, psychoanalysis provides a method and theory to understand human minds and mentalities, helping the patient know his mind and transform action into reflection. Mental activities, including social skills, develop in the social context, depending on the social environment's demands and resources put onto the individual. Encoding emotional signals, markers of meaning for the individual, is ontogenetically necessary and has influences on memory encoding. Beyond theoretical understanding, implicit relational knowledge is actualized in the therapeutic setting. With a strong focus on experiencing emotional reconsolidation of memories, previous relationships' repercussions are enriched with broadening viewpoints in the analytic environment. The long-term effects of psychotherapeutic treatments have been examined. A sufficient explanation of the specific factors contributing to success or an answer when an impact is lacking is still under investigation. When investigating subliminal and implicit mechanisms leading to memory reconsolidation and the formation of functional object relations and interaction patterns, the focus is set on affective interplay and processing prior/during and after social interactions. The present paper discusses which parameters might contribute to the reshaping of memories and the linkage of memory with the emotional load of experience. Providing insights into such dynamic mental phenomena could enhance process research by investigating moment by moment interactions in psychoanalysis, treatment, and learning processes. Due to the research subject's complexity, different research methods and integration of associated research fields are required.

Key Words: Psychoanalysis; Hermeneutic circle; Evidence-based medicine; Bias; Affective interplay; Micro-process

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Core Tip: The mind's ability to interact and assess the external world's reality and integrate new experiences into existing conceptions is determined by the affective load the respective interplay is assigned. Gaining a picture of the world at an acceptable reliability level requires a curious mind and openness for a discursive dispute with encountered findings.

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INTRODUCTION

"The only true wisdom is in knowing you know nothing." – Socrates.

The illusion of certainty is constantly eroded when the amplification of questions is generated by research. Nevertheless, integrating scientific findings following an interdisciplinary approach is as challenging as inspiring, even more when dealing with a presumably still unknowable research object like the human mind. Creating a scientific dialogue dedicated to integrating balanced evidence while still constantly questioning results for their probability towards an approximation to truths requires openness to innovation. This dialogue leads to an integration of different perspectives; all concerned with overlapping research topics.

THE CIRCLE OF UNDERSTANDING

Being in the world involves acquiring experience, knowledge, and assumptions. Only from the observer's background, it is possible to enter a circle of understanding and re-experience in practice the hermeneutic circle. Developing a sense of the whole means acquiring a better sense of each part – the interpretation of findings depends on the conceptions and vice versa.

Psychodynamic theorizing and therapeutic work explore the unconscious elements not intelligible to conscious thinking but impacting our cognitive and affective abilities. Therapeutic work makes part of applied sciences to apply care based on up-to-date scientific findings continually. It contributes to research by generating a hypothesis and collecting data again, feeding back to research and quality control. "How do we know what we know" remains a sophisticated question, especially when it comes to 'implicit' and 'embodied' knowledge like social skills, relational knowledge, and interactional patterns.

Relevance to the daily routine and therapeutic work is evident as investigating mechanisms of change in this field determines patients' future options and the therapists' attitudes toward what she/he can influence. Generating meaning and giving value to one's life is something very individual and so are conceptions regarding the outcome. However, attachment to relevant others and life itself is often disturbed in mental disorders. Mental conditions confound and trouble emotional well-being and overall psychosocial functioning, with innumerable consequences on a person's path of life, catapulting them in an awkward position. Compassion fatigue marks the borders of empathy and resilience even of socially skilled and socially minded persons.

LEVELS OF EVIDENCE

To answer clinical questions and support clinical decision-making recommendations, evidence-based medicine should rely on the highest level of evidence available. Expert opinion and case reports are at the lowest level of evidence followed by case series. However, when it comes to the relevance of an individual case, this is not only determined by the incidence of the condition in question and thus by the possibility of carrying out extensive investigations (*e.g.*, in rare diseases). To follow a hypothesis-

generating approach, such study designs including qualitative methods (video- or text-analyses, interviews, *etc*.) can be of specific value and can be combined in a mixed-methods design to build a clinical theory - of course without claiming the stance of a scientific theory. Strong recommendations demand several adequately conducted randomized controlled trials and systematic reviews/meta-analyses on the research question. However, consistent evidence from lower-level studies (high-quality prospective cohort study with adequate power) and evidence from a lesser quality type of evidence with a predefined study design (*e.g.*, retrospective cohort study, a case-control study) support a strong recommendation[1]. The quality of possible findings in a meta-analysis depends on the quality of available evidence. Nevertheless, both approaches, a quantitative, natural scientific and a more qualitative, social scientific or even including the humanities, can be interesting for the research field of processing and facilitating change and learning, but we have to take the different levels of evidence into account.

Interpretation of knowledge from different levels of evidence can be challenging. However, when prioritizing information, the need for randomized controlled trials to improve evidence is relevant for psychodynamic theorizing. Confirmation[2] and publication bias[3] can only be avoided by reproduction of results in large systematic replication projects, transparency and completeness in reporting methods, data, and analysis in a scientific publication[4,5]. To avoid constructed consensus, Socrates developed the Socratic dialogue as a form of cooperative argumentative dialogue based on asking and answering questions to stimulate critical thinking[6]. Awareness of the complexity of investigations, of the questionability of truth and value of one's own opinions, leads to careful and in-depth thinking[6]. Popper's concept of critical rationalism as a method of inquiry claims that scientific theories should be criticized; a hypothesis must be subjected to tests that might falsify them[7,8]. Critical rationalists believe in progress without believing in the concept of truth in an absolute sense. However, in postmodernism, a diversity of voices is accepted as an acceptable endpoint of scientific research[8]. The human mind's ability to falsify hypotheses might be limited by its premises as its ability to generate them. Anti-positivists doubted the existence of facts. A problem-oriented, or even case-based, approach, instead of focusing on a method-oriented approach, has been claimed by both postmodernists and critical rationalists[8].

THE SCIENCE OF THE UNCONSCIOUS

In his search of the genesis of human knowledge and the role memory has in our having experience, Freud[9] concluded that plenty of human mental processes might happen unconsciously but influence behavior. In his everyday work, Freud[9] observed clinical phenomena and effects worth investigating further, thus facilitating subsequent research, with his theories also being subject to controversy. In his analysis of symptoms, he postulated that each of them makes sense when the mind's operations taking place below the conscious awareness level are considered (also compare[10]). Drives connected with basic needs (*i.e.* basic biological instincts) and societal demands posed to the individual by environments and context form human personalities, intrapsychic structures (ego, id, and super-ego), and mental abilities. Social and human science methodologists developed a multitude of research strategies, termed 'qualitative'. With Lacan[11], among other psychoanalytic theoretical developments, psychoanalytical science became a symbolization process and a way of obliterating and dissolving the phenomena of life. The imaginary realm (*e.g.*, images, shapes) is transformed in the symbolical realm of scientific experience (*e.g.*, measurement, numbers, formulae, methodological standards)[12] (Figure 1).

Contemporary views on whether research has a role in justifying and developing psychoanalytic theory and the limitations of research in this field root in a controversy with a long history[13]. Psychiatry, conceptualized as applied clinical neuroscience, had been focusing on pharmacotherapy in the 1990s. In contrast, integrating the psychoanalytic method into other psychological methods and establishing a research culture had been missed[14].

Nevertheless, clinical observations were invaluable to all known thinkers in this field. Repeated interactions with the caregiver and relevant others in early childhood shape how reality is experienced and perceived. Those affectively loaded and lived experiences result in implicit knowledge and assumptions and determine later behavior (*i.e.* patterns)[15]. That is why infant research has a long history within psychoanalysis[16-20].

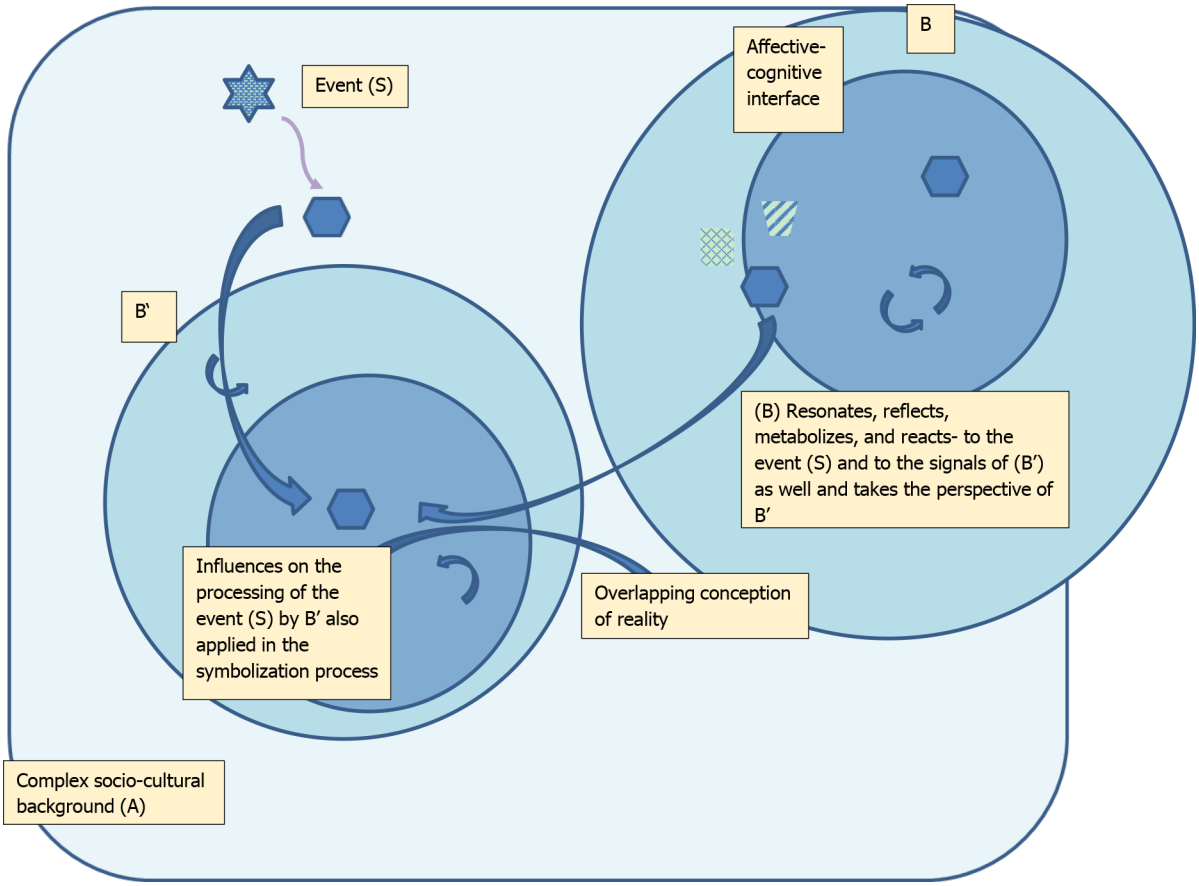

Figure 1 Symbolization process. Within a more complex sociocultural background (A), two individuals meet (B, B'). Something (S) affects them both in their (shared conception of) reality. An individual's behavior and inner states and reaction to this stimulus depend on its own symbolization abilities and experiencing. This processing evolves in tight interrelation with others and happens on a somatic and a cognitive layer. The relevant other (B) resonates, reflects, metabolizes, and reacts to the event (S) and to the signals of (B') as well and takes the perspective of B'. This reaction again influences the processing of the event (S) by B', also applied in the symbolization process.

PSYCHOTHERAPY RESEARCH

Adaptation to reality is one of the principal goals in psychoanalytic therapy, with reality as the derivation point of unconscious fantasies[9] exposed by the therapeutic work. Psychodynamic work considers subliminal signals (*i.e.* enacted through language, gesture, facial expressions) and latent perceptions of those stimuli. Importance of unconscious and embodied knowledge in the processing of such perceptions applies. Psychodynamic interventions aim at reshaping cognitive processing (*e.g.*, perception, attention, and memory)[21] by creating new viewpoints and experiences in the (analytic) environment.

Several high-quality studies reviewed in an updated meta-analysis have shown the efficacy of short-term psychodynamic therapy for depression and its equivalence with other psychotherapies[22-24]. However, several reviews with very high effect sizes had to be excluded from this analysis due to their statistical methodology. Long-term psychoanalytic therapy effectiveness is supported by evidence from systematic reviews of empirical studies[25]. Regardless of these findings, concerns about the consistency of the research methodology have been raised. Due to the lack of meta-analyses reviewing robust, high-quality data, high-level evidence is missing[25]. Overall, identifying predictors for long-term effects would help yield hope for individual patients and allocate treatments. Nowadays, health care providers demand the highest achievable evidence when deciding upon the allocation of resources. When confronting the efficacy of cognitive-behavioral therapy and psychodynamic therapy in treating major depression, the two methods applied in the randomized controlled trials showed no significant differences but were equally effective[23]. However, when long-lasting effects (3 years) were investigated, psychoanalytic therapy was better, possibly due to a dose effect[26]. Additionally, mediators predicting treatment success specific for each treatment method have been proposed[27-31]. Investigating dreams and patients' fantasies and focusing on memories or reconstructions of childhood were

found to explain some of the differences between the two methods.

When creating common ground in psychotherapy research, this involves many therapeutic approaches, claiming to have the recipe for healing the human psyche. One of the characteristic traits of humans, most probably distinguishing them from other primates, is their ability to form societies and carry on negotiations between different groups within individual societies and at an international level. The ability to hypothesize and adopt different perspectives to understand other viewpoints (*i.e.* mentalizing) is necessary.

As to psychotherapy research, given that many different approaches lead to improved symptoms, common factor models (including alliance, empathy[32], attitude [33], expectations, cultural adaptation, and therapist differences)[34-36] have been proposed, including the clients' contributions[37]. Essential skills for all psychotherapists are relationship skills, attachment, and emotional intelligence abilities. For psychodynamic therapy, technical neutrality was found to correlate with success[38].

INTEGRATION OF KNOWLEDGE

Nowadays, embedding psychodynamic thinking with an evidence-based approach aims at integrating different kinds of research, looking at cognitive processes from different perspectives.

The constant questioning of "truths" leads to openness to innovations and engagement with associated research fields (*e.g.*, neuropsychology, neurosciences, communication-sciences). As outlined above, a mixed-method approach is necessary when generating evidence in a real-world scenario. The choice of the method depends on the research question, but independent of the method considered, quality depends on preventing bias (*e.g.*, recall bias, selection bias, observation bias, confirmation bias, and publishing bias). As mentioned above, the approach should be a problem-solving one. Collaboration, support (*e.g.*, methodological support, guidelines), peer review, and open science reforms call for openness in the scientific discourse[39].

Developing substantial research questions requires excellent knowledge of the investigated research topic and the problem identified. The uncertainty and complexity of knowledge and parties involved limit the academic debate, and already the possible questions impact answers. Thus, integrating new theories and strains of expertise and strategies in existing frameworks and dynamic systems (*e.g.*, *via* a public/patient involving design) requires an adequate understanding of the system, influencing factors, and a generalization across its states and the ones of the observing unit/system. This integration of findings might be challenging and time-consuming [40]. Scientific theorizing involves acknowledging uncertainty and expressing the limitation of results.

Applying this to the example of research in emotion and behavior will demonstrate the rise of a new research field by integrating different approaches and awareness of limitations in research. Emotion has been a mainstream topic in the last decades[41]. Psychoanalysts and neuropsychologists have equally been interested in understanding emotional processes. The interest in this research field is understandable because of the influence emotion has on cognitive abilities. This impact is especially true in directing an individual's attention, perception of reality, motivation, and memory[42]. Human emotions determine how an individual uses its resources, and they have importance not only when triggered by internal stimuli but also when interacting with external triggers (compare, *e.g.*, mentalization based therapy)[43].

Generation of meaning is bound to the interplay between individual and (social) environment under specific conditions and frames memory traces. Each selection between different action options (and thoughts) influences subsequent decisions. When relying on experience, actualization is facilitated if adaptation to the current environment is perceived as sufficient. Implicit bias refers to unconscious assumptions, categories, and attitudes influencing our perception and appraisal[42]. Cognitive bias enables fast cognitive processing and roots in evolutionary advantage arising from this stereotype judgment, with evident affective influences.

The world of science seeks to study phenomena through observation and experiment. The impact of the flexibility of analytical approaches was investigated recently for the field of neuroimaging: the analysis of a single neuroimaging dataset by many teams showed substantial variability despite significant consensus in activated regions [42]. The authors stress the importance of validating complex workflows and analyzing data[42] through different research teams, taking into account implicit bias. Also, for the field of explainable artificial intelligence, a paradigm shift has been

suggested to avoid confirmation bias and increase transparency and validity[44].

Emotion theories from various research fields were concerned with components of emotional processes. Emotions include preceding mental and bodily states, appraisal and consequences like consciousness, generation of symbolic meaning, and/or enactment *via* behavior. The importance of process in addition to outcome research has been emphasized. Looking at micro processes prior/during and after social interactions makes sense in emotion research as emotional reactions arise during interactions with others and are perceived and regulated moment by moment[45-47].

As the science of the unconscious, psychoanalysis investigates human minds and mentality, aiming to provide an environment for the transformation of enactment into reflection, preventing recurring patterns if identified as destructive or harmful[48]. This process of adaptation occurs in the individual as well as in society. However, how does this happen? An "analytic environment" provides an actualization of memories and related implicit and unconscious knowledge and affective linkages. The psychoanalytic method aims at broadening the field of experience and perception. Providing a revalidation and reinterpretation of existing viewpoints leads to freedom of thought and action and reshaping memories or appraisal. Integration of so far indigestible contents in a more favorable narrative leads to a changed perception of reality and perspectives. The focus is on the affective interplay and processing in the actualized situation, thus demanding time to analyze ongoing interactions[47,49]. Leading affects in the early dyadic interplays directly affect conceptions of the self. A child's internal abilities to cope with reality depend on whether specific representational structures (self, others, relationships) have been created in the early interactions[50,51]. Interactional patterns are socially transmittable, and their modification is challenging.

Psychotherapy research is concerned with process and outcome investigation of how specific factors contribute to therapy success or alliance rupture and failure. Observational research often assumes that behavior is more or less proving of mental and affective states. However, modifiers and moderators must be considered when aiming at attributing results to specific therapeutic interventions. For mice, facial expressions have been linked to emotional states and their neuronal correlates[50,52]. While in the mouse model and under laboratory circumstances, this might be more straightforward, generalization to real-life scenarios requires caution when interpreting findings.

When it comes to investigating persons with disturbances or diseases of their mental health, their vulnerability[53] must be acknowledged in therapy as well as when conceptualizing research[54,55] (1949 Nuremberg Code, updated in the 2008 World Medical Association Declaration of Helsinki, and in the 1979 Belmont Report). On the other hand, excluding persons only because they belong to vulnerable groups has been discussed as equally unethical and contributing to research bias[56,57]. Each case must be considered, especially when dealing with persons with (temporarily, fluctuating, or permanently) impaired mental state. In psychoanalytic therapy, investigation of therapy dropouts revealed that multiple factors contribute to the decision to continue or to dismiss treatments. Goals, readiness to change, awareness and insight capacity, resistance, and transference are well-known factors[55]. However, when Lacan[57] attempts to conceptualize psychoanalytical ethics, he places the problem of desire at the center of his ethics[56]. "At every moment we need to know what our effective relationship is to the desire to do good, to the desire to cure." Lacan[57] keeps reminding us that the sphere of human subjectivity, including unconscious fantasies, is a dimension the analyst cannot pretend to know. Lacan[57] emphasizes that not only the patients' unconscious wishes are present, but also the analyst's own desires. Acknowledging this is the starting point in preventing the psychoanalyst's application of personal reality and desire as a normative ideology to the patient[58]. This includes "hidden agendas of economic power and status" and morality[56].

Self-related processing, the wish to be the agent of one's actions in the world, and orientation towards relevant others (*i.e.* innate attachment motive) through repetitive interactional interplay leads to creating social bonds as to the human's impact on the environment. Interactive resonance contributes to attachment formation with relevant others[46]. Medical knowledge integration is ambitious due to the heterogonous field involving biological, behavioral, and social sciences providing data (bottom-up)[59]. Top-down organismic systems medicine has been proposed as an integrative approach [40].

When merging psychoanalytical with neuroscientific conceptions, both assume that major adaptations and developments related to cognitive abilities merely take place in the first decades of life. This goes in hand with current attempts to detect and treat vulnerable subjects already early in their life to prevent mental disorders later on[37]. Following systems theory, a rather integrative approach, and complex systems can

only be understood in their context, influencing each other[60] through a web of connections depending on their complexity.

Subliminal affective reactions can be hints for targeting specific interventions[61-63]. The ability to infer mental and affective states evolves early in life, but different interpersonal and arousal contexts influence available strategies[64]. When dealing with a subject's memories, this is supposed to be emotionally challenging because only subjectively valuable content is stored. However, when experiences are overwhelming, accessibility of memory content might be reduced. Containment also depends on the attitudes and competencies of the containing person[33,48]. Memories are not unchangeable. However, defense against arbitrary manipulation is adaptive and intelligible due to obvious reasons. Psychodynamic therapies aim to explore and interpret internal conflicts to assist people when earlier experiences influence a destructive and distorting way on present options[63].

Providing an opportunity to model oneself by reconsidering our mind, various core factors apply. This remodeling would imply a reconceptualization of the self and others and the relationships between them and anchoring this process in the embodied self[64]. When interacting with the world, self-representations and world-representations are actualized. Hence, psychotherapy constitutes a setting where this process is supposed to happen in a sphere of expanded subjectivity (involving the therapist), considering rational aspects and experiencing[19,40,46].

CONCLUSION

In conclusion, integrating relevant findings into psychoanalytic theories requires a top-down approach (*i.e.* a meta-theory) constantly metabolizing up-to-date empirical evidence. Thus, differentiation of knowledge about mental conditions evolves dynamically in a sphere of unification of multiple features contributing to the whole, also very subjective contributions to the topic of facilitating change.

Almost any phenomenon can be studied qualitatively and quantitatively. However, applied techniques determine results, and choosing the adequate research method according to the scope and research question is critical for gaining an in-depth picture of the addressed topic.

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REFERENCES

1 **Burns PB**, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg* 2011; **128**: 305-310 [PMID: 21701348 DOI: 10.1097/PRS.0b013e318219c171]

2 **Begley CG**, Ellis LM. Drug development: Raise standards for preclinical cancer research. *Nature* 2012; **483**: 531-533 [PMID: 22460880 DOI: 10.1038/483531a]

3 **Fanelli D**. Do pressures to publish increase scientists' bias? *PLoS One* 2010; **5**: e10271 [PMID: 20422014 DOI: 10.1371/journal.pone.0010271]

4 **Bakker M**, Wicherts JM. The (mis)reporting of statistical results in psychology journals. *Behav Res Methods* 2011; **43**: 666-678 [PMID: 21494917 DOI: 10.3758/s13428-011-0089-5]

5 **Nuijten MB**, Hartgerink CH, van Assen MA, Epskamp S, Wicherts JM. The prevalence of statistical reporting errors in psychology (1985-2013). *Behav Res Methods* 2016; **48**: 1205-1226 [PMID: 26497820 DOI: 10.3758/s13428-015-0664-2]

6 **van Rossem K**. Meeting Socrates. How to do Socratic consultations. *Philos Pract: J APPA* 2014; **9**: 1344-1351

7 **Compston A**. From the Archives Muscular atrophy, after measles, in three members of a family. By J.A. Ormerod, M.D. Brain (October) 1884; 7 (part XXVII): 334-342; with The peroneal type of progressive muscular atrophy. By Howard H. Tooth, M.A, M.D., M.R.C.P (H.K Lewis, London). 1886; pages 44: with Critical Digests. Recent observations on progressive muscular atrophy. By H. H. Tooth, M.D. Brain (July) 1887; 10 (part XXXVIII): 243-253; with The peroneal form or leg-type of progressive muscular atrophy. By B. Sachs, M.D. (New York). Professor of Mental and Nervous Diseases in the New York Polyclinic, Brain 1890; 12: 447-459. *Brain* 2019; **142**: 2538-2543 [PMID: 31292617 DOI: 10.1093/brain/awz200]

8 **Holtz P**. Does Postmodernism Really Entail a Disregard for the Truth? *Front Psychol* 2020; **11**:

545959 [PMID: 33041913 DOI: 10.3389/fpsyg.2020.545959]
9 **Freud S**. Das Ich und das Es. GW XIII, Frankfurt am Main: S. Fischer Verlag, 1923: 237-289
10 **Hevesi Z**, Zelena D, Romanov RA, Hanics J, Ignácz A, Zambon A, Pollak DD, Lendvai D, Schlett K, Palkovits M, Harkany T, Hökfelt TGM, Alpár A. Secretagogin marks amygdaloid PKCδ interneurons and modulates NMDA receptor availability. *Proc Natl Acad Sci U S A* 2021; **118**: e1921123118 [PMID: 33558223 DOI: 10.1073/pnas.1921123118]
11 **Lacan J**. Symbol and imaginary (Seminar II: session 22nd June 1955: part 4). In: Blonsky M, editor. Baltimore MD: The Johns Hopkins University Press, 1985: 206-209
12 **Zwart H**. Conceptual and methodological framework: Lacanian psychoanalysis. In: Tales of research misconduct. Library of ethics and applied philosophy. Springer: Cham, 2017: 25-55 [DOI: 10.1007/978-3-319-65554-3_2]
13 **Davies R**, Sandler A-M, Sandler J. Clinical and observational psychoanalytic research: roots of a controversy - Andre Green & Daniel Stern. 1st ed. London: Routledge, 2000: 1-184
14 **Paris J**. An evidence-based critique of contemporary Psychoanalysis. Research, theory, and clinical practice. 1st ed. London, UK: Routledge, 2019: i–174
15 **Balint M**. Die drei seelischen Bereiche. *Psyche Z Psychoanaly* 1957; **11**: 321-344
16 **Sherwin-White S**. Melanie Klein and infant observation. *Infant Observation* 2017; **20**: 5-26 [DOI: 10.1080/13698036.2017.1311235]
17 **Dix M**. Beziehungserfahrungen und Fantasietätigkeit von Säuglingen in den Theorien von Melanie Klein und Daniel Stern. *Forum Psychoanal* 2017; **33** [DOI: 10.1007/s00451-017-0274-y]
18 **Brierley M**. Affects in theory and practice. *Int J Psycho-Anal* 1937; **18**: 256-268
19 **Fonagy P**, Gergely G, Jurist EL, Target M. Affect regulation, mentalization, and the development of the self. New York: Other Press, 2002: 1-592
20 **Bowlby J**. A secure base: Clinical applications of attachment theory. 1st ed. London: Routledge, 2005: 1-225
21 **Freud S**. Entwurf einer Psychologie. 1950 [cited 10 January 2021]. Available from: https://www.semanticscholar.org/paper/Entwurf-einer-Psychologie-Freud/48bfc3c82b7384f61bd25b8611046eabd7ee6139
22 **Driessen E**, Hegelmaier LM, Abbass AA, Barber JP, Dekker JJ, Van HL, Jansma EP, Cuijpers P. The efficacy of short-term psychodynamic psychotherapy for depression: A meta-analysis update. *Clin Psychol Rev* 2015; **42**: 1-15 [PMID: 26281018 DOI: 10.1016/j.cpr.2015.07.004]
23 **Driessen E**, Van HL, Don FJ, Peen J, Kool S, Westra D, Hendriksen M, Schoevers RA, Cuijpers P, Twisk JW, Dekker JJ. The efficacy of cognitive-behavioral therapy and psychodynamic therapy in the outpatient treatment of major depression: a randomized clinical trial. *Am J Psychiatry* 2013; **170**: 1041-1050 [PMID: 24030613 DOI: 10.1176/appi.ajp.2013.12070899]
24 **Shedler J**. The efficacy of psychodynamic psychotherapy. *Am Psychol* 2010; **65**: 98-109 [PMID: 20141265 DOI: 10.1037/a0018378]
25 **de Maat S**, de Jonghe F, de Kraker R, Leichsenring F, Abbass A, Luyten P, Barber JP, Rien Van, Dekker J. The current state of the empirical evidence for psychoanalysis: a meta-analytic approach. *Harv Rev Psychiatry* 2013; **21**: 107-137 [PMID: 23660968 DOI: 10.1097/HRP.0b013e318294f5fd]
26 **Huber D**, Zimmermann J, Henrich G, Klug G. Comparison of cognitive-behaviour therapy with psychoanalytic and psychodynamic therapy for depressed patients - a three-year follow-up study. *Z Psychosom Med Psychother* 2012; **58**: 299-316 [PMID: 22987495 DOI: 10.13109/zptm.2012.58.3.299]
27 **Brown J**. Specific Techniques Vs. Common Factors? *Am J Psychother* 2015; **69**: 301-316 [PMID: 26414311 DOI: 10.1176/appi.psychotherapy.2015.69.3.301]
28 **Taurke EA**, Flegenheimer W, McCullough L, Winston A, Pollack J, Trujillo M. Change in patient affect/defense ratio from early to late sessions in brief psychotherapy. *J Clin Psychol* 1990; **46**: 657-656 [PMID: 2246376 DOI: 10.1002/1097-4679(199009)46:5<657::aid-jclp2270460519>3.0.co;2-g]
29 **McCullough ME**, Worthington EL Jr, Rachal KC. Interpersonal forgiving in close relationships. *J Pers Soc Psychol* 1997; **73**: 321-336 [PMID: 9248052 DOI: 10.1037//0022-3514.73.2.321]
30 **Winston RB**. Student housing and residential life: A handbook for professionals committed to student development goals. The Jossey-Bass higher and adult education series. San Francisco: Jossey-Bass, Inc., 1993: 1-628
31 **Høglend P**, Hersoug AG, Bøgwald KP, Amlo S, Marble A, Sørbye Ø, Røssberg JI, Ulberg R, Gabbard GO, Crits-Christoph P. Effects of transference work in the context of therapeutic alliance and quality of object relations. *J Consult Clin Psychol* 2011; **79**: 697-706 [PMID: 21859184 DOI: 10.1037/a0024863]
32 **Schmidsberger F**, Löffler-Stastka H. Empathy is proprioceptive: the bodily fundament of empathy - a philosophical contribution to medical education. *BMC Med Educ* 2018; **18**: 69 [PMID: 29622015 DOI: 10.1186/s12909-018-1161-y]
33 **Pastner B**, Schechtner C, Billeth S, Preusche I, Alexopoulos J, Löffler-Stastka H. Development of therapeutic attitudes: Teaching and learning in psychotherapy. *Procedia - Social and Behav Sci* 2014; **116**: 1170-1175 [DOI: 10.1016/j.sbspro.2014.01.364]
34 **Wampold BE**. How important are the common factors in psychotherapy? *World Psychiatry* 2015; **14**: 270-277 [PMID: 26407772 DOI: 10.1002/wps.20238]
35 **Lambert MJ**. Prevention of treatment failure: The use of measuring, monitoring, and feedback in clinical practice. Washington, DC: APA, 2010 [DOI: 10.1037/12141-000]

36 **Drisko J**. The common factors model: Its place in clinical practice and research. *Smith Coll Stud Soc* 2013; **83**: 398-413 [DOI: 10.1080/00377317.2013.833435]

37 **Eversmann J**, Schöttke H, Wiedl KH, Rogner J. Die Beobachtungsskala „Therapie-relevante interpersonelle Verhaltensweisen" (TRIB) in der Auswahl von Teilnehmern der Psychotherapieausbildung. *Z Klin Psychol Psychother: Forschung und Praxis* 2011; **40**: 11-21 [DOI: 10.1026/1616-3443/a000062]

38 **McDonald S**. Emotions Are Rising: The Growing Field of Affect Neuropsychology. *J Int Neuropsychol Soc* 2017; **23**: 719-731 [PMID: 29198275 DOI: 10.1017/S1355617717000844]

39 **Fidler F**, Wilcox J. Reproducibility of scientific results. [cited 22 April 2021]. In: Stanford Encyclopedia of Philosophy [Internet]. Available from: https://plato.stanford.edu/entries/scientific-reproducibility/

40 **Tretter F**, Löffler-Stastka H. Medical knowledge integration and "systems medicine": Needs, ambitions, limitations and options. *Med Hypotheses* 2019; **133**: 109386 [PMID: 31541780 DOI: 10.1016/j.mehy.2019.109386]

41 **Tyng CM**, Amin HU, Saad MNM, Malik AS. The Influences of Emotion on Learning and Memory. *Front Psychol* 2017; **8**: 1454 [PMID: 28883804 DOI: 10.3389/fpsyg.2017.01454]

42 **Botvinik-Nezer R**, Holzmeister F, Camerer CF, Dreber A, Huber J, Johannesson M, Kirchler M, Iwanir R, Mumford JA, Adcock RA, Avesani P, Baczkowski BM, Bajracharya A, Bakst L, Ball S, Barilari M, Bault N, Beaton D, Beitner J, Benoit RG, Berkers RMWJ, Bhanji JP, Biswal BB, Bobadilla-Suarez S, Bortolini T, Bottenhorn KL, Bowring A, Braem S, Brooks HR, Brudner EG, Calderon CB, Camilleri JA, Castrellon JJ, Cecchetti L, Cieslik EC, Cole ZJ, Collignon O, Cox RW, Cunningham WA, Czoschke S, Dadi K, Davis CP, Luca A, Delgado MR, Demetriou L, Dennison JB, Di X, Dickie EW, Dobryakova E, Donnat CL, Dukart J, Duncan NW, Durnez J, Eed A, Eickhoff SB, Erhart A, Fontanesi L, Fricke GM, Fu S, Galván A, Gau R, Genon S, Glatard T, Glerean E, Goeman JJ, Golowin SAE, González-García C, Gorgolewski KJ, Grady CL, Green MA, Guassi Moreira JF, Guest O, Hakimi S, Hamilton JP, Hancock R, Handjaras G, Harry BB, Hawco C, Herholz P, Herman G, Heunis S, Hoffstaedter F, Hogeveen J, Holmes S, Hu CP, Huettel SA, Hughes ME, Iacovella V, Iordan AD, Isager PM, Isik AI, Jahn A, Johnson MR, Johnstone T, Joseph MJE, Juliano AC, Kable JW, Kassinopoulos M, Koba C, Kong XZ, Koscik TR, Kucukboyaci NE, Kuhl BA, Kupek S, Laird AR, Lamm C, Langner R, Lauharatanahirun N, Lee H, Lee S, Leemans A, Leo A, Lesage E, Li F, Li MYC, Lim PC, Lintz EN, Liphardt SW, Losecaat Vermeer AB, Love BC, Mack ML, Malpica N, Marins T, Maumet C, McDonald K, McGuire JT, Melero H, Méndez Leal AS, Meyer B, Meyer KN, Mihai G, Mitsis GD, Moll J, Nielson DM, Nilsonne G, Notter MP, Olivetti E, Onicas AI, Papale P, Patil KR, Peelle JE, Pérez A, Pischedda D, Poline JB, Prystauka Y, Ray S, Reuter-Lorenz PA, Reynolds RC, Ricciardi E, Rieck JR, Rodriguez-Thompson AM, Romyn A, Salo T, Samanez-Larkin GR, Sanz-Morales E, Schlichting ML, Schultz DH, Shen Q, Sheridan MA, Silvers JA, Skagerlund K, Smith A, Smith DV, Sokol-Hessner P, Steinkamp SR, Tashjian SM, Thirion B, Thorp JN, Tinghög G, Tisdall L, Tompson SH, Toro-Serey C, Torre Tresols JJ, Tozzi L, Truong V, Turella L, van 't Veer AE, Verguts T, Vettel JM, Vijayarajah S, Vo K, Wall MB, Weeda WD, Weis S, White DJ, Wisniewski D, Xifra-Porxas A, Yearling EA, Yoon S, Yuan R, Yuen KSL, Zhang L, Zhang X, Zosky JE, Nichols TE, Poldrack RA, Schonberg T. Variability in the analysis of a single neuroimaging dataset by many teams. *Nature* 2020; **582**: 84-88 [PMID: 32483374 DOI: 10.1038/s41586-020-2314-9]

43 **Bateman A**, Fonagy P. Mentalization-Based Treatment. *Psychoanal Inq* 2013; **33**: 595-613 [PMID: 26157198 DOI: 10.1080/07351690.2013.835170]

44 **Rosenfeld A**. Better metrics for evaluating explainable artificial intelligence. In: AAMAS '21: Proceedings of the 20th International Conference on Autonomous Agents and Multi Agent Systems. Richland: International Foundation for Autonomous Agents and Multiagent Systems, 2021: 45–50

45 **Anstadt T**, Merten J, Ullrich B, Krause R. Affective dyadic behavior, core conflictual relationship themes, and success of treatment. *Psychother Res* 1997; **7**: 397-417 [DOI: 10.1080/10503309712331332103]

46 **Krause R**. The development of different selves on the basis of leading maternal affects: Metatheoretical, clinical and technical reflections. *Int Forum Psychoanal* 2020; **30**: 22-23 [DOI: 10.1080/0803706x.2020.1749300]

47 **Datz F**, Wong G, Löffler-Stastka H. Interpretation and Working through Contemptuous Facial Micro-Expressions Benefits the Patient-Therapist Relationship. *Int J Environ Res Public Health* 2019; **16**: 4901 [PMID: 31817282 DOI: 10.3390/ijerph16244901]

48 **Steinmair D**, Richter F, Löffler-Stastka AH. Relationship between Mentalizing and Working Conditions in Health Care. *Int J Environ Res Public Health* 2020; **17**: 2420 [PMID: 32252375 DOI: 10.3390/ijerph17072420]

49 **Fonagy P**, Campbell C. Future directions in personality pathology. *Curr Opin Psychol* 2021; **37**: 145-151 [PMID: 33571731 DOI: 10.1016/j.copsyc.2021.01.001]

50 **Dolensek N**, Gehrlach DA, Klein AS, Gogolla N. Facial expressions of emotion states and their neuronal correlates in mice. *Science* 2020; **368**: 89-94 [PMID: 32241948 DOI: 10.1126/science.aaz9468]

51 **Klein M**. Love, guilt, and reparation and other works. In: The writings of Melanie Klein. 1st ed. London: Hogarth Press, 1975

52 **Moccia L**, Mazza M, Di Nicola M, Janiri L. The Experience of Pleasure: A Perspective Between Neuroscience and Psychoanalysis. *Front Hum Neurosci* 2018; **12**: 359 [PMID: 30233347 DOI:

10.3389/fnhum.2018.00359]
53 **Milic B**, Feller C, Schneider M, Debbané M, Löffler-Stastka H. Social cognition in individuals with 22q11 deletion syndrome linked to psychopathology and social outcomes: A review. *BMC Psychiatry* 2021 [DOI: 10.1186/s12888-020-02975-5]
54 **Novaes MRCG**, Rodrigues CS, Guilhem DB. Scientific integrity and copyright in codes of professional ethics. *Rev Bioét* 2018; **26**: 387-96 [DOI: 10.1590/1983-80422018263258]
55 **González-Duarte A**, Zambrano-González E, Medina-Franco H, Alberú-Gómez J, Durand-Carbajal M, Hinojosa CA, Aguilar-Salinas CA, Kaufer-Horwitz M. II. The research ethics involving vulnerable groups. *Rev Invest Clin* 2019; **71**: 217-225 [PMID: 31448777 DOI: 10.24875/RIC.19002812]
56 **Kirshner LA**. Toward an ethics of psychoanalysis: a critical reading of Lacan's ethics. *J Am Psychoanal Assoc* 2012; **60**: 1223-1242 [PMID: 23118239 DOI: 10.1177/0003065112457876]
57 **Lacan J**. The Seminar of Jacques Lacan Book VII. In: The ethics of Psychoanalysis. 1st ed. Miller JA, editor. London, UK: Routledge; 1992: i-352
58 **Bion WR**. Notes on memory and desire. *Psychoanalytic Forum* 1967; **2**: 272-280
59 **Camilleri N**, Chiarenza GA, Cosmiou A, Debbané M, Garcia-Lopez LJ, Gergov V, Girini K, Hochgerner M, Löffler-Stastka H, Markovska-Simoska S, Milic B, Podina IR, Poulsen S, Prevendar T, Sacco R, Saliba A, Saliba E, Torres S, Tulbure BT, Ulberg R, Fondacaro DV, Vousoura E. Predictors and moderators of psychotherapy outcome for mental disorders in young people: Protocol for a systematic review. PROSPERO 2020 CRD42020166756. [cited 10 January 2021]. In: National Institute for Health Research [Internet]. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020166756
60 **McFarquhar T**, Luyten P, Fonagy P. Changes in interpersonal problems in the psychotherapeutic treatment of depression as measured by the Inventory of Interpersonal Problems: A systematic review and meta-analysis. *J Affect Disord* 2018; **226**: 108-123 [PMID: 28968563 DOI: 10.1016/j.jad.2017.09.036]
61 **van Leeuwen WA**, van Wingen GA, Luyten P, Denys D, van Marle HJF. Attachment in OCD: A meta-analysis. *J Anxiety Disord* 2020; **70**: 102187 [PMID: 31951931 DOI: 10.1016/j.janxdis.2020.102187]
62 **Luyten P**, Campbell C, Allison E, Fonagy P. The Mentalizing Approach to Psychopathology: State of the Art and Future Directions. *Annu Rev Clin Psychol* 2020; **16**: 297-325 [PMID: 32023093 DOI: 10.1146/annurev-clinpsy-071919-015355]
63 **Thabrew H**, Stasiak K, Hetrick SE, Donkin L, Huss JH, Highlander A, Wong S, Merry SN. Psychological therapies for anxiety and depression in children and adolescents with long-term physical conditions. *Cochrane Database Syst Rev* 2018; **12**: CD012488 [PMID: 30578633 DOI: 10.1002/14651858.CD012488.pub2]
64 **Newen A**. The Embodied Self, the Pattern Theory of Self, and the Predictive Mind. *Front Psychol* 2018; **9**: 2270 [PMID: 30532721 DOI: 10.3389/fpsyg.2018.02270]

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REVIEW

Binge eating and psychostimulant addiction

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Abstract

Many of the various factors, characteristics, and variables involved in the addictive process can determine an individual's vulnerability to develop drug addiction. Hedonic eating, based on pleasure rather than energy needs, modulates the same reward circuits, as do drugs of abuse. According to the last report of the World Health Organization, the worldwide obesity rate has more than doubled since 1980, reaching especially critical levels in children and young people, who are overexposed to high-fat, high-sugar, energy-dense foods. Over the past few decades, there has been an increase in the number of studies focused on how eating disorders can lead to the development of drug addiction and on the comorbidity that exists between the two disorders. Herein, we review the most recent research on the subject, focusing especially on animal models of binge eating disorders and drug addiction. The complex profile of patients with substance use and binge eating disorders requires an integrated response to dually diagnosed patients. Nutritional patterns should be considered an important variable in the treatment of substance use disorders, and future studies need to focus on specific treatments and interventions in individuals who show a special vulnerability to shift from one addiction to the other.

Key Words: Binge eating; Psychostimulant; Dopamine; Obesity; Reward; Addiction

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Core Tip: In recent years there has been an increased interest in the relationship between food rewarding properties and drug abuse. Binge eating and drug abuse are associated with loss of control and share clinical morbidity. The comorbidity complicates the evaluation and treatment of both disorders, affecting inhibitory control

conflicting interests.

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and decision making. This is the first mini-review exploring the most recent research about how bingeing on palatable food can potentially influence vulnerability to develop psychostimulant addiction. It includes the behavioral and neurobiological commonalities between binge eating disorder and drug addiction, especially focusing on recent animal studies.

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INTRODUCTION

The aim of the present review is to throw light on the similarities between binge eating disorder and substance use disorders by exploring the most recent research about how bingeing on palatable food can influence vulnerability to the development of psychostimulant addiction. We address how the two disorders co-occur, and discuss the need for new forms of treatment and therapies that approach the problem as a dual pathology.

In all species of the animal kingdom, nutrition is crucial for the maintenance of adequate energy stores for survival. Mammals need to maintain a stable body temperature, and as they have a high metabolic rate, they require a constant supply of large amounts of energy[1]. That is the reason why mammalian brains have evolved to develop several neuronal systems that drive feeding behavior, with the rewarding nature of eating being one of the most potent drives behind feeding[2]. Beyond the homeostatic regulation of food intake, and in order to promote survival, the complex neural networks within the brain drive individuals to seek the most caloric foods. During evolution, our organism has developed in a context of nutritional shortage, so we have an innate biological preference for that type of food. That is why palatable foods high in fat, sugar, and salt induce a potent release of dopamine in our brain reward system, producing a great feeling of pleasure[3].

As a consequence of the brain's bias towards palatable food, overeating and obesity are global diseases of our modern society, even though both are preventable. For many years, malnutrition was a common problem, but now, according to the most recent report of the World Health Organization[4], worldwide obesity rates have more than tripled since 1975, and it now kills more people than undernourishment. In 2016, 39% of the world population over 18 years of age was overweight and 13% were obese. This problem is especially critical in children and young people, who are more vulnerable to inadequate dietary habits and are overexposed to high-fat, high-sugar, high-salt, energy-dense foods of lower nutritional quality. In 2016, 41 million children under 5 years of age worldwide were overweight or obese. The progressive and continuous increase in metabolic diseases and overweight is related to obesogenic environmental factors, such as the high number of fast food establishments, the decrease in physical activity associated with the sedentary nature of many forms of work, transportation choices, and increased urbanization[4,5]. The rise in obesity rates worldwide has encouraged extensive research to improve our understanding of the problem, particularly the excessive intake of food, and especially that of sugary and fatty foods, which has become a serious health problem for our society.

The 21st century society is characterized by the consumption of ultraprocessed food that is high in fat and sugar and is often eaten for pleasure rather than survival; in this context, Gold[6] defined "hedonic eating" as *eating based on pleasure rather than energy needs*. Research to date shows that hedonic eating modulates neural mechanisms related to reward processing[7], the same circuits activated by drugs of abuse, which explains the maintenance and escalation of this behavior. The brain reward system is designed to play a crucial role in basic survival activities, such as eating, sex or sleep [1]. However, we are currently facing a situation in which palatable food not only supports our survival but also modulates our brain function and behavior.

Drugs of abuse target the abovementioned reward system, inducing an overstimulation of the circuitry that eventually overrides the pleasurable effects of other basic activities[8]. As with other psychiatric disorders, not all humans have the same risk of

developing an addiction, and the risk varies considerably from one person to another. There are many different factors, characteristics, and variables involved in the addictive process, and they determine an individual's vulnerability to develop this disease. In general, the more risk factors found in a person, the greater is the probability of developing a substance use disorder after taking drugs occasionally[9]. Among the environmental and lifestyle variables under investigation in recent years are nutritional habits and eating patterns, which not only contribute to the obesity epidemic, but also affect our mental health and can lead to the development of a substance use disorder[10].

The latest research suggests that both drug addiction and obesity are disorders in which the value of drug or food reinforcement, respectively is abnormally increased in relation to and at the expense of other reinforcements[7,10]. Both drugs and food have powerful rewarding effects mediated by increases in dopamine release in the limbic system that, under certain circumstances or in vulnerable subjects, can alter the homeostatic control mechanisms of hunger and satiety[7,11,12]. For example, it has been shown that individuals with a substance use disorder or obesity have a reduced number of dopamine receptors in the nucleus accumbens[7], and the neuroadaptation has been directly related to a decrease in the basal activity of the frontal regions involved in reward and inhibitory control[13].

Adolescent populations today are often characterized by abnormal dietary habits and lower levels of physical activity, resulting in an increased percentage of overweight adolescents that will later become obese adults. Apart from the risk of developing obesity-derived cardiovascular diseases such as diabetes, it is important to bear in mind that adolescents are more prone than adults to develop eating disorders, such as anorexia, bulimia, and binge eating[14]. Moreover, nonclinical binge eating behavior is very common among the adolescent population, as every weekend a high percentage of this age group engages in episodes of excessive intake of fast food combined with the consumption of large amounts of alcohol and other substances of abuse. The adolescent brain works in a promotivational state, with a strong, fully developed reward system, but still developing inhibitory control areas, such as the prefrontal cortex[15]. Although basal levels of synaptic dopamine are lower during adolescence, there is an increase in drug-induced dopamine release during this period [16,17]. As a consequence, teenagers exposed too early to these potent rewards may suffer from an unbalanced brain reward system when they become adults[18,19].

As several studies have reported that drug use early on in life often predicts an increased likelihood of continued use into adulthood[20], a gateway theory has also been applied to eating disorders[21]. According to the theory, binge eating can lead to the development of another maladaptive behavior, such as drug abuse. The literature available to date points to the mutual influence of palatable diets and psychostimulants, but there is a need to increase awareness of the problem and to perform more studies in humans to confirm the data obtained in preclinical studies.

COMMONALITIES BETWEEN BINGE EATING DISORDER AND DRUG ADDICTION

Behavioral commonalities between binge eating disorder and substance use disorder

The interaction between drug abuse and food, hunger, and appetite, has not inspired interest only in recent times. Since the earliest recorded use of cocaine, indigenous peoples have consumed the drug in order to boost energy levels that allow them to work at high altitude and also to reduce appetite[22]. When cocaine consumption spread to other cultures, cocaine abusers in the United States would report forgetting to eat on many occasions, and had multiple nutritional deficiencies, anorexia and weight loss. Similar observations have been made with respect to methamphetamine, amphetamine, and ecstasy consumers. Under these circumstances, psychostimulants and food compete, and drugs would seem to be the winner[6]. Moreover, although psychostimulants like cocaine or amphetamine produce few withdrawal symptoms, they lead to multiple alterations in appetite and mood[23].

Among eating disorders, binge eating is highly prevalent. The DSM-5 defines binge eating as recurring episodes of rapid and excessive food consumption in a short period of time, marked by feelings of lack of control, and not necessarily driven by hunger or metabolic need[24]. Although binge eating is related to obesity, many people who binge are not obese, and most obese people do not present binge eating disorder[25].

Binge eating and substance use disorders belong to the family of intermittent excessive behaviors, which are associated with loss of control and are clinically comorbid[26,27]. Forms of psychostimulant consumption vary considerably among individuals, with the appearance of a binge pattern being very frequent. Binges or "runs" are defined as the way cocaine is consumed in an intense and repetitive manner over several hours and days[28]. This pattern of cocaine intake is associated with increased medical and psychiatric consequences and is linked to worse health and social outcomes[29,30].

To date, research has revealed a high comorbidity between binge eating and substance use disorders[31], which complicates the evaluation and treatment of both disorders[32] and increases low adherence to treatment[33,34]. An early study at the Center for Addiction and Substance Abuse of the University of Columbia[35] reported that the prevalence of drug abuse was 50% in the case of individuals suffering from eating disorders, while it was around 9% in the general population. On the other hand, 35% of people diagnosed with a substance use disorder exhibited comorbidity with eating disorders, compared with 1%-3% of the general population. More recently, a study performed by an Addictive Behavior Treatment Unit in Spain demonstrated a higher prevalence of eating disorders in a population with substance use disorder[36]. Participants who presented with a substance use disorder had higher scores on all scales indicating the presence of an eating disorder, with values proving especially high in women. A recent study in a university sample showed that binge eating and fat intake were positively related to binge drinking in students[37].

Current research is focused on the symptomatic and neurobiological similarity between alterations in appetite and satiety, obsessive and impulsive disorders, self-destructive behaviors and medical consequences[38]. Among the shared characteristics, several drug addiction symptoms were also observed in individuals with a binge eating disorder[39,40]. Consuming drugs or eating palatable food are both motivated appetitive behaviors with common aspects, and both can evolve into addictive behavior[41]. Both eating disorders and drug abuse commonly begin during a vulnerable period, such as adolescence. In the same way as an individual with a drug addiction ignores responsibilities or obligations in order to take drugs, people with a binge eating disorder devote all their energy to bingeing, purging, exercising, and making efforts to lose weight[42]. Similar to drug abuse, individuals engage in eating disorders despite the serious consequences of the acts in question, making them vulnerable to relapse after periods of regular behavior[43].

Common neurobiology: The dopaminergic, opioid and cannabinoid systems

The brain reward system is clearly the most important neurotransmitter system involved in binge eating and substance use disorders, which are characterized by the impulsive and compulsive intake of drugs or highly palatable food[44,45]. Although multiple neurotransmitters are implicated, the dopamine and opioid systems are the main regulators of feeding behaviors and drug addiction[44,46]. While dopamine is involved in the motivation toward a rewarding activity and its subsequent conditioning, opioids participate in the enjoyment and pleasurable effects of the rewarding activity[47,48]. However, the two pathways do not function independently, and both can be altered by other neurotransmitters[47]. For example, dopaminergic signals can be modified by endogenous opioids, while opioid signaling needs a dopamine D2 receptor to work correctly. In line with this, Smith and Robbins[49] reported that both substance use disorders and binge eating disorder are related by dysfunctional dopaminergic and opioid signaling as well as decreased activity in the prefrontal cortex area, a brain area associated with inhibitory control and decision making. Other studies have found common polymorphisms in the mu-opioid receptor gene and the D2 receptor gene in a sample of individuals with binge eating and substance use disorders, and it has been proposed that the polymorphisms increase vulnerability to the rewarding effects of food and drugs[47,50].

The predisposition to emotion-based impulsive actions observed in both binge eating disorder and substance use disorders[51] can also be explained by neurobiology. Every time an individual takes a drug there is a massive dopamine release that results in a pronounced subjective perception of reward[52]. This experience leads the individual to choose this option to regulate their positive or negative emotional state. Over time, drug use induces changes in neuroplasticity that increase the brain's reward threshold, so that the user requires more drug more frequently to achieve the same pleasurable effects[53]. At this stage, the brain produces neuroadaptations; the effectiveness of dopamine D2 receptors decreases, which is accompanied by a reduced sensitivity to the rewarding effects of other natural reinforcers[54]. These decreased striatal dopamine D2 receptor levels are present in humans with substance use disorder and in animal models of compulsive drug intake

[55].

Regarding binge eating disorder, research shows that women with bulimia nervosa tend to have lower levels of dopamine receptors, and a negative correlation has been highlighted between episodes of binge eating, purging, and striatal dopamine response[56]. Similar to that seen with drugs of abuse, increasingly higher amounts of dopamine need to be released to obtain the same pleasurable effect of palatable food [57]. A decrease in dopamine D2 receptors in the striatum and nucleus accumbens has been described in rats bingeing on sugar[58]. Similarly, after 30 d of intermittent access to a high-sugar beverage, a decrease in dopamine D2 receptors and an increase in dopamine D1 receptors in the dorsal striatum and nucleus accumbens have been described in the same species[59]. Alterations in D2 regulation are related with compulsive drug abuse and binge eating in rodents, with a shift from reward-directed consumption to a compulsive drug and food intake[60,61]. On the other hand, studies in humans have reported alterations in dopamine turnover and receptors in individuals with binge eating disorder[7,62].

Endogenous opioids play an important role in the positive experience associated with eating, both in humans and in animals[63]. Activation of the mu-opioid receptor increases dopamine release in the nucleus accumbens by inhibiting GABAergic neurons in the ventral tegmental area[64,65]. Normally, these neurons provide a tonic-like inhibition of dopamine neurons, but inhibiting this process results in an increase in dopamine release[66]. Studies to date have shown how nutritional conditions can significantly dysregulate the function of the endogenous opioid system, contributing to a worsening of different eating disorders, including binge eating disorder. In fact, some eating disorders have been shown to modify plasma beta-endorphin levels and induce alterations in mu-receptor function[67,68]. We have recently reported decreased gene expression of the mu-opioid receptor in the nucleus accumbens of animals that binged on fat[69]. As an example of the important role that opioids play in binge eating, medications like naltrexone, an opioid antagonist used to treat substance use disorders, work by reducing the frequency of binge eating and purging in bulimia nervosa, and through the positive perception of highly palatable foods[70].

Lastly, a promising therapeutic target is the endocannabinoid system, which is a key point of the regulatory network that controls energy homeostasis[71]. While the opioid is dopamine-anticipating food, the endocannabinoid system is related to the homeostatic control of intake and positive feedback of the specific intake of fatty food [72]. Hypothalamic endocannabinoids control food intake by decreasing satiety signals and increasing orexigenic signals[73]. Moreover, they modulate reward mechanisms by interacting with the mesolimbic pathways, increasing the motivation to eat and possibly reinforcing the incentive or hedonic value of food[74]. Some studies have discovered alterations in anandamide, an endogenous cannabinoid ligand, in patients with anorexia and binge eating disorder, but not in those with bulimia nervosa, suggesting a possible involvement of endocannabinoids in the rewarding aspects of aberrant eating behaviors[75]. Recent animal studies have highlighted changes in brain levels of anandamide in rats that binge on fat[76] and changes in *CB1r* gene expression in the prefrontal cortex and nucleus accumbens[69]. The neurobiological relationship between substance use disorders and binge eating disorder is shown in Figure 1.

ANIMAL STUDIES: PALATABLE FOOD SENSITIZES TO DRUG ADDICTION

In this section we will review a series of basic studies focused on intermittent and limited access to palatable food, which mimics binge eating disorder and induces an escalation in intake over time. Currently, there is evidence that the composition of a diet, such as the percentage of sugar or fat, can affect the intake of drugs of abuse. Laboratory animal models are useful for understanding the factors that contribute to both disorders, helping to broaden horizons and open new perspectives of treatment [42]. As we have previously explained, psychological and biological similarities between palatable food intake and addiction to drugs of abuse have previously been reported, highlighting common reward mechanisms and suggesting that nutritional status is an important factor in the development of addiction[7].

Some authors have implied that, rather than the food itself, it is the way food is consumed that alters the reward system and contributes to vulnerability to other addictive disorders[77,78]. Current research mainly concentrates on two animal eating patterns that modulate reward system function, continuous access *vs* limited access models. While continuous ad libitum access to palatable diets creates animal models of obesity and metabolic syndrome, the limited access model resembles binge eating in

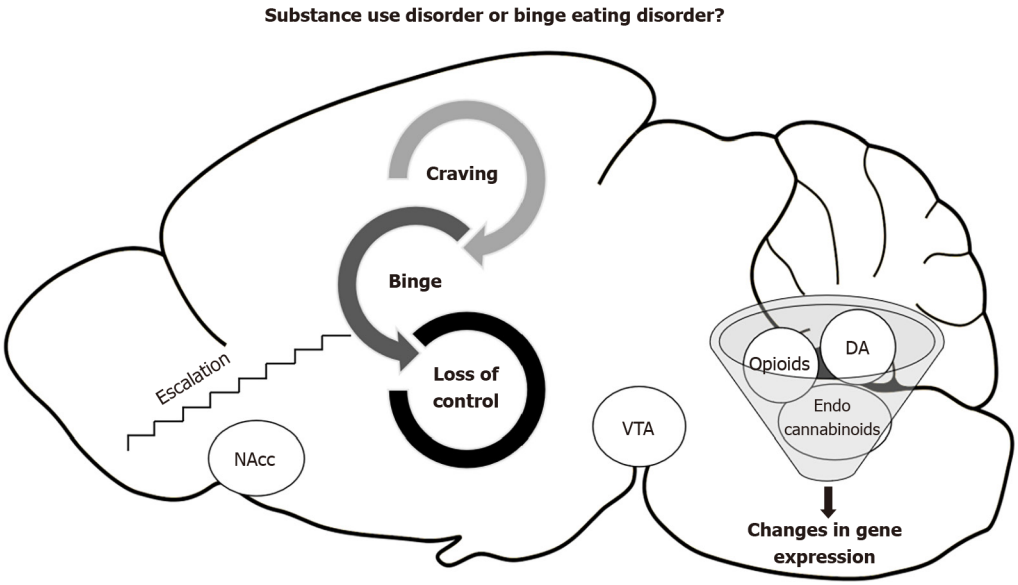

Figure 1 Relationship between substance use disorders and binge eating disorder. DA: Dopamine; NAcc: Nucleus accumbens; VTA: Ventral tegmental area.

its intermittent pattern[78]. Although animal models of binge eating reveal behaviors similar to those seen in humans, they mimic only some of the characteristics of the human disorder. They do not include blame, guilt, the sense of losing control, or the social influence of human eating behavior[79]. Despite these limitations, they share numerous features with human patterns of eating; for example, animals ingest a large amount of food in a brief period of time, exceeding the quantity that an animal maintained on a standard diet would eat in similar circumstances[80].

There are three binge eating models that have been the most widely used to date. The model of sugar bingeing proposed by Avena[58] was the first animal model of food addiction. In that model, animals have intermittent access to a 10% sugar beverage and develop behaviors and brain changes that are analogous to those produced by drugs of abuse in addition to a withdrawal syndrome similar to that induced by opioids. Artiga *et al*[81] described another model, a history of dieting and stress that induces binge eating behavior with palatable and nonpalatable foods. In that model, rats are subjected to cycles of food restriction and refeeding. For 5 d, they are administered only 66% of the standard diet given to control animals. For the next 2 d, animals have ad libitum access to chow and chocolate cookies, *etc.* The repetitive cycle is a good model to mimic what occurs in disorders like bulimia nervosa, as a prior history of energy deprivation is the most critical trigger of binge eating. The third program is the limited access model of Corwin *et al*[82]. It is a non-food-deprivation model in which rats have sporadic, intermittent, and limited access to high-fat food that allows an escalation of food intake to occur[83]. Eating in the absence of hunger is one of the most important characteristics of binge eating in humans, which demonstrates its hedonic nature[80,84].

Research on the link between binge eating disorder and vulnerability to drug addiction points to two main behavioral outcomes, cross-sensitization and the gateway theory[85]. The cross-sensitization phenomenon refers to the effects of bingeing on palatable foods, which leads to long-lasting neuroadaptations that increase the acute response to another drug. Early research in this area focused on the locomotor response to different drugs of abuse after exposure to different binge eating patterns. The majority of studies showed that animals developed a pattern of bingeing on palatable food, and exhibited enhanced locomotor sensitization to amphetamine[86,87] and cocaine[88-90]. These initial studies indicated that the compulsive behavior of bingeing on palatable food sensitizes the same system on which psychostimulants exert their action[86]. Intermittent access to palatable food promptly promotes a compulsion in intake and stimulation of the dopamine circuits in the nucleus accumbens that is sustained over time[62]. The response of the nucleus accumbens is similar to that observed after consumption of psychostimulants. Initially, when food is novel and palatable, dopamine levels in the shell increase, while those in the core are released independently of the reward's novelty[91]. Avena *et al*[77] suggested that

dopamine release derived from bingeing on palatable food is not subject to habituation, as it remains elevated even after repeated bingeing episodes.

After having shown that binge eating behavior induces increased sensitivity to the locomotor effects of psychostimulants, subsequent studies went further and investigated whether animals were also more prone to develop a substance use disorder, such as an increase in cocaine seeking and consuming. Most studies used operant self-administration (SA) and conditioning place preference (CPP) paradigms. The SA paradigm directly assesses a mouse's disposition to take the drug, as animals have to press a lever to experience the drug's rewarding effect. The animal is free to choose to consume or not, and the paradigm directly measures motivation for the drug[92]. On the other hand, the CPP focuses on the role of contextual cues associated with the pleasurable effect of the drug. Mice associate a place or compartment with the rewarding experience of the drug and eventually develop a conditioned preference for that place[93]. Both paradigms provide a complete picture of what occurs in human addiction, when people consume to enjoy the pleasurable effects of the drug, but also because they find themselves in certain social contexts. These aspects play a crucial role in relapse into drug seeking.

To evaluate whether bingeing on palatable food alters an animal's disposition and motivation to take a drug, a 2011 study that used the limited access model of Corwin found a tendency toward an increase in intravenous cocaine SA, but the effect was not significant[94]. Consequently, we performed several mouse studies in our laboratory to further investigate this phenomenon, confirming that bingeing on fat during an early period of life, such as adolescence, enhanced intravenous cocaine SA and motivation to obtain the drug in adulthood[69]. We also used Corwin's limited access model, in which adolescent mice had limited access to a high-fat chow for 2 h, 3 d/wk, with continuous access to a standard diet in their home cages. We observed an escalation in the intake of fat from the second week onwards, which confirmed the rapid development of fat bingeing behavior. Mice exposed to the high-fat binge sessions during adolescence showed an increase in cocaine SA compared with those fed a healthy standard diet. After acquiring a sustained cocaine SA, animals under-went an extinction process. When the operant behavior of pressing the lever to obtain cocaine was extinguished, mice were exposed once again to a single high-fat binge, which induced a strong reinstatement of the cocaine SA. Similarly, Barnea *et al*[85] observed that restricted access to a palatable diet was a risk factor for cocaine SA and drug craving and for binge eating state and trait, especially in the latter case. A binge eating state is induced by intermittent access to palatable diets, while the binge eating trait is a phenotypical proneness for overeating.

Regarding the key role of environmental clues in psychostimulant reward, a series of studies was performed in which animals that binged on fat during adolescence developed CPP for the drug-paired compartment, even with very low doses of cocaine [69] that were not effective in animals on a standard diet. The results confirmed that bingeing on fat increases sensitivity to the rewarding effects of cocaine and strengthens contextual memories associated with the pleasant experience.

Finally, palatable food can also induce withdrawal or craving for specific kinds of foods that are generally high in fat, salt, and sugar, much like that observed in drug addiction. For example, patients have described intense feelings of panic and anxiety when they are forced to postpone a binge eating episode or when they remove certain types of palatable food from their diet, leading to headaches, irritability, and anxiety [56,95]. Studies in animals also confirm that withdrawal symptoms are experienced when binge eating of specific kinds of food is stopped, confirming its potent effect on the brain[69,96,97]. The withdrawal-like symptoms common to cessation of any palatable diet arise following an increase in corticosterone and anxiety levels[98-100].

The effects of cessation of palatable food bingeing on the reward system have also been studied. For example, there is a significant increase in the locomotor response to cocaine after withdrawal from sugar[88,101]. Furthermore, animals that stop bingeing on fat are more resistant to forgetting the contextual memories associated with cocaine, and are more liable to relapse after lower cocaine doses[69]. All the studies suggest that bingeing on palatable food not only increases sensitivity to the rewarding effects of cocaine, but also heightens vulnerability to relapse into drug seeking.

CONCLUSION

Based on the literature published to date, we can conclude that the relationship between binge eating disorder and substance use disorders is a two-way street. On one

hand, binge eating can be a risk factor or a gateway to drug addiction, and on the other, psychostimulant addiction can lead to several eating disorders. While we have referred to binge eating disorder throughout the review, binge eating may produce the same effects without necessarily meeting the diagnostic criteria for binge eating. In the same way as substance abuse, binge eating interferes with daily life and is characterized by persistence of the behavior despite the associated negative consequences, which include guilt, stress, and compensatory behaviors[6]. In relation to the binge cycle, an important common factor between eating disorders and drug abuse is relapse. Nair and colleagues[102] described how, on many occasions, people decide to diet and exercise, but that the resolve only lasts a few weeks, with a rapid return (relapse) of old (bad) habits. In that way, dieting induces changes in the reward system that can subsequently result in relapse into binge eating episodes and overeating.

In this review we have drawn a picture of bingeing on palatable food as something that is as harmful as substance abuse. If feeding is a risk factor that affects the same neurobiological mechanisms as drugs of abuse, early exposure to certain types of ultraprocessed food could be a gateway to increased sensitivity to reward. The high comorbidity that exists between the two disorders supports the hypothesis and highlights the importance of identifying and treating both conditions.

In the same manner that clinicians observe multiple nutritional deficiencies, anorexia and weight loss in cocaine abusers, which is described at the beginning of the review, the opposite effect can be observed after drug withdrawal[103]. Overeating during the rehabilitation phase is often recommended as part of detoxification programs as a way of counteracting craving. In this context, the concept of "addiction transfer," where one addiction is replaced by another, has been proposed[104]. Indeed, increase in the rate of obesity among patients undergoing detoxification can be so dramatic that current substance addiction programs are beginning to complement treatment with physical exercise and diet programs to avoid it.

Most professionals focus on their area of expertise, resulting in the vital need for integrated services to deal with dually diagnosed patients who have a complex profile because of their substance use and binge eating disorders[105]. Until now, there have been no guidelines for experts to treat this comorbid condition. It is surprising that most specialists in substance abuse centers do not follow protocols that broach eating disorders among their patients. Likewise, most clinicians dealing with eating disorders are not trained to detect or investigate the possible misuse of substances of abuse.

Nutritional patterns should be considered an important variable in the treatment of people with substance use disorder, as an eating disorder may develop in parallel to detoxification from the drug, consequently affecting social relationships, cognitive functions, and lifestyle. Future studies should focus on specific treatments and interventions for individuals who have a special vulnerability to transfer from one addiction to another. It is now necessary to discover new therapeutic targets of food and drugs in order to improve public health solutions. In this context, new nutritional interventions are the focus of increasing investigation as possible modulators of reward and other diseases.

REFERENCES

1 **Leonard WR**. Human Nutritional Evolution. In: Stinson S, Bogin B, O'Rourke D. Human Biology: An Evolutionary and Biocultural Perspective. 2nd ed. New York (NY): Wiley, 2012: 251-324 [DOI: 10.1002/9781118108062.ch7]

2 **Saper CB**, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. *Neuron* 2002; **36**: 199-211 [PMID: 12383777 DOI: 10.1016/s0896-6273(02)00969-8]

3 **Kelley AE**, Schiltz CA, Landry CF. Neural systems recruited by drug- and food-related cues: studies of gene activation in corticolimbic regions. *Physiol Behav* 2005; **86**: 11-14 [PMID: 16139315 DOI: 10.1016/j.physbeh.2005.06.018]

4 **World Health Organization**. Obesity and overweight. [cited 9 June 2021]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

5 **Meldrum DR**, Morris MA, Gambone JC. Obesity pandemic: causes, consequences, and solutions-but do we have the will? *Fertil Steril* 2017; **107**: 833-839 [PMID: 28292617 DOI: 10.1016/j.fertnstert.2017.02.104]

6 **Gold MS**. From bedside to bench and back again: a 30-year saga. *Physiol Behav* 2011; **104**: 157-161 [PMID: 21530563 DOI: 10.1016/j.physbeh.2011.04.027]

7 **Volkow ND**, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev* 2013; **14**: 2-18 [PMID: 23016694 DOI: 10.1111/j.1467-789X.2012.01031.x]

8 **Berridge KC**. 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. *Physiol Behav* 2009; **97**: 537-550 [PMID: 19336238 DOI: 10.1016/j.physbeh.2009.02.044]

9 **National Institute on Drug Abuse**. Media Guide. [cited 29 November 2019]. Available from: https://www.drugabuse.gov/publications/media-guide

10 **Avena NM**, Gold JA, Kroll C, Gold MS. Further developments in the neurobiology of food and addiction: update on the state of the science. *Nutrition* 2012; **28**: 341-343 [PMID: 22305533 DOI: 10.1016/j.nut.2011.11.002]

11 **Davis C**, Carter JC. Compulsive overeating as an addiction disorder. A review of theory and evidence. *Appetite* 2009; **53**: 1-8 [PMID: 19500625 DOI: 10.1016/j.appet.2009.05.018]

12 **Koob GF**, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* 2001; **24**: 97-129 [PMID: 11120394 DOI: 10.1016/S0893-133X(00)00195-0]

13 **Moreno-Lopez L**, Contreras-Rodriguez O, Soriano-Mas C, Stamatakis EA, Verdejo-Garcia A. Disrupted functional connectivity in adolescent obesity. *Neuroimage Clin* 2016; **12**: 262-268 [PMID: 27504261 DOI: 10.1016/j.nicl.2016.07.005]

14 **Swanson SA**, Crow SJ, Le Grange D, Swendsen J, Merikangas KR. Prevalence and correlates of eating disorders in adolescents. Results from the national comorbidity survey replication adolescent supplement. *Arch Gen Psychiatry* 2011; **68**: 714-723 [PMID: 21383252 DOI: 10.1001/archgenpsychiatry.2011.22]

15 **Rodríguez-Arias M**, Aguilar MA. Polydrug use in adolescence. In: Addictions-From Pathophysiology to Treatment. *IntechOpen* 2021 [DOI: 10.5772/47961]

16 **Badanich KA**, Adler KJ, Kirstein CL. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. *Eur J Pharmacol* 2006; **550**: 95-106 [PMID: 17011546 DOI: 10.1016/j.ejphar.2006.08.034]

17 **Laviola G**, Pascucci T, Pieretti S. Striatal dopamine sensitization to D-amphetamine in periadolescent but not in adult rats. *Pharmacol Biochem Behav* 2001; **68**: 115-124 [PMID: 11274716 DOI: 10.1016/s0091-3057(00)00430-5]

18 **Bisetto Pons D**, Botella Guijarro Á, Sancho Muñoz A. [Eating Disorders and drug use in adolescents]. *Adicciones* 2012; **24**: 9-16 [PMID: 22508012 DOI: 10.20882/adicciones.112]

19 **Herpertz-Dahlmann B**. Adolescent eating disorders: update on definitions, symptomatology, epidemiology, and comorbidity. *Child Adolesc Psychiatr Clin N Am* 2015; **24**: 177-196 [PMID: 25455581 DOI: 10.1016/j.chc.2014.08.003]

20 **Degenhardt L**, Chiu WT, Conway K, Dierker L, Glantz M, Kalaydjian A, Merikangas K, Sampson N, Swendsen J, Kessler RC. Does the 'gateway' matter? *Psychol Med* 2009; **39**: 157-167 [PMID: 18466664 DOI: 10.1017/S0033291708003425]

21 **Blanco-Gandía MC**, Rodríguez-Arias M. Bingeing on fat increases cocaine reward. *Oncotarget* 2017; **8**: 16105-16106 [PMID: 28199956 DOI: 10.18632/oncotarget.15260]

22 **Hoebel BG**. Three anorectic drugs: similar structures but different effects on brain and behavior. *Int J Obes* 1978; **2**: 157-166 [PMID: 101472]

23 **D'Souza MS**, Markou A. Neural substrates of psychostimulant withdrawal-induced anhedonia. In: Behavioral neuroscience of drug addiction. Springer, Berlin, Heidelberg, 2010: 119-178 [DOI: 10.1007/7854_2009_20]

24 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders. *BMC Med* 2013; **17**: 133-137

25 **Hudson JI**, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry* 2007; **61**: 348-358 [PMID: 16815322 DOI: 10.1016/j.biopsych.2006.03.040]

26 **Corwin RL**. Bingeing rats: a model of intermittent excessive behavior? *Appetite* 2006; **46**: 11-15 [PMID: 16188345 DOI: 10.1016/j.appet.2004.09.002]

27 **Wiederman MW**, Pryor T. Substance use and impulsive behaviors among adolescents with eating disorders. *Addict Behav* 1996; **21**: 269-272 [PMID: 8730530 DOI: 10.1016/0306-4603(95)00062-3]

28 **Daniulaityte R**, Carlson RG, Siegal HA. "Heavy users," "controlled users," and "quitters": understanding patterns of crack use among women in a midwestern city. *Subst Use Misuse* 2007; **42**: 129-152 [PMID: 17366129 DOI: 10.1080/10826080601174678]

29 **Juteau LC**, Roy É, Berbiche D, Arruda N, Bruneau J, Jutras-Aswad D. Examining the Association Between Psychiatric Disorders and Cocaine Binges: Results From the COSMO Study. *J Addict Med* 2018; **12**: 136-142 [PMID: 29283956 DOI: 10.1097/ADM.0000000000000378]

30 **Roy É**, Arruda N, Jutras-Aswad D, Berbiche D, Perreault M, Bertrand K, Dufour M, Bruneau J. Examining the link between cocaine binging and individual, social and behavioral factors among street-based cocaine users. *Addict Behav* 2017; **68**: 66-72 [PMID: 28103534 DOI: 10.1016/j.addbeh.2017.01.012]

31 **Escrivá-Martínez T**, Herrero R, Molinari G, Rodríguez-Arias M, Verdejo-García A, Baños RM. Binge Eating and Binge Drinking: A Two-Way Road? *Curr Pharm Des* 2020; **26**: 2402-2415 [PMID: 32175840 DOI: 10.2174/1381612826666200316153317]

32 **Merlo LJ**, Stone AM, Gold MS. Co-occurring addiction and eating disorders. In: Miller S, Ries RK, Saitz K, Fiellin DA. Principles of addiction medicine. Lippincott Williams & Wilkins, 2009

33 **Elmquist J**, Shorey RC, Anderson SE, Stuart GL. The relationship between early maladaptive schemas and eating-disorder symptomatology among individuals seeking treatment for substance dependence. *Addict Res Theory* 2015; **23**: 429-436 [PMID: 27375373 DOI: 10.3109/16066359.2015.1025063]

34 **Harrop EN**, Marlatt GA. The comorbidity of substance use disorders and eating disorders in

women: prevalence, etiology, and treatment. *Addict Behav* 2010; **35**: 392-398 [PMID: 20074863 DOI: 10.1016/j.addbeh.2009.12.016]

35 **National Center on Addiction and Substance Abuse at Columbia University**. The National Center on Addiction and Substance Abuse (CASA) at Columbia University's analysis of 1999 CASA teen survey data. 2003

36 **Flores-Fresco MJ**, Blanco-Gandía MC, Rodríguez-Arias M. Alterations in eating behavior in patients with substance abuse disorders. *Clínica y Salud* 2018; **29**: 125-132 [DOI: 10.5093/clysa2018a18]

37 **Escrivá-Martínez T**, Galiana L, Herrero R, Rodríguez-Arias M, Baños RM. Understanding the Influence of Eating Patterns on Binge Drinking: A Mediation Model. *Int J Environ Res Public Health* 2020; **17** [PMID: 33348581 DOI: 10.3390/ijerph17249451]

38 **Root TL**, Pisetsky EM, Thornton L, Lichtenstein P, Pedersen NL, Bulik CM. Patterns of co-morbidity of eating disorders and substance use in Swedish females. *Psychol Med* 2010; **40**: 105-115 [PMID: 19379530 DOI: 10.1017/S0033291709005662]

39 **Avena NM**. Examining the addictive-like properties of binge eating using an animal model of sugar dependence. *Exp Clin Psychopharmacol* 2007; **15**: 481-491 [PMID: 17924782 DOI: 10.1037/1064-1297.15.5.481]

40 **Meule A**, Gearhardt AN. Food addiction in the light of DSM-5. *Nutrients* 2014; **6**: 3653-3671 [PMID: 25230209 DOI: 10.3390/nu6093653]

41 **Volkow ND**, Wise RA. How can drug addiction help us understand obesity? *Nat Neurosci* 2005; **8**: 555-560 [PMID: 15856062 DOI: 10.1038/nn1452]

42 **Murray S**, Gordillo M, Avena NM. Animal models of eating disorders, substance use disorders, and addictions. In: Eating Disorders, Addictions and Substance Use Disorders. Springer, Berlin, Heidelberg, 2014: 3-21 [DOI: 10.1007/978-3-642-45378-6_1]

43 **Barbarich-Marsteller NC**, Foltin RW, Walsh BT. Does anorexia nervosa resemble an addiction? *Curr Drug Abuse Rev* 2011; **4**: 197-200 [PMID: 21999694 DOI: 10.2174/1874473711104030197]

44 **Kessler RM**, Hutson PH, Herman BK, Potenza MN. The neurobiological basis of binge-eating disorder. *Neurosci Biobehav Rev* 2016; **63**: 223-238 [PMID: 26850211 DOI: 10.1016/j.neubiorev.2016.01.013]

45 **Avena NM**, Bocarsly ME. Dysregulation of brain reward systems in eating disorders: neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology* 2012; **63**: 87-96 [PMID: 22138162 DOI: 10.1016/j.neuropharm.2011.11.010]

46 **Bello NT**, Walters AL, Verpeut JL, Caverly J. Dietary-induced binge eating increases prefrontal cortex neural activation to restraint stress and increases binge food consumption following chronic guanfacine. *Pharmacol Biochem Behav* 2014; **125**: 21-28 [PMID: 25158105 DOI: 10.1016/j.pbb.2014.08.003]

47 **Davis CA**, Levitan RD, Reid C, Carter JC, Kaplan AS, Patte KA, King N, Curtis C, Kennedy JL. Dopamine for "wanting" and opioids for "liking": a comparison of obese adults with and without binge eating. *Obesity (Silver Spring)* 2009; **17**: 1220-1225 [PMID: 19282821 DOI: 10.1038/oby.2009.52]

48 **Wise RA**. Dopamine, learning and motivation. *Nat Rev Neurosci* 2004; **5**: 483-494 [PMID: 15152198 DOI: 10.1038/nrn1406]

49 **Smith DG**, Robbins TW. The neurobiological underpinnings of obesity and binge eating: a rationale for adopting the food addiction model. *Biol Psychiatry* 2013; **73**: 804-810 [PMID: 23098895 DOI: 10.1016/j.biopsych.2012.08.026]

50 **Wang GJ**, Volkow ND, Thanos PK, Fowler JS. Similarity between obesity and drug addiction as assessed by neurofunctional imaging: a concept review. *J Addict Dis* 2004; **23**: 39-53 [PMID: 15256343 DOI: 10.1300/J069v23n03_04]

51 **Pearson CM**, Guller L, Smith GT. Dimensions of personality and neuropsychological function in eating disorders, substance use disorders, and addictions. In: Eating Disorders, Addictions and Substance Use Disorders. Springer, Berlin, Heidelberg, 2014: 107-126 [DOI: 10.1007/978-3-642-45378-6_6]

52 **Volkow ND**, Wang GJ, Fowler JS, Gatley SJ, Ding YS, Logan J, Dewey SL, Hitzemann R, Lieberman J. Relationship between psychostimulant-induced "high" and dopamine transporter occupancy. *Proc Natl Acad Sci U S A* 1996; **93**: 10388-10392 [PMID: 8816810 DOI: 10.1073/pnas.93.19.10388]

53 **Koob GF**, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology* 2010; **35**: 217-238 [PMID: 19710631 DOI: 10.1038/npp.2009.110]

54 **Volkow ND**, Fowler JS. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex* 2000; **10**: 318-325 [PMID: 10731226 DOI: 10.1093/cercor/10.3.318]

55 **Johnson PM**, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci* 2010; **13**: 635-641 [PMID: 20348917 DOI: 10.1038/nn.2519]

56 **Broft A**, Shingleton R, Kaufman J, Liu F, Kumar D, Slifstein M, Abi-Dargham A, Schebendach J, Van Heertum R, Attia E, Martinez D, Walsh BT. Striatal dopamine in bulimia nervosa: a PET imaging study. *Int J Eat Disord* 2012; **45**: 648-656 [PMID: 22331810 DOI: 10.1002/eat.20984]

57 **Volkow ND**, Wang GJ, Maynard L, Jayne M, Fowler JS, Zhu W, Logan J, Gatley SJ, Ding YS, Wong C, Pappas N. Brain dopamine is associated with eating behaviors in humans. *Int J Eat Disord*

2003; **33**: 136-142 [PMID: 12616579 DOI: 10.1002/eat.10118]
58 **Avena NM**. The study of food addiction using animal models of binge eating. *Appetite* 2010; **55**: 734-737 [PMID: 20849896 DOI: 10.1016/j.appet.2010.09.010]
59 **Colantuoni C**, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, Schwartz GJ, Moran TH, Hoebel BG. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport* 2001; **12**: 3549-3552 [PMID: 11733709 DOI: 10.1097/00001756-200111160-00035]
60 **Everitt BJ**, Robbins TW. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. *Neurosci Biobehav Rev* 2013; **37**: 1946-1954 [PMID: 23438892 DOI: 10.1016/j.neubiorev.2013.02.010]
61 **Murray SM**, Tulloch AJ, Chen EY, Avena NM. Insights revealed by rodent models of sugar binge eating. *CNS Spectr* 2015; **20**: 530-536 [PMID: 26510689 DOI: 10.1017/S1092852915000656]
62 **Bello NT**, Hajnal A. Dopamine and binge eating behaviors. *Pharmacol Biochem Behav* 2010; **97**: 25-33 [PMID: 20417658 DOI: 10.1016/j.pbb.2010.04.016]
63 **Yeomans MR**, Gray RW. Opioid peptides and the control of human ingestive behaviour. *Neurosci Biobehav Rev* 2002; **26**: 713-728 [PMID: 12479844 DOI: 10.1016/s0149-7634(02)00041-6]
64 **Kalivas PW**. Neurotransmitter regulation of dopamine neurons in the ventral tegmental area. *Brain Res Brain Res Rev* 1993; **18**: 75-113 [PMID: 8096779 DOI: 10.1016/0165-0173(93)90008-n]
65 **Spanagel R**, Shippenberg TS. Modulation of morphine-induced sensitization by endogenous kappa opioid systems in the rat. *Neurosci Lett* 1993; **153**: 232-236 [PMID: 8392157 DOI: 10.1016/0304-3940(93)90329-j]
66 **Chefer VI**, Denoroy L, Zapata A, Shippenberg TS. Mu opioid receptor modulation of somatodendritic dopamine overflow: GABAergic and glutamatergic mechanisms. *Eur J Neurosci* 2009; **30**: 272-278 [PMID: 19614973 DOI: 10.1111/j.1460-9568.2009.06827.x]
67 **Bencherif B**, Guarda AS, Colantuoni C, Ravert HT, Dannals RF, Frost JJ. Regional mu-opioid receptor binding in insular cortex is decreased in bulimia nervosa and correlates inversely with fasting behavior. *J Nucl Med* 2005; **46**: 1349-1351 [PMID: 16085593]
68 **Waller DA**, Kiser RS, Hardy BW, Fuchs I, Feigenbaum LP, Uauy R. Eating behavior and plasma beta-endorphin in bulimia. *Am J Clin Nutr* 1986; **44**: 20-23 [PMID: 2942030 DOI: 10.1093/ajcn/44.1.20]
69 **Blanco-Gandía MC**, Cantacorps L, Aracil-Fernández A, Montagud-Romero S, Aguilar MA, Manzanares J, Valverde O, Miñarro J, Rodríguez-Arias M. Effects of bingeing on fat during adolescence on the reinforcing effects of cocaine in adult male mice. *Neuropharmacology* 2017; **113**: 31-44 [PMID: 27666001 DOI: 10.1016/j.neuropharm.2016.09.020]
70 **Drewnowski A**, Krahn DD, Demitrack MA, Nairn K, Gosnell BA. Naloxone, an opiate blocker, reduces the consumption of sweet high-fat foods in obese and lean female binge eaters. *Am J Clin Nutr* 1995; **61**: 1206-1212 [PMID: 7762518 DOI: 10.1093/ajcn/61.6.1206]
71 **Cota D**, Woods SC. The role of the endocannabinoid system in the regulation of energy homeostasis. *Curr Opin Endocrinol Diabetes Obes* 2005; **12**: 338-351 [DOI: 10.1097/01.med.0000178715.87999.69]
72 **Koch JE**. Delta(9)-THC stimulates food intake in Lewis rats: effects on chow, high-fat and sweet high-fat diets. *Pharmacol Biochem Behav* 2001; **68**: 539-543 [PMID: 11325410 DOI: 10.1016/s0091-3057(01)00467-1]
73 **Bermudez-Silva FJ**, Viveros MP, McPartland JM, Rodriguez de Fonseca F. The endocannabinoid system, eating behavior and energy homeostasis: the end or a new beginning? *Pharmacol Biochem Behav* 2010; **95**: 375-382 [PMID: 20347862 DOI: 10.1016/j.pbb.2010.03.012]
74 **Kirkham TC**. Endogenous cannabinoids: a new target in the treatment of obesity. *Am J Physiol Regul Integr Comp Physiol* 2003; **284**: R343-R344 [PMID: 12529283 DOI: 10.1152/ajpregu.00706.2002]
75 **Monteleone P**, Matias I, Martiadis V, De Petrocellis L, Maj M, Di Marzo V. Blood levels of the endocannabinoid anandamide are increased in anorexia nervosa and in binge-eating disorder, but not in bulimia nervosa. *Neuropsychopharmacology* 2005; **30**: 1216-1221 [PMID: 15841111 DOI: 10.1038/sj.npp.1300695]
76 **Satta V**, Scherma M, Piscitelli F, Usai P, Castelli MP, Bisogno T, Fratta W, Fadda P. Limited Access to a High Fat Diet Alters Endocannabinoid Tone in Female Rats. *Front Neurosci* 2018; **12**: 40 [PMID: 29456490 DOI: 10.3389/fnins.2018.00040]
77 **Avena NM**, Rada P, Hoebel BG. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. *Neurosci Biobehav Rev* 2008; **32**: 20-39 [PMID: 17617461 DOI: 10.1016/j.neubiorev.2007.04.019]
78 **Corwin RL**, Avena NM, Boggiano MM. Feeding and reward: perspectives from three rat models of binge eating. *Physiol Behav* 2011; **104**: 87-97 [PMID: 21549136 DOI: 10.1016/j.physbeh.2011.04.041]
79 **Perello M**, Valdivia S, García Romero G, Raingo J. Considerations about rodent models of binge eating episodes. *Front Psychol* 2014; **5**: 372 [PMID: 24808881 DOI: 10.3389/fpsyg.2014.00372]
80 **Corwin RL**, Buda-Levin A. Behavioral models of binge-type eating. *Physiol Behav* 2004; **82**: 123-130 [PMID: 15234600 DOI: 10.1016/j.physbeh.2004.04.036]
81 **Artiga AI**, Viana JB, Maldonado CR, Chandler-Laney PC, Oswald KD, Boggiano MM. Body composition and endocrine status of long-term stress-induced binge-eating rats. *Physiol Behav* 2007; **91**: 424-431 [PMID: 17498757 DOI: 10.1016/j.physbeh.2007.04.001]
82 **Corwin RL**, Wojnicki FH, Fisher JO, Dimitriou SG, Rice HB, Young MA. Limited access to a

dietary fat option affects ingestive behavior but not body composition in male rats. *Physiol Behav* 1998; **65**: 545-553 [PMID: 9877422 DOI: 10.1016/s0031-9384(98)00201-7]

83 **Corwin RL**. Binge-type eating induced by limited access in rats does not require energy restriction on the previous day. *Appetite* 2004; **42**: 139-142 [PMID: 15010177 DOI: 10.1016/j.appet.2003.08.010]

84 **Marcus MD**, Kalarchian MA. Binge eating in children and adolescents. *Int J Eat Disord* 2003; **34** Suppl: S47-S57 [PMID: 12900986 DOI: 10.1002/eat.10205]

85 **Barnea R**, Bekker L, Zifman N, Marco A, Yadid G, Weller A. Trait and state binge eating predispose towards cocaine craving. *Addict Biol* 2017; **22**: 163-171 [PMID: 26419743 DOI: 10.1111/adb.12315]

86 **Avena NM**, Hoebel BG. A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine. *Neuroscience* 2003; **122**: 17-20 [PMID: 14596845 DOI: 10.1016/s0306-4522(03)00502-5]

87 **McGuire BA**, Baladi MG, France CP. Eating high-fat chow enhances sensitization to the effects of methamphetamine on locomotion in rats. *Eur J Pharmacol* 2011; **658**: 156-159 [PMID: 21371470 DOI: 10.1016/j.ejphar.2011.02.027]

88 **Gosnell BA**. Sucrose intake enhances behavioral sensitization produced by cocaine. *Brain Res* 2005; **1031**: 194-201 [PMID: 15649444 DOI: 10.1016/j.brainres.2004.10.037]

89 **Serafine KM**, Bentley TA, Koek W, France CP. Eating high fat chow, but not drinking sucrose or saccharin, enhances the development of sensitization to the locomotor effects of cocaine in adolescent female rats. *Behav Pharmacol* 2015; **26**: 321-325 [PMID: 25485647 DOI: 10.1097/FBP.0000000000000114]

90 **Baladi MG**, Horton RE, Owens WA, Daws LC, France CP. Eating high fat chow decreases dopamine clearance in adolescent and adult male rats but selectively enhances the locomotor stimulating effects of cocaine in adolescents. *Int J Neuropsychopharmacol* 2015; **18**: pyv024 [PMID: 25805560 DOI: 10.1093/ijnp/pyv024]

91 **Bassareo V**, Di Chiara G. Differential influence of associative and nonassociative learning mechanisms on the responsiveness of prefrontal and accumbal dopamine transmission to food stimuli in rats fed ad libitum. *J Neurosci* 1997; **17**: 851-861 [PMID: 8987806 DOI: 10.1523/JNEUROSCI.17-02-00851.1997]

92 **Sanchis-Segura C**, Spanagel R. Behavioural assessment of drug reinforcement and addictive features in rodents: an overview. *Addict Biol* 2006; **11**: 2-38 [PMID: 16759333 DOI: 10.1111/j.1369-1600.2006.00012.x]

93 **Aguilar MA**, Rodríguez-Arias M, Miñarro J. Neurobiological mechanisms of the reinstatement of drug-conditioned place preference. *Brain Res Rev* 2009; **59**: 253-277 [PMID: 18762212 DOI: 10.1016/j.brainresrev.2008.08.002]

94 **Puhl MD**, Cason AM, Wojnicki FH, Corwin RL, Grigson PS. A history of bingeing on fat enhances cocaine seeking and taking. *Behav Neurosci* 2011; **125**: 930-942 [PMID: 21988520 DOI: 10.1037/a0025759]

95 **McaLeavey KM**, Fiumara MC. Eating disorders: Are they addictions? *J Soc Work Pract Addict* 2001; **1**: 107-113 [DOI: 10.1300/J160v01n02_09]

96 **Teegarden SL**, Scott AN, Bale TL. Early life exposure to a high fat diet promotes long-term changes in dietary preferences and central reward signaling. *Neuroscience* 2009; **162**: 924-932 [PMID: 19465087 DOI: 10.1016/j.neuroscience.2009.05.029]

97 **Teegarden SL**, Bale TL. Effects of stress on dietary preference and intake are dependent on access and stress sensitivity. *Physiol Behav* 2008; **93**: 713-723 [PMID: 18155095 DOI: 10.1016/j.physbeh.2007.11.030]

98 **Avena NM**, Rada P, Hoebel BG. Sugar and fat bingeing have notable differences in addictive-like behavior. *J Nutr* 2009; **139**: 623-628 [PMID: 19176748 DOI: 10.3945/jn.108.097584]

99 **Avena NM**, Carrillo CA, Needham L, Leibowitz SF, Hoebel BG. Sugar-dependent rats show enhanced intake of unsweetened ethanol. *Alcohol* 2004; **34**: 203-209 [PMID: 15902914 DOI: 10.1016/j.alcohol.2004.09.006]

100 **Blanco-Gandía MC**, Miñarro J, Rodríguez-Arias M. Behavioral profile of intermittent *vs* continuous access to a high fat diet during adolescence. *Behav Brain Res* 2019; **368**: 111891 [PMID: 31009646 DOI: 10.1016/j.bbr.2019.04.005]

101 **Le Merrer J**, Stephens DN. Food-induced behavioral sensitization, its cross-sensitization to cocaine and morphine, pharmacological blockade, and effect on food intake. *J Neurosci* 2006; **26**: 7163-7171 [PMID: 16822973 DOI: 10.1523/JNEUROSCI.5345-05.2006]

102 **Nair SG**, Adams-Deutsch T, Epstein DH, Shaham Y. The neuropharmacology of relapse to food seeking: methodology, main findings, and comparison with relapse to drug seeking. *Prog Neurobiol* 2009; **89**: 18-45 [PMID: 19497349 DOI: 10.1016/j.pneurobio.2009.05.003]

103 **Leeman RF**, O'Malley SS, White MA, McKee SA. Nicotine and food deprivation decrease the ability to resist smoking. *Psychopharmacology (Berl)* 2010; **212**: 25-32 [PMID: 20585761 DOI: 10.1007/s00213-010-1902-z]

104 **Chechlacz M**, Rotshtein P, Klamer S, Porubská K, Higgs S, Booth D, Fritsche A, Preissl H, Abele H, Birbaumer N, Nouwen A. Diabetes dietary management alters responses to food pictures in brain regions associated with motivation and emotion: a functional magnetic resonance imaging study. *Diabetologia* 2009; **52**: 524-533 [PMID: 19139843 DOI: 10.1007/s00125-008-1253-z]

105 **Dennis AB**, Pryor T. The complex relationship between eating disorders and substance use

disorders. *Clin Handbook Complex Atypical Eating Disorders* 2017; 60-78 [DOI: 10.1093/med-psych/9780190630409.003.0004]

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MINIREVIEWS

Genetics of adult attachment: An updated review of the literature

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Abstract

Attachment style, which has been theorized to be rooted in childhood bonding experiences, influences adult cognitive, emotional and interpersonal functioning. Despite its relationship with early experiences, research indicates that the continuity of attachment style across childhood and adulthood is only partial,

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being a malleable tendency that is shaped throughout development, with an increasing influence of genetics, as it occurs in other cognitive and behavioral phenotypes. Genetic research indicates that up to 45% of the variability in anxious and 39% in avoidant adult attachment style could be explained by genetic causes, but the precise mechanisms remain unclear. A narrative review is conducted analyzing the existing literature regarding the implication of candidate genes related to oxytocin, dopaminergic pathways, serotonergic pathways and brain-derived neurotrophic factor in adult attachment, with both vulnerability and differential susceptibility approaches, yielding mixed results. We highlight the lack of genome-wide studies and the scarcity of epigenetic investigation. Based on the existing data, we conclude that the genetics of adult attachment is an area that requires further research to clarify its etiological role and that it should be preferably approached as an interaction between nature and nurture.

Key Words: Genetics; Adult attachment; Oxytocin; Dopamine; Serotonin; Brain-derived neurotrophic factor; Methylation

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Core Tip: Attachment style influences adult cognitive, emotional and interpersonal functioning. Despite its relationship with early experiences, it is a malleable tendency that is shaped throughout development. Genetic research indicates that up to 45% of the variability in anxious and 39% in avoidant adult attachment style could be explained by genetic causes. A narrative review is conducted analyzing the existing literature regarding the implication of candidate genes, with vulnerability and differential susceptibility approaches. We highlight the lack of genome-wide studies and scarcity of epigenetic investigation, concluding that further research is needed to clarify the etiological role of genetics on adult attachment.

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INTRODUCTION

Attachment has been defined as the tendency of human beings to create strong affective bonds towards specific figures and explains the various forms of emotional stress and personality pathology, including anxiety, anger, depression and emotional detachment, that result from unwanted separation or loss of such figures[1]. During childhood, the relationship with the parent is the primary attachment, and this will be gradually replaced, during adolescence and adulthood, by social and romantic relationships.

Broadly speaking, the type of attachment can be defined as secure or insecure. Different proposals describe distinct types of insecure attachment, as we will detail below, although the most widely used is the two-dimensional one that distinguishes anxious and avoidant attachment styles. Secure attachment is seen as an internal resource that allows for the management of negative emotions and the recovery of calm, as well as a source of resilience. In contrast, an insecure attachment style facilitates the development of psychological distress and eventual psychopathology [2]. It has been shown that the attachment style plays a determining role in cognitive, emotional and social-interactional aspects of the individual.

ATTACHMENT STYLES

The concept of attachment style was first proposed by Ainsworth in the 1970s to

describe children's response patterns to separation from their mothers during the Strange Situation Procedure, designed to assess attachment pattern[3]. Children were described as secure if they showed separation distress and sought contact and calmed down with the mother after the reunion. On the other hand, children were classified as insecure-avoidant if they showed little separation distress and avoided contact with their mother after the reunion. Finally, insecure-ambivalent/resistant children were those who showed extreme distress before separation and ambivalent behaviors after the meeting with the mother. It has been proposed that deactivation of the attachment system occurs in avoidant children and hyperactivation in ambivalent/resistant children. Later, Main and Solomon[4] added the disorganized attachment style to describe those children who did not present coherent attachment strategies, oscillating between different types or presenting bizarre behavior after the reunion.

Beginning in the 1980s, several researchers developed new measures to assess attachment style in order to extend the study to adolescents and adults. Maintaining a developmental perspective, George *et al*[5] developed the Adult Attachment Interview (AAI), which assessed the mental representations of attachment (or states of mind in relation to attachment) towards the parents in relation to childhood. Through this interview, the attachment style was classified as secure, dismissing, preoccupied or unresolved/disorganized[5].

In the same period, Hazan and Shaver[6] developed a self-administered questionnaire to assess attachment in adult relationships, and based on Ainsworth's styles, the individual was classified as secure, avoidant or anxious/ambivalent[6]. With a similar focus, Bartholomew and Horowitz[7] developed another proposal, in which attachment was also assessed by means of a self-administered questionnaire and classified as secure, dismissive, preoccupied or fearful. It gradually became evident that adult attachment could be assessed along two main dimensions: Anxiety and avoidance[8]. Anxiety explores concern regarding the availability and responsiveness of the other, and avoidance, on the other hand, evaluates interindividual differences regarding the degree of comfort with closeness and interdependence. It has been proposed that low scores on both anxiety and avoidance are suggestive of secure attachment; high scores on anxiety alone would indicate an anxious type of insecure attachment; high scores on avoidance alone would indicate an avoidant type of insecure attachment; and high scores on both dimensions would be suggestive of disorganized attachment, although a solely dimensional treatment of the two variables is recommended[2].

STABILITY AND CHANGE OF THE ATTACHMENT SYSTEM

Adult attachment research, therefore, has been conducted using the two aforementioned models. The first is based on the AAI, a semi-structured interview that explores the adult's current state of mind and the coherence of discourse in relation to childhood attachment experiences, and the second is based on the evaluation through self-administered questionnaires of beliefs and experiences related to attachment in the adult's current relationships with significant others. Nevertheless, although both maintain the same theoretical background, divergences have been found in the results obtained between the two models, with correlations interpreted as trivial to small[9]. These results suggest that there is no significant equivalence between attachment measured with the AAI, more focused on childhood experiences, and that assessed with self-administered questionnaires in relation to current significant figures.

A lack of continuity has also been observed even between childhood attachment and that assessed in adults using the AAI or equivalents, despite the fact that both assess the quality and style of the relationship with the parents during childhood. A meta-analysis concluded that the overall stability in the type of attachment assessed by the Strange Situation Procedure (or equivalents) in childhood and by the AAI (or equivalents) in adulthood was 0.39, which is interpreted as medium-sized stability. However, there was no significant stability for intervals longer than 15 years. Interestingly, and in relation to subgroups with psychosocial risks, it was observed that securely attached children that belonged to these groups were less likely to maintain attachment security, whereas insecurely attached children were most likely to maintain insecurity[10].

These results suggest the existence of other variables that would act throughout development and that would intervene in the shaping of adult attachment. In this sense, it has been described that in addition to the relationship with caregivers in childhood, emerging social competence (the socialization skills of children assessed by

their teachers at school) and the quality of the relationship with best friends in childhood-adolescence independently and significantly influence adult attachment style[11].

Working models of attachment formed in infancy are sensorimotor, procedural and nonlinguistic in nature, reflecting interactions between the infant and caregiver that occurred prior to the emergence of linguistic and introspective abilities. Thus, different theorists have contributed to the development of a "prototype" theory that posits the coexistence of current working models and early prototypical models. Prototypical working models formed during early life would continue to exist and exert a shaping effect on attachment patterns throughout life, both by attempting to match new experiences to pre-existing models and by reinforcing them through behaviors that elicit reactions consistent with the individual's expectations. In addition, current ones would be revised and updated as relevant attachment experiences arise that differ from, or challenge, previous experiences and knowledge (such as the loss of an attachment figure or infidelities), thus enabling and explaining variations in attachment style across the lifespan[2]. In the same line, other authors also describe that children's attachment patterns are malleable and shaped by multiple experiences in the transition to adulthood, pointing out that socialization and selection effects have a differential influence according to the life stage[12].

ADULT ATTACHMENT AND PERSONALITY

The relationship between attachment style and personality is also an aspect to be considered in this area of investigation. Although attachment research tends not to emphasize the temperamental contribution to attachment styles, Bowlby[13] himself suggested that there may be preexisting temperamental differences in children and that attachment experiences would modulate, interact with or overcome these differences. In this line, several authors have described a certain degree of overlap in the heritability of personality features and attachment styles in studies carried out using self-administered questionnaires to explore adult attachment[14-16]. It has been reported that 63% of the association between attachment anxiety and personality dimensions was attributable to common genetic effects[14]. Other authors described that genetic influence on neuroticism contributed to 35% of the variance in anxiety and 11% in avoidance, whereas genetic influence on extraversion contributed to 6% of the variance in avoidance[15].

In a study conducted by our group with a general population sample, we found that a functional polymorphism in the catechol-o-methyltransferase (COMT) gene had a common influence on avoidant attachment and inhibitedness personality dimension. This was not due to a poor discriminative capacity of the instruments, since independent associations were observed, for example, between a polymorphism in the serotonin transporter (5HTT) gene and both variables[16].

In this regard, it has been proposed that temperamental characteristics, which are strongly influenced by genetics, would influence internal working models of attachment in complex ways, including person-environment interaction and gene-environment interaction[15]. In addition to the genetic conditioning that may exist, and that will constitute the temperamental basis by which the individual tends to experience certain affects in his or her experience of the other, starting from primary object relations, there is a continuous and close interaction between personality and attachment style throughout development. It will determine the social choices and the way in which the individual perceives relationships throughout life. The greater capacity of the adult to make these social decisions, determined in part by temperamental aspects, could explain to some degree the discrepancies observed between samples of children and adults in genetic research of attachment, which are detailed below.

GENETICS OF ADULT ATTACHMENT

Methods

A literature search was performed to identify studies on genetics of adult attachment. Articles published until December 28, 2020 were retrieved from the PubMed database using broad search terms in order to identify as many potentially eligible studies as possible: [(attachment OR "adult attachment") AND (genetic* OR dopamine* OR

COMT OR serotonin* OR oxytocin* OR brain-derived OR BDNF)]. An age filter was added: "Adults: 19+ years". The reference lists of the selected studies and reviews were also checked to identify additional relevant articles using a snowballing approach. Studies were included if: (1) They investigated the influence of genetics/epigenetics on adult attachment using any approach (twin-studies, genome-wide studies or candidate gene studies); (2) They used standard measures of adult attachment (AAI or self-administered questionnaires); (3) They were systematic reviews, meta-analyses, narrative reviews or original research studies; and (4) They were written in English or Spanish.

This is not a systematic review but a narrative one; it summarizes the findings described in the selected reports and, in this way, provides an overview on the subject.

Heritability of attachment: Twin-studies

In twin-studies of children, the combination of shared and nonshared environmental variables seems to explain most of the variability in attachment style, with no significant weight of genetics observed[17-19]. Shared environmental factors have been described as the environmental influences responsible for resemblance between family members, and nonshared environmental factors as those influences that contribute to differences between family members[20].

In contrast to what has been observed in children, independent twin studies in adolescents and adults describe that attachment is mainly conditioned by genetic and nonshared environmental factors[14,15,21-24]. The only study of adolescent twins to date was conducted using the Child Attachment Interview, a childhood adaptation of the AAI that explores coherence of discourse and childhood attachment experiences in relation to parents. They found that genetic effects accounted for 35% of the variance in attachment security and that the remaining 65% was estimated to be due to the nonshared environment[22].

Most of the twin-studies in adults have been conducted using self-reported questionnaires, but the results are generally similar to those obtained in the adolescent study. The heritability of anxious attachment has been described to be between 37% and 40% in two different studies, the rest being explained by nonshared environmental factors[14,21]. These two groups did not observe avoidant attachment to be explained by genetics. In other studies, however, the heritability of anxious attachment was replicated, and genetic influence was also described for the avoidant style. Additive genetic effects were described to account for 45% of the variability in anxiety and 39% in avoidance in the Michigan State University Twin Study of Behavioral Adjustment[15]. These figures were similar to those obtained in another study, where genetic effects accounted for 45% of individual differences in anxiety and 36% in avoidant attachment[23]. The only report exploring attachment with the AAI in adult twins described that attachment styles were determined by genetics and shared environment[24]; nonetheless, it was a pilot study with a limited sample size.

The differences in heritability observed between studies carried out with samples of children and adult samples are consistent with the lack of stability in attachment style described in longitudinal studies, as we have previously mentioned. They could be due to the way the exploration of attachment is operationalized depending on age; whereas in children it is based on differences in observed attachment behaviors, in adults it is focused on the way individuals think about their attachment relations, in relation to their parents (with the AAI) or in relation to their current close relationships (with self-administered questionnaires).

In addition, age-related increases in genetic influences on various cognitive, behavioral and psychiatric phenotypes have been well-documented, some authors suggesting that shared environmental effects may be relatively restricted to infancy and, when present, may not be stable beyond childhood[25]. The influence of the environment would decrease with age, as the children undergo a variety of influences outside the family, and are more able to shape their own environments[26]. In this line, an increasing influence of genetics has also been observed in relation to affiliation with peers in a relatively short range of years, concretely in the transition from adolescence to adulthood (between the ages of 15 and 21)[27].

Genome-wide association studies

The first genome-wide association study (GWAS) on attachment patterns was conducted in children, providing evidence of novel genes (HDAC1, ZNF675, BSCD1) associated with attachment disorganization[28], but these findings have not been replicated. A subsequent epigenome-wide association study reported that infant attachment was also significantly associated with a principal component that

accounted for 11.9% of the variation in genome-wide DNA methylation[29]. Methylation is associated with lower levels of transcription of a gene when it occurs in the promoter region. The observed effects were most apparent when comparing children with a secure *vs* a disorganized attachment style, and most pronounced in females, providing preliminary evidence for a molecular signature of infant attachment. The complexity of child attachment assessment makes it difficult to conduct studies that involve the analysis of the whole genome and thus require large samples, being the samples of both studies of limited size (samples sizes of 657 and 226, respectively) compared to others of this type. To date, no GWAS on adult attachment have been published.

Candidate gene studies

The bulk of research in adult attachment genetics has been conducted based on a candidate gene approach and has mainly involved polymorphisms in the oxytocin receptor (OXTR) gene and in those involved in dopaminergic and serotonergic pathways, although more recent work has also studied brain-derived neurotrophic factor (BDNF). Candidate gene studies have been conducted reporting either direct associations or gene-by-environment interactions (known respectively as vulnerability and plasticity genes, see Belsky *et al*[30]). We will describe the main findings using both approaches. The findings are summarized in Table 1.

OXTR: Oxytocin (OXT) is a neuropeptide synthesized in the hypothalamus whose known role in the periphery is as an initiator of childbirth and lactation. It also has a central role in social and emotional behavior, insofar as it participates in the formation of emotional bonds across the lifespan[31]. In fact, OXTR are concentrated in brain regions involved in social behavior, including the olfactory processing regions, limbic brain structures, hippocampus, hypothalamus and brainstem[32].

Plasma concentrations of OXT and genetic polymorphisms that involve OTX action, mainly the OXTR gene, have been studied in relation to different aspects of socialization in animals and humans, including attachment. OXTR gene is located on the short arm of chromosome 3 (3p25) and has three introns and four exons. Several dozens of single-nucleotide polymorphisms (SNP) have been identified in the OXTR gene region[33]; among them, rs53576 and rs2254298, located in intron 3, are the most extensively studied in relation to social behavior. In both cases, they consist of mutations in which a guanine (G) base is replaced by an adenine (A) base.

The functionality of these polymorphisms remains unclear[34]. They do not change the amino acid sequence of the encoded protein, and thus it has been proposed that they should exert their effects through variations in brain structure and function[35]. The A allele of rs53576 has been associated with morphometric and functional alterations in hypothalamus and amygdala that predicted lower levels of reward dependence[36]. The rs2254298 OXTR A allele has been associated with larger amygdala volume in different populations[37,38]. These studies provide evidence of a possible convergent impact of OXTR polymorphisms on this key limbic structure.

In relation to adult attachment, an association of the GG genotype of rs53576 with greater insecurity according to self-administered questionnaires has been described [39], and conversely, that this genotype is associated with lower anxiety and avoidance [40]. With regard to rs2254298, the GG genotype has been associated with greater avoidance[39] and lower anxiety[41], the latter in women. Other authors, however, have not found significant associations between these two polymorphisms and attachment styles[11,42,43].

Further, it has been described that rs53576 acts as a moderator in the continuity of secure attachment from childhood to adulthood, so that in those individuals with the GG genotype, infant attachment security predicted romantic attachment security in adulthood[44].

Finally, when we study the interaction of the OXTR gene genotypes with environmental variables, a role in the intergenerational transmission of attachment, in interaction with childrearing style, has been reported[45], whereas other authors have not found any interaction with parental sensitivity[11]. Recent epigenetic studies coincide in describing that the higher the methylation in the promoter region of the OXTR gene, the higher the avoidant attachment score[46,47]. These studies have been conducted on saliva and peripheral blood samples, respectively.

Dopaminergic system: Regarding the dopaminergic pathway, the genes of the dopaminergic receptors D2 (DRD2) and D4 (DRD4) and of the COMT have been mainly studied.

Table 1 Summary of candidate gene studies on adult attachment

Gene	Marker	Ref.	Adult attachment measure	Result
OXTR	rs53576	Costa *et al*[39], 2009	ASQ	GG greater insecurity
		Monin *et al*[39], 2019	ECR	GG lower anxiety and avoidance
		Raby *et al*[44], 2013	CRI	GG predicts continuity of attachment security
		Fraley *et al*[11], 2013	RSQ	No significant associations or interactions with maternal sensitivity
		Gillath *et al*[42], 2008	ECR	No significant associations
		Gong *et al*[43], 2020	RAAS	No significant associations
	rs2254298	Costa *et al*[39], 2009	ASQ	GG higher avoidance
		Chen and Johnson[41], 2012	ECR	GG lower anxiety in females
		Fraley *et al*[11], 2013	ECR	No significant associations or interactions with maternal sensitivity
		Gong *et al*[43], 2020	RAAS	No significant associations
	Methylation promoter region	Ebner *et al*[46], 2019	ECR	Higher methylation associated with higher avoidance
		Ein-Dor *et al*[47], 2018	AAS	Higher methylation associated with higher avoidance
DRD2	rs1800497	Gong *et al*[43], 2020	RAAS	A1 homozygotes higher anxiety than A2 carriers
		Fraley *et al*[11], 2013	ECR	No significant associations or interactions with maternal sensitivity
DRD4	VNTR	Reiner and Spangler[51], 2010	AAI	7R carriers greater security
		Bakermans-Kranenburg *et al*[52], 2011	AAI	7R carriers greater susceptibility to environmental factors
COMT	rs4680	Erkoreka *et al*[16], 2018	ECR	ValMet heterozygotes higher avoidance than either homozygotes
5HT1A	rs6295	Gong *et al*[43], 2020	RAAS	G carriers less comfortable in close relationships
5HT2A	rs6313	Gillath *et al*[42], 2008	ECR	T homozygotes higher avoidance than C homozygotes
		Salo *et al*[62], 2011	RSQ	T homozygotes greater susceptibility to environmental factors
		Fraley *et al*[11], 2013	ECR/RSQ	C homozygotes higher anxiety (RSQ)
5HTTLPR	rs4795541	Caspers *et al*[64], 2009	AAI	Higher unresolved attachment
		Reiner and Spangler[51], 2010	AAI	No significant associations
		Bakermans-Kranenburg *et al*[52], 2011	AAI	No significant associations
		Erkoreka *et al*[16], 2018	ECR	No significant associations
	Methylation promoter region	van IJzendoorn *et al*[65], 2010	AAI	Higher methylation in L homozygotes increased risk or unresolved loss or trauma; higher methylation in S homozygotes less unresolved loss or trauma
		Jones-Mason *et al*[66], 2016	AAI	Methylation interacts with socioeconomic status
BDNF	rs6265	Suzuki *et al*[68], 2012	PBI	Met carriers with low maternal care greater interpersonal sensitivity
		Ibarra *et al*[69], 2014	PBI	Met carriers greater susceptibility to childrearing style

5HT1A: Serotonin receptor A1; 5HT2A: Serotonin receptor A2; 5HTTLPR: Serotonin transporter-linked polymorphic region; AAI: Adult Attachment

Interview; ASQ: Attachment Style Questionnaire; BDNF: Brain-derived neurotrophic factor; COMT: Catechol-o-methyltransferase; CRI: Current Relationship Interview; DRD2: Dopaminergic receptor D2; DRD4: Dopaminergic receptor D4; ECR: Experiences in Close Relationships; OXTR: Oxytocin receptor; PBI: Parental Bonding Instrument; RAAS: Revised Adult Attachment Scale; RSQ: Relationship Questionnaire.

The gene that encodes DRD2 contains a SNP (TaqIA, rs1800497) that gives rise to the A1 allele (when thymine [T] is present) or A2 allele (when cytosine [C] is present). A1 allele is associated with a reduced number of dopamine binding sites in the brain [48]. Individuals with two A1 alleles were found to score higher on attachment anxiety than those with only one, or none A1-alleles[42]. A subsequent study, however, found no relationship between this polymorphism and attachment style, either directly or in interaction with maternal sensitivity[11]. Both studies were carried out with the same self-administered questionnaire, so there was no methodological variability that could explain the differences in results.

The DRD4 gene contains a functional polymorphism consisting on a variable number of tandem repeats, in which a 48 base pair sequence exists as a 2-fold to 10-fold repeat[49]. The 7-repeat (7R) allele has been described to have a reduced ability to inhibit neuronal firing in the prefrontal cortex and thus, proposed to associate higher dopaminergic stimulation at that level[50]. There is an extensive literature on infant attachment and its relationship with this gene; however, only two studies have studied its effect on adult attachment. In both studies, the assessment of attachment style was carried out using the AAI. According to the first study, carriers of the 7R allele were significantly more likely to be securely attached, although this was only true for subjects reporting unloving caregiver recollections[51]. The authors of the second study, on their part, did not find a direct association of the polymorphism with the type of attachment. Instead, they observed that 7R allele carriers showed a heightened susceptibility to environmental influences[52], so that the carriers that reported parental problems had the highest scores for unresolved loss or trauma and the carriers without parental problems had the lowest scores. No differences according to parental problems were found among participants without the 7R allele.

COMT participates in the breakdown of dopamine and noradrenaline. Its gene contains a functional SNP (COMT Val158Met, rs4680), a substitution of G for A, which translates into an exchange of valine (Val) for methionine (Met) in the protein. MetMet homozygote individuals have four times less enzymatic activity than ValVal homozygotes, whereas heterozygotes show an intermediate level of activity. Activity associated with this polymorphism is particularly important in the prefrontal cortex, and it has been associated with numerous psychopathological phenotypes[53].

Individual heterozygous for COMT Val158Met were found to exert a more avoidant attachment pattern than homozygotes for either allele in the general population[16]. The pattern observed, in which heterozygotes scored higher than either homozygote, is called molecular heterosis. One of the explanations proposed for this fact is that on the cellular level, heterozygosity confers a broader range of genetic expressions and provides greater plasticity[54]. Although no previous or latter studies on adults have replicated this finding, they were coherent with previous research conducted in children[55].

Serotonergic system: Regarding the serotonergic system, both serotonin 1A (5HT1A) and 2A (5HT2A) receptor genes and the 5HTT gene have been studied.

Five-5HT1A is one of the most abundantly expressed serotonin receptors in the brain, acting at both pre- and post-synaptic neurons in several brain areas[56]. A SNP (C1019G, rs6295) in the gene has been suggested to regulate the 5HT1A receptor expression in presynaptic raphe neurons[57,58]. Compared with the C allele, the G allele is associated with higher expression in raphe neurons, leading to a decrease in firing frequency and serotonin level in synaptic cleft[57,59]. Individuals with the CG and GG genotypes have been associated with feeling less comfortable in close relationships than individuals with the CC genotype[60].

The gene that encodes 5HT2A contains a functional SNP (T102C, rs6313); the presence of T allele has been associated with reduced serotonin binding in the prefrontal cortex and, thus, with reduced serotonergic activity[61]. Individuals homozygote for T allele were found to score significantly higher on avoidant attachment than those homozygotes for C allele[42]. However, this finding was not replicated in a subsequent study, which reported that homozygotes for C allele scored higher on anxiety than T allele carriers[11]. An interaction of this polymorphism with maternal nurturance in childhood has also been observed, such that high childhood maternal nurturance predicted low avoidant attachment in the TT homozygotes but

not in carriers of C allele, whereas low maternal nurturance was associated with high avoidance in TT homozygotes but not in C allele carriers. It suggests that a gene-environmental interaction exists, with T homozygotes showing a heightened susceptibility to environmental factors[62].

The 5HTT is responsible for the recapture of serotonin from the synaptic cleft. Its gene includes a 44 base pair deletion/insertion polymorphism in the promoter region (5HTTLPR, rs4795541) and is one of the most widely studied genetic variants in psychiatric research. The long (L) allele in the promoter is associated with raised serotonin transporter messenger RNA levels, which translates into elevated transcription activity, greater transporter density and, therefore, serotonin hypofunction. The short (S) allele has the opposite effect, that is, it is associated with lower transcription activity, less transporter density and, therefore, a greater concentration of serotonin in the synapse. Further, the S allele behaves in a dominant manner [63].

An association between the S allele of 5HTTLPR and increased risk for unresolved attachment according to the AAI was described[64], although it has not been replicated. No direct effect of 5HTTLPR on attachment styles has been subsequently found, either assessed with self-report questionnaires[16] or when explored by means of the AAI[51,52].

Two studies examining methylation of the 5HTTLPR have been published so far, both of them exploring attachment styles using the AAI. Higher levels of methylation of 5HTTPR in DNA obtained from peripheral lymphoblasts were described to be associated with an increased risk of unresolved loss or trauma in homozygotes for the L allele. Higher levels of methylation in S allele homozygotes were associated with less unresolved loss or other trauma[65]. More recent research examining methylation of the 5HTTLPR gene in DNA from peripheral lymphocytes, as well as socioeconomic status (SES), concluded that lower methylation and low-SES were associated with higher unresolved loss, and higher methylation and low-SES with higher unresolved trauma. Within the unresolved category, low-SES unresolved participants had higher levels of methylation than mid/upper-SES participants, whereas SES was unrelated to methylation within the secure and organized categories[66]. Although these results require careful analysis, it appears that both gene-environment interaction and epigenetic mechanisms may play a role in the contribution of 5HTTLPR to attachment style.

BDNF: BDNF is one of the proteins of the neurotrophin family. It acts by promoting the survival of existing neurons, contributes to the growth and differentiation of new neurons and synapses and protects against stress-related neuronal damage. The gene encoding BDNF contains a functional SNP-like polymorphism, the BDNF Val66Met (rs6265), in which a G for A base change in the gene results in the substitution of Val for Met in the protein[67]. The presence of Met in the protein is associated with lower concentration of pro-BDNF in dendrites and secretory glands and a lower secretion of the molecule into the synaptic space.

With respect to this polymorphism, a synergistic effect has been described between being a Met carrier and low maternal care according to the Parental Bonding Instrument, leading to a greater interpersonal sensitivity[68]. In another study, Met carriers showed greater sensitivity to the childrearing style, according to the Parental Bonding Instrument, in relation to developing anxiety and somatization in adulthood [69].

CONCLUSION

The evidence about a significant influence of genetics on adult attachment comes mainly from twin-studies, but the specific ways and mechanisms remain unclear. Research has been focused on candidate gene studies, and although some markers such as the rs53576 and rs2254298 polymorphisms in the OXTR gene seemed promising, no consistent results have been found across the studies. The same is true for the described functional polymorphisms affecting dopaminergic and serotonergic systems (in the DRD2, DRD4, COMT, 5HT1A, 5HT2A, 5HTT genes). It should be noted that the only replicated finding is the association between methylation of the promoter region of the OXTR gene and higher attachment avoidance, even using different attachment measures (in both cases, self-reports). Carrying the Met allele in the BDNF rs6265 polymorphism also seems to confer certain vulnerability to environmental factors related to childrearing, although the studies published so far have been conducted with different methodology, making it difficult to compare the results.

Admittedly, the scarcity of data, the methodological differences in relation to the exploration of the adult attachment (AAI *vs* self-administered questionnaires) and the doubts raised about the comparability of data obtained in children (more abundant) and adults make it difficult to draw conclusions regarding the specific contribution of genetics to adult attachment. Different authors propose that the weight of genetics and environment on attachment styles differs in childhood and adulthood, so that during childhood the shared environment would be the main contributor to attachment style, whereas the biological-temperamental and the nonshared environment would acquire greater importance in adulthood[12,26,70]. These differences in the weight of genetics depending on the life stage are not unique to attachment style and have been observed in other cognitive and behavioral phenotypes as well[25,71-73].

In addition, the importance of gene-environment interaction to explain the contribution of genetics to the formation of attachment styles has also been emphasized, suggesting that research should focus more on the search for differential susceptibility or plasticity genes than on direct associations. Epigenetic research, currently in its embryonic stage in the area of attachment, has also been highlighted[26]. The studies exploring differential susceptibility, as well as epigenetic research, are precisely the ones that have yielded the most promising results to date and on which future research should probably be based.

We could therefore conclude that: (1) More research is needed to understand the precise contribution of genetics to adult attachment style; (2) Future research should take into account that the patterns observed in children and adults may differ; and (3) Additional studies should include the study of environmental variables that could affect affiliative behaviors.

REFERENCES

1 **Bowlby J**. The Making & Breaking of Affectional Bonds. London: Tavistock, 1979
2 **Nelson JK**, Mikulincer M, Shaver PR. Attachment in Adulthood. Structure, Dynamics, and Change. *Clin Soc Work J* 2009; **37**: 179-180 [DOI: 10.1007/s10615-009-0193-5]
3 **Ainsworth M**, Blehar M, Waters E, Wall S. Patterns of attachment: Assessed in the Strange Situation and at home. Hillsdale, NJ: Erlbaum, 1978
4 **Main M**, Solomon J. Procedures for identifying infants as disorganized/disoriented during the Ainsworth Strange Situation. In: Attachment in the preschool years: Theory, research, and intervention. Chicago, IL: University of Chicago Press, 1990: 121-160
5 **George C**, Main M, Kaplan N. Adult Attachment Interview (AAI). *APA PsycNe*t 1985 [DOI: 10.1037/t02879-000]
6 **Hazan C**, Shaver P. Romantic love conceptualized as an attachment process. *J Pers Soc Psychol* 1987; **52**: 511-524 [PMID: 3572722 DOI: 10.1037//0022-3514.52.3.511]
7 **Bartholomew K**, Horowitz LM. Attachment styles among young adults: a test of a four-category model. *J Pers Soc Psychol* 1991; **61**: 226-244 [PMID: 1920064 DOI: 10.1037//0022-3514.61.2.226]
8 **Brennan KA**, Clark CL, Shaver PR. Self-report measurement of adult attachment: An integrative overview. In: Simpson JA, Rholes WS. Attachment theory and close relationships. New York, NY: Guilford Press, 1998: 46-76
9 **Roisman GI**, Holland A, Fortuna K, Fraley RC, Clausell E, Clarke A. The Adult Attachment Interview and self-reports of attachment style: an empirical rapprochement. *J Pers Soc Psychol* 2007; **92**: 678-697 [PMID: 17469952 DOI: 10.1037/0022-3514.92.4.678]
10 **Pinquart M**, Feussner C, Ahnert L. Meta-analytic evidence for stability in attachments from infancy to early adulthood. *Attach Hum Dev* 2013; **15**: 189-218 [PMID: 23210665 DOI: 10.1080/14616734.2013.746257]
11 **Fraley RC**, Roisman GI, Booth-LaForce C, Owen MT, Holland AS. Interpersonal and genetic origins of adult attachment styles: a longitudinal study from infancy to early adulthood. *J Pers Soc Psychol* 2013; **104**: 817-838 [PMID: 23397970 DOI: 10.1037/a0031435]
12 **Fraley RC**, Roisman GI. The development of adult attachment styles: four lessons. *Curr Opin Psychol* 2019; **25**: 26-30 [PMID: 29510301 DOI: 10.1016/j.copsyc.2018.02.008]
13 **Bowlby J**. Attachment and Loss. Vol 2. Separation: anxiety and anger. New York: Basic Books, 1974
14 **Crawford TN**, Livesley WJ, Jang KL, Shaver PR, Cohen P, Ganiban J. Insecure attachment and personality disorder: a twin study of adults. *Eur J Personal* 2007; **21**: 191-208 [DOI: 10.1002/per.602]
15 **Donnellan MB**, Burt SA, Levendosky AA, Klump KL. Genes, personality, and attachment in adults: a multivariate behavioral genetic analysis. *Pers Soc Psychol Bull* 2008; **34**: 3-16 [PMID: 18162654 DOI: 10.1177/0146167207309199]
16 **Erkoreka L**, Zumárraga M, Macías I, Angel Gonzalez-Torres M. The COMT Val158Met polymorphism exerts a common influence on avoidant attachment and inhibited personality, with a pattern of positive heterosis. *Psychiatry Res* 2018; **262**: 345-347 [PMID: 28807501 DOI:

10.1016/j.psychres.2017.07.053]
17 **Bokhorst CL**, Bakermans-Kranenburg MJ, Fearon RM, van IJzendoorn MH, Fonagy P, Schuengel C. The importance of shared environment in mother-infant attachment security: a behavioral genetic study. *Child Dev* 2003; **74**: 1769-1782 [PMID: 14669895 DOI: 10.1046/j.1467-8624.2003.00637.x]
18 **O'Connor TG**, Croft CM. A twin study of attachment in preschool children. *Child Dev* 2001; **72**: 1501-1511 [PMID: 11699684 DOI: 10.1111/1467-8624.00362]
19 **Roisman GI**, Fraley RC. A behavior-genetic study of parenting quality, infant attachment security, and their covariation in a nationally representative sample. *Dev Psychol* 2008; **44**: 831-839 [PMID: 18473647 DOI: 10.1037/0012-1649.44.3.831]
20 **Plomin R**, DeFries J, McClearn G, McGuffin P. Behavioral genetics. 4th ed. New York: W. H. Freeman and Company, 2012: 505
21 **Brussoni MJ**, Jang KL, Livesley WJ, Macbeth TM. Genetic and environmental influences on adult attachment styles. *Pers Relatsh* 2000; **7**: 283-289 [DOI: 10.1111/j.1475-6811.2000.tb00017.x]
22 **Fearon P**, Shmueli-Goetz Y, Viding E, Fonagy P, Plomin R. Genetic and environmental influences on adolescent attachment. *J Child Psychol Psychiatry* 2014; **55**: 1033-1041 [PMID: 24256475 DOI: 10.1111/jcpp.12171]
23 **Picardi A**, Fagnani C, Nisticò L, Stazi MA. A twin study of attachment style in young adults. *J Pers* 2011; **79**: 965-991 [PMID: 21204839 DOI: 10.1111/j.1467-6494.2010.00707.x]
24 **Torgersen AM**, Grova BK, Sommerstad R. A pilot study of attachment patterns in adult twins. *Attach Hum Dev* 2007; **9**: 127-138 [PMID: 17508313 DOI: 10.1080/14616730701349705]
25 **Plomin R**, DeFries J, Knopik V, Neiderhiser J. Behavioral Genetics. 6th ed. New York: Worth Publishers, 2013: 560
26 **Bakermans-Kranenburg MJ**, Van Ijzendoorn MH. Attachment, Parenting, and Genetics. In: Handbook of Attachment. 3rd ed. Guilford Press, 2016: 155-179
27 **Tarantino N**, Tully EC, Garcia SE, South S, Iacono WG, McGue M. Genetic and environmental influences on affiliation with deviant peers during adolescence and early adulthood. *Dev Psychol* 2014; **50**: 663-673 [PMID: 24015689 DOI: 10.1037/a0034345]
28 **Pappa I**, Szekely E, Mileva-Seitz VR, Luijk MP, Bakermans-Kranenburg MJ, van IJzendoorn MH, Tiemeier H. Beyond the usual suspects: a multidimensional genetic exploration of infant attachment disorganization and security. *Attach Hum Dev* 2015; **17**: 288-301 [PMID: 25939396 DOI: 10.1080/14616734.2015.1037316]
29 **Garg E**, Chen L, Nguyen TTT, Pokhvisneva I, Chen LM, Unternaehrer E, MacIsaac JL, McEwen LM, Mah SM, Gaudreau H, Levitan R, Moss E, Sokolowski MB, Kennedy JL, Steiner MS, Meaney MJ, Holbrook JD, Silveira PP, Karnani N, Kobor MS, O'Donnell KJ; Mavan Study Team. The early care environment and DNA methylome variation in childhood. *Dev Psychopathol* 2018; **30**: 891-903 [PMID: 30068421 DOI: 10.1017/S0954579418000627]
30 **Belsky J**, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? *Mol Psychiatry* 2009; **14**: 746-754 [PMID: 19455150 DOI: 10.1038/mp.2009.44]
31 **Hurlemann R**, Scheele D. Dissecting the Role of Oxytocin in the Formation and Loss of Social Relationships. *Biol Psychiatry* 2016; **79**: 185-193 [PMID: 26122876 DOI: 10.1016/j.biopsych.2015.05.013]
32 **Russell JA**, Brunton PJ. Oxytocin: Control of Secretion by the Brain and Central Roles. *Ref Module Neur Biob Psychol* 2017 [DOI: 10.1016/B978-0-12-809324-5.02246-X]
33 **International HapMap Consortium**, Frazer KA, Ballinger DG, Cox DR, Hinds DA, Stuve LL, Gibbs RA, Belmont JW, Boudreau A, Hardenbol P, Leal SM, Pasternak S, Wheeler DA, Willis TD, Yu F, Yang H, Zeng C, Gao Y, Hu H, Hu W, Li C, Lin W, Liu S, Pan H, Tang X, Wang J, Wang W, Yu J, Zhang B, Zhang Q, Zhao H, Zhou J, Gabriel SB, Barry R, Blumenstiel B, Camargo A, Defelice M, Faggart M, Goyette M, Gupta S, Moore J, Nguyen H, Onofrio RC, Parkin M, Roy J, Stahl E, Winchester E, Ziaugra L, Altshuler D, Shen Y, Yao Z, Huang W, Chu X, He Y, Jin L, Liu Y, Sun W, Wang H, Wang Y, Xiong X, Xu L, Waye MM, Tsui SK, Xue H, Wong JT, Galver LM, Fan JB, Gunderson K, Murray SS, Oliphant AR, Chee MS, Montpetit A, Chagnon F, Ferretti V, Leboeuf M, Olivier JF, Phillips MS, Roumy S, Sallée C, Verner A, Hudson TJ, Kwok PY, Cai D, Koboldt DC, Miller RD, Pawlikowska L, Taillon-Miller P, Xiao M, Tsui LC, Mak W, Song YQ, Tam PK, Nakamura Y, Kawaguchi T, Kitamoto T, Morizono T, Nagashima A, Ohnishi Y, Sekine A, Tanaka T, Tsunoda T, Deloukas P, Bird CP, Delgado M, Dermitzakis ET, Gwilliam R, Hunt S, Morrison J, Powell D, Stranger BE, Whittaker P, Bentley DR, Daly MJ, de Bakker PI, Barrett J, Chretien YR, Maller J, McCarroll S, Patterson N, Pe'er I, Price A, Purcell S, Richter DJ, Sabeti P, Saxena R, Schaffner SF, Sham PC, Varilly P, Stein LD, Krishnan L, Smith AV, Tello-Ruiz MK, Thorisson GA, Chakravarti A, Chen PE, Cutler DJ, Kashuk CS, Lin S, Abecasis GR, Guan W, Li Y, Munro HM, Qin ZS, Thomas DJ, McVean G, Auton A, Bottolo L, Cardin N, Eyheramendy S, Freeman C, Marchini J, Myers S, Spencer C, Stephens M, Donnelly P, Cardon LR, Clarke G, Evans DM, Morris AP, Weir BS, Mullikin JC, Sherry ST, Feolo M, Skol A, Zhang H, Matsuda I, Fukushima Y, Macer DR, Suda E, Rotimi CN, Adebamowo CA, Ajayi I, Aniagwu T, Marshall PA, Nkwodimmah C, Royal CD, Leppert MF, Dixon M, Peiffer A, Qiu R, Kent A, Kato K, Niikawa N, Adewole IF, Knoppers BM, Foster MW, Clayton EW, Watkin J, Muzny D, Nazareth L, Sodergren E, Weinstock GM, Yakub I, Birren BW, Wilson RK, Fulton LL, Rogers J, Burton J, Carter NP, Clee CM, Griffiths M, Jones MC, McLay K, Plumb RW, Ross MT, Sims SK, Willey DL, Chen Z, Han H, Kang L, Godbout M, Wallenburg JC, L'Archevêque P, Bellemare G, Saeki K, An D, Fu H, Li Q, Wang Z, Wang R, Holden AL, Brooks LD, McEwen JE, Guyer MS, Wang VO, Peterson JL, Shi M, Spiegel J, Sung LM,

Zacharia LF, Collins FS, Kennedy K, Jamieson R, Stewart J. A second generation human haplotype map of over 3.1 million SNPs. *Nature* 2007; **449**: 851-861 [PMID: 17943122 DOI: 10.1038/nature06258]

34 **GeneCards**. GeneCards-Human Gene Database. [cited 1 May 2021]. In: GeneCards [Internet]. Available from: https://www.genecards.org/

35 **Meyer-Lindenberg A**, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci* 2011; **12**: 524-538 [PMID: 21852800 DOI: 10.1038/nrn3044]

36 **Tost H**, Kolachana B, Hakimi S, Lemaitre H, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A. A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proc Natl Acad Sci U S A* 2010; **107**: 13936-13941 [PMID: 20647384 DOI: 10.1073/pnas.1003296107]

37 **Furman DJ**, Chen MC, Gotlib IH. Variant in oxytocin receptor gene is associated with amygdala volume. *Psychoneuroendocrinology* 2011; **36**: 891-897 [PMID: 21208749 DOI: 10.1016/j.psyneuen.2010.12.004]

38 **Inoue H**, Yamasue H, Tochigi M, Abe O, Liu X, Kawamura Y, Takei K, Suga M, Yamada H, Rogers MA, Aoki S, Sasaki T, Kasai K. Association between the oxytocin receptor gene and amygdalar volume in healthy adults. *Biol Psychiatry* 2010; **68**: 1066-1072 [PMID: 20832055 DOI: 10.1016/j.biopsych.2010.07.019]

39 **Costa B**, Pini S, Gabelloni P, Abelli M, Lari L, Cardini A, Muti M, Gesi C, Landi S, Galderisi S, Mucci A, Lucacchini A, Cassano GB, Martini C. Oxytocin receptor polymorphisms and adult attachment style in patients with depression. *Psychoneuroendocrinology* 2009; **34**: 1506-1514 [PMID: 19515497 DOI: 10.1016/j.psyneuen.2009.05.006]

40 **Monin JK**, Goktas SO, Kershaw T, DeWan A. Associations between spouses' oxytocin receptor gene polymorphism, attachment security, and marital satisfaction. *PLoS One* 2019; **14**: e0213083 [PMID: 30818381 DOI: 10.1371/journal.pone.0213083]

41 **Chen FS**, Johnson SC. An Oxytocin Receptor Gene Variant Predicts Attachment Anxiety in Females and Autism-Spectrum Traits in Males. *Soc Psychol Personal Sci* 2012; **3**: 93-99 [DOI: 10.1177/1948550611410325]

42 **Gillath O**, Shaver PR, Baek JM, Chun DS. Genetic correlates of adult attachment style. *Pers Soc Psychol Bull* 2008; **34**: 1396-1405 [PMID: 18687882 DOI: 10.1177/0146167208321484]

43 **Gong P**, Wang Q, Liu J, Xi S, Yang X, Fang P, Wang B, He L, Guo W, Zhang M. The OXTR polymorphisms are not associated with attachment dimensions: A three-approach study. *Psychoneuroendocrinology* 2020; **120**: 104780 [PMID: 32634747 DOI: 10.1016/j.psyneuen.2020.104780]

44 **Raby KL**, Cicchetti D, Carlson EA, Egeland B, Collins WA. Genetic contributions to continuity and change in attachment security: a prospective, longitudinal investigation from infancy to young adulthood. *J Child Psychol Psychiatry* 2013; **54**: 1223-1230 [PMID: 23731038 DOI: 10.1111/jcpp.12093]

45 **Fujiwara T**, Weisman O, Ochi M, Shirai K, Matsumoto K, Noguchi E, Feldman R. Genetic and peripheral markers of the oxytocin system and parental care jointly support the cross-generational transmission of bonding across three generations. *Psychoneuroendocrinology* 2019; **102**: 172-181 [PMID: 30572177 DOI: 10.1016/j.psyneuen.2018.12.004]

46 **Ebner NC**, Lin T, Muradoglu M, Weir DH, Plasencia GM, Lillard TS, Pournajafi-Nazarloo H, Cohen RA, Sue Carter C, Connelly JJ. Associations between oxytocin receptor gene (OXTR) methylation, plasma oxytocin, and attachment across adulthood. *Int J Psychophysiol* 2019; **136**: 22-32 [PMID: 29410310 DOI: 10.1016/j.ijpsycho.2018.01.008]

47 **Ein-Dor T**, Verbeke WJMI, Mokry M, Vrtička P. Epigenetic modification of the oxytocin and glucocorticoid receptor genes is linked to attachment avoidance in young adults. *Attach Hum Dev* 2018; **20**: 439-454 [PMID: 29513137 DOI: 10.1080/14616734.2018.1446451]

48 **Pohjalainen T**, Rinne JO, Någren K, Lehikoinen P, Anttila K, Syvälahti EK, Hietala J. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. *Mol Psychiatry* 1998; **3**: 256-260 [PMID: 9672901 DOI: 10.1038/sj.mp.4000350]

49 **Oak JN**, Oldenhof J, Van Tol HH. The dopamine D(4) receptor: one decade of research. *Eur J Pharmacol* 2000; **405**: 303-327 [PMID: 11033337 DOI: 10.1016/s0014-2999(00)00562-8]

50 **D'Souza UM**, Russ C, Tahir E, Mill J, McGuffin P, Asherson PJ, Craig IW. Functional effects of a tandem duplication polymorphism in the 5'flanking region of the DRD4 gene. *Biol Psychiatry* 2004; **56**: 691-697 [PMID: 15522254 DOI: 10.1016/j.biopsych.2004.08.008]

51 **Reiner I**, Spangler G. Adult attachment and gene polymorphisms of the dopamine D4 receptor and serotonin transporter (5-HTT). *Attach Hum Dev* 2010; **12**: 209-229 [PMID: 20473794 DOI: 10.1080/14616731003759674]

52 **Bakermans-Kranenburg MJ**, van IJzendoorn MH, Caspers K, Philibert R. DRD4 genotype moderates the impact of parental problems on unresolved loss or trauma. *Attach Hum Dev* 2011; **13**: 253-269 [PMID: 21506030 DOI: 10.1080/14616734.2011.562415]

53 **Witte AV**, Flöel A. Effects of COMT polymorphisms on brain function and behavior in health and disease. *Brain Res Bull* 2012; **88**: 418-428 [PMID: 22138198 DOI: 10.1016/j.brainresbull.2011.11.012]

54 **Comings DE**, MacMurray JP. Molecular heterosis: a review. *Mol Genet Metab* 2000; **71**: 19-31 [PMID: 11001792 DOI: 10.1006/mgme.2000.3015]

55 **Raby KL**, Cicchetti D, Carlson EA, Cutuli JJ, Englund MM, Egeland B. Genetic and caregiving-based contributions to infant attachment: unique associations with distress reactivity and attachment security. *Psychol Sci* 2012; **23**: 1016-1023 [PMID: 22829464 DOI: 10.1177/0956797612438265]

56 **Drago A**, Ronchi DD, Serretti A. 5-HT1A gene variants and psychiatric disorders: a review of current literature and selection of SNPs for future studies. *Int J Neuropsychopharmacol* 2008; **11**: 701-721 [PMID: 18047755 DOI: 10.1017/S1461145707008218]

57 **Lemonde S**, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, Sequeira A, Kushwaha N, Morris SJ, Basak A, Ou XM, Albert PR. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J Neurosci* 2003; **23**: 8788-8799 [PMID: 14507979 DOI: 10.1523/JNEUROSCI.23-25-08788.2003]

58 **Wu S**, Comings DE. A common C-1018G polymorphism in the human 5-HT1A receptor gene. *Psychiatr Genet* 1999; **9**: 105-106 [PMID: 10412191 DOI: 10.1097/00041444-199906000-00010]

59 **Czesak M**, Le François B, Millar AM, Deria M, Daigle M, Visvader JE, Anisman H, Albert PR. Increased serotonin-1A (5-HT1A) autoreceptor expression and reduced raphe serotonin levels in deformed epidermal autoregulatory factor-1 (Deaf-1) gene knock-out mice. *J Biol Chem* 2012; **287**: 6615-6627 [PMID: 22232550 DOI: 10.1074/jbc.M111.293027]

60 **Gong P**, Liu J, Li S, Zhou X. Serotonin receptor gene (5-HT1A) modulates alexithymic characteristics and attachment orientation. *Psychoneuroendocrinology* 2014; **50**: 274-279 [PMID: 25247748 DOI: 10.1016/j.psyneuen.2014.09.001]

61 **Turecki G**, Brière R, Dewar K, Antonetti T, Lesage AD, Séguin M, Chawky N, Vanier C, Alda M, Joober R, Benkelfat C, Rouleau GA. Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide. *Am J Psychiatry* 1999; **156**: 1456-1458 [DOI: 10.1176/appi.ajp.158.1.148]

62 **Salo J**, Jokela M, Lehtimäki T, Keltikangas-Järvinen L. Serotonin receptor 2A gene moderates the effect of childhood maternal nurturance on adulthood social attachment. *Genes Brain Behav* 2011; **10**: 702-709 [PMID: 21649857 DOI: 10.1111/j.1601-183X.2011.00708.x]

63 **Lesch KP**, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996; **274**: 1527-1531 [PMID: 8929413 DOI: 10.1126/science.274.5292.1527]

64 **Caspers KM**, Paradiso S, Yucuis R, Troutman B, Arndt S, Philibert R. Association between the serotonin transporter promoter polymorphism (5-HTTLPR) and adult unresolved attachment. *Dev Psychol* 2009; **45**: 64-76 [PMID: 19209991 DOI: 10.1037/a0014026]

65 **van IJzendoorn MH**, Caspers K, Bakermans-Kranenburg MJ, Beach SR, Philibert R. Methylation matters: interaction between methylation density and serotonin transporter genotype predicts unresolved loss or trauma. *Biol Psychiatry* 2010; **68**: 405-407 [PMID: 20591416 DOI: 10.1016/j.biopsych.2010.05.008]

66 **Jones-Mason K**, Allen IE, Bush N, Hamilton S. Epigenetic marks as the link between environment and development: examination of the associations between attachment, socioeconomic status, and methylation of the SLC6A4 gene. *Brain Behav* 2016; **6**: e00480 [PMID: 27458544 DOI: 10.1002/brb3.480]

67 **Egan MF**, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003; **112**: 257-269 [PMID: 12553913 DOI: 10.1016/s0092-8674(03)00035-7]

68 **Suzuki A**, Matsumoto Y, Shibuya N, Ryoichi S, Kamata M, Enokido M, Goto K, Otani K. Interaction effect between the BDNF Val66Met polymorphism and parental rearing for interpersonal sensitivity in healthy subjects. *Psychiatry Res* 2012; **200**: 945-948 [PMID: 22542952 DOI: 10.1016/j.psychres.2012.03.014]

69 **Ibarra P**, Alemany S, Fatjó-Vilas M, Córdova-Palomera A, Goldberg X, Arias B, González-Ortega I, González-Pinto A, Nenadic I, Fañanás L. The BDNF-Val66Met polymorphism modulates parental rearing effects on adult psychiatric symptoms: a community twin-based study. *Eur Psychiatry* 2014; **29**: 293-300 [PMID: 24768157 DOI: 10.1016/j.eurpsy.2014.03.001]

70 **Oliveira P**, Fearon P. The biological bases of attachment. *Adopt Foster* 2019; **43**: 274-293 [DOI: 10.1177/0308575919867770]

71 **Bergen SE**, Gardner CO, Kendler KS. Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. *Twin Res Hum Genet* 2007; **10**: 423-433 [PMID: 17564500 DOI: 10.1375/twin.10.3.423]

72 **Haworth CM**, Kovas Y, Petrill SA, Plomin R. Developmental origins of low mathematics performance and normal variation in twins from 7 to 9 years. *Twin Res Hum Genet* 2007; **10**: 106-117 [PMID: 17539370 DOI: 10.1375/twin.10.1.106]

73 **Wadsworth SJ**, Corley RP, Hewitt JK, Defries JC; Colorado Adoption Project. Stability of genetic and environmental influences on reading performance at 7, 12, and 16 years of age in the Colorado Adoption Project. *Behav Genet* 2001; **31**: 353-359 [PMID: 11720121 DOI: 10.1023/a:1012218301437]

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MINIREVIEWS

Recent advances in the treatment of opioid use disorders–focus on long-acting buprenorphine formulations

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Abstract

Oral methadone or sublingual buprenorphine are first-line medications for pharmacotherapy of opioid use disorders (OUDs). Three long-acting buprenorphine depot or implant formulations are currently available for the treatment of OUDs: (1) CAM 2038 (Buvidal) for subcutaneous weekly and monthly application; (2) RBP-6000 (Sublocade™) as a monthly depot formulation; and (3) A six-month buprenorphine implant [Probuphine™]. The pharmacology, clinical efficacy and prospects of these medications are discussed.

Key Words: Opioids; Opioid dependence; Maintenance treatment; Methadone; Buprenorphine; Depot; Implant

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Core Tip: Although opioid maintenance therapy with methadone or buprenorphine is the widely accepted first line treatment in opioid use disorders (OUDs) the risk of diversion and low retention rates limit its use. While previous attempts to introduce long-acting methadone analogues have failed due to cardiac side effects in recent years, three different long-acting buprenorphine formulations have been developed and successfully studied in opioid users, two weekly or monthly depot injections (CAM 2038, RBP-6000) and one implant (probuphine). The prospects of these new medications are significant by optimizing retention and compliance and minimizing the risk of diversion. Thus, these novel medications can facilitate treatment of OUDs significantly.

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INTRODUCTION

Opioid use disorder (OUD) is defined as a chronic relapsing substance use disorder that causes psychological and physical harm. The economic burden and health costs of OUD are also very significant[1-4].

PREVALENCE

OUD has a prevalence of approximately 0.2%-0.4% in the adult population in many countries[5-7]. In Europe, heroin is the most frequently abused opioid. However, in other countries, the use of synthetic opioids and opioid pain killers, such as fentanyl or oxycodone, has been exploding and is the predominant form of opioid use. In particular, the United States is facing an epidemic of opioid pain killer abuse[8]. Recent data indicate that in Europe, there are 1.3 million high-risk opioid users and 644000 opioid users in substitution treatment[5]. Opioid use accounts for 40% of all drug requests in the European Union.

The high mortality in opioid dependence remains a significant problem. Opioids are involved in 82% of fatal drug-related overdoses[5]. Most opioid-related deaths are caused by overdose and respiratory depression. Other frequent causes of death include suicide, accidents, injuries, and numerous somatic disorders, such as infectious diseases (human immunodeficiency virus, hepatitis, others). In many fatal drug intoxications, polysubstance abuse is involved, especially alcohol or other sedative drugs[9].

TREATMENT AIMS

Opioid maintenance treatment (OMT) and psychosocial interventions are key elements in the treatment of OUD[2,8,10,11]. Major aims in the treatment of OUD are reduction of opioid use or even abstinence[12,13] as measured by self-reports or toxicological analysis, reduction of other substance use, improved social functioning and health outcome and reduction of criminal behavior[12,14,15].

There are numerous clinical and longitudinal studies on treatment outcomes in OUD. However, many long-term studies only address substance use or abstinence rates, whereas other outcome parameters are less often reported. An interesting study on outcome criteria has recently been described by Wiessing *et al*[16], who assessed reported outcome domains in 27 longitudinal studies (Table 1). Data indicate that many domains, especially social functioning or health economics, are often neglected as outcome parameters.

Several medications are currently available for the treatment of OUDs (Table 2). For approximately five decades, OMT has been the established and widely accepted first-line treatment of OUD[11,14,17-20]. In addition, a number of pharmacological options are available. Medications used in OMT control craving for opioids and withdrawal symptoms. The two widely examined gold standards in OMT are methadone and buprenorphine[21].

Oral methadone (standard doses 60-100/120 mg daily) and sublingual buprenorphine (standard doses 8-12, max 24-32 mg daily) are the primarily used drugs in the treatment of opioid dependence. Their efficacy has been shown in many clinical studies[17-19]. Some distinct pharmacological differences are noted between methadone and buprenorphine.

Methadone is a pure nonselective opioid receptor agonist of the mu, delta and kappa opioid receptors. Methadone induces the typical clinical effects of full opioid agonists, such as analgesia, sedation, respiratory depression, euphoria and tolerance. Methadone causes a significant physical dependence. Methadone has a half-life of approximately 22 h (13-50 h). Methadone blocks the opioid receptor for approximately 24 h, so it is suitable for daily dosing. Methadone suppresses opioid withdrawal symptoms for 24 h. There is broad evidence for the efficacy of methadone in OMT[14,17-19]. The drug is widely accepted and used.

Table 1 Large variations in outcome measures in longitudinal studies of opioid dependence[16]

Domain	Reported among 27 studies included
Drug use	21 of 27
Crime	13 of 27
Health	13 of 27
Treatment-related outcomes	16 of 27
Social functioning	13 of 27
Harms	8 of 27
Mortality	13 of 27
Economic estimates	2 of 27

Results are based on 27 studies included. Eight domains were defined. Each domain was reported x-times among 27 studies.

Table 2 Pharmacological options in the treatment of opioid use disorders

Drug	Onset of action, duration	Route of administration	Clinical use
Opioid antagonists			
Naloxone	Few minutes	i.v., nasal (spray)	Opioid overdose
Naltrexone	Daily	Oral	Abstinence
Naltrexone (depot)	One month	i.m.	Abstinence
Partial agonists			
Buprenorphine	Daily	Sublingual	Maintenance
Buvidal	Weekly, monthly	Subcutaneous	Maintenance
RB_6000 (sublocade)	Monthly	Subcutaneous	Maintenance
Probuphine	6 mo	Implant	Maintenance
Full agonists			
Methadone	Daily	Oral	Maintenance
Heroin	Hours	i.v.	Maintenance
Morphine sulfate (retarded)	Daily	Oral	Maintenance
Morphine sulfate	Daily	Oral	Maintenance

Buprenorphine, being a partial agonist at the mu-opioid receptor[11,19], has to be administered sublingually because of a strong first pass effect. Regarding opioid receptors, the use of buprenorphine is associated with a ceiling effect at these receptors. Compared to methadone, buprenorphine is at lower risk to induce depression of respiration. Numerous studies indicate that buprenorphine is associated with fewer fatal intoxications or overdose deaths than methadone. Other full opioid agonists used for the treatment of OUD include morphine sulfate and diacetylmorphine (heroin). Both are second line medications for OMT[11,14,22].

There are some significant problems in OMT. The most important factor is the risk of diversion of methadone or buprenorphine. Other major problems are concomitant opioid or other substance use as well as limited compliance and retention in treatment [20,23,24]. The latter is of great importance. A recent systematic review on retention in OMT[25] included four randomized clinical trials and 63 observational cohort studies with a total of 294592 patients. The overall findings indicate a 1-year retention rate of 57% and a 3-year retention rate of 38.4%. The retention rate is higher in patients with older age and depends on an adequate dose of the maintenance drug. Several studies indicate that a too low dosage is associated with a higher dropout rate[26].

Dosing issues are of great relevance in OMT. Adherence to treatment depends on adequate dosing, and retention can be improved by adequate dosing[13,27-29]. Too low doses of methadone or buprenorphine are associated with low retention and risk

of further substance use.

Methadone remains the most frequently used medication in OMT. The other first-line medication is buprenorphine[18,19,24,26,30,31]. The retention rate for buprenorphine was reported to be lower than that of methadone in some studies[19,26,30]. The risk for respiratory depression by buprenorphine in cases of overdose is lower than that for full opioid agonists[24,32].

Buprenorphine is used as a sublingual tablet. It is marketed as a monoproduct or in combination with naloxone (buprenorphine:naloxone ratio 4:1)[9,27]. Naloxone is a short-acting opioid antagonist and is pharmacologically active only as an i.v. medication and as a nasal spray for the prevention of overdose death. Naloxone will rapidly induce opioid withdrawal. The risk of precipitated opioid withdrawal should prevent the patient from injecting buprenorphine and thus reduce the risk of diversion or i.v. use of buprenorphine.

Both methadone and buprenorphine are administered as once a day doses, and both suppress symptoms of opioid withdrawal for 24 h. Longer dosing intervals have been a major aim in OMT research. A long-acting methadone analog was previously studied but had to be withdrawn over potential adverse cardiac effects[33,34].

Clinical and social reasons for long-acting opioids in OMT include a reduced risk of diversion, improved compliance, easier home dosing and longer treatment intervals. The recent coronavirus disease 2019 (COVID-19) epidemic has demonstrated that prolonged dosing and treatment intervals and consequently less time spent in the outpatient clinic or at the office-based physician, respectively, and reduced use of social and medical resources are important goals for many clinicians.

Recent developments

Exciting developments have occurred in recent years: Three different long-acting buprenorphine formulations have been developed, approved and in part introduced into clinical practice in many countries. These agents will be reviewed briefly.

RBP-6000 (Sublocade™)

RBP-6000 is a buprenorphine depot injection. It has been marketed in the United States since 2018 and will soon be available in Europe. Medication and dosing intervals: Monthly s.c. injections are available with dosages of 100 and 300 mg. Dosages recommended for the treatment of OUD (www.sublocade.com) include two initial 300 mg injections monthly followed by monthly 100 mg injections.

RBP-6000 has been studied in several pharmacological and clinical studies. Nasser *et al*[35] studied the effects of RBP-6000 in patients with opioid dependence. RBP was found to block the effects of a strong opioid, hydromorphone, such as opioid cravings. Other studies showed effective μ-opioid receptor blockade with different dosages of RBP-6000[35,36]. These findings suggest that RBP-6000 is a suitable medication for OMT. A recent combined analysis of phase II and III trials with 570 subjects[37] showed that therapeutic concentrations can be achieved from the first injection. These therapeutic concentrations were achieved during the entire treatment duration. The data suggest that the drug provided therapeutic plasma concentrations over the entire treatment duration.

Clinical data indicate that RBP-6000 is effective in OMT. Haight *et al*[38] performed a multicenter phase III study being double-blind and placebo-controlled. Dosing regimen among the opioid dependent patients was as follows: One group received monthly injections of RBP-6000 subcutaneously (6 × 300 mg or 2 × 300 mg) followed by 4 × 100 mg, the other group received placebo. Abstinence rates as a major outcome in both buprenorphine depot groups (n = 203 and n = 201 patients, respectively) were significantly higher than those in the placebo group (n = 100) (41.3% and 42.7% in the respective buprenorphine groups compared to 5.0% in the placebo group; P < 0.0001 for both buprenorphine groups). No differences in outcome were noted between the buprenorphine groups. Both studied dosing regimens were equally effective. In addition, the rate of hospital admissions was also lower in both buprenorphine groups compared with the placebo group[39]. Overall, these data indicate that RBP-6000 is effective. Andorn *et al*[40] performed an open-label multicenter study in 257 patients. A total of 13.2% of OUD patients had injection-site adverse events. Although these events are usually mild and transient, they may affect acceptance of this or other depot injections. Otherwise, the safety profile was good with fewer adverse events in the second 6 mo of treatment *vs* the first 6 mo. The retention rate was approximately 50% after 12 mo.

CAM 2038 (Buvidal®)

CAM 2038 is another novel depot buprenorphine injection. The drug is injected subcutaneously. Buvidal is approved in Europe[41,42]. Dosing regimen: Four different dosages are available: 8, 16, 24 or 32 mg for weekly injections and 64, 96, 128 or 160 mg for monthly injections. CAM 2038 treatment is typically initiated with weekly injections. Later, the patient can be transferred from weekly to monthly depot injections.

Several pharmacological studies have been conducted to explore the pharmacological effects of RBP-6000[43-45]. In sum, adequate plasma concentrations and bioavailability were demonstrated for the compound. Albayaty *et al*[45] showed that monthly or weekly subcutaneously administered depots of CAM 2038 (dosages: 96 mg and 192 mg) exhibited 5.7- to 7.7-fold increased bioavailability than sublingual buprenorphine (8, 16 or 24 mg). In addition, 24 mg and 32 mg Buvidal block the subjective effects of intramuscularly administered hydromorphone[44].

The efficacy of Buvidal has also been demonstrated in several clinical trials. In a phase III study being double-blind with double-dummy, with 428 patients[46], flexible weekly injections of CAM 2038 were used in the first 12 wk rather than monthly injections in the following 12 wk and tested against sublingual buprenorphine (flexible dose up to 24 mg daily maximum). Buvidal was found to be noninferior to sublingual buprenorphine with respect to opioid use (primary outcome) and opioid-free urine (secondary outcome). The average weekly CAM 2038 dosages were 24 mg, and monthly injections ranged over 100 mg. No novel adverse events were noted. The side effect profile of RBP-6000 is similar to that of sublingual buprenorphine[47]. With respect to the injection, mild local reactions were reported by 18%-22% of the participants. In a very recent study, injection site reactions of mild intensity were the most frequent adverse drug reaction[48]. Further safety data are being collected in an ongoing nonrandomized prospective observational study[49].

Buprenorphine implant (Probuphine™, Sixmo)

The third long-acting buprenorphine is an implant[1]. Probuphine was approved by the Food and Drug Administration (FDA) in 2016 for the long-term treatment of opioid dependent patients who were on a stable medication regimen of 8 mg buprenorphine sublingually or less. Buprenorphine (8 mg) is typically considered a moderate dose in OMT with an upper limit of daily sublingual buprenorphine dose of 24-32 mg. In Europe, the implant was approved by the European Medicine Agency in 2019. Buprenorphine is linked to a polymer that delivers the drug steadily to the body. Four implants are inserted. The dose of the buprenorphine released by the implant is equivalent to 8 mg sublingual buprenorphine or less[50-52]. Subdermal insertion of the implant requires minimal surgery. The implant is inserted in the upper arm and remains there for 6 mo before it is removed again. Plasma concentrations peak 12 h after the implant is inserted. Steady state conditions were noted after 3-4 wk[52].

Several relevant clinical studies of Probuphine are available. The efficacy of the buprenorphine implant was demonstrated in three double-blind studies (309 patients included) with a follow-up of up to 6 mo.

In a randomized controlled trial Ling *et al*[53] assessed 163 participants with opioid dependence over a period of 6 mo. After initial treatment with sublingual buprenorphine, the patients were transferred to either 4 × 80 mg buprenorphine or placebo implants. The retention rate in the implant group (71 of 108 patients) was significantly higher than that in the placebo group (17 of 55 patients; 65.7% *vs* 30.9%, $P < 0.001$). In the buprenorphine implant group, the number of opioid-free urine samples was higher.

Rosenthal *et al*[54] conducted a placebo-controlled randomized clinical trial in opioid-dependent patients who either received 4 × 80 mg buprenorphine ($n = 114$) or 4 placebo implants ($n = 54$). In an open design, the control group was treated with sublingual buprenorphine at a dose of 12-16 mg daily. In total, 119 participants were included in the control group. Compared to the placebo group, the retention rate of the implant group was significantly higher ($P < 0.0001$) (64 *vs* 26%). Furthermore, regarding the mean number of urine samples being opioid-free, the implant group was also found to be superior to the placebo group and noninferior to the sublingual buprenorphine group. Side effects: Negligible (local) reactions among the patients of the implant group were more or less frequent (25%-27%).

Furthermore, Rosenthal *et al*[55] studied OMT patients being stably adjusted to a sublingual dose of 8 mg (or less). Patients were given sublingual placebo plus four buprenorphine implants or sublingual buprenorphine plus four placebo implants over a period of 24 wk. In total, 177 patients were included. Over a time period of 6 mo, the

rate of abstinence among patients in the buprenorphine implant group was found to be noninferior to that in the control group treated with sublingual buprenorphine (85.7% *vs* 71.9%). The retention rate was 93%. The response rate was 96.4% in the buprenorphine implant group and 87.6% in the control group ($P < 0.01$). In addition, 85% of patient in the implant group were opioid free compared to 72% of the patients of the control group.

According to the FDA there is the necessity of a special risk management for this treatment. The "Probuphine Risk Evaluation and Mitigation Strategy" program was initiated (https://probuphinerems.com).

In addition, Titan Pharmaceuticals announced discontinuing United States Probuphine implant sales on October 15, 2020. No specific medical reasons were given for this decision.

DISCUSSION

OMT is the established first-line treatment in OUD, and methadone and buprenorphine serve as the pharmacological "frontrunners"[21]. Buprenorphine has a good safety profile[56] but modest and somehow lower retention rates than methadone. Retention to treatment is of overwhelming importance for treatment outcome and mortality in OUD, especially the induction phase and the period after leaving treatment[15]. Other common problems include diversion and i.v. use of buprenorphine[3,57]. Whether the combination of buprenorphine and naloxone lowers the risk of buprenorphine diversion is controversial[58].

Emerging or approved long-acting buprenorphine (depot or implant) formulations significantly widen the therapeutic arena in OMT[42,59]. Weekly and monthly s.c. buprenorphine injections as well as 6-mo depot formulations are available or will be available in the near future. It is clear and self-evident that the retention to treatment in patients with a depot formulation will be greater than that noted in patients in conventional OMT, and the risk of diversion is especially minimal to nonexistent. The data reviewed indicate that long-acting buprenorphine formulations are as efficient as sublingual buprenorphine with respect to opioid use with a similar side effect profile–with the exception of effects linked to injection or insertion of the compound. To date, some other observational studies on these medications are ongoing to provide further safety data[49,60].

The clinical question is: Who will benefit?

With the long-term French buprenorphine experience in mind, Vorspan *et al*[61] suggest prolonged-release buprenorphine depot formulations, such as Buvidal, as a promising treatment option in the following scenarios: (1) OMT initiation, including in nonspecialized medicine care; (2) Discharge from prison or hospital; (3) Diversion /Misuse of buprenorphine or methadone; and (4) Clinically stabilized patients wishing to avoid daily oral taking of the medication.

In addition, clinically stabilized patients wishing to receive an injection or implantation of the compound can be transferred to a buprenorphine depot.

This covers a wide range of patients. Other authors have similar views. Ling *et al*[39] stated that "Anyone with an OUD who can benefit from oral buprenorphine can benefit from the injectable".

Patients who want to avoid daily oral intake of the medication may be attracted by the prospect of more personal freedom.

In addition to benefits at the individual level, this novel medication also provides public health benefits. Retention rates may be increased–which has to be shown in future studies–and the risk for diversion may be reduced. In addition, the utilization of health care resources will be reduced. These effects are relevant, especially during the COVID-19 pandemic when social distancing is required[42].

Arunogiri and Lintzeris[62] argued that the use of long-acting buprenorphine formulations may help during the COVID-19 pandemic, and some health care organizations have advocated its use[42]. For example, a rapid upscaling of Buvidal use in custodial settings occurred in Australia during the COVID-19 epidemic[63].

Depot formulations are already used in prisons or forensic psychiatry settings to avoid diversion of the drug[61]. Broad empirical evidence suggests that OMT can reduce criminality in OUD[64-68] as reported in a meta-analysis by Moore *et al*[69]. The risk of diversion and misuse of opioid medication is significant in prison settings. Depot medications may reduce this risk significantly.

There are also some practical aspects to be considered. Although transfer from sublingual to depot buprenorphine will likely not represent a major problem, the introduction of depot buprenorphine to a patient previously treated with methadone is more complicated. Moreover, there are few studies on this issue. Switching the patient from methadone to sublingual buprenorphine first before transferring him to a depot formulation seems to be the most appropriate method at present.

Patient preferences and attitudes toward treatment are of great relevance for OMT. Many patients prefer certain OMT medications.

There are very few qualitative studies on this issue[70-73]. Patients cite spending less time with drug-treatment services, having more time for other activities and avoiding the stigma of being in OMT as reasons for preferring depot medications[39].

CONCLUSION

In conclusion, novel depot buprenorphine formations are a promising therapeutic option in OMT. There is no doubt about the efficacy of these compounds, but the practical value has to be shown in real life conditions.

REFERENCES

1 **Degenhardt L**, Charlson F, Mathers B, Hall WD, Flaxman AD, Johns N, Vos T. The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. *Addiction* 2014; **109**: 1320-1333 [PMID: 24661272 DOI: 10.1111/add.12551]

2 **Degenhardt L**, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, Bruneau J, Altice FL, Henderson G, Rahimi-Movaghar A, Larney S. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. *Lancet* 2019; **394**: 1560-1579 [PMID: 31657732 DOI: 10.1016/S0140-6736(19)32229-9]

3 **Neusser S**, Treutner A, Pomorin N Wasem A, Neumann A. Krankheitskosten der Opioidabhängigkeit in Deutschland. *Suchtmed* 2020; **22**: 205-216

4 **Schuckit MA**. Treatment of Opioid-Use Disorders. *N Engl J Med* 2016; **375**: 1596-1597 [PMID: 27797302 DOI: 10.1056/NEJMc1610830]

5 **EMCDDA**. European Monitoring Centre for drugs and Drug addiction (2020) European Drug Report. Lisbon: EMCDDA. [cited 10 January 2021]. Available from: https://www.drugsandalcohol.ie/33049/

6 **Merz F**. United Nations Office on Drugs and Crime (2017) World Drug Report. *SIRIUS-Zeitschrift für Strategische Analysen* 2017; 85-86 [DOI: 10.1515/sirius-2018-0016]

7 **United Nations**. United Nations Office on Drugs and Crime (2020) International Standards on Drug Use Prevention. Second updated Edition. [cited 10 January 2021]. Available from: https://www.unodc.org/

8 **Blanco C**, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. *Lancet* 2019; **393**: 1760-1772 [PMID: 30878228 DOI: 10.1016/S0140-6736(18)33078-2]

9 **Soyka M**, Batra A, Heinz A, Moggi F, Walter M. Suchtmedizin. München: Elsevier, 2019: 177-202

10 **Volkow ND**, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies--tackling the opioid-overdose epidemic. *N Engl J Med* 2014; **370**: 2063-2066 [PMID: 24758595 DOI: 10.1056/NEJMp1402780]

11 **Volkow ND**, Blanco C. Medications for opioid use disorders: clinical and pharmacological considerations. *J Clin Invest* 2020; **130**: 10-13 [PMID: 31763992 DOI: 10.1172/JCI134708]

12 **Gossop M**, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. *Drug Alcohol Depend* 2001; **62**: 255-264 [PMID: 11295330 DOI: 10.1016/s0376-8716(00)00211-8]

13 **Bell J**. Pharmacological maintenance treatments of opiate addiction. *Br J Clin Pharmacol* 2014; **77**: 253-263 [PMID: 23210630 DOI: 10.1111/bcp.12051]

14 **Bell J**, Strang J. Medication Treatment of Opioid Use Disorder. *Biol Psychiatry* 2020; **87**: 82-88 [PMID: 31420089 DOI: 10.1016/j.biopsych.2019.06.020]

15 **Sordo L**, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* 2017; **357**: j1550 [PMID: 28446428 DOI: 10.1136/bmj.j1550]

16 **Wiessing L**, Ferri M, Darke S, Simon R, Griffiths P. Large variation in measures used to assess outcomes of opioid dependence treatment: A systematic review of longitudinal observational studies. *Drug Alcohol Rev* 2018; **37** Suppl 1: S323-S338 [PMID: 28971544 DOI: 10.1111/dar.12608]

17 **Amato L**, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments *vs* agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev* 2011; CD004147 [PMID: 21975742 DOI: 10.1002/14651858.CD004147.pub4]

18 **Mattick RP**, Breen C, Kimber J, Davoli M. Methadone maintenance therapy *vs* no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2003; CD002209 [DOI: 10.1002/14651858.cd002209]

19 **Mattick RP**, Breen C, Kimber J. Davoli M. Buprenorphine maintenance *vs* placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014; CD002207 [DOI: 10.1002/14651858.CD002207]

20 **Soyka M**, Strehle J, Rehm J, Bühringer G, Wittchen HU. Six-Year Outcome of Opioid Maintenance Treatment in Heroin-Dependent Patients: Results from a Naturalistic Study in a Nationally Representative Sample. *Eur Addict Res* 2017; **23**: 97-105 [PMID: 28376505 DOI: 10.1159/000468518]

21 **Crotty K**, Freedman KI, Kampman KM. Executive Summary of the Focused Update of the ASAM National Practice Guideline for the Treatment of Opioid Use Disorder. *J Addict Med* 2020; **14**: 99-112 [PMID: 32209915 DOI: 10.1097/ADM.0000000000000635]

22 **Strang J**, Groshkova T, Uchtenhagen A, van den Brink W, Haasen C, Schechter MT, Lintzeris N, Bell J, Pirona A, Oviedo-Joekes E, Simon R, Metrebian N. Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction†. *Br J Psychiatry* 2015; **207**: 5-14 [PMID: 26135571 DOI: 10.1192/bjp.bp.114.149195]

23 **Bell J**. The global diversion of pharmaceutical drugs: opiate treatment and the diversion of pharmaceutical opiates: a clinician's perspective. *Addiction* 2010; **105**: 1531-1537 [PMID: 20626373 DOI: 10.1111/j.1360-0443.2010.03014.x]

24 **Bell J**, Trinh L, Butler B, Randall D, Rubin G. Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment. *Addiction* 2009; **104**: 1193-1200 [PMID: 19563562 DOI: 10.1111/j.1360-0443.2009.02627.x]

25 **O'Connor AM**, Cousins G, Durand L, Barry J, Boland F. Retention of patients in opioid substitution treatment: A systematic review. *PLoS One* 2020; **15**: e0232086 [PMID: 32407321 DOI: 10.1371/journal.pone.0232086]

26 **Hser YI**, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, Wiest K, Cohen A, Ling W. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction* 2014; **109**: 79-87 [PMID: 23961726 DOI: 10.1111/add.12333]

27 **Fareed A**, Vayalapalli S, Casarella J, Drexler K. Effect of buprenorphine dose on treatment outcome. *J Addict Dis* 2012; **31**: 8-18 [PMID: 22356665 DOI: 10.1080/10550887.2011.642758]

28 **Greenwald MK**, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug Alcohol Depend* 2014; **144**: 1-11 [PMID: 25179217 DOI: 10.1016/j.drugalcdep.2014.07.035]

29 **Greenwald MK**, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 2003; **28**: 2000-2009 [PMID: 12902992 DOI: 10.1038/sj.npp.1300251]

30 **Hser YI**, Evans E, Huang D, Weiss R, Saxon A, Carroll KM, Woody G, Liu D, Wakim P, Matthews AG, Hatch-Maillette M, Jelstrom E, Wiest K, McLaughlin P, Ling W. Long-term outcomes after randomization to buprenorphine/naloxone *vs* methadone in a multi-site trial. *Addiction* 2016; **111**: 695-705 [PMID: 26599131 DOI: 10.1111/add.13238]

31 **Jordan CJ**, Cao J, Newman AH, Xi ZX. Progress in agonist therapy for substance use disorders: Lessons learned from methadone and buprenorphine. *Neuropharmacology* 2019; **158**: 107609 [PMID: 31009632 DOI: 10.1016/j.neuropharm.2019.04.015]

32 **Kimber J**, Larney S, Hickman M, Randall D, Degenhardt L. Mortality risk of opioid substitution therapy with methadone *vs* buprenorphine: a retrospective cohort study. *Lancet Psychiatry* 2015; **2**: 901-908 [PMID: 26384619 DOI: 10.1016/S2215-0366(15)00366-1]

33 **Deamer RL**, Wilson DR, Clark DS, Prichard JG. Torsades de pointes associated with high dose levomethadyl acetate (ORLAAM). *J Addict Dis* 2001; **20**: 7-14 [PMID: 11760927 DOI: 10.1300/J069v20n04_02]

34 **Wieneke H**, Conrads H, Wolstein J, Breuckmann F, Gastpar M, Erbel R, Scherbaum N. Levo-alpha-acetylmethadol (LAAM) induced QTc-prolongation - results from a controlled clinical trial. *Eur J Med Res* 2009; **14**: 7-12 [PMID: 19258204 DOI: 10.1186/2047-783x-14-1-7]

35 **Nasser AF**, Heidbreder C, Gomeni R, Fudala PJ, Zheng B, Greenwald MK. A population pharmacokinetic and pharmacodynamic modelling approach to support the clinical development of RBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid dependence. *Clin Pharmacokinet* 2014; **53**: 813-824 [PMID: 25015174 DOI: 10.1007/s40262-014-0155-0]

36 **Laffont CM**, Gomeni R, Heidbreder C, Jones JP 3rd, Nasser AF. Population Pharmacokinetic Modeling After Repeated Administrations of RBP-6000, a New, Subcutaneously Injectable, Long-Acting, Sustained-Release Formulation of Buprenorphine, for the Treatment of Opioid Use Disorder. *J Clin Pharmacol* 2016; **56**: 806-815 [PMID: 26479717 DOI: 10.1002/jcph.665]

37 **Jones AK**, Ngaimisi E, Gopalakrishnan M, Young MA, Laffont CM. Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase II and Phase III Trials. *Clin Pharmacokinet* 2021; **60**: 527-540 [PMID: 33135125 DOI: 10.1007/s40262-020-00957-0]

38 **Haight BR**, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, Greenwald MK, Nadipelli

VR, Ling W, Heidbreder C; RB-US-13-0001 Study Investigators. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2019; **393**: 778-790 [PMID: 30792007 DOI: 10.1016/S0140-6736(18)32259-1]

39 **Ling W**, Shoptaw S, Goodman-Meza D. Depot Buprenorphine Injection In The Management Of Opioid Use Disorder: From Development To Implementation. *Subst Abuse Rehabil* 2019; **10**: 69-78 [PMID: 31819701 DOI: 10.2147/SAR.S155843]

40 **Andorn AC**, Haight BR, Shinde S, Fudala PJ, Zhao Y, Heidbrecher C, Learned SM, Fox NL, Nadipelli VR, Hassman D, Rutrick D. Treating Opioid Use Disorder with a Monthly Subcutanaeous Buprenorphine depot Injection: 12-Month Safety, tolerability, and Efficacy Analysis. *J Clin Psychopharmacol* 2020; **40**: 231-239 [DOI: 10.1097/jcp.0000000000001195]

41 **Coe MA**, Lofwall MR, Walsh SL. Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations. *J Addict Med* 2019; **13**: 93-103 [PMID: 30531584 DOI: 10.1097/ADM.0000000000000457]

42 **Soyka M**. Novel Long-Acting Buprenorphine Medications for Opioid Dependence: Current Update. *Pharmacopsychiatry* 2021; **54**: 18-22 [PMID: 33212514 DOI: 10.1055/a-1298-4508]

43 **Haasen C**, Linden M, Tiberg F. Pharmacokinetics and pharmacodynamics of a buprenorphine subcutaneous depot formulation (CAM2038) for once-weekly dosing in patients with opioid use disorder. *J Subst Abuse Treat* 2017; **78**: 22-29 [PMID: 28554599 DOI: 10.1016/j.jsat.2017.04.008]

44 **Walsh SL**, Comer SD, Lofwall MR, Vince B, Levy-Cooperman N, Kelsh D, Coe MA, Jones JD, Nuzzo PA, Tiberg F, Sheldon B, Kim S. Effect of buprenorphine weekly depot (CAM 2038) and hydromorphone blockade in individuals with opioid use disorder: a randomised clinical trial. *JAMA Psychiatry* 2017; **74**: 894-902 [PMID: 28655025 DOI: 10.1001/jamapsychiatry.2017.1874]

45 **Albayaty M**, Linden M, Olsson H, Johnsson M, Strandgarden K, Tiberg F. Pharmacokinetic evaluation of one-weekly and once-monthly buprenorphine subcutaneous injection depots (CAM 2038) *vs* intravenous and sublingual buprenorphine in healthy volunteers under naltrexone blockade: an open-label phase 1 study. *Adv Ther* 2017; **34**: 560-575 [PMID: 28070862 DOI: 10.1007/s12325-016-0472-9]

46 **Lofwall MR**, Walsh SL, Nunes EV, Bailey GL, Sigmon SC, Kampman KM, Frost M, Tiberg F, Linden M, Sheldon B, Oosman S, Peterson S, Chen M, Kim S. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations *vs* Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. *JAMA Intern Med* 2018; **178**: 764-773 [PMID: 29799968 DOI: 10.1001/jamainternmed.2018.1052]

47 **Frost M**, Bailey GL, Lintzeris N, Strang J, Dunlop A, Nunes EV, Jansen JB, Frey LC, Weber B, Haber P, Oosman S, Kim S, Tiberg F. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. *Addiction* 2019; **114**: 1416-1426 [PMID: 31013390 DOI: 10.1111/add.14636]

48 **Lintzeris N**, Dunlop AJ, Haber PS, Lubman DI, Graham R, Hutchinson S, Arunogiri S, Hayes V, Hjelmström P, Svedberg A, Peterson S, Tiberg F. Patient-Reported Outcomes of Treatment of Opioid Dependence With Weekly and Monthly Subcutaneous Depot *vs* Daily Sublingual Buprenorphine: A Randomized Clinical Trial. *JAMA Netw Open* 2021; **4**: e219041 [PMID: 33970256 DOI: 10.1001/jamanetworkopen.2021.9041]

49 **Schulte B**, Lehmann K, Schmidt CS, Rühling E, Weber B, Schäfer I, Reimer J, Verthein U. Addiction Recovery Among Opioid-Dependent Patients Treated With Injectable Subcutaneous Depot Buprenorphine: Study Protocol of a Non-randomized Prospective Observational Study (ARIDE). *Front Psychiatry* 2020; **11**: 580863 [PMID: 33363483 DOI: 10.3389/fpsyt.2020.580863]

50 **Barnwal P**, Das S, Mondal S, Ramasamy A, Maiti T, Saha A. Probuphine® (buprenorphine implant): a promising candidate in opioid dependence. *Ther Adv Psychopharmacol* 2017; **7**: 119-134 [PMID: 28348732 DOI: 10.1177/2045125316681984]

51 **Itzoe M**, Guarnieri M. New developments in managing opioid addiction: impact of a subdermal buprenorphine implant. *Drug Des Devel Ther* 2017; **11**: 1429-1437 [PMID: 28546740 DOI: 10.2147/DDDT.S109331]

52 **White J**, Bell J, Saunders JB, Williamson P, Makowska M, Farquharson A, Beebe KL. Open-label dose-finding trial of buprenorphine implants (Probuphine) for treatment of heroin dependence. *Drug Alcohol Depend* 2009; **103**: 37-43 [PMID: 19403243 DOI: 10.1016/j.drugalcdep.2009.03.008]

53 **Ling W**, Casadonte P, Bigelow G, Kampman KM, Patkar A, Bailey GL, Rosenthal RN, Beebe KL. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. *JAMA* 2010; **304**: 1576-1583 [PMID: 20940383 DOI: 10.1001/jama.2010.1427]

54 **Rosenthal RN**, Ling W, Casadonte P, Vocci F, Bailey GL, Kampman K, Patkar A, Chavoustie S, Blasey C, Sigmon S, Beebe KL. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. *Addiction* 2013; **108**: 2141-2149 [PMID: 23919595 DOI: 10.1111/add.12315]

55 **Rosenthal RN**, Lofwall MR, Kim S, Chen M, Beebe KL, Vocci FJ; PRO-814 Study Group. Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial. *JAMA* 2016; **316**: 282-290 [PMID: 27434441 DOI: 10.1001/jama.2016.9382]

56 **Pendergrass SA**, Crist RC, Jones LK, Hoch JR, Berrettini WH. The importance of buprenorphine research in the opioid crisis. *Mol Psychiatry* 2019; **24**: 626-632 [PMID: 30617273 DOI: 10.1038/s41380-018-0329-5]

57 **Timko C**, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. *J Addict Dis* 2016; **35**: 22-35 [PMID: 26467975 DOI: 10.1080/10550887.2016.1100960]

58 **Kelty E**, Cumming C, Troeung L, Hulse G. Buprenorphine alone or with naloxone: Which is safer? *J Psychopharmacol* 2018; **32**: 344-352 [PMID: 29433352 DOI: 10.1177/0269881118756015]

59 **Allikmets S**, Vink JP. Clinical applications of buprenorphine depot injection for opioid use disorder. *Addiction* 2020; **115**: 190 [PMID: 31521065 DOI: 10.1111/add.14818]

60 **Larance B**, Byrne M, Lintzeris N, Nielsen S, Grebely J, Degenhardt L, Shahbazi J, Shanahan M, Lancaster K, Dore G, Ali R, Farrell M; CoLAB study team. Open-label, multicentre, single-arm trial of monthly injections of depot buprenorphine in people with opioid dependence: protocol for the CoLAB study. *BMJ Open* 2020; **10**: e034389 [PMID: 32737087 DOI: 10.1136/bmjopen-2019-034389]

61 **Vorspan F**, Hjelmström P, Simon N, Benyamina A, Dervaux A, Brousse G, Jamain T, Kosim M, Rolland B. What place for prolonged-release buprenorphine depot-formulation Buvidal® in the treatment arsenal of opioid dependence? *Expert Opin Drug Deliv* 2019; **16**: 907-914 [PMID: 31364884 DOI: 10.1080/17425247.2019.1649252]

62 **Arunogiri S**, Lintzeris N. Depot buprenorphine during COVID-19 in Australia: Opportunities and challenges. *J Subst Abuse Treat* 2021; **124**: 108221 [PMID: 33303254 DOI: 10.1016/j.jsat.2020.108221]

63 **Roberts J**, White B, Attalla D, Ward S, Dunlop AJ. Rapid upscale of depot buprenorphine (CAM2038) in custodial settings during the early COVID-19 pandemic in New South Wales, Australia. *Addiction* 2021; **116**: 426-427 [PMID: 32888226 DOI: 10.1111/add.15244]

64 **Bukten A**, Skurtveit S, Strangeland P, Gossop M, Willersrud AB, Waal H, Havnes I, Clausen T. Reductions in convictions for violent crime during opioid maintenance during a 3-year period prior to opioid maintenance treatment: a longitudinal national cohort study. *J Subst Abuse Treat* 2012; **41**: 407-414 [DOI: 10.1016/j.jsat.2011.06.006]

65 **Havnes I**, Bukten A, Gossop M, Waal H, Stangeland P, Clausen T. Reductions in convictions for violent crime during opioid maintenance treatment: a longitudinal national cohort study. *Drug Alcohol Depend* 2012; **124**: 307-310 [PMID: 22382045 DOI: 10.1016/j.drugalcdep.2012.02.005]

66 **Soyka M**, Träder A, Klotsche J, Haberthür A, Bühringer G, Rehm J, Wittchen H-U. Criminal behavior in opioid-dependent patients before and during maintenance therapy: 6-year follow-up of a nationally representative cohort sample. *J Forsenic Sci* 2012; **57**: 1524-1530 [DOI: 10.1111/j.1556-4029.2012.02234.x]

67 **Russolillo A**, Moniruzzaman A, McCandless LC, Patterson M, Somers JM. Associations between methadone maintenance treatment and crime: a 17-year longitudinal cohort study of Canadian provincial offenders. *Addiction* 2018; **113**: 656-667 [PMID: 28987068 DOI: 10.1111/add.14059]

68 **Vorma H**, Sokero P, Aaltonen M, Turtiainen S, Hughes LA, Savolainen J. Participation in opioid substitution treatment reduces the rate of criminal convictions: evidence from a community study. *Addict Behav* 2013; **38**: 2313-2316 [PMID: 23584191 DOI: 10.1016/j.addbeh.2013.03.009]

69 **Moore KE**, Roberts W, Reid HH, Smith KMZ, Oberleitner LMS, McKee SA. Effectiveness of medication assisted treatment for opioid use in prison and jail settings: A meta-analysis and systematic review. *J Subst Abuse Treat* 2019; **99**: 32-43 [PMID: 30797392 DOI: 10.1016/j.jsat.2018.12.003]

70 **Kenney SR**, Anderson BJ, Bailey GL, Stein MD. Buprenorphine treatment formulations: Preferences among persons in opioid withdrawal management. *J Subst Abuse Treat* 2018; **94**: 55-59 [PMID: 30243418 DOI: 10.1016/j.jsat.2018.08.011]

71 **Larance B**, Degenhardt L, Grebely J, Nielsen S, Bruno R, Dietze P, Lancaster K, Larney S, Santo T Jr, Shanahan M, Memedovic S, Ali R, Farrell M. Perceptions of extended-release buprenorphine injections for opioid use disorder among people who regularly use opioids in Australia. *Addiction* 2020; **115**: 1295-1305 [PMID: 31860767 DOI: 10.1111/add.14941]

72 **Tompkins CNE**, Neale J, Strang J. Opioid users' willingness to receive prolonged-release buprenorphine depot injections for opioid use disorder. *J Subst Abuse Treat* 2019; **104**: 64-71 [PMID: 31370986 DOI: 10.1016/j.jsat.2019.06.007]

73 **Neale J**, Tompkins CNE, Strang J. Prolonged-release opioid agonist therapy: qualitative study exploring patients' views of 1-week, 1-month, and 6-month buprenorphine formulations. *Harm Reduct J* 2019; **16**: 25 [PMID: 30943990 DOI: 10.1186/s12954-019-0296-4]

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MINIREVIEWS

Is there a place for cellular therapy in depression?

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Abstract

Although efforts have been made to improve the pharmacological treatment of depression, approximately one-third of patients with depression do not respond to conventional therapy using antidepressants. Other potential non-pharmacological therapies have been studied in the last years, including the use of mesenchymal stem cell therapies to treat depression. These therapies are reviewed here since it is clinically relevant to develop innovative therapeutics to treat psychiatric patients. Experimental data corroborate that mesenchymal stem cell therapy could be considered a potential treatment for depression based on its anti-inflammatory and neurotrophic properties. However, some clinical trials involving treatment of depression with stem cells are in progress, but with no published results. These studies and other future clinical investigations will be crucial to define how much mesenchymal stem cells can effectively be used in psychiatric clinics as a strategy for supporting depression treatment.

Key Words: Mood disorders; Stem cells transplant; Mesenchymal stem-cells transplant; Inflammation; Immunomodulation; Depression

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authors declare that they have no conflict of interest.

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INTRODUCTION

Depression is a highly prevalent disorder that affects the entire life span. In adults, the 12-mo prevalence of the major depressive disorder is approximately 6%[1], and the lifetime risk is 15%-18%[2]. It is one of the leading causes of disability worldwide[3]. In clinical terms, depression is a complex disorder with devastating consequences for patients and their families, provoking psychological suffering due to sadness, anxiety, anguish, and guilt; diminished cognitive performance; and impaired attention, memory, and reasoning. Moreover, depression has negative influences on decision-making and interpretation of facts, leading to wrong decisions. Depression is also a risk factor for the development and outcome of many chronic non-transmissible diseases, such as cardiovascular diseases and diabetes[4-6]. Evidence also suggests a small and positive association between depression and the overall risk of cancer, including liver and lung cancer[7].

Pharmacological treatment for depression has been available since 1957, when imipramine, a tricyclic antidepressant, and iproniazid, a monoamine oxidase inhibitor, were released[8,9]. In more than six decades, many drugs have been released commercially, improving the tolerability and safety of antidepressant treatment. However, with few exceptions, these medications' intended mechanism was to increase serotonin, noradrenaline, and dopamine availability. Although efforts have been made to improve pharmacological treatment of depression, approximately one-third of patients fail to respond to conventional antidepressants[10]. This limitation in the antidepressive efficiency is possibly related to the mechanism of action of the available antidepressants. Therefore, it is clinically relevant to develop innovative therapeutic strategies based on the pathophysiological aspects of depression.

Several lines of evidence suggest that chronic inflammatory states may be related to depression etiopathogenesis in recent years. This evidence made way for researchers to develop new anti-inflammatory therapies that could alleviate symptoms and the progression of depression[11,12]. In a previous study, our group investigated the possible use of stem cell therapy. Our hypothesis was based on the anti-inflammatory and neurodegenerative properties of stem cells, which could treat the pathogenic state that maintains depression.

Here, we performed a narrative review regarding the role of inflammation in depression and investigated the evidence suggesting that the use of stem cell therapies could be a realistic, safe, and effective strategy for treating depression.

INFLAMMATION PROVOKING DEPRESSION

A colossal research effort has been made in the last 60 years to unravel and understand the neurobiological processes underlying depression. This process started since tricyclic and monoamine-oxidase effectiveness in depression treatment was proven in 1957[13], and pharmacological drugs have been introduced in clinical practice. The attempt to identify the neurobiological processes and causes of depression started with understanding the antidepressant mechanisms of action. This strategy led to the identification of monoamines and their role in depression. Further, the development of almost all antidepressant medications was based on these discoveries.

In 1968, Carrol *et al*[14] postulated the role of the hypothalamus-hypophysis-adrenal axis (HPA axis) in depression etiopathogenesis, subsidizing the HPA axis hypothesis. The role of glucocorticoid hippocampal receptors in HPA-axis modulation in

depression has been extensively studied. Chronic stress modulates the inflammatory process that plays a crucial role in the neurobiological aspects underlying depression [15]. However, this research strategy has not led to the development of antidepressant medications.

The interest in the role of immunological and inflammatory mechanisms in depression is a natural consequence of HPA axis studies since cortisol can modulate these responses. Furthermore, consistent data on the role of psychological stress on depression development involves alterations in immune functions, mainly due to chronic inflammatory states[16,17].

The link between emotional stress, depression, and inflammation seems to involve evolutionary issues. Several lines of evidence suggest that metabolic, endocrine, and immune responses co-evolved, helping animal surveillance since animals need to actively seek food by exposing themselves to injury or predation and also need to defend themselves from pathogens[18].

In addition to triggering a fight or flight response, stress is characterized by increases in heart rate, blood pressure, cortisol, and catecholamines. It also activates inflammatory pathways in peripheral blood mononuclear cells[9]. However, when stress exposure occurs continuously without being resolved, metabolic and physiological responses are triggered that contribute to the formation of chronic inflammatory states[19]. Figure 1 shows the association between stress and neuroinflammation in depression etiopathogenesis based on several previous reviews[14,18,20].

HOW CHRONIC STRESS, THROUGH INFLAMMATION, CAN TRIGGER DEPRESSION?

Although acute stress induces an immunosuppressed state, chronic stress exposure has an antagonistic pro-inflammatory effect. As a result, the anti-inflammatory state develops to a chronic inflammatory condition due to the factors produced by exposure to chronic stress, such as catecholamines[19].

Catecholamines released by psychological stress can promote damage-associated molecular patterns (DAMPs), including high mobility group box 1 (HMGB1), ATP, and heat shock proteins. DAMPs are inflammatory signaling proteins released by different stress levels, including psychological factors[21,22]. For example, HMGB1 is a nuclear protein that is present in all cell types.

Once released, it activates through TLR4 and RAGE receptor inflammatory cascades, including the pyrin domain-containing protein 3 (NLRP3) inflammasome[20,23]. Inflammasomes are cytosolic protein complexes formed in myeloid cells, such as monocytes, in response to pathogenic microorganisms or sterile stressors, such as psychological stress. Activation of the NLRP3 inflammasome subsequently leads to caspase-1 activation, which in turn provokes cleavage of the pro-inflammatory cytokines interleukine-1β (IL-1β) and IL-18[20], and nuclear factor-κB (NF-κB) pathway activation with subsequent IL-6 release[21].

All events occurring outside the brain must change the brain physiology to trigger depression. There are three mechanisms by which inflammation in peripheral tissues reaches the brain, overcoming the blood-brain barrier (BBB). In the humoral pathway, pro-inflammatory cytokines, such as IL-1β, IL-18, IL-6, and TNFa, enter the brain through the leaky region of the BBB, such as circumventricular organs, or the binding of these cytokines to saturable transport molecules in the BBB[9]. In the neural pathway, the same cytokines bind peripheral afferent nerve fibers, such as the vagus nerve, which stimulates catecholaminergic fibers in the brain and translates into central cytokine signals. Moreover, activated immune cells, such as monocytes, reach the brain vasculature and parenchyma through trafficking mechanisms[9]. These different mechanisms act in coordination to trigger inflammation in the brain. For example, peripheral TNFa can stimulate microglia to produce CC-chemokine ligand 2 (CCL2), a chemokine that attracts monocytes to the brain[24]. Cytokines such as IL-1β and TNFa can also stimulate astrocytes to produce chemokines such as CCL2 or CXC chemokine ligand 1, thus attracting immune cells to the brain[25].

Peripheral inflammatory molecules induce astrocytes and microglia activation into the brain, triggering a complex inflammatory cascade. This cascade interferes with neurotransmission, the HPA axis, and neurotrophin balance synapses. An example of the peripheral effects on neuroinflammation is the expression of IL-1β and TNFa. These cytokines can induce the overexpression of some molecules, such as p38 mitogen-activated protein kinase, which alters the serotonin transporter, leading to a

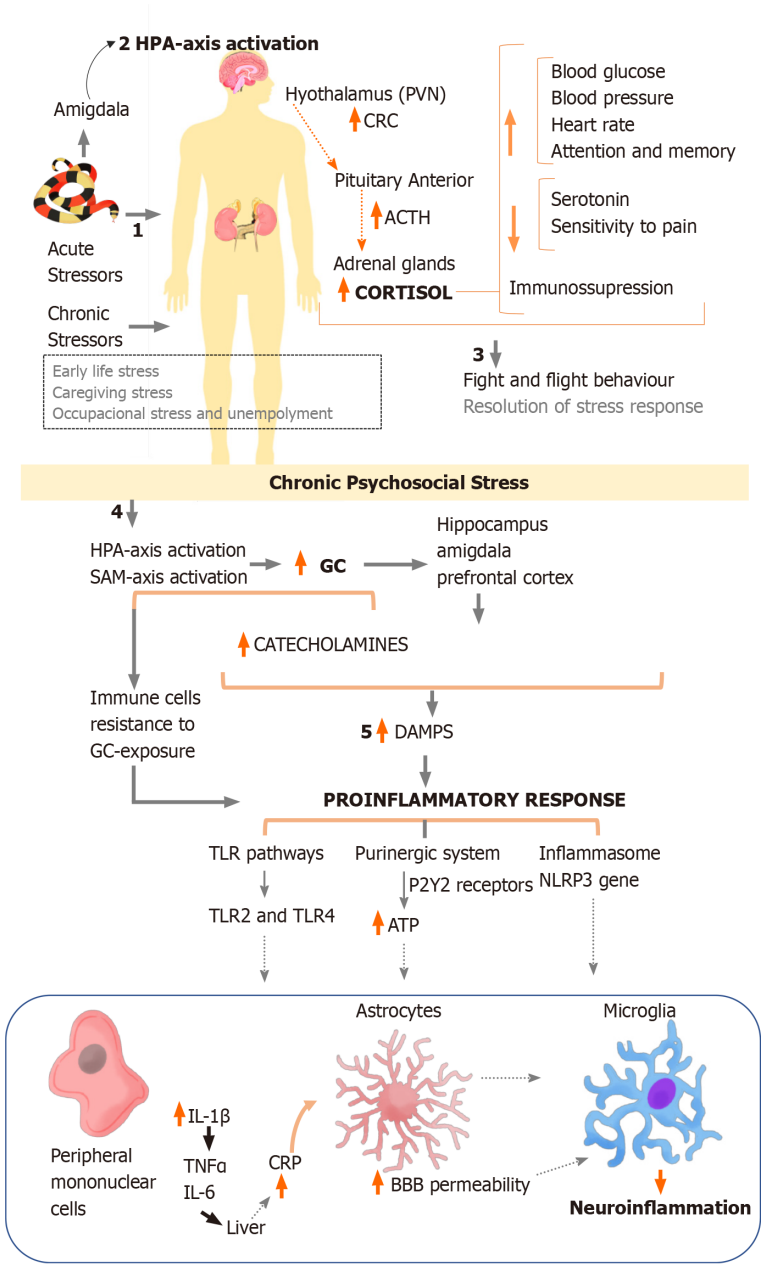

Figure 1 Synthesis of stress acute and chronic response on the inflammatory pathway. (1-2) Stressors trigger a primary neuroendocrine response from the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamic Parvocellular neurons from the paraventricular nucleus secrete a corticotrophin-releasing hormone (CRH) and vasopressin. CRC induces, subsequently, the anterior hypophysis to release the adrenocorticotropic hormone, leading to a glucocorticoid secretion (cortisol in humans and corticosterone in rodents) by the adrenal cortex; (3) Acute physiological alterations prepare the human to fight or flight from stressors. These are evolutionary adaptive behaviors related to surveillance. Therefore, stress induces transient activation of HPA- axis activity paralleled by temporary increases in CRH transcription. Sympathetic-Adreno-Medullar axis is also activated in the stress response causing several physiological systemic changes. Acute stress also leads to an immunosuppressive state; (4) On the contrary, the exposure to chronic stress leads to excessive sustained elevated levels of stress hormones, including CRH and corticosterone, can be harmful and predispose to risk of several chronic non-transmissible diseases, including psychiatric disturbs; (5) And mechanisms involving an increase in neural apoptosis an in the levels of some molecules associated to stress response, especially catecholamines. These processes induce the production of immunogenic Damage-associated molecular patterns (DAMPs) molecules. (6) DAMPs can activate at least three inflammatory pathways that contribute to the increase of brain-blood barrier permeability, promoting ingress of some systemic peripheral inflammatory cells into the brain contributing to the neuroinflammatory states cause dysfunction and increase the risk of depression. HPA: Hypothalamic-pituitary-adrenal; PVN: Paraventricular nucleus; CRH: Corticotrophin-releasing hormone; VP: Vasopressin; ACTH: Adrenocorticotropic hormone; GC: Glucocorticoid; SAM: Sympathetic-Adreno-Medullar; DAMPs: Damage-associated molecular patterns; BBB: Brain-blood barrier.

decrease in the availability of serotonin in the synaptic cleft[9].

IL-6, another pro-inflammatory cytokine, contributes to the generation of high levels of reactive oxygen and nitrogen species, which cause oxidative stress. This reaction decreases tetrahydrobiopterin (BH4) availability, a cofactor enzyme in monoamine synthesis, diminishing serotonin, noradrenaline, and dopamine availability. The cytokines, particularly IL-1β and TNFa molecules, alter the kynurenine pathway by

increasing quinolinic acid levels (QA). The elevation of QA levels occurs by the activity of the indoleamine 2,3-dioxygenase enzyme, which catalyzes tryptophan into kynurenine. As QA synthesis involves tryptophan, depletion of this amino acid directly affects serotonin production. Furthermore, QA has a dangerous effect on the brain by increasing oxidative stress, astrocyte degeneration, and neuronal apoptosis. Therefore, inflammatory activation generates metabolic alterations that can contribute to the risk of depression and suicide[9,16,26-28].

QA and cytokines also have a critical synergistic effect on glutamate metabolism. QA directly stimulates N-methyl-D-aspartate receptors (NMDA), decreasing glutamate re-uptake and stimulating glutamate release by astrocytes[9]. In astrocytes, pro-inflammatory cytokines decrease the expression of glutamate re-uptake pumps, increasing glutamate release. This combined action triggers high glutamate levels inside and outside the synapses, allowing the activation of extra-synaptic NMDA receptors. Alterations in the glutamatergic pathway induce a decrease in molecules with neurogenic functions, particularly brain-derived neurotrophic factor (BDNF)[9,29,30]. It should be noted that conventional antidepressant medication acts by increasing monoamine availability in the synapse, thereby increasing BDNF and consequently promoting neurogenesis through BDNF action on its receptor TrkB[31,32].

The effect of neuroinflammation has an impact on neurocircuit function. Inflammation has been associated with a decrease in responsiveness to reward stimuli, particularly in the ventral striatum. For example, in healthy volunteers, the administration of low doses of endotoxin, which can increase pro-inflammatory cytokine levels more safely, is associated with the development of depressive mood. This effect was related to the diminished activity of the ventral striatum to the anticipated reward measured by functional magnetic resonance imaging (fMRI)[33]. Interferon-a administration to treat chronic hepatitis virus C infection-induced depression, anhedonia, and fatigue. This administration reduced ventral striatum activation with reward-anticipatory stimuli during fMRI. In the same study, positron emission tomography demonstrated an association between the behavior and fMRI results with 18F-dopa turnover in the ventral striatum; changing presynaptic dopamine function was consistent with decreased dopamine synthesis or release[34]. Evidence also described that typhoid immunization could produce inflammation by IL-6 augmentation and activation of the subgenual anterior cingulate cortex (sgACC), a region implicated in depression and depressive symptoms. Moreover, the elevation in IL-6 concentrations decreases the connectivity between the sgACC and amygdala, medial prefrontal cortex, superior temporal sulcus, and ventral striatum[35].

Many of these brain changes induced by peripheral inflammation and neuroinflammation have been described in experimental and epidemiological studies that involve chronic exposure to social stress. Exposure to social stress can increase soluble TNFa receptors and IL-6 molecules. The elevation of soluble TNFa receptor can increase the dorsal ACC and anterior insula activity, two brain regions that process rejection-related distress and negative affect[36,37]. Experimental protocols where stress was induced in the laboratory conditions described the increased feelings of social and rejection behaviors associated with inflammatory activation by increasing IL-6 Levels and high left amygdala activity, a brain area directly related to detection and response threats[38].

Child abuse is one of the main risk factors for chronic stress and inflammation in the etiopathogenesis of depression. Early adversity is considered a risk factor for developing depression, and emotional abuse shows the strongest association, followed by neglect[39]. A growing body of literature showed that early adversity could shape immune cells and inflammatory cascades. A meta-analysis performed by Baumeister *et al*[40] showed that adult individuals exposed to childhood trauma had elevated baseline blood levels of C-reactive protein, IL-6, and TNFa.

Therefore, the pieces of evidence commented here can support the hypothesis that depression is an inflammatory disease. A meta-analysis showed higher peripheral levels of IL-6, TNFa, IL-10, IL-12, IL-13, IL-18, CCL2, IL-1b receptor antagonist, soluble IL-2 receptor, and soluble TNF receptor 2 in depressive patients. In comparison, the INFγ blood levels were lower in these individuals. Moreover, the concentrations of IL-1b, IL-2, IL-4, IL-8, IL-5, CCL3, IL-17, the soluble IL-6 receptor, and the transforming growth factor-beta one did not present differences associated with depression[41].

ANTIDEPRESSANTS AND ANTI-INFLAMMATORY DRUGS ON DEPRESSION

As inflammation could trigger depression, the logical question is that anti-inflammatory drugs could positively affect depression. A recent meta-analysis on this issue included studies involving the impact of anti-depressive drugs on different pro and anti-inflammatory cytokines (IL-1b, IL-2, IL-4, IL5, IL-6, IL-8, IL-10, IL-12, TNFa, INFy, and others)[42]. Moreover, the meta-analysis found that antidepressant responders had lower levels of IL-8 than non-responders. Antidepressant treatment only decreased TNFa levels, IL-5, and granulocyte-macrophage colony-stimulating factor in responsive patients. However, when treatment-resistant patients were compared to non-depressed controls, IL-6, IL-8, TNFa, C-reactive protein (CRP), and macrophage inflammatory protein-1 were associated with poor treatment outcomes[43].

Furthermore, it has been tested for its potential anti-inflammatory use in the attenuation of depressive symptoms. A meta-analysis of randomized controlled trials showed an antidepressant effect of anti-cytokine drugs[44]. The anti-TNFa adalimumab and etanercept, except infliximab, showed an antidepressant effect. Previous studies have also described some antidepressant effects of dupilumab, an antagonist drug of the alpha subunit of the IL-4 receptor, and ustekinumab, which inactivates IL-12 and IL-23 cytokines[45]. Randomized controlled clinical trials have described the anti-depressive effect of some anti-inflammatory drugs such as (1) Glycyrrhizic acid, an HMGB1 inhibitor, was useful as an add-on with selective serotonin re-uptake inhibitor in the treatment[45]; (2) Minocycline, a tetracycline antibiotic, that lowers neuroinflammation by inhibiting microglial activation and inhibiting the release of HMGB1[46]. However, minocycline was effective only in patients with baseline levels of CRP > 2.8 mg/L[47]; and (3) Although bipolar disorder (BD) is not in the scope of this review, a clinical trial stands out here describing that coadministration of N-acetylcysteine and aspirin for 16 wk was associated with a reduction in depressive symptoms in BD-patients[48].

Despite the evidence suggesting that anti-inflammatory drugs could help treat depression, further investigations are needed to evaluate the safety of prolonged periods of anti-inflammatory co-treatments in patients with depression[49]. In this context, the search for non-pharmacological anti-inflammatory therapeutic strategies is of great interest to the psychiatric clinic, as in the case of stem cell treatments, which have been applied in other clinical areas, has been intensively investigated for more than 10 years[50,51].

CLINICAL USE OF ADULT STEM CELLS

Stem cells are defined as adult unspecialized cells with self-renewal ability and high regenerative potential[52,53]. Adult stem cells can differentiate into several cell lines and activate or inhibit a sequence of molecules involved in anti-inflammatory and anti-apoptotic pathways[52,53]. Mesenchymal stem cells (MSCs) were first detected in the bone marrow. However, they can also be isolated from the umbilical cord tissue and adipose tissue, among other sources[52-57].

Stem cells were first described in the middle of the 20th century in mouse models [58,59], and stem cell transplantation was first applied in humans in 1957[60,61]. In the following decades, bone marrow stem cells-transplants have saved the lives of patients suffering from a great variety of diseases, mainly conditions affecting the hematopoietic or immunological system. Due to relatively low MSC-immunogenicity, the transplantation of these cells presents a low risk of tumorigenicity and less complicated ethical/regulatory issues compared to embryonic pluripotent stem cells [57,62].

Studies of therapeutic MSCs applications have expanded, showing that both allogeneic and autologous transplantation is possible due to the low immunogenicity of these cells and immunomodulatory effects[63]. These studies, including experimental investigations performed in several animal models of inflammatory and autoimmune-mediated disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and myasthenia gravis[64-66] and other conditions associated with inflammatory disturbances such as sepsis[67], lung fibrosis[68], diabetes[69], atherosclerosis [70], and osteoarthritis[71].

STEM CELLS-BASED THERAPIES FOR NEUROINFLAMMATORY DISORDERS

Stem cell therapies have emerged as a standard for the treatment of both subacute and chronic inflammatory processes and neurological disorders. Investigations have suggested the potential use of adult stem cells therapy to treat several neurological conditions, such as multiple sclerosis[72], autoimmune encephalomyelitis[73], Alzheimer's disease, and other dementia conditions[74], Parkinson's disease[75], and epilepsy[76]. Most studies emphasize the immunomodulatory nature of adult stem cells, with its therapeutic efficiency related to neurological diseases, particularly triggering anti-inflammatory states.

For example, in epilepsy, seizure activity can induce pro-inflammatory molecules, therefore affecting the severity and frequency of seizures[77]. Transplantation of bone marrow mononuclear cells (BMMCs) or human umbilical cord blood mononuclear cells in experimental epilepsy models induced significant improvements in neurological function[78,79]. After a seizure, brain injury induces a highly regulated cascade of biological events, characterized by the release of cytokines, chemokines, and protectins in the neuronal microenvironment[80,81], which was attenuated by adult stem cell transplantation, decreased the inflammatory states, and promoted tissue repair through cell-cell interactions and paracrine effects[80-83]. Furthermore, some evidence showed that adult stem cells stimulate angiogenesis and endothelial repair through paracrine actions[82,83]. In Alzheimer's disease, MSCs have been shown to reduce IL-1, IL-2, TNFa, and IFN-γ in the serum and oxidative stress, which showed an anti-inflammatory effect[84].

Among the most relevant stem cells' action mechanisms is the release of extracellular vesicles carrying soluble factors, microRNAs, and organelles[85]. Initially, the release of extracellular vesicles was thought to represent a disposal mechanism by which cells eliminate unwanted proteins and other molecules. Among the extracellular vesicle subtypes, significant attention has been given to exosomes. Exosomes are small membrane vesicles with a diameter between 40 and 100 nm[86], and different biological molecules, including proteins, lipids, and nucleic acids that may be captured and act in a biologically active manner on recipient cells. Various studies have described the beneficial actions of MSCs by delivering exosomes instead of cells[87, 88]. Therefore, MSC cells or exosome transplantation could offer an efficient and safe non-pharmacological therapy to treat neurological conditions.

POTENTIAL USE OF BMMCS AND MSCS IN DEPRESSION: EVIDENCE FROM PRECLINICAL STUDIES IN EXPERIMENTAL MODELS

The optimistic results obtained from experimental studies involving BMMCs and MSCs in the therapy of neurological conditions open the perspective of developing non-pharmacological cell treatments for psychiatric disorders. The main results of these studies are presented in Table 1. The potential therapeutic effects of adult cells-based therapies have been well characterized across *in vivo* studies of depression models, including an investigation performed by our research team[89]. This study evaluated the effect of BMMCs transplantation on the restoration of sucrose preference in rats subjected to chronic stress. This well-established model triggers depressive symptoms in animals. The study also evaluated the potential inflammatory modulation of BMMCs in stressed rats. The levels of pro-and anti-inflammatory cytokines in different brain areas, blood, and spleen were also quantified. In this protocol, escitalopram was used as a positive antidepressant control. The results demonstrated that BMMCs transplantation in stressed rats: (1) Restored spontaneous sucrose consumption in stressed rats; (2) Had a robust anti-inflammatory effect, increasing the levels of the anti-inflammatory cytokine IL-10 in the amygdala, hippocampus, frontal cortex, other brain areas, and in the spleen and blood; a lowering effect on pro-inflammatory cytokine levels (IL-1 β, IL-6, TNFa, and INF-γ) was also detected in the same brain and peripheral tissues; and (3) Decreased levels of oxidized DNA quantified by 8'2-deoxyguanosine. In summary, the therapeutic use of BMMCs presented a positive impact on symptoms of depressed rats, and possible mechanisms involved in this effect include immunomodulation of inflammatory states in both the peripheral and central nervous systems.

Another recent study performed by Huang *et al*[90] team verified the results involving potential therapeutic MSC-transplantation in depression by anti-inflam-

Table 1 Concise information of some studies on the effects of administration of mesenchymal stem cells with different sources and exosomes

Ref.	Type and characteristics of animal model used	Timing of intervention with cells after insult	Type of cells infused and route of administration	Major finding
do Prado-Lima *et al*[89], 2019	Wistar rats; depression, induced with CMS	30th day of the CMS protocol	BMMCs from mice. Single-dose (1 × 10^{7} cells). i.v.	Anti-inflammatory effects; Reduction of pro-inflammatory cytokines; increased expression of anti-inflammatory cytokines; BMMCs decreased 8'2-deoxyguanosine level
Huang *et al*[90], 2020	C57BL/6 mice; depression-induced with CMS	21th day of the CMS protocol	ADSCs from C57BL/6 mice; Repeated i.v. (3 times) 1 × 10^{6} cells/dose	ADSC treatment improved depressive-like behaviors. Reduced the expression of inflammatory factors in the serum Reduced microglial activation in the hippocampus
Kin *et al* [91], 2020	Wistar Kyoto rats model of treatment-resistant depression	Day zero	MSCs from the bone marrow of Wistar rats. Single-dose 3 × 10^{5} cells/5 µl i.v.	MSCs encapsulation enhanced the treatment effects of MSCs in an animal model of treatment-resistant depression
Li *et al* [92], 2020	Mice model depression induced by CUMS	14th to the 42nd day CUMS protocol	MSCs lines from human umbilical cords (hUC-MSCs); Repeated (4 times) 1 × 10^{6}/ dose i.v.	The hUC-MSCs treatment improved the anxiety-like behaviors of CUMS, decreased pro-inflammatory factor levels, and increased anti-inflammatory factor levels. The hUC-MSCs inhibit microglial M1 polarization and the level of inflammation factors. The hUC-MSCs can alter the polarization of microglia by inhibiting C3a-C3aR signaling from reducing neuroinflammation. The hUC-MSCsdecreased neuronal damage and synaptic deficits
Guo *et al* [93], 2020	Sprague Dawley rats; Depression model by corticosterone injection	Day zero	BMSCs-derived exosomes 1 mL exosomes (100 µg/ 1 mL PBS) i.v.	BMSCs-derived exosomes improved hippocampal neuron injury of rats with depression by upregulating miR-26a
Li *et al* [94], 2020	Male BALB/c mice depression, induced by CS	After 30 days of the CMS protocol	Exosomes from NK cells one time. Exosomes 66.42 µg i.v.	The exosomes miRNA-containing from NK cells could alleviate symptoms of chronic mild stress in mice. miRNA decreased the levels of pro-inflammatory cytokines (I L-1β, IL-6, and TNFα) released by astrocytes in vivo; Exosomes with low miR-207 levels showed decreased antidepressant activity in vivo experiments. Exosomes with low miR-207 levels showed decreased antidepressant activity MiR-207 could reduce the release of pro-inflammatory cytokines in vitro

BMMCs: Bone marrow mononuclear cells; ADSCs: Adipose-derived mesenchymal stem cells; CMS: Chronic mild stress; CS: Chronic stress; BDNF: Brain-derived neurotrophic factor; TrkB: Tyrosine receptor kinase B; BV2: Microglial cells; eMSC: Capsules with MSCs; hUC-MSCs: Human umbilical cord mesenchymal stem cells; CUMS: Chronic unpredictable mild stress model; miR-26a: MicroRNA-26a; SOD: Superoxide dismutase; MDA: Malondialdehyde; LDH: Lactate dehydrogenase; TNFα: Tumor necrosis factor α; IL-1β: Interleukin-1β; NK: Natural killer cells; i.v.: Intravenously injected.

matory action. The experimental protocol used adipose-derived mesenchymal stem cells (ADSCs) injected into C57BL/6 mice on the 21st day of a protocol of 42 d of chronic mild stress (CMS). The animals were tested by three behavioral assays: sucrose preference, tail suspension, and forced swimming test. All tests are broadly recognized as behavioral assays to identify depressive and anti-depressive chemical and behavioral factors. ADSC transplantation remedied depressive-like behaviors. The authors also observed that ADSC treatment reversed and prevented the increase in the production of some pro-inflammatory cytokines (CCL2, TNFa, IL-1β, and IL-6) in the serum and promoted the expression of BDNF and its receptor TrkB in the brain tissue. ADSC treatment increased the nuclear factor-E2 related factor 2 (Nrf2), which in turn has an anti-inflammatory effect by inhibiting TLR4/NF-κB pathway activation. Immunofluorescence detection revealed that the number of ionized calcium-binding adaptor molecule 1 (Iba1+), a protein expressed only in microglia and involved in its activation, decreased after ADSC treatment. In the same study, Nrf2-modified ADSCs were co-cultured with microglia cells and then exposed to lipopolysaccharide (LPS). Nrf2 downregulation decreased the protective effects of ADSCs against LPS-induced microglial activation and M1 polarization; however, Nrf2 overexpression markedly suppressed LPS-induced TLR4/NF-κB expression in microglial cells[90].

Kin *et al*[91] implanted the encapsulated MSCs (eMSCs) into the lateral ventricle and observed antidepressant effects *via* neurogenic pathways in Wistar Kyoto rats. These rats exhibited congenitally higher depression-like behaviors and resistance to conventional antidepressant treatments. Therefore, Kyoto rats are considered a promising model for treatment-resistant depression. The implantation of eMSCs counteracted

depressive-like behavior on days 13 to 15 after implantation and enhanced endogenous neurogenesis in the subventricular zone and the dentate gyrus of the hippocampus. The eMSCs displayed a robust and stable secretion of vascular endothelial growth factor, BDNF, fibroblast growth factor 2, and ciliary neurotrophic factor. Implantation of eMSCs into the lateral ventricle activated relevant pathways associated with these growth factors.

Li *et al*[92] described the therapeutic action of human umbilical cord MSCs (hUC-MSCs) on chronic middle stress in mice. The animals were induced with hUC-MSCs once a week for four weeks for 42 d. The hUC-MSCs treatment induced downregulation of some pro-inflammatory genes (GFAP, Iba1, Il-1, TNF, IL-1b, and TNFa). Moreover, the treatment also downregulated IL-10, transforming growth factor-β and AMPA gene expression. The authors reported a modulation in the microglia M1/M2 polarization balance and a decrease in neuroinflammation involving complement C3 molecules, specifically in the C3a-C3aR pathway.

Therapy efficacy using BMMCs-derived exosomes in rats with depression induced by corticosterone treatment was performed by Guo *et al*[93]. The exosome therapy upregulated miR-26a microRNA, increased hippocampal tissue proliferation, and suppressed apoptosis in depressive-like rats. Treatment decreased oxidative stress and inflammation by inducing high superoxide dismutase antioxidant enzyme levels and decreasing lipoperoxidation, TNFa, and IL-1β levels in both serum and hippocampus.

Another study administered natural killer (NK)-cell-derived exosomes carrying miR-207, capable of inhibiting the NF-κB signaling pathway in astrocytes. This exosome treatment was effective in diminishing depressive symptoms in mice submitted to CMS and decreased the levels of IL-1b, IL-6, and TNFa released by astrocytes. The critical element of the exosome effect was the presence of the miR-207 molecule. When NK-cells were transfected with miR-207 inhibitor and exosomes were produced by and injected in astrocytes, the impact on IL-1b, IL-6, and TNFa levels was no longer observed[94].

CLINICAL TRIALS IN DEPRESSIVE PATIENTS

The results from different experimental studies strongly support the potential therapeutic use of stem cells in treating depression. However, while data from experimental models have shown beneficial effects in depression, gaps remain to be explored. Further studies are needed to clarify whether any MSCs type could be as effective and safe as an antidepressant therapy. For example, MSCs from the bone marrow have the best potential to treat depression, considering the significant data regarding them. However, ethical problems are to be considered when it comes to autologous transplants that require surgical intervention to obtain these cells. Moreover, allogeneic cell transplantation could be an acceptable clinical strategy. However, further studies are needed to assess the safety of using these cells from donors with a different genetic background than the patient.

In addition, further studies are needed to establish the optimal dose, administration route, and fundamental mechanisms of action. The translation ability of such experimental models to the target human population, possibly composed of refractory and polypharmacy patients, merits further discussion. For instance, previous efforts with several compounds that passed through animal studies with promising results have failed in clinical trials, partially due to the poor validity of such models to represent the target patient population[95].

Due to these gaps, the first clinical trials involving cell-based products or exosomes to treat depression have been registered to international platforms. At Clintrial.gov, the keywords "depression," "depressive disorder," and "cell therapy" were used to perform the search. This research led us to find four registered clinical studies involving the use of MSCs as a treatment for patients with depression. Currently, four clinical studies (phases 1 and 2) are under evaluation for the safety, efficacy, and tolerability of the administration of MSCs and exosomes (Table 2). However, most of the results are not yet available, as these studies are still in the patient recruitment phase. Therefore, the results are anticipated to be published from these trials soon.

CONCLUSION

Cell therapy, through BMMCs or MSCs transplantation or the administration of cell products such as exosomes, may have a place in treatment-resistant depression. The

Table 2 List of registered cell-based clinical trials for treating depression

Study	Country	Target population	Product	Study design	Outcomes
NCT02675556	United States	Treatment-resistant depression; (n = 80)	Allogeneic MSCs; 10^8 cells single i.v. infusion; source not reported	Phase I, placebo-controlled 1:1	Incidence of any treatment-emergent serious adverse events; Reduction of Inflammation.
NCT03522545	United States	Treatment-resistant bipolar depression; (n = 30)	Allogeneic bone marrow-derived MSCs; dose not reported	Phase I, placebo-controlled	Change in depression as assessed by the MADRS Scale.
NCT03265808	United States	Alcohol use disorder and major depression; (n = 80)	Allogeneic MSCs; 10^8 cells single i.v. infusion; source not reported	Phase I/II	An incident of treatment emergent-serious adverse events
NCT04202770	United States	Refractory depression; anxiety disorders; neurodegenerative diseases; (n = 300)	Focused ultrasound and exosomes	Single group assignment	Beck depression inventory (BDI-II)

MSCs: Mesenchymal stem cells.

number of preclinical studies is still limited; therefore, further development of clinical trials is encouraged.

As technology and knowledge involving all aspects of cells or cell-based products develop, the easier it is to identify the best alternative (cells or exosomes) to try as an antidepressant treatment, the lower the costs and the more established the routines. A significant development should be expected to understand its potential and possible side effects better.

Despite the limited number of preclinical studies, many issues have not been identified, such as how long the antidepressant effect persists. It is a critical question that has consequences for the feasibility of these procedures as treatment. Because of the challenge that represents the treatment of resistant depression, the possibility of an effective treatment in this chronic, severe, and prevalent condition must be explored.

For this, a more significant number of clinical studies are needed to evaluate several open questions considering the variability of the effectiveness of the use of stem cells in the treatment of depression.

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REFERENCES

1 **Kessler RC**, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health* 2013; **34**: 119-138 [PMID: 23514317 DOI: 10.1146/annurev-publhealth-031912-114409]

2 **Bromet E**, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, de Graaf R, Demyttenaere K, Hu C, Iwata N, Karam AN, Kaur J, Kostyuchenko S, Lépine JP, Levinson D, Matschinger H, Mora ME, Browne MO, Posada-Villa J, Viana MC, Williams DR, Kessler RC. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med* 2011; **9**: 90 [PMID: 21791035 DOI: 10.1186/1741-7015-9-90]

3 **Global Burden of Disease Study 2013 Collaborators**. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386**: 743-800 [PMID: 26063472 DOI: 10.1016/S0140-6736(15)60692-4]

4 **van Sloten T**, Schram M. Understanding depression in type 2 diabetes: a biological approach in observational studies. *F1000Res* 2018; **7** [PMID: 30135724 DOI: 10.12688/f1000research.13898.1]

5 **Bucciarelli V**, Caterino AL, Bianco F, Caputi CG, Salerni S, Sciomer S, Maffei S, Gallina S. Depression and cardiovascular disease: The deep blue sea of women's heart. *Trends Cardiovasc Med* 2020; **30**: 170-176 [PMID: 31109802 DOI: 10.1016/j.tcm.2019.05.001]

6 **Bădescu SV**, Tătaru C, Kobylinska L, Georgescu EL, Zahiu DM, Zăgrean AM, Zăgrean L. The association between Diabetes mellitus and Depression. *J Med Life* 2016; **9**: 120-125 [PMID: 27453739]

7 **Jia Y**, Li F, Liu YF, Zhao JP, Leng MM, Chen L. Depression and cancer risk: a systematic review

and meta-analysis. *Public Health* 2017; **149**: 138-148 [PMID: 28641155 DOI: 10.1016/j.puhe.2017.04.026]
8 **Kuhn R**. [Treatment of depressive states with an iminodibenzyl derivative (G 22355)]. *Schweiz Med Wochenschr* 1957; **87**: 1135-1140 [PMID: 13467194]
9 **Bruel O**. [Treatment of depressive states with hematoporphyrin Nencki; a survey based on 320 personal ambulant cases]. *Psychiatr Neurol (Basel)* 1957; **133**: 1-17 [PMID: 13420229]
10 **Rush AJ**, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006; **163**: 1905-1917 [PMID: 17074942 DOI: 10.1176/ajp.2006.163.11.1905]
11 **Miller AH**, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 2016; **16**: 22-34 [PMID: 26711676 DOI: 10.1038/nri.2015.5]
12 **Beurel E**, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. *Neuron* 2020; **107**: 234-256 [PMID: 32553197 DOI: 10.1016/j.neuron.2020.06.002]
13 **Thuillier J**. Then years that changed the face of mental illness. London: Martin Dunitz Ltd, 1999
14 **Carroll BJ**, Martin FI, Davies B. Pituitary-adrenal function in depression. *Lancet* 1968; **1**: 1373-1374 [PMID: 4172674 DOI: 10.1016/s0140-6736(68)92072-2]
15 **Juruena MF**, Bocharova M, Agustini B, Young AH. Atypical depression and non-atypical depression: Is HPA axis function a biomarker? *J Affect Disord* 2018; **233**: 45-67 [PMID: 29150144 DOI: 10.1016/j.jad.2017.09.052]
16 **Franklin TC**, Xu C, Duman RS. Depression and sterile inflammation: Essential role of danger associated molecular patterns. *Brain Behav Immun* 2018; **72**: 2-13 [PMID: 29102801 DOI: 10.1016/j.bbi.2017.10.025]
17 **Gałecki P**, Talarowska M. Inflammatory theory of depression. *Psychiatr Pol* 2018; **52**: 437-447 [PMID: 30218560 DOI: 10.12740/PP/76863]
18 **Fumagalli M**, Sironi M, Pozzoli U, Ferrer-Admetlla A, Pattini L, Nielsen R. Signatures of environmental genetic adaptation pinpoint pathogens as the main selective pressure through human evolution. *PLoS Genet* 2011; **7**: e1002355 [PMID: 22072984 DOI: 10.1371/journal.pgen.1002355]
19 **Rohleder N**. Stress and inflammation - The need to address the gap in the transition between acute and chronic stress effects. *Psychoneuroendocrinology* 2019; **105**: 164-171 [PMID: 30826163 DOI: 10.1016/j.psyneuen.2019.02.021]
20 **Leonard BE**. Inflammation and depression: a causal or coincidental link to the pathophysiology? *Acta Neuropsychiatr* 2018; **30**: 1-16 [PMID: 28112061 DOI: 10.1017/neu.2016.69]
21 **Fleshner M**. Stress-evoked sterile inflammation, danger associated molecular patterns (DAMPs), microbial associated molecular patterns (MAMPs) and the inflammasome. *Brain Behav Immun* 2013; **27**: 1-7 [PMID: 22964544 DOI: 10.1016/j.bbi.2012.08.012]
22 **Fleshner M**, Frank M, Maier SF. Danger Signals and Inflammasomes: Stress-Evoked Sterile Inflammation in Mood Disorders. *Neuropsychopharmacology* 2017; **42**: 36-45 [PMID: 27412959 DOI: 10.1038/npp.2016.125]
23 **Rana T**, Behl T, Mehta V, Uddin MS, Bungau S. Molecular insights into the therapeutic promise of targeting HMGB1 in depression. *Pharmacol Rep* 2021; **73**: 31-42 [PMID: 33015736 DOI: 10.1007/s43440-020-00163-6]
24 **D'Mello C**, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. *J Neurosci* 2009; **29**: 2089-2102 [PMID: 19228962 DOI: 10.1523/JNEUROSCI.3567-08.2009]
25 **Hennessy E**, Griffin ÉW, Cunningham C. Astrocytes Are Primed by Chronic Neurodegeneration to Produce Exaggerated Chemokine and Cell Infiltration Responses to Acute Stimulation with the Cytokines IL-1β and TNF-α. *J Neurosci* 2015; **35**: 8411-8422 [PMID: 26041910 DOI: 10.1523/JNEUROSCI.2745-14.2015]
26 **Maes M**, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; **35**: 702-721 [PMID: 21185346 DOI: 10.1016/j.pnpbp.2010.12.017]
27 **Steiner J**, Walter M, Gos T, Guillemin GJ, Bernstein HG, Sarnyai Z, Mawrin C, Brisch R, Bielau H, Meyer zu Schwabedissen L, Bogerts B, Myint AM. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? *J Neuroinflammation* 2011; **8**: 94 [PMID: 21831269 DOI: 10.1186/1742-2094-8-94]
28 **Bansal Y**, Singh R, Parhar I, Kuhad A, Soga T. Quinolinic Acid and Nuclear Factor Erythroid 2-Related Factor 2 in Depression: Role in Neuroprogression. *Front Pharmacol* 2019; **10**: 452 [PMID: 31164818 DOI: 10.3389/fphar.2019.00452]
29 **Hardingham GE**, Fukunaga Y, Bading H. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. *Nat Neurosci* 2002; **5**: 405-414 [PMID: 11953750 DOI: 10.1038/nn835]
30 **Chiba S**, Numakawa T, Ninomiya M, Richards MC, Wakabayashi C, Kunugi H. Chronic restraint stress causes anxiety- and depression-like behaviors, downregulates glucocorticoid receptor

expression, and attenuates glutamate release induced by brain-derived neurotrophic factor in the prefrontal cortex. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **39**: 112-119 [PMID: 22664354 DOI: 10.1016/j.pnpbp.2012.05.018]

31 **Duman RS**, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med* 2016; **22**: 238-249 [PMID: 26937618 DOI: 10.1038/nm.4050]

32 **Malhi GS**, Mann JJ. Depression. *Lancet* 2018; **392**: 2299-2312 [PMID: 30396512 DOI: 10.1016/S0140-6736(18)31948-2]

33 **Eisenberger NI**, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. *Biol Psychiatry* 2010; **68**: 748-754 [PMID: 20719303 DOI: 10.1016/j.biopsych.2010.06.010]

34 **Capuron L**, Pagnoni G, Drake DF, Woolwine BJ, Spivey JR, Crowe RJ, Votaw JR, Goodman MM, Miller AH. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Arch Gen Psychiatry* 2012; **69**: 1044-1053 [PMID: 23026954 DOI: 10.1001/archgenpsychiatry.2011.2094]

35 **Harrison NA**, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol Psychiatry* 2009; **66**: 407-414 [PMID: 19423079 DOI: 10.1016/j.biopsych.2009.03.015]

36 **Slavich GM**, Way BM, Eisenberger NI, Taylor SE. Neural sensitivity to social rejection is associated with inflammatory responses to social stress. *Proc Natl Acad Sci U S A* 2010; **107**: 14817-14822 [PMID: 20679216 DOI: 10.1073/pnas.1009164107]

37 **Felger JC**. Imaging the Role of Inflammation in Mood and Anxiety-related Disorders. *Curr Neuropharmacol* 2018; **16**: 533-558 [PMID: 29173175 DOI: 10.2174/1570159X15666171123201142]

38 **Muscatell KA**, Dedovic K, Slavich GM, Jarcho MR, Breen EC, Bower JE, Irwin MR, Eisenberger NI. Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. *Brain Behav Immun* 2015; **43**: 46-53 [PMID: 25016200 DOI: 10.1016/j.bbi.2014.06.201]

39 **Mandelli L**, Petrelli C, Serretti A. The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. *Eur Psychiatry* 2015; **30**: 665-680 [PMID: 26078093 DOI: 10.1016/j.eurpsy.2015.04.007]

40 **Baumeister D**, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Mol Psychiatry* 2016; **21**: 642-649 [PMID: 26033244 DOI: 10.1038/mp.2015.67]

41 **Köhler CA**, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, Stubbs B, Solmi M, Veronese N, Herrmann N, Raison CL, Miller BJ, Lanctôt KL, Carvalho AF. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand* 2017; **135**: 373-387 [PMID: 28122130 DOI: 10.1111/acps.12698]

42 **Liu JJ**, Wei YB, Strawbridge R, Bao Y, Chang S, Shi L, Que J, Gadad BS, Trivedi MH, Kelsoe JR, Lu L. Peripheral cytokine levels and response to antidepressant treatment in depression: a systematic review and meta-analysis. *Mol Psychiatry* 2020; **25**: 339-350 [PMID: 31427752 DOI: 10.1038/s41380-019-0474-5]

43 **Strawbridge R**, Hodsoll J, Powell TR, Hotopf M, Hatch SL, Breen G, Cleare AJ. Inflammatory profiles of severe treatment-resistant depression. *J Affect Disord* 2019; **246**: 42-51 [PMID: 30578945 DOI: 10.1016/j.jad.2018.12.037]

44 **Kappelmann N**, Lewis G, Dantzer R, Jones PB, Khandaker GM. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol Psychiatry* 2018; **23**: 335-343 [PMID: 27752078 DOI: 10.1038/mp.2016.167]

45 **Cao ZY**, Liu YZ, Li JM, Ruan YM, Yan WJ, Zhong SY, Zhang T, Liu LL, Wu R, Wang B, Wang W, Bi XY, Wang YX, Su WJ, Jiang CL. Glycyrrhizic acid as an adjunctive treatment for depression through anti-inflammation: A randomized placebo-controlled clinical trial. *J Affect Disord* 2020; **265**: 247-254 [PMID: 32090748 DOI: 10.1016/j.jad.2020.01.048]

46 **Wang B**, Huang X, Pan X, Zhang T, Hou C, Su WJ, Liu LL, Li JM, Wang YX. Minocycline prevents the depressive-like behavior through inhibiting the release of HMGB1 from microglia and neurons. *Brain Behav Immun* 2020; **88**: 132-143 [PMID: 32553784 DOI: 10.1016/j.bbi.2020.06.019]

47 **Nettis MA**, Lombardo G, Hastings C, Zajkowska Z, Mariani N, Nikkheslat N, Worrell C, Enache D, McLaughlin A, Kose M, Sforzini L, Bogdanova A, Cleare A, Young AH, Pariante CM, Mondelli V. Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial. *Neuropsychopharmacology* 2021; **46**: 939-948 [PMID: 33504955 DOI: 10.1038/s41386-020-00948-6]

48 **Bauer IE**, Green C, Colpo GD, Teixeira AL, Selvaraj S, Durkin K, Zunta-Soares GB, Soares JC. A Double-Blind, Randomized, Placebo-Controlled Study of Aspirin and N-Acetylcysteine as Adjunctive Treatments for Bipolar Depression. *J Clin Psychiatry* 2018; **80** [PMID: 30549489 DOI: 10.4088/JCP.18m12200]

49 **Adzic M**, Brkic Z, Mitic M, Francija E, Jovicic MJ, Radulovic J, Maric NP. Therapeutic Strategies for Treatment of Inflammation-related Depression. *Curr Neuropharmacol* 2018; **16**: 176-209 [PMID: 28847294 DOI: 10.2174/1570159X15666170828163048]

50 **Brown C**, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, Svinarich D, Dodds R, Govind CK,

Chaudhry GR. Mesenchymal stem cells: Cell therapy and regeneration potential. *J Tissue Eng Regen Med* 2019; **13**: 1738-1755 [PMID: 31216380 DOI: 10.1002/term.2914]

51 **Mirzaei H**, Sahebkar A, Sichani LS, Moridikia A, Nazari S, Sadri Nahand J, Salehi H, Stenvang J, Masoudifar A, Mirzaei HR, Jaafari MR. Therapeutic application of multipotent stem cells. *J Cell Physiol* 2018; **233**: 2815-2823 [PMID: 28475219 DOI: 10.1002/jcp.25990]

52 **Abdelmawgoud H**, Saleh A. Anti-inflammatory and antioxidant effects of mesenchymal and hematopoietic stem cells in a rheumatoid arthritis rat model. *Adv Clin Exp Med* 2018; **27**: 873-880 [PMID: 29905411 DOI: 10.17219/acem/73720]

53 **Méndez-Ferrer S**, Michurina TV, Ferraro F, Mazloom AR, Macarthur BD, Lira SA, Scadden DT, Ma'ayan A, Enikolopov GN, Frenette PS. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. *Nature* 2010; **466**: 829-834 [PMID: 20703299 DOI: 10.1038/nature09262]

54 **Mezey E**. The therapeutic potential of bone marrow-derived stromal cells. *J Cell Biochem* 2011; **112**: 2683-2687 [PMID: 21678464 DOI: 10.1002/jcb.23216]

55 **Patrikoski M**, Sivula J, Huhtala H, Helminen M, Salo F, Mannerström B, Miettinen S. Different culture conditions modulate the immunological properties of adipose stem cells. *Stem Cells Transl Med* 2014; **3**: 1220-1230 [PMID: 25122689 DOI: 10.5966/sctm.2013-0201]

56 **Ra JC**, Shin IS, Kim SH, Kang SK, Kang BC, Lee HY, Kim YJ, Jo JY, Yoon EJ, Choi HJ, Kwon E. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. *Stem Cells Dev* 2011; **20**: 1297-1308 [PMID: 21303266 DOI: 10.1089/scd.2010.0466]

57 **Bowen JE**. Technical issues in harvesting and concentrating stem cells (bone marrow and adipose). *PM R* 2015; **7**: S8-S18 [PMID: 25864664 DOI: 10.1016/j.pmrj.2015.01.025]

58 **Lorenz E**, Uphoff D, Reid TR, Shelton E. Modification of irradiation injury in mice and guinea pigs by bone marrow injections. *J Natl Cancer Inst* 1951; **12**: 197-201 [PMID: 14874130 DOI: 10.1093/jnci/12.1.197]

59 **Perry AR**, Linch DC. The history of bone-marrow transplantation. *Blood Rev* 1996; **10**: 215-219 [PMID: 9012918 DOI: 10.1016/S0268-960X(96)90004-1]

60 **Barnes DW**, Corp MJ, Loutit JF, Neal FE. Treatment of murine leukaemia with X rays and homologous bone marrow; preliminary communication. *Br Med J* 1956; **2**: 626-627 [PMID: 13356034 DOI: 10.1136/bmj.2.4993.626]

61 **Thomas ED**, Lochte HL Jr, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N Engl J Med* 1957; **257**: 491-496 [PMID: 13464965 DOI: 10.1056/nejm195709122571102]

62 **Lee M**, Jeong SY, Ha J, Kim M, Jin HJ, Kwon SJ, Chang JW, Choi SJ, Oh W, Yang YS, Kim JS, Jeon HB. Low immunogenicity of allogeneic human umbilical cord blood-derived mesenchymal stem cells in vitro and in vivo. *Biochem Biophys Res Commun* 2014; **446**: 983-989 [PMID: 24657442 DOI: 10.1016/j.bbrc.2014.03.051]

63 **Griffin MD**, Ryan AE, Alagesan S, Lohan P, Treacy O, Ritter T. Anti-donor immune responses elicited by allogeneic mesenchymal stem cells: what have we learned so far? *Immunol Cell Biol* 2013; **91**: 40-51 [PMID: 23207278 DOI: 10.1038/icb.2012.67]

64 **Sun L**, Akiyama K, Zhang H, Yamaza T, Hou Y, Zhao S, Xu T, Le A, Shi S. Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans. *Stem Cells* 2009; **27**: 1421-1432 [PMID: 19489103 DOI: 10.1002/stem.68]

65 **Freitag J**, Bates D, Wickham J, Shah K, Huguenin L, Tenen A, Paterson K, Boyd R. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. *Regen Med* 2019; **14**: 213-230 [PMID: 30762487 DOI: 10.2217/rme-2018-0161]

66 **Yu J**, Zheng C, Ren X, Li J, Liu M, Zhang L, Liang L, Du W, Han ZC. Intravenous administration of bone marrow mesenchymal stem cells benefits experimental autoimmune myasthenia gravis mice through an immunomodulatory action. *Scand J Immunol* 2010; **72**: 242-249 [PMID: 20696022 DOI: 10.1111/j.1365-3083.2010.02445.x]

67 **Németh K**, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, Robey PG, Leelahavanichkul K, Koller BH, Brown JM, Hu X, Jelinek I, Star RA, Mezey E. Bone marrow stromal cells attenuate sepsis *via* prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nat Med* 2009; **15**: 42-49 [PMID: 19098906 DOI: 10.1038/nm.1905]

68 **Rojas M**, Xu J, Woods CR, Mora AL, Spears W, Roman J, Brigham KL. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. *Am J Respir Cell Mol Biol* 2005; **33**: 145-152 [PMID: 15891110 DOI: 10.1165/rcmb.2004-0330OC]

69 **Päth G**, Perakakis N, Mantzoros CS, Seufert J. Stem cells in the treatment of diabetes mellitus - Focus on mesenchymal stem cells. *Metabolism* 2019; **90**: 1-15 [PMID: 30342065 DOI: 10.1016/j.metabol.2018.10.005]

70 **Xing X**, Li Z, Yang X, Li M, Liu C, Pang Y, Zhang L, Li X, Liu G, Xiao Y. Adipose-derived mesenchymal stem cells-derived exosome-mediated microRNA-342-5p protects endothelial cells against atherosclerosis. *Aging (Albany NY)* 2020; **12**: 3880-3898 [PMID: 32096479 DOI: 10.18632/aging.102857]

71 **Luque-Campos N**, Contreras-López RA, Jose Paredes-Martínez M, Torres MJ, Bahraoui S, Wei M, Espinoza F, Djouad F, Elizondo-Vega RJ, Luz-Crawford P. Mesenchymal Stem Cells Improve Rheumatoid Arthritis Progression by Controlling Memory T Cell Response. *Front Immunol* 2019; **10**: 798 [PMID: 31040848 DOI: 10.3389/fimmu.2019.00798]

72 **Genc B**, Bozan HR, Genc S, Genc K. Stem Cell Therapy for Multiple Sclerosis. *Adv Exp Med Biol*

2019; **1084**: 145-174 [PMID: 30039439 DOI: 10.1007/5584_2018_247]

73 **Zappia E**, Casazza S, Pedemonte E, Benvenuto F, Bonanni I, Gerdoni E, Giunti D, Ceravolo A, Cazzanti F, Frassoni F, Mancardi G, Uccelli A. Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. *Blood* 2005; **106**: 1755-1761 [PMID: 15905186 DOI: 10.1182/blood-2005-04-1496]

74 **Zhang L**, Dong ZF, Zhang JY. Immunomodulatory role of mesenchymal stem cells in Alzheimer's disease. *Life Sci* 2020; **246**: 117405 [PMID: 32035129 DOI: 10.1016/j.lfs.2020.117405]

75 **Vilaça-Faria H**, Salgado AJ, Teixeira FG. Mesenchymal Stem Cells-derived Exosomes: A New Possible Therapeutic Strategy for Parkinson's Disease? *Cells* 2019; **8** [PMID: 30717429 DOI: 10.3390/cells8020118]

76 **Costa-Ferro ZS**, Vitola AS, Pedroso MF, Cunha FB, Xavier LL, Machado DC, Soares MB, Ribeiro-dos-Santos R, DaCosta JC. Prevention of seizures and reorganization of hippocampal functions by transplantation of bone marrow cells in the acute phase of experimental epilepsy. *Seizure* 2010; **19**: 84-92 [PMID: 20080419 DOI: 10.1016/j.seizure.2009.12.003]

77 **Vezzani A**, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. *Nat Rev Neurol* 2011; **7**: 31-40 [PMID: 21135885 DOI: 10.1038/nrneurol.2010.178]

78 **Zanirati G**, Azevedo PN, Marinowic DR, Rodrigues F, de Oliveira Dias AC, Venturin GT, Greggio S, Simão F, DaCosta JC. Transplantation of bone marrow mononuclear cells modulates hippocampal expression of growth factors in chronically epileptic animals. *CNS Neurosci Ther* 2015; **21**: 463-471 [PMID: 25645708 DOI: 10.1111/cns.12382]

79 **Costa-Ferro ZS**, de Borba Cunha F, de Freitas Souza BS, Leal MM, da Silva AA, de Bellis Kühn TI, Forte A, Sekiya EJ, Soares MB, Dos Santos RR. Antiepileptic and neuroprotective effects of human umbilical cord blood mononuclear cells in a pilocarpine-induced epilepsy model. *Cytotechnology* 2014; **66**: 193-199 [PMID: 23929461 DOI: 10.1007/s10616-013-9557-3]

80 **Leal MM**, Costa-Ferro ZS, Souza BS, Azevedo CM, Carvalho TM, Kaneto CM, Carvalho RH, Dos Santos RR, Soares MB. Early transplantation of bone marrow mononuclear cells promotes neuroprotection and modulation of inflammation after status epilepticus in mice by paracrine mechanisms. *Neurochem Res* 2014; **39**: 259-268 [PMID: 24343530 DOI: 10.1007/s11064-013-1217-7]

81 **Walker LE**, Janigro D, Heinemann U, Riikonen R, Bernard C, Patel M. WONOEP appraisal: Molecular and cellular biomarkers for epilepsy. *Epilepsia* 2016; **57**: 1354-1362 [PMID: 27374986 DOI: 10.1111/epi.13460]

82 **Abi Chahine NH**, Wehbe TW, Hilal RA, Zoghbi VV, Melki AE, Habib EB. Treatment of Cerebral Palsy with Stem Cells: A Report of 17 Cases. *Int J Stem Cells* 2016; **9**: 90-95 [PMID: 27426090 DOI: 10.15283/ijsc.2016.9.1.90]

83 **Wehbe T**, Abi Saab M, Abi Chahine N, Margossian T. Mesenchymal stem cell therapy for refractory scleroderma: a report of 2 cases. *Stem Cell Investig* 2016; **3**: 48 [PMID: 27777937 DOI: 10.21037/sci.2016.09.03]

84 **Wei W**, Huang Y, Li D, Gou HF, Wang W. Improved therapeutic potential of MSCs by genetic modification. *Gene Ther* 2018; **25**: 538-547 [PMID: 30254305 DOI: 10.1038/s41434-018-0041-8]

85 **Rani S**, Ryan AE, Griffin MD, Ritter T. Mesenchymal Stem Cell-derived Extracellular Vesicles: Toward Cell-free Therapeutic Applications. *Mol Ther* 2015; **23**: 812-823 [PMID: 25868399 DOI: 10.1038/mt.2015.44]

86 **Karlsen TA**, Aae TF, Brinchmann JE. Robust profiling of microRNAs and isomiRs in human plasma exosomes across 46 individuals. *Sci Rep* 2019; **9**: 19999 [PMID: 31882820 DOI: 10.1038/s41598-019-56593-7]

87 **Álvarez-Viejo M**. Mesenchymal stem cells from different sources and their derived exosomes: A pre-clinical perspective. *World J Stem Cells* 2020; **12**: 100-109 [PMID: 32184935 DOI: 10.4252/wjsc.v12.i2.100]

88 **Boulestreau J**, Maumus M, Rozier P, Jorgensen C, Noël D. Mesenchymal Stem Cell Derived Extracellular Vesicles in Aging. *Front Cell Dev Biol* 2020; **8**: 107 [PMID: 32154253 DOI: 10.3389/fcell.2020.00107]

89 **do Prado-Lima PAS**, Onsten GA, de Oliveira GN, Brito GC, Ghilardi IM, de Souza EV, Dos Santos PG, Salamoni SD, Machado DC, Duarte MMF, Barbisan F, da Cruz IBM, Costa-Ferro ZSM, daCosta JC. The antidepressant effect of bone marrow mononuclear cell transplantation in chronic stress. *J Psychopharmacol* 2019; **33**: 632-639 [PMID: 31018809 DOI: 10.1177/0269881119841562]

90 **Huang X**, Fei GQ, Liu WJ, Ding J, Wang Y, Wang H, Ji JL, Wang X. Adipose-derived mesenchymal stem cells protect against CMS-induced depression-like behaviors in mice *via* regulating the Nrf2/HO-1 and TLR4/NF-κB signaling pathways. *Acta Pharmacol Sin* 2020; **41**: 612-619 [PMID: 31796867 DOI: 10.1038/s41401-019-0317-6]

91 **Kin K**, Yasuhara T, Kameda M, Tomita Y, Umakoshi M, Kuwahara K, Kin I, Kidani N, Morimoto J, Okazaki M, Sasaki T, Tajiri N, Borlongan CV, Date I. Cell encapsulation enhances antidepressant effect of the mesenchymal stem cells and counteracts depressive-like behavior of treatment-resistant depressed rats. *Mol Psychiatry* 2020; **25**: 1202-1214 [PMID: 30108315 DOI: 10.1038/s41380-018-0208-0]

92 **Li J**, Wang H, Du C, Jin X, Geng Y, Han B, Ma Q, Li Q, Wang Q, Guo Y, Wang M, Yan B. hUC-MSCs ameliorated CUMS-induced depression by modulating complement C3 signaling-mediated microglial polarization during astrocyte-microglia crosstalk. *Brain Res Bull* 2020; **163**: 109-119 [PMID: 32681971 DOI: 10.1016/j.brainresbull.2020.07.004]

93 **Guo H**, Huang B, Wang Y, Zhang Y, Ma Q, Ren Y. Bone marrow mesenchymal stem cells-derived exosomes improve injury of hippocampal neurons in rats with depression by upregulating microRNA-26a expression. *Int Immunopharmacol* 2020; **82**: 106285 [PMID: 32088640 DOI: 10.1016/j.intimp.2020.106285]

94 **Li D**, Wang Y, Jin X, Hu D, Xia C, Xu H, Hu J. NK cell-derived exosomes carry miR-207 and alleviate depression-like symptoms in mice. *J Neuroinflammation* 2020; **17**: 126 [PMID: 32321532 DOI: 10.1186/s12974-020-01787-4]

95 **Belzung C**, Willner P, Philippot P. Depression: from psychopathology to pathophysiology. *Curr Opin Neurobiol* 2015; **30**: 24-30 [PMID: 25218233 DOI: 10.1016/j.conb.2014.08.013]

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MINIREVIEWS

Antiglutamatergic agents for obsessive-compulsive disorder: Where are we now and what are possible future prospects?

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Abstract

Recent data suggest that obsessive-compulsive disorder (OCD) is driven by an imbalance among the habit learning system and the goal-directed system. The frontostriatal loop termed cortico-striatal-thalamo-cortical (CSTC) circuitry loop is involved in habits and their dysfunction plays an important role in OCD. Glutamatergic neurotransmission is the principal neurotransmitter implicated in the CSTC model of OCD. Hyperactivity in the CSTC loop implies a high level of glutamate in the cortical-striatal pathways as well as a dysregulation of *GABA* ergic transmission, and could represent the pathophysiology of OCD. Moreover, the dysregulation of glutamate levels can lead to neurotoxicity, acting as a neuronal excitotoxin. The hypothesis of a role of neurotoxicity in the pathophysiology of OCD clinically correlates to the importance of an early intervention for patients. Indeed, some studies have shown that a reduction of duration of untreated illness is related to an earlier onset of remission. Although robust data supporting a progression of such brain changes are not available so far, an early intervention could help interrupt damage from neurotoxicity. Moreover, agents targeting glutamate neurotransmission may represent promising therapeutical option in OCD patients.

Key Words: Obsessive-compulsive disorder; Antiglutamatergic agents; Glutammate; Early intervention; Neurophysiopathology; Duration of untreated illness

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Core Tip: In pathophysiology of obsessive-compulsive disorder (OCD), dysfunction of the cortico-striatal-thalamo-cortical (CSTC) loop could provoke an imbalance between goal-directed system and habit learning system. Glutamate is the principal neurotransmitter implicated in the CSTC model of OCD. Glutammate dysregulation and

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neurotoxicity seem to be correlated, thus, an early intervention and a reduction of duration of untreated illness appear central in treatment of OCD, as well as the use of glutamate-modulating drugs that could help to interrupt damage from neurotoxicity.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a severe and debilitating neuropsychiatric condition that affects 2.5%-3.0% of the general population[1,2].

OCD usually occurs in childhood or adolescence[3] and is associated with important distress, disability and suicidality[4]. Conventionally, OCD is driven by irrational beliefs (obsessions) considered as the product of a cognitive bias (including overestimation of threat, increased personal responsibility and thought-action fusion) and compulsions, which are rational avoidance responses triggered by these irrational beliefs that form a coping mechanism to neutralize anxiety and reduce the likelihood that fears will be realized. Preceding DSM-5[5], OCD was considered an anxiety disorder: Anxiety symptoms are indeed commonly expressed by patients[6]. Nevertheless, anxiety is not essential for OCD diagnosis and the condition was considered to be more similar to other disorders, therefore OCD was moved to a separated section of DSM-5[7].

First-line treatments include cognitive behavior therapy (CBT) and pharmacological treatment with serotonin reuptake inhibitors (SRIs)[8]. Unfortunately, around 40% of patients with OCD do not achieve remission of their symptoms with these therapies [6]. Even when an alternate selective serotonin re-uptake inhibitor or clomipramine treatment is given, or when an atypical antipsychotic is added, a considerable portion of refractory patients (30%) remain with the diagnosis, which is associated with serious social disability, patient's and family's suffering as well as a high suicide rate [9]. To understand the mechanisms underlying the development of OCD, a variety of hypothesis have been proposed, one of which is a dysfunction of the serotonergic and dopaminergic systems[10]. More recently, different studies focused their attention on the role of the glutamatergic system in OCD pathology[11]. Glutamate is the principal neurotransmitter involved in cortico-striatal-thalamic circuits (CSTC)[12] and, according to recent hypotheses (CSTC model of OCD), it would seem implicated in the pathogenesis of OCD. Moreover, there is consensus among experts on the importance of early intervention in OCD patients to reduce the duration of untreated illness (DUI) as well as to reduce the 'toxic' effect of an extended DUI in OCD[13]. The first aim of this mini review is an overview of the role of glutamate in CSTC models of OCD and the use of antiglutamatergic agents. Moreover we propose an intervention on the DUI in order to optimize fundamental time, due to the supposed toxic damages, and subsequently an early use of antiglutamatergic agents. Therefore, an early intervention could be both reduce the toxic effect of an extended DUI and, if necessary, encourage early use of antiglutamatergic agents.

WHAT DRIVES THE NEUROPHYSIOPATHOLOGY OF OCD?

As previously mentioned, conventionally OCD is driven by obsessions, while compulsions would be a rational avoidance response triggered by irrational beliefs. Patients report that, despite the repetitive and ritualistic nature of such behaviors, which are unproductive and frequently without any purpose, they are unable to discontinue them.

Recent data[14,15] suggest that OCD is driven by interference in the balance between the habit learning system and the goal-directed system. The habit learning system is based on historical information, regardless of past rewards, and it can lead to behavioural rigidity even in the face of rapid changes in the environment; on the other

hand, the goal-directed system applies control over habits in light of changes, including changes in response to the evaluation of actions and outcomes. A neurocomputational study[16] found that OCD patients made choices mostly based on model-free (*i.e.*, habit) rather than model-based (*i.e.*, executive control) learning. It is difficult for patients with OCD to modulate their future behavior based on immediate feedback. Therefore, in light of these hypotheses, habit formation appears to be abnormal in patients affected by OCD. According to the contemporary habit hypothesis, compulsive behaviours would not be driven by irrational and intrusive thoughts, but would be the consequences of a deficit in the control over goal-directed actions, leading to amplified reliance on habitual thoughts.

Orbitofrontal and cingulate cortices and the caudate nucleus are involved in habit learning[17,18] and in goal-directed control[19-21]. The frontostriatal loop termed CSTC circuitry is involved in habits and there is consensus that dysfunction of these areas plays an important role in OCD[22-24]. Dysfunction of the CSTC could cause disruptions between the goal-directed system and habitual control[25], which would cause an overreliance on the latter. Neuroimaging studies have shown that dysfunction of these areas has been implicated in OCD, including structural abnormalities, altered brain activation and connectivity[22,26]. The hypothesis is that in patients with OCD, the hyperactivation or hyperconnection of CSTC leads to a uncontrolled positive feedback loop[24,27]. This would trigger the impulse to perform compulsions, which would in turn consolidate the habit of executing compulsions, increasing the need to perform them[10].

In line with this behavioural hypothesis, OCD has been removed from anxiety disorders in DSM-5 and placed into its own category of "obsessive-compulsive and related disorders".

STATE OF ART ABOUT THE USE OF ANTIGLUTAMATERGIC AGENTS IN OCD

Traditionally, OCD medications have targeted serotonergic pathways. SRIs are commonly administered to treat patients with OCD and although the exact mechanism of their action remains elusive, SRIs are considered to exert their effects by influencing the CSTC[28]. However, the proportion of non-responder patients suggests a role of other neurotransmitter systems outside of the serotonergic in the pathophysiology of OCD[10].

Glutamate is the principal neurotransmitter implicated in the CSTC model of OCD [12]. In the neuropathophysiology of OCD, a dysregulation of the glutamatergic signal within the cortico-striatal circuitry has been suggested, which would lead to a reduced concentration of glutamate in the anterior cingulate cortex on the one hand, and overactivity of glutamatergic signalling in the striatum and orbitofrontal cortex on the other[29]. Hyperactivity in the CSTC loop implies a high level of glutamate in the cortical-striatal pathways and a dysregulation of GABAergic transmission that could represent the pathophysiology of OCD[10]. Furthermore, both ionotropic and metabotropic glutamate receptors are located in the candidate brain circuits of OCD and have been virtually associated with every form of learning in the brain, including habit learning[14,30]. Additionally, several studies showed an increase in glutamate in the cerebrospinal fluid of OCD patients compared to controls[1,31,32]. Genetics studies have also found an association between glutamate genes and OCD[33-35]. A polymorphism encoding for *N*-methyl-D-aspartic acid receptor (NMDAR) has been associated with OCD in families[33].

In light of a possible role of glutamatergic signal dysregulation in OCD, it is possible to find in glutamatergic drugs candidates for the augmentation strategy of OCD's therapy. Glutamate-modulating drugs have shown promise as potential therapeutic agents in other psychiatric disorders with a high comorbidity with OCD such as depression, bipolar disorder and suicide[36-38]. Moreover, several studies suggested that neuromodulation techniques using noninvasive devices, such as transcranial magnetic stimulation (TMS), or invasive procedures, such as deep brain stimulation (DBS), could offer additional support for the CSTC model of OCD. Based on the results of a recent randomized controlled trials (RCT), the Food and Drug Administration approved deep TMS, for the treatment of OCD[39,40]. Also DBS, which involves implantation of electrodes that modulate specific brain function, is approved for treatment of refractory OCD[41]. The first trials on DBS for OCD were conducted in the 2003 by Gabriëls *et al*[42] showed that DBS targeted at striatal areas is effective and safe for patients with refractory OCD.

This background has motivated the interest in studying glutamate modulators in patients who are unresponsive to standard pharmacotherapeutic approaches. Several clinical studies were conducted to evaluate the effect of glutamate-modulating drugs in OCD, however, they differed significantly in terms of treatment resistance, comorbidities, age and gender of the patients[29].

In particular, some studies using memantine and riluzole reported promising benefits[43]. Other studies have explored the role of stimulants and nutritional supplements such as *N*-acetylcysteine (NAC) and glycine[44-46]. Glutamate-modulating RCT for refractory OCD are reported in Table 1. To be more precise we describe the principal studies reported in the literature:

Memantine

Memantine, a low-to-moderate affinity noncompetitive NMDAR antagonist[47] currently approved for the treatment of Alzheimer's disease, is used as an augmentative agent to SRIs in the treatment of moderate to severe OCD. Four RCTs [48-51] were conducted using memantine *vs* placebo as an adjunctive treatment to SRIs [48,50,51] or fluvoxamine[49]. In three of these, conducted on 40, 42 and 32 patients, respectively[48-50], the adjunction of memantine (in the target dose of 5-10 mg/d for 12 wk[48] or 20 mg/d for 8 wk[49] or 12 wk[50] showed a reduction in scores at the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). In the last RCT[51] conducted on 99 patients, the use of memantine (in the target dose of 10 mg/d for 8 wk) *vs* placebo and *vs* gabapentin did not lead to the reduction of Y-BOCS scores.

A recent review on the subject conducted by Marinova *et al*[29] concluded that memantine is the compound that most consistently showed a positive effect as an augmentation therapy in OCD. However, a critical letter[52], exposed some concern on this conclusion mainly due to some methodological gaps and because all four RCTs were conducted in the same geographic area. Andrade[52] concluded that, in the light of these limitations, it is still premature to recommend the use of memantine as an OCD augmentation therapy and that more studies are needed.

Amantadine

Amantadine, a weak noncompetitive NMDAR antagonist originally used in the treatment and prophylaxis of viral infections, has been used in the treatment of some neurological conditions including Parkinson's disease, dementia, multiple sclerosis, cocaine withdrawal, pain and depression[53-55]. In one RCT, conducted on 100 patients diagnosed with moderate to severe OCD[56] the use of amantadine *vs* placebo as an adjunctive treatment to SRIs, showed a significant effect on Y-BOCS compared to placebo.

Riluzole

Riluzole acts through voltage-gated ion channels modulating the outflow of glutamate and enhancing the reuptake of extracellular glutamate. It is approved for the treatment of amyotrophic lateral sclerosis and some data report benefit in the use of riluzole for depression and anxiety[57]. Three RCTs were conducted using riluzole *vs* placebo adjunctive to SRIs[58,59] or fluvoxamine[60]. Only one study, conducted on 50 patients [60], using riluzole at a final dose of 100 mg/d for 10 wk, showed a reduction in the Y-BOCS score; while the other two, conducted on 38[58] and 60 patients[59], respectively, both using riluzole at a final dose of 100 mg/d for 12 wk, did not lead to the reduction in the Y-BOCS scores.

Ketamine

Ketamine, a noncompetitive NMDA receptor antagonist, is approved for the treatment of depression. An RCT by Rodriguez and colleagues[61], conducted on 15 drug-free adults with OCD (intravenous infusions of ketamine 0.5 mg/kg *vs* placebo) reported significant improvement of OCD symptoms in patients that received ketamine *vs* placebo. This study was the first RCT that proved the effect of antiglutamatergic agents on OCD symptoms without the presence of an SRIs.

Glycine

Glycine is an amino acid, NMDA glutamate receptor agonist. Only one RCT[46] conducted on a sample of 24 patients with OCD used glycine augmentation (60 g/d for 12 wk) *vs* placebo. This study had a high dropout rate due to the adverse effects of glycine. However, nearly significant improvements in Y-BOCS scores were observed in evaluable patients.

Table 1 Glutamate-modulating randomized controlled trials for refractory obsessive-compulsive disorder

Ref.	Drugs	Adjunctive/ monotherapy	Subjects	Duration & dose	Results
Haghighi *et al*[48], 2013	Memantine	Adjunctive to SRIs	40 pt	12 wk. Dose: 5-10 mg/d	Significant reduction. Y-BOCS score
Ghaleiha *et al*[49], 2013	Memantine	Adjunctive to fluvoxamine	42 pt	8 wk. Dose: 20 mg/d	Significant reduction. Y-BOCS score
Modarresi *et al*[50], 2018	Memantine	Adjunctive to SRIs	32 pt	12 wk. Dose: 20 mg/d	Significant reduction. Y-BOCS score
Farnia *et al*[51], 2018	Memantine	Adjunctive to SRIs	99 pt	8 wk. Dose: 10 mg/d	No significant reduction. Y-BOCS score
Naderi *et al*[56] , 2019	Amantadine	Adjunctive to SRIs	100 pt	12 wk. Dose: 100 mg/d	Significant reduction. Y-BOCS score
Grant *et al*[59], 2014	Riluzole	Adjunctive to SRIs	60 pt	12 wk. Final dose: 100 mg/d	No significant reduction. Y-BOCS score
Pittenger *et al*[58], 2015	Riluzole	Adjunctive to SRIs	38 pt	12 wk. Final dose: 100 mg/d	No significant reduction. Y-BOCS score
Emamzadehfar *et al* [60], 2016	Riluzole	Adjunctive to fluvoxamine	50 pt	10 wk. Final dose: 100 mg/d	Significant reduction. Y-BOCS score
Rodriguez *et al*[61], 2013	Ketamine	Monotherapy	15 pt	Intravenous infusions dose: 0.5 mg/kg	Significant reduction. Y-BOCS score
Greenberg *et al*[46], 2009	Glycine	Adjunctive pharmacological or psychotherapeutic treatment	24 pt	12 wk. Dose: 60 mg/d	No significant reduction. Y-BOCS score
Afshar *et al*[44], 2012	N-acetylcysteine	Adjunctive to SRIs	48 pt	12 wk. Dose: 2.4 g/d	Significant reduction. Y-BOCS score
Sarris *et al*[68], 2015	N-acetylcysteine	Adjunctive to SRIs	44 pt	16 wk. Dose: 3 g/d	No significant reduction. Y-BOCS score
Paydary *et al*[45], 2016	N-acetylcysteine	Adjunctive to fluvoxamine	44 pt	10 wk. Dose: 2 g/d	Significant reduction. Y-BOCS score
Costa *et al*[69], 2017	N-acetylcysteine	Adjunctive to SRIs	40 pt	16 wk. Dose: 3 g/d	No significant reduction. Y-BOCS score
Ghanizadeh *et al*[70], 2017	N-acetylcysteine	Adjunctive to SRIs	34 pt	10 wk. Dose: 2.4 g/d	Significant reduction. Y-BOCS score
Li *et al*[71], 2020	N-acetylcysteine	Adjunctive to SRIs	11 pt	12 wk. Dose: 2.7 g/d	Significant reduction. Y-BOCS score
Esalatmanesh *et al*[75], 2016	Minocycline	Adjunctive to fluvoxamine	102 pt	10 wk. Dose: 200 mg/d	Significant reduction. Y-BOCS score
Kushner *et al*[78], 2007	D-cycloserine	Adjunctive to CBT	32 pt	125 mg	Significant reduction. Y-BOCS score
Wilhelm *et al*[79], 2008	D-cycloserine	Adjunctive to CBT	23 pt	100 mg	Significant reduction. Y-BOCS score
Farrell *et al*[80], 2013	D-cycloserine	Adjunctive to CBT	17 pt	25-50 mg	Significant reduction. Y-BOCS score
Andersson *et al*[81], 2015	D-cycloserine	Adjunctive to CBT	128 pt	12 wk. Dose: 50 mg	Significant reduction. Y-BOCS score
Mataix-Cols *et al*[82], 2014	D-cycloserine	Adjunctive to CBT	27 pt	50 mg	Significant reduction. Y-BOCS score
Storch *et al*[83], 2007	D-cycloserine	Adjunctive to CBT	24 pt	250 mg	No significant reduction. Y-BOCS score
Storch *et al*[85], 2010	D-cycloserine	Adjunctive to CBT	30 pt	25 mg	No significant reduction. Y-BOCS score
Storch *et al*[84], 2016	D-cycloserine	Adjunctive to CBT	142 pt	50 mg	No significant reduction. Y-BOCS score

RCT: Randomized controlled trials; OCD: Obsessive-compulsive disorder; SRIs: Serotonin reuptake inhibitors; CBT: Cognitive behaviour therapy; pt:

Patients; Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

Nicotine

Some studies have also suggested that nicotine acts by promoting glutamatergic transmission as well as by stabilizing the glutamatergic hyperactivity of the loop running from the orbitofrontal cortex to the cyngulate gyrus, the striatum and the thalamus[62-65]. Nicotine acts on the desensitisation of nAChRs by increasing both glutamatergic transmission and, transiently, *GABA*ergic transmission. In particular, nAChR on GABA neurons are more desensitized then those on the glutamatergic system. This would lead to a shift toward excitation, reducing inhibitory inputs[65]. According to these data and with the complexity of OCD's pathophysiology, nicotine can be considered as a possible add-on therapeutic option in OCD resistant subjects, due to its peculiar mechanism of action. Only one study[66] was conducted on 5 patients using nicotine. Patients who received nicotine reported a reduction in Y-BOCS scores, especially in the compulsive score. A recent systematic review on the efficacy of nicotine administration suggested the need to test nicotine use in OCD in a large RCT. However, such suggestion raises ethical issues related to nicotine administration for its potential addiction effect[67].

NAC

NAC is a glutamate-modulating drug acting through the inhibition of the synaptic glutamate release. Five RCTs were conducted on adults[44,45,68-70] and one on children[71] using NAC *vs* placebo as an adjunctive therapy to SRIs[44,68-71] or fluvoxamine[45]. In three studies, conducted on 48, 44, 34 and 11 patients, respectively [44,45,70,71], the use of NAC (in the dose of 2.4 g/d for 12 wk[44] or 2 g/d for 10 wk [45] or of 2.4 g/d for 10 wk[70] or 2.7 g/d for 12 wk[71] showed improvement in the severity of OCD symptoms. On the other hands, in two studies conducted on 44[68] and 40 patients[69], respectively, the use of NAC (in the dose of 3 g/d for 16 wk)[68, 69] did not lead to a reduction of OCD symptoms.

Minocycline

Minocycline is an antibiotic that crosses the blood-brain barrier and has a neuroprotective effect that decreases glutamate-induced neurotoxicity[72]. It is used in some neurodegenerative diseases such as amyotrophic lateral sclerosis and Parkinson[73, 74]. Only one RCT was conducted on 102 patients using minocycline (200 mg/d for 10 wk) *vs* placebo as an adjunctive treatment to fluvoxamine. The results showed a reduction in Y-BOCS scores in the group that received minocycline[75].

D-cycloserine

D-cycloserine is a partial agonist at the *N*-methyl-d-aspartate receptor in the amygdala and some data have suggested a role of this receptor in fear extinction. For this reason, it was hypothesized that d-cycloserine may increase the efficacy of exposure therapy, a component of CBT for anxiety and OCD[76,77].

Eight RCTs were conducted on OCD patients using d-cycloserine *vs* placebo as an augmentation treatment of CBT with exposure and response prevention. Among these RCTs, four studies, conducted on 32[78], 23[79], 17[80] and 128 patients[81], respectively, used d-cycloserine in doses of 25[82] to 125 mg[78] close to each CBT session, reporting a significant amelioration of OCD symptom. In the other four studies, conducted on 27[82], 24[83], 30[45] and 142[84] patients, respectively, used d-cycloserine in doses of 25[85] to 250 mg[84] close to each CBT session, but did not show any statistically significant improvement.

In light of such contrasting results, it is not yet possible to give a clear answer on the use of glutamate-modulating drugs in OCD.

Therefore, further randomized placebo-controlled trials in larger study populations are essential to draw definitive indications on the efficacy of the use of antiglutamatergic agents in OCD.

THE REASON WHY EARLY INTERVENTION COULD BE IMPORTANT FOR OCD

As we underline, glutamate neurotransmission plays a crucial role in the CSTC of

OCD[12]. Furthermore, glutamate is also implicated in neuronal plasticity, learning, and memory[86]. Dysregulation of glutamate levels may bring glutamate receptor hyperactivity or even excitotoxicity in neurons and, in pathological situations, glutamate could lead to neurotoxicity by acting as a neuronal excitotoxin[87].

In support of this hypothesis, neuroimaging studies found changes in multiple sites of age-related brain structures suggesting that OCD is characterized by complex and nonlinear neurophysiopathological mechanisms[88,89].

The hypothesis of the role of neurotoxicity in the neurophysiopathology of OCD is clinically related to the importance of early intervention for patients. Indeed, some studies showed that a faster onset in the treatment of OCD correlates with an earlier onset of remission[90]. On the contrary, late intervention is associated with increased comorbidity, disability, reduced treatment response and remission[91-93].

The DUI for OCD is very high compared to other mental disorders[94]. Most cases of OCD arise in childhood or adolescence[92] and symptoms are often ignored[95] extending the time for diagnosis (from 2 to 10 year) and consequently for starting treatment[92,96,97] with average DUI of two to three years[98,99]. Although there is a paucity of data to support a progression of such brain changes so far, it is assumed that early intervention, even with the use of glutamate-modulating drugs, could help to stop neurotoxic damage[13]. A crucial point may be the switch from a time-dependent neurotransmitter dysfunction to an irreversible structural damage. This may explain both refractory to SSRI and the unresponsiveness to anti-glutamatergic agents.

Identifying and confirming the efficacy and safety of new therapeutic approaches for OCD could also be very useful for early intervention in these patients. An international group of expert clinicians and scientists with extensive OCD experience are documenting the negative impact associated with the delayed treatment on clinical outcomes, suggesting the importance of a greater emphasis on targeted early intervention for OCD patients as is already is the case for psychotic disorders. Early intervention is more promising for reducing chronicity as well as the economic and social burdens associated with OCD.

CONCLUSION

The hypothesis of a hyperactive CSTC loop that implies a high level of glutamate in the cortical-striatal pathways and a dysregulation of *GABA*ergic transmission may represent the pathophysiology of OCD. Despite the effectiveness of SRIs in treating OCD, the treatment-resistant symptoms observed in 40% of patients present enormous clinical issues. The refractory to SRIs and the unresponsiveness to antiglutamatergic agents may be explained by a time-dependent neurotransmitter dysfunction, which may lead to an irreversible structural damage. There is a need to develop novel pharmacological strategies, which are not exclusively related to refractory subjects. If glutamate-neurotoxicity is extensively confirmed, the time from OCD onset will be the most important variable to take into consideration. In such a scenario, agents targeting glutamate neurotransmission may represent a promising treatment, especially in the case of a timely prescription.

REFERENCES

1 **Ruscio AM**, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry* 2010; **15**: 53-63 [PMID: 18725912 DOI: 10.1038/mp.2008.94]

2 **Kessler RC**, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 593-602 [PMID: 15939837 DOI: 10.1001/archpsyc.62.6.593]

3 **Dell'Osso B**, Benatti B, Hollander E, Fineberg N, Stein DJ, Lochner C, Nicolini H, Lanzagorta N, Palazzo C, Altamura AC, Marazziti D, Pallanti S, Van Ameringen M, Karamustafalioglu O, Drummond LM, Hranov L, Figee M, Grant JE, Zohar J, Denys D, Menchon JM. Childhood, adolescent and adult age at onset and related clinical correlates in obsessive-compulsive disorder: a report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS). *Int J Psychiatry Clin Pract* 2016; **20**: 210-217 [PMID: 27433835 DOI: 10.1080/13651501.2016.1207087]

4 **Carmi L**, Fineberg N, Ben Arush O, Zohar J. Epidemiology of OCD. In: Geddes JR, Andreasen NC, Goodwin GM, editors. New Oxford Textbook of Psychiatry, Third Edition. Oxford: Oxford University Press, 2020

5 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington: American Psychiatric Publishing, 2013

6 **Stein DJ**, Fineberg NA, Bienvenu OJ, Denys D, Lochner C, Nestadt G, Leckman JF, Rauch SL, Phillips KA. Should OCD be classified as an anxiety disorder in DSM-V? *Depress Anxiety* 2010; **27**: 495-506 [PMID: 20533366 DOI: 10.1002/da.20699]

7 **Phillips KA**, Stein DJ, Rauch SL, Hollander E, Fallon BA, Barsky A, Fineberg N, Mataix-Cols D, Ferrão YA, Saxena S, Wilhelm S, Kelly MM, Clark LA, Pinto A, Bienvenu OJ, Farrow J, Leckman J. Should an obsessive-compulsive spectrum grouping of disorders be included in DSM-V? *Depress Anxiety* 2010; **27**: 528-555 [PMID: 20533367 DOI: 10.1002/da.20705]

8 **Skapinakis P**, Caldwell DM, Hollingworth W, Bryden P, Fineberg NA, Salkovskis P, Welton NJ, Baxter H, Kessler D, Churchill R, Lewis G. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2016; **3**: 730-739 [PMID: 27318812 DOI: 10.1016/S2215-0366(16)30069-4]

9 **Hollander E**, Kwon JH, Stein DJ, Broatch J, Rowland CT, Himelein CA. Obsessive-compulsive and spectrum disorders: overview and quality of life issues. *J Clin Psychiatry* 1996; **57** Suppl 8: 3-6 [PMID: 8698678]

10 **Dougherty DD**, Brennan BP, Stewart SE, Wilhelm S, Widge AS, Rauch SL. Neuroscientifically Informed Formulation and Treatment Planning for Patients With Obsessive-Compulsive Disorder: A Review. *JAMA Psychiatry* 2018; **75**: 1081-1087 [PMID: 30140845 DOI: 10.1001/jamapsychiatry.2018.0930]

11 **Albelda N**, Bar-On N, Joel D. The role of NMDA receptors in the signal attenuation rat model of obsessive-compulsive disorder. *Psychopharmacology (Berl)* 2010; **210**: 13-24 [PMID: 20238210 DOI: 10.1007/s00213-010-1808-9]

12 **Ting JT**, Feng G. Neurobiology of obsessive-compulsive disorder: insights into neural circuitry dysfunction through mouse genetics. *Curr Opin Neurobiol* 2011; **21**: 842-848 [PMID: 21605970 DOI: 10.1016/j.conb.2011.04.010]

13 **Fineberg NA**, Dell'Osso B, Albert U, Maina G, Geller D, Carmi L, Sireau N, Walitza S, Grassi G, Pallanti S, Hollander E, Brakoulias V, Menchon JM, Marazziti D, Ioannidis K, Apergis-Schoute A, Stein DJ, Cath DC, Veltman DJ, Van Ameringen M, Fontenelle LF, Shavitt RG, Costa D, Diniz JB, Zohar J. Early intervention for obsessive compulsive disorder: An expert consensus statement. *Eur Neuropsychopharmacol* 2019; **29**: 549-565 [PMID: 30773387 DOI: 10.1016/j.euroneuro.2019.02.002]

14 **Gillan CM**, Papmeyer M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW, de Wit S. Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *Am J Psychiatry* 2011; **168**: 718-726 [PMID: 21572165 DOI: 10.1176/appi.ajp.2011.10071062]

15 **Gillan CM**, Morein-Zamir S, Urcelay GP, Sule A, Voon V, Apergis-Schoute AM, Fineberg NA, Sahakian BJ, Robbins TW. Enhanced avoidance habits in obsessive-compulsive disorder. *Biol Psychiatry* 2014; **75**: 631-638 [PMID: 23510580 DOI: 10.1016/j.biopsych.2013.02.002]

16 **Voon V**, Derbyshire K, Rück C, Irvine MA, Worbe Y, Enander J, Schreiber LR, Gillan C, Fineberg NA, Sahakian BJ, Robbins TW, Harrison NA, Wood J, Daw ND, Dayan P, Grant JE, Bullmore ET. Disorders of compulsivity: a common bias towards learning habits. *Mol Psychiatry* 2015; **20**: 345-352 [PMID: 24840709 DOI: 10.1038/mp.2014.44]

17 **Yin HH**, Knowlton BJ, Balleine BW. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *Eur J Neurosci* 2004; **19**: 181-189 [PMID: 14750976 DOI: 10.1111/j.1460-9568.2004.03095.x]

18 **Coutureau E**, Killcross S. Inactivation of the infralimbic prefrontal cortex reinstates goal-directed responding in overtrained rats. *Behav Brain Res* 2003; **146**: 167-174 [PMID: 14643469 DOI: 10.1016/j.bbr.2003.09.025]

19 **Killcross S**, Coutureau E. Coordination of actions and habits in the medial prefrontal cortex of rats. *Cereb Cortex* 2003; **13**: 400-408 [PMID: 12631569 DOI: 10.1093/cercor/13.4.400]

20 **Tricomi EM**, Delgado MR, Fiez JA. Modulation of caudate activity by action contingency. *Neuron* 2004; **41**: 281-292 [PMID: 14741108 DOI: 10.1016/s0896-6273(03)00848-1]

21 **Tanaka SC**, Balleine BW, O'Doherty JP. Calculating consequences: brain systems that encode the causal effects of actions. *J Neurosci* 2008; **28**: 6750-6755 [PMID: 18579749 DOI: 10.1523/JNEUROSCI.1808-08.2008]

22 **Saxena S**, Rauch SL. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. *Psychiatr Clin North Am* 2000; **23**: 563-586 [PMID: 10986728 DOI: 10.1016/s0193-953x(05)70181-7]

23 **Menzies L**, Williams GB, Chamberlain SR, Ooi C, Fineberg N, Suckling J, Sahakian BJ, Robbins TW, Bullmore ET. White matter abnormalities in patients with obsessive-compulsive disorder and their first-degree relatives. *Am J Psychiatry* 2008; **165**: 1308-1315 [PMID: 18519525 DOI: 10.1176/appi.ajp.2008.07101677]

24 **Graybiel AM**, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. *Neuron* 2000; **28**: 343-347 [PMID: 11144344 DOI: 10.1016/s0896-6273(00)00113-6]

25 **Alexander GE**, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986; **9**: 357-381 [PMID: 3085570 DOI: 10.1146/annurev.ne.09.030186.002041]

26 **Burguière E**, Monteiro P, Mallet L, Feng G, Graybiel AM. Striatal circuits, habits, and implications for obsessive-compulsive disorder. *Curr Opin Neurobiol* 2015; **30**: 59-65 [PMID: 25241072 DOI: 10.1016/j.conb.2014.08.008]

27 **Milad MR**, Rauch SL. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. *Trends Cogn Sci* 2012; **16**: 43-51 [PMID: 22138231 DOI: 10.1016/j.tics.2011.11.003]

28 **Shin DJ**, Jung WH, He Y, Wang J, Shim G, Byun MS, Jang JH, Kim SN, Lee TY, Park HY, Kwon JS. The effects of pharmacological treatment on functional brain connectome in obsessive-compulsive disorder. *Biol Psychiatry* 2014; **75**: 606-614 [PMID: 24099506 DOI: 10.1016/j.biopsych.2013.09.002]

29 **Marinova Z**, Chuang DM, Fineberg N. Glutamate-Modulating Drugs as a Potential Therapeutic Strategy in Obsessive-Compulsive Disorder. *Curr Neuropharmacol* 2017; **15**: 977-995 [PMID: 28322166 DOI: 10.2174/1570159X15666170320104237]

30 **Lovinger DM**. Neurotransmitter roles in synaptic modulation, plasticity and learning in the dorsal striatum. *Neuropharmacology* 2010; **58**: 951-961 [PMID: 20096294 DOI: 10.1016/j.neuropharm.2010.01.008]

31 **Chakrabarty K**, Bhattacharyya S, Christopher R, Khanna S. Glutamatergic dysfunction in OCD. *Neuropsychopharmacology* 2005; **30**: 1735-1740 [PMID: 15841109 DOI: 10.1038/sj.npp.1300733]

32 **Bhattacharyya S**, Khanna S, Chakrabarty K, Mahadevan A, Christopher R, Shankar SK. Anti-brain autoantibodies and altered excitatory neurotransmitters in obsessive-compulsive disorder. *Neuropsychopharmacology* 2009; **34**: 2489-2496 [PMID: 19675532 DOI: 10.1038/npp.2009.77]

33 **Arnold PD**, Rosenberg DR, Mundo E, Tharmalingam S, Kennedy JL, Richter MA. Association of a glutamate (NMDA) subunit receptor gene (GRIN2B) with obsessive-compulsive disorder: a preliminary study. *Psychopharmacology (Berl)* 2004; **174**: 530-538 [PMID: 15083261 DOI: 10.1007/s00213-004-1847-1]

34 **Dickel DE**, Veenstra-VanderWeele J, Cox NJ, Wu X, Fischer DJ, Van Etten-Lee M, Himle JA, Leventhal BL, Cook EH Jr, Hanna GL. Association testing of the positional and functional candidate gene SLC1A1/EAAC1 in early-onset obsessive-compulsive disorder. *Arch Gen Psychiatry* 2006; **63**: 778-785 [PMID: 16818867 DOI: 10.1001/archpsyc.63.7.778]

35 **Hanna GL**, Veenstra-VanderWeele J, Cox NJ, Boehnke M, Himle JA, Curtis GC, Leventhal BL, Cook EH Jr. Genomewide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. *Am J Med Genet* 2002; **114**: 541-552 [DOI: 10.1002/ajmg.10519]

36 **Niciu MJ**, Henter ID, Luckenbaugh DA, Zarate CA Jr, Charney DS. Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. *Annu Rev Pharmacol Toxicol* 2014; **54**: 119-139 [PMID: 24392693 DOI: 10.1146/annurev-pharmtox-011613-135950]

37 **Price RB**, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* 2009; **66**: 522-526 [PMID: 19545857 DOI: 10.1016/j.biopsych.2009.04.029]

38 **Murphy DL**, Moya PR, Fox MA, Rubenstein LM, Wendland JR, Timpano KR. Anxiety and affective disorder comorbidity related to serotonin and other neurotransmitter systems: obsessive-compulsive disorder as an example of overlapping clinical and genetic heterogeneity. *Philos Trans R Soc Lond B Biol Sci* 2013; **368**: 20120435 [PMID: 23440468 DOI: 10.1098/rstb.2012.0435]

39 **Carmi L**, Tendler A, Bystritsky A, Hollander E, Blumberger DM, Daskalakis J, Ward H, Lapidus K, Goodman W, Casuto L, Feifel D, Barnea-Ygael N, Roth Y, Zangen A, Zohar J. Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial. *Am J Psychiatry* 2019; **176**: 931-938 [PMID: 31109199 DOI: 10.1176/appi.ajp.2019.18101180]

40 **Goodman WK**, Storch EA, Sheth SA. Harmonizing the Neurobiology and Treatment of Obsessive-Compulsive Disorder. *Am J Psychiatry* 2021; **178**: 17-29 [PMID: 33384007 DOI: 10.1176/appi.ajp.2020.20111601]

41 **Goodman WK**, Alterman RL. Deep brain stimulation for intractable psychiatric disorders. *Annu Rev Med* 2012; **63**: 511-524 [PMID: 22034866 DOI: 10.1146/annurev-med-052209-100401]

42 **Gabriëls L**, Cosyns P, Nuttin B, Demeulemeester H, Gybels J. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: psychopathological and neuropsychological outcome in three cases. *Acta Psychiatr Scand* 2003; **107**: 275-282 [PMID: 12662250]

43 **Pittenger C**, Krystal JH, Coric V. Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder. *NeuroRx* 2006; **3**: 69-81 [PMID: 16490414 DOI: 10.1016/j.nurx.2005.12.006]

44 **Afshar H**, Roohafza H, Mohammad-Beigi H, Haghighi M, Jahangard L, Shokouh P, Sadeghi M, Hafezian H. N-acetylcysteine add-on treatment in refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2012; **32**: 797-803 [PMID: 23131885 DOI: 10.1097/JCP.0b013e318272677d]

45 **Paydary K**, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. *J Clin Pharm Ther* 2016; **41**: 214-219 [PMID: 26931055 DOI: 10.1111/jcpt.12370]

46 **Greenberg WM**, Benedict MM, Doerfer J, Perrin M, Panek L, Cleveland WL, Javitt DC. Adjunctive glycine in the treatment of obsessive-compulsive disorder in adults. *J Psychiatr Res* 2009; **43**: 664-

670 [PMID: 19046587 DOI: 10.1016/j.jpsychires.2008.10.007]
47 **Parsons CG**, Danysz W, Quack G. Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist--a review of preclinical data. *Neuropharmacology* 1999; **38**: 735-767 [PMID: 10465680 DOI: 10.1016/s0028-3908(99)00019-2]
48 **Haghighi M**, Jahangard L, Mohammad-Beigi H, Bajoghli H, Hafezian H, Rahimi A, Afshar H, Holsboer-Trachsler E, Brand S. In a double-blind, randomized and placebo-controlled trial, adjuvant memantine improved symptoms in inpatients suffering from refractory obsessive-compulsive disorders (OCD). *Psychopharmacology (Berl)* 2013; **228**: 633-640 [PMID: 23525525 DOI: 10.1007/s00213-013-3067-z]
49 **Ghaleiha A**, Entezari N, Modabbernia A, Najand B, Askari N, Tabrizi M, Ashrafi M, Hajiaghaee R, Akhondzadeh S. Memantine add-on in moderate to severe obsessive-compulsive disorder: randomized double-blind placebo-controlled study. *J Psychiatr Res* 2013; **47**: 175-180 [PMID: 23063327 DOI: 10.1016/j.jpsychires.2012.09.015]
50 **Modarresi A**, Sayyah M, Razooghi S, Eslami K, Javadi M, Kouti L. Memantine Augmentation Improves Symptoms in Serotonin Reuptake Inhibitor-Refractory Obsessive-Compulsive Disorder: A Randomized Controlled Trial. *Pharmacopsychiatry* 2018; **51**: 263-269 [PMID: 29100251 DOI: 10.1055/s-0043-120268]
51 **Farnia V**, Gharehbaghi H, Alikhani M, Almasi A, Golshani S, Tatari F, Davarinejad O, Salemi S, Sadeghi Bahmani D, Holsboer-Trachsler E, Brand S. Efficacy and tolerability of adjunctive gabapentin and memantine in obsessive compulsive disorder: Double-blind, randomized, placebo-controlled trial. *J Psychiatr Res* 2018; **104**: 137-143 [PMID: 30044966 DOI: 10.1016/j.jpsychires.2018.07.008]
52 **Andrade C**. Augmentation With Memantine in Obsessive-Compulsive Disorder. *J Clin Psychiatry* 2019; **80** [PMID: 31846244 DOI: 10.4088/JCP.19f13163]
53 **Huber TJ**, Dietrich DE, Emrich HM. Possible use of amantadine in depression. *Pharmacopsychiatry* 1999; **32**: 47-55 [PMID: 10333162 DOI: 10.1055/s-2007-979191]
54 **Pud D**, Eisenberg E, Spitzer A, Adler R, Fried G, Yarnitsky D. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial. *Pain* 1998; **75**: 349-354 [PMID: 9583771 DOI: 10.1016/s0304-3959(98)00014-1]
55 **Stryjer R**, Strous RD, Shaked G, Bar F, Feldman B, Kotler M, Polak L, Rosenzcwaig S, Weizman A. Amantadine as augmentation therapy in the management of treatment-resistant depression. *Int Clin Psychopharmacol* 2003; **18**: 93-96 [PMID: 12598820 DOI: 10.1097/00004850-200303000-00005]
56 **Naderi S**, Faghih H, Aqamolaei A, Mortazavi SH, Mortezaei A, Sahebolzamani E, Rezaei F, Akhondzadeh S. Amantadine as adjuvant therapy in the treatment of moderate to severe obsessive-compulsive disorder: A double-blind randomized trial with placebo control. *Psychiatry Clin Neurosci* 2019; **73**: 169-174 [PMID: 30488617 DOI: 10.1111/pcn.12803]
57 **Pittenger C**, Coric V, Banasr M, Bloch M, Krystal JH, Sanacora G. Riluzole in the treatment of mood and anxiety disorders. *CNS Drugs* 2008; **22**: 761-786 [PMID: 18698875 DOI: 10.2165/00023210-200822090-00004]
58 **Pittenger C**, Bloch MH, Wasylink S, Billingslea E, Simpson R, Jakubovski E, Kelmendi B, Sanacora G, Coric V. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a pilot randomized placebo-controlled trial. *J Clin Psychiatry* 2015; **76**: 1075-1084 [PMID: 26214725 DOI: 10.4088/JCP.14m09123]
59 **Grant PJ**, Joseph LA, Farmer CA, Luckenbaugh DA, Lougee LC, Zarate CA Jr, Swedo SE. 12-week, placebo-controlled trial of add-on riluzole in the treatment of childhood-onset obsessive-compulsive disorder. *Neuropsychopharmacology* 2014; **39**: 1453-1459 [PMID: 24356715 DOI: 10.1038/npp.2013.343]
60 **Emamzadehfard S**, Kamaloo A, Paydary K, Ahmadipour A, Zeinoddini A, Ghaleiha A, Mohammadinejad P, Akhondzadeh S. Riluzole in augmentation of fluvoxamine for moderate to severe obsessive-compulsive disorder: Randomized, double-blind, placebo-controlled study. *Psychiatry Clin Neurosci* 2016; **70**: 332-341 [PMID: 27106362 DOI: 10.1111/pcn.12394]
61 **Rodriguez CI**, Kegeles LS, Levinson A, Feng T, Marcus SM, Vermes D, Flood P, Simpson HB. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. *Neuropsychopharmacology* 2013; **38**: 2475-2483 [PMID: 23783065 DOI: 10.1038/npp.2013.150]
62 **Heresco-Levy U**, Javitt DC. The role of N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in the pathophysiology and therapeutics of psychiatric syndromes. *Eur Neuropsychopharmacol* 1998; **8**: 141-152 [PMID: 9619693 DOI: 10.1016/s0924-977x(97)00050-3]
63 **Girod R**, Barazangi N, McGehee D, Role LW. Facilitation of glutamatergic neurotransmission by presynaptic nicotinic acetylcholine receptors. *Neuropharmacology* 2000; **39**: 2715-2725 [PMID: 11044742 DOI: 10.1016/s0028-3908(00)00145-3]
64 **Araki H**, Suemaru K, Gomita Y. Neuronal nicotinic receptor and psychiatric disorders: functional and behavioral effects of nicotine. *Jpn J Pharmacol* 2002; **88**: 133-138 [PMID: 11928712 DOI: 10.1254/jjp.88.133]
65 **Mansvelder HD**, Keath JR, McGehee DS. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. *Neuron* 2002; **33**: 905-919 [PMID: 11906697 DOI: 10.1016/s0896-6273(02)00625-6]
66 **Lundberg S**, Carlsson A, Norfeldt P, Carlsson ML. Nicotine treatment of obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28**: 1195-1199 [PMID: 15610934 DOI:

10.1016/j.pnpbp.2004.06.014]

67 **Piacentino D**, Maraone A, Roselli V, Berardelli I, Biondi M, Kotzalidis GD, Pasquini M. Efficacy of nicotine administration on obsessions and compulsions in OCD: a systematic review. *Ann Gen Psychiatry* 2020; **19**: 57 [PMID: 33014119 DOI: 10.1186/s12991-020-00309-z]

68 **Sarris J**, Oliver G, Camfield DA, Dean OM, Dowling N, Smith DJ, Murphy J, Menon R, Berk M, Blair-West S, Ng CH. N-Acetyl Cysteine (NAC) in the Treatment of Obsessive-Compulsive Disorder: A 16-Week, Double-Blind, Randomised, Placebo-Controlled Study. *CNS Drugs* 2015; **29**: 801-809 [PMID: 26374743 DOI: 10.1007/s40263-015-0272-9]

69 **Costa DLC**, Diniz JB, Requena G, Joaquim MA, Pittenger C, Bloch MH, Miguel EC, Shavitt RG. Randomized, Double-Blind, Placebo-Controlled Trial of N-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder. *J Clin Psychiatry* 2017; **78**: e766-e773 [PMID: 28617566 DOI: 10.4088/JCP.16m11101]

70 **Ghanizadeh A**, Mohammadi MR, Bahraini S, Keshavarzi Z, Firoozabadi A, Alavi Shoshtari A. Efficacy of N-Acetylcysteine Augmentation on Obsessive Compulsive Disorder: A Multicenter Randomized Double Blind Placebo Controlled Clinical Trial. *Iran J Psychiatry* 2017; **12**: 134-141 [PMID: 28659986]

71 **Li F**, Welling MC, Johnson JA, Coughlin C, Mulqueen J, Jakubovski E, Coury S, Landeros-Weisenberger A, Bloch MH. N-Acetylcysteine for Pediatric Obsessive-Compulsive Disorder: A Small Pilot Study. *J Child Adolesc Psychopharmacol* 2020; **30**: 32-37 [PMID: 31800306 DOI: 10.1089/cap.2019.0041]

72 **Pi R**, Li W, Lee NT, Chan HH, Pu Y, Chan LN, Sucher NJ, Chang DC, Li M, Han Y. Minocycline prevents glutamate-induced apoptosis of cerebellar granule neurons by differential regulation of p38 and Akt pathways. *J Neurochem* 2004; **91**: 1219-1230 [PMID: 15569265 DOI: 10.1111/j.1471-4159.2004.02796.x]

73 **Traynor BJ**, Bruijn L, Conwit R, Beal F, O'Neill G, Fagan SC, Cudkowicz ME. Neuroprotective agents for clinical trials in ALS: a systematic assessment. *Neurology* 2006; **67**: 20-27 [PMID: 16832072 DOI: 10.1212/01.wnl.0000223353.34006.54]

74 **NINDS NET-PD Investigators**. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. *Neurology* 2006; **66**: 664-671 [PMID: 16481597 DOI: 10.1212/01.wnl.0000201252.57661.e1]

75 **Esalatmanesh S**, Abrishami Z, Zeinoddini A, Rahiminejad F, Sadeghi M, Najarzadegan MR, Shalbafan MR, Akhondzadeh S. Minocycline combination therapy with fluvoxamine in moderate-to-severe obsessive-compulsive disorder: A placebo-controlled, double-blind, randomized trial. *Psychiatry Clin Neurosci* 2016; **70**: 517-526 [PMID: 27488081 DOI: 10.1111/pcn.12430]

76 **Davis M**, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. *Biol Psychiatry* 2006; **60**: 369-375 [PMID: 16919524 DOI: 10.1016/j.biopsych.2006.03.084]

77 **Lewin AB**, Wu MS, McGuire JF, Storch EA. Cognitive behavior therapy for obsessive-compulsive and related disorders. *Psychiatr Clin North Am* 2014; **37**: 415-445 [PMID: 25150570 DOI: 10.1016/j.psc.2014.05.002]

78 **Kushner MG**, Kim SW, Donahue C, Thuras P, Adson D, Kotlyar M, McCabe J, Peterson J, Foa EB. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biol Psychiatry* 2007; **62**: 835-838 [PMID: 17588545 DOI: 10.1016/j.biopsych.2006.12.020]

79 **Wilhelm S**, Buhlmann U, Tolin DF, Meunier SA, Pearlson GD, Reese HE, Cannistraro P, Jenike MA, Rauch SL. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry* 2008; **165**: 335-41; quiz 409 [PMID: 18245177 DOI: 10.1176/appi.ajp.2007.07050776]

80 **Farrell LJ**, Waters AM, Boschen MJ, Hattingh L, McConnell H, Milliner EL, Collings N, Zimmer-Gembeck M, Shelton D, Ollendick TH, Testa C, Storch EA. Difficult-to-treat pediatric obsessive-compulsive disorder: feasibility and preliminary results of a randomized pilot trial of D-cycloserine-augmented behavior therapy. *Depress Anxiety* 2013; **30**: 723-731 [PMID: 23722990 DOI: 10.1002/da.22132]

81 **Andersson E**, Hedman E, Enander J, Radu Djurfeldt D, Ljótsson B, Cervenka S, Isung J, Svanborg C, Mataix-Cols D, Kaldo V, Andersson G, Lindefors N, Rück C. D-Cycloserine vs Placebo as Adjunct to Cognitive Behavioral Therapy for Obsessive-Compulsive Disorder and Interaction With Antidepressants: A Randomized Clinical Trial. *JAMA Psychiatry* 2015; **72**: 659-667 [PMID: 25970252 DOI: 10.1001/jamapsychiatry.2015.0546]

82 **Mataix-Cols D**, Turner C, Monzani B, Isomura K, Murphy C, Krebs G, Heyman I. Cognitive-behavioural therapy with post-session D-cycloserine augmentation for paediatric obsessive-compulsive disorder: pilot randomised controlled trial. *Br J Psychiatry* 2014; **204**: 77-78 [PMID: 24262813 DOI: 10.1192/bjp.bp.113.126284]

83 **Storch EA**, Merlo LJ, Bengtson M, Murphy TK, Lewis MH, Yang MC, Jacob ML, Larson M, Hirsh A, Fernandez M, Geffken GR, Goodman WK. D-cycloserine does not enhance exposure-response prevention therapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2007; **22**: 230-237 [PMID: 17519647 DOI: 10.1097/YIC.0b013e32819f8480]

84 **Storch EA**, Wilhelm S, Sprich S, Henin A, Micco J, Small BJ, McGuire J, Mutch PJ, Lewin AB, Murphy TK, Geller DA. Efficacy of Augmentation of Cognitive Behavior Therapy With Weight-Adjusted d-Cycloserine vs Placebo in Pediatric Obsessive-Compulsive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* 2016; **73**: 779-788 [PMID: 27367832 DOI:

10.1001/jamapsychiatry.2016.1128]

85 **Storch EA**, Murphy TK, Goodman WK, Geffken GR, Lewin AB, Henin A, Micco JA, Sprich S, Wilhelm S, Bengtson M, Geller DA. A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. *Biol Psychiatry* 2010; **68**: 1073-1076 [PMID: 20817153 DOI: 10.1016/j.biopsych.2010.07.015]

86 **Javitt DC**, Schoepp D, Kalivas PW, Volkow ND, Zarate C, Merchant K, Bear MF, Umbricht D, Hajos M, Potter WZ, Lee CM. Translating glutamate: from pathophysiology to treatment. *Sci Transl Med* 2011; **3**: 102mr2 [PMID: 21957170 DOI: 10.1126/scitranslmed.3002804]

87 **Sanacora G**, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov* 2008; **7**: 426-437 [PMID: 18425072 DOI: 10.1038/nrd2462]

88 **Boedhoe PS**, Schmaal L, Abe Y, Ameis SH, Arnold PD, Batistuzzo MC, Benedetti F, Beucke JC, Bollettini I, Bose A, Brem S, Calvo A, Cheng Y, Cho KI, Dallaspezia S, Denys D, Fitzgerald KD, Fouche JP, Giménez M, Gruner P, Hanna GL, Hibar DP, Hoexter MQ, Hu H, Huyser C, Ikari K, Jahanshad N, Kathmann N, Kaufmann C, Koch K, Kwon JS, Lazaro L, Liu Y, Lochner C, Marsh R, Martínez-Zalacaín I, Mataix-Cols D, Menchón JM, Minuzzi L, Nakamae T, Nakao T, Narayanaswamy JC, Piras F, Pittenger C, Reddy YC, Sato JR, Simpson HB, Soreni N, Soriano-Mas C, Spalletta G, Stevens MC, Szeszko PR, Tolin DF, Venkatasubramanian G, Walitza S, Wang Z, van Wingen GA, Xu J, Xu X, Yun JY, Zhao Q; ENIGMA OCD Working Group, Thompson PM, Stein DJ, van den Heuvel OA. Distinct Subcortical Volume Alterations in Pediatric and Adult OCD: A Worldwide Meta- and Mega-Analysis. *Am J Psychiatry* 2017; **174**: 60-69 [PMID: 27609241 DOI: 10.1176/appi.ajp.2016.16020201]

89 **Boedhoe PSW**, Schmaal L, Abe Y, Alonso P, Ameis SH, Anticevic A, Arnold PD, Batistuzzo MC, Benedetti F, Beucke JC, Bollettini I, Bose A, Brem S, Calvo A, Calvo R, Cheng Y, Cho KIK, Ciullo V, Dallaspezia S, Denys D, Feusner JD, Fitzgerald KD, Fouche JP, Fridgeirsson EA, Gruner P, Hanna GL, Hibar DP, Hoexter MQ, Hu H, Huyser C, Jahanshad N, James A, Kathmann N, Kaufmann C, Koch K, Kwon JS, Lazaro L, Lochner C, Marsh R, Martínez-Zalacaín I, Mataix-Cols D, Menchón JM, Minuzzi L, Morer A, Nakamae T, Nakao T, Narayanaswamy JC, Nishida S, Nurmi E, O'Neill J, Piacentini J, Piras F, Reddy YCJ, Reess TJ, Sakai Y, Sato JR, Simpson HB, Soreni N, Soriano-Mas C, Spalletta G, Stevens MC, Szeszko PR, Tolin DF, van Wingen GA, Venkatasubramanian G, Walitza S, Wang Z, Yun JY; ENIGMA-OCD Working Group, Thompson PM, Stein DJ, van den Heuvel OA; ENIGMA OCD Working Group. Cortical Abnormalities Associated With Pediatric and Adult Obsessive-Compulsive Disorder: Findings From the ENIGMA Obsessive-Compulsive Disorder Working Group. *Am J Psychiatry* 2018; **175**: 453-462 [PMID: 29377733 DOI: 10.1176/appi.ajp.2017.17050485]

90 **Mancebo MC**, Boisseau CL, Garnaat SL, Eisen JL, Greenberg BD, Sibrava NJ, Stout RL, Rasmussen SA. Long-term course of pediatric obsessive-compulsive disorder: 3 years of prospective follow-up. *Compr Psychiatry* 2014; **55**: 1498-1504 [PMID: 24952937 DOI: 10.1016/j.comppsych.2014.04.010]

91 **Dell'Osso B**, Benatti B, Buoli M, Altamura AC, Marazziti D, Hollander E, Fineberg N, Stein DJ, Pallanti S, Nicolini H, Van Ameringen M, Lochner C, Hranov G, Karamustafalioglu O, Hranov L, Menchon JM, Zohar J; ICOCS group. The influence of age at onset and duration of illness on long-term outcome in patients with obsessive-compulsive disorder: a report from the International College of Obsessive Compulsive Spectrum Disorders (ICOCS). *Eur Neuropsychopharmacol* 2013; **23**: 865-871 [PMID: 23791074 DOI: 10.1016/j.euroneuro.2013.05.004]

92 **Albert U**, Barbaro F, Bramante S, Rosso G, De Ronchi D, Maina G. Duration of untreated illness and response to SRI treatment in Obsessive-Compulsive Disorder. *Eur Psychiatry* 2019; **58**: 19-26 [PMID: 30763828 DOI: 10.1016/j.eurpsy.2019.01.017]

93 **Rufer M**, Hand I, Alsleben H, Braatz A, Ortmann J, Katenkamp B, Fricke S, Peter H. Long-term course and outcome of obsessive-compulsive patients after cognitive-behavioral therapy in combination with either fluvoxamine or placebo: a 7-year follow-up of a randomized double-blind trial. *Eur Arch Psychiatry Clin Neurosci* 2005; **255**: 121-128 [PMID: 15812606 DOI: 10.1007/s00406-004-0544-8]

94 **Altamura AC**, Buoli M, Albano A, Dell'Osso B. Age at onset and latency to treatment (duration of untreated illness) in patients with mood and anxiety disorders: a naturalistic study. *Int Clin Psychopharmacol* 2010; **25**: 172-179 [PMID: 20305566 DOI: 10.1097/YIC.0b013e3283384c74]

95 **Rapoport JL**, Inoff-Germain G, Weissman MM, Greenwald S, Narrow WE, Jensen PS, Lahey BB, Canino G. Childhood obsessive-compulsive disorder in the NIMH MECA study: parent versus child identification of cases. Methods for the Epidemiology of Child and Adolescent Mental Disorders. *J Anxiety Disord* 2000; **14**: 535-548 [PMID: 11918090 DOI: 10.1016/s0887-6185(00)00048-7]

96 **Geller D**, Biederman J, Faraone SV, Frazier J, Coffey BJ, Kim G, Bellordre CA. Clinical correlates of obsessive compulsive disorder in children and adolescents referred to specialized and non-specialized clinical settings. *Depress Anxiety* 2000; **11**: 163-168 [PMID: 10945136 DOI: 10.1002/1520-6394(2000)11:4<163::AID-DA3>3.0.CO;2-3]

97 **García-Soriano G**, Rufer M, Delsignore A, Weidt S. Factors associated with non-treatment or delayed treatment seeking in OCD sufferers: a review of the literature. *Psychiatry Res* 2014; **220**: 1-10 [PMID: 25108591 DOI: 10.1016/j.psychres.2014.07.009]

98 **Walitza S**, Zellmann H, Irblich B, Lange KW, Tucha O, Hemminger U, Wucherer K, Rost V, Reinecker H, Wewetzer C, Warnke A. Children and adolescents with obsessive-compulsive disorder and comorbid attention-deficit/hyperactivity disorder: preliminary results of a prospective follow-up

study. *J Neural Transm (Vienna)* 2008; **115**: 187-190 [PMID: 18200431 DOI: 10.1007/s00702-007-0841-2]

99 **Zellmann H**, Jans T, Irblich B, Hemminger U, Reinecker H, Sauer C, Lange KW, Tucha O, Wewetzer C, Warnke A, Walitza S. [Children and adolescents with obsessive-compulsive disorders]. *Z Kinder Jugendpsychiatr Psychother* 2009; **37**: 173-182 [PMID: 19415602 DOI: 10.1024/1422-4917.37.3.173]

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MINIREVIEWS

The renin-angiotensin system, mood, and suicide: Are there associations?

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Abstract

Available evidence points to a possible role of the renin-angiotensin system (RAS) in the pathophysiology of mood disorders and suicide. We carried out a critical analysis of literature data regarding this role, with a focus on the proposed association between RAS dysfunction and suicidal behavior. Epidemiological, genetic, and biochemical findings are described, and the pathophysiological hypothesis aiming at explaining the possible relationship between RAS and suicide are discussed. Available findings do support the involvement of the RAS in the neurobiology of suicide, although the exact mechanisms underlying this involvement are still unknown.

Key Words: Renin-angiotensin system; Suicide; Mood disorders; Depression; Bipolar disorder

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Core Tip: This is a minireview on the proposed role of renin-angiotensin system dysfunctions in the pathophysiology of suicide.

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INTRODUCTION

Despite the large amount of research aiming at understanding its clinical, epidemiological, and neurobiological correlates, suicide remains a leading cause of death worldwide[1,2]. Data from the World Health Organization indicate that, during 2015, 800000 suicides took place worldwide, corresponding to 1.4% of premature deaths[3]. Suicide represents the second leading cause of death during the second and third decades of life, with more than 45000 deaths by suicide reported in the United States alone during 2016[4]. From a psychiatric and epidemiological standpoint, there is a strong association between suicidal behavior and psychiatric disorders, particularly mood disorders (unipolar depression and bipolar disorder). Approximately 50% of all completed suicides are associated with mood disorders, with a 20-fold increase in the risk of suicide among individuals suffering from depression or other mood disorders compared to healthy individuals[5-7].

In order to characterize the pathophysiology of suicide, most authors adopt a stress-diathesis model, according to which certain individuals with genetic vulnerability exhibit increased risk of suicidal behavior when exposed to external stressors or life events[8,9]. A large amount of evidence supports the involvement of neurobiological factors in the pathogenesis of suicidal behavior, although the search for suicide biomarkers has not yet produced consistent findings. In addition to abnormalities in the serotonergic system, the most consistent neurobiological findings associated with suicide are related to dysregulation in stress response and its downstream effects[10,11].

Over the last several years, the renin-angiotensin system (RAS) has been the object of great interest due to its possible involvement in the pathophysiology of mood disorders and suicide[12,13]. At a systemic level, the RAS plays an important role in blood pressure regulation and in the maintenance of body homeostasis. Furthermore, the existence of a brain RAS is well-established, with angiotensin-II receptors being found in brain areas involved in the processing of emotions, including the amygdala, the hippocampus, and the prefrontal cortex[14,15]. Evidence points to associations between increased RAS activity and depression, with angiotensin conversion enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) having been hypothesized as having protective and possibly therapeutic effects against mood disorders[12,16,17]. On the other hand, some epidemiological studies have raised concerns about possible associations between the use of medications targeting the RAS and increased risk of suicide. In particular, the results of a recent study pointing to the association between the use of angiotensin receptor blockers and suicide[18] have been discussed not only by the specialized literature but also in the mass media due to the potential implications and the widespread use of these medications in the treatment of hypertension and other cardiovascular conditions[19,20].

The current mini-review critically analyzes the putative relationships between the RAS, mood disorders, and suicide, in light of available evidence. Clinical and epidemiological data are discussed, in addition to considerations on the hypothesized neurobiological mechanisms involved in the interface between RAS and suicidal behavior.

MOOD DISORDERS AND THE RENIN-ANGIOTENSIN SYSTEM

Alterations in systemic markers of RAS activity among mood disorder patients have been reported, and studies have shown lower rates of depressive symptomatology among patients receiving angiotensin receptor antagonists and ACE inhibitors for the treatment of hypertension or diabetic nephropathy[13,17]. Further, improvements in depressive symptoms and interpersonal sensitivity among patients with diabetes type II using angiotensin receptor blockers have been observed[21].

Nevertheless, the relationship between RAS activity and mood disorders seems to be more complex, involving interactions among the RAS, inflammation, the hypothalamic-pituitary-adrenal (HPA) axis, and mood regulation. A large amount of evidence supports the notion that increases in RAS activity result in the activation of the HPA axis. For example, stimulation of the angiotensin II receptor type 1 (AT1) in the hypothalamic paraventricular nucleus brings about increases in the release of corticotrophin releasing hormone, ultimately contributing to HPA axis hyperactivation in animal models[22]. Furthermore, certain variants of the *ACE* gene, such as rs4291 and the D allele, related with higher ACE serum activity and increased HPA axis activity, have been found to be associated with depressive disorders[23,24].

In addition, there are multiple interactions among RAS, inflammation, and psychiatric disorders[13,15,25,26], with strong evidence from *in vitro* and *in vivo* studies supporting the effects of angiotensin II as a potent pro-inflammatory agent[27]. Recently, it was hypothesized that the RAS is composed by two arms with opposite actions in terms of inflammatory activity and effects on the pathophysiology of mental illnesses. The first arm, composed by ACE, angiotensin II, and AT1, shows pro-inflammatory effects, while the second arm, comprised of ACE2, Ang (1-7), and angiotensin receptor type II (AT2) seems to have anti-inflammatory effects and a putatively protective effect against the development of neuropsychiatric conditions[15]. Moreover, decreases in angiotensin II activity induced by ACE inhibitors or angiotensin II receptor blockers have been found to significantly reduce the concentrations of inflammatory mediators such as IL-6, TNF-α, and CRP, and have been found to be of benefit for patients with inflammatory diseases[27-29].

Furthermore, it is not yet clear whether different patterns of associations with the RAS are found across distinct subtypes of mood disorders. Studies specifically examining the role of the RAS in bipolar disorder are scant and the cyclic nature of that condition adds an extra layer of complexity to the investigation of RAS-related abnormalities and their involvement in the pathophysiology of BD different mod states. Our group recently described decreased ACE levels among individuals with BD in acute mood states (irrespective of type of mood episode) when compared to controls, but no significant correlations were specifically found between ACE levels and depressive or manic symptoms[14]. Based on findings from animal models, it has been proposed that candesartan, an angiotensin receptor antagonist, may have antimanic-like properties[16] but, given the proposed antidepressive properties of RAS modulators, as described above, a possible the association between increased RAS activity and mania seems to be of difficult interpretation. Of notice, one anecdotal report described associations between ACE use and the onset of acute mania[30].

In summary, even though the exact neurobiological mechanisms underlying the relationship between RAS and mood are not yet completely clarified, there is strong evidence suggesting that the relationship in question is mediated by possible effects of the RAS on the HPA and on inflammatory processes. That is of particular importance when analyzing possible interactions between RAS and suicide, as discussed in the next section.

THE RENIN-ANGIOTENSIN SYSTEM AND SUICIDE

Epidemiological data

The first studies looking at possible relationships between the RAS and suicide were published in the later 1990s and early 2000s. For example, in a cross-sectional ecological study carried out in 152 municipalities in Sweden[31], the use of ACE inhibitors by patients with hypertension, in contrast with calcium channel blockers, was not associated with increased suicide rates. In another study, which utilized data from a 5-year Danish cohort comprised by 58529 subjects receiving beta blockers, calcium channel blockers, or ACE inhibitors[32], there was a slight, non-significant elevation in the standardized mortality ratio (SMR) for suicide among patients on ACE inhibitors [SMR: 1.2; 95% confidence interval (CI): 0.7-1.8]. Similarly, in a subsequent nested case-control study analyzing 743 cases of completed suicide and 14860 matched controls [33], ACE inhibitors were not significantly associated with suicide (OR: 1.11; 95%CI: 0.68-1.83). In the same study, based on five of the cases exposed, current use of ARBs was associated with elevations in suicide risk (OR: 3.52; 95%CI: 1.33-9.30). Nonetheless, when a subsequent restricted analysis (which excluded subjects with a history of psychotropic drug use) was performed, the associations between current ARB use and risk of suicide became non-significant (OR: 3.32; 95%CI: 0.93-11.8).

While in the studies mentioned above the possibility of increased suicide risk among individuals receiving RAS medications was analyzed in a broader context, *i.e.*, studies of the possible associations between suicide and use of cardiovascular drugs, more recent studies have specifically focused on the hypothesis that ACEs and ARBs could be related to elevation in the risk of suicide. Mamdani *et al*[18] carried out a population-based nested case-control study involving 964 individuals aged 66 years and older who died by suicide and 3856 matched controls. Data were obtained from administrative claims databases in Canada, over a period of 20 years (1995 to 2015). The authors reported significant associations between the use of ARBs (but not ACE inhibitors) and higher suicide risk (adjusted OR: 1.63; 95%CI: 1.33-2.00). Of notice, the findings remained significant even after individuals with a previous history of self-

harm were excluded from the analysis (OR: 1.60; 95%CI: 1.29-1.98). However, data on past history of substance abuse and personality disorders among cases and controls was not available.

On the other hand, in a similarly designed study using data from the Veterans Health administration in the United States[34], no significant associations between the use of ARBs or ACE inhibitors and elevations in suicide risk were found. Data of 1309 cases of completed suicide and matched 5217 controls, collected between 2015 and 2017, were included in the analysis. The adjusted suicide OR for ARBs was 0.98 (95%CI: 0.83-1.16), whereas the crude suicide OR for ARBS *vs* ACE inhibitors was 0.966 (95%CI: 0.828-1.127).

Moreover, a study using information from the National Health Insurance Research Database in Taiwan looked at associations between ARB use and suicidal behavior [35]. The authors conducted a retrospective population-based cohort study and estimated the rates of suicide attempts among ARB users, propensity-score matched with non-users. The suicide attempt rates were significantly lower among ARB users than among non-users (adjusted hazard ratio: 0.48; 95%CI: 0.26-0.87), and a Kaplan Meyer survivor analysis showed a lower cumulative incidence of suicide attempts among ARB users compared to non-users.

Last, Köhler-Forsberg *et al*[36] recently performed a register-based nationwide cohort study comparing individuals started on a selective serotonin reuptake inhibitor (SSRI) with and without concomitant use of a RAS medication. Both groups were propensity-score matched and were followed over a period of up to three years. Individuals in the group receiving SSRIs plus RAS medications showed reduced risks for psychiatric hospital contacts and lower mortality rates when compared to those receiving only SSRIs. Differences between groups in terms of suicidal behavior were not statistically significant (hazard rate ratio: 1.06; 95%CI: 0.79-1.42).

In summary, available data from epidemiological studies suggesting relationships between use of RAS medications and suicide are inconsistent, with important variations in terms of the direction of such interactions (increased *vs* decreased risk of suicide in association with RAS medications) and of possible differences between different classes of RAS medications (ACE inhibitors and ARBs). Additionally, it is not totally clear, in light of current available evidence, whether these relationships, if present, are modulated by other factors, such as previous psychiatric history, age, and other demographic data. Methodological issues might explain at least part of the discrepant findings across different studies, as explained in the discussion section.

Biological findings

To date, the neurobiological evidence analyzing the relationship between RAS activity and suicidality is scant. One early study described increases in ACE activity in the substantia nigra of individuals who completed suicide[37]. More recently, Hallberg *et al*[38] looked at the levels of renin and aldosterone among depressive disorder patients [major depressive disorder (MDD), dysthymic disorder, and adjustment disorder] with and without a history of suicide attempt, as well as healthy controls. Serum levels of aldosterone were significantly lower among MDD patients with a history of suicidal behavior when compared to the other groups. Interestingly, no association between history of suicide attempt and aldosterone levels was found among individuals with other depressive disorders, and MDD patients without a history of suicidal attempt were similar to healthy controls in terms of their aldosterone levels. Together, these findings suggest that decreased aldosterone could represent a marker of suicidality among patients with MDD.

Given the evidence suggesting that increased RAS activity may be associated with depressive symptomatology, Hong *et al*[39] investigated the distribution of the ACE gene insertion/deletion (ACE I/D) polymorphism among major depressive disorder patients with and without a history of suicide attempts. The authors hypothesized that D allele (which has been associated with increases in RAS activity compared to I allele) would be found at a higher frequency among suicide attempters. No statistically significant differences between groups regarding the polymorphisms in question were found. Nevertheless, other studies have reported positive findings regarding the association between the ACE D allele and suicidal behavior. In one of them[40], significant differences in the distribution of ACE I/D polymorphisms between suicide attempters and non-attempters were reported, with higher frequencies of the DD genotype among attempters. Furthermore, the results of two other unrelated case-control studies were jointly reported by Sparks *et al*[41]. In the first study, 64 subjects who completed suicide were compared to 90 controls, with higher rates of the ACE DD allele in the completed suicide group. Among individuals carrying the DD allele, the OR for completed suicide was 2.4 (95%CI: 1.2-4.8) when compared to II and ID

bearers. In the second study, 588 patients hospitalized following a suicide attempt were compared to 639 healthy controls. While statistically significant higher frequencies of the D allele were reported among cases, differences between groups with respect to genotype frequencies were not statistically significant.

On the other hand, a 2006 study carried out in Japan[42] looked at possible associations between suicide and functional polymorphisms in ACE gene and three other RAS-related genes: angiotensin, angiotensin type-1 receptor, and GNB3. A total of 166 completed suicides and an equal number of unrelated controls were included in the analysis. While there were no statistically significant differences between groups with regards to genotype distributions, the I allele frequency of the ACE insertion/deletion (ACE I/D) polymorphism was significantly higher in the complete suicide group, specifically in males. The risk of suicide among male individuals with the I allele was found to be more than 50% higher (OR: 1.55, 95%CI: 1.07-2.26). Furthermore, among male I/I homozygotes, the risk of suicide was estimated as more than 80% higher (OR: 1.84, 95%CI: 1.08–3.12). Even though the results in question did not remain positive after correction for multiple comparisons, since the I allele is associated with low ACE levels, these results suggest that decreased RAS activity could contribute to elevations in suicide risk. These findings were partially replicated by Fudalej *et al*[43], who described an increased frequency of the ACE I allele among male victims of suicide compared to male controls (OR: 1.69, $P < 0.006$).

DISCUSSION

The evidence outlined above points to associations between RAS activity and suicide risk. Despite the great variability of the results, the most replicated findings suggest a higher risk of suicidal behavior among carriers of the ACE gene DD allele. Results from epidemiological studies are less consistent, with different patterns of association between suicidal behavior and use of RAS medications.

Several theories aiming at explaining the putative pathophysiological mechanisms responsible for the relationship between RAS activity and suicidal behavior have been formulated. One of the most frequently discussed hypothesis is based on the described interactions between RAS, stress regulation, and the HPA axis. This is of particular importance given the recent attention given to the role of HPA axis hyperactivation as a possible diagnostic-independent suicide biomarker[44]. Elevated HPA activity contributes to the development of depression, which, on its turn, is associated with higher risks of suicide. Therefore, this mechanism provides a simple and straightforward explanation for the hypothesized relationship between increased RAS function and suicide risk, as suggested by the genetic studies describing higher rates of suicide among ACE D allele carriers (who show increased ACE activity) and the epidemiological data pointing to lower risk of suicidal behavior in individuals receiving RAS medications.

On the other hand, there are also findings indicating that suicidal patients with depression, in comparison to non-suicidal ones, might show decreased HPA response and lower cerebrospinal fluid levels of CRH[45,46]. In consonance with the results of the studies pointing to correlations between suicide and the ACE I allele, associated with decreased ACE activity, and the description of reduced aldosterone levels among suicidal MDD patients, those findings suggest that, in fact, decreased RAS activity could contribute to elevation in the risk of suicide.

How to explain these apparently conflicting findings? It has been proposed that the relationship between RAS activity and HPA axis might actually be bidirectional, with the RAS system not only having direct effects in the regulation of the HPA axis but also suffering downstream effects of increased HPA activity[14]. In rats, the expression of angiotensin 1 receptors seems to increase as a result of stress exposure[22], and this effect might be mediated by HPA axis-modulated increases in cortisol levels. As demonstrated in another animal study, the number of angiotensin 1 receptors in the brain was significantly decreased by adrenalectomy, and this effect was reversed by the administration of corticosteroids[47]. Therefore, one can hypothesize that, in some suicidal individuals, elevations in the HPA axis could bring about reductions in angiotensin 1 receptor expression which could lead to increases in the circulating brain levels of angiotensin II and, in its turn, produce compensatory reductions in ACE levels and downstream RAS activity through negative feedback. The exact mechanisms involved in this putative self-regulatory interaction between HPA axis and RAS are still poorly understood, and it is not clear either, in light of available evidence, whether the different ACE gene polymorphisms described above could have

distinct impacts on the modulation of this interaction.

Moreover, the different case-control studies reported show different patterns of association between use of RAS medications and suicide risk. While the study by Mamdani *et al*[18] pointed to increased risk of suicide associated with the use of ARBs but not ACE inhibitors, other studies failed to identify increases in suicide risk among ARB users. The study in question has received some criticism with respect to certain methodological limitations, some of which related to the age range of the subjects included in the study (which included only individuals 65 years and older), the lack of better characterization of the groups in terms of their psychiatric history and comorbidity, and other limitations inherent to case-control studies[19]. Still, one possible explanation to the reported elevation in suicide risk associated with ARBs but not ACE inhibitors involves interactions between RAS and substance P. Evidence indicates that the RAS plays a role in the regulation of substance P, with increases in ACE activity resulting in correspondent angiotensin II-mediated elevations in substance P levels in the brain[24,34,48]. The D allele of the ACE gene, which is associated with a higher risk of affective disorders, is correlated with elevated levels of substance P in the basal ganglia and substantia nigra[24]. Further, increases in substance P activity seem to be associated with anxiety and mood symptomatology, and substance P receptor antagonists have been investigated as for their possible antidepressant properties[49,50]. It has been proposed that ARBs use could result in compensatory elevations in the circulating levels of angiotensin II, leading to increases in the levels of substance P and, consequently, with elevations in the risk of suicide.

CONCLUSION

While available evidence does support the existence of an association between RAS dysfunctions and suicide, there are inconsistent findings with respect to the direction of this association. In other words, in contrast to the findings strongly suggesting that a hyperactive RAS seems to play a role in the pathophysiology of mood disorders, in the case of suicidal behavior, it is not possible to pinpoint whether increased or decreased RAS contributes to elevations in the risk of suicide and even if a direct cause-and-effect relationship does exist. Moreover, it is not yet clear whether this relationship, if present, corresponds an indirect effect, modulated by a putative role of RAS dysfunctions in the development of mood disorders and other psychiatric conditions (which would, by default, bring about increases in the risk of suicide) or results from an independent effect of RAS dysfunctions on the neurobiological mechanisms associated with suicide. Given the importance of suicide and the urgent need for interventions aiming at improving its prevention, a better understanding of the involvement of the RAS in its pathophysiology would have profound implications for psychiatry, neuroscience, and public health.

REFERENCES

1 **Capuzzi E**, Caldiroli A, Capellazzi M, Tagliabue I, Buoli M, Clerici M. Biomarkers of suicidal behaviors: A comprehensive critical review. *Adv Clin Chem* 2020; **96**: 179-216 [PMID: 32362318 DOI: 10.1016/bs.acc.2019.11.005]

2 **Naguy A**, Elbadry H, Salem H. Suicide: A Précis! *J Family Med Prim Care* 2020; **9**: 4009-4015 [PMID: 33110803 DOI: 10.4103/jfmpc.jfmpc_12_20]

3 **Bachmann S**. Epidemiology of Suicide and the Psychiatric Perspective. *Int J Environ Res Public Health* 2018; **15** [PMID: 29986446 DOI: 10.3390/ijerph15071425]

4 **Sisti DA**, Joffe S. Implications of Zero Suicide for Suicide Prevention Research. *JAMA* 2018; **320**: 1633-1634 [PMID: 30286223 DOI: 10.1001/jama.2018.13083]

5 **Lépine JP**, Briley M. The increasing burden of depression. *Neuropsychiatr Dis Treat* 2011; **7**: 3-7 [PMID: 21750622 DOI: 10.2147/NDT.S19617]

6 **Tondo L**, Vázquez GH, Baldessarini RJ. Prevention of suicidal behavior in bipolar disorder. *Bipolar Disord* 2021; **23**: 14-23 [PMID: 33037692 DOI: 10.1111/bdi.13017]

7 **Isometsä ET**. Suicides in Mood Disorders in Psychiatric Settings in Nordic National Register-Based Studies. *Front Psychiatry* 2020; **11**: 721 [PMID: 32848909 DOI: 10.3389/fpsyt.2020.00721]

8 **Oquendo MA**, Sullivan GM, Sudol K, Baca-Garcia E, Stanley BH, Sublette ME, Mann JJ. Toward a Biosignature for Suicide. *American Journal of Psychiatry* 2014; **171**: 1259-1277 [PMID: 25263730 DOI: 10.1176/appi.ajp.2014.14020194]

9 **Mann JJ**, Rizk MM. A Brain-Centric Model of Suicidal Behavior. *Am J Psychiatry* 2020; **177**: 902-916 [PMID: 32998550 DOI: 10.1176/appi.ajp.2020.20081224]

10 **Pandey GN**. Biological basis of suicide and suicidal behavior. *Bipolar Disord* 2013; **15**: 524-541 [PMID: 23773657 DOI: 10.1111/bdi.12089]

11 **Courtet P**, Olié E. Neurobiology of suicidal behavior and social stress. *J Neurosci Res* 2020; **98**: 579-580 [PMID: 31984501 DOI: 10.1002/jnr.24573]

12 **de Góis Queiroz AI**, Medeiros CD, Ribeiro BM, de Lucena DF, Macêdo DS. Angiotensin receptor blockers for bipolar disorder. *Med Hypotheses* 2013; **80**: 259-263 [PMID: 23265360 DOI: 10.1016/j.mehy.2012.11.043]

13 **Rocha NP**, Simoes E Silva AC, Prestes TRR, Feracin V, Machado CA, Ferreira RN, Teixeira AL, de Miranda AS. RAS in the Central Nervous System: Potential Role in Neuropsychiatric Disorders. *Curr Med Chem* 2018; **25**: 3333-3352 [PMID: 29484978 DOI: 10.2174/0929867325666180226102358]

14 **Sanches M**, Colpo GD, Cuellar VA, Bockmann T, Rogith D, Soares JC, Teixeira AL. Decreased Plasma Levels of Angiotensin-Converting Enzyme Among Patients With Bipolar Disorder. *Front Neurosci* 2021; **15**: 617888 [PMID: 33642980 DOI: 10.3389/fnins.2021.617888]

15 **Mohite S**, Sanches M, Teixeira AL. Exploring the Evidence Implicating the Renin-Angiotensin System (RAS) in the Physiopathology of Mood Disorders. *Protein Pept Lett* 2020; **27**: 449-455 [PMID: 31868144 DOI: 10.2174/0929866527666191223144000]

16 **de Souza Gomes JA**, de Souza GC, Berk M, Cavalcante LM, de Sousa FC, Budni J, de Lucena DF, Quevedo J, Carvalho AF, Macêdo D. Antimanic-like activity of candesartan in mice: Possible involvement of antioxidant, anti-inflammatory and neurotrophic mechanisms. *Eur Neuropsychopharmacol* 2015; **25**: 2086-2097 [PMID: 26321203 DOI: 10.1016/j.euroneuro.2015.08.005]

17 **Braszko JJ**, Karwowska-Polecka W, Halicka D, Gard PR. Captopril and enalapril improve cognition and depressed mood in hypertensive patients. *J Basic Clin Physiol Pharmacol* 2003; **14**: 323-343 [PMID: 15198305 DOI: 10.1515/jbcpp.2003.14.4.323]

18 **Mamdani M**, Gomes T, Greaves S, Manji S, Juurlink DN, Tadrous M, Kennedy SH, Antoniou T. Association Between Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and Suicide. *JAMA Netw Open* 2019; **2**: e1913304 [PMID: 31617924 DOI: 10.1001/jamanetworkopen.2019.13304]

19 **Andrade C**. Angiotensin Receptor Blockers and the Risk of Suicide: An Exercise in the Critical Examination of a Case-Control Study. *J Clin Psychiatry* 2020; **81** [PMID: 31967746 DOI: 10.4088/JCP.20f13238]

20 **Katz IR**. Concerns Raised by a Study of Suicide as an Adverse Drug Effect-Replicating Findings From Real-World Data. *JAMA Netw Open* 2019; **2**: e1913284 [PMID: 31617919 DOI: 10.1001/jamanetworkopen.2019.13284]

21 **Pavlatou MG**, Mastorakos G, Lekakis I, Liatis S, Vamvakou G, Zoumakis E, Papassotiriou I, Rabavilas AD, Katsilambros N, Chrousos GP. Chronic administration of an angiotensin II receptor antagonist resets the hypoth-alamic-pituitary-adrenal (HPA) axis and improves the affect of patients with diabetes mellitus type 2: preliminary results. *Stress* 2008; **11**: 62-72 [PMID: 17853061 DOI: 10.1080/10253890701476621]

22 **Castren E**, Saavedra JM. Repeated stress increases the density of angiotensin II binding sites in rat paraventricular nucleus and subfornical organ. *Endocrinology* 1988; **122**: 370-372 [PMID: 3335214 DOI: 10.1210/endo-122-1-370]

23 **Baghai TC**, Binder EB, Schule C, Salyakina D, Eser D, Lucae S, Zwanzger P, Haberger C, Zill P, Ising M, Deiml T, Uhr M, Illig T, Wichmann HE, Modell S, Nothdurfter C, Holsboer F, Müller-Myhsok B, Möller HJ, Rupprecht R, Bondy B. Polymorphisms in the angiotensin-converting enzyme gene are associated with unipolar depression, ACE activity and hypercortisolism. *Mol Psychiatry* 2006; **11**: 1003-1015 [PMID: 16924268 DOI: 10.1038/sj.mp.4001884]

24 **Arinami T**, Li L, Mitsushio H, Itokawa M, Hamaguchi H, Toru M. An insertion/deletion polymorphism in the angiotensin converting enzyme gene is associated with both brain substance P contents and affective disorders. *Biol Psychiatry* 1996; **40**: 1122-1127 [PMID: 8931914 DOI: 10.1016/s0006-3223(95)00597-8]

25 **Ren L**, Lu X, Danser AHJ. Revisiting the Brain Renin-Angiotensin System-Focus on Novel Therapies. *Curr Hypertens Rep* 2019; **21**: 28 [PMID: 30949864 DOI: 10.1007/s11906-019-0937-8]

26 **Saavedra JM**. Angiotensin II AT(1) receptor blockers as treatments for inflammatory brain disorders. *Clin Sci (Lond)* 2012; **123**: 567-590 [PMID: 22827472 DOI: 10.1042/CS20120078]

27 **Dagenais NJ**, Jamali F. Protective effects of angiotensin II interruption: evidence for antiinflammatory actions. *Pharmacotherapy* 2005; **25**: 1213-1229 [PMID: 16164395 DOI: 10.1592/phco.2005.25.9.1213]

28 **Du YC**, Xu JY, Zhang SJ. Effects of angiotensin II receptor antagonist on expression of collagen III, collagen V, and transforming growth factor beta1 in the airway walls of sensitized rats. *Chin Med J (Engl)* 2004; **117**: 908-912 [PMID: 15198897]

29 **Hammer A**, Stegbauer J, Linker RA. Macrophages in neuroinflammation: role of the renin-angiotensin-system. *Pflugers Arch* 2017; **469**: 431-444 [PMID: 28190090 DOI: 10.1007/s00424-017-1942-x]

30 **Mesure G**, Fallet A, Chevalier JF. [Psychotropic effects of angiotensin-converting enzyme inhibitors: what are the arguments? *Encephale* 1995; **21**: 609-614 [PMID: 8529571]

31 **Lindberg G**, Bingefors K, Ranstam J, Råstam L, Melander A. Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population based cohort study. *BMJ* 1998; **316**: 741-745 [PMID: 9529409 DOI: 10.1136/bmj.316.7133.741]

32 **Sùrensen HT**, Mellemkjĩr L, Olsen JH. Risk of suicide in users of b-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. *Br J Clin Pharmacol* 2001; **52**: 313-318 [PMID: 11560564 DOI: 10.1046/j.0306-5251.2001.01442.x]

33 **Callréus T**, Agerskov Andersen U, Hallas J, Andersen M. Cardiovascular drugs and the risk of suicide: a nested case-control study. *Eur J Clin Pharmacol* 2007; **63**: 591-596 [PMID: 17468865 DOI: 10.1007/s00228-007-0293-5]

34 **Dent KR**, Griffin CA, McCarthy JF, Katz IR. Hypertension Treatment Modality and Suicide Risk Among Veterans in Veterans Health Administration Care From 2015 to 2017. *JAMA Netw Open* 2020; **3**: e2020330 [PMID: 33044550 DOI: 10.1001/jamanetworkopen.2020.20330]

35 **Lin SY**, Lin CL, Lin CC, Hsu WH, Lin CD, Wang IK, Hsieh MH, Hsu CY, Kao CH. Association between angiotensin receptor blockers and suicide: nationwide population-based propensity score matching study. *J Affect Disord* 2020; **276**: 815-821 [PMID: 32738666 DOI: 10.1016/j.jad.2020.07.106]

36 **Köhler-Forsberg O**, Petersen L, Berk M, Gasse C, Østergaard SD. The effect of combined treatment with SSRIs and renin-angiotensin system (RAS) drugs: A propensity score matched cohort study. *Eur Neuropsychopharmacol* 2020; **32**: 120-130 [PMID: 32001138 DOI: 10.1016/j.euroneuro.2020.01.004]

37 **Arregui A**, Mackay AV, Spokes EG, Iversen LL. Reduced activity of angiotensin-converting enzyme in basal ganglia in early onset schizophrenia. *Psychol Med* 1980; **10**: 307-313 [PMID: 6247736 DOI: 10.1017/s0033291700044068]

38 **Hallberg L**, Westrin A, Isaksson A, Janelidze S, Träskman-Bendz L, Brundin L. Decreased aldosterone in the plasma of suicide attempters with major depressive disorder. *Psychiatry Res* 2011; **187**: 135-139 [PMID: 20797799 DOI: 10.1016/j.psychres.2010.07.038]

39 **Hong CJ**, Wang YC, Tsai SJ. Association study of angiotensin I-converting enzyme polymorphism and symptomatology and antidepressant response in major depressive disorders. *J Neural Transm (Vienna)* 2002; **109**: 1209-1214 [PMID: 12203048 DOI: 10.1007/s00702-001-0686-z]

40 **Ghorbani E**, Mohammadi M, Malakouti SK, Mohammadi-Kangarani H, Abdollahi E, Torab M, Rahimi-Moghaddam P. Association of ACE Gene Insertion/Deletion Polymorphism with Suicidal Attempt in an Iranian Population. *Biochem Genet* 2021; **59**: 31-41 [PMID: 32720141 DOI: 10.1007/s10528-020-09986-7]

41 **Sparks DL**, Hunsaker JC 3rd, Amouyel P, Malafosse A, Bellivier F, Leboyer M, Courtet P, Helbecque N. Angiotensin I-converting enzyme I/D polymorphism and suicidal behaviors. *Am J Med Genet B Neuropsychiatr Genet* 2009; **150B**: 290-294 [PMID: 18521860 DOI: 10.1002/ajmg.b.30793]

42 **Hishimoto A**, Shirakawa O, Nishiguchi N, Hashimoto T, Yanagi M, Nushida H, Ueno Y, Maeda K. Association between a functional polymorphism in the renin-angiotensin system and completed suicide. *J Neural Transm (Vienna)* 2006; **113**: 1915-1920 [PMID: 16736244 DOI: 10.1007/s00702-006-0483-9]

43 **Fudalej S**, Fudalej M, Kostrzewa G, Kuźniar P, Franaszczyk M, Wojnar M, Krajewski P, Płoski R. Angiotensin-converting enzyme polymorphism and completed suicide: an association in Caucasians and evidence for a link with a method of self-injury. *Neuropsychobiology* 2009; **59**: 151-158 [PMID: 19439995 DOI: 10.1159/000218077]

44 **Berardelli I**, Serafini G, Cortese N, Fiaschè F, O'Connor RC, Pompili M. The Involvement of Hypothalamus-Pituitary-Adrenal (HPA) Axis in Suicide Risk. *Brain Sci* 2020; **10** [PMID: 32967089 DOI: 10.3390/brainsci10090653]

45 **Träskman-Bendz L**, Ekman R, Regnéll G, Ohman R. HPA-related CSF neuropeptides in suicide attempters. *Eur Neuropsychopharmacol* 1992; **2**: 99-106 [PMID: 1378770 DOI: 10.1016/0924-977x(92)90018-4]

46 **Pfennig A**, Kunzel HE, Kern N, Ising M, Majer M, Fuchs B, Ernst G, Holsboer F, Binder EB. Hypothalamus-pituitary-adrenal system regulation and suicidal behavior in depression. *Biol Psychiatry* 2005; **57**: 336-342 [PMID: 15705348 DOI: 10.1016/j.biopsych.2004.11.017]

47 **Castrén E**, Saavedra JM. Angiotensin II receptors in paraventricular nucleus, subfornical organ, and pituitary gland of hypophysectomized, adrenalectomized, and vasopressin-deficient rats. *Proc Natl Acad Sci U S A* 1989; **86**: 725-729 [PMID: 2911602 DOI: 10.1073/pnas.86.2.725]

48 **Ebner K**, Singewald N. The role of substance P in stress and anxiety responses. *Amino Acids* 2006; **31**: 251-272 [PMID: 16820980 DOI: 10.1007/s00726-006-0335-9]

49 **Lang UE**, Borgwardt S. Molecular mechanisms of depression: perspectives on new treatment strategies. *Cell Physiol Biochem* 2013; **31**: 761-777 [PMID: 23735822 DOI: 10.1159/000350094]

50 **Argyropoulos SV**, Nutt DJ. Substance P antagonists: novel agents in the treatment of depression. *Expert Opin Investig Drugs* 2000; **9**: 1871-1875 [PMID: 11060783 DOI: 10.1517/13543784.9.8.1871]

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MINIREVIEWS

Cognitive attentional syndrome and metacognitive beliefs as potential treatment targets for metacognitive therapy in bipolar disorder

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Abstract

Most treatment guidelines emphasize the use of psychotropic drugs for both the acute and maintenance treatment of bipolar disorder (BD). However, relying only on psychotropics without adjunctive psychosocial interventions may be insufficient in treating patients with BD. Given its unique view in the explanation of psychopathological states, metacognitive therapy (MCT) might be helpful for BD. Metacognitive theory posits that psychopathology is a result of the cognitive attentional syndrome (CAS) and that it is influenced and maintained by dysfunctional metacognitive beliefs, perseverative thinking, attentional biases, and dysfunctional coping strategies. In this review, literature data regarding these areas in BD are examined. Studies suggest that perseverative thinking might be among the emotion regulation strategies endorsed in individuals with BD. Regarding attentional biases, literature data show that state-dependent, mood-changing attentional biases and a ruminative self-focused attention are present. Studies also suggest that cognitive self-consciousness is higher in BD compared to controls. It is seen that maladaptive coping strategies are frequently reported in BD, and that these strategies are associated with depression severity, negative affect and relapse risk. Studies focusing on dysfunctional metacognitive beliefs in BD reported that individuals with BD had higher scores for negative metacognitive beliefs, self-consciousness, need to control thoughts, and a lack of cognitive confidence. Also, dysfunctional metacognitive beliefs were associated with depressive symptomatology. These findings suggest that the components of CAS

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and dysfunctional metacognitive beliefs are evident in BD. For a subgroup of patients with BD who fail to respond to evidence-based psychopharmacological and adjunctive psychotherapeutic interventions, MCT might be an alternative way to consider as a treatment option. In conclusion, taken the available data together, we propose a sequential treatment protocol for BD, mainly based on the MCT treatment plan of depressive disorders.

Key Words: Attentional biases; Bipolar disorder; Dysfunctional coping; Metacognition; Metacognitive therapy; Perseverative thinking; Threat monitoring

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Core Tip: Relying only on psychotropics without adjunctive psychosocial interventions may be insufficient in treating patients with bipolar disorder (BD). Given its unique view in the explanation of psychopathological states, metacognitive therapy (MCT) might be helpful. In this review, literature data regarding dysfunctional metacognitive beliefs, perseverative thinking, attentional biases, and dysfunctional coping strategies in BD are examined. Findings suggest that dysfunctional metacognitive beliefs are evident in BD. Taken the available data together, we lastly propose a sequential treatment protocol for BD, mainly based on the MCT treatment plan of depressive disorders.

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INTRODUCTION

Treatment of bipolar disorder (BD) is complex. Most treatment guidelines emphasize the use of psychotropic drugs for both the acute and maintenance treatment of BD[1-4]. However, psychotropics alone without adjunctive psychosocial interventions does not come close to meeting the outcome expectations of providers and patients[5]. Therefore, the effectiveness of many psychotherapeutic interventions has been investigated[6-9]. A recent meta-analysis concluded that adjunctive psychotherapy that emphasizes illness management strategies and enhances adaptive coping skills may benefit individuals with BD[10]. Unfortunately, current psychotherapies also suffer from many shortcomings, and many areas of psychotherapy for BD still need to be explored[11]. Developments in the understanding of psychopathology beyond the current and conventional approaches may help clinicians to provide more efficacious and acceptable treatments to individuals with BD. Given its unique view in the explanation of psychopathological states, metacognitive therapy (MCT) may offer one of these advanced approaches.

MCT AND THEORY

Metacognitive theory posits that psychopathology results from cognitive attentional syndrome (CAS)[12], which involves perseverative thinking styles, attentional biases, and dysfunctional coping strategies. The theory also proposes that CAS is influenced and maintained by dysfunctional metacognitive beliefs. As a treatment modality, MCT targets CAS and metacognitive beliefs to break the vicious cycle in which the patient is mentally stuck.

Perseverative thinking style may manifest as worry and rumination. While worry is generally defined as asking "what if" questions about future events, rumination mostly involves asking "why" questions about past events. These forms of extended thinking cause the person to be trapped in an inescapable thought process. Persev-

erative thinking increases the negative emotional consequences of the situation at hand, takes long periods of time, and does not aid those who engage in it in solving the problems they faced in the first place. Attentional biases are presented as fixed attention on threats (threat monitoring) or focused attention on the self. As a result, those with attentional biases become more aware of their internal experiences, many of which are negative in essence, which creates a vicious cycle in which they begin to believe that their feelings reflect the reality and that feeling that particular way is appropriate. The more focused they are on their thoughts, feelings, or sensations, the greater their reactions to such stimuli. Focusing on threat cues also increases the likelihood that they will feel distressed by them. Dysfunctional coping strategies, such as thought suppression, avoidance, or substance use, are applied to reduce the feelings of distress, but conversely, those strategies backfire and make the situation worse[12]. Components of CAS are maintained by underlying metacognitive beliefs, which may be either positive or negative. Positive metacognitive beliefs generally relate to the advantageous aspects of CAS, whereas negative metacognitive beliefs mainly center on the uncontrollability of perseverative thinking or the negative consequences of engaging with the CAS[12].

Regarding depressive disorders, metacognitive theory suggests that the person, in response to negative internal experiences—mostly negative automatic thoughts or beliefs—decides to focus attention specifically to dwell on the past or on some real or imagined personal failure. This overthinking pattern may also involve focusing on worries about what may happen in the future, like the recurrence of a new depressive episode. Consequently, this selective and self-referential attentional process extends the negative thinking style, eventually forming a trap from which the person cannot escape. At the same time, the theory also proposes that the person holds some positive beliefs about the benefits of extended thinking, which may be associated with a belief that rumination will help to solve problems or to identify the root cause of negative feelings. On the other hand, the person may also believe that the excessive ruminating is uncontrollable and that it may harm his or her physical or mental well-being or result in social exclusion[13]. In addition, the person with a depressive disorder will engage in dysfunctional, backfiring coping behaviors, which may include inactivity, social withdrawal, alcohol and substance use, repetitive mood- and energy-level checking, self-harming or suicidal behaviors, avoidance of feelings and thoughts, efforts at thought control, and so on. Such beliefs about rumination and such coping behaviors are thought to be the underlying maintenance factors in depressive disorders[12].

To this end, for those with depressive disorders, an MCT therapist first identifies a trigger thought, which generally corresponds to the ruminative thinking style of the patient, and then tries to eliminate, or at least limit, the amount of time the patient spends on rumination. The therapist also works with the patient to find ways to abandon any attentional biases, which generally consist of self-referential, self-focused attention and threat monitoring, and ways to stop engaging with any dysfunctional, backfiring coping strategies. In MCT, additionally, the therapist focuses on identifying and reality-checking any positive and negative metacognitive beliefs so that any maintaining factor is targeted and eliminated[13].

A recent meta-analysis concluded that MCT may be at least as effective as cognitive behavioral therapy for treating depressive disorders[14]. Whether MCT may also be effective for treating BD has yet to be explored. Currently, the literature on the effectiveness of MCT for treating BD is minimal. In the only case series on the application of MCT in individuals with BD type II published thus far, MCT was found to effectively make clinically significant improvements within 7-12 therapy sessions[15].

This review aimed to focus on any developments in the literature that highlight factors associated with the metacognitive model of BD therapy and to propose a theoretical framework for applying MCT for BD. We begin this paper with a summary of what is already known and reported in the literature and identify where the gaps in the research lie, and we end with a theoretical suggestion for the application of MCT for BD patients.

CAS IN BD

Since MCT is transdiagnostic in its approach to psychopathology, CAS in BD also consists of perseverative thinking, attentional biases, and dysfunctional coping strategies. Dysfunctional metacognitive beliefs are the underlying maintenance factors in BD, as they are in any other psychiatric disorder. Some examples of CAS and

dysfunctional metacognitive beliefs that may be encountered in patients with BD are presented in Table 1.

PERSEVERATIVE (EXTENDED) THINKING (RUMINATION AND WORRY)

Adaptive and maladaptive emotion regulation strategies have been defined as transdiagnostic processes[16]. Two recent articles discussed reviews that examined how individuals with BD try to regulate their internal experiences[17,18]. These articles stated that perseverative thinking may be among the emotion regulation strategies endorsed in individuals with BD and in individuals at risk for mania. Although many other forms of perseverative thinking exist, most studies have focused on rumination and, to a lesser extent, on worry in BD patients.

Two earlier reviews on rumination related to BD suggested that rumination, which was present in all phases of the disorder, was independent of the mood state of the individual, although closely related to it. In addition to depressive rumination, which was commonly associated with depressive phases in both major depressive disorder and BD, individuals with BD additionally and uniquely ruminated on positive affect, which can influence the triggering of new episodes. Rumination was also found to have negative consequences on cognitive and executive functions, most importantly, inhibitory control[19,20]. Another review proposed that spontaneous thoughts can predict depressive episodes and BD *via* the mediation of rumination, particularly if it is self-focused, past-focused, or associated with abstract processing and if cognitive control is reduced. Such spontaneous thoughts may be relevant for future BD episodes if they are characterized by goal-striving and if they are frequent, self-centered, and focused on grandiose successes[21].

A recent meta-analysis on rumination associated with BD revealed no significant differences in rumination in general or in depressive rumination between individuals with BD and those with major depressive disorder. However, individuals with BD reported ruminating more often on positive affect than those with major depressive disorder. The results also demonstrated that, albeit non-significant, when comparing BD subtypes with major depressive disorder, a tendency toward more rumination in general in favor of BD type I was observed. This tendency was not observed for individuals with BD type II[22].

Studies published since, or not included in, this meta-analysis have demonstrated similar findings regarding the frequency of rumination and maladaptive emotion regulation strategies in BD patients. Interestingly, increased rumination was found to be a mediator between anxiety levels and suicide behaviors in individuals with BD[23, 24]. Negative rumination has also been proposed as a mediator between traumatic distress and hypomania levels[25]. Another study comparing euthymic BD individuals with healthy controls indicated that both subtypes ruminated more frequently but that they did not worry more. The researchers of that study also suggested that depressive rumination may be a trait-specific feature of BD[26]. Trait rumination—specifically, rumination on positive emotions—was reported to be a characteristic of individuals with remitted BD[27]. Based on a study in which individuals with BD types I and II were compared with individuals with major depressive disorder and healthy controls, the researchers reported that individuals with both BD subtypes ruminated more frequently than the healthy controls did but not more than the individuals with unipolar depression[28]. Further, in a study for which individuals with both subtypes of BD who were either in an acute depressive episode or in remission were recruited, the participants were found to score higher on the rumination scale than the healthy controls. In this study, however, individuals with BD did not differ significantly from the healthy controls on self-focused positive rumination, and they even scored significantly lower than the control subjects on emotion-focused positive rumination [29]. An earlier study with a controversial result claimed that rumination was more evident in individuals with BD in the remitted phase than in the depressive phase[30]. The authors of another research paper concluded that the processes of dampening and emotion-focused positive rumination played important roles for individuals with BD [31]. Additional research focusing on positive rumination in individuals with BD revealed that these individuals endorsed more responses focused on positive affect and that these responses were explained by the level of hypomanic symptoms[32-34]. Unexpectedly, depressive rumination was also associated with hypomania severity in previous reports[35-38]. Moreover, depressive rumination was associated with lower self-esteem scores in individuals who were considered at high risk for BD[39].

Table 1 Examples of the components of the cognitive attentional syndrome and dysfunctional metacognitive beliefs in bipolar disorder

	Depressive phase	Hypo/manic phase
Perseverative thinking	"Why am I so depressed? What is the point in living any more? What is the root cause of my depression? Why can't I just snap out of this feeling?"	"I can do whatever I like, I have never been stronger! I feel so great, and this feeling must last forever."
	"What if I never get better? Will I always feel like this? What if I have a recurrence?"	"How dare they think that I should not be doing the things I want to? Nobody has the right to tell me what I am allowed to do."
		"What if my mood deteriorates? What if I start to feel depressed again? Will my health never be like everyone else's?"
Attentional biases and threat monitoring	Constant mood monitoring, self-focused attention, focusing on any changes in depressive symptomatology, checking energy levels, body scanning for early warning signs of recurrence	Constant mood monitoring, self-focused attention, focusing on any changes in hypo/manic symptomatology, checking energy levels, body scanning for early warning signs of recurrence
Dysfunctional coping strategies	Thought control, inactivity, self-harm, alcohol/substance use, emotional avoidance, social withdrawal	Thought control, hyperactivity, impulsivity, alcohol/substance use, emotional overindulgence, increased social interaction
Negative metacognitive beliefs	"Rumination is uncontrollable. Worrying will harm me. If my energy level changes during the day, this means that I am about to get depressed."	"Rumination is out of my control. Worrying too much might harm me. I have a broken brain. My genes are responsible for my disorder, and there is no way to cure it."
	"My friends will leave me because of my never-ending rumination."	"I can not form stable relationships because of my bipolar disorder. This has ruined my life."
Positive metacognitive beliefs	"Rumination will help me identify the cause of my depression. Worrying keeps me prepared for any unwanted consequences. Checking my mood will tell me when I am at risk for depression."	"Thinking about my positive mood will make my day better. The more time I spend time on my heightened energy, the less probable that I fall back to my depression. Worrying that I may experience a relapse will help me identify any early warning signs."

The subject of worry in BD patients has not attracted the same amount of scholarly attention as rumination. Nevertheless, individuals with BD type I and II were found to worry more frequently than healthy controls but not more than individuals with unipolar depression[28]. Similar results indicating individuals with BD worried more than healthy controls were also found in an earlier study[40]. However, these results were not replicated in a more recent study[26]. An examination of the frequency of worry in the different phases of BD revealed that worry was more often endorsed by individuals in their depressed phase compared to individuals in their manic phase, underlying the importance of mood state[41].

In summary, perseverative thinking has been found to be an important feature of BD, and many studies have identified its role in the severity, risk of relapse, and maintenance of BD. However, still unclear is how exactly perseverative thinking is associated with BD and whether any change in its frequency may impact the prognosis for BD. Also as yet undetermined are whether rumination and worry may differentially affect individuals with BD and whether targeting them specifically may be appropriate according to the phase of BD. More research is undoubtedly necessary to clarify if and to what degree MCT is effective in reducing perseverative thinking in BD patients. To this end, carefully designed, randomized controlled trials with sample sizes sufficient to detect clinically significant effect sizes are needed.

ATTENTIONAL BIASES (SELF-FOCUSED ATTENTION AND THREAT MONITORING)

To date, many studies have been conducted on the neurocognition of BD that have produced conflicting results due to cognitive heterogeneity and methodological differences. Factors such as different clinical and neuropsychological presentations of BD, different tools used in neuropsychological measurements, difficulties in excluding drug effects, and insufficient statistical power of sample sizes are some of the challenges to reaching consensus on the neurocognition of BD[42]. Nevertheless, more consistent results have been obtained regarding the neurocognition of BD in some domains, such as executive functions, verbal memory, and sustained attention[43].

In the literature, sustained attention is often measured with a computerized test called continuous performance test (CPT), while distinct attentional domains can be evaluated with tests like the Trail Making Test, Stroop Color-Word Association Test, and Digit Span[44]. In the CPT, a selection of stimuli is presented to the subject in an unpredictable way to focus the subject's attention. Several outcome criteria may be

obtained, such as omission error (failure to respond to the required target, which is a measure of target sensitivity), commission error (erroneous response to a non-target, which is a measure of false alarm), total number of correct responses, and reaction time[45]. Impairments have been suggested to be present in different attentional domains in particular episodes of BD[46].

In the first review regarding the attentional processes of BD patients, commission and omission errors were reported to be significantly present in manic patients and target detection (omission) errors were reported as persisting in patients with BD during remission[44]. Sustained attention deficit in BD, which is persistent in euthymia and is exacerbated in the active disorder period, has been suggested as a state-modulated deficit[47]. This finding was replicated in subsequent studies; additionally, state-dependent impairments have been proposed to be unrelated to medication, while deficits that become widespread in the acute episode may be partially related to medication[48]. Study findings have also indicated that distinguishing drug-related deficits from disease-related deficits is difficult and that drugs may have a certain degree of adverse effects on psychomotor speed and sustained attention. However, in first-episode and drug-naive patients, the cognitive deficits detected were similar to those of patients with long-term drug use[49]. This reflects the need for appropriately designed studies that can demonstrate drug effects more clearly.

Regarding attentional processes in BD subtypes, although several prior studies suggested that BD type I may be related to worse attentional performance, more recent studies uncovered that both subtypes were associated with similar attentional impairment during euthymia and that the differences between them may be related to antipsychotics, which were more likely to be used in BD type I[50]. Current meta-analyses and reviews regarding the differences between BD types I and II also suggest that the severity of attentional impairment in BD type II is similar to the severity of such impairment in BD type I[42,43,49,51]. The effect size related to attentional impairment in BD has been reported as small to medium[43,52].

Attentional bias is one of the areas that has been increasingly investigated in BD studies in recent years. In the literature, attentional bias is investigated by using tests like the dot-probe task and the affective go/no-go test and by examining attentional biases against faces and words that have affective components. In one of the earliest studies in this field, Jongen *et al*[53] found that mildly depressed patients directed their attention away from depression-related and positive words and reported this finding was mood state-dependent. They also found that the bias away from positive words could also be seen in euthymia, which may be part of a trait effect. In a study that evaluated these findings in both BD patients and their relatives, the relatives did not differ significantly from the control group in terms of attentional biases. However, mildly depressed patients exhibited attentional biases similar to those observed in the study from Jabben *et al*[54]. In another study involving people on the bipolar spectrum, the subjects were found to have a negative self-referent information processing bias that was partially mediated by depressive symptomatology[55]. On the other part of the spectrum, manic patients were found to show no attentional vigilance to happy or sad expressions, but they avoided sad expressions and focused more on happy expressions in later emotion processing[56]. Like the study by Liu *et al* [56], Gruber *et al*[57] investigated the relationship between attentional biases and hypomania proneness. Gruber and associates found that hypomania proneness was positively associated with attentional bias toward happy, but not angry or fearful, faces. These findings show distinct attentional biases may be present in both depressive and manic episodes.

These consistent results regarding attentional biases in BD, especially in depressive episodes, were confirmed in subsequent studies. However, results regarding attentional biases in euthymia were conflicting. Several studies revealed that, regardless of the episode, attentional biases were present and an increased attention to threat may be a trait-based vulnerability[58,59]. However, in a larger sampled study, no differences in attentional bias were found compared to controls in euthymia[60]. Factors such as the inability to exclude drug effects, small sample sizes, and different clinical and neuropsychological presentations of BD may have caused these inconsistent results. Taken together, attentional bias is especially apparent in the depressive episode in BD, and this effect may be state-dependent.

Recent studies also suggest the existence of biases regarding threat in BD. Increased threat sensitivity is characterized by enhanced attentional biases toward negative stimuli and away from positive stimuli and it has been viewed as enhancing the need for cognitive control[61,62]. Threat sensitivity has also been associated with depressive and anxiety disorders in the past, and recently, findings have shown that it may also

be associated with BD[63-65]. One study demonstrated that threat sensitivity is increased in those with BD, in which anxiety disorder comorbidity is up to 60%[66]. Similar findings were found in another study conducted in a pediatric BD group that revealed that children with BD and anxiety disorder comorbidity had a bias toward threat compared to those without anxiety[67]. The same study also showed that hypo/mania scores were related to a greater bias toward threatening faces, with the authors stating that "current mood state also influences threat-related attention biases" [67]. These findings, which were also present in the pediatric group, indicate that further research is required on neurodevelopmental effects on attentional biases.

A particular way of threat monitoring encountered in individuals with BD is constant mood monitoring and body scanning to determine if energy levels are somehow predictive of a new depressive episode. An early study concluded that mood monitoring implied that individuals had to be vigilant to track any changes in their mood state, which could result in repeatedly checking it but remaining confused about its nature. With an analogy to hypochondriasis, the authors suggested that the individuals' judgments about their moods could be clouded by an absorption in their mood state. Indeed, mood monitoring has been repeatedly associated with an increased self-focus, resulting in rumination and negative affectivity[68]. More recent research also demonstrated that, despite evidence to the contrary, some individuals may shift into a more depressive mood state after frequent assessment of their negative symptoms[69]. In fact, over 10% of individuals with BD reported that self-monitoring did not help to maintain their health, whereas over 25% of the participants in this survey reported that they were not sure whether self-monitoring had any effect on their health[70], confirming the earlier suggestion that repeated assessments may cloud their judgments. Such concerns were echoed in more recent surveys. Participants informed the researchers that their mood monitoring could potentially become preoccupying and unhelpful and that they might interpret their conclusions about their mood as negative when they were actually feeling well. Participants were also concerned that such practices may not seem normal and that engaging in them may draw additional attention from the general public[71]. Additionally, mood monitoring did not result in significantly decreasing mania scores[72]. Given the controversies over the effectiveness of mood monitoring in BD, experts recently published recommendations on how to implement it in routine practice. They suggested that without a clear rationale for using mood monitoring, and without reviewing the procedure with the patient, this practice can be detrimental. The experts also highlighted the need to normalize everyday mood fluctuations and to distinguish them from actual signs of relapse. The recommendations also included suggestions to respond to mood changes without mood monitoring. This set of recommendations calls for caution in employing mood monitoring in individuals with BD[73].

Studies on the attentional bias in BD have brought forward the investigation of the role of self-focused attention in BD. In past studies regarding the cognition of unipolar depression, self-focused style was found to contribute to the onset and maintenance of depression[74]. In a 3.5-year follow-up study examining the effects of self-focused attention on different stages of BD, controlling for depressive and manic symptoms, bipolar patients were found to experience significantly higher levels of depressive rumination and private self-consciousness than the controls[75]. These findings seem consistent with the findings from Johnson *et al*[33] that patients with BD have a ruminative response pattern to both depressive and positive moods. Self-focused attention research seems to mostly be conducted with anxiety and depression; thus, further studies regarding the relationship between self-focused attention and BD are needed.

In terms of cognitive self-consciousness, previous research demonstrated that patients with BD reflected more frequently on themselves than patients with schizophrenia, but they did so at rates similar to those of healthy subjects. Further, focusing on the self negatively correlated with excitement and hostility[76]. The researchers of another study, comparing individuals with BD and schizophrenia, arrived at the same conclusion, indicating that self-reflection was higher in the BD group[77]. Conversely, these findings were not demonstrated in a more recent study in which individuals with BD failed to discriminate not only from individuals with schizophrenia but also from healthy controls[78]. A similar non-significant difference was reported in individuals with BD subtypes and healthy controls[26]. Cognitive self-consciousness was found to be higher in patients with BD compared to controls, and it also correlated with an earlier age of onset of an affective disorder and with the severity of depression. The severity of depressive symptomatology was the only predictor of self-focused attention, highlighting the possibility of the specific role of depressive episodes in cognitive self-consciousness[79]. However, other studies have not

replicated this finding; instead, they reported that self-focused attention may more specifically correlate with anxiety levels. Interestingly, the previous study also did not find any significant differences between individuals with unipolar or bipolar depression and healthy controls[80]. This result was obtained in a later study as well [28]. However, another study claimed that, although individuals with unipolar and bipolar depression did not differ from each other on a measure of self-focused attention, both scored higher than healthy controls. This study also reported that cognitive self-consciousness correlated weakly with both manic and depressive symptom severity[81]. On the other hand, another study showed that individuals with BD did not differ from healthy controls on cognitive self-consciousness, but cognitive self-consciousness significantly correlated with worsening in executive functioning, according to the researchers[82]. Further, a comparative study identified that the need to control thoughts was associated with thought disturbance, whereas this was not valid for individuals with schizophrenia[78]. Focusing particularly on suicide attempts in BD patients, another study reported that self-focused attention may be protective against suicide attempts. The authors suggested that being aware of one's own thoughts may alert the individual about any threatening suicidal ideations, which may prompt the individual to seek help. In this study, cognitive self-consciousness was significantly lower in the group of individuals who previously attempted suicide[83]. Given that this is a rather controversial finding and interpretation of the metacognitive model, we strongly urge waiting for further studies to confirm this finding.

In summary, the literature data on attentional biases illustrate the following: deficits in attentional processes in the euthymic period in BD, the presence of mostly commission errors, that these impairments can also be seen in people with genetic risk for BD, and that attentional impairments are widespread in patients with mania. Although not consistent, in euthymia and in relatives of patients with BD, the literature shows that state-dependent, mood-changing attentional biases and a ruminative self-focused attention are present. Studies on cognitive bias modification demonstrate that attentional biases that are present in depression may be modified and that this may lead to changes in mood and reactivity to stressful events[84,85]. In BD patients, reducing the severity of symptoms and the risk of relapse may be possible with metacognitive interventions regarding self-focused attention and attention biases.

DYSFUNCTIONAL (BACKFIRING) COPING STRATEGIES

Patients diagnosed with BD need to cope with the various problems they encounter, the outcomes of their mental disorder, and unpleasant situations in general to stay healthy[86]. Coping has various definitions. Lazarus defined coping as both thoughts and behaviors that individuals use to control the internal and external requirements of conditions that are perceived as stressful[87]. Compas *et al*[88] described coping as a self-regulatory process volitionally and purposely explicitly established in response to stress. Considering the executive dysfunction due to neurotoxicity in BD, coping abilities have been reported to play a key role in modulating the relationship between stress and episodic recurrence[89]. It was reported by Goossens *et al*[86] that, among those with euthymic BD, those who had had 10 or more acute depressive episodes throughout their lives chose a more passive coping style. In addition, outpatients with BD had a less active reaction pattern and a more avoidant coping style compared with healthy people[86].

Green *et al*[90] compared the use of certain cognitive strategies for regulating negative emotions in patients with BD type I, unaffected relatives of BD patients, and healthy controls. The results were interesting: The BD group reported more frequently using maladaptive regulatory strategies, such as rumination, catastrophizing, and self-blame, which were previously associated with depression[90]. In a paper describing another study, Paans *et al*[91] reported that better executive functioning and fewer depressive symptoms were associated with more active coping in older adults with BD. In addition, they noted that associations between executive functioning and coping styles became non-significant when the depressive symptoms in euthymic participants were considered, indicating that even subclinical depressive symptoms may negatively influence active coping[91].

Fletcher *et al*[92] aimed to address the cognitive and coping styles in patients diagnosed with BD types I or II. They indicated positive relationships existed between both BD subtypes and depressive severity and maladaptive coping styles. Furthermore, a wider variety of negative cognitive styles were associated with BD type II depression symptoms[92]. An editorial by Grunze[93] underlined the results of the

study by Fletcher *et al*[92] and stated that only low levels of seeking support to cope with stress as a coping style, which increased the likelihood of a depressive episode at follow-up, predicted BD type I depression. Grunze[93] suggested that subtype-specific identification of cognitive and coping styles may identify and quantify the risk of relapse, which may provide clinicians with a way to reduce the risk of relapse by modifying specific areas of negative cognition and maladaptive coping styles.

Pavlickova *et al*[36] reported that adaptive coping significantly predicted an increase in self-esteem, which was associated with a decrease in ruminative thinking in a specified period. Similarly, Leung *et al*[94] showed that the level of adaptive coping predicted an increase in positive affect in patients with BD.

Another study examining BD aimed to calculate the cumulative effect of childhood abuse, neuroticism, social support, and coping style on depressive symptoms. The results showed that emotional childhood abuse, neuroticism, social support use, and active coping style affected depressive symptoms and indicated that 45.6% variability in depressive symptoms could be explained by these factors[95].

Suh *et al*[96] recently studied the similarities and differences in coping styles between BD and depressive disorder patients. More avoidant and task-oriented coping was associated with individuals with BD independent of the effect of depressive symptoms. The results revealed significant negative correlations between the severity of depression and both task and avoidance-oriented coping styles in both the BD group and the depressive group. However, avoidance-related coping had a significant negative correlation with depression scores only in the BD group.

Individuals with BD tended to believe that they needed to control their thoughts more frequently than healthy controls [34,82], which was evident for both BD subtypes [26,28]. The need to control thoughts seemed to negatively affect neurocognitive functioning[82]; furthermore, individuals with BD who had previously attempted suicide scored higher than those who had never attempted suicide, suggesting that the need to control thoughts was associated with increased risk for suicide attempts[83]. Additionally, thought control strategies were associated with an earlier age of onset of an affective disorder and with the severity of a depressive episode. Individuals with BD used worry and self-punishment more frequently than the control subjects as thought control strategies, whereas they used distraction and social control less frequently than the controls[34]. However, patients with BD in a depressive episode did not differ significantly from patients with unipolar depression in the frequency of their need to control thoughts, but the need to control thoughts did positively correlate with depression severity[80,81].

In summary, maladaptive coping strategies were frequently reported in patients with BD. These strategies are found to be associated with depression severity, negative affect, and relapse risk. Metacognitive interventions that aim to change these maladaptive coping strategies may improve both disorder severity and relevant BD aspects.

DYSFUNCTIONAL (MALADAPTIVE) METACOGNITIVE BELIEFS IN BD

Dysfunctional metacognitive beliefs are known to be transdiagnostic processes. A previously published meta-analysis included participants with BD. This meta-analysis concluded that negative metacognitive beliefs (beliefs about the uncontrollability and dangerousness of thoughts), lack of cognitive confidence, heightened cognitive self-consciousness, and the need to control thoughts were more prevalent in various psychiatric disorders. The authors also suggested that although metacognitive beliefs were transdiagnostic, specificity of higher dysfunctional metacognitive beliefs was also found in different diagnostic categories[97].

Studies specifically focusing on dysfunctional metacognitive beliefs in BD individuals have recently gained interest among researchers. Compared to healthy controls, individuals with BD reported higher scores for negative metacognitive beliefs, lack of cognitive confidence, and the need to control thoughts[26,80,82]. Other studies also suggested that higher self-consciousness was evident in individuals with BD[34,81]. Contradicting previous results, Favaretto *et al*[26] further claimed that positive metacognitive beliefs were more frequently endorsed by individuals with BD type II than by healthy controls. Other research has also pointed out that fewer metacognitive deficits may be present in those with BD than in those with schizophrenia[76-78]. Additionally, other researchers indicated that metacognitive beliefs may mediate the effect of early emotional abuse on psychotic symptoms through an affective pathway[98]. Dysfunctional metacognitive beliefs were more strongly

associated with depressive symptomatology[82] and with suicide attempts in individuals with BD type I[83]. In a study that compared healthy controls with individuals with both BD subtypes and with major depressive disorder on their metacognitive beliefs, the diagnostic groups did not differ significantly from each other, but they scored higher than the control group on negative metacognitive beliefs, lack of cognitive confidence, and the need to control thoughts. However, the diagnostic groups did not separate from the healthy controls on positive metacognitive beliefs and cognitive self-consciousness. This study also investigated metacognitive beliefs about rumination of the participants. The results revealed that, while negative beliefs about rumination (uncontrollability, danger, and negative interpersonal and social consequences) were higher in the diagnostic groups, scores on the positive beliefs about rumination did not differ between the groups[28]. In addition, preliminary results demonstrated that metacognitive interventions may be useful for individuals with BD[15,76,99].

In summary, although individuals with BD are known to present with dysfunctional metacognitive beliefs, further studies are still needed to clarify how these beliefs are associated with depressive symptomatology and whether they may also have an impact on hypomanic/manic symptomatology. Further studies focusing specifically on BD subtypes and different phases of the disorder are also needed. Assessment instruments developed for individuals for BD are also lacking. The effectiveness of MCT in BD needs to be investigated in large-scale, randomized controlled studies.

PROPOSED THEORETICAL FRAMEWORK FOR MCT IN BD

As summarized in the previous sections, components of CAS and dysfunctional metacognitive beliefs are evident in BD. Despite the minimal research on the effectiveness of MCT for BD, acknowledging the transdiagnostic nature of MCT, a theoretical framework for applying MCT for BD patients may be proposed. Following the treatment steps of the only published study on applying MCT in BD[15], which was based on the generic structure of MCT[12], we propose a sequential treatment protocol for BD (Figure 1): (1) Case conceptualization; (2) Socialization to the model and treatment; (3) Shifting the patient to the metacognitive mode and increasing meta-awareness of perseverative thinking; (4) Implementing the attention training technique (ATT); (5) Practicing detached mindfulness (DM); (6) Postponing perseverative thinking; (7) Modifying the uncontrollability of perseverative thinking beliefs and challenging other negative metacognitive beliefs; (8) Exploring and abandoning dysfunctional coping strategies, including all kinds of threat monitoring strategies, and suggesting behavioral activation; (9) Challenging positive beliefs about perseverative thinking; (10) Identifying and modifying negative beliefs about mood states; (11) Working on a relapse prevention plan with the patient; (12) Targeting fears of recurrence; and (13) Scheduling booster sessions.

This proposed treatment protocol is mainly based on the MCT treatment plan for depressive disorders[12]. However, for the plan to be compatible with the needs of individuals with BD, the therapist must make some adjustments and modifications. For the metacognitive case conceptualization of the patient, the therapist may need to focus on positive trigger thoughts (or other positive internal experiences), as well as negative ones. To identify the perseverative thinking style of the patient, the therapist may need to make note of any responses to positive affect and worries in addition to depressive rumination. The negative consequences section of the case conceptualization diagram needs to be completed with consideration of any increase in self-reported energy levels, hypomanic/manic affective tendencies, hyperactivity, increased goal-directed activities, changes in sexual interest, impulsivity, increased self-esteem, and grandiosity, in addition to conventional thoughts, affect, and behaviors observed in depression. The therapist and patient must work collaboratively to identify ruminative thinking styles and worrying, with a special focus on positive rumination and how that may interfere with the patient's goal to stay in remission. The role of positive rumination on unwanted consequences should be explored, and postponement and/or abandonment of positive rumination must be encouraged, as it is for depressive rumination and worrying. The uncontrollability and dangerousness of all types of perseverative thinking styles need to be challenged. Modifying beliefs about the negative interpersonal consequences of perseverative thinking need to incorporate a discussion on the responses to positive affect in addition to the conventional discussion about depressive rumination and worrying. Any beliefs about the advantages of perseverative thinking need to be questioned, specifically questioning

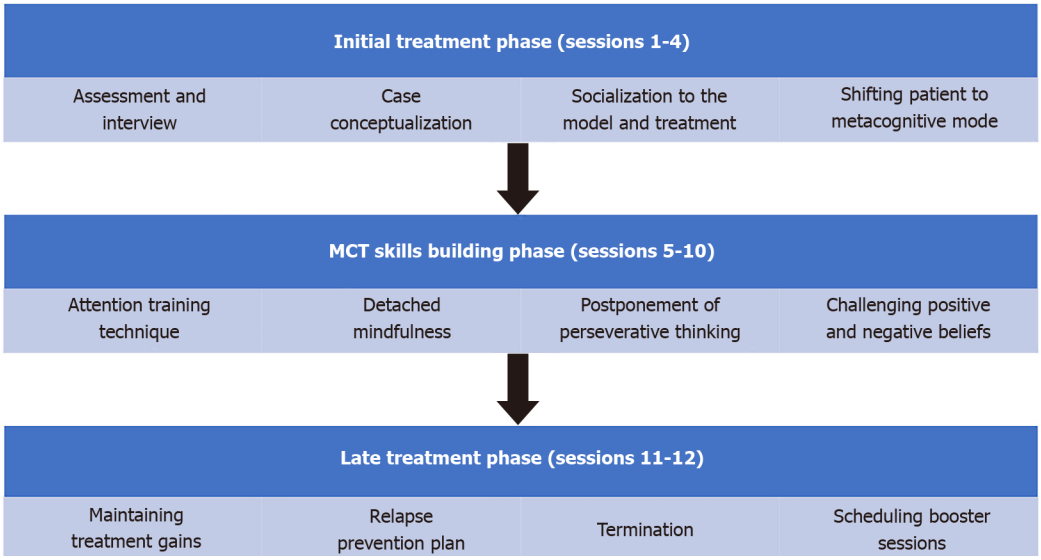

Figure 1 Structure of the proposed metacognitive treatment protocol for bipolar disorder. MCT: Metacognitive therapy.

the perceived positive effects of positive rumination along with the conventional work on depressive rumination and worrying. Dysfunctional coping strategies involving thought control strategies, inactivity, self-harm, alcohol/substance use, emotional avoidance, social withdrawal, and so on may be targeted as they are with a patient with depressive disorder. For the BD patient, the therapist also must acknowledge the possibility of increased goal-directed activity, hyperactivity, staying up all night to keep up with high expectations of self, impulsive behaviors, and related behaviors. Additionally, self-focused attention and constantly monitoring energy levels and mood states may be problematic for the patient. Since a recurrence may be feared and warning signs for new episodes may be in focus, the patient may wake up every day with an initial body scanning for any signs and symptoms suggestive of a new mood episode. The patient needs to abandon such biased and backfiring threat monitoring strategies. Although this is discussed with patients with depressive disorder, the therapist may also spend some time with BD patients focusing on the effects of incessantly looking for possible early warning signs and how this strategy may interfere with the patient's interpretation of naturally occurring mood swings. Other MCT techniques, such as ATT, DM, relapse prevention strategies, and setting up booster sessions, may follow the guidelines for patients with depressive disorders with modifications for patients with BD where necessary.

CONCLUSION

In conclusion, the metacognitive model of BD may provide a new perspective to further understand the underlying psychological mechanisms in patients with BD. Therefore, for a subgroup of patients with BD who fail to respond to evidence-based psychopharmacological and adjunctive psychotherapeutic interventions, MCT may be an alternative treatment option. More randomized controlled research undertaken in large samples is necessary to present more evidence on the effectiveness of MCT in BD.

REFERENCES

1 **Fountoulakis KN**, Grunze H, Vieta E, Young A, Yatham L, Blier P, Kasper S, Moeller HJ. The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 3: The Clinical Guidelines. *Int J Neuropsychopharmacol* 2017; **20**: 180-195 [PMID: 27941079 DOI: 10.1093/ijnp/pyw109]

2 **Goodwin GM**, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, Coghill DR, Fazel S, Geddes JR, Grunze H, Holmes EA, Howes O, Hudson S, Hunt N, Jones I, Macmillan IC, McAllister-Williams H, Miklowitz DR, Morriss R, Munafò M, Paton C, Saharkian BJ, Saunders K, Sinclair J, Taylor D, Vieta E, Young AH. Evidence-based guidelines for treating bipolar disorder: Revised third

edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2016; **30**: 495-553 [PMID: 26979387 DOI: 10.1177/0269881116636545]

3 **Malhi GS**, Bell E, Singh AB, Bassett D, Berk M, Boyce P, Bryant R, Gitlin M, Hamilton A, Hazell P, Hopwood M, Lyndon B, McIntyre RS, Morris G, Mulder R, Porter R, Yatham LN, Young A, Murray G. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: Major depression summary. *Bipolar Disord* 2020; **22**: 788-804 [PMID: 33320412 DOI: 10.1111/bdi.13035]

4 **Yatham LN**, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, Sharma V, Goldstein BI, Rej S, Beaulieu S, Alda M, MacQueen G, Milev RV, Ravindran A, O'Donovan C, McIntosh D, Lam RW, Vazquez G, Kapczinski F, McIntyre RS, Kozicky J, Kanba S, Lafer B, Suppes T, Calabrese JR, Vieta E, Malhi G, Post RM, Berk M. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* 2018; **20**: 97-170 [PMID: 29536616 DOI: 10.1111/bdi.12609]

5 **Fountoulakis KN**, Vieta E, Young A, Yatham L, Grunze H, Blier P, Moeller HJ, Kasper S. The International College of Neuropsychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 4: Unmet Needs in the Treatment of Bipolar Disorder and Recommendations for Future Research. *Int J Neuropsychopharmacol* 2017; **20**: 196-205 [PMID: 27677983 DOI: 10.1093/ijnp/pyw072]

6 **Dean OM**, Gliddon E, Van Rheenen TE, Giorlando F, Davidson SK, Kaur M, Ngo TT, Williams LJ. An update on adjunctive treatment options for bipolar disorder. *Bipolar Disord* 2018; **20**: 87-96 [PMID: 29369487 DOI: 10.1111/bdi.12601]

7 **Novick DM**, Swartz HA. Psychosocial Interventions for Bipolar II Disorder. *Am J Psychother* 2019; **72**: 47-57 [PMID: 31070452 DOI: 10.1176/appi.psychotherapy.20190008]

8 **Salcedo S**, Gold AK, Sheikh S, Marcus PH, Nierenberg AA, Deckersbach T, Sylvia LG. Empirically supported psychosocial interventions for bipolar disorder: Current state of the research. *J Affect Disord* 2016; **201**: 203-214 [PMID: 27243619 DOI: 10.1016/j.jad.2016.05.018]

9 **Xuan R**, Li X, Qiao Y, Guo Q, Liu X, Deng W, Hu Q, Wang K, Zhang L. Mindfulness-based cognitive therapy for bipolar disorder: A systematic review and meta-analysis. *Psychiatry Res* 2020; **290**: 113116 [PMID: 32480120 DOI: 10.1016/j.psychres.2020.113116]

10 **Miklowitz DJ**, Efthimiou O, Furukawa TA, Scott J, McLaren R, Geddes JR, Cipriani A. Adjunctive Psychotherapy for Bipolar Disorder: A Systematic Review and Component Network Meta-analysis. *JAMA Psychiatry* 2021; **78**: 141-150 [PMID: 33052390 DOI: 10.1001/jamapsychiatry.2020.2993]

11 **Popovic D**, Yildiz A, Murphy P, Colom F. Unexplored areas of psychotherapy in bipolar disorder. *Harv Rev Psychiatry* 2014; **22**: 373-378 [PMID: 25377613 DOI: 10.1097/HRP.0000000000000015]

12 **Wells A**. Metacognitive therapy for anxiety and depression. New York: Guilford Press, 2009

13 **Wells A**. Fisher P. Treating Depression: MCT, CBT, and Third Wave Therapies. Oxford: John Wiley & Sons, 2015

14 **Normann N**, Morina N. The Efficacy of Metacognitive Therapy: A Systematic Review and Meta-Analysis. *Front Psychol* 2018; **9**: 2211 [PMID: 30487770 DOI: 10.3389/fpsyg.2018.02211]

15 **Callesen P**, Pedersen ML, Andersen CK, Wells A. Metacognitive therapy for bipolar II disorder: A single case series study. *Neurol Psychiat Br* 2020; **38**: 107-113 [DOI: 10.1016/j.npbr.2020.08.004]

16 **Cludius B**, Mennin D, Ehring T. Emotion regulation as a transdiagnostic process. *Emotion* 2020; **20**: 37-42 [PMID: 31961175 DOI: 10.1037/emo0000646]

17 **Dodd A**, Lockwood E, Mansell W, Palmier-Claus J. Emotion regulation strategies in bipolar disorder: A systematic and critical review. *J Affect Disord* 2019; **246**: 262-284 [PMID: 30590289 DOI: 10.1016/j.jad.2018.12.026]

18 **McGrogan CL**, Dodd AL, Smith MA. Emotion regulation strategies in mania risk: A systematic review. *J Clin Psychol* 2019; **75**: 2106-2118 [PMID: 31385293 DOI: 10.1002/jclp.22841]

19 **Ghaznavi S**, Deckersbach T. Rumination in bipolar disorder: evidence for an unquiet mind. *Biol Mood Anxiety Disord* 2012; **2**: 2 [PMID: 22738363 DOI: 10.1186/2045-5380-2-2]

20 **Silveira Éde M Jr**, Kauer-Sant'Anna M. Rumination in bipolar disorder: a systematic review. *Braz J Psychiatry* 2015; **37**: 256-263 [PMID: 26176599 DOI: 10.1590/1516-4446-2014-1556]

21 **Marchetti I**, Koster EHW, Klinger E, Alloy LB. Spontaneous Thought and Vulnerability to Mood Disorders: The Dark Side of the Wandering Mind. *Clin Psychol Sci* 2016; **4**: 835-857 [PMID: 28785510 DOI: 10.1177/2167702615622383]

22 **Kovács LN**, Takacs ZK, Tóth Z, Simon E, Schmelowszky Á, Kökönyei G. Rumination in major depressive and bipolar disorder - a meta-analysis. *J Affect Disord* 2020; **276**: 1131-1141 [PMID: 32777651 DOI: 10.1016/j.jad.2020.07.131]

23 **Simon NM**, Pollack MH, Ostacher MJ, Zalta AK, Chow CW, Fischmann D, Demopulos CM, Nierenberg AA, Otto MW. Understanding the link between anxiety symptoms and suicidal ideation and behaviors in outpatients with bipolar disorder. *J Affect Disord* 2007; **97**: 91-99 [PMID: 16820212 DOI: 10.1016/j.jad.2006.05.027]

24 **Stange JP**, Hamilton JL, Burke TA, Kleiman EM, O'Garro-Moore JK, Seligman ND, Abramson LY, Alloy LB. Negative cognitive styles synergistically predict suicidal ideation in bipolar spectrum disorders: a 3-year prospective study. *Psychiatry Res* 2015; **226**: 162-168 [PMID: 25660736 DOI: 10.1016/j.psychres.2014.12.042]

25 **Steel C**. Cognitive Emotion Regulation as a Mediator between Posttraumatic Stress Symptoms and Hypomanic Personality within a Non-Clinical Population. *Behav Cogn Psychother* 2016; **44**: 104-111

[PMID: 26365097 DOI: 10.1017/S1352465815000508]
26 **Favaretto E**, Bedani F, Offredi A, Schroffenegger M, Sassaroli S, Ruggiero G, Fagiolini A, Caselli G. Metacognitions and repetitive negative thinking in bipolar disorder and healthy controls: A comparative study. *J Affect Disord* 2020; **276**: 152-158 [PMID: 32697694 DOI: 10.1016/j.jad.2020.07.013]
27 **Gruber J**, Eidelman P, Johnson SL, Smith B, Harvey AG. Hooked on a feeling: rumination about positive and negative emotion in inter-episode bipolar disorder. *J Abnorm Psychol* 2011; **120**: 956-961 [PMID: 21553935 DOI: 10.1037/a0023667]
28 **Çakmak S**. Depresyonla giden duygudurum bozukluklarında ruminasyonla ilgili üstbilişler. [Metacognitions about rumination in mood disorders with depression] [Turkish]. Medical Specialization Thesis. Tokat, Turkey: Psychiatry Department Gaziosmanpasa University, 2016
29 **Yesilyaprak N**, Batmaz S, Yildiz M, Songur E, Akpinar Aslan E. Automatic thoughts, cognitive distortions, dysfunctional attitudes, core beliefs, and ruminative response styles in unipolar major depressive disorder and bipolar disorder: a comparative study. *Psychiat Clin Psych* 2019; **29**: 854-863 [DOI: 10.1080/24750573.2019.1690815]
30 **Thomas J**, Knowles R, Tai S, Bentall RP. Response styles to depressed mood in bipolar affective disorder. *J Affect Disord* 2007; **100**: 249-252 [PMID: 17134763 DOI: 10.1016/j.jad.2006.10.017]
31 **Kraiss JT**, Ten Klooster PM, Chrispijn M, Stevens AWMM, Kupka RW, Bohlmeijer ET. Psychometric properties and utility of the Responses to Positive Affect questionnaire (RPA) in a sample of people with bipolar disorder. *J Clin Psychol* 2019; **75**: 1850-1865 [PMID: 31240732 DOI: 10.1002/jclp.22819]
32 **Dempsey RC**, Gooding PA, Jones SH. Positive and negative cognitive style correlates of the vulnerability to hypomania. *J Clin Psychol* 2011; **67**: 673-690 [PMID: 21425259 DOI: 10.1002/jclp.20789]
33 **Johnson SL**, McKenzie G, McMurrich S. Ruminative Responses to Negative and Positive Affect Among Students Diagnosed with Bipolar Disorder and Major Depressive Disorder. *Cognit Ther Res* 2008; **32**: 702-713 [PMID: 20360996 DOI: 10.1007/s10608-007-9158-6]
34 **Olofsson ME**, Boersma K, Engh J, Wurm M. A psychometric evaluation of the Swedish version of the Responses to Positive Affect questionnaire. *Nord J Psychiatry* 2014; **68**: 588-593 [PMID: 24724927 DOI: 10.3109/08039488.2014.898792]
35 **Knowles R**, Tai S, Christensen I, Bentall R. Coping with depression and vulnerability to mania: a factor analytic study of the Nolen-Hoeksema (1991) Response Styles Questionnaire. *Br J Clin Psychol* 2005; **44**: 99-112 [PMID: 15826347 DOI: 10.1348/014466504X20062]
36 **Pavlickova H**, Varese F, Smith A, Myin-Germeys I, Turnbull OH, Emsley R, Bentall RP. The dynamics of mood and coping in bipolar disorder: longitudinal investigations of the inter-relationship between affect, self-esteem and response styles. *PLoS One* 2013; **8**: e62514 [PMID: 23638104 DOI: 10.1371/journal.pone.0062514]
37 **Rowland JE**, Hamilton MK, Lino BJ, Ly P, Denny K, Hwang EJ, Mitchell PB, Carr VJ, Green MJ. Cognitive regulation of negative affect in schizophrenia and bipolar disorder. *Psychiatry Res* 2013; **208**: 21-28 [PMID: 23499232 DOI: 10.1016/j.psychres.2013.02.021]
38 **Thomas J**, Bentall RP. Hypomanic traits and response styles to depression. *Br J Clin Psychol* 2002; **41**: 309-313 [PMID: 12396257 DOI: 10.1348/014466502760379154]
39 **Bentall RP**, Myin-Germeys I, Smith A, Knowles R, Jones SH, Smith T, Tai SJ. Hypomanic personality, stability of self-esteem and response styles to negative mood. *Clin Psychol Psychother* 2011; **18**: 397-410 [PMID: 21887813 DOI: 10.1002/cpp.780]
40 **Gruber J**, Eidelman P, Harvey AG. Transdiagnostic emotion regulation processes in bipolar disorder and insomnia. *Behav Res Ther* 2008; **46**: 1096-1100 [PMID: 18684436 DOI: 10.1016/j.brat.2008.05.004]
41 **Kertz SJ**, Bigda-Peyton JS, Rosmarin DH, Björgvinsson T. The importance of worry across diagnostic presentations: prevalence, severity and associated symptoms in a partial hospital setting. *J Anxiety Disord* 2012; **26**: 126-133 [PMID: 22078242 DOI: 10.1016/j.janxdis.2011.10.005]
42 **Cotrena C**, Damiani Branco L, Ponsoni A, Samamé C, Milman Shansis F, Paz Fonseca R. Executive functions and memory in bipolar disorders I and II: new insights from meta-analytic results. *Acta Psychiatr Scand* 2020; **141**: 110-130 [PMID: 31697843 DOI: 10.1111/acps.13121]
43 **Bora E**. Neurocognitive features in clinical subgroups of bipolar disorder: A meta-analysis. *J Affect Disord* 2018; **229**: 125-134 [PMID: 29306692 DOI: 10.1016/j.jad.2017.12.057]
44 **Clark L**, Goodwin GM. State- and trait-related deficits in sustained attention in bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* 2004; **254**: 61-68 [PMID: 15146334 DOI: 10.1007/s00406-004-0460-y]
45 **Conners CK**, Staff M, Connelly V, Campbell S, MacLean M, Barnes J. Conners' continuous performance Test II (CPT II v. 5). North Tonawanda: Multi-Health Syst Inc., 2000: 175-196
46 **Kolur US**, Reddy YC, John JP, Kandavel T, Jain S. Sustained attention and executive functions in euthymic young people with bipolar disorder. *Br J Psychiatry* 2006; **189**: 453-458 [PMID: 17077437 DOI: 10.1192/bjp.bp.106.022921]
47 **Najt P**, Glahn D, Bearden CE, Hatch JP, Monkul ES, Kaur S, Villarreal V, Bowden C, Soares JC. Attention deficits in bipolar disorder: a comparison based on the Continuous Performance Test. *Neurosci Lett* 2005; **379**: 122-126 [PMID: 15823428 DOI: 10.1016/j.neulet.2004.12.051]
48 **Bora E**, Vahip S, Akdeniz F. Sustained attention deficits in manic and euthymic patients with bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; **30**: 1097-1102 [PMID: 16740350 DOI:

10.1016/j.pnpbp.2006.04.016]
49 **Tsitsipa E**, Fountoulakis KN. The neurocognitive functioning in bipolar disorder: a systematic review of data. *Ann Gen Psychiatry* 2015; **14**: 42 [PMID: 26628905 DOI: 10.1186/s12991-015-0081-z]
50 **Pålsson E**, Figueras C, Johansson AG, Ekman CJ, Hultman B, Östlind J, Landén M. Neurocognitive function in bipolar disorder: a comparison between bipolar I and II disorder and matched controls. *BMC Psychiatry* 2013; **13**: 165 [PMID: 23758923 DOI: 10.1186/1471-244X-13-165]
51 **Bora E**, Yücel M, Pantelis C, Berk M. Meta-analytic review of neurocognition in bipolar II disorder. *Acta Psychiatr Scand* 2011; **123**: 165-174 [PMID: 21092023 DOI: 10.1111/j.1600-0447.2010.01638.x]
52 **Robinson LJ**, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, Moore PB. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord* 2006; **93**: 105-115 [PMID: 16677713 DOI: 10.1016/j.jad.2006.02.016]
53 **Jongen EM**, Smulders FT, Ranson SM, Arts BM, Krabbendam L. Attentional bias and general orienting processes in bipolar disorder. *J Behav Ther Exp Psychiatry* 2007; **38**: 168-183 [PMID: 17107657 DOI: 10.1016/j.jbtep.2006.10.007]
54 **Jabben N**, Arts B, Jongen EM, Smulders FT, van Os J, Krabbendam L. Cognitive processes and attitudes in bipolar disorder: a study into personality, dysfunctional attitudes and attention bias in patients with bipolar disorder and their relatives. *J Affect Disord* 2012; **143**: 265-268 [PMID: 22840633 DOI: 10.1016/j.jad.2012.04.022]
55 **Molz Adams A**, Shapero BG, Pendergast LH, Alloy LB, Abramson LY. Self-referent information processing in individuals with bipolar spectrum disorders. *J Affect Disord* 2014; **152-154**: 483-490 [PMID: 24074480 DOI: 10.1016/j.jad.2013.07.039]
56 **Liu YH**, Liu TB, Zhao J, Huang SW, Lai WT, Yang HC, Xu D, Zhang M, Rong H. A study on attentional bias and response inhibition of facial expressions in manic patients: evidence from eye movement. *Int J Psychiatry Clin Pract* 2019; **23**: 164-170 [PMID: 31035798 DOI: 10.1080/13651501.2019.1569238]
57 **Gruber J**, Maclaine E, Avard E, Purcell J, Cooper G, Tobias M, Earls H, Wieland L, Bothe E, Boggio P, Palermo R. Associations between hypomania proneness and attentional bias to happy, but not angry or fearful, faces in emerging adults. *Cogn Emot* 2021; **35**: 207-213 [PMID: 32883181 DOI: 10.1080/02699931.2020.1810638]
58 **García-Blanco A**, Salmerón L, Perea M. Attentional capture by emotional scenes across episodes in bipolar disorder: Evidence from a free-viewing task. *Biol Psychol* 2015; **108**: 36-42 [PMID: 25796341 DOI: 10.1016/j.biopsycho.2015.03.010]
59 **Montel S**, Scott J, Dubois M, M'bailara K, Henry C. Attentional deficits and emotional bias in bipolar disorders: comparison at different stages of the disease. *Eur Arch Psychiatry Clin Neurosci* 2014; **264**: 743-745 [PMID: 24338031 DOI: 10.1007/s00406-013-0477-1]
60 **Peckham AD**, Johnson SL, Tharp JA. Eye Tracking of Attention to Emotion in Bipolar I Disorder: Links to Emotion Regulation and Anxiety Comorbidity. *Int J Cogn Ther* 2016; **9**: 295-312 [PMID: 28127416 DOI: 10.1521/ijct_2016_09_12]
61 **Armstrong T**, Olatunji BO. Eye tracking of attention in the affective disorders: a meta-analytic review and synthesis. *Clin Psychol Rev* 2012; **32**: 704-723 [PMID: 23059623 DOI: 10.1016/j.cpr.2012.09.004]
62 **Cavanagh JF**, Shackman AJ. Frontal midline theta reflects anxiety and cognitive control: meta-analytic evidence. *J Physiol Paris* 2015; **109**: 3-15 [PMID: 24787485 DOI: 10.1016/j.jphysparis.2014.04.003]
63 **Britton JC**, Lissek S, Grillon C, Norcross MA, Pine DS. Development of anxiety: the role of threat appraisal and fear learning. *Depress Anxiety* 2011; **28**: 5-17 [PMID: 20734364 DOI: 10.1002/da.20733]
64 **Pornpattananangkul N**, Hu X, Nusslock R. Threat/reward-sensitivity and hypomanic-personality modulate cognitive-control and attentional neural processes to emotional stimuli. *Soc Cogn Affect Neurosci* 2015; **10**: 1525-1536 [PMID: 25887153 DOI: 10.1093/scan/nsv042]
65 **Meyer B**, Johnson SL, Winters R. Responsiveness to Threat and Incentive in Bipolar Disorder: Relations of the BIS/BAS Scales With Symptoms. *J Psychopathol Behav Assess* 2001; **23**: 133-143 [PMID: 21765592 DOI: 10.1023/A:1010929402770]
66 **Muhtadie L**, Johnson SL. Threat sensitivity in bipolar disorder. *J Abnorm Psychol* 2015; **124**: 93-101 [PMID: 25688436 DOI: 10.1037/a0038065]
67 **Brotman MA**, Rich BA, Schmajuk M, Reising M, Monk CS, Dickstein DP, Mogg K, Bradley BP, Pine DS, Leibenluft E. Attention bias to threat faces in children with bipolar disorder and comorbid lifetime anxiety disorders. *Biol Psychiatry* 2007; **61**: 819-821 [PMID: 17338904 DOI: 10.1016/j.biopsych.2006.08.021]
68 **Swinkels A**, Giuliano TA. The measurement and conceptualization of mood awareness: Monitoring and labeling one's mood states. *Pers Soc Psychol B* 1995; **21**: 934-949 [DOI: 10.1177/0146167295219008]
69 **Broderick JE**, Vikingstad G. Frequent assessment of negative symptoms does not induce depressed mood. *J Clin Psychol Med Settings* 2008; **15**: 296-300 [PMID: 19104986 DOI: 10.1007/s10880-008-9127-6]
70 **Murnane EL**, Cosley D, Chang P, Guha S, Frank E, Gay G, Matthews M. Self-monitoring practices, attitudes, and needs of individuals with bipolar disorder: implications for the design of technologies to manage mental health. *J Am Med Inform Assoc* 2016; **23**: 477-484 [PMID: 26911822 DOI:

10.1093/jamia/ocv165]
71 **Saunders KE**, Bilderbeck AC, Panchal P, Atkinson LZ, Geddes JR, Goodwin GM. Experiences of remote mood and activity monitoring in bipolar disorder: A qualitative study. *Eur Psychiatry* 2017; **41**: 115-121 [PMID: 28135594 DOI: 10.1016/j.eurpsy.2016.11.005]
72 **van der Watt ASJ**, Odendaal W, Louw K, Seedat S. Distant mood monitoring for depressive and bipolar disorders: a systematic review. *BMC Psychiatry* 2020; **20**: 383 [PMID: 32698802 DOI: 10.1186/s12888-020-02782-y]
73 **Palmier-Claus J**, Lobban F, Mansell W, Jones S, Tyler E, Lodge C, Bowe S, Dodd A, Wright K. Mood monitoring in bipolar disorder: Is it always helpful? *Bipolar Disord* 2021; **23**: 429-431 [PMID: 33570820 DOI: 10.1111/bdi.13057]
74 **Ingram RE**. Self-focused attention in clinical disorders: review and a conceptual model. *Psychol Bull* 1990; **107**: 156-176 [PMID: 2181521 DOI: 10.1037/0033-2909.107.2.156]
75 **Alloy LB**, Abramson LY, Flynn M, Liu RT, Grant DA, Jager-Hyman S, Whitehouse WG. Self-focused Cognitive Styles and Bipolar Spectrum Disorders: Concurrent and Prospective Associations. *Int J Cogn Ther* 2009; **2**: 354 [PMID: 20161631 DOI: 10.1521/ijct.2009.2.4.354]
76 **Lysaker PH**, Irarrázaval L, Gagen EC, Armijo I, Ballerini M, Mancini M, Stanghellini G. Metacognition in schizophrenia disorders: Comparisons with community controls and bipolar disorder: Replication with a Spanish language Chilean sample. *Psychiatry Res* 2018; **267**: 528-534 [PMID: 29980133 DOI: 10.1016/j.psychres.2018.06.049]
77 **Tas C**, Brown EC, Aydemir O, Brüne M, Lysaker PH. Metacognition in psychosis: comparison of schizophrenia with bipolar disorder. *Psychiatry Res* 2014; **219**: 464-469 [PMID: 25017619 DOI: 10.1016/j.psychres.2014.06.040]
78 **Popolo R**, Smith E, Lysaker PH, Lestingi K, Cavallo F, Melchiorre L, Santone C, Dimaggio G. Metacognitive profiles in schizophrenia and bipolar disorder: Comparisons with healthy controls and correlations with negative symptoms. *Psychiatry Res* 2017; **257**: 45-50 [PMID: 28719831 DOI: 10.1016/j.psychres.2017.07.022]
79 **Østefjells T**, Melle I, Aminoff SR, Hellvin T, Hagen R, Lagerberg TV, Lystad JU, Røssberg JI. An exploration of metacognitive beliefs and thought control strategies in bipolar disorder. *Compr Psychiatry* 2017; **73**: 84-92 [PMID: 27918949 DOI: 10.1016/j.comppsych.2016.11.008]
80 **Sarisoy G**, Pazvantoğlu O, Ozturan DD, Ay ND, Yilman T, Mor S, Korkmaz IZ, Kaçar OF, Gümüş K. Metacognitive beliefs in unipolar and bipolar depression: a comparative study. *Nord J Psychiatry* 2014; **68**: 275-281 [PMID: 23902127 DOI: 10.3109/08039488.2013.814710]
81 **Batmaz S**, Ulusoy Kaymak S, Kocbiyik S, Turkcapar MH. Metacognitions and emotional schemas: a new cognitive perspective for the distinction between unipolar and bipolar depression. *Compr Psychiatry* 2014; **55**: 1546-1555 [PMID: 24974282 DOI: 10.1016/j.comppsych.2014.05.016]
82 **Van Camp L**, Sabbe BGC, Oldenburg JFE. Metacognitive functioning in bipolar disorder *vs* controls and its correlations with neurocognitive functioning in a cross-sectional design. *Compr Psychiatry* 2019; **92**: 7-12 [PMID: 31202082 DOI: 10.1016/j.comppsych.2019.06.001]
83 **Cesur E**, Şahmelikoğlu Onur Ö, Erten E. Differences in metacognitive beliefs among patients with bipolar disorder with or without previous suicide attempts. *Nord J Psychiatry* 2019; **73**: 433-440 [PMID: 31393750 DOI: 10.1080/08039488.2019.1649722]
84 **MacLeod C**, Rutherford E, Campbell L, Ebsworthy G, Holker L. Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. *J Abnorm Psychol* 2002; **111**: 107-123 [PMID: 11866165]
85 **Wadlinger HA**, Isaacowitz DM. Looking happy: the experimental manipulation of a positive visual attention bias. *Emotion* 2008; **8**: 121-126 [PMID: 18266522 DOI: 10.1037/1528-3542.8.1.121]
86 **Goossens PJ**, Knoppert-van der Klein EA, van Achterberg T. Coping styles of outpatients with a bipolar disorder. *Arch Psychiatr Nurs* 2008; **22**: 245-253 [PMID: 18809117 DOI: 10.1016/j.apnu.2007.07.001]
87 **Lazarus RS**, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company, 1984
88 **Compas BE**, Connor-Smith JK, Saltzman H, Thomsen AH, Wadsworth ME. Coping with stress during childhood and adolescence: problems, progress, and potential in theory and research. *Psychol Bull* 2001; **127**: 87-127 [PMID: 11271757]
89 **Kapczinski F**, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, Kauer-Sant'anna M, Grassi-Oliveira R, Post RM. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. *Neurosci Biobehav Rev* 2008; **32**: 675-692 [PMID: 18199480 DOI: 10.1016/j.neubiorev.2007.10.005]
90 **Green MJ**, Lino BJ, Hwang EJ, Sparks A, James C, Mitchell PB. Cognitive regulation of emotion in bipolar I disorder and unaffected biological relatives. *Acta Psychiatr Scand* 2011; **124**: 307-316 [PMID: 21644938 DOI: 10.1111/j.1600-0447.2011.01718.x]
91 **Paans NPG**, Dols A, Comijs HC, Stek ML, Schouws SNTM. Associations between cognitive functioning, mood symptoms and coping styles in older age bipolar disorder. *J Affect Disord* 2018; **235**: 357-361 [PMID: 29665519 DOI: 10.1016/j.jad.2018.04.052]
92 **Fletcher K**, Parker G, Manicavasagar V. The role of psychological factors in bipolar disorder: prospective relationships between cognitive style, coping style and symptom expression. *Acta Neuropsychiatr* 2014; **26**: 81-95 [PMID: 24855886 DOI: 10.1017/neu.2013.41]
93 **Grunze H**. Coping style and bipolarity. *Acta Neuropsychiatr* 2014; **26**: 67-68 [PMID: 24983090 DOI: 10.1017/neu.2014.7]

94 **Leung MH**, So SH, Kwok NT, Ng IH, Chan PS, Lo CC, Na S, Mak AD, Lee S. Moment-to-moment interaction between affectivity and coping behaviours in bipolar disorder and the role of cognitive appraisals. *BJPsych Open* 2019; **5**: e44 [PMID: 31530307 DOI: 10.1192/bjo.2019.35]

95 **Zhou J**, Feng L, Hu C, Pao C, Xiao L, Wang G. Associations Among Depressive Symptoms, Childhood Abuse, Neuroticism, Social Support, and Coping Style in the Population Covering General Adults, Depressed Patients, Bipolar Disorder Patients, and High Risk Population for Depression. *Front Psychol* 2019; **10**: 1321 [PMID: 31231288 DOI: 10.3389/fpsyg.2019.01321]

96 **Suh H**, Kang TU, Moon E, Park JM, Lee BD, Lee YM, Jeong HJ, Kim SY, Lee K, Lim HJ. Similarities and Differences of Strategies between Bipolar and Depressive Disorders on Stress Coping. *Psychiatry Investig* 2020; **17**: 71-77 [PMID: 31995974 DOI: 10.30773/pi.2019.0152]

97 **Sun X**, Zhu C, So SHW. Dysfunctional metacognition across psychopathologies: A meta-analytic review. *Eur Psychiatry* 2017; **45**: 139-153 [PMID: 28763680 DOI: 10.1016/j.eurpsy.2017.05.029]

98 **Østefjells T**, Lystad JU, Berg AO, Hagen R, Loewy R, Sandvik L, Melle I, Røssberg JI. Metacognitive beliefs mediate the effect of emotional abuse on depressive and psychotic symptoms in severe mental disorders. *Psychol Med* 2017; **47**: 2323-2333 [PMID: 28397634 DOI: 10.1017/S0033291717000848]

99 **Haffner P**, Quinlivan E, Fiebig J, Sondergeld LM, Strasser ES, Adli M, Moritz S, Stamm TJ. Improving functional outcome in bipolar disorder: A pilot study on metacognitive training. *Clin Psychol Psychother* 2018; **25**: 50-58 [PMID: 28857347 DOI: 10.1002/cpp.2124]

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MINIREVIEWS

Gastrointestinal disease in children with autism spectrum disorders: Etiology or consequence?

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Abstract

Chronic gastrointestinal (GI) symptoms and disorders are common in children with autism spectrum disorder and have been shown to be significantly correlated with the degree of behavioral and cognitive impairment. In this unique population, GI symptoms often arise very early in development, during infancy or toddlerhood, and may be misdiagnosed - or not diagnosed at all – due in part to the challenges associated with recognition of symptoms in a minimally or non-communicative child. Evidence demonstrating that the gut-brain-axis can communicate gut dysbiosis and systemic immune dysregulation in a bidirectional manner raises the question as to whether an untreated gastrointestinal disorder can directly impact neurodevelopment or, conversely, whether having a neurodevelopmental disorder predisposes a child to chronic GI issues. From the data presented in this mini review, we conclude that the preponderance of available evidence would suggest the former scenario is more strongly supported.

Key Words: Autism spectrum disorder; Gastrointestinal disease; Immune dysregulation; Neurodevelopment

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Core Tip: Children with autism spectrum disorder are at a significantly increased risk for chronic gastrointestinal issues from an early age. Clinicians and caregivers should be made aware of this association and provided with the tools necessary for recognition of gastrointestinal (GI) symptoms in these children. Because the first several years is a critical developmental window in the life of a child, and because of the demonstrated

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correlation between GI symptom severity and severity of autism spectrum disorder behaviors and cognition, it is plausible that a neurodevelopmental diagnosis may result from an untreated, persistent state of GI/immune dysregulation.

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INTRODUCTION

Children with autism spectrum disorder (ASD) display gastrointestinal (GI) signs (*i.e.*, abnormalities noted by an observer) more frequently than their neurotypical counterparts[1]. These signs may present as constipation, diarrhea, abdominal pain, vomiting, food refusal, gastroesophageal reflux, malodorous macroscopic malabsorption, failure to thrive, or weight loss and although nearly all children experience gastrointestinal issues at some point during childhood, the reasons for this increased prevalence of GI signs in children with ASD has not been clearly established. This raises the question as to whether autism renders children more vulnerable to chronic GI issues, or whether chronic GI issues, especially in infancy and early childhood, increases the risk for developmental delay and/or ASD.

Verbally (or non-verbally) communicative children with ASD who can express what they are feeling are known to experience GI symptoms (the self-expressed feeling of an abnormality such as pain) at a greater frequency than their neurotypical counterparts, whereas children with ASD who have an underlying GI disorder, but who are unable to express what they are feeling, are known to manifest GI symptoms as extremes of behaviors, such as aggression, self-injury, and excessive self-repetitive behaviors[2]. It is this group of (treatable) children that is most at risk for not receiving a GI diagnosis and not receiving the proper clinical care.

Finally, core ASD features are more pronounced in GI symptomatic children with ASD, and the severity of GI signs and symptoms have been shown correlate with the severity of ASD features[3]. The constellation of GI sign/symptom presentations in ASD, as well as the GI-behavioral association, has been reviewed elsewhere[4] and will not be the focus of this review. It is worth noting here, however, that the frequent anecdotal reports of improvement (from modest to remarkable) in core ASD features following successful treatment of an underlying GI disorder provides compelling evidence that the two are interrelated.

In this mini review, the fundamental conundrum we wish to explore is: (1) Does chronic gastrointestinal dysfunction, especially at a very young age, predispose a child to developmental delay or disorder (etiology); or (2) Does having a developmental delay or disorder increases the risk of gastrointestinal dysfunction in children (consequence).

IMPORTANCE TO THE MENTAL HEALTH PROFESSIONAL

The relevance and importance of this information to the mental health professional cannot be overstated. Although it is clear that all core ASD features or their extremes cannot be explained solely by an underlying GI pathology, the documented relationship between these two demands vigilance on the part of those who interact with and care for the child with ASD. If a caregiver or medical professional suspects and/or is made aware that GI signs/symptoms exist, then appropriate pediatric gastroenterology referral is warranted. The logical consequence of acknowledging this relationship between GI signs/symptoms and ASD behaviors (documented[5], though not yet formally addressed in most of the medical literature) is that it will allow for accurate identification and treatment of GI pathology to commence and, when treatment is successful, will ultimately decrease the unfortunate dependence on often unnecessary behavior modifying medications and their associated adverse effect profiles. Most importantly, this strategy directly targets the underlying pathology as opposed to simply modifying the resultant disease related behaviors.

HOW DOES GASTROINTESTINAL DYSFUNCTION INFLUENCE BEHAVIOR IN AUTISM SPECTRUM DISORDER?

The vast autism-GI literature provides an additional layer of fundamental mechanistic questions regarding the notion that central nervous system (CNS) pathology alone is responsible for ASD behaviors. If GI signs/symptoms correlate with the degree of ASD features in children with ASD, and if they are in some cases the sole presenting indication of an underlying cognitive/behavioral disorder, what might the mechanism be? Although it is tempting to attribute behaviors as directly resulting from unattended pain (an"acting out"of sorts), abundant anecdotal experience with communicative children with ASD reveals that they experience intense compulsions, thoughts, and feelings during active GI symptoms, even in the absence of pain. This question of an underlying mechanism to explain how GI dysfunction can impact ASD behaviors has led to speculation that a "gut-brain-axis", in which the products of one or more pathological GI processes contributes to CNS dysfunction, is the nexus.

The obligatory first step then in answering this pathophysiologic question lies in the clinical approach taken by the gastroenterologist when confronted with these signs/symptoms in the child with ASD. The standard of care for these children is to address their GI signs/symptoms in identical fashion as one would the child who is neurotypical, while at the same time being mindful of the unique behaviors that may be the only sign of underlying GI pathology. GI evaluation is therefore sign/symptom driven, and when standard non-invasive diagnostic tests (blood, stool, urine, imaging studies) are unrevealing, empiric finite trials of medication (*e.g.*, H2 blockers, laxatives, *etc.*) may be warranted. If unsuccessful, the standard of care at that point is usually endoscopy with biopsy.

The most important clues as to the mechanism of the unidirectional GI-CNS linkage (beyond the simple behavioral response to pain) would be expected to lie within the GI mucosa, and in our experience treating > 1500 GI-symptomatic children with ASD, the most common pathologic finding at endoscopy in such cases is non-specific inflammation. Therefore, the putative mechanism that will be described in the following sections differs from existing mechanistic hypotheses that have been put forth thus far in the literature in that it is based solely on human GI mucosal pathology, identified specifically (and often uniquely) in children with ASD, that has been published over the past twenty years. A mechanistic theory will then be proposed that incorporates these findings into the published systemic and CNS pathology of ASD.

GASTROINTESTINAL INFLAMMATION IN AUTISM SPECTRUM DISORDER

Kanner[6]'s seminal paper that describes 11 children with autism mentions the finding of GI disturbances in many of them, but it was not until more than 50 years later, in 1998, that the first histologic evaluation and description of GI inflammation of GI symptomatic children with ASD was published. The ongoing and evolving story of ASD related GI inflammation might appear to be better suited for a gastroenterology journal, however since GI disease is being evaluated in the context of ASD, journals focused on autism or psychiatry (ASD is diagnosed as a psychiatric illness, after all) are equally well suited. Regardless of the venue, the story itself is illuminating in so many respects that academic fidelity dictates that if we are to provide meaningful context, any discussion of this topic must necessarily include the chronologic appearances in the literature of evidence of gastrointestinal inflammation.

In 1998, led by world renowned pediatric gastroenterologist John Walker-Smith, the inflammatory bowel disease (IBD) study group at the Royal Free Hospital in London published a case report in the lancet about 12 children with regressive pervasive developmental disorder, characteristic of autism, who underwent diagnostic endoscopy for evaluation of chronic GI symptoms including diarrhea, abdominal pain, abdominal distention, and food intolerance[7]. Chronic colitis (the excessive presence of lymphocytes - primarily plasma cells - in the lamina propria) was found in 11 of the12 children, and active colitis (neutrophilic infiltration of the epithelium and lamina propria) was found in 5. Intraepithelial lymphocytosis of the cecum was observed in 1 patient. Importantly, and unlike the "classic" inflammatory bowel diseases Crohn's disease (CD) and ulcerative colitis (UC), the chronic inflammatory changes in these children were present in areas of the colon that appeared endoscopically normal. The publication of this case series created a media frenzy at the time because of questions it raised regarding pediatric vaccination safety, ultimately prompting a "retraction of an interpretation" six years later in 2004[8]. Full retraction of the paper by the lancet

occurred in 2010 following a four-year investigation of the paper's findings by England's General Medical Council (GMC), a body that concluded patients were not in fact consecutively referred and that the Institutional Review Board authorization was not appropriately obtained. But, as will be described next, by the time the GMC findings had been rendered, the histologic findings had already been replicated and expanded upon by these and other investigators, at other institutions, and using additional methodologies.

The following year, in 1999, Horvath *et al*[9] published a clinical report describing the histologic (but not endoscopic) findings in 36 children with ASD and GI symptoms of diarrhea, flatulence, nighttime awakening, unexplained irritability, and abdominal distention. In that study it was found that 25 (69.4%) of the children had histologic gastroesophageal reflux, almost all of whom had unexplained irritability as a key symptom. Additionally, Paneth cell hyperplasia, a measure of increased crypt mitotic activity secondary to inflammatory mucosal damage, was significantly increased. The authors do not discuss therapeutic interventions.

Before proceeding further through this brief review of the ASD-GI inflammation literature, it is important to note that not all "inflammation" is equal. For example, the cellular infiltrate of acid related disease is composed of different cellular lineages and intensities than, for example, CD. Even within the classification of classic IBD (CD and UC), the types of inflammatory cells differ between the differing IBD diagnoses. Using tissue immunostaining, Furlano *et al*[10] demonstrated not only a significant non-specific lymphocytic inflammatory plasma cell, CD3, and CD8 T-cell elevation in the colon of GI symptomatic children with ASD compared to healthy controls, but that there was also an excess γδ-T-cell presence that distinguishes autistic colitis from classic IBD.

Attention then turned to the upper gastrointestinal tract where, in 2002, the use of immunohistochemical staining again showed the non-specific increased CD3 and CD8 T-cell inflammatory infiltrate in the mucosa with the additional finding of a thickened basement membrane, a feature often found in the intestine of patients with systemic autoimmune disease such as diabetes, rheumatoid arthritis, and gluten sensitive enteropathy (celiac disease)[11]. However, what distinguished the duodenal inflammation from all previously reported forms of childhood enteropathy was the presence of a unique feature of autoimmunity, namely the presence of IgG colocalizing with complement c1q on the basolateral enterocyte membrane.

Next, in 2003, Ashwood *et al*[12] reproduced the findings of Furlano and Torrente using the newer technique of flow cytometry (as opposed to immunostaining). This group demonstrated elevated CD3 and CD8 cellular infiltrate in the mucosa (duodenum, terminal ileum, and colon) of 52 GI symptomatic children with ASD when compared to inflamed and non-inflamed mucosal tissues from 54 non ASD controls. They also reported statistically similar degrees of infiltrate compared to inflamed controls having other diagnoses (*e.g.*, IBD, indeterminate colitis, food allergy, celiac disease, *etc.*). Additionally, intraepithelial lymphocytosis and B-cell infiltration were present in GI symptomatic children with ASD but not in healthy children. The authors noted that this study confirmed and expanded upon the previously described unique nature of the combined inflammatory components in GI symptomatic children with ASD. Importantly, it was the first time that this pathology was shown to exist simultaneously in the small and large intestine.

In 2004, Torrente *et al*[13] described unique inflammatory pathology in the stomach of 20 (out of 25; 80%) GI symptomatic children with ASD when compared to 30 non-ASD controls. This pathology profile, like the one described by Torrente in the small bowel, was unique and unlike the focal enhanced gastritis seen in CD. Specifically, it consisted of a markedly elevated CD8 T-cell infiltration, marked presence of intraepithelial lymphocytes, and had the same subepithelial basement membrane IgG deposition colocalization with complement c1q seen in the small bowel.

In 2005, Balzola *et al*[14] reported similar chronic active colitis and gastritis (with gastric pseudopolyps) in a 28-year-old patient with regressive autism. Importantly, capsule endoscopy was also performed and revealed jejunal and ileal erosions and ulcerations. This remains the only published report of capsule endoscopic findings in a patient with autism. The authors suggested that their findings of small bowel disease beyond the limits of the duodenum and terminal ileum "demonstrate the potential for involvement of the entire bowel in this inflammatory disease".

A 2008 case report of two GI-symptomatic patients (one 18-year-old male; one 19-year-old female) with autism describes the precise histopathologic findings previously reported [*i.e.*, non-specific gastritis, focal active colitis, and lymphonodular hyperplasia (LNH) of the terminal ileum] and reported clinical GI symptom improvement in the male patient following a course of steroids after a failed trial of high dose 5-ASA[15].

In their discussion of the findings, the authors commented that "although the idea of a shared pathophysiology between GI disease and autism remains controversial, the evidence presented so far warrants further exploration at the very least" and they advocated for a heightened awareness and lower threshold for work-up and management on this population.

In 2010, Krigsman *et al*[16] reported on the retrospective histologic findings (on routine H&E staining) as reported by the hospital pathologists, of 143 consecutive children with ASD and chronic GI symptoms. It remains the largest study of GI symptomatic ASD mucosal biopsy tissue to date. Based on H&E staining, the authors found ileitis in one third (35%), and ileal or colonic chronic active inflammation in nearly three fourths (74%) of the children. LNH, a feature of inflammation that may be observed at any site while not by itself meeting the definition for inflammation, was present in nearly three fourths (73.2%) of the patients, and for this patient series the presence of LNH predicted the presence of inflammation. Regarding LNH in general, and specifically in children with ASD, this finding represented an important observation because although the prominent presence of LNH in GI-symptomatic children with ASD had been noted (and vigorously debated) in the literature, this case series, due to the large size of the cohort, was the first to report a statistically significant link between LNH and actual mucosal inflammation. Regressive or plateau autism was more strongly linked to ileocolitis than early onset autism. This case series did not seek to identify inflammatory characteristics unique to ASD.

In 2013, Walker *et al*[17] expanded upon the uniqueness of the ASD-associated enterocolitis with characterization of the infiltrates at the molecular level. This case-control study utilized mRNA transcriptome profiling of inflamed ileal and colonic tissue from GI-symptomatic children with ASD and from controls consisting of anatomically matched (ileal and colonic) GI biopsy tissues from GI-symptomatic non-ASD control patients with either: (1) No histologic evidence of pathology; (2) CD; or (3) Ulcerative colitis. Comparison of differentially expressed transcripts between the ASD samples and each of the non-ASD groups showed a clear distinction between the ASD-inflamed mucosa and all other groups. Of particular interest, while there was some degree of overlap between gene expression in inflamed tissue from GI-symptomatic children with ASD and the control samples from non-ASD children with IBD (both CD and UC), no significant overlap existed between ASD and non-diseased controls. The authors noted that this correlates well with the similarities of GI symptom expression and response to therapy as seen in their clinical experience with these patients. Nearly identical molecular profile patterns emerged from both the ileal and colonic mucosal specimens from GI-symptomatic children with ASD which served to confirm the notion of unique ASD inflammatory patterns in both the small and large intestine. The differentially expressed mucosal transcripts unique to ASD that were identified in this study were subsequently evaluated in a follow up 2016 study that compared mucosal gene expression to blood gene expression simultaneously obtained in the same patients, to identify which of these biomarkers might serve as a molecular signature (*i.e.*, a "blood test") for the presence of ASD-specific inflammatory bowel disease[18].

A subsequent 2016 report by Kushak *et al*[19] evaluated intestinal function in GI-symptomatic children with autism by measuring duodenal disaccharidase activity (lactase, sucrase, and palmitase), intestinal permeability (endoscopic infusion of rhamnose and lactulose followed by measurements in urine over the next 5 h), and fecal markers of intestinal inflammation (stool calprotectin). Results suggested that intestinal permeability, brush border enzyme activity, and the frequency of inflammation did not differ between children with or without autism. Routine H&E staining showed no significant difference in the frequency of gastric or intestinal inflammation between GI symptomatic ASD and non-ASD children and although 52% of children in the ASD group had some inflammation in the gastrointestinal tract, "it was generally mild and nondiagnostic". The authors concluded that children with autism who have symptoms of GI disorders exhibit objective findings that are similar to those in children without autism.

Lastly, Alessandria *et al*[20] investigated the distribution of human leukocyte antigen-DQ2/DQ8 typing in GI-symptomatic patients with ASD, together with its correlation with duodenal histology and response to a gluten free casein-free diet. The study found unexplained duodenal intraepithelial lymphocytosis in 37% (56/151) of GI symptomatic ASD children, none of which were found to have celiac disease serologic markers. The authors concluded that their results suggest that GI-symptomatic children with ASD seem to have a high prevalence of duodenal histologic inflammation that is not linked to celiac disease.

INTESTINAL MUCOSAL PRO-INFLAMMATORY CYTOKINE ACTIVITY IN AUTISM SPECTRUM DISORDER

Evaluation and comparison of biopsy obtained mucosal tissue from the terminal ileum, ascending, and descending colon from GI-symptomatic children with pervasive developmental disorder (PDD) with age matched controls was first reported in 2003 by DeFelice *et al*[21]. Study subjects consisted of 6 children with PDD (3 with a specific diagnosis of autism or ASD) and 9 neurotypical controls. Using an ELISA kit assay of organ culture supernatants, the authors found no statistically significant differences in the concentration of IL-6, IL-8, and IL-1β between PDD and controls. Histologic findings for all patients, based on H&E staining, were nonpathological. The authors concluded that the data failed to support an association between autism and GI inflammation.

In 2004, Ashwood *et al*[22] prospectively tested the hypothesis that GI-symptomatic children with ASD demonstrated increased numbers of pro-inflammatory cytokine producing CD3+ lymphocytes. As compared to the previously cited 2003 study, this prospective and larger study of 21 children with ASD and 65 neurotypical pediatric controls focused on the intracellular content of pro-inflammatory cytokines as opposed to the cellular supernatant and evaluated the number of pro-inflammatory cytokine containing CD3+ lymphocytes using multicolor flow cytometry. Significant findings included elevated pro-inflammatory cytokine containing lymphocyte counts in children with ASD *vs* controls, particularly lymphocytes containing TNF-α, IL-2, IL-4, and IFN-γ. Significantly, the counterregulatory IL-10 was reduced in ASD as compared to controls. These trends were found in both the duodenum and colon, as well as in both the epithelium and lamina propria. The authors concluded that that there is a consistent profile of CD3+ lymphocyte cytokines in the small and large intestinal mucosa of GI-symptomatic children with ASD, providing further evidence of a diffuse mucosal immunopathology that may respond to dietary and immunomodulatory therapeutic approaches.

In 2006 Ashwood *et al*[23] using a different prospective patient cohort consisting of GI-symptomatic children with ASD (n = 18), and typically developing controls (n = 27), including non-inflamed controls (NIC), and inflamed GI control children with CD, further elaborated on their 2004 findings. As in the earlier study, the group used flow cytometry to assess the CD3+ lymphocyte intracellular pro-inflammatory and counter-regulatory cytokine profiles, this time in mucosal tissue from the terminal ileum. In this study, the CD3+ lymphocyte cytokine profiles were also measured in peripheral blood and correlated to those from the mucosa. In both the peripheral blood and mucosa, CD3+ TNFα+ and CD3+ IFNγ+ were increased in children with ASD compared to NIC, reaching levels similar to those seen in CD. In contrast, peripheral and mucosal counterregulatory CD3+ IL-10+ were markedly lower in GI-symptomatic children with ASD compared to NIC and CD controls. The authors concluded that there was a unique pattern of peripheral blood and mucosal CD3+ lymphocyte intracellular cytokines, consistent with significant immune dysregulation, in that ASD cohort. This 2006 paper marks the last published investigation of mucosal inflammatory cytokine findings in children with ASD and chronic gastrointestinal disease.

In the years between 2006 and 2018, as the incidence of autism continued to rise (according to official reporting from the CDC) and the interest in identifying biomarkers for ASD was high, there was a renewed focus (and a concomitant rise in peer-reviewed publication activity) on peripheral cytokine activity in children with autism. A 2019 meta-analysis on all circulating (blood, serum, or plasma) pro-inflammatory cytokine related literature in ASD identified 38 studies, with a total of 2487 participants (1393 with ASD and 1094 non-ASD controls) and found evidence for higher concentrations of IFN-γ, IL-1β, IL-6 and TNF-α in participants with autism[24]. A second meta-analysis by the same group, also published in 2019, examined levels of circulating anti-inflammatory cytokines in ASD[25]. This report summarized data from 25 studies with a total of 1754 participants (1022 patients with ASD and 732 controls) and found lower concentrations of IL-10 and IL-1Ra in ASD subjects compared to controls.

MUCOSAL BRUSH BORDER DIGESTIVE ENZYMES

Disaccharidases, the enzymes that break down dietary carbohydrates, reside in the brush border lining of the small bowel. Deficiencies in the level of these enzymes and/or their activity can lead to unabsorbed carbohydrates reaching the colon where

they are fermented by colonic bacteria. Aside from causing symptoms of diarrhea and gaseousness, these fermentation products have been hypothesized to play a role in exacerbating behavioral symptoms in children with ASD, possibly through abnormal absorption in the permeable GI mucosa. Due to the accessibility of the duodenum *via* endoscopic biopsy, the levels and activity of these enzymes in the mucosa can be measured relatively easily and as a result, several studies have been able to explore disaccharidase activity deficiencies in children with ASD.

For example, in 1999, Horvath *et al*[9] evaluated the structure and function of the upper GI tract in a group of 36 GI-symptomatic children with autism and found that 58% (21/36) had deficiencies in at least one brush border disaccharidase enzyme, most often lactase (14/21). Kushak *et al*[26] measured disaccharidase activity in duodenal biopsies from 199 GI-symptomatic individuals with autism and reported a lactase deficiency in 58% of autistic children < 5 years old and 65% in older patients. Finally, Williams *et al*[27] in a small case control study that investigated impaired carbohydrate digestion and transport in the GI tract of children with autism and GI disease compared to controls (GI disease alone), found deficient ileal mRNA transcripts encoding intestinal disaccharidases and hexose transporters in the children with ASD. This approach, though novel, did not ultimately measure actual enzyme activity, but the finding of deficient transcript levels provided additional support for the findings reported by Horvath *et al*[9] and Kushak *et al*[19].

Of interest is the case-control 2016 study by Kushak *et al*[19] which again found a similarly high frequency of lactase and other brush border enzyme deficiencies in GI symptomatic children with ASD, but also a similarly high frequency of disaccharidase deficiency in GI symptomatic neurotypical children undergoing diagnostic endoscopy. While disaccharidase deficiency is by no means a unique feature in autism, this finding in persons with ASD suggests it may play an important role in cognitive/behavioral function in conjunction with numerous other pathophysiologic GI activity known to occur in ASD.

INTESTINAL MUCOSAL PERMEABILITY

Intestinal mucosal permeability, or "leaky gut", has been linked to developmental and behavioral changes in children. For example, a study published in 2010 that evaluated alterations in the intestinal barrier in patients with ASD and their first-degree relatives found a high percentage of abnormal intestinal permeability among patients (36.7%) and their relatives (21.2%) as compared to normal subjects (4.8%)[28]. The authors concluded that their results provided support for the leaky gut hypothesis.

A recent 2019 review of the concept of 'leaky gut' discusses how intestinal barrier integrity is commonly measured, what clinical impact a compromised intestinal barrier can have in humans, and sheds light on the nuances of this of this complex topic[29]. Although the review was not specifically about the leaky gut hypothesis in ASD-associated GI disease, the author's conclusion that "clinicians should be aware of the potential of barrier dysfunction in GI diseases and of the barrier as a target for future therapy" is highly relevant to this discussion.

Between 1996-2016 at least five investigations into the frequency and extent of intestinal permeability in children with ASD were published[19,30-33], but the heterogeneity in study design and the exclusion of GI symptomatic children in some of the studies makes it difficult to draw meaningful conclusions as to the contribution of an excessively permeable membrane to cognitive and behavioral dysfunction in children with ASD and inflammatory GI disease. However, taken together, these studies report an overall greater frequency of increased intestinal permeability in ASD as compared to non-ASD controls, though it appears that this finding does not reach statistical significance in the more rigorous studies.

Lastly, in a study investigating blood-brain barrier and intestinal epithelial barrier function, Fiorentino *et al*[34] using duodenal mucosal biopsies from GI-symptomatic children with ASD (n = 12) and healthy controls (n = 9), found that 75% of the ASD samples had reduced expression of barrier-forming tight junction proteins, suggesting an impaired gut barrier integrity.

INFLUENCE OF THE MICROBIOTA

Human health and well-being are inextricably linked to a balanced microbiome and it is well established that intestinal dysbiosis can alter GI physiology, immune function,

and even behavior in children with ASD, a population in which microbial gut dysbiosis is common[35]. In the context of the gut-brain-axis in ASD, the influence of the microbiome is an area of intense interest and research activity. Although published studies report imbalances in intestinal microbiome composition in children with ASD [36-38] and have investigated the relationship between dysbiosis and ASD-related cognition, behavior, and GI symptomatology[39], the mechanisms by which the microbiota are thought to alter GI function and behavior are still actively being investigated. A more comprehensive understanding of mechanisms by which dysbiosis occurs, and how it impacts host function, will accelerate the development of clinically relevant mitigation and therapeutic strategies[40].

CLINICAL ENDOSCOPIC AND LABORATORY OBSERVATIONS/EXPERIENCE OF THE AUTHORS

Serum antibodies to luminal bacterial and fungal microbes

In clinical gastroenterology, the presence of serological antibodies to normal intestinal flora and their association with IBD has been well established. Though not used clinically as a diagnostic tool, the presence of these antibodies distinguishes one form of IBD from another and emphasizes the prominent role of enteric bacteria and fungi as antigenic stimuli in IBD; only rarely are they present in the general and disease control populations. Their presence does not inform specific treatment strategies, but they do suggest an important microbiome related pathogenic pathway for development of intestinal mucosa inflammation in IBD.

To date, there have not been published studies that have investigated the frequency of these serologic markers in ASD-associated IBD. It has been the experience of the authors that, although the frequency with which they are present in ASD-IBD is somewhat less than in CD[41,42], they occur with much greater frequency than in the general population. As with CD, there is age-related appearance of these markers such that the anti-flagellan antibodies are prominent in children under 10 years of age, whereas the anti-glycan antibodies (*e.g.*, ASCA) are more dominant in the teenage and young adult patients[43].

Focal patchy lymphangiectasia

Intestinal lymphangiectasia (the presence of lipid and protein-rich fluid within dilated small intestinal villi) is another endoscopic finding commonly encountered by the authors in teenage and young adult patients with ASD and enteritis who have a long-standing history of untreated gastrointestinal symptoms. Although lymphangiectasia may be found in any number of disease states that prevent the free lymphatic flow away from the intestinal lumen (*e.g.*, elevated central venous pressure secondary to right sided cardiac failure, lymphoma of draining lymph nodes causing distal obstruction, *etc.*), it has also been noted in intestinal inflammatory states such as CD where the obstruction to outward lymph flow occurs in the intestinal wall layers as it does in ASD-enteritis[44]. Examples of intestinal lymphangiectasia in ASD enteritis co-occurring in the same region as classic IBD aphthous ulcers, and in adjacent mucosa in the same patient is presented in Figure 1. To date, the authors have not encountered protein-losing enteropathy resulting from lymphangiectasia.

In the experience of the authors, a third type of endoscopic lesion frequently seen in younger ASD-GI children (less than 10 years of age) is that of white spots, either singular or in clusters, that are prominent in the proximal small bowel and present, but much less frequent, in the distal small bowel (Figure 2). They are often, but not always, seen in conjunction with mildly erythematous mucosa, and inflammatory infiltrate is typically not noted on routine H&E staining. Upon histologic multiple sectioning of the biopsy specimen, truncated villi are noted (single or contiguous) that demonstrate a protective fibrous plume emanating from the core of the decapitated villi. Villous decapitation allows luminal contents to evade the highly evolved system of selective absorption and results in increased permeability (Figure 3). In these cases, capsule endoscopy does not reveal the typical lipid filled villi, but rather a white spot on the surface of the mucosa not within a villous structure.

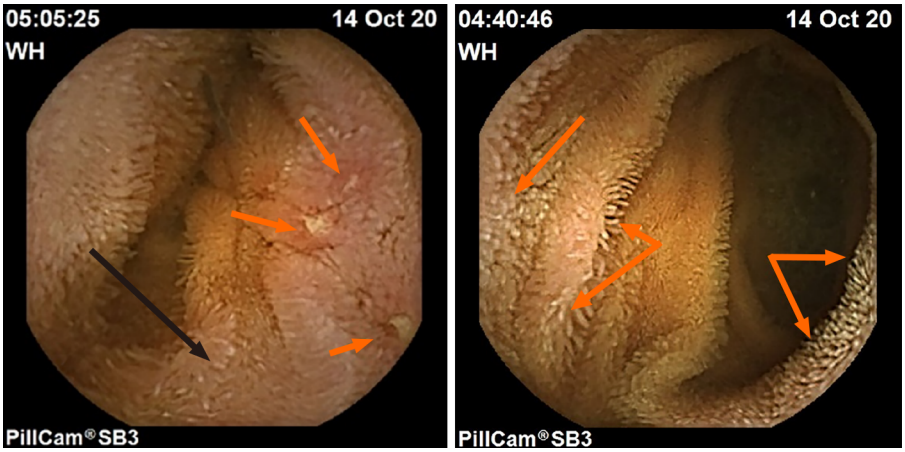

Figure 1 Pillcam images from the small bowel of a gastrointestinal-symptomatic patient with autism spectrum disorder. Lymphangiectasia in patient with autism spectrum disorder-associated enteritis (left panel, black arrow); the patient also exhibited aphthous ulcerations (orange arrows); Jejunal lymphangiectasia (orange arrows) in adjacent mucosa of same patient (right panel).

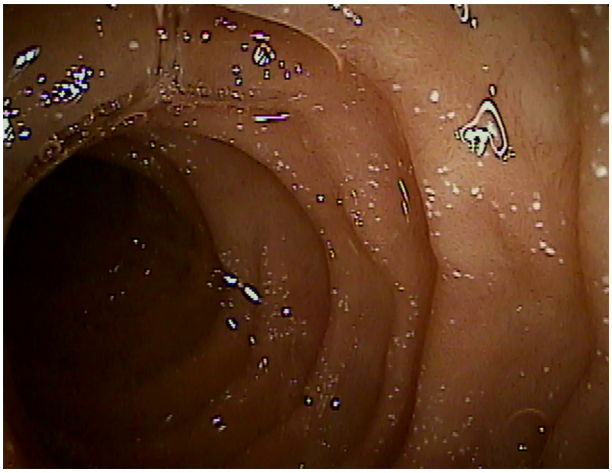

Figure 2 Endoscopic image of white spot lesions of the proximal small bowel in a gastrointestinal-symptomatic child with autism spectrum disorder.

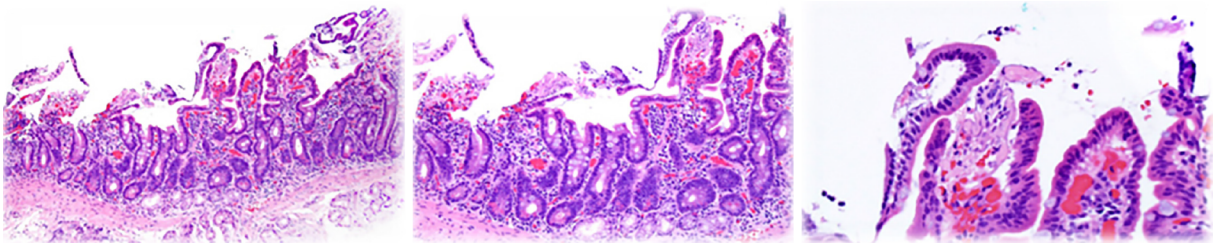

Figure 3 Histologic staining of a mucosal biopsy specimen from the proximal small bowel of a patient with autism spectrum disorder-associated enteritis. White spot lesions (truncated villi) can be seen in low (left); medium (middle); and high magnification (right) of the H&E-stained images.

POTENTIAL MECHANISMS OF CNS INJURY SECONDARY TO UNIQELY INFLAMED GI MUCOSA

Based on the cumulative published literature discussed to this point detailing what is known about the pathology of the inflamed GI mucosa in GI-symptomatic children with ASD, a unidirectional (bowel to brain) mechanism of enterogenous CNS injury in ASD is proposed (Figure 4).

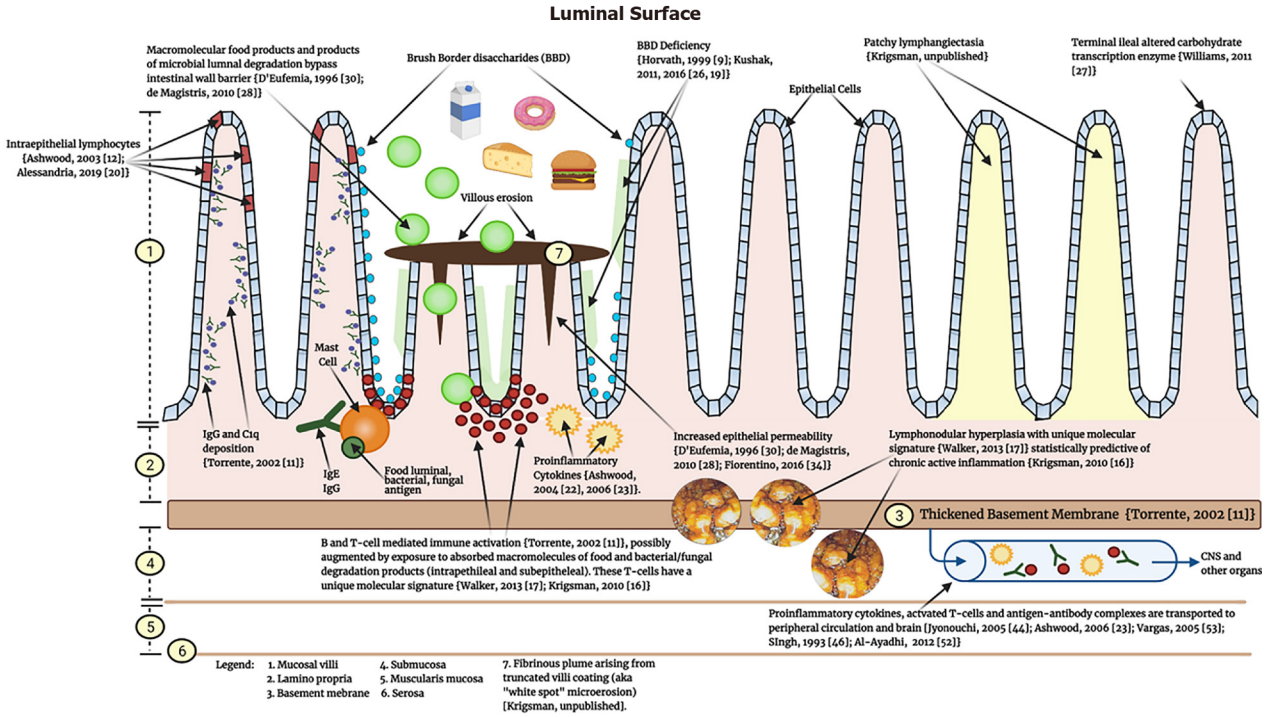

Figure 4 Schematic diagram depicting pathological findings in a portion of the gastrointestinal tract of a representative gastrointestinal-symptomatic child with autism spectrum disorder[9,11,12,16,17,19,20,22,23,26,27,28,30,34,46,52,53]. Key landmarks are identified in the legend (#1-7) and key findings are described throughout the diagram.

For reasons that are not yet entirely clear - but that include environmental, epigenetic, maternal-fetal, and perhaps genetic factors - the immune response in ASD is primed towards over-responsiveness. This over-responsiveness manifests as a heavy lamina propria B and T-cell presence, IgG colocalization with complement c1q on the basolateral enterocyte membrane[11], and intraepithelial lymphocytosis[12,20]. Excessive levels of pro-inflammatory cytokines produced by these cell lineages, as well as deficiencies in counter-regulatory IL-10, are consistently present[22,23]. Marked LNH, a persistently occurring feature of GI immunopathology, is typically present and predicts the presence of cellular inflammation[16]. The combination of hypertrophied reactive LNH and the thickened fibrous basement membrane[11] may serve to obstruct, in whole or in part, lymphatic flow away from the mucosa, resulting in lymphangiectasia. The gene transcriptional profile of the inflammatory infiltrate is unique to children with autism and overlaps significantly with CD[17]. Luminal bacteria are antigens known to be targeted by the mucosal antibodies (Krigsman, unpublished observation).

This persistent inflammatory presence in the intestinal mucosa eventually results in mucosal and epithelial architectural damage. Villous destruction occurs (truncated decapitated villi) with attempts at self-reparation by villous production of a fibrinous covering. Inflammatory villous damage and destruction results, as always, in the loss of resident brush border enzymes[9,26] and increased intestinal permeability[28,30,34]. The clinical implications of the latter two findings are that luminal contents (food, degradation products of resident flora, medications) can more easily evade the highly developed mechanisms for selective absorption and enter the mucosa and capillaries of the GI tract as macro, not micro, molecules, thus exposing the local and systemic immune system to unrecognized antigens. The result of this immunologic activity at the level of the intestinal mucosa is the production of activated B and T cells, as well as numerous pro-inflammatory cytokines, antibodies, and antigen-antibody complexes, that may then enter the peripheral circulation. Once in the peripheral circulation, the effects of such a wide array of active inflammatory activity is largely unknown, but would help explain the observation by Jyonouchi[45] who in 2005 described an increase in GI symptoms and systemic pro-inflammatory cytokines after exposure to specific dietary antigens in GI symptomatic ASD children.

The presence of autoantibodies to the GI epithelium, *i.e.*, autoimmunity, often heralds the formation of autoantibodies directed against other organs as well[46] and thus, the inflammatory activity emanating from the bowel may contribute to the

development of the numerous CNS autoantibodies described in the literature[47-49]. Additionally, cytokines produced locally in the GI mucosa travel peripherally and can cross the blood brain barrier[50].

Of note, the mechanisms of brain inflammation originating in the bowel may be entirely independent of immune dysregulation of peripheral origin that results in production of anti-CNS antibodies or intracranial cellular and molecular mediators of inflammation. The tendency of autoimmune processes to co-exist in the body and even to augment each other has been discussed elsewhere[46].

Finally, although a number of studies have investigated the role of immunomodulating therapy, targeting inflammatory pathways, as a treatment for autism have appeared over the years (reviewed in 51), the focus of the current review is to understand how the existence of a unique inflammatory bowel disease might impact the brain, and, by extension, how treatment of this IBD might ameliorate core symptoms of ASD. Although "classic" IBD such as CD is not known to affect cognition and behavior in the manner described in ASD, the difference may lie in the unique inflammatory features of ASD-associated enteritis that distinguishes it from CD (as already discussed), and the early age of onset of the ASD enteritis, a time when the brain is most susceptible to toxic insult.

CONCLUSION

We have presented a mechanistic concept, based on published pathologic immunologic processes occurring in the gastrointestinal tract of GI-symptomatic children with autism, describing how such pathology may be contributing to the cognitive and behavioral deficits seen in ASD. The logical next step is to conduct a prospective treatment study to determine whether standard immunotherapy for IBD results in improvement in GI symptoms and histologic disease, and if this improvement correlates with improvement in the ASD cognitive and behavioral domains as well.

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REFERENCES

1 **McElhanon BO**, McCracken C, Karpen S, Sharp WG. Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. *Pediatrics* 2014; **133**: 872-883 [PMID: 24777214 DOI: 10.1542/peds.2013-3995]

2 **Buie T**, Fuchs GJ 3rd, Furuta GT, Kooros K, Levy J, Lewis JD, Wershil BK, Winter H. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. *Pediatrics* 2010; **125** Suppl 1: S19-S29 [PMID: 20048084 DOI: 10.1542/peds.2009-1878D]

3 **Chakraborty P**, Carpenter KLH, Major S, Deaver M, Vermeer S, Herold B, Franz L, Howard J, Dawson G. Gastrointestinal problems are associated with increased repetitive behaviors but not social communication difficulties in young children with autism spectrum disorders. *Autism* 2021; **25**: 405-415 [PMID: 32972215 DOI: 10.1177/1362361320959503]

4 **Restrepo B**, Angkustsiri K, Taylor SL, Rogers SJ, Cabral J, Heath B, Hechtman A, Solomon M, Ashwood P, Amaral DG, Nordahl CW. Developmental-behavioral profiles in children with autism spectrum disorder and co-occurring gastrointestinal symptoms. *Autism Res* 2020; **13**: 1778-1789 [PMID: 32767543 DOI: 10.1002/aur.2354]

5 **Buie T**, Campbell DB, Fuchs GJ 3rd, Furuta GT, Levy J, Vandewater J, Whitaker AH, Atkins D, Bauman ML, Beaudet AL, Carr EG, Gershon MD, Hyman SL, Jirapinyo P, Jyonouchi H, Kooros K, Kushak R, Levitt P, Levy SE, Lewis JD, Murray KF, Natowicz MR, Sabra A, Wershil BK, Weston SC, Zeltzer L, Winter H. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics* 2010; **125** Suppl 1: S1-18 [PMID: 20048083 DOI: 10.1542/peds.2009-1878C]

6 **Kanner L**. Autistic disturbances of affective contact. *Acta Paedopsychiatr* 1968; **35**: 100-136 [PMID: 4880460]

7 **Wakefield AJ**, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. Ileal-lymphoid-nodular

hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637-641 [PMID: 9500320 DOI: 10.1016/s0140-6736(97)11096-0]

8 **Wakefield AJ**, Harvey P, Linnell J. MMR--responding to retraction. *Lancet* 2004; **363**: 1327-8; discussion 1328 [PMID: 15094289 DOI: 10.1016/S0140-6736(04)16017-0]

9 **Horvath K**, Papadimitriou JC, Rabsztyn A, Drachenberg C, Tildon JT. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr* 1999; **135**: 559-563 [PMID: 10547242 DOI: 10.1016/s0022-3476(99)70052-1]

10 **Furlano RI**, Anthony A, Day R, Brown A, McGarvey L, Thomson MA, Davies SE, Berelowitz M, Forbes A, Wakefield AJ, Walker-Smith JA, Murch SH. Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. *J Pediatr* 2001; **138**: 366-372 [PMID: 11241044 DOI: 10.1067/mpd.2001.111323]

11 **Torrente F**, Ashwood P, Day R, Machado N, Furlano RI, Anthony A, Davies SE, Wakefield AJ, Thomson MA, Walker-Smith JA, Murch SH. Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. *Mol Psychiatry* 2002; **7**: 375-382, 334 [PMID: 11986981 DOI: 10.1038/sj.mp.4001077]

12 **Ashwood P**, Anthony A, Pellicer AA, Torrente F, Walker-Smith JA, Wakefield AJ. Intestinal lymphocyte populations in children with regressive autism: evidence for extensive mucosal immunopathology. *J Clin Immunol* 2003; **23**: 504-517 [PMID: 15031638 DOI: 10.1023/b:joci.0000010427.05143.bb]

13 **Torrente F**, Anthony A, Heuschkel RB, Thomson MA, Ashwood P, Murch SH. Focal-enhanced gastritis in regressive autism with features distinct from Crohn's and Helicobacter pylori gastritis. *Am J Gastroenterol* 2004; **99**: 598-605 [PMID: 15089888 DOI: 10.1111/j.1572-0241.2004.04142.x]

14 **Balzola F**, Barbon V, Repici A, Rizzetto M, Clauser D, Gandione M, Sapino A. Panenteric IBD-like disease in a patient with regressive autism shown for the first time by the wireless capsule enteroscopy: another piece in the jigsaw of this gut-brain syndrome? *Am J Gastroenterol* 2005; **100**: 979-981 [PMID: 15784047 DOI: 10.1111/j.1572-0241.2005.41202_4.x]

15 **Galiatsatos P**, Gologan A, Lamoureux E. Autistic enterocolitis: fact or fiction? *Can J Gastroenterol* 2009; **23**: 95-98 [PMID: 19214283 DOI: 10.1155/2009/394317]

16 **Krigsman A**, Boris M, Goldblatt A, Stott C. Clinical presentation and histologic findings at ileocolonoscopy in children with autistic spectrum disorder and chronic gastrointestinal symptoms. *Autism Insights* 2010; **2**: 1-11 [DOI: 10.4137/aui.s3252]

17 **Walker SJ**, Fortunato J, Gonzalez LG, Krigsman A. Identification of unique gene expression profile in children with regressive autism spectrum disorder (ASD) and ileocolitis. *PLoS One* 2013; **8**: e58058 [PMID: 23520485 DOI: 10.1371/journal.pone.0058058]

18 **Walker SJ**, Beavers DP, Fortunato J, Krigsman A. A Putative Blood-Based Biomarker for Autism Spectrum Disorder-Associated Ileocolitis. *Sci Rep* 2016; **6**: 35820 [PMID: 27767057 DOI: 10.1038/srep35820]

19 **Kushak RI**, Buie TM, Murray KF, Newburg DS, Chen C, Nestoridi E, Winter HS. Evaluation of Intestinal Function in Children With Autism and Gastrointestinal Symptoms. *J Pediatr Gastroenterol Nutr* 2016; **62**: 687-691 [PMID: 26913756 DOI: 10.1097/MPG.0000000000001174]

20 **Alessandria C**, Caviglia GP, Campion D, Nalbone F, Sanna C, Musso A, Abate ML, Rizzetto M, Saracco GM, Balzola F. HLA-DQ Genotyping, Duodenal Histology, and Response to Exclusion Diet in Autistic Children With Gastrointestinal Symptoms. *J Pediatr Gastroenterol Nutr* 2019; **69**: 39-44 [PMID: 31232884 DOI: 10.1097/MPG.0000000000002293]

21 **DeFelice ML**, Ruchelli ED, Markowitz JE, Strogatz M, Reddy KP, Kadivar K, Mulberg AE, Brown KA. Intestinal cytokines in children with pervasive developmental disorders. *Am J Gastroenterol* 2003; **98**: 1777-1782 [PMID: 12907332 DOI: 10.1111/j.1572-0241.2003.07593.x]

22 **Ashwood P**, Anthony A, Torrente F, Wakefield AJ. Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: mucosal immune activation and reduced counter regulatory interleukin-10. *J Clin Immunol* 2004; **24**: 664-673 [PMID: 15622451 DOI: 10.1007/s10875-004-6241-6]

23 **Ashwood P**, Wakefield AJ. Immune activation of peripheral blood and mucosal CD3+ lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms. *J Neuroimmunol* 2006; **173**: 126-134 [PMID: 16494951 DOI: 10.1016/j.jneuroim.2005.12.007]

24 **Saghazadeh A**, Ataeinia B, Keynejad K, Abdolalizadeh A, Hirbod-Mobarakeh A, Rezaei N. A meta-analysis of pro-inflammatory cytokines in autism spectrum disorders: Effects of age, gender, and latitude. *J Psychiatr Res* 2019; **115**: 90-102 [PMID: 31125917 DOI: 10.1016/j.jpsychires.2019.05.019]

25 **Saghazadeh A**, Ataeinia B, Keynejad K, Abdolalizadeh A, Hirbod-Mobarakeh A, Rezaei N. Anti-inflammatory cytokines in autism spectrum disorders: A systematic review and meta-analysis. *Cytokine* 2019; **123**: 154740 [PMID: 31228728 DOI: 10.1016/j.cyto.2019.154740]

26 **Kushak RI**, Lauwers GY, Winter HS, Buie TM. Intestinal disaccharidase activity in patients with autism: effect of age, gender, and intestinal inflammation. *Autism* 2011; **15**: 285-294 [PMID: 21415091 DOI: 10.1177/1362361310369142]

27 **Williams BL**, Hornig M, Buie T, Bauman ML, Cho Paik M, Wick I, Bennett A, Jabado O, Hirschberg DL, Lipkin WI. Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. *PLoS One* 2011; **6**: e24585 [PMID: 21949732 DOI: 10.1371/journal.pone.0024585]

28 **de Magistris L**, Familiari V, Pascotto A, Sapone A, Frolli A, Iardino P, Carteni M, De Rosa M,

Francavilla R, Riegler G, Militerni R, Bravaccio C. Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. *J Pediatr Gastroenterol Nutr* 2010; **51**: 418-424 [PMID: 20683204 DOI: 10.1097/MPG.0b013e3181dcc4a5]

29 **Camilleri M**. Leaky gut: mechanisms, measurement and clinical implications in humans. *Gut* 2019; **68**: 1516-1526 [PMID: 31076401 DOI: 10.1136/gutjnl-2019-318427]

30 **D'Eufemia P**, Celli M, Finocchiaro R, Pacifico L, Viozzi L, Zaccagnini M, Cardi E, Giardini O. Abnormal intestinal permeability in children with autism. *Acta Paediatr* 1996; **85**: 1076-1079 [PMID: 8888921 DOI: 10.1111/j.1651-2227.1996.tb14220.x]

31 **Robertson MA**, Sigalet DL, Holst JJ, Meddings JB, Wood J, Sharkey KA. Intestinal permeability and glucagon-like peptide-2 in children with autism: a controlled pilot study. *J Autism Dev Disord* 2008; **38**: 1066-1071 [PMID: 18311517 DOI: 10.1007/s10803-007-0482-1]

32 **Boukthir S**, Matoussi N, Belhadj A, Mammou S, Dlala SB, Helayem M, Rocchiccioli F, Bouzaidi S, Abdennebi M. [Abnormal intestinal permeability in children with autism]. *Tunis Med* 2010; **88**: 685-686 [PMID: 20812190]

33 **Navarro F**, Pearson DA, Fatheree N, Mansour R, Hashmi SS, Rhoads JM. Are 'leaky gut' and behavior associated with gluten and dairy containing diet in children with autism spectrum disorders? *Nutr Neurosci* 2015; **18**: 177-185 [PMID: 24564346 DOI: 10.1179/1476830514Y.0000000110]

34 **Fiorentino M**, Sapone A, Senger S, Camhi SS, Kadzielski SM, Buie TM, Kelly DL, Cascella N, Fasano A. Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. *Mol Autism* 2016; **7**: 49 [PMID: 27957319 DOI: 10.1186/s13229-016-0110-z]

35 **Vuong HE**, Hsiao EY. Emerging Roles for the Gut Microbiome in Autism Spectrum Disorder. *Biol Psychiatry* 2017; **81**: 411-423 [PMID: 27773355 DOI: 10.1016/j.biopsych.2016.08.024]

36 **Yang Y**, Tian J, Yang B. Targeting gut microbiome: A novel and potential therapy for autism. *Life Sci* 2018; **194**: 111-119 [PMID: 29277311 DOI: 10.1016/j.lfs.2017.12.027]

37 **Settanni CR**, Bibbò S, Ianiro G, Rinninella E, Cintoni M, Mele MC, Cammarota G, Gasbarrini A. Gastrointestinal involvement of autism spectrum disorder: focus on gut microbiota. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 599-622 [PMID: 33356668 DOI: 10.1080/17474124.2021.1869938]

38 **Hazan S**, Spradling-Reeves KD, Papoutsis A, Walker SJ. Shotgun Metagenomic Sequencing Identifies Dysbiosis in Triplet Sibling with Gastrointestinal Symptoms and ASD. *Children (Basel)* 2020; **7** [PMID: 33255785 DOI: 10.3390/children7120255]

39 **Kang DW**, Adams JB, Coleman DM, Pollard EL, Maldonado J, McDonough-Means S, Caporaso JG, Krajmalnik-Brown R. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. *Sci Rep* 2019; **9**: 5821 [PMID: 30967657 DOI: 10.1038/s41598-019-42183-0]

40 **Eshraghi RS**, Davies C, Iyengar R, Perez L, Mittal R, Eshraghi AA. Gut-Induced Inflammation during Development May Compromise the Blood-Brain Barrier and Predispose to Autism Spectrum Disorder. *J Clin Med* 2020; **10** [PMID: 33374296 DOI: 10.3390/jcm10010027]

41 **Lamberts SW**, de Herder WW, Kwekkeboom DJ, Bruining HA, Krenning EP. [Insulinoma and octreotide]. *Ned Tijdschr Geneeskd* 1992; **136**: 907-910 [PMID: 1594063]

42 **Schoepfer AM**, Schaffer T, Mueller S, Flogerzi B, Vassella E, Seibold-Schmid B, Seibold F. Phenotypic associations of Crohn's disease with antibodies to flagellins A4-Fla2 and Fla-X, ASCA, p-ANCA, PAB, and NOD2 mutations in a Swiss Cohort. *Inflamm Bowel Dis* 2009; **15**: 1358-1367 [PMID: 19253375 DOI: 10.1002/ibd.20892]

43 **Rieder F**, Hahn P, Finsterhoelzl L, Schleder S, Wolf A, Dirmeier A, Lopez R, Shen B, Rogler G, Klebl F, Lang T. Clinical utility of anti-glycan antibodies in pediatric Crohn's disease in comparison with an adult cohort. *Inflamm Bowel Dis* 2012; **18**: 1221-1231 [PMID: 22147427 DOI: 10.1002/ibd.21854]

44 **Cui Y**, Lu SY, Xu J, Peng YS, Miao Q, Wang XQ, Chen XY, Ran ZH. Microscopic features of small bowel mucosa of patients with Crohn's disease. *BMC Gastroenterol* 2019; **19**: 232 [PMID: 31888502 DOI: 10.1186/s12876-019-1138-2]

45 **Jyonouchi H**, Geng L, Ruby A, Reddy C, Zimmerman-Bier B. Evaluation of an association between gastrointestinal symptoms and cytokine production against common dietary proteins in children with autism spectrum disorders. *J Pediatr* 2005; **146**: 605-610 [PMID: 15870662 DOI: 10.1016/j.jpeds.2005.01.027]

46 **Anaya JM**, Corena R, Castiblanco J, Rojas-Villarraga A, Shoenfeld Y. The kaleidoscope of autoimmunity: multiple autoimmune syndromes and familial autoimmunity. *Expert Rev Clin Immunol* 2007; **3**: 623-635 [PMID: 20477166 DOI: 10.1586/1744666X.3.4.623]

47 **Singh VK**, Warren RP, Odell JD, Warren WL, Cole P. Antibodies to myelin basic protein in children with autistic behavior. *Brain Behav Immun* 1993; **7**: 97-103 [PMID: 7682457 DOI: 10.1006/brbi.1993.1010]

48 **Singh VK**, Lin SX, Yang VC. Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism. *Clin Immunol Immunopathol* 1998; **89**: 105-108 [PMID: 9756729 DOI: 10.1006/clin.1998.4588]

49 **Connolly AM**, Chez M, Streif EM, Keeling RM, Golumbek PT, Kwon JM, Riviello JJ, Robinson RG, Neuman RJ, Deuel RM. Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. *Biol Psychiatry* 2006; **59**: 354-363 [PMID: 16181614 DOI: 10.1016/j.biopsych.2005.07.004]

50 **Banks WA**, Kastin AJ, Broadwell RD. Passage of cytokines across the blood-brain barrier. *Neuroimmunomodulation* 1995; **2**: 241-248 [PMID: 8963753 DOI: 10.1159/000097202]

51 **Hafizi S**, Tabatabaei D, Lai MC. Review of Clinical Studies Targeting Inflammatory Pathways for

Individuals With Autism. *Front Psychiatry* 2019; **10**: 849 [PMID: 31824351 DOI: 10.3389/fpsyt.2019.00849]

52 **Al-Ayadhi LY**, Mostafa GA. Elevated serum levels of interleukin-17A in children with autism. *J Neuroinflammation* 2012; **9**: 158 [PMID: 22748016 DOI: 10.1186/1742-2094-9-158]

53 **Vargas DL**, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol* 2005; **57**: 67-81 [PMID: 15546155 DOI: 10.1002/ana.20315]

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ORIGINAL ARTICLE

Observational Study

Evaluating the emotion regulation of positive mood states among people with bipolar disorder using hierarchical clustering

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Author contributions: Chan SHW conceived and guided the study; Liu KHK, Lau C and Fung AOY completed the literature search; Liu KHK, Lau C and Fung AOY coordinated the data collection; Chan SHW and Yu CH performed the statistical analyses; Chan SHW and Tse S wrote and revised the paper; all authors approved the final version of the manuscript.

Institutional review board statement: The study was conducted according to the Declaration of Helsinki and the ethical guidelines established by the University of Hong Kong/West Cluster of the Hong Kong Hospital Authority.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Abstract

BACKGROUND

People with bipolar disorder (BD) frequently struggle with the recurrence of affective symptoms. However, the interplay between coping mechanism and positive mood state remains under-researched.

AIM

To explore the associations among behavioral approach system (BAS) sensitivity level, coping, and positive mood states among people with BD.

METHODS

Using a cross-sectional study design, 90 participants with BD were presented with four BAS-activating life event scenarios and assessed with regard to their BAS trait sensitivity, coping flexibility, and mood states. A hierarchical clustering method was used to identify different groups with different styles of coping. Multiple hierarchical regression analyses were conducted to examine the mediating and moderating roles of different components of coping on mood states.

RESULTS

A three-cluster solution was found to best fit the present data set. The findings showed that a low mass of coping combined with low BAS sensitivity level protects people with BD from detrimentally accentuating mood states when they encounter BAS-activating life events. Moreover, coping flexibility is demonstrated to mediate and moderate the relationships between BAS sensitivity level and

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author. Participants gave informed consent for data sharing in which the presented data are anonymized and risk of identification is low.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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mood states. Specifically, subduing the perceived controllability and reducing the use of behavioral-activation/emotion-amplifying coping strategies could help buffer the effect of positive affect.

CONCLUSION

The judicious use of coping in emotion regulation for people with BD when encountering BAS-activating life events was indicated. Practical applications and theoretical implications are highlighted.

Key Words: Bipolar disorder; Mood regulation; Cluster analysis; Coping style; Positive emotions

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Core Tip: Individuals with bipolar disorder (BD) essentially fail to regulate their emotions and behavior effectively due to their behavioral approach system (BAS) hypersensitivity. This research, based on the BAS dysregulation theory, explores the dynamic role of coping in emotion regulation for managing positive mood states due to BAS-activating life events. Results show that a low mass of coping combined with low BAS sensitivity level protects people with BD from detrimentally accentuating mood states. Practical applications for the improvement of stress management programs and theoretical implication for the extension of coping frameworks to include positive mood states are highlighted.

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INTRODUCTION

Bipolar disorder (BD) is a biologically-based disorder with significant neurobiological underpinnings[1,2]. Nonetheless, the evidence was mixed and independent of the argument for a psychological dimension in explaining the emotion dysregulation of BD[3-5]. One of the fundamental psychobiological features of BD is the behavioral approach system (BAS) sensitivity level[6], which can lay a foundation for understanding the emotion dysregulation in BD. Individuals with high BAS sensitivity levels are significantly more likely to have lifetime BD[7]. In particular, they tend to be over-responsive in relation to reward-relevant environmental cues.

As such, BAS is postulated to be a system that integrates motivational factors, personality traits, and behavioral tendencies entailed in goal-seeking and reward responsiveness (RR)[8]. More specifically, the BAS dysregulation theory[9] proposes that weak regulation of the BAS is involved in the fluctuations between high and low mood that characterize BDs. While the excessive increase in BAS activity leads to manic symptoms, the undue decrease in BAS activity would result in depressive symptoms.

In addition, according to the BAS dysregulation theory, individuals with BD essentially fail to regulate their emotions and behavior effectively due to their BAS hypersensitivity. Specifically, the emotion dysregulation in BD is manifested as excessive variability in BAS activity in response to BAS relevant signals. Thus, BAS is justified as a good measure of emotion dysregulation in which individuals with BD would easily show elevated responses on psychophysiological indices of BAS sensitivity[9-11]. Particularly, BAS hypersensitivity and vulnerability to dysregulation may be an "endophenotype that mediates the effects of the genetic predisposition to bipolar disorder"[12].

Difficulties in achieving positive emotion regulation may contribute to the development of mania in people with BD[13,14]. Thus, exploring strategies in managing positive affects in BD was accordingly called for[15]. Alloy *et al*[12]

proposed different longitudinal predictors of mood states among people with BD along a proximal-distal continuum, starting from the most proximal predictors (prodromes), to recent environmental factors (BAS-relevant life events), and lastly the most distal temperamental features (BAS sensitivity level). However, the model as proposed by Alloy *et al*[6] did not consider the feasible role of coping during the interaction between BAS sensitivity level and BAS-relevant life events.

In essence, coping is a dynamic process that alters according to changing demands and appraisals of situations. In terms of cognitive appraisal, perceived controllability has been seen as one of the key elements[16,17]. With regard to coping patterns, the traditional dimensions include problem-focused and emotion-focused coping[18-20], which can be adaptive in controllable and uncontrollable situations, respectively, according to the good-fit criteria[21]. Regarding coping in BD, previous studies postulated two essential dimensions, one behavioral and one emotional. On one hand, it has been proposed that coping strategies in the behavioral dimension - including "behavioral deactivation" or "behavioral activation" - regulate the mania and depression prodromes, respectively[22-24]. On the other hand, Edge *et al*[25] put forward similar notions but with regard to the emotional dimension. They found that, in response to positive emotions and rewards, people with BD tend to adopt "emotion diminishing" coping strategies instead of "emotion amplifying" coping tactics. This study is therefore focused on exploring the dynamic role of coping in regard to BAS sensitivity level and BAS-relevant life events. Research has indicated the moderating role of stress coping in life events related to BAS[26,27]. When taking BAS dimensions into account, different mood episodes are developed according to the nature of the life events. Therefore, specific coping strategies are necessary for the BAS-relevant life events. In particular, the fit and adaptability of coping should be emphasized. For example, the use of rumination or self-blame can be positively associated with depression, whereas the use of positive appraisal can be negatively associated with these symptoms. Therefore, different forms of coping may help to explain "how" or "why" BAS sensitivity level predicts or causes emotional responses, or meanwhile, it can play a protective role against different BAS sensitivity level as well as BAS-relevant life events.

This study explored the effects of BAS sensitivity levels and coping with BAS-activating life events on mood states among people with BD. Specifically, different clusters were identified in connection with different types of coping strategies. Research has shown that manic BD participants would have a tendency to habitual use of coping strategies more frequently[28] or putting greater effort in spontaneously regulating emotions[29] than healthy controls. Thus, an objective measure of number of coping strategies is implied in this study. Moreover, investigations were performed to test whether coping can play a mediating or buffering role for different BAS sensitivity levels. It was hypothesized that a higher BAS sensitivity level is associated with over-accentuated mood states, in which the use of a higher sense of behavioral-activation/emotion-amplifying (AA) coping should augment the effect on mood states. Alternatively, the use of behavioral-deactivation/emotion-diminishing (DD) coping should further help to regulate heighted mood states.

MATERIALS AND METHODS

Participants

Ethical approval was obtained from the Institutional Review Board of the University of Hong Kong/West Cluster of the Hong Kong Hospital Authority (UW13-176). Ninety participants with BD were recruited from a regional hospital's outpatient clinic. The inclusion criteria were: meeting the criteria cited in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[30] for diagnosis of bipolar I or II disorder; a required state of full remission for more than 2 mo[31], confirmed by the attending psychiatrists and strictly checked with the corresponding medical records; having been educated to primary level or above; being between the ages of 18 years and 65 years; and being of Chinese ethnicity. Psychiatric diagnoses and remissions were strictly checked with medical records in the hospital. People with a comorbid diagnosis of schizophrenia, schizoaffective disorder, substance abuse, organic brain syndrome, or mental retardation were excluded.

Measures

BAS trait sensitivity: This was measured using the behavioral-inhibition system (BIS)/BAS scales[32]. This self-report scale consists of one BIS subscale and three BAS

subscales: RR, drive (D), and fun-seeking (FS). Specifically, RR measures the sensitivity to pleasant reinforcers in the environment, D measures the motivation to follow one's goals, and FS measures the motivation to find novel rewards spontaneously. Higher scores indicate a higher sensitivity level. Adequate internal consistencies (Cronbach's alphas ranging from 0.66 to 0.81) and good test-retest reliabilities (ranging from 0.59 to 0.69) were established for all of the subscales[32-34]. For this study, translations and cultural adaptations of the scale have been made[35]. The internal consistency reliability (Cronbach's alpha) of the subscales was established ranging from 0.70 to 0.78. Specifically, only the three BAS subscales were used for further analysis.

Coping: This was measured using the Coping Flexibility Questionnaire[16,36], which attempts to capture the simultaneous person-situation transactional processes. At first, 10 BAS activation-relevant life event scenarios were developed with reference to the life events scale[37]. These 10 life events have been discussed, agreed upon, and modified by a pilot focus group of people with BD, *i.e.*, all life events were proven to have comparable BAS-activating effects. All of them were role-played and videotaped by the first author (Chan SHW) and a research assistant. Each scenario was role played for a couple of minutes. The character who needs to make decision in coping was clearly presented. Examples of the 10 events include: "At work, your boss gave you a compliment on your work performance" or "You won an important award due to achievement at work." Then, in the actual field study, two compulsory and two elective scenarios, as chosen by the participants, were presented accordingly. As different individuals may have distinct stressful experiences (and may interpret those experiences differently depending on their illness), exposing each individual to the same nature and number of stressful situations could mitigate this problem[12,38]. Besides, in order to enhance the self-determination level of the participants, they were also advised to make a choice on their own; each was asked to choose two extra life-event scenarios that could be more or less related to his or her living condition, on top of the original two designated life-event scenarios.

The coping indices included the following scores: (1) The perceived controllability score. The participants were asked to view the video clips and vividly imagine encountering in real life the situation portrayed in the life event scenarios. Then, they rated the perceived controllability of the life events on a 6-point scale, with a higher score indicating greater perceived controllability. The scores included the average and the variance of the perceived controllability across the four BAS-activating life events; and (2) The coping strategies score. A list of coping strategies was compiled that included strategies of behavioral-activation and behavioral-deactivation coping[22-24], and emotion-amplifying and emotion-diminishing coping[25]. Participants reported their repertoire of coping responses after their cognitive appraisal. The operationalization of the coping strategies score included the mean and variability (variance) in the number of AA copings (sample items include keeping oneself busy, stimulating coping, self- and emotion-focused coping as well as encouraging rewarding activities) and DD copings (sample items include modifying excessive behavior, engaging in calming activities, avoiding rewarding activities, and dampening responses) across the four different life events.

Mood states: Baseline pre-event affective symptoms (including depressive and manic mood) were measured using the Modified Hamilton Rating Scale for Depression (commonly known as the MHRSD)[39] and the Bech-Rafaelsen Mania Scale (commonly known as the BRMS)[40], respectively. Both scales use a standardized interview format, with higher scores representing higher symptom severity. Post-event mood states were measured using the internal state scale (ISS)[41], which consists of four subscales: Activation (ACT), well-being (WB), perceived conflict, and the depression index. Adequate internal consistencies (Cronbach's alphas ranging from 0.81 to 0.92) have been previously established for all of the subscales. The ISS is a self-report instrument that is sensitive to changes in affective states. Higher scores, specifically in the subscales of ACT and WB, indicate elevated mood states. Translations and cultural adaptations of the scale were also carried out[35], and only the ACT and WB subscales were reported for the present study. Specifically, ACT was used to classify hypomanic (ACT ≥ 200) or euthymic (ACT < 200); whereas, WB was used to classify depressed (WB < 125) or non-depressed (WB ≥ 125). The internal consistency reliability (Cronbach's alpha) of the subscales ranged from 0.61 to 0.85. In the present study, Mansell and Lam[42]'s present state version of the ISS was used. The assessment was completed immediately post-mood induction, enabling the tracking of participants' instant mood states following their viewing of the videotaped vignettes.

Sociodemographic factors

Each participant's sex, age, marital status, educational level, employment status, and residential status were recorded; these were the sociodemographic factors used in this study.

Procedures

First, a list of people with BD attending the outpatient clinic at a regional hospital in Hong Kong was generated. Potential participants who met the inclusion criteria were individually approached by the first author (Chan SHW). After signing a consent form, the participants' baseline pre-event affective symptoms and BAS sensitivity levels were assessed. Subsequently, they were shown video clips depicting two compulsory and two elective BAS-activating life events in a random order. Perceived controllability and corresponding coping strategies for each of these life event scenarios were reported. Finally, the participants' overall post-event mood states were assessed. Each participant was offered a coupon worth Hong Kong $20 (or United States $2.50) for taking part in the study.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 24.0 (IBM Corp., Armonk, NY, United States). First, Ward's hierarchical agglomerative clustering method was used to identify the participants' different styles of coping, based on their degrees of perceived controllability and corresponding numbers of coping strategies. The squared Euclidean distance was used as the proximity measure in clustering the data. The stability of the cluster analysis was determined by dendrogram and data visualization method. Cluster differences of various particulars (including BAS sensitivity level, coping, and post-event mood states) were examined through a multivariate analysis of variance or chi-square analysis. A post-hoc Bonferroni's comparison was then employed. *F*-tests were used to assess significant differences between the clusters; partial η^2 values were used to represent effect sizes. To establish evidence of the proposed mediating effect of coping with regard to the relationship between BAS sensitivity level and mood states, the hierarchical regression analyses were carried out according to the procedures advised by Baron and Kenny[43]. Residual plots were checked to determine the random distribution around zero. When determining the moderating effect of coping, hierarchical regression analyses were performed. These strictly followed the procedures recommended by Frazier *et al*[44]. The predictor and moderator variables were standardized to reduce multicollinearity.

RESULTS

General participants' characteristics

A total of 90 participants with bipolar I or bipolar II disorder were successfully recruited for the study (Figure 1). Their mean age was 43.32 years (SD = 11.26), and one-third of them were male (37.7%). Nearly 80% had an educational level above secondary 5. More than a half (55%) were still single, and a majority (80%) were living with others. Regarding employment status, half (50%) were still unemployed. Their relatively low symptom levels resulted in low mean scores of 1.24 and 0.33 in the MHRSD and BRMS, respectively (theoretical ranges of 0-52 and 0-55, respectively). On average, the participants generated 4.56 (SD = 1.93) and 2.24 (SD = 1.31) numbers of AA coping and DD coping, respectively. The associations of all variables in terms of Pearson's correlation are presented in Table 1. Regarding those excluded participants, their mean age was 45 years (SD = 10.34), and nearly 47.3% were male. Within this group, about 63% were unemployed which was comparable with the study group. Thus, there was no significant difference between the consented and non-consented groups.

Identification and comparison of three clusters based on AA and DD coping

To analyze AA and DD coping, a 90 × 12 data matrix was constructed. The unique identification numbers of the 90 participants were entered in the rows, and the raw scores on the perceived controllability of each life event (the first four columns), the number of AA coping (the following four columns), and the number of DD coping (the last four columns) were entered in the columns. There were four sets of three columns, as each participant responded to four life-event scenarios in total. After the data had

Table 1 Correlations of major variables

Variable	BAS_D	BAS_FS	BAS_RR	CTR	AA	DD	ISS_ACT	ISS_WB
BAS_D	1	0.29[b]	0.41[b]	-0.11	-0.05	0.13	0.01	0.02
BAS_FS		1	0.36[b]	0.01	0.18	0.14	0.20	0.07
BAS_RR			1	0.06	0.33[b]	0.30[b]	0.24[a]	0.34[b]
CTR				1	0.42[b]	0.28[b]	0.04	0.30[b]
AA					1	0.57[b]	0.18	0.29[b]
DD						1	0.06	-0.01
ISS_ACT							1	0.70[b]
ISS_WB								1

[a]$P < 0.05$.
[b]$P < 0.01$.
AA: Behavioral-activation/emotion-amplifying coping; ACT: Activation; BAS: Behavioral approach system; CTR: Perceived controllability; D: Drive; DD: Behavioral-deactivation/emotion-diminishing coping; FS: Fun-seeking; ISS: Internal state scale; RR: Reward responsiveness; WB: Well-being.

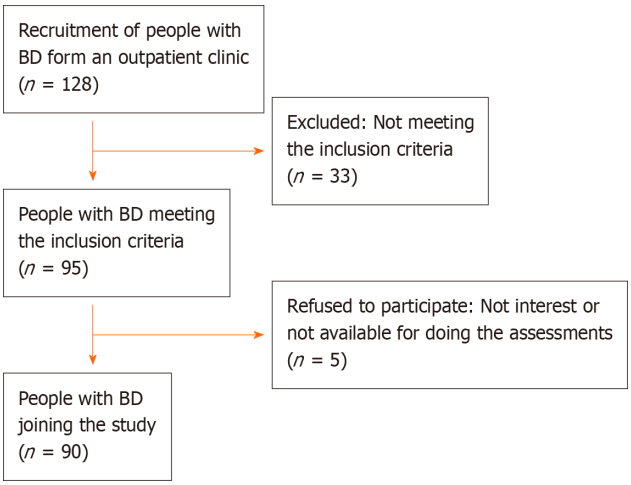

Figure 1 A flow chart of recruitment of participants. BD: Bipolar disorder.

been clustered, a three-cluster solution was found to be the most meaningful and stable (Figure 2 and Table 2). The dendrogram presented in Figure 1 displays all possible options of clustering. In the rightmost part, all participants were grouped together, meaning that there was no clustering at all; whereas, in the leftmost, each participant was paired with another, resulting in too many groups. If there were too many clusters, the subsequent modeling would be too complicated to be interpretable. Conversely, if there were too few clusters (*e.g.*, 2), there would not be distinct coping patterns in each group. This data visualization suggested that the optimal number of clusters should be set at three.

There were no significant differences in the sociodemographic profiles of the three clusters, except in terms of the age of the cluster members. In addition, as long as the baseline affective symptoms were comparable among the three clusters, it was therefore possible to perform further comparison of post-event mood states. Regarding BAS trait sensitivity, there was a statistically significant cluster main effect on the overall BIS/BAS scores (Wilks' $\lambda = 0.798$, $F(6170) = 3.388$, $P = 0.004$, partial $\eta^2 = 0.107$). In further multiple comparisons, an adjusted alpha level of 0.017 (0.05/3) was adopted to correct for the overall Type I errors with regard to three BAS subscales. The members of clusters 1 and 3 were found to be persistent in pursuing their desired goals, as indicated by their significantly higher BAS (D) scores. The members of cluster 1 also had significantly higher BAS (RR) scores than other two clusters; this indicates that their responses to the anticipation of receiving rewards were more positive.

Table 2 Descriptive statistics and comparison of major variables for the three clusters

	Cluster 1, *n* = 26		Cluster 2, *n* = 26		Cluster 3, *n* = 38		
Variables	**Goal achievers with a high mass of coping**		**Goal preservers with a high mass of coping**		**Goal achievers with a low mass of coping**		
	n	**%**	***n***	**%**	***n***	**%**	**Statistics**
Sociodemographic factors							
Sex							χ^2 = 2.13 (P = 0.345)
Female	19	73.1	14	53.8	23	60.5	
Male	7	26.9	12	46.2	15	39.5	
Education level							χ^2 = 7.46 (P = 0.281)
Primary	8	30.8	4	15.4	9	23.7	
Secondary	10	38.4	8	30.8	6	15.8	
Tertiary	8	30.8	14	53.8	23	60.5	
Marital status							χ^2 = 6.72 (P = 0.347)
Single	12	46.2	19	73.1	19	50.0	
Married/cohabited	14	53.8	7	26.9	19	50.0	
Living status							χ^2 = 0.345 (P = 0.987)
Living alone	6	23.0	5	19.3	7	18.4	
Living with others	20	77.0	21	80.7	31	81.6	
Working status							χ^2 = 18.8 (P = 0.171)
Unemployed	17	65.4	11	42.3	17	44.7	
Employed	9	34.6	15	57.7	21	55.3	
	M	SD	M	SD	M	SD	Statistics
Age	48.04	9.64	41.31	12.27	41.47	10.89	F = 3.378 (P = 0.039), 1 > 2, 1 > 3
Baseline affective symptoms							
MHRSD	1.19	1.13	1.38	1.47	1.18	1.25	F = 0.217 (P = 0.805)
BRMS	0.50	1.03	0.38	0.80	0.18	0.56	F = 1.31 (P = 0.275)
BAS sensitivity level							
BAS_D	12.85	1.62	11.62	1.68	12.79	1.76	F = 4.622 (P = 0.012) 1 > 2, 3 > 2
BAS_FS	12.19	2.43	11.42	2.47	11.13	2.70	F = 1.351 (P = 0.264)
BAS_RR	17.85	2.05	15.65	3.11	16.05	2.27	F = 5.924 (P = 0.004) 1 > 2, 1 > 3
Coping							
CTR	2.80	0.74	2.5	0.64	1.68	0.66	F = 23.505 (P < 0.001) 1 > 3, 2 > 3
VCTR	2.70	2.41	1.88	1.10	2.90	2.30	F = 1.998 (P = 0.142)
AA	5.90	1.25	4.68	0.94	2.72	1.27	F = 58.999 (P < 0.001) 1 > 2, 1 > 3, 2 > 3
VAA	1.46	1.83	1.95	1.33	2.08	2.10	F = 0.919 (P = 0.403)
DD	4.28	0.88	2.19	0.61	1.72	0.99	F = 71.542 (P < 0.001) 1 > 2, 1 > 3, 2 > 3
VDD	1.23	0.92	0.94	0.79	0.74	0.62	F = 3.242 (P = 0.044)
Post-event mood states							
ISS_ACT	226.15	99.08	162.31	111.94	182.89	116.90	F = 2.281 (P = 0.108)

ISS_WB	194.62	65.38	139.62	79.22	156.84	77.50	F = 3.728 (P = 0.028)

AA: Behavioral-activation/emotion-amplifying coping; ACT: Activation; BAS: Behavioral approach system; BRMS: Bech-rafaelsen mania scale; CTR: Perceived controllability; D: Drive; DD: Behavioral-deactivation/emotion-diminishing coping; FS: Fun-seeking; ISS: Internal state scale; MHRSD: Modified Hamilton Rating Scale for Depression; RR: Reward responsiveness; VAA: Variance of behavioral-activation/emotion-amplifying coping; VCTR: Variance of perceived controllability; VDD: Variance of behavioral-deactivation/emotion-diminishing coping; WB: Well-being.

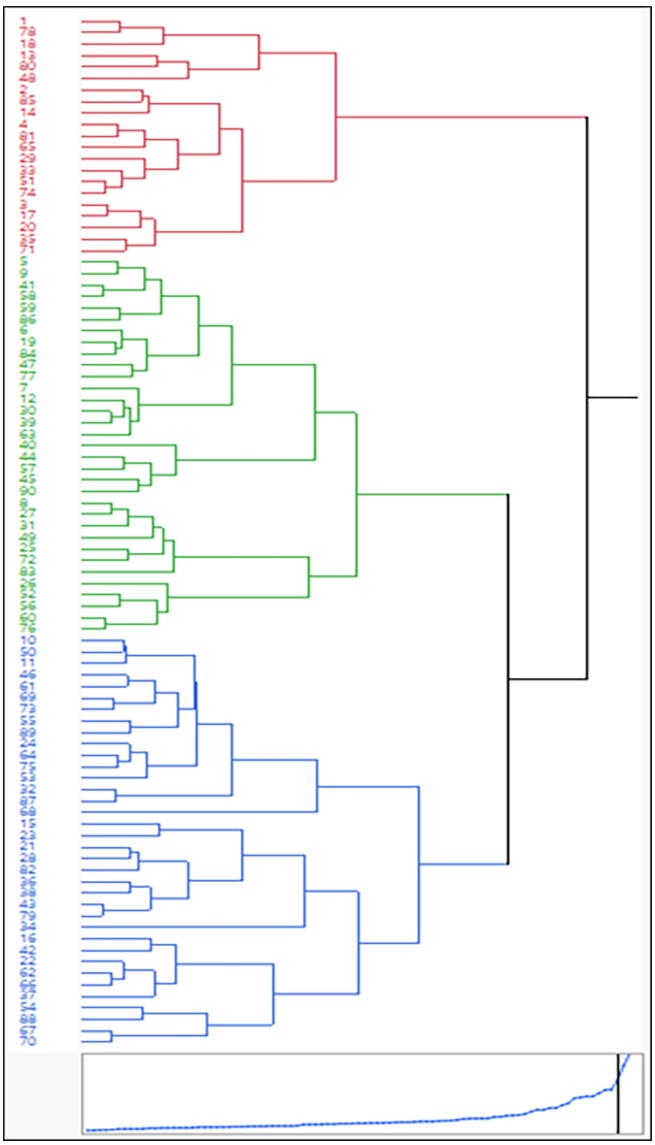

Figure 2 Dendrogram of hierarchical cluster analysis.

Regarding coping scores, there was a statistically significant cluster main effect on the overall scores (Wilks' λ = 0.173, $F(12164)$ = 19.172, P < 0.001, partial η^2 = 0.584). In further multiple comparisons, an adjusted alpha level of 0.008 (0.05/6) was adopted in response to the six different scores that comprised the coping indices. Specifically, the members of cluster 1 (labeled "Goal achievers with a high mass of coping") were characterized by a high level of BAS sensitivity and as using the greatest number of coping strategies with higher degree of perceived controllability. The members of cluster 2 (labeled "Goal preservers with a high mass of coping strategies") were characterized by a low BAS sensitivity level and as using a moderately large number of coping strategies with higher degree of perceived controllability. The members of cluster 3 (labeled "Goal achievers with a low mass of coping") were characterized by a high BAS sensitivity level but also as using the smallest number of coping strategies with lower degree of perceived controllability. For post-event mood states, there was no statistically significant cluster main effect on the overall ISS scores (Wilks' λ = 0.920,

F(4172) = 1.838, *P* = 0.124, partial η^2 = 0.041). However, the members of the "Goal achievers with a high mass of coping" cluster 1 had the highest ISS scores. The effect sizes were small to moderate, as indicated by the partial η^2 values (which ranged from 0.050 to 0.079).

Mediating effect of coping

As the sample size of each cluster was relatively small, the entire sample was used for calculation of the mediation or moderation effects. Following the analyses, only AA coping was found to meet the three conditions stipulated by Baron and Kenny[43]. The results are presented in Table 3. First, ISS (WB) was positively related to BAS (RR) (β = 0.335, *P* < 0.001). When BAS (RR) and AA coping were taken together in the regression analysis, the relationship between BAS (RR) and ISS (WB) was found to be weaker but still significant (β = 0.268, *P* < 0.001). Baron and Kenny[43] suggested that it was a partial mediation model. This partial mediation model was verified by the Sobel *z*-test [45] (*Z* = 2.156, *P* < 0.05).

Moderating effect of coping

The results are shown in Table 4. When the effects of sex and age were controlled for in block 1, some of the components of coping — including AA coping, perceived controllability, and variability of perceived controllability — were found to moderate the association between BAS sensitivity level and mood states. As recommended by Aiken and West[46], simple slope tests were performed to compare the effect of BAS sensitivity level on the mood states of individuals with high (1 SD above the mean) and low (1 SD below the mean) levels of coping. The results showed that the associations between BAS sensitivity level and mood states were negative among individuals with low levels of coping including AA coping, perceived controllability, and variability of perceived controllability (β = -0.735 to -0.019), whereas the associations were positive among individuals with high levels of coping (β = 0.202 to 0.497).

DISCUSSION

This study demonstrates how the judicious use of coping can help in emotion regulation for people with BD when encountering BAS-activating life events. Echoing previous research findings, it was found that higher BAS sensitivity levels[6,11] resulted in higher mood states. By comparing individuals between clusters 1 and 2, it was demonstrated that a higher degree of perceived controllability and using higher numbers of coping strategies can further over-activate an individual's mood state. Alternatively, when comparing clusters 1 and 3, with similar levels of BAS sensitivity, a lower degree of perceived controllability and using lower numbers of coping strategies were found to regulate heightened mood states.

With regard to the cognitive appraisal in terms of the high degree of perceived controllability, the judgment on an appraisal in the coping process may be colored by individual affective state[47], which should be related to the BAS sensitivity level, as shown in this study. Perceived controllability may connote taking an active role or exerting effort to alter the environment. Therefore, reducing the perceived controllability of life events seems to imply the notion of "non-striving," which is one of the core ideas in mindfulness[48-50]; as such, it is no wonder that mindfulness-based intervention is a plausible way to enhance mood regulation in BD[51].

Particularly, the mediation model showed that if an individual has a higher level of BAS sensitivity, this results in over-activation of mood states by stimulating the use of AA coping strategies. These results supplement previous findings[6,12,34] by verifying the role of the BAS dysregulation system in people with BD. The emotion amplifying intention is also in line with the findings of Stange *et al*[52], who suggested that individuals with high levels of BAS sensitivity exhibit greater emotion-focused rumination that may result in manic/hypomanic-like symptoms.

In addition, the moderation model suggests that subduing the use of AA coping, perceived controllability, and variability of perceived controllability was advantageous for people with high levels of BAS sensitivity, as it prevents the detrimental accentuation of mood states. That is, to attenuate their mood states, individuals with high levels of BAS sensitivity should utilize relatively less strategies — such as keeping oneself busy or encouraging rewarding activities — after exposure to BAS-activating life events. This kind of adaptation in coping should also extend the application of the dual process theory of coping flexibility[53] in mood regulation for people with BD. However, the alternative approach of increasing use of DD coping

Table 3 Mediating effect of behavioral-activation/emotion-amplifying coping between behavioral approach system sensitivity level and mood states (with dependent variable as internal state scale_well-being)

Variables	*B*	*SE B*	*β*
Step 1			
Outcome: ISS_WB			
Predictor: BAS_RR	9.841	2.953	0.335[b]
Step 2			
Outcome: AA			
Predictor: BAS_RR	0.244	0.074	0.332[b]
Step 3			
Outcome: ISS_WB			
Mediator: AA	8.054	4.186	0.202[a]
Predictor: BAS_RR	7.873	3.084	0.268[b]

[a]$P < 0.05$.
[b]$P < 0.01$.
AA: Behavioral-activation/emotion-amplifying coping; BAS: Behavioral approach system; ISS: Internal state scale; RR: Reward responsiveness; WB: Well-being.

could not be confirmed from the present results. Perhaps people with BD may tend to avoid use of some strategies, such as dampening response, by classifying them as maladaptive strategies[14]. Some individuals may even express ambivalence towards self-help strategies for the managing of high mood episodes[54]. It is necessary for there to be further investigation into the effectiveness of interventions for BD that emphasize the utilization of DD coping.

Nevertheless, cautions have to be taken in interpreting the findings. A general BAS sensitivity level and overall mood states were used for discussion here, despite there being different subscales presented in the BAS scale or ISS. There could exist a differential relationship between different subscales. ISS (WB) was found to be the common significant outcome in both mediation and moderation models; yet, the predictors involved were distinct. Only BAS (RR) was found in the former; whereas, BAS (D) and BAS (FS) were indicated in the latter. Perhaps the AA coping can be used to explain the contributing reason of sensitivity towards pleasant reinforcers leading to increased mood states. On the other hand, the reduced use of AA coping or perceived controllability can help to reduce the effects on elated mood due to motivation to goals or rewards. Future research is worthwhile for investigating the differences of various BAS or mood states' representation, especially for the mediating or moderating roles of coping. Moreover, videos were used as stimuli in this study. Despite having been found to be a reliable means by which to induce positive mood change[55], future research can be considered to compare different natural *vs* artificial means for eliciting varied mood states.

People who experience positive affect should have better psychological health, but over-elevated mood may not be adaptive for people with BD[56]. The judicious use of coping appears to be vital in managing positive affect or over-elevated mood among people with BD. Originally, the framework of coping was applied only to "negative" or stressful life events[57,58]; applying this framework to "positive" life events, as in the present study, has the potential to generate another conceptual viewpoint. Undoubtedly, people "cope" with positive events in order to cultivate higher positive affect and greater life satisfaction[59,60]. Folkman and Moskowitz[61] have also highlighted the beneficial effect or adaptational significance of positive affect in the midst of stress. However, positive affect as induced by positive events may do harm to people with impaired emotion regulation[37,62]. Coping with both positive effect and negative affect play equivalent roles in cases of people with BD. Broadening models of coping in the present study will help people with BD to gain greater insight into enhancing their competencies in emotion regulation.

This study also has important clinical significance and practical implications for the improvement of stress management programs for people with BD. Conventionally, and in most previous programs[63,64], participants have learned only general coping

Table 4 Moderating effect of coping between behavioral approach system sensitivity level and mood states (with dependent variable as internal state scale_well-being)

Variables	*B*	*SE B*	*β*	R^2	R^2 change	*F* change
Moderator: AA coping						
Block 2				0.137	0.069	3.405[a]
BAS_D	-0.236	7.417	-0.003			
AA	15.417	7.861	0.200			
Block 3				0.234	0.097	10.609[b]
BAS_D × AA	24.777	7.607	0.323[b]			
Moderator: CTR						
Block 2				0.153	0.085	4.256[a]
BAS_D	1.107	7.552	0.014			
CTR	18.150	7.757	0.236[a]			
Block 3				0.214	0.061	6.570[a]
BAS_D × CTR	16.691	6.512	0.258[a]			
Moderator: VCTR						
Block 2				0.086	0.019	0.864
BAS_FS	7.192	8.021	0.093			
VCTR	8.918	7.934	0.116			
Block 3				0.142	0.056	5.437[a]
BAS_FS × VCTR	-15.334	6.576	-0.239[a]			

[a]$P < 0.05$.
[b]$P < 0.01$.
AA: Behavioral-activation/emotion-amplifying coping; BAS: Behavioral approach system; CTR: Perceived controllability; D: Drive; FS: Fun-seeking; ISS: Internal state scale; VCTR: Variance of perceived controllability; WB: Well-being.

skills but not situation-specific ones. Enhancing individuals' understanding of how to differentiate effectively between various stressful situations may enhance their use of coping. Moreover, the emphasis of such a program has typically focused on negative life events. In fact, positive life events also play a significant role for people with BD with regard to life stress in general. This study promotes maintaining the balance of helping people with BD to cope with the later. Taking into account an individual difference in BAS sensitivity level, people with BD can deploy appropriate coping strategies to meet the different challenges that arise from various stressors. For example, "low degree" coping may help to stabilize the mood state of an individual with BD in situations where they are exposed to BAS-activating life events. Echoing the findings of Edge *et al*[25] that people with BD intentionally find appropriate ways to avoid mania so as to allow them to stay well[65], modification of such individuals' coping repertoire should lead to beneficial changes in their mood states. Thus, teaching the judicious use of various coping strategies in terms of AA or DD coping as well as facilitating proper attitude in reducing perceived controllability can further enhance the treatment effects of the stress management program for BD.

This study had some notable limitations. First, "polarity-specific" life events[66,67] either activate or deactivate the BAS in a dynamic process. However, this study focused only on a single pathway with respect to BAS-activating life events. Second, this study examined only people with BD, without a control group for comparison. People without BD should have lower BAS trait sensitivity levels, which may require a less emotion-driven consideration, so it may bring in a distinctive representation for individuals without BD. In addition, persistent cognitive deficits are common in people with BD even when they are euthymic[68], in which ventrolateral prefrontal cortex dysfunction was also demonstrated as a trait-related abnormality in people with euthymic BD[69]. Thus, future studies that compare euthymic BD with a healthy control group regarding the decision making in choosing coping strategies would be

of interest. Third, because only cross-sectional correlation statistics were utilized in this study, no definitive statement on causality can be made. Using a lower number of coping strategies can regulate heightened mood states, but it is also possible that the effect goes the other way around. Further longitudinal research is needed to achieve an understanding of the directionality. Moreover, the small sample size of this study may have affected the findings. In particular, the size of each cluster was quite small, and this may have affected the validity of the findings.

Despite these limitations, this study does provide novel insights into the landscape in which BAS sensitivity level and coping affect the mood states of people with BD. Investigations of this kind significantly improve our ability to identify potential vulnerabilities or protective factors that influence the course of recovery for people with BD. BAS-activating life events have been reckoned to have a prospective association with people's propensity to experience increasingly severe manic symptoms[33]. Thus, people with BD may be likely to over-activate their positive emotions or develop manic/hypomanic mood symptoms after exposure to the corresponding events. In essence, BD is characterized by amplified emotionality[13] together with difficulty in regulating emotion[70,71]. The ability to regulate their emotions, using appropriate coping strategies for various different life events, is therefore of paramount importance for people with BD.

CONCLUSION

Using a small number of coping strategies appears to be an adaptive emotion regulation strategy[72] for maintaining an euthymic state for people with BD. More specifically, as shown in this study, reducing the use of AA coping should be effective in countering high BAS sensitivity level, especially when coping with BAS-activating life events.

ARTICLE HIGHLIGHTS

Research background

Individuals with bipolar disorder (BD) frequently struggle with the recurrence of affective symptoms. However, the interplay between coping mechanism and positive mood state remains under-researched.

Research motivation

To add to the current knowledge about the role of coping in emotion regulation in people with BD.

Research objectives

The main objective was to explore the associations between the behavioral approach system (BAS) sensitivity level, coping flexibility, and mood states among people with BD after they encounter BAS-activating life events.

Research methods

Using a cross-sectional study design, 90 participants with BD were presented with four BAS-activating life event scenarios and assessed with regard to their BAS trait sensitivity, coping flexibility, and mood states. A hierarchical clustering method was used to identify different groups with different styles of coping. Multiple hierarchical regression analyses were conducted in order to examine the mediating and moderating roles of different components of coping on mood states.

Research results

A three-cluster solution was found to best fit the present data set. The findings showed that a low mass of coping combined with low BAS sensitivity level protects people with BD from detrimentally accentuating mood states when they encounter BAS-activating life events. Moreover, coping flexibility is demonstrated to mediate and moderate the relationships between BAS sensitivity level and mood states. Specifically, subduing the perceived controllability and reducing the use of behavioral-activation/emotion-amplifying coping strategies could help buffer the effect of positive affect.

Research conclusions

The judicious use of coping in emotion regulation for people with BD when encountering BAS-activating life events was indicated.

Research perspectives

The findings of this study have practical implications for the improvement of stress management programs. Theoretically, this study helps integrate the concept of coping flexibility into the BAS dysregulation theory as it applies to mental illness.

REFERENCES

1 **Duffy A**, Horrocks J, Doucette S, Keown-Stoneman C, Grof P, Andreazza A, Young LT. Immunological and neurotrophic markers of risk status and illness development in high-risk youth: understanding the neurobiological underpinnings of bipolar disorder. *Int J Bipolar Disord* 2014; **2**: 29 [PMID: 26092400 DOI: 10.1186/2194-7511-2-4]

2 **Newberg AR**, Catapano LA, Zarate CA, Manji HK. Neurobiology of bipolar disorder. *Expert Rev Neurother* 2008; **8**: 93-110 [PMID: 18088203 DOI: 10.1586/14737175.8.1.93]

3 **Green MJ**, Cahill CM, Malhi GS. The cognitive and neurophysiological basis of emotion dysregulation in bipolar disorder. *J Affect Disord* 2007; **103**: 29-42 [PMID: 17328959 DOI: 10.1016/j.jad.2007.01.024]

4 **Keener MT**, Phillips ML. Neuroimaging in bipolar disorder: a critical review of current findings. *Curr Psychiatry Rep* 2007; **9**: 512-520 [PMID: 18221633 DOI: 10.1007/s11920-007-0070-2]

5 **Johnson SL**, Tharp JA, Peckham AD, McMaster KJ. Emotion in bipolar I disorder: Implications for functional and symptom outcomes. *J Abnorm Psychol* 2016; **125**: 40-52 [PMID: 26480234 DOI: 10.1037/abn0000116]

6 **Alloy LB**, Abramson LY. The Role of the Behavioral Approach System (BAS) in Bipolar Spectrum Disorders. *Curr Dir Psychol Sci* 2010; **19**: 189-194 [PMID: 20606725 DOI: 10.1177/0963721410370292]

7 **Alloy LB**, Abramson LY, Walshaw PD, Cogswell A, Smith JM, Neeren AM, Hughes ME, Iacoviello BM, Gerstein RK, Keyser J, Urosevic S, Nusslock R. Behavioral approach system (BAS) sensitivity and bipolar spectrum disorders: A retrospective and concurrent behavioral high-risk design. *Motiv Emot* 2006; **30**: 143-155 [DOI: 10.1007/s11031-006-9003-3]

8 **Depue RA**, Iacono WG. Neurobehavioral aspects of affective disorders. *Annu Rev Psychol* 1989; **40**: 457-492 [PMID: 2648983 DOI: 10.1146/annurev.ps.40.020189.002325]

9 **Nusslock R**, Abramson LY, Harmon-Jones E, Alloy LB, Coan JA. Psychosocial Interventions for Bipolar Disorder: Perspective from the Behavioral Approach System (BAS) Dysregulation Theory. *Clin Psychol (New York)* 2009; **16**: 449-469 [PMID: 20161456 DOI: 10.1111/j.1468-2850.2009.01184.x]

10 **Gray JA**. Three fundamental emotion systems. In: Ekman P, Davidson RJ. The nature of emotion: Fundamental questions. New York: Oxford University Press, 1994: 243-247

11 **Urosević S**, Abramson LY, Harmon-Jones E, Alloy LB. Dysregulation of the behavioral approach system (BAS) in bipolar spectrum disorders: review of theory and evidence. *Clin Psychol Rev* 2008; **28**: 1188-1205 [PMID: 18565633 DOI: 10.1016/j.cpr.2008.04.004]

12 **Alloy LB**, Abramson LY, Urosevic S, Bender RE, Wagner CA. Longitudinal Predictors of Bipolar Spectrum Disorders: A Behavioral Approach System (BAS) Perspective. *Clin Psychol (New York)* 2009; **16**: 206-226 [PMID: 20161008 DOI: 10.1111/j.1468-2850.2009.01160.x]

13 **Gruber J**, Kogan A, Mennin D, Murray G. Real-world emotion? *J Abnorm Psychol* 2013; **122**: 971-983 [PMID: 24364600 DOI: 10.1037/a0034425]

14 **Dodd A**, Lockwood E, Mansell W, Palmier-Claus J. Emotion regulation strategies in bipolar disorder: A systematic and critical review. *J Affect Disord* 2019; **246**: 262-284 [PMID: 30590289 DOI: 10.1016/j.jad.2018.12.026]

15 **Painter JM**, Mote J, Peckham AD, Lee EH, Campellone TR, Pearlstein JG, Morgan S, Kring AM, Johnson SL, Moskowitz JT. A positive emotion regulation intervention for bipolar I disorder: Treatment development and initial outcomes. *Gen Hosp Psychiatry* 2019; **61**: 96-103 [PMID: 31439286 DOI: 10.1016/j.genhosppsych.2019.07.013]

16 **Cheng C**. Assessing coping flexibility in real-life and laboratory settings: a multimethod approach. *J Pers Soc Psychol* 2001; **80**: 814-833 [PMID: 11374752 DOI: 10.1037//0022-3514.80.5.814]

17 **Haines SJ**, Gleeson J, Kuppens P, Hollenstein T, Ciarrochi J, Labuschagne I, Grace C, Koval P. The Wisdom to Know the Difference. *Psychol Sci* 2016; **27**: 1651-1659 [PMID: 27738099 DOI: 10.1177/0956797616669086]

18 **Carver CS**, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. *J Pers Soc Psychol* 1989; **56**: 267-283 [PMID: 2926629 DOI: 10.1037//0022-3514.56.2.267]

19 **Holahan CJ**, Moos RH, Schaefer JA. Coping, stress resistance, and growth: Conceptualizing adaptive functioning. In: Zeidner M, Endler NS. Handbook of coping. New York: Wiley, 1996: 24-43

20 **Lazarus RS**, Folkman S. Stress, appraisal, and coping. New York: Springer, 1984

21 **Lazarus RS**. Stress and emotion: A new synthesis. New York: Springer, 1999

22 **Lam D**, Wong G. Prodromes, coping strategies, insight and social functioning in bipolar affective disorders. *Psychol Med* 1997; **27**: 1091-1100 [PMID: 9300514 DOI: 10.1017/s0033291797005540]

23 **Wong G**, Lam D. The development and validation of the coping inventory for prodromes of mania. *J Affect Disord* 1999; **53**: 57-65 [PMID: 10363667 DOI: 10.1016/s0165-0327(98)00096-2]

24 **Lam D**, Wong G, Sham P. Prodromes, coping strategies and course of illness in bipolar affective disorder--a naturalistic study. *Psychol Med* 2001; **31**: 1397-1402 [PMID: 11722154 DOI: 10.1017/s003329170100472x]

25 **Edge MD**, Miller CJ, Muhtadie L, Johnson SL, Carver CS, Marquinez N, Gotlib IH. People with bipolar I disorder report avoiding rewarding activities and dampening positive emotion. *J Affect Disord* 2013; **146**: 407-413 [PMID: 23021378 DOI: 10.1016/j.jad.2012.07.027]

26 **Kemner SM**, Mesman E, Nolen WA, Eijckemans MJ, Hillegers MH. The role of life events and psychological factors in the onset of first and recurrent mood episodes in bipolar offspring: results from the Dutch Bipolar Offspring Study. *Psychol Med* 2015; **45**: 2571-2581 [PMID: 25865058 DOI: 10.1017/S0033291715000495]

27 **Kemner SM**, van Haren NE, Bootsman F, Eijkemans MJ, Vonk R, van der Schot AC, Nolen WA, Hillegers MH. The influence of life events on first and recurrent admissions in bipolar disorder. *Int J Bipolar Disord* 2015; **3**: 6 [PMID: 25717427 DOI: 10.1186/s40345-015-0022-4]

28 **Thomas J**, Knowles R, Tai S, Bentall RP. Response styles to depressed mood in bipolar affective disorder. *J Affect Disord* 2007; **100**: 249-252 [PMID: 17134763 DOI: 10.1016/j.jad.2006.10.017]

29 **Gruber J**, Harvey AG, Gross JJ. When trying is not enough: emotion regulation and the effort-success gap in bipolar disorder. *Emotion* 2012; **12**: 997-1003 [PMID: 22251049 DOI: 10.1037/a0026822]

30 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th ed. Washington, DC: APA, 2013

31 **Tohen M**, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN, Malhi GS, Calabrese JR, Nolen WA, Vieta E, Kapczinski F, Goodwin GM, Suppes T, Sachs GS, Chengappa KR, Grunze H, Mitchell PB, Kanba S, Berk M. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord* 2009; **11**: 453-473 [PMID: 19624385 DOI: 10.1111/j.1399-5618.2009.00726.x]

32 **Carver CS**, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. *J Pers Soc Psychol* 1994; **67**: 319-333 [DOI: 10.1037/0022-3514.67.2.319]

33 **Alloy LB**, Abramson LY, Walshaw PD, Cogswell A, Grandin LD, Hughes ME, Iacoviello BM, Whitehouse WG, Urosevic S, Nusslock R, Hogan ME. Behavioral Approach System and Behavioral Inhibition System sensitivities and bipolar spectrum disorders: prospective prediction of bipolar mood episodes. *Bipolar Disord* 2008; **10**: 310-322 [PMID: 18271911 DOI: 10.1111/j.1399-5618.2007.00547.x]

34 **Urosević S**, Abramson LY, Alloy LB, Nusslock R, Harmon-Jones E, Bender R, Hogan ME. Increased rates of events that activate or deactivate the behavioral approach system, but not events related to goal attainment, in bipolar spectrum disorders. *J Abnorm Psychol* 2010; **119**: 610-615 [PMID: 20677850 DOI: 10.1037/a0019533]

35 **Wild D**, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005; **8**: 94-104 [PMID: 15804318 DOI: 10.1111/j.1524-4733.2005.04054.x]

36 **Cheng C**. Cognitive and motivational processes underlying coping flexibility: a dual-process model. *J Pers Soc Psychol* 2003; **84**: 425-438 [PMID: 12585814 DOI: 10.1037/0022-3514.84.2.425]

37 **Francis-Raniere EL**, Alloy LB, Abramson LY. Depressive personality styles and bipolar spectrum disorders: prospective tests of the event congruency hypothesis. *Bipolar Disord* 2006; **8**: 382-399 [PMID: 16879139 DOI: 10.1111/j.1399-5618.2006.00337.x]

38 **Ruggero CJ**, Johnson SL. Reactivity to a laboratory stressor among individuals with bipolar I disorder in full or partial remission. *J Abnorm Psychol* 2006; **115**: 539-544 [PMID: 16866593 DOI: 10.1037/0021-843X.115.3.539]

39 **Miller IW**, Bishop S, Norman WH, Maddever H. The Modified Hamilton Rating Scale for Depression: reliability and validity. *Psychiatry Res* 1985; **14**: 131-142 [PMID: 3857653 DOI: 10.1016/0165-1781(85)90057-5]

40 **Bech P**, Bolwig TG, Kramp P, Rafaelsen OJ. The Bech-Rafaelsen Mania Scale and the Hamilton Depression Scale. *Acta Psychiatr Scand* 1979; **59**: 420-430 [PMID: 433633 DOI: 10.1111/j.1600-0447.1979.tb04484.x]

41 **Bauer MS**, Crits-Christoph P, Ball WA, Dewees E, McAllister T, Alahi P, Cacciola J, Whybrow PC. Independent assessment of manic and depressive symptoms by self-rating. Scale characteristics and implications for the study of mania. *Arch Gen Psychiatry* 1991; **48**: 807-812 [PMID: 1929771 DOI: 10.1001/archpsyc.1991.01810330031005]

42 **Mansell W**, Lam D. "I won't do what you tell me! *Behav Res Ther* 2006; **44**: 1787-1801 [PMID: 16487480 DOI: 10.1016/j.brat.2006.01.002]

43 **Baron RM**, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; **51**: 1173-1182 [PMID: 3806354 DOI: 10.1037//0022-3514.51.6.1173]

44 **Frazier PA**, Tix AP, Barron KE. Testing moderator and mediator effects in counseling psychology research. *J Couns Psychol* 2004; **51**: 115-134 [DOI: 10.1037/0022-0167.51.1.115]

45 **Sobel ME**. Asymptotic CIs for indirect effects in structural equation models. In: Leinhardt S. Sociological methodology 1982. Washington, DC: American Sociological Association, 1982: 290-312

46 **Aiken LS**, West SG. Multiple regression: Testing and interpreting interactions. Newbury Park, CA: Sage, 1991

47 **Forgas JP**, Eich E. Affective influences on cognition: Mood congruence, mood dependence, and mood effects on processing strategies. In: Forgas JP, Eich E, editors. Handbook of psychology: Experimental psychology. 2nd ed. Hoboken: John Wiley & Sons Inc, 2013: 61-82

48 **Kabat-Zinn J**. Full catastrophe living: Using the wisdom of your body and mind to face stress, pain, and illness. New York: Delta Books, 1990

49 **Hayes SC**. Acceptance, mindfulness, and Science. *Clin Psychol (NY)* 2002; **9**: 101-106 [DOI: 10.1093/clipsy.9.1.101]

50 **Kabat-Zinn J**. Wherever you go there you are: Mindfulness meditations in everyday life. New York: Hyperion, 1994

51 **Deckersbach T**, Hozel B, Eisner L, Lazar SW. Mindfulness-based cognitive therapy for bipolar disorder. New York: Guilford Publications, 2014

52 **Stange JP**, Shapero BG, Jager-Hyman S, Grant DA, Abramson LY, Alloy LB. Behavioral Approach System (BAS)-Relevant Cognitive Styles in Individuals with High vs. Moderate BAS Sensitivity: A Behavioral High-Risk Design. *Cognit Ther Res* 2013; **37**: 139-149 [PMID: 23459574 DOI: 10.1007/s10608-012-9443-x]

53 **Kato T**. Testing of the coping flexibility hypothesis based on the dual-process theory: Relationships between coping flexibility and depressive Symptoms. *Psychiatry Res* 2015; **230**: 137-142 [PMID: 26342281 DOI: 10.1016/j.psychres.2015.07.030]

54 **Tse S**, Yuen YM, Suto M. Expected possible selves and coping skills among young and middle-aged adults with bipolar disorder. *East Asian Arch Psychiatry* 2014; **24**: 117-124 [PMID: 25316803]

55 **Lomax CL**, Barnard PJ, Lam D. Cognitive processing in bipolar disorder conceptualized using the Interactive Cognitive Subsystems (ICS) model. *Psychol Med* 2009; **39**: 773-783 [PMID: 18796173 DOI: 10.1017/S003329170800425X]

56 **Ford BQ**, Mauss IB, Gruber J. Valuing happiness is associated with bipolar disorder. *Emotion* 2015; **15**: 211-222 [PMID: 25603134 DOI: 10.1037/emo0000048]

57 **Gan Y**, Liu Y, Zhang Y. Flexible coping responses to severe acute respiratory syndrome-related and daily life stressful events. *Asian J Soc Psychol* 2004; **7**: 55-66 [DOI: 10.1111/j.1467-839X.2004.00134.x]

58 **Cheng C**, Lau HP, Chan MP. Coping flexibility and psychological adjustment to stressful life changes: a meta-analytic review. *Psychol Bull* 2014; **140**: 1582-1607 [PMID: 25222637 DOI: 10.1037/a0037913]

59 **Nelis S**, Holmes EA, Palmieri R, Bellelli G, Raes F. Thinking Back about a Positive Event: The Impact of Processing Style on Positive Affect. *Front Psychiatry* 2015; **6**: 3 [PMID: 25806003 DOI: 10.3389/fpsyt.2015.00003]

60 **Gable SL**, Reis HT, Impett EA, Asher ER. What do you do when things go right? *J Pers Soc Psychol* 2004; **87**: 228-245 [PMID: 15301629 DOI: 10.1037/0022-3514.87.2.228]

61 **Folkman S**, Moskowitz JT. Positive affect and the other side of coping. *Am Psychol* 2000; **55**: 647-654 [PMID: 10892207 DOI: 10.1037//0003-066x.55.6.647]

62 **Kang Y**, Gruber J. Harnessing happiness? *Emotion* 2013; **13**: 290-301 [PMID: 23205524 DOI: 10.1037/a0030780]

63 **Zaretsky AE**, Rizvi S, Parikh SV. How well do psychosocial interventions work in bipolar disorder? *Can J Psychiatry* 2007; **52**: 14-21 [PMID: 17444074 DOI: 10.1177/070674370705200104]

64 **Miklowitz DJ**, Otto MW, Frank E, Reilly-Harrington NA, Kogan JN, Sachs GS, Thase ME, Calabrese JR, Marangell LB, Ostacher MJ, Patel J, Thomas MR, Araga M, Gonzalez JM, Wisniewski SR. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. *Am J Psychiatry* 2007; **164**: 1340-1347 [PMID: 17728418 DOI: 10.1176/appi.ajp.2007.07020311]

65 **Murray G**, Suto M, Hole R, Hale S, Amari E, Michalak EE. Self-management strategies used by 'high functioning' individuals with bipolar disorder: from research to clinical practice. *Clin Psychol Psychother* 2011; **18**: 95-109 [PMID: 20572206 DOI: 10.1002/cpp.710]

66 **Johnson SL**. Life events in bipolar disorder: towards more specific models. *Clin Psychol Rev* 2005; **25**: 1008-1027 [PMID: 16129530 DOI: 10.1016/j.cpr.2005.06.004]

67 **Johnson SL**, Cueller AK, Ruggero C, Winett-Perlman C, Goodnick P, White R, Miller I. Life events as predictors of mania and depression in bipolar I disorder. *J Abnorm Psychol* 2008; **117**: 268-277 [PMID: 18489203 DOI: 10.1037/0021-843X.117.2.268]

68 **Elshahawi HH**, Essawi H, Rabie MA, Mansour M, Beshry ZA, Mansour AN. Cognitive functions among euthymic bipolar I patients after a single manic episode *vs* recurrent episodes. *J Affect Disord* 2011; **130**: 180-191 [PMID: 21074274 DOI: 10.1016/j.jad.2010.10.027]

69 **Foland-Ross LC**, Bookheimer SY, Lieberman MD, Sugar CA, Townsend JD, Fischer J, Torrisi S, Penfold C, Madsen SK, Thompson PM, Altshuler LL. Normal amygdala activation but deficient ventrolateral prefrontal activation in adults with bipolar disorder during euthymia. *Neuroimage* 2012; **59**: 738-744 [PMID: 21854858 DOI: 10.1016/j.neuroimage.2011.07.054]

70 **Johnson SL**, Gruber J, Eisner L. Emotion in bipolar disorder. In: Rottenberg J, Johnson SL. Emotion and psychopathology: Bridging affective and clinical science. Washington: American Psychological Association, 2007: 123-150
71 **Phillips ML**, Vieta E. Identifying functional neuroimaging biomarkers of bipolar disorder: toward DSM-V. *Schizophr Bull* 2007; **33**: 893-904 [PMID: 17562698 DOI: 10.1093/schbul/sbm060]
72 **Wolkenstein L**, Zwick JC, Hautzinger M, Joormann J. Cognitive emotion regulation in euthymic bipolar disorder. *J Affect Disord* 2014; **160**: 92-97 [PMID: 24445131 DOI: 10.1016/j.jad.2013.12.022]

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SYSTEMATIC REVIEWS

Thinking about worry: A systematic review and meta-analysis on the assessment of metacognitions in children and adolescents

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Abstract

BACKGROUND

The metacognitive model of generalized anxiety disorder identifies three forms of metacognition: Positive metacognitive beliefs about worry (POS), negative metacognitive beliefs about worry (NEG), and meta-worry. Though this model was originally developed relying on adult samples, it has since been applied to children and youth in different studies, and results mostly support its validity for this group. As the roles of POS, meta-worry, and age-effects do not appear to be fully clarified for children and adolescents yet, an integration of studies on children and adolescents and the metacognitive model is both timely and worthwhile.

AIM

To summarize the current research on relationships, age-effects, and measurements for POS, NEG, and meta-worry in childhood and youth.

METHODS

We carried out a literature search in the electronic databases PsycINFO, PubMed, PSYNDEX, and ERIC in 2017 and updated in 2020. Empirical research in German or English language on metacognition was included with child and adolescent samples diagnosed with anxiety disorders or healthy controls if POS, NEG, or meta-worry were measured. Studies were included for meta-analysis if they reported correlations between these metacognitions and anxiety or worry. Consensus rating for eligibility was done for 20.89% of full-texts with 90.32% agreement. Risk of bias was assessed with the appraisal tool for cross-sectional studies and consensus rating of appraisal tool for cross-sectional studies for 20.83% of included studies attaining agreement of intraclass correlation = 0.898. Overall, correlations between metacognitions, anxiety and worry were calculated with RevMan 5.4.1, assuming random-effects models. Meta-regressions with

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mean age as the covariate were performed *via* the online tool MetaMar 2.7.0. PROSPERO-ID: CRD42018078852.

RESULTS

Overall, k = 763 records and k = 78 additional records were identified. Of those, k = 48 studies with 12839 participants were included and of those, k = 24 studies were included for meta-analysis. Most studies showed consistent NEG correlations with worry and anxiety, as well as higher values for clinical than for non-clinical samples. POS findings were less consistent. Meta-analysis revealed large effects for NEG correlating with worry and anxiety, small to medium effects for POS correlating with worry and anxiety, as well as small to medium effects for POS correlating with NEG. Meta-regressions did not reveal mean age as a significant covariate. Meta-worry was assessed in only one study. We identified eight questionnaires and one interview-format that assess metacognition about worry in children and adolescents.

CONCLUSION

POS and NEG are measurable from the age of seven upwards and correlate with anxiety and worry without influences by age. Meta-worry requires further investigation.

Key Words: Metacognition; Anxiety; Child; Adolescent; Measures; Meta-analysis

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Core Tip: Systematic review and meta-analysis showed that positive metacognitive beliefs about worry and negative metacognitive beliefs about worry correlate with worry and anxiety, as claimed in the metacognitive model of generalized anxiety disorder. Studies tended not to report significant correlations between age and positive metacognitive beliefs about worry or negative metacognitive beliefs about worry. Mean age was not a significant covariate in meta-regressions. No conclusions about meta-worry's influence can be drawn. We need an adequate measurement of meta-worry, and measurements applying to young children should undergo further investigation. Studies showed moderate to large heterogeneity, and the power of meta-regression might have been low. As mostly cross-sectional data were collected, no causal conclusions can be drawn.

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INTRODUCTION

Anxiety disorders in children and adolescents reveal a 6.5% prevalence, making them the most prevalent mental disorder in this age group worldwide[1]. They are associated with various negative effects, *e.g.*, impaired school performance, sleep and social functions, increased risk of comorbidities (such as depression or other anxiety disorders), and persistence into adulthood[2-5]. A key feature of anxiety is worry. Worries are understood as repetitive, chained thoughts about potentially negative future events, and they are fear-related[6,7]. These thoughts are common, occurring in 60.1% of children and adolescents[8]. Almost every second preschooler has worries, and even more children worry as they grow older[9]. Worry is associated with anxiety symptoms in community samples as well as in samples consisting of children with anxiety disorders[10,11]. Children with anxiety disorders suffer more intense worries than healthy children[12]. The frequency of worry itself, however, does not seem to be problematic. However, worries seem to become pathological when they are experienced as intense and uncontrollable[13]. Excessive worry is a core criterion of

general anxiety disorder (GAD)[14], and domain-specific worries are a diagnostic criterion of separation anxiety disorder (SAD)[13]. When compared specifically, children with diagnosed anxiety disorders reveal significantly more self-reported worry than healthy children, and children with GAD scored higher on worry assessments than children suffering from other anxiety disorders[11]. Worry is thus a central feature of anxiety in childhood and youth.

In line with the importance of evaluating worries as intense and uncontrollable, both worry itself and "thinking about worry" play key roles in anxiety disorders. Such higher-level thinking is described as metacognition, a concept first defined by Flavell [15] as "knowledge and cognition about cognitive phenomena" (S. 906). Metacognitions are known to be involved in the development and maintenance of mental disorders such as depression and anxiety or obsessive-compulsive disorders (OCD) [16-20]. For pathological worries to develop, Wells[19-21] emphasizes three forms of metacognition that play decisive roles: Positive metacognitive beliefs about worry (POS), negative metacognitive beliefs about worry (NEG), and meta-worry. POS refer to the usefulness of various thoughts (*e.g.*, "Worrying helps me to avoid problems in the future"[22]). NEG can be understood as trait-beliefs that a person generally holds about worries[21]. They include the appraisal of one's own thoughts as uncontrollable and imply negative consequences of worries (*e.g.*, "Worrying is dangerous for me"[22]). Meta-worry can be described as the state of worrying about worry[21]. Wells describes his assumptions about how these metacognitive constructs interact with each other and with worry, behavior, thought control strategies, and emotion in the metacognitive model of GAD[19-21].

The metacognitive model of GAD postulates that an intense, negative thought is what initially triggers worry. Worrying is then especially likely to become a coping strategy when someone tends to think about worry's usefulness (POS). If general beliefs that worry is dangerous or uncontrollable (NEG) have been activated, one starts to worry about current worries (meta-worry). Meta-worry provokes emotions such as anxiety, which only exacerbates worry and meta-worry. Anxiety is misattributed as a consequence of the worries themselves, which in turn reinforces NEG. As this thought spiral continues, meta-worry triggers coping strategies such as reassurance, avoidance behavior, or substance abuse. As these dysfunctional attempts prevent the person from experiencing that worries are controllable and harmless, meta-worry and NEG about the danger of worries are reinforced. Meta-worry can also lead to thought-control strategies such as suppression, and if these fail, meta-worry and NEG will persist (for details and figural display of the metacognitive model of GAD see Wells[21]).

The metacognitive model has been investigated in children and adolescents in different studies. Esbjørn *et al*[23] showed that metacognitive processes, in addition to the effects of gender, age, and anxiety, account for 14% of the variance of worry and an additional 11% of the variance of anxiety in a healthy sample of children. In a second study, patients with GAD reported more POS and NEG than children with other anxiety disorders or healthy controls, and children with anxiety disorders reported more NEG than healthy controls[23]. Another study by Ellis and Hudson[24] also showed that adolescents with anxiety disorders described more POS and NEG than a control group. These findings support assumptions of the metacognitive model of GAD and support its validity in childhood and youth. However, there are also contradictory findings that question this validity. For example, some studies failed to detect any significant relationships between POS and worry or anxiety in children[25,26] or found no differences in either POS or NEG between clinical and non-clinical participants[27,28].

In addition, the question arises as to the age that these metacognitions about worry develop and whether they change with age. Ellis and Hudson[29] noted that few studies on the metacognitive model included children under 12 years of age. There have also been mixed results about the relationship with age, as some studies show correlations between metacognitions and age[24] while other studies do not[30]. When transferring adult models like the metacognitive model of GAD to children, the experience and cognitive skills of children must be taken into account[24]. Metacognitive skills are assumed to be gradually acquired[31]: At 3 years of age, children can name mental processes and distinguish them from the external environment[32,33]. From the age of four, children understand that thoughts can refer to non-real or non-present things[34]. Seven-year-old children know when, what, and at what frequency they themselves or others are thinking[33-35]. However, more recent results indicate that already 3- to 5-year-old children can demonstrate metacognitive knowledge when measured with an age-appropriate interview[36].

To evaluate the age at which children first think about their worries (*i.e.* metacognition about worry), an age-appropriate assessment is needed. Many studies use questionnaires to measure metacognition in children[23,24,27]. However, a recent review's authors concluded that questionnaires for younger children yield mixed results for factor structure, internal consistency, and age-appropriateness, and they emphasize the need for further development and psychometric analysis of assessments for metacognition in childhood[37].

The present systematic review synthesizes the latest findings about metacognition on worry in children and adolescents. Current knowledge for POS, NEG, and meta-worry as well as their development is summarized, as are available assessments of POS, NEG, and meta-worry for children and adolescents. In so doing, we posed the questions below:

What evidence is there for positive relationships between POS, NEG, and meta-worry with each other and with worry and anxiety in children and adolescents?

At what age do children report POS, NEG, and meta-worry, and does age play any role in relationships with worry and anxiety?

Which methods are currently applicable to assess POS, NEG, and meta-worry in childhood and youth?

To answer these questions, we conducted a systematic review of the recent literature. We synthesized the tested relationships between POS, NEG, meta-worry with each other, worry, and anxiety in order to compare those results with the postulated relationships in the metacognitive model of GAD. For further validation, we compared non-clinical samples and clinical samples consisting of children and adolescents with anxiety disorders, as the latter are likely to exhibit more NEG and meta-worry according to the metacognitive model of GAD, while that does not necessarily apply to POS (compare Wells[21]). To assess potential age effects, we summarized results for age of onset and developmental patterns for POS, NEG, and meta-worry. Different methods of assessing POS, NEG, and meta-worry and reported reliability measures, their usage in age-ranges, and the numbers of studies are resumed.

Depending on the studies identified, we conducted additional meta-analysis based on effect sizes of POS, NEG, and meta-worry correlations with each other and with anxiety and worry. Whenever possible, we performed meta-regressions to analyze whether age is a significant covariate for these relationships.

MATERIALS AND METHODS

Literature search

This systematic review was registered with PROSPERO (International prospective register of systematic reviews, PROSPERO-ID: CRD42018078852, last update: January 26, 2021) and is based on the PRISMA Statement[38] and the PRISMA-P Statement [39]. The literature search was first run on September 24, 2017 and updated on February 6, 2020.

The search string "(children OR adolescents*) AND (meta cognition* OR metacognition* OR meta-cognitive belief* OR meta cognitive belief*) AND (anxiety OR worry OR phobia)" was used in the following databases: PsycINFO, PubMed, and PSYNDEX. In addition, available full-texts of the database ERIC were searched with the same search string. In the first search (2017), we set no limitations to obtain a preferably broad impression of the state of research. In the second search (2020), the period was limited to publication dates between 2017 and 2020. We identified additional studies through a backward search of reference lists by screening additive publications of research groups and, to include the gray literature, the screening of doctoral theses. After identifying records through the databases and additional searches, duplicates were removed. Afterwards, titles, key words, and abstracts in all records were screened by the first author. The full-text versions of the remaining records were analyzed for eligibility. Doctoral theses were only included if the data had not been published in a journal. In case of the latter, the publication was included and the doctoral thesis was excluded from analysis. The study selection process was conducted by one reviewer (Köcher LM). Additionally, 20.89% (k = 33) of the full-texts were independently rated for eligibility by another reviewer (Schneider K). Overall, 90.32% of the ratings were in agreement. In case of discrepancies, a third reviewer (Christiansen H) was consulted, and consensus was reached for the remaining 9.68% (k = 3) of records.

Study selection

Empirical studies reporting quantitative data were included in the systematic review, which fulfilled the following criteria: (1) Participants were 18 years of age or younger; (2) Non-clinical samples and/or clinical samples with anxiety disorders were investigated. We followed the classification for anxiety disorders in the fifth edition of the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-5)[40], including the following diagnoses: GAD, SAD, social anxiety disorder (SoD), specific phobia, agoraphobia, and panic disorder; (3) POS, NEG, and/or meta-worry were assessed as an outcome variable; (4) The study was published in English or German language; and (5) The study had been published by February 6, 2020.

To be included in our meta-analysis, studies also had to fulfill these criteria: (6) Bivariate correlation coefficients for relationships between POS/NEG/meta-worry with each other/anxiety/worry were reported; and (7) Data were not reported in a study that had already been included in our meta-analysis.

Data extraction

The first author extracted the following information from the included studies: Author(s), year of publication, title, country, study design, sample size, study population (non-clinical and/or clinical, and related diagnoses), participants' age range and/or mean age, gender distribution, measurement of POS/NEG/meta-worry and reliability, anxiety measurement, worry measurement, relationship of POS/NEG/meta-worry with each other/anxiety/worry/age, and group differences between clinical and non-clinical subgroups in POS/NEG/meta-worry.

The study characteristics coded for meta-analysis and meta-regression by the first author were: Effect sizes of correlations between POS/NEG/meta-worry with each other/anxiety/worry, sample size, and mean age. If studies reported correlational coefficients split for different subgroups such as male or female participants, or clinical or non-clinical participants, correlations were coded separately for subgroups and then combined to a single correlation according to the following procedure: Correlations were transformed into Fisher's z scores and weighted by subsample size, then the mean of both values was inversely z-transformed into product-moment-correlation coefficients. If a study reported a subsample's data in a previous study that we had already included in the meta-analysis, only the other subsample's data were coded for this study. For meta-regressions, studies were only included if they reported the mean age of their samples. If mean age was reported for split subgroups, values were coded for each of these subgroups and mean of the mean ages, weighted by subsample sizes, was calculated and used for meta-regression.

Risk of bias

To assess the risk of bias, each study was rated on the Appraisal tool for Cross-Sectional Studies (AXIS)[41] by one reviewer (Köcher LM). AXIS-scores range between 0 and 20 and were clustered in the categories high (0-6), moderate (7-13), and low risk of bias (14-20) for a global rating. Additionally, 20.83% of studies (k = 10) were rated by an independent reviewer in our working group. Our interrater agreement (intraclass correlation = 0.898) can be considered as good[42].

Statistical analysis

Statistical analysis was performed by the first author and reviewed by the third author at the Department of Psychology, Philipps University Marburg. Coded correlation coefficients were transformed into Fisher's z scale for meta-analysis. For reports of summary correlations, all summary Fisher's z were back-transformed into Pearson's product-moment correlations. Cohen's criteria[43] were used to interpret overall effect sizes. Random-effect models were used for analysis because of assumed heterogeneity in addition to sampling error. Calculations were computed using the computer program RevMan, version 5.4.1[44]. To show actual dispersion of overall effects, prediction intervals are reported in addition to CIs, as proposed by IntHout *et al*[45], and calculated based on the T^2-estimate[46]. Heterogeneity was tested using Q-statistic and I^2. Interpretations of I^2 are based on benchmarks proposed by Higgins *et al*[47]. Results of each meta-analysis are graphically illustrated in forest plots. A set of meta-regressions was conducted to test whether mean age of the included studies moderated the analyzed correlations significantly. Other potential covariates such as sample type (clinical *vs* non-clinical) were not examined due to the low number of k = 1 study[25] included in the meta-analysis with a clinical sample only. Meta-regressions were run using the free online meta-analysis tool Meta-Mar, version 2.7.0[48].

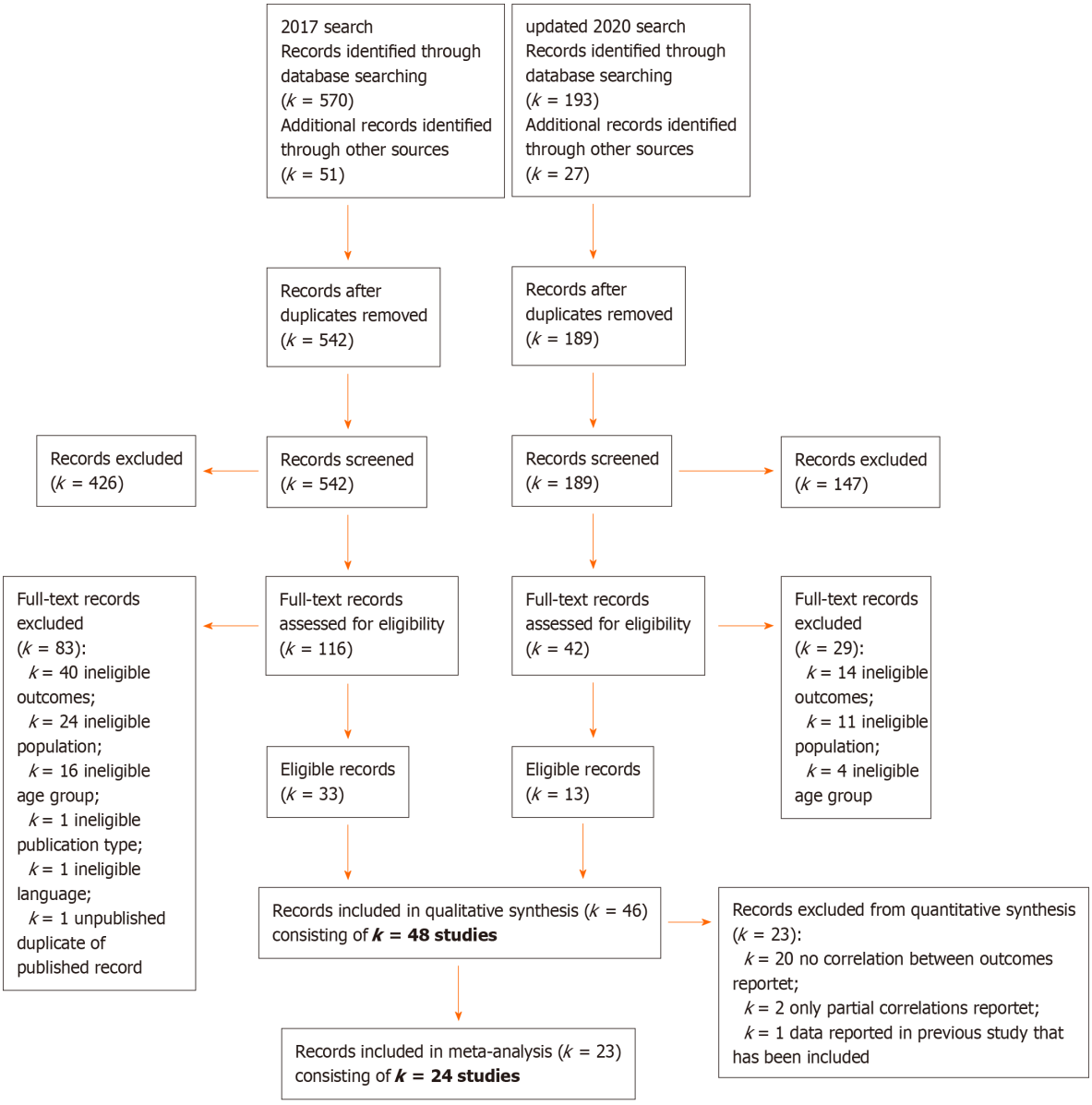

Figure 1 Adapted PRISMA Flowchart for study selection in this systematic review and meta-analysis.

RESULTS

Study selection

Figure 1 shows this review's selection process divided into the first search in 2017 and the search updated in 2020. Overall, k = 763 records were identified through database searching. A total of k = 78 additional records were identified through other sources. Initially, a total of k = 110 duplicates were removed. Next, the first author screened the titles and abstracts of the identified studies. k = 158 records remained in the selection process after screening. Overall, k = 46 records fulfilled our inclusion criteria. Of those, each of two records reported two studies[23,49], resulting in k = 48 studies overall included in this systematic literature review. In two cases, working groups analyzed the same datasets in two independently published records[27,28,50,51]. For quantitative synthesis, k = 24 studies fulfilled our inclusion criteria and were included in meta-analysis.

Characteristics of studies included in this systematic review

An overview of the included studies and study characteristics is found in Table 1. They contain k = 47 published studies carried out in Australia, Canada, Denmark, Germany, Italy, Iran, Turkey, the United Kingdom or Ireland, and United States between 2003 and 2020. The k = 1 remaining study is characterized as gray literature and was submitted in 2014 to qualify for a doctorate degree at a German university.

Table 1 Overview of studies included in the systematic review

Ref.	Sample	*n*	Female (%)	Age in year (range), mean ± SD	Risk of bias	POS/NEG/meta-worry	Worry	Anxiety
Babaei *et al*[55]	NC	200	NA	NA	Mod (9)	MCQ-30	-	GHQ-scale
Bacow *et al*[27]	Total/C[1,2,3,4]/NC	98/78/20	NA/63%/65%	(7-17) NA/(NA) 11.9 ± 3.1/(NA) 12.4 ± 3.0	Low (14)	MCQ-C	ADIS-C-section	ADIS-C/P
Bacow *et al*[28]	Total/C[1,2,3,4]/NC	98/78/20	NA/63%/65%	(7-17) NA/(NA) 11.9 ± 3.1/(NA) 12.4 ± 3.0	Low (14)	MCQ-C	PSWQ-C; ADIS-C-section	ADIS-C/P
Benedetto *et al*[64]	NC	184	53%	(11-13) 12.0 ± 0.9	Mod (13)	MCQ-C	PSWQ-C	RCMAS-2
Benedetto *et al*[49], study1	NC	191	49%	(13-18) 16.4 ± 1.76[a]	Mod (13)	MCQ-C	-	RCMAS-2
Benedetto *et al*[49], study2	C[1,5]/NC[b]	14/14	57%/NA	(12-17) 14.9 ± 1.6/NA	Low (14)	MCQ-C	-	RCMAS-2
Boysan *et al*[92]	NC	805	49%	(11-17) 13.9 ± 1.4	Low (14)	MCQ-C	-	STAI-C
Carr and Szabó[72]	NC	93	48%	(7-12) 10.0 ± 1.2	Low (16)	MCQ-C	CAWS	-
Cartwright-Hatton *et al*[53]	C[6]/NC	(11)/166	(64%)/66%	NA/(13-17) 15.3 ± NA	Mod (12)	MCQ-A	-	RCMAS
Donovan *et al*[80]	Total/C[1]/NC	50/25/25	60%/NA/NA	(7-12) 9.9 ± 1.5/NA/NA	Low (14)	MCQ-C	PSWQ-C	ADIS-C
Donovan *et al*[65]	NC	114	51%	(8-12) 9.9 ± 1.3	Low (15)	MCQ-C	PSWQ-C	-
Ellis and Hudson[24]	Total/C[1,5]/NC	123/81/42	NA/57%/52%	(12-17) NA/(NA) 14.1 ± 1.5/(NA) 13.7 ± 1.4	Low (15)	MCQ-A	PSWQ	ADIS-C/P; SCAS-C/P
Esbjørn *et al*[23], study1	NC	587	55%	(9-17) 12.5 ± 0.9[a]	Mod (12)	MCQ-C_{30}	PSWQ-C	SCARED-R
Esbjørn *et al*[23], study2	Total/C[1,4,7,3]/NC	93/50/43	NA/NA/NA	(7-12) 9.8 ± 1.6/NA/NA	Mod (13)	MCQ-C_{30}	-	ADIS-C/P
Esbjørn *et al*[93]	NC	111	64%	(8-12) 10.1 ± 1.4	Low (15)	MCQ-C_{30}	PSWQ-C	ADIS-C/P; RCADS
Esbjørn *et al*[66]	NC	974	55%	(9-17)	Low (15)	MCQ-C_{30}	PSWQ-C	SCARED-R
Esbjørn *et al*[56]	C[1]	44	50%	(7-13) 9.7 ± 1.6	Low (15)	MCQ-C_{30}	PSWQ-C	ADIS; RCADS
Fergus and Limbers[57]	NC (TG)/NC (CG)	39/34	62%/71%	(NA) 13.8 ± 0.5/(NA) 13.8 ± 0.7	Low (17)	MCQ-C	-	CTAS
Fisak *et al*[73]	NC	175	66%	(11-18) 13.9 ± 1.5	Mod (12)	MCQ-C;MWQ	PSWQ-C	-
Francis *et al*[50]	NC	312	55%	(9-15) 11.9 ± 1.2	Low (15)	MCQ-C	PSWQ-C	SCAS;MASC
Francis *et al*[51]	NC	312	55%	(9-15) 11.9 ± 1.2	Mod (14)	MCQ-C	PSWQ-C	-
Gallagher and Cartwright-Hatton[94]	NC	168	85%	(16-18) 17.2 ± 0.9	Mod (11)	MCQ-30	-	STAI-T
Gini *et al*[67]	NC	1169	48%	(14-17) 15.8 ± 1.1	Mod (11)	MCQ-30	PSWQ-C	GAD7
Hearn *et al*[25]	C[3]	126	60%	(8-17) 11.3 ± 2.7	Mod (13)	MCQ-C	PSWQ-C(SF)	ADIS;SPAI-10-C/P

Hearn *et al*[74]	Total/C[1,3]/NC	60/40/20	70%/NA/NA	(8-12) 9.9 ± 1.3/NA/NA	Low (15)	MCQ-C	PSWQ-C(SF)	ADIS; SCAS
Hearn *et al*[26]	Total/C[3] (TG)/C[3] (WL)	125/95/30	60%/NA/NA	(8-17) 11.3 ± 2.7/NA/NA	Low (17)	MCQ-C	PSWQ-C(SF)	ADIS; SPAI-10
Holmes *et al*[59]	C[1]	1	0%	10	Low (16)	MCQ-C	PSWQ-C	ADIS-C/P;SCAS-C/P
Holmes *et al*[58]	Total/C[1] (TG)/C[1] (WL)	42/20/22	67%/NA/NA	(7-12) 9.6 ± 1.4/NA/NA	Low (17)	MCQ-C	PSWQ-C	ADIS-C/P;SCAS-C/P
Irak[78]	NC	470	44%	(8-17) 12.2 ± 2.8	Mod (12)	MCQ-C	-	STAI-C
Kertz and Woodruff-Borden [75]	NC	80	71%	(8-12) 9.6 ± 1.1	Mod (12)	MCQ-C	PSWQ-C(SF)	RCMAS
Laugesen *et al*[71]	NC	528	49%	(14-18) 15.6 ± 0.9	Low (15)	WW-II	PSWQ-C	WAQ
Lønfeldt *et al*[76]	NC	188	66%	(7-12) 10.0 ± 1.4	Low (14)	MCQ-C_{30}	-	ADIS-P; RCADS
Lønfeldt *et al*[77]	NC	1062	55%	(9-17) 12.3 ± 1.7	Low (14)	MCQ-C_{30}	-	SCARED-R
Mather and Cartwright-Hatton[95]	NC	166	66%	(13-17) 15.1 ± 1.4	Mod (12)	MCQ-A	-	RCMAS
Matthews *et al* [81]	NC	223	56%	(13-16) NA	Mod (13)	MCQ-A	-	-
Naumann[68]	NC	972	52%	(7-14) 10.6 ± 1.5	Low (14)	MKF-K	PSWQ-C	SCAS
Normann *et al*[60]	C[1,4,3,7]	44	50%	(7-12) 9.9 ± 1.6	Low (14)	MCQ-C_{30}	-	ADIS-C/P; SCARED-R
Reinholdt-Dunne *et al*[79]	C[1,4,3,7]/NC	169/182	53%/55%	(7-14) 9.9 ± 1.8/(7-12) 10.0 ± 1.4	Low (16)	MCQ-C_{30}	-	RCADS
Sanger and Dorjee[61]	NC (TG)/NC (CG)	20/25	50%/68%	(16-18) 16.6 ± 0.6/(16-18) 17.1 ± 0.6	Mod (12)	MCQ-A	-	-
Simons and Vloet [62]	C[7]	3	100%	(14-17) 15.3 ± 1.5	Mod (13)	MCQ-A	SCAS-scale	SCAS
Smith and Hudson[52]	Total/C[1,3,2,7,4,8]/NC	83/49/34	60%/NA/NA	(7-12) 9.2 ± 1.6/NA/NA	Mod (13)	MCQ-C	-	ADIS-C/P; SCAS
Thorslund *et al* [63]	C[1,3,9]	10	70%	(14-17) 15.2 ± NA	Low (14)	MCQ-C	PSWQ-C	MINIKid
White and Hudson[30]	NC	187	31%	(7-12) 10.6 ± 1.7	Low (15)	MCQ-CR	PSWQ-C	SCAS
Wilson *et al*[82]	NC	72	54%	(11-16) 13.2 ± 1.0	Mod (13)	MCQ-A	PSWQ-C	MASC
Wilson and Hall [69]	NC	151	56%	(13-16) 15.1 ± 1.0	Mod (12)	MCQ-A	TCQ-scale	-
Wilson and Hughes[70]	NC	57	61%	(6-10) NA	Mod (12)	Interview	PSWQ-C	MASC
Yavuz *et al*[96]	NC	1817	54%	(14-17) 15.4 ± 1.1	Mod (12)	MCQ-C	-	NMP-Q
Zimmermann *et al*[54]	NC	221	55%	(13-17) 14.9 ± 1.4	Mod (12)	MCQ-A	-	SBB-ANZ

[a]Mean was only reported for subsamples and has been weighted on sample size.
[b]Subsample from study 1.
Superscript numbers show diagnosis of clinical groups in descending order:

[1]Generalized Anxiety disorder.
[2]Obsessive-compulsive-disorder.
[3]Social Anxiety Disorder.
[4]Separation Anxiety disorder.
[5]Other Anxiety disorder.
[6]Any emotional disorder.
[7]Specific Phobia.
[8]Post-traumatic stress disorder.
[9]Panic disorder/agora phobia.

NA: Not available; TG: Treatment group; WL: Waiting list; CG: Control group; POS: Positive beliefs about worry; NEG: Negative beliefs about worry; Mod: Moderate; MCQ-30: Metacognitions Questionaire-30-Item Version; MCQ-C: Metacognitions Questionnaire for children; MCQ-A: Metacognitions Questionnaire-Adolescent Version; MKF-K: Metakognitions-Fragebogen für Kinder; MCQ-CR: Revised Metacognitions Questionnaire for Children; MCQ-$C_{30:}$ Metacognitions Questionnaire for Children–30Item Version; MWQ: Meta-Worry Questionnaire; ADIS-C/P: Anxiety Disorders Interview Schedule Child/Parent Versions; PSWQ: Penn State Worry Questionnaire; PSWQ-C: Penn State Worry Questionnaire for Children; WAQ: Worry and Anxiety Questionnaire; RCMAS,RCMAS-2: Revised Children's Manifest Anxiety Scale; STAI-C: State-Trait Anxiety Inventory for Children; CAWS: Child and Adolescent Worry Scale; SCAS: Spence Children's Anxiety Scale; SCARED-R: Revised Version of the Screen for Child Anxiety Related Emotional Disorders; MASC: Multidimensional Anxiety Scale for Children; GHQ: General Health Questionnaire; TCQ: Thought Control Questionnaire; SPAI-10: Social Phobia and Anxiety Inventory for Children; CTAS: Children´s Test Anxiety Scale; MINI Kid: Mini International Neuropsychiatric Interview for Children and Adolescents; GAD7: 7-item Generalized Anxiety Disorder scale; NMP-Q: Nomophobia Questionnaire; SBB-ANZ: Diagnostik-System für Psychische Störungen nach ICD-10 und DSM-IV für Kinder und Jugendliche – Selbstbeurteilungsfragebogen Angst- und Zwangsstörungen; SD: Standard deviation.

A total of n = 12839 participants were examined in the included studies. Median sample size was n = 138.50 per study, range n = 1 to n = 1817. Gender distribution was reported in k = 46 studies. Overall, a mean of 56.84% of participants per study described themselves as female, ranging from 0% to 100% per study. The age of participants ranged from 6 to 18 years. k = 30 studies involved a non-clinical sample, k = 8 studies involved a purely clinical sample, and k = 10 studies included both a clinical group and a non-clinical group. The non-clinical samples were usually convenience samples recruited from schools. Studies with clinical samples included the primary diagnoses GAD, SAD, SoD, panic disorder/agoraphobia, and specific phobia. In three studies, OCD or post-traumatic stress disorder were classified as anxiety disorders[27,28,52]. Patients with these primary disorders represented a percentage of 8.1% to 18.4% of patients included with anxiety disorders. Most studies revealed a cross-sectional design. Three studies included a retest-measurement to assess test-retest correlations for validating different questionnaires[53-55]. Nine studies followed a longitudinal design in the form of intervention studies with pre-post- (and follow-up) measurement points[26,56-63].

Risk of bias

We used the AXIS-tool to assess the risk of bias. Most of the studies were classified as low risk of bias (k = 25) and moderate risk of bias (k = 23), whereas no study was classified as having a high risk of bias (see Table 1).

What evidence is there for positive relationships between POS, NEG, and meta-worry with each other, worry, and anxiety for children and adolescents?

Relationships between POS, NEG, meta-worry, and worry: Table 2 provides an overview of the relationships reported in the included studies. In total, k = 18 studies researched the relationships between POS, NEG, and worry. Most thereof demonstrated correlations between worry and both POS and NEG[24,51,64-70]. Moreover, two studies collected POS exclusively and reported significant correlations between worry and POS[71,72]. Two studies showed that POS and NEG contribute to worry as unique predictors[23,73], and another study that exclusively measured POS identified it as a unique predictor of worry[72]. However, other studies found that worry correlated only with NEG, not with POS[26,30,74,75]. Another study detected a correlation between POS and worry that disappeared after the authors controlled for worry contents, while worry nevertheless continued to correlate with NEG[28]. One study detected no group differences in worry between participants who described POS or NEG verbally in open-ended questions and those who did not[70]. Only one study investigated the relationship between meta-worry and worry and observed positive correlations between them[73].

Results of meta-analysis: Table 3 shows our meta-analysis results. Meta-analysis (k = 13) for correlation between POS and worry resulted in an overall small to medium effect size [r = 0.27 (0.22, 0.33), P < 0.001]. Q-Test for heterogeneity was significant (Q =

Table 2 Extracted correlational coefficient on measures of positive beliefs about worry/negative beliefs about worry and worry/anxiety

Ref.	Worry		Anxiety		POS	Age	
	POS	NEG	POS	NEG	NEG	POS	NEG
Babaei *et al*[55]	-	-	-0.053	-0.303[b]	0.21[b]	-	-
Bacow *et al*[27]	-	-	-	-	-	NA	NA
Bacow *et al*[28]	0.21[a]	0.55[b]	-	-	-	-	-
Benedetto *et al*[64]	0.23[b]	0.70[b]	0.29[b]	0.65[b]	0.30[b]		
Benedetto *et al*[49], study1	-	-	0.20[3,a]; 0.01[4]	0.56[3,b]; 0.48[4,b]	0.17[3]; 0.31[4,b]	-	-
Benedetto *et al*[49], study2	-	-	-0.68[1,a]; 0.38[2]	0.56[1,a]; 0.42[2]	-0.41[1]; 0.69[2,b]	-	-
Boysan *et al*[92]	-	-	-	-	-	-	-
Carr and Szabó[72]	0.35[c]	-	-	-	-	0.02	-
Cartwright-Hatton *et al*[53]	-	-	0.32[c]	0.67[c]	-	-	-
Donovan *et al*[80]	-	-	-	-	-	-	-
Donovan *et al*[65]	0.22[a]	0.72[b]	-	-	0.20[a]	-	-
Ellis and Hudson[24]	0.49[b]	0.84[b]	0.46[b]	0.72[b]	-	0.16	0.16
Esbjørn *et al*[23], study1	-	-	-	-	-	-	-
Esbjørn *et al*[23], study2	-	-	-	-	-	-	-
Esbjørn *et al*[93]	-	-	-	-	-	-	-
Esbjørn *et al*[66]	0.25[c]	0.31[c]	0.17[c]	0.55[c]	0.25[c]	-	-
Esbjørn *et al*[56]	-	-	-	-	-	-	-
Fergus and Limbers[57]	-	-	-	-	-	-	-
Fisak *et al*[73]	-	-	-	-	-	-	-
Francis *et al*[50]	-	-	-	-	-	-	-
Francis *et al*[51]	0.39[b]	0.69[b]	-	-	0.31[b]	-	-
Gallagher and Cartwright-Hatton[94]			-	-	-	-	-
Gini *et al*[67]	0.32[c]	0.65[c]	0.22[c]	0.60[c]	0.16[c]	-	-
Hearn *et al*[25]	0.16	0.50[b]	0.02	0.39[b]	0.08	-	-
Hearn *et al*[74]	-	-	-	-	-	-	-
Hearn *et al*[26]	0.02	0.48[b]	0.01	0.36[b]	-	-	-
Holmes *et al*[59]	-	-	-	-	-	-	-
Holmes *et al*[58]	-	-	-	-	-	-	-
Irak[78]	-	-	0.194[c]	0.412[c]	-	-	-
Kertz and Woodruff-Borden[75]	0.14 (P)	0.53[c] (P)	-	-	-	-	-
Laugesen *et al*[71]	0.37[c] (P)	-	-	-	-	-	-
Lønfeldt *et al*[76]	-	-	0.31[b]	0.57[b]	0.30[b]	0.10	0.06
Lønfeldt *et al*[77]	-	-	0.19[a]	0.58[a]	0.23[c]	-0.01	-0.08[a]
Mather and Cartwright-Hatton[95]	-	-	-	-	-	-	-
Matthews *et al*[81]	-	-	-	-	0.47[a]	-0.05	-0.18[b]
Naumann[68]	0.20[b]	0.63[b]	0.20[b]	0.55[b]	0.07	-	-
Normann *et al*[60]	-	-	-	-	-	-	-
Reinholdt-Dunne *et al*[79]	-	-	0.09[1]; 0.36[2,b]	0.62[1,b]; 0.68[2,b]	0.05[1]; 0.29[2,b]	0.10[1]; -0.10[2]	0[1]; 0[2]
Sanger and Dorjee[61]	-	-	-	-	-	-	-
Simons and Vloet[62]	-	-	-	-	-	-	-

Smith and Hudson[52]	-	-	0.30[b]	0.47[b]	0.36[b]	-	-
Thorslund *et al*[63]	-	-	-	-	-	-	-
White and Hudson[30]	0.08	0.65[b]	0.20[b]	0.56[b]	0.27[a]	0.06	0.07
Wilson *et al*[82]	0.35[b]	0.74[b]	0.19	0.51[a]	NA	< 0.16	< 0.16
Wilson and Hall[69]	0.33[c]	0.51[c]	-	-	0.29[c]	-	-
Wilson and Hughes[70]	-	-	-	-	-	-	-
Yavuz *et al*[96]	-	-	-	-	-	-	-
Zimmermann *et al*[54]	-	-	0.22[b]	0.57[b]	-	0.16[a]	0.12

[1]Clinical group.
[2]Non-clinical group.
[3]Female subsample.
[4]Male subsample.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
NA: Not available; POS: Positive beliefs about worry; NEG: Negative beliefs about worry; (P): Partial correlation.

Table 3 Summary of results for random effect models for meta-analysis on correlational coefficient on measures of positive beliefs about worry/negative beliefs about worry and worry/anxiety

	Overall effect							Heterogenity test		
Meta-analysis	***k***	***r***	**95%CI, *r***	**95%PI, *r***	**Fisher's z**	**95%CI, z**	**Z**	**Q**	**I^2**	**T^2**
POS and worry	13	0.27	(0.22, 0.33)	(0.08, 0.45)	0.28	(0.22, 0.34)	9.56, $P <$ 0.001	36.14, $P < 0.001$	67 %	0.01
NEG and worry	12	0.64	(0.55, 0.72)	(0.27, 1.25)	0.76	(0.62, 0.90)	10.49, $P <$ 0.001	233.90, $P < 0.001$	95 %	0.06
POS and anxiety	18	0.20	(0.16, 0.25)	(0.00, 0.38)	0.20	(0.16, 0.25)	8.54, $P <$ 0.001	52.11, $P < 0.001$	67 %	0.01
NEG and anxiety	18	0.53	(0.46, 0.60)	(0.19, 0.76)	0.59	(0.50, 0.69)	12.32, $P <$ 0.001	234.07, $P < 0.001$	93 %	0.04
POS and NEG	17	0.24	(0.18, 0.28)	(0.04, 0.41)	0.24	(0.18, 0.29)	8.49, $P <$ 0.001	66.44, $P < 0.001$	76 %	0.01

k: Number of studies included in meta-analysis; *r*: Pearson's product-moment correlation; CI: Confidence interval; PI: Prediction interval; SE: Standard error; POS: Positive beliefs about worry; NEG: Negative beliefs about worry.

36.14, $P < 0.001$), and inconsistency can be described as moderate to high ($I^2 = 67\%$). For correlation between NEG and worry ($k = 12$), the overall correlation coefficient was $r = 0.64$ (0.55, 0.72), $P < 0.001$, indicating a large effect. Heterogeneity tests resulted in significant and substantial inconsistency: $I^2 = 95\%$, $Q = 233.90$, $P < 0.001$. Forest plots for meta-analysis are depicted in Figures 2 and 3. As only one study examined meta-worry[73], we could not conduct a meta-analysis for a correlation with worry.

Relationships between POS, NEG, meta-worry, and anxiety: $k = 21$ studies analyzed the association between POS and NEG and anxiety symptoms. Correlations between POS, NEG, and anxiety were demonstrated in the majority of studies[24,30,52-54,64,66-68,76-78]. However, other study findings contradict those results. Three studies revealed correlations between anxiety and NEG, while anxiety failed to correlate with POS[25,26,70]. NEG contributed to anxiety as a unique predictor in one study, while POS did not predict anxiety significantly[23]. In study 1 by Benedetto *et al*[49], anxiety did correlate with NEG in female and male participants, whereas POS and anxiety correlated significantly in female subjects only. In study 2, those two correlations were proven in adolescents with an anxiety disorder only but not in a non-clinical sample [49]. Another study showed that NEG correlated with anxiety in clinical and non-clinical groups, while POS were only associated with anxiety in a clinical group[79]. In the study by Wilson and Hughes[70], children's anxiety scores did not differ as to

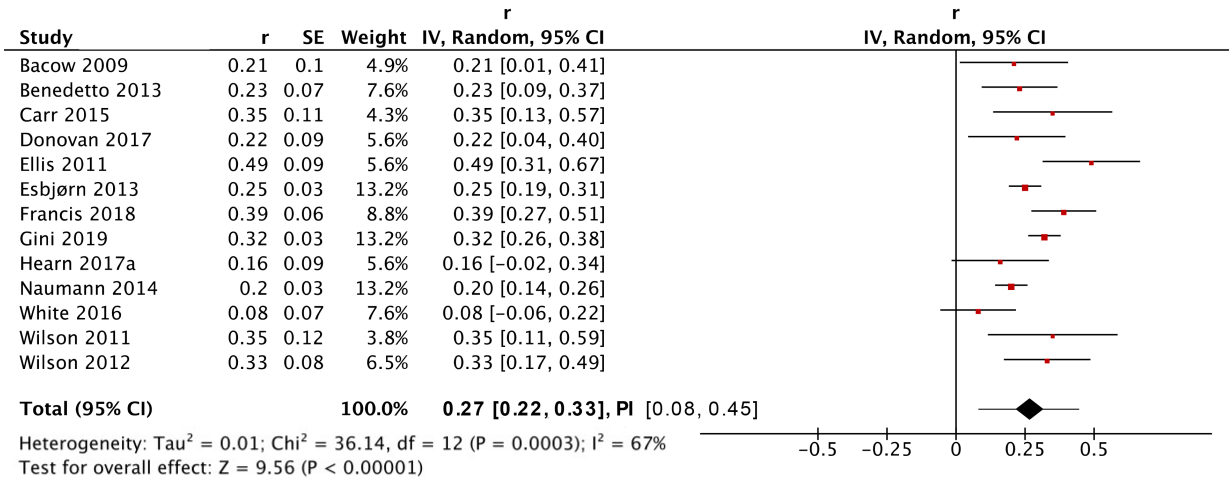

Figure 2 Meta-analysis forest plot on the correlation between measures of positive metacognitive beliefs about worry and worry. CI: Confidence interval; SE: Standard error.

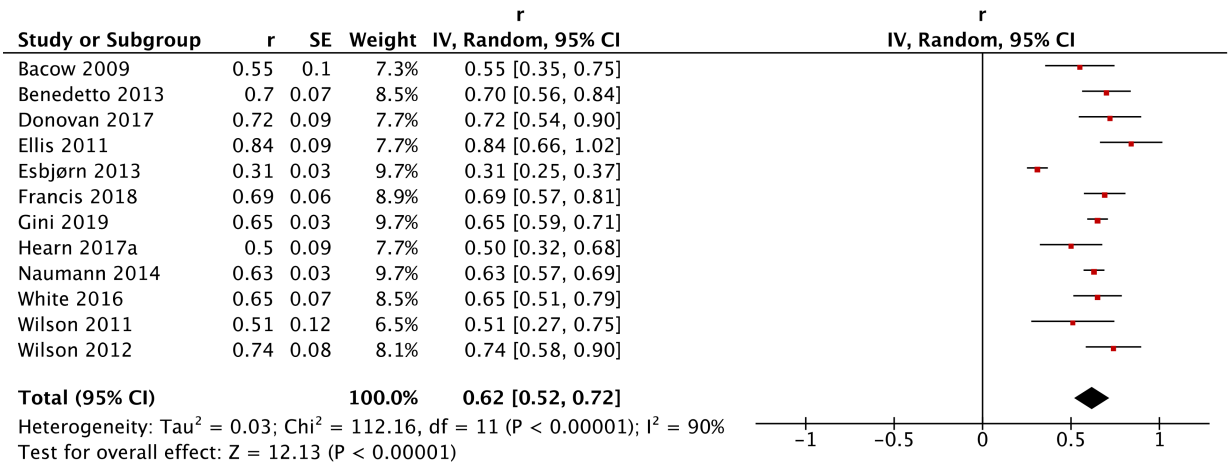

Figure 3 Meta-analysis forest plot on the correlation between measures of negative metacognitive beliefs about worry and worry. CI: Confidence interval; SE: Standard error.

whether they reported NEG or POS. One study even identified a negative correlation between NEG and anxiety, while POS did not correlate with anxiety[55]. No study examined whether meta-worry was related to anxiety. Extracted relationships are shown in Table 2.

Results of meta-analysis: For the correlation between POS and anxiety, we identified k = 18 studies for meta-analysis. The overall effect size was small [r = 0.20, 95%CI (0.16, 0.25), P < 0.001]. Q-Test for heterogeneity was significant (Q = 52.11, P < 0.001) and the amount of inconsistency is moderate to high (I^2 = 67%). Testing of overall-effect size when correlating NEG and anxiety (k = 18) resulted in a large effect [r = 0.53 (0.46, 0.60), P < 0.001]. With respect to heterogeneity, the Q-statistic is significant (Q = 234.07, P < 0.001), and results speak for inconsistency (I^2 = 93%). Our meta-analysis results are displayed in Table 3, the forest plots in Figures 4 and 5. No meta-analyses for correlations between worry and meta-worry were possible as no study investigated potential relationships between those variables.

Clinical *vs* non-clinical groups: A total of k = 10 studies included both clinical and non-clinical samples. Three studies showed that their clinical sample held significantly higher POS and NEG than the non-clinical group[24,52,79]. In other studies, clinical participants reported more NEG than non-clinical participants, POS revealed no group difference[49,53,74,80]. One study found that both investigated clinical samples (GAD, other anxiety disorders) held significant higher NEG than a non-clinical group, but only patients with GAD differed from healthy controls in case of POS[23]. Two studies

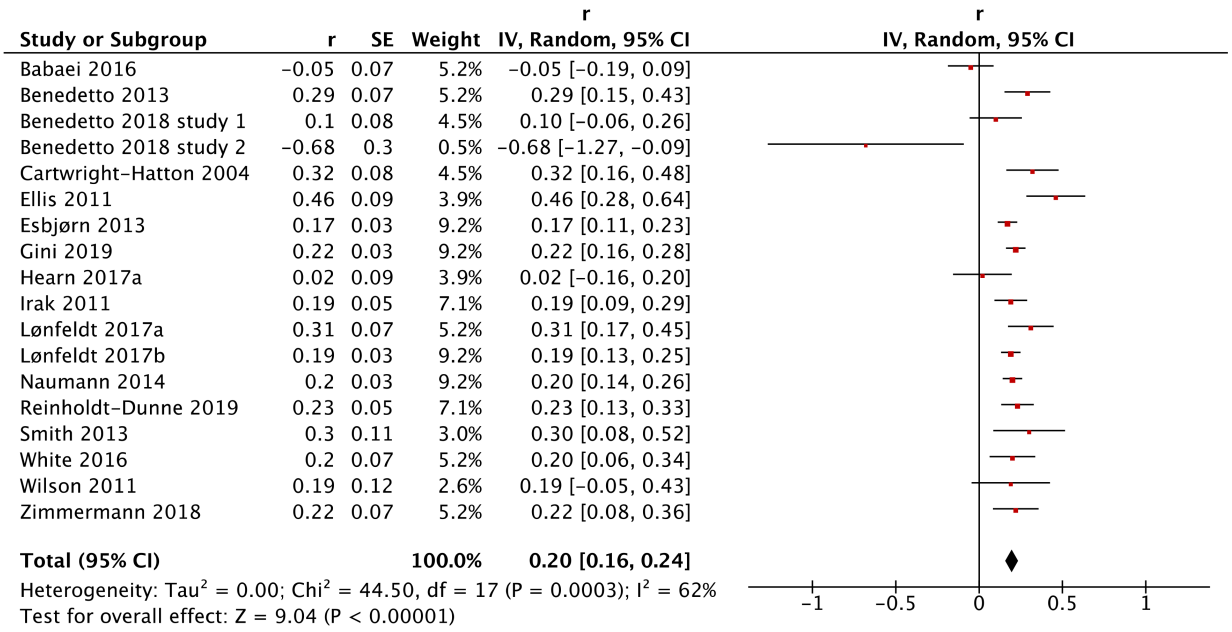

Figure 4 Meta-analysis forest plot on the correlation between measures of positive metacognitive beliefs about worry and anxiety. CI: Confidence interval; SE: Standard error.

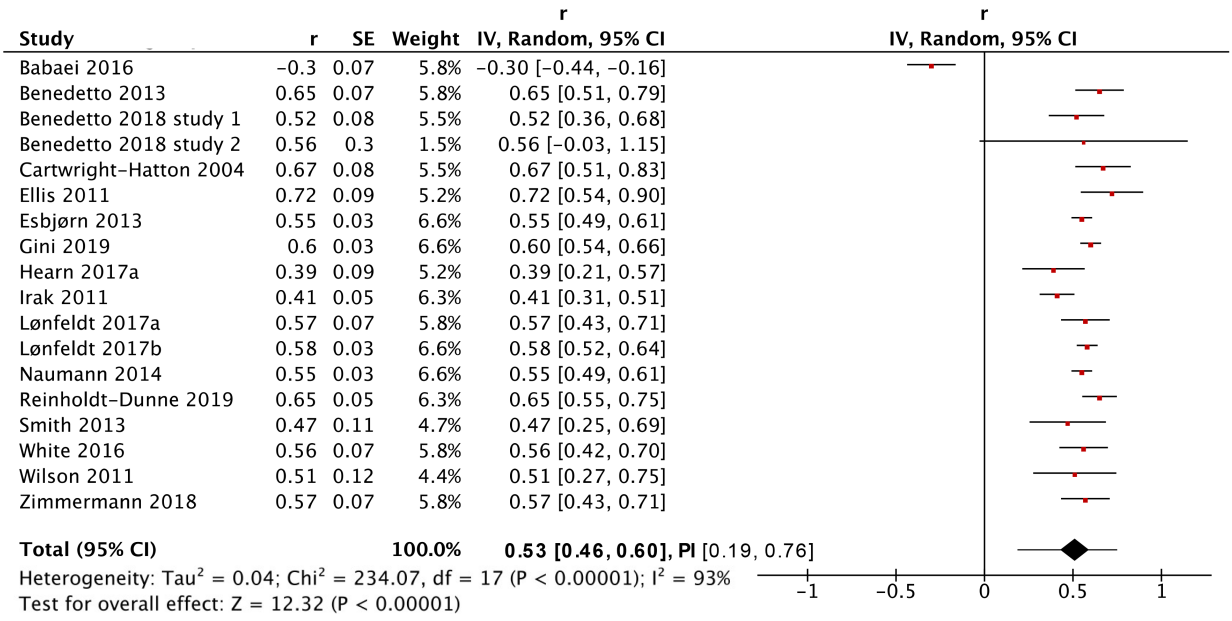

Figure 5 Meta-analysis forest plot on the correlation between measures of negative metacognitive beliefs about worry and anxiety. CI: Confidence interval; SE: Standard error.

failed to demonstrate significant differences between a non-clinical sample and patients with anxiety disorders for POS or NEG[27,28]. Furthermore, k = 4 studies compared different anxiety disorders with each another specifically. The findings by Bacow *et al*[27] indicate that children and adolescents with OCD, SAD, SoD, and non-clinical controls do not differ in POS or NEG. Another study reported no group differences between patients with GAD and patients with SoD for POS or NEG[74]. Ellis and Hudson[24] detected no differences either between their sample with GAD and one with other anxiety disorders. Nevertheless, in their study 2, Esbjørn *et al*[23] demonstrated that patients with GAD had higher NEG than those with other anxiety disorders, whereas POS did not differ between groups.

Relationships between POS, NEG, and meta-worry: Correlations between POS and NEG were explored in k = 19 studies, as shown in Table 2. Most studies identified a

positive correlation between POS and NEG[30,51,52,55,64-67,69,76,77,81]. In Benedetto *et al*[49] study 1, POS and NEG correlated positively with each other for male but not female participants. In their second study, a correlation between POS and NEG only became evident in a non-clinical sample, not a clinical one. Reinholdt-Dunne *et al*[79] reported the same result. Still other working groups failed to demonstrate any significant correlation between POS and NEG[25,26,68,82], and none analyzed relationships between POS and NEG with meta-worry.

Results of meta-analysis: We excluded one study from meta-analysis that showed a correlation between POS and NEG since they reported no effect size for correlation [82]. Overall effect size for the POS with NEG correlation (k = 17) was small to medium, r = 0.24 (0.18, 0.28), P < 0.001. Heterogeneity was shown to be significant (Q = 66.44, P < 0.001), and inconsistency was high (I^2 = 76%). Results are displayed in Table 3 and Figure 6.

At what age do children report POS, NEG, and meta-worry, and does age play a role in relationships with worry and anxiety?

Onset of metacognitive beliefs about worry: k = 31 studies examined metacognitive beliefs in children under the age of 12 years, and k = 14 studies included populations from age 7 years upwards. Only one study investigated metacognition in children as young as six[70]. Those authors asked children between 6 and 10 years of age to fill out open-ended questions about POS and NEG. Fifty-six percent of children expressed one or more POS, and 77% of children expressed one or more NEG; they observed no age-related differences in the numbers who named POS or NEG[70]. Six-year-old children thus do not seem to differ from older children in their POS and NEG. Other studies analyzed how well young children understand metacognitive questionnaires. Smith and Hudson[52] found that six items on the often used Metacognitions Questionnaire for Children[28] were not adequately understood by 35.8% to 78.6% of the 7- and 8-year-olds they investigated. White and Hudson[30] changed those six items and included a fifth answer option, "I don't understand". Their new instrument, the Revised Metacognitions Questionnaire for Children[30], was tested in a sample of 187 7- to 12-year-old children. No item, including the six newly changed items, was marked as "I don't understand" by more than 25% of 7-year-olds and 17% of 8-year-olds, indicating that the vast majority of this age group (75%-83%) was indeed able to rate their POS and NEG[30]. A small negative correlation was found between age and the number of not-understood items, and a similar significant group difference between 7- to 8-year-olds and 9- to 12-year-olds appeared, indicating that children understand POS and NEG better as they age[30].

Relationship between age and metacognition about worry: Table 2 contains an overview of extracted relationships. Of all included studies, only a minority investigated whether metacognitive beliefs change with age (k = 12). Most of those studies did not detect any correlation between POS and NEG, neither with participants' age nor age-related differences[24,27,28,30,72,77,79,82]. In the open-ended questions asked verbally by Wilson and Hughes[70], 56% of children claimed to have at least one POS and 77% at least one NEG. The authors revealed no age-related difference in these answers from children aged 6 to 10 years. In contrast, another study's results suggest that NEG may decline with age, as age did not correlate with POS, but NEG did correlate with age (with a small negative effect[76]). Interestingly, another study identified a small positive correlation between POS and age, but no significant correlation between NEG and age[54]. Another study also demonstrated a significant age effect for POS but none for NEG[78].

Results of meta-regressions with age as covariate: Results of the meta-regressions with mean age as covariate are presented in Table 4. Z-tests for latitudes did not reach significance in any meta-regression, therefore the null hypothesis of no effect cannot be rejected. We therefore found that mean age was not a significant covariate in any of the tested correlations.

Which methods are currently applicable to assess POS, NEG, and meta-worry in childhood and youth?

In total, the authors administered six different questionnaires to assess POS and NEG together. These include the Metacognitions Questionnaire-30-Item Version (MCQ-30) [83], MCQ - Adolescent Version[53], and MCQ for Children (MCQ-C)[28]. The Revised MCQ for Children (MCQ-CR)[30], MCQ for Children-30-Item version (MCQ-C_{30})[66],

Table 4 Results of meta-regressions on correlational coefficient on measures of positive beliefs about worry/negative beliefs about worry and worry/anxiety with mean age as covariate

Meta-regression		*B*	*SEB*	95%lower	95% upper	*Z*	*P*
POS and	Intercept	0.5082	0.356	-0.254	1.271	1.429	0.175
Anxiety[1]	Latitude	-0.0265	0.028	-0.086	0.033	-0.958	0.354
POS and	Intercept	-0.0905	0.195	-0.525	0.344	-0.464	0.652
Worry[2]	Latitude	0.0302	0.016	-0.005	0.065	1.911	0.085
NEG and	Intercept	0.4427	0.128	0.168	0.718	3.450	0.004[b]
Anxiety[3]	Latitude	0.0094	0.010	-0.012	0.031	0.940	0.363
NEG and	Intercept	0.6482	0.225	0.139	1.157	2.881	0.018[a]
Worry[4]	Latitude	0.0004	0.018	-0.040	0.041	0.021	0.984
POS and	Intercept	0.5256	0.260	-0.042	1.093	2.019	0.066
NEG[5]	Latitude	-0.0286	0.021	-0.074	0.017	-1.357	0.200

[1]Based on *k*: 16 studies.
k: 2 studies[55,67] were excluded as no mean age was reported;
[2]Based on *k*: 12 studies.
k: 1 study[67] was excluded as no mean age was reported;
[3]Based on *k*: 16 studies.
k: 2 studies[55,67] were excluded as no mean age was reported;
[4]Based on *k*: 11 studies.
k: 1 study[67] was excluded as no mean age was reported;
[5]Based on *k*: 14 studies.
k: 3 studies[55,67,81] were excluded as no mean age was reported.
[a]$P < 0.05$.
[b]$P < 0.01$.
B: Point estimate; *SEB*: Standard error of point estimate; POS: Positive metacognitive beliefs about worry; NEG: Negative metacognitive beliefs about worry.

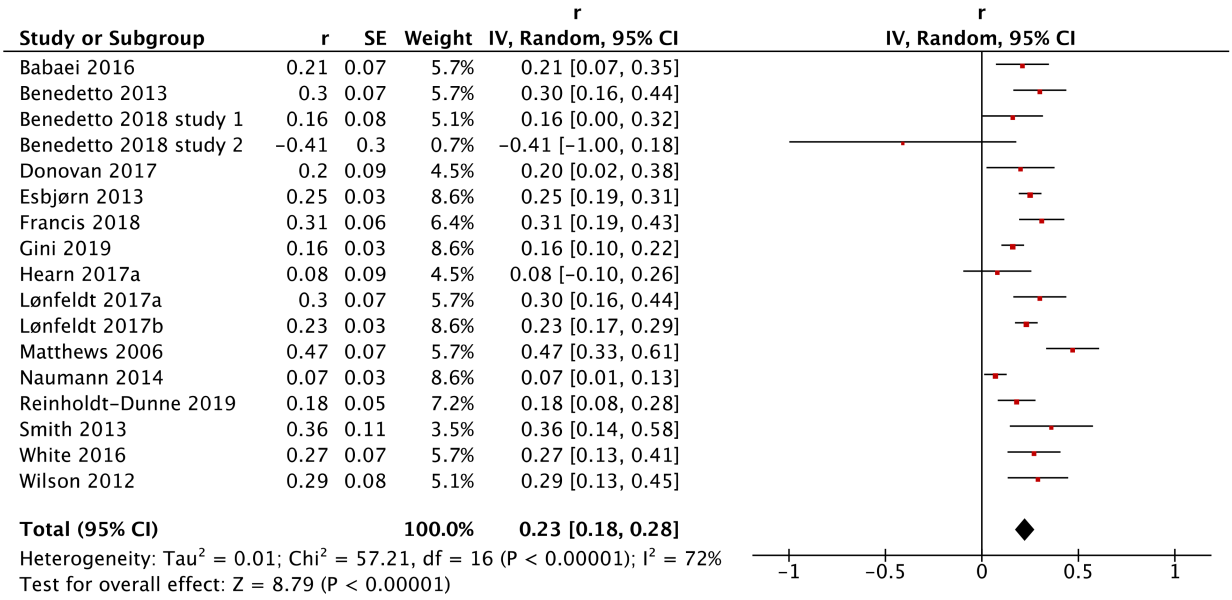

Figure 6 Meta-analysis forest plot on the correlation between measures of positive metacognitive beliefs about worry and negative metacognitive beliefs about worry. CI: Confidence interval; SE: Standard error.

and Metakognitionsfragebogen für Kinder[68] are more recent adaptations. All those questionnaires are variations of the MCQ developed by Cartwright-Hatton and Wells [22]. Despite POS and NEG, it also covers cognitive confidence, the need for control, and cognitive self-consciousness[22]. Furthermore, with Why Worry-II[84], we

extracted one questionnaire that exclusively measures POS. Only one study assessed meta-worry[73]. Its authors administered the meta-worry questionnaire[21] for this purpose.

Of the studies included, only one assessed POS and NEG in children as young as 6 years of age[70]. Due to the lack of reading skills at this age, the children were orally asked these open-ended questions: "Worry can sometimes be helpful and good. Tell me some reasons why worry is good" and "Worry can sometimes be unhelpful and bad. Tell me some reasons why worry is bad"[70]. The authors assigned the children's responses to the categories POS (*e.g.*, solves problems, motivates you, keeps you safe) and NEG (*e.g.*, impacts on activity, is uncontrollable, makes you unwell). An overview of the measurements used in these studies is found in Table 5.

DISCUSSION

To the best of our knowledge, this review is the first to describe systematically measuring instruments for POS and NEG as well as results on the validity of the metacognitive model by meta-analysis on correlations between POS and NEG with each other, worry, and anxiety. Presenting 48 studies, we provide a broad overview of this topic, upon which future research can build. We conducted a consensus rating of 20.89% of full-texts with agreement in 90.32%. Good interrater agreement was attained regarding the risk of bias assessment. No study was rated as showing a high risk of bias. Data from 24 studies could be included in quantitative synthesis to meta-analyze the strength of effect sizes. We were also able to analyze mean age as a moderator in meta-regressions and identify various measurement instruments for different age ranges and newer adaptations like MCQ-CR and MCQ-C_{30} that enable better coverage of POS and NEG in younger children. The use of orally posed open questions reveals another approach for assessing POS and NEG in even younger children, thus enabling us to investigate the onset of such beliefs about worry[70].

What evidence is there for positive relationships between POS, NEG, and meta-worry with each other, worry, and anxiety in children and adolescents?

NEG correlated in all 14 studies[24,25,26,28,30,51,64-69,75,82] with worry and proved to be an independent predictor of worry in three[23,65,73] out of three studies. Meta-analysis showed large overall correlation between NEG and worry.

NEG also correlated with anxiety in 17[24-26,30,52-55,64,66-68,76-79,82] of 19 studies. Benedetto *et al*[49] study 2 revealed a correlation in their clinical sample only. Surprisingly, another study showed a significant negative relationship of medium effect size between NEG measured with MCQ-30 and anxiety in high school students [55]. The questionnaires used had not been adapted or evaluated for use in adolescents; their contradictory result may be attributable to their not mentioning any specific age range[55]. Overall, the correlation between NEG and anxiety in our meta-analysis revealed was large. NEG predicted anxiety uniquely in three[23,68,75] out of four studies. One study found that NEG was not a significant predictor of anxiety, however[25]. Eight[23,24,49,52,53,74,79,80] out of 10 studies that compared clinical and non-clinical samples showed higher NEG in participants with anxiety disorders, a finding that also supports the metacognitive model. Two studies[27,28] detected no significant group differences.

For POS, 12[24,28,51,64-69,71,72,82] out of 16 studies showed a significant positive relationship with worry, while correlations failed to reach significance in four studies [26,30,48,74]. Meta-analysis resulted in a small overall effect size for the correlation between POS and worry. POS predicted worry in three[23,71,73] out of four studies, while it was not significant in one study[65].

POS correlated with anxiety in 12[24,30,52-54,64,66-68,76-78] out of 19 studies. Studies 1 and 2 of Benedetto *et al*[49] did identify significant correlations but only in their clinical subgroup, while Reinholdt-Dunne *et al*[79] detected a significant correlation in their non-clinical subgroup. In fact, four studies[25,26,55,82] failed to indicate any significant correlations between POS and anxiety. Meta-analysis demonstrated a small to medium effect size for the correlation between POS and anxiety. POS proved to be unique predictors of anxiety in one[68] of three studies, while two studies[73,80] failed to prove POS as a significant predictor. Clinical groups scored higher on POS than non-clinical groups in four[23,24,52,79] out of 10 studies, while six[27,28,49,53,74,80] studies revealed no significant group differences.

Table 5 Measurements of metacognitive beliefs about worry and meta-worry

Measure	Items	Scales	Answer format	Values for reliability	Age	*k*
MCQ-C	24	4	Do not agree (1) to agree very much (4)	POS: α = 0.46 - 0.89, *rtt* = 0.82; NEG: α = 0.60 - 0.95, *rtt* = 0.76[25-28,49,51,52,57,64,65,72,73,74,78]	7-17	22
MCQ-A	30	5	Do not agree (1) to agree very much (4)	POS: α = 0.80 - 0.90, *rtt* = 0.66; NEG: α = 0.80 - 0.87, *rtt* = 0.71[24,53,54,81,82]	11-17	9
MCQ-C_{30}	30	5	Not at all (1) to completely (4)	POS: α = 0.64 - 0.73; NEG: α = 0.71 - 0.79[23,76,93]	7-17	8
MCQ-30	30	5	Do not agree (1) to agree very much (4)	POS: α = 0.88; NEG: α = 0.77[67]	15-18	3
MCQ-CR	30	5	Not true (1) to Very true (4); I do not understand	POS: α = 0.77; NEG: α = 0.80[30]	7-12	1
MKF-K	30	4	Not at all (1) to completely (4)	POS: α = 0.73; NEG: α = 0.70[68]	7-14	1
MWQ	7	2	Never (1) to almost always (4)	α = 0.80 - 0.82[73]	11-18	1
WW-II	25	5	Not at all (0) to incapacitating (4)	α = 0.90[71]	7-18	1
Interview	2	2	Open questions	κ = 0.61[70]	6-10	1

α: Cronbach's Alpha; *rtt:* Test-retest-reliability; κ: Cohen's kappa; *k*: Number of included studies which used the measure; MCQ-30: Metacognitions Questionnaire - 30-Item Version; MCQ-A: Metacognitions Questionnaire - Adolescent Version; MCQ-C: Metacognitions Questionnaire for Children; MCQ-CR: Revised Metacognitions Questionnaire for Children; MCQ-C30: Metacognitions Questionnaire for Children - 30 Item version; MKF-K: Metacognition questionnaire for children; MWQ: Meta-Worry Questionnaire; WW-II: Why Worry-II; POS: Positive beliefs about worry; NEG: Negative beliefs about worry.

Correlations between POS and NEG were reported as significant in 12[30,51,52,55,64-69,76,77,81] out of 19 studies, whereas that finding applied to only one of two subgroups in Studies 1 and 2 of Benedetto *et al*[49] and a study by Reinholdt-Dunne *et al*[79]. Meta-analysis demonstrated a small to medium effect size.

These mixed results partly support the metacognitive model as well, but NEG seem to have a generally more stable effect on worry and anxiety than POS. POS correlations were quite smaller (small to medium effect sizes) while NEG correlations were large. This is not surprising since NEG revealed medium to large correlations with anxiety and worry in adults, while POS result in small to medium correlations with anxiety and worry[83,85,86]. Meta-analysis revealed a smaller effect for the correlation between POS and NEG (small to medium), while correlations for NEG with anxiety and worry are large - evidence that concurs with studies from adult research[83,85,86]. To evaluate conclusively the causal claims of the metacognitive model for children, longitudinal studies are needed. However, most of the studies we included applied a cross-sectional design that precludes such conclusions. Only 10 studies compared clinical to non-clinical samples. Future studies should compare POS, NEG, and meta-worry in clinical and non-clinical samples to validate further the metacognitive model of GAD in childhood and youth. For more information about the specific influence of NEG and meta-worry in the development of GAD, patients presenting different anxiety disorders should be compared also, since the results here are far from clear. In total, the overall situation that this systematic review and meta-analysis portrays indicates that NEG play an especially relevant role in worry and anxiety in children and adolescents, and that there is ample evidence from studies that supports the applicability of the metacognitive model of GAD in childhood and youth.

At what age do children report POS, NEG, and meta-worry, and does age play a role in the relationships with worry and anxiety?

Fourteen studies in total included samples of children aged 7 years and upwards. None of those studies investigated the age of onset of metacognition about worry explicitly. To explore how well children understand questionnaire items, White and Hudson[30] added a response option for not-understanding in the MCQ-CR, and their results support an improvement in how well items are understood from the age 7 to 12 years. Nevertheless, at least 75% of 7- to eight-year-olds understood every MCQ-CR

item. Only one study investigated even younger children[70]. The authors posed open-ended questions verbally to assess POS and NEG in 6-year-olds and concluded that these children are capable of understanding and can describe beliefs about worry, as more than half of the 6- to 10-year-olds stated POS, and almost 8 out of 10 children stated NEG. Response frequencies did not differ with age. Although children are less capable of introspection at 5 years of age than 7- or 8-year-olds[33,35], this result implicates that the metacognitive abilities needed to perceive and describe when worry arises and what feelings and thoughts are associated with it are already developed by the age of 6 years. It thus seems possible that we are underestimating the metacognitive ability of young children[36]. This could also be because POS and NEG are usually surveyed using questionnaires.

Most of the included studies revealed no significant associations between the participants' age and NEG[24,27,30,54,76,79,82] or POS[24,27,30,72,76,77,79,81,82]. Two studies even demonstrated negative correlations between age and NEG[77,81]. We cannot therefore assume any increase in POS and NEG with rising age. However, one study[54] did show a positive correlation between POS and age. We analyzed mean age as a covariate in meta-regressions as a potential source of variance, but the results were not significant, thus we cannot assume that mean age is a relevant source of variance. Because of the rather small number of included studies in meta-regressions (range: k = 11-16) and the substantial heterogeneity as demonstrated by Q- and I^2-statistics, there might be insufficient power to demonstrate mean age's moderating effect[87]. Our results therefore do not allow us to assume that mean age has a zero-effect on correlations between POS and NEG with each other, worry, and anxiety. Nevertheless, our overall results suggest that POS and NEG do not vary much with age and that the metacognitive model of GAD can be applied to a broad age range of seven to 18 years.

Which methods are currently applicable to assess POS, NEG, and meta-worry in childhood and youth?

The studies included in this review indicate that MCQ-family of questionnaires are the ones most widely used in research and clinical practice to measure metacognitive beliefs in childhood and youth. We identified six derivates of the MCQ in this review. The MCQ-C, applied in 22 studies, was most frequently administered in children and adolescents aged 7 to 18 years. For youth between 11 and 17 years, the MCQ - Adolescent Version was used in nine studies. MCQ-C_{30} was also used in 7- to 17-year-olds in eight studies. Since each study we included originated from a single research group, we may have overestimated the frequency of use. The MCQ-30, designed for adults, was administered by three study groups in adolescents between 15 and 18 years of age without any adaptations for that age group. Other MCQ-derivates were only used in one study each. The MCQ-CR was especially designed to be better understandable for 7- and 8-year-olds[30] but was not distributed further. One study used the German questionnaire Metakognitionsfragebogen für Kinder[68]. To measure exclusively POS, Why Worry-II was used without pretesting or adaptation in a sample of 7- to 18 year-olds[71].

One study posed open-questions to assess verbally POS and NEG in children from the age of 6 to 10 years but detected no age-related differences in POS or NEG[70]. Such interview approaches represent an alternative method when surveying young children who may not yet be able to read well enough. To define the onset of POS and NEG more specifically, future research should also attempt to replicate the results of Wilson and Hughes[70] with a larger sample and perhaps include even younger children. An interview-format was also applied in the dissertation of Bacow[88], the MCQ-C author who designed the "Evaluations of Worries and Thoughts Interview for Children" (EWTI-C) to survey worry and associated beliefs. While the MCQ-C's results were covered in the paper of Bacow *et al*[28], no EWTI-C data have been published yet. Interestingly, when measured with the EWTI-C, POS and NEG did not correlate with worry at all, and participants with anxiety disorder reported more NEG, but not POS, than non-clinical controls[88]. This indicates a need for valid and reliable methods to measure metacognition in childhood and youth. More recently, thanks to the availability of the MCQ-CR and MCQ-C_{30}, two promising adaptations of the MCQ have been added and should be further investigated. Although meta-worry plays an important role in the metacognitive model, only one study investigated this construct using the meta-worry questionnaire with children aged 11 years[73]. This questionnaire has not yet been validated or adapted for children and adolescents. We need to improve and modify suitable instruments for measuring meta-worry, and it deserves more attention in future research.

Limitations

Some limitations need to be considered: First, the results we extracted are mainly cross-sectional and thus preclude any causal conclusions. Longitudinal studies are needed to support the metacognitive model's causal assumptions despite the overall relationship trends the cross-sectional data from this review has revealed so far.

Second, the broad heterogeneity revealed across the various meta-analyses we conducted should be considered a limitation. The amount of genuine variance not attributable to chance was medium to large, as the heterogeneity values indicate (I^2 = 67% and 95%). Mean age was assessed as a covariate by meta-regression to see whether age plays a role in relationships between POS and NEG with worry and anxiety, but it did not explain variance. Other sources of variance might include differences in assessment methods for POS, NEG, anxiety and worry, sample types (clinical *vs* non-clinical), percentage of comorbid disorders in clinical samples, and gender distribution. Additional meta-regressions for these potential covariates could help to explain the amount of variance among the included studies.

Third, some studies covered a broad age range[28,51,69,78,79], limiting specific interpretations of potential developmental patterns specific to different age groups. We chose mean age as a covariate for meta-regression, but the ages of all participants might not have been accurately represented. Our results can thus only reflect the mean age of the samples and must be interpreted with caution for aggregation bias[89].

Fourth, only studies with clinical samples were included if they exclusively assessed patients with DSM-5[40] listed anxiety disorders, but three studies[27,28,52] contained clinical subgroups with post-traumatic stress disorder or OCD, as they had been included in anxiety disorders in the DSM's earlier fourth edition[90]. Moreover, 60% of non-clinical participants in one study presented subclinical anxiety symptoms[28].

Fifth, to measure POS and NEG, some Cronbach's alpha values for the MCQ-C[25,27,28,52,57,64,65,72,73] and MCQ-C_{30}[60,76] fell below the recommended level of 0.70 for exploratory research as recommended by Nunnaly and Bernstein[91]. Moreover, the MCQ-C does not seem to be ideally suitable for use in younger children, as 35.8% to 78.6% of children aged 7 to 8 years did not fully understand six items[52]. As the MCQ-C was used in k = 22 studies and the MCQ-C_{30} in k = 8 studies, this factor should be considered a limitation.

Sixth, we could include only one unpublished study as gray literature[68], therefore the risk of publication bias should be considered a limiting factor.

CONCLUSION

In conclusion, the studies included in this review demonstrate that POS and NEG are measurable by administering questionnaires in children from 7 years of age upwards, and even children aged as young as 6 years can already name them verbally. Furthermore, POS and NEG do not seem to vary with age in childhood and youth. NEG shows strong overall correlations with worry and anxiety over different age groups, highlighting their relevance in the development and maintenance of anxiety disorders and confirming the metacognitive model's implications. POS' smaller effect sizes and inconsistent findings suggest that these play a subordinate role, in line with the evidence from adult studies[83,85,86]. The current research data reveal quite large heterogeneity between studies that cannot be attributed to the influence of mean age. Nor can any conclusions about the influence of meta-worry on anxiety disorders be drawn. Measurements of meta-worry in children and adolescents are thus needed, and measurements of POS and NEG for young children require further research. Longitudinal studies could enable clearer conclusions to be made on causal relationships between the metacognitive model's relevant constructs.

ARTICLE HIGHLIGHTS

Research background

The metacognitive model of generalized anxiety disorder has been applied to children and youth in different studies. Results mostly support its validity, but the roles of positive metacognitive beliefs about worry (POS), meta-worry, and age-effects do not appear to be fully clarified yet.

Research motivation

Summarizing the current research on relationships, age-effects, and measurements for POS, negative metacognitive beliefs about worry (NEG) and meta-worry in childhood and youth are both timely and worthwhile.

Research objectives

Relationships between POS, NEG, and meta-worry with each other, worry, and anxiety, and possible age-effects for these relationships were analyzed. Assessment methods POS, NEG and meta-worry for children and adolescents were examined.

Research methods

A literature search was carried out in the electronic databases PsycINFO, PubMed, PSYNDEX, and ERIC in 2017 and updated in 2020. Empirical research in German or English language on metacognition was included with child and adolescent samples diagnosed with anxiety disorders or healthy controls if POS, NEG, or meta-worry was measured. Meta-analysis for reported correlations between these metacognitions and anxiety or worry was carried out with RevMan 5.4.1, assuming random-effects models. Meta-regressions with mean age as the covariate were performed *via* the online tool MetaMar 2.7.0.

Research results

Overall, we included k = 48 studies in this systematic literature review and of those, k = 24 studies fulfilled our inclusion criteria for meta-analysis. Systematic review and meta-analysis showed that POS and NEG correlate with worry and anxiety. Mean age was not a significant covariate in meta-regressions. Only one study measured meta-worry. We identified eight questionnaires and one interview approach for assessment of metacognitive beliefs.

Research conclusions

Our overall results support the applicability of the metacognitive model of generalized anxiety disorder in childhood and youth. NEG play an especially relevant role in worry and anxiety in children and adolescents, while conclusions about meta-worry's influence cannot be drawn. Most included studies used a cross-sectional design and thus preclude causal conclusions. Metacognitive beliefs do not seem to vary with age and appear to be measurable in children from 7 years upwards.

Research perspectives

Longitudinal studies and research on the impact and measurement of meta-worry would be beneficial. Measurements applying to young children should undergo further investigation.

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REFERENCES

1 **Polanczyk GV**, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry* 2015; **56**: 345-365 [PMID: 25649325 DOI: 10.1111/jcpp.12381]

2 **Kim-Cohen J**, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry* 2003; **60**: 709-717 [PMID: 12860775 DOI: 10.1001/archpsyc.60.7.709]

3 **Woodward LJ**, Fergusson DM. Life course outcomes of young people with anxiety disorders in adolescence. *J Am Acad Child Adolesc Psychiatry* 2001; **40**: 1086-1093 [PMID: 11556633 DOI: 10.1097/00004583-200109000-00018]

4 **Hill C**, Waite P, Creswell C. Anxiety disorders in children and adolescents. *Paediatr Child Health* 2016; **26**: 548-553 [DOI: 10.1016/j.paed.2016.08.007]

5 **Ford T**, Goodman R, Meltzer H. The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders. *J Am Acad Child Adolesc Psychiatry* 2003; **42**: 1203-1211 [PMID:

14560170 DOI: 10.1097/00004583-200310000-00011]
6 **Borkovec TD**, Robinson E, Pruzinsky T, DePree JA. Preliminary exploration of worry: some characteristics and processes. *Behav Res Ther* 1983; **21**: 9-16 [PMID: 6830571 DOI: 10.1016/0005-7967(83)90121-3]
7 **Watkins ER**. Constructive and unconstructive repetitive thought. *Psychol Bull* 2008; **134**: 163-206 [PMID: 18298268 DOI: 10.1037/0033-2909.134.2.163]
8 **Muris P**, Merckelbach H, Meesters C, Van Den Brand K. Cognitive development and worry in normal children. *Cognit Ther Res* 2002; **26**: 775-787 [DOI: 10.1023/A:1021241517274]
9 **Muris P**, Merckelbach H, Gadet B, Moulaert V. Fears, worries, and scary dreams in 4- to 12-year-old children: their content, developmental pattern, and origins. *J Clin Child Psychol* 2000; **29**: 43-52 [PMID: 10693031 DOI: 10.1207/S15374424jccp2901_5]
10 **Weems CF**, Silverman WK, La Greca AM. What do youth referred for anxiety problems worry about? *J Abnorm Child Psychol* 2000; **28**: 63-72 [PMID: 10772350 DOI: 10.1023/a:1005122101885]
11 **Esbjørn BH**, Reinholdt-Dunne ML, Caspersen ID, Christensen LB, Chorpita BF. Penn State Worry Questionnaire: Findings Form Normative and Clinical Samples in Denmark. *J Psychopathol Behav Assess* 2013; **35**: 113-122 [DOI: 10.1007/s10862-012-9320-7]
12 **Perrin S**, Last CG. Worrisome thoughts in children clinically referred for anxiety disorder. *J Clin Child Psychol* 1997; **26**: 181-189 [PMID: 9169378 DOI: 10.1207/s15374424jccp2602_6]
13 **Wilson C**. Pathological Worry in Children: What is Currently Known? *J Exp Psychopathol* 2010; **1**: 6-33 [DOI: 10.5127/jep.008110]
14 **Remschidt H**, Schmidt M, Poustka F. Multiaxiales Klassifikationsschema für psychische Störungen des Kindes- und Jugendalters nach ICD-10 der WHO: Mit einem synoptischen Vergleich von ICD-10 und DSM-IV. 7th ed. Bern: Hogrefe, 2017 [DOI: 10.1024/85759-000]
15 **Flavell JH**. Metacognition and cognitive monitoring: A new area of cognitive-developmental inquiry. *Am Psychol* 1979; **34**: 906-911 [DOI: 10.1037/0003-066X.34.10.906]
16 **Fisher PL**, Wells A. Experimental modification of beliefs in obsessive-compulsive disorder: a test of the metacognitive model. *Behav Res Ther* 2005; **43**: 821-829 [PMID: 15890171 DOI: 10.1016/j.brat.2004.09.002]
17 **Papageorgiou C**, Wells A. Metacognitive beliefs about rumination in recurrent major depression. *Cogn Behav Pract* 2001; **8**: 160-164 [DOI: 10.1016/S1077-7229(01)80021-3]
18 **Papageorgiou C**, Wells A. An empirical test of a clinical metacognitive model of rumination and depression. *Cognit Ther Res* 2003; **27**: 261-273 [DOI: 10.1023/A:1023962332399]
19 **Wells A**. Meta-Cognition and Worry: A Cognitive Model of Generalized Anxiety Disorder. *Behav Cogn Psychother* 1995; **23**: 301-320 [DOI: 10.1017/S1352465800015897]
20 **Wells A**. A cognitive model of generalized anxiety disorder. *Behav Modif* 1999; **23**: 526-555 [PMID: 10533439 DOI: 10.1177/0145445599234002]
21 **Wells A**. The metacognitive model of GAD: Assessment of meta-worry and relationship with DSM-IV generalized anxiety disorder. *Cognit Ther Res* 2005; **29**: 107-121 [DOI: 10.1007/s10608-005-1652-0]
22 **Cartwright-Hatton S**, Wells A. Beliefs about worry and intrusions: the Meta-Cognitions Questionnaire and its correlates. *J Anxiety Disord* 1997; **11**: 279-296 [PMID: 9220301 DOI: 10.1016/s0887-6185(97)00011-x]
23 **Esbjørn BH**, Lønfeldt NN, Nielsen SK, Reinholdt-Dunne ML, Sømhovd MJ, Cartwright-Hatton S. Meta-worry, worry, and anxiety in children and adolescents: relationships and interactions. *J Clin Child Adolesc Psychol* 2015; **44**: 145-156 [PMID: 24555865 DOI: 10.1080/15374416.2013.873980]
24 **Ellis DM**, Hudson J. Test of the Metacognitive Model of Generalized Anxiety Disorder in Anxiety-Disordered Adolescents. *J Exp Psychopathol* 2011; **2**: 28-43 [DOI: 10.5127/jep.011910]
25 **Hearn CS**, Donovan CL, Spence SH, March S. A worrying trend in Social Anxiety: To what degree are worry and its cognitive factors associated with youth Social Anxiety Disorder? *J Affect Disord* 2017; **208**: 33-40 [PMID: 27744124 DOI: 10.1016/j.jad.2016.09.052]
26 **Hearn CS**, Donovan CL, Spence SH, March S. Do worry and its associated cognitive variables alter following CBT treatment in a youth population with Social Anxiety Disorder? *J Anxiety Disord* 2018; **53**: 46-57 [PMID: 29195187 DOI: 10.1016/j.janxdis.2017.11.005]
27 **Bacow TL**, May JE, Brody LR, Pincus DB. Are there specific metacognitive processes associated with anxiety disorders in youth? *Psychol Res Behav Manag* 2010; **3**: 81-90 [PMID: 22110332 DOI: 10.2147/PRBM.S11785]
28 **Bacow TL**, Pincus DB, Ehrenreich JT, Brody LR. The metacognitions questionnaire for children: development and validation in a clinical sample of children and adolescents with anxiety disorders. *J Anxiety Disord* 2009; **23**: 727-736 [PMID: 19362445 DOI: 10.1016/j.janxdis.2009.02.013]
29 **Ellis DM**, Hudson JL. The metacognitive model of generalized anxiety disorder in children and adolescents. *Clin Child Fam Psychol Rev* 2010; **13**: 151-163 [PMID: 20352491 DOI: 10.1007/s10567-010-0065-0]
30 **White JA**, Hudson JL. The Metacognitive Model of Anxiety in Children: Towards a Reliable and Valid Measure. *Cognit Ther Res* 2016; **40**: 92-106 [DOI: 10.1007/s10608-015-9725-1]
31 **Kuhn D**. Metacognitive Development. In: Balter L, Tamis-LeMonda C. Child Psychology: A handbook of contemporary issues. Philadelphia: Psychology Press, 1999: 259–286
32 **Estes D**, Wellman HM, Woolley JD. Children's Understanding of Mental Phenomena. In: Advances in Child Development and Behavior. San Diego: Academic Press, 1989: 41–87
33 **Flavell JH**, Miller P. Social cognition. In: Damon W, Kuhn D. Handbook of child psychology. New

York: Wiley, 1997: 851-898
34 **Flavell JH**. Cognitive development: children's knowledge about the mind. *Annu Rev Psychol* 1999; **50**: 21-45 [PMID: 10074674 DOI: 10.1146/annurev.psych.50.1.21]
35 **Flavell JH**, Green FL, Flavell ER. The mind has a mind of its own: Developing knowledge about mental uncontrollability. *Cogn Dev* 1998; **13**: 127-138 [DOI: 10.1016/S0885-2014(98)90024-7]
36 **Marulis LM**, Palincsar AS, Berhenke AL, Whitebread D. Assessing metacognitive knowledge in 3–5 year olds: the development of a metacognitive knowledge interview (McKI). *Metacognit Learn* 2016; **11**: 339-368 [DOI: 10.1007/s11409-016-9157-7]
37 **Myers SG**, Solem S, Wells A. The Metacognitions Questionnaire and Its Derivatives in Children and Adolescents: A Systematic Review of Psychometric Properties. *Front Psychol* 2019; **10**: 1871 [PMID: 31551843 DOI: 10.3389/fpsyg.2019.01871]
38 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]
39 **Moher D**, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; **4**: 1 [PMID: 25554246 DOI: 10.1186/2046-4053-4-1]
40 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlingon (VA): American Psychiatric Publishing, 2013
41 **Downes MJ**, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open* 2016; **6**: e011458 [PMID: 27932337 DOI: 10.1136/bmjopen-2016-011458]
42 **Koo TK**, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med* 2016; **15**: 155-163 [PMID: 27330520 DOI: 10.1016/j.jcm.2016.02.012]
43 **Cohen J**. A power primer. *Psychol Bull* 1992; **112**: 155-159 [PMID: 19565683 DOI: 10.1037//0033-2909.112.1.155]
44 **The Cochrane Collaboration**. Review Manager (RevMan). [cited 10 January 2021]. Available from: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman
45 **IntHout J**, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* 2016; **6**: e010247 [PMID: 27406637 DOI: 10.1136/bmjopen-2015-010247]
46 **Borenstein M**, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Res Synth Methods* 2017; **8**: 5-18 [PMID: 28058794 DOI: 10.1002/jrsm.1230]
47 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]
48 **Beheshti A**, Chavanon M-L, Albrecht B, Christiansen H. Meta-Mar: a free online meta-analysis service. [cited 10 January 2021]. In: Meta-Mar [Internet]. Available from: https://www.meta-mar.com/
49 **Benedetto L**, La Fauci E, Ingrassia M. Exploring meta-worry and perceived parenting behaviors in adolescents' anxiety. *Life Span Disabil* 2018; **2**: 117-141
50 **Francis R**, Hawes DJ, Abbott M, Costa DSJ. Development and Preliminary Validation of the Threat Appraisal Questionnaire for Children (TAQ-C). *J Psychopathol Behav Assess* 2017; **39**: 322-341 [DOI: 10.1007/s10862-016-9584-4]
51 **Francis R**, Hawes DJ, Abbott MJ, Costa DSJ. Cognitive mechanisms for worry in early adolescence: Re-examining the role of high verbal intelligence. *Pers Individ Dif* 2018; **120**: 179-184 [DOI: 10.1016/j.paid.2017.08.044]
52 **Smith KE**, Hudson JL. Metacognitive beliefs and processes in clinical anxiety in children. *J Clin Child Adolesc Psychol* 2013; **42**: 590-602 [PMID: 23356384 DOI: 10.1080/15374416.2012.755925]
53 **Cartwright-Hatton S**, Mather A, Illingworth V, Brocki J, Harrington R, Wells A. Development and preliminary validation of the Meta-cognitions Questionnaire-Adolescent Version. *J Anxiety Disord* 2004; **18**: 411-422 [PMID: 15125986 DOI: 10.1016/S0887-6185(02)00294-3]
54 **Zimmermann M**, Glemser M, Ertle A. Dysfunktionale Metakognitionen im Jugendalter: Psychometrische Evaluation einer deutschsprachigen Version des Meta-cognitions Questionaire - Adolescent Version (MCQ-A). *Z Kinder Jugendpsychiatr Psychother* 2018; **47**: 264-273 [DOI: 10.1026/1616-3443/a000492]
55 **Babaei S**, Ranjbar Varandi S, Hatami Z, Gharechahi M. Metacognition Beliefs and General Health in Predicting Alexithymia in Students. *Glob J Health Sci* 2015; **8**: 117-125 [PMID: 26383206 DOI: 10.5539/gjhs.v8n2p117]
56 **Esbjørn BH**, Normann N, Christiansen BM, Reinholdt-Dunne ML. The efficacy of group metacognitive therapy for children (MCT-c) with generalized anxiety disorder: An open trial. *J Anxiety Disord* 2018; **53**: 16-21 [PMID: 29145078 DOI: 10.1016/j.janxdis.2017.11.002]
57 **Fergus TA**, Limbers CA. Reducing Test Anxiety in School Settings: A Controlled Pilot Study Examining a Group Format Delivery of the Attention Training Technique Among Adolescent Students. *Behav Ther* 2019; **50**: 803-816 [PMID: 31208689 DOI: 10.1016/j.beth.2018.12.001]
58 **Holmes MC**, Donovan CL, Farrell LJ, March S. The efficacy of a group-based, disorder-specific treatment program for childhood GAD--a randomized controlled trial. *Behav Res Ther* 2014; **61**: 122-135 [PMID: 25193003 DOI: 10.1016/j.brat.2014.08.002]
59 **Holmes MC**, Donovan CL, Farrell LJ. A Disorder-Specific, Cognitively Focused Group Treatment

for Childhood Generalized Anxiety Disorder: Development and Case Illustration of the No Worries! *J Cogn Psychother* 2015; **29**: 275-301 [PMID: 32755939 DOI: 10.1891/0889-8391.29.4.275]

60 **Normann N**, Lønfeldt NN, Reinholdt-Dunne ML, Esbjørn BH. Negative Thoughts and Metacognitions in Anxious Children Following CBT. *Cognit Ther Res* 2016; **40**: 188-197 [DOI: 10.1007/s10608-015-9740-2]

61 **Sanger KL**, Dorjee D. Mindfulness training with adolescents enhances metacognition and the inhibition of irrelevant stimuli: Evidence from event-related brain potentials. *Trends Neurosci Educ* 2016; **5**: 1-11 [DOI: 10.1016/j.tine.2016.01.001]

62 **Simons M**, Vloet TD. Emetophobia - A Metacognitive Therapeutic Approach for an Overlooked Disorder. *Z Kinder Jugendpsychiatr Psychother* 2018; **46**: 57-66 [PMID: 27685192 DOI: 10.1024/1422-4917/a000464]

63 **Thorslund J**, McEvoy PM, Anderson RA. Group metacognitive therapy for adolescents with anxiety and depressive disorders: A pilot study. *J Clin Psychol* 2020; **76**: 625-645 [PMID: 31916590 DOI: 10.1002/jclp.22914]

64 **Benedetto L**, Di Blasi D, Pacicca P. Worry and Meta-Cognitive Beliefs in Childhood Anxiety Disorders. *Mediterr J Clin Psychol* 2013; **1**: 1-14 [DOI: 10.6092/2282-1619/2013.1.932]

65 **Donovan CL**, Holmes MC, Farrell LJ, Hearn CS. Thinking about worry: Investigation of the cognitive components of worry in children. *J Affect Disord* 2017; **208**: 230-237 [PMID: 27792968 DOI: 10.1016/j.jad.2016.09.061]

66 **Esbjørn BH**, Sømhovd MJ, Holm JM, Lønfeldt NN, Bender PK, Nielsen SK, Reinholdt-Dunne ML. A structural assessment of the 30-item Metacognitions Questionnaire for Children and its relations to anxiety symptoms. *Psychol Assess* 2013; **25**: 1211-1219 [PMID: 23876156 DOI: 10.1037/a0033793]

67 **Gini G**, Marino C, Spada MM. The Role of Metacognitions and Thinking Styles in the Negative Outcomes of Adolescents' Peer Victimization. *Violence Vict* 2019; **34**: 752-769 [PMID: 31575813 DOI: 10.1891/0886-6708.VV-D-18-00016]

68 **Naumann L**. Understanding and assessing worrying - analyzing relevant psychopathological mechanisms relevant for generalized anxiety disorder across the lifespan. Doctoral Thesis, The University of Cologne. 2014. Available from: https://kups.ub.uni-koeln.de/6135/

69 **Wilson C**, Hall M. Thought control strategies in adolescents: links with OCD symptoms and meta-cognitive beliefs. *Behav Cogn Psychother* 2012; **40**: 438-451 [PMID: 22380705 DOI: 10.1017/S135246581200001X]

70 **Wilson C**, Hughes C. Worry, beliefs about worry and problem solving in young children. *Behav Cogn Psychother* 2011; **39**: 507-521 [PMID: 21878136 DOI: 10.1017/S1352465811000269]

71 **Laugesen N**, Dugas MJ, Bukowski WM. Understanding adolescent worry: the application of a cognitive model. *J Abnorm Child Psychol* 2003; **31**: 55-64 [PMID: 12597699 DOI: 10.1023/a:1021721332181]

72 **Carr I**, Szabó M. Worry in Children: Changing Associations With Fear, Thinking, and Problem-Solving. *J Early Adolesc* 2015; **35**: 120-135 [DOI: 10.1177/0272431614529366]

73 **Fisak B**, Mentuccia M, Przeworski A. Meta-worry in adolescents: examination of the psychometric properties of the meta-worry questionnaire in an adolescent sample. *Behav Cogn Psychother* 2014; **42**: 491-496 [PMID: 23735158 DOI: 10.1017/S1352465813000374]

74 **Hearn CS**, Donovan CL, Spence SH, March S, Holmes MC. What's the Worry with Social Anxiety? *Child Psychiatry Hum Dev* 2017; **48**: 786-795 [PMID: 27917455 DOI: 10.1007/s10578-016-0703-y]

75 **Kertz S**, Woodruff-Borden J. The role of metacognition, intolerance of uncertainty, and negative problem orientation in children's worry. *Behav Cogn Psychother* 2013; **41**: 243-248 [PMID: 22877861 DOI: 10.1017/S1352465812000641]

76 **Lønfeldt NN**, Esbjørn BH, Normann N, Breinholst S, Francis SE. Do Mother's Metacognitions, Beliefs, and Behaviors Predict Child Anxiety-Related Metacognitions? *Child Youth Care Forum* 2017; **46**: 577-599 [DOI: 10.1007/s10566-017-9396-z]

77 **Lønfeldt NN**, Marin CE, Silverman WK, Reinholdt-Dunne ML, Esbjørn BH. The Role of Metacognitions in the Association between Children's Perceptions of Maternal Control and Anxiety. *J Child Fam Stud* 2017; **26**: 1398-1408 [DOI: 10.1007/s10826-017-0664-1]

78 **Irak M**. Standardization of Turkish form of metacognition questionnaire for children and adolescents: the relationships with anxiety and obsessive-compulsive symptoms. *Turk Psikiyatri Derg* 2012; **23**: 46-52 [PMID: 22374631]

79 **Reinholdt-Dunne ML**, Blicher A, Nordahl H, Normann N, Esbjørn BH, Wells A. Modeling the Relationships Between Metacognitive Beliefs, Attention Control and Symptoms in Children With and Without Anxiety Disorders: A Test of the S-REF Model. *Front Psychol* 2019; **10**: 1205 [PMID: 31231273 DOI: 10.3389/fpsyg.2019.01205]

80 **Donovan CL**, Holmes MC, Farrell LJ. Investigation of the cognitive variables associated with worry in children with Generalised Anxiety Disorder and their parents. *J Affect Disord* 2016; **192**: 1-7 [PMID: 26702733 DOI: 10.1016/j.jad.2015.12.003]

81 **Matthews L**, Reynolds S, Derisley J. Examining Cognitive Models of Obsessive Compulsive Disorder in Adolescents. *Behav Cogn Psychother* 2006; **35**: 149-163 [DOI: 10.1017/S1352465806003213]

82 **Wilson C**, Budd B, Chernin R, King H, Leddy A, Maclennan F, Mallandain I. The role of meta-cognition and parenting in adolescent worry. *J Anxiety Disord* 2011; **25**: 71-79 [PMID: 20828983 DOI: 10.1016/j.janxdis.2010.08.005]

83 **Wells A**, Cartwright-Hatton S. A short form of the metacognitions questionnaire: properties of the

MCQ-30. *Behav Res Ther* 2004; **42**: 385-396 [PMID: 14998733 DOI: 10.1016/S0005-7967(03)00147-5]

84 **Gosselin P**, Ladouceur R, Langlois F, Freeston MH, Dugas MJ, Bertrand J. Development and validation of a new instrument to evaluate erroneous beliefs about worries. *Eur Rev Appl Psychol* 2003; **53**: 199-211

85 **Cho Y**, Jahng S, Chai S. The factor structure and concurrent validity of the Korean version of the Metacognitions Questionnaire 30 (K-MCQ-30). *J Clin Psychol* 2012; **68**: 349-391 [PMID: 22307959 DOI: 10.1002/jclp.20867]

86 **Quattropani MC**, Lenzo V, Mucciardi M, Toffle ME. Psychometric properties of the Italian version of the Short Form of the Metacognitions Questionnaire (MCQ-30). *Boll di Psicol Appl* 2014; **62**: 29-41

87 **Hempel S**, Miles JN, Booth MJ, Wang Z, Morton SC, Shekelle PG. Risk of bias: a simulation study of power to detect study-level moderator effects in meta-analysis. *Syst Rev* 2013; **2**: 107 [PMID: 24286208 DOI: 10.1186/2046-4053-2-107]

88 **Bacow TL**. Metacognitive processes in anxious children: Associations with diagnostic status. Doctoral Thesis, The University of Boston, 2008

89 **Baker WL**, White CM, Cappelleri JC, Kluger J, Coleman CI; Health Outcomes, Policy, and Economics (HOPE) Collaborative Group. Understanding heterogeneity in meta-analysis: the role of meta-regression. *Int J Clin Pract* 2009; **63**: 1426-1434 [PMID: 19769699 DOI: 10.1111/j.1742-1241.2009.02168.x]

90 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Arlingon (VA): American Psychiatric Publishing, 1994

91 **Nunnaly JC**, Bernstein IH. Psychometric Theory. 3rd ed. New York: McGraw-Hill, 1994

92 **Boysan M**, Kadak MT, Tarakcioglu MC, Sertdurak ZS, Demirel OF. Psychometric Properties of Turkish versions of the Leyton Obsessional Inventory-Child Version (LOI-CV) and Obsessive Beliefs Questionnaire-Child Version (OBQ-CV). *Klin Psikofarmakol Bülteni-Bulletin Clin Psychopharmacol* 2016; **26**: 382-396 [DOI: 10.5455/bcp.20151203125902]

93 **Esbjørn BH**, Normann N, Lønfeldt NN, Tolstrup M, Reinholdt-Dunne ML. Exploring the relationships between maternal and child metacognitions and child anxiety. *Scand J Psychol* 2016; **57**: 201-206 [PMID: 27119255 DOI: 10.1111/sjop.12286]

94 **Gallagher B**, Cartwright-Hatton S. The relationship between parenting factors and trait anxiety: mediating role of cognitive errors and metacognition. *J Anxiety Disord* 2008; **22**: 722-733 [PMID: 17766082 DOI: 10.1016/j.janxdis.2007.07.006]

95 **Mather A**, Cartwright-Hatton S. Cognitive predictors of obsessive-compulsive symptoms in adolescence: a preliminary investigation. *J Clin Child Adolesc Psychol* 2004; **33**: 743-749 [PMID: 15498741 DOI: 10.1207/s15374424jccp3304_9]

96 **Yavuz M**, Altan B, Bayrak B, Gündüz M, Bolat N. The relationships between nomophobia, alexithymia and metacognitive problems in an adolescent population. *Turk J Pediatr* 2019; **61**: 345-351 [PMID: 31916711 DOI: 10.24953/turkjped.2019.03.005]

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SYSTEMATIC REVIEWS

Deep brain stimulation for obsessive-compulsive disorder: A systematic review of worldwide experience after 20 years

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Abstract

BACKGROUND

Twenty years after its first use in a patient with obsessive-compulsive disorder (OCD), the results confirm that deep brain stimulation (DBS) is a promising therapy for patients with severe and resistant forms of the disorder. Nevertheless, many unknowns remain, including the optimal anatomical targets, the best stimulation parameters, the long-term (LT) effects of the therapy, and the clinical or biological factors associated with response. This systematic review of the articles published to date on DBS for OCD assesses the short and LT efficacy of the therapy and seeks to identify predictors of response.

AIM

To summarize the existing knowledge on the efficacy and tolerability of DBS in treatment-resistant OCD.

METHODS

A comprehensive search was conducted in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020, using the following strategy: "(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS)." Clinical trials and observational studies published in English and evaluating the effectiveness of DBS for OCD in humans were included and screened for relevant information using a standardized collection

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tool. The inclusion criteria were as follows: a main diagnosis of OCD, DBS conducted for therapeutic purposes and variation in symptoms of OCD measured by the Yale-Brown Obsessive-Compulsive scale (Y-BOCS) as primary outcome. Data were analyzed with descriptive statistics.

RESULTS

Forty articles identified by the search strategy met the eligibility criteria. Applying a follow-up threshold of 36 mo, 29 studies (with 230 patients) provided information on short-term (ST) response to DBS in, while 11 (with 155 patients) reported results on LT response. Mean follow-up period was 18.5 ± 8.0 mo for the ST studies and 63.7 ± 20.7 mo for the LT studies. Overall, the percentage of reduction in Y-BOCS scores was similar in ST (47.4%) and LT responses (47.2%) to DBS, but more patients in the LT reports met the criteria for response (defined as a reduction in Y-BOCS scores > 35%: ST, 60.6% *vs* LT, 70.7%). According to the results, the response in the first year predicts the extent to which an OCD patient will benefit from DBS, since the maximum symptom reduction was achieved in most responders in the first 12-14 mo after implantation. Reports indicate a consistent tendency for this early improvement to be maintained to the mid-term for most patients; but it is still controversial whether this improvement persists, increases or decreases in the long term. Three different patterns of LT response emerged from the analysis: 49.5% of patients had good and sustained response to DBS, 26.6% were non responders, and 22.5% were partial responders, who might improve at some point but experience relapses during follow-up. A significant improvement in depressive symptoms and global functionality was observed in most studies, usually (although not always) in parallel with an improvement in obsessive symptoms. Most adverse effects of DBS were mild and transient and improved after adjusting stimulation parameters; however, some severe adverse events including intracranial hemorrhages and infections were also described. Hypomania was the most frequently reported psychiatric side effect. The relationship between DBS and suicide risk is still controversial and requires further study. Finally, to date, no clear clinical or biological predictors of response can be established, probably because of the differences between studies in terms of the neuroanatomical targets and stimulation protocols assessed.

CONCLUSION

The present review confirms that DBS is a promising therapy for patients with severe resistant OCD, providing both ST and LT evidence of efficacy.

Key Words: Deep brain stimulation; Obsessive-compulsive disorder; Predictors of response; Side effects; Short-term; Long-term

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Core Tip: This systematic review describes worldwide experience in the use of deep brain stimulation (DBS) in severe resistant patients with obsessive-compulsive disorder over the last twenty years, comparing short-term (ST) and long-term (LT) response to the treatment (in 230 and 155 patients respectively). Both ST and LT studies report similar, stable reductions in severity of around 47%, although the number of patients who met the criteria for response was significantly higher in the LT studies (60.6% *vs* 70.7%). DBS is a safe and well-tolerated technique, since most side effects are mild and reversible on adjusting stimulation parameters. However, no clear predictors of response can be established at present.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by the presence of persistent intrusive thoughts, images or urges (obsessions) that lead to compulsions, repetitive mental or motor acts, or avoidance behaviors, in order to reduce anxiety[1]. OCD has a lifetime prevalence of 2%-3%. It begins in childhood, puberty or early adult life, and thus affects a critical period in relational and academic development[2,3]. The standard treatment for OCD combines psychotropic medication - typically serotonin reuptake inhibitors and antipsychotic potentiation - and cognitive behavioral therapy (CBT), mainly exposure with response prevention. However, around 10% of patients continue to present chronic and severe obsessive-compulsive symptoms despite exhausting all available pharmacological strategies and undergoing intensive behavior therapy[4,5]. In this group of severely disabled OCD patients, for some decades now neurosurgical interventions have been considered as a potential treatment, in spite of the possible risks.

Beyond ablative surgery, advances in many areas of neurosurgery and neuroimaging over the last 20 years have made it possible to test the capacity of different brain stimulation techniques. These techniques include deep brain stimulation (DBS) for modulating the activity of dysfunctional brain areas located in, or intimately connected with, the cortico-striato-thalamo-cortical circuitry in treatment-refractory OCD[6]. DBS was first used in 1999 as a surgical option for patients with severe OCD who had not responded to other treatments[7], but it was not until 2009 that the US Food and Drug Administration and Conformité Européenne approved it under the Humanitarian Device Exemption Program[8]. This new status means that DBS may be used as an alternative to more invasive procedures, such as anterior capsulotomy, for the treatment of chronic, severe, treatment-resistant OCD. Indeed, DBS is a reversible, focal, and adjustable neuromodulation technique that is usually well tolerated. Serious adverse effects are infrequent; they are typically psychiatric (*e.g.*, hypomania, sleep complaints, disinhibition, and depression)[9,10], and can be minimized by adjusting the stimulation parameters[11]. Although adverse effects have been described in somatic domains (*e.g.*, weight change, sexual complaints, infection, and gastrointestinal symptoms) and neurological domains (*e.g.*, headache, paresthesia, sensorial complaints, or cognitive difficulties), they are relative-ly rare[12,13].

Literature reports indicate that, to date, more than 300 patients with OCD have undergone surgery for DBS implantation. Among these reports, three meta-analyses[9-11] have reported that approximately 60% achieved reductions of > 35% on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS, the gold standard of OCD symptom assessment), a rate accepted as indicating response to treatment[14,15]. This mean reduction in the Y-BOCS score is reported to range from 38.6% to 45.1%, and the major differences between studies has been attributed to the heterogeneity of the targets stimulated and the parameters programmed[16,17]. Recently, studies have begun to publish data on the long-term (LT) outcome of these patients[18-22]. Despite all these advances, however, and 20 years after the first DBS implantation in a patient with OCD, our knowledge of the benefits and risks of DBS use in OCD is still limited, due to the small sample sizes, the lack of adequate control conditions, and the heterogeneity of the anatomical targets and stimulation parameters applied. Therefore, a systematic and critical review of all the data published to date can help us resolve some of the doubts regarding the extension and likelihood of treatment response to DBS, the need for concomitant pharmacological or behavioral treatments after implantation, the recommended duration of stimulation in both responsive and non-responsive patients, and the risk of severe adverse effects.

Therefore, the aim of this systematic review is to summarize the existing knowledge on the efficacy and tolerability of DBS in treatment-resistant OCD and to compare the short-term (ST) and LT results. This analysis should indicate whether differential response patterns exist and whether response predictors can be established so as to optimize the use of DBS in patients with OCD.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance[23,24]. Studies with ST and LT follow-up periods are referred to as “ST studies” and “LT studies” respectively.

Search strategy

A comprehensive search was conducted in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020, using the following strategy: "(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS)." The search identified a limited number of studies and was therefore completed by manual selection of relevant studies included in the reference lists of previously published articles. Any available meta-analyses and systematic reviews were also assessed in order to include all references.

Eligibility criteria

We conducted a systematic review of studies evaluating the effectiveness of DBS for OCD in humans, searching for both clinical trials and observational studies. The inclusion criteria were as follows: (1) A main diagnosis of severe and disabling OCD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth or fifth edition[1,25], regardless of comorbidities; (2) DBS conducted for therapeutic purposes; (3) A primary outcome of variation in OCD symptoms measured by the Y-BOCS[14,15]. The Y-BOCS is the gold standard for OCD symptom assessment and was used in all studies assessing response to DBS in OCD; (4) Publication in English; and (5) Randomized clinical trials (parallel or crossover) or observational studies designs. Articles were excluded if their focus was sham stimulation, neuroanatomy, functional imaging, or neurophysiology.

Study selection and outcome measures

Articles were initially extracted and screened (title, abstract, and full article) by one reviewer (Mar-Barrutia L) with regard to the eligibility criteria and were subsequently reviewed by a second reviewer (Alonso P) to confirm their eligibility. Disagreements were resolved by consensus. The following data were then extracted: authors, year of publication, sample size, and study design; patient age, sex, and illness duration; DBS target site and follow-up since implantation; Y-BOCS, depression assessment, and global function (*e.g.*, Global Assessment of Functioning, GAF score) at baseline and last follow-up; adverse effects; and suicide attempts and/or death by suicide. Data were double-checked to exclude duplication. If a patient was included in more than one study, only their most recent/most detailed data were considered.

Risk of bias assessment

We used the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias in randomized controlled trials (RCT)[26], classifying the risk as low, high, or unclear risk in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. To assess the risk of bias in observational studies we used the Newcastle-Ottawa Scale[27] (Table 1 and Table 2).

Ethics

The review did not require ethics committee approval because it analyses anonymous, previously published information.

RESULTS

Study characteristics: ST vs LT follow-up

Using the search strategy, we identified 896 articles for abstract review. Of these, 40 met the eligibility criteria (Figure 1), and a further three meta-analyses were also assessed[9-11]. Based on a follow-up threshold of 36 mo, we classified 29 articles as ST (230 cases) and eleven as LT (155 cases). Some LT studies described the LT follow-up of patients who had previously been included in ST studies (a total of 41 cases).

To assess the differences between ST and LT studies, the mean values for clinical and methodological variables were compared between the two study types (Table 3). Most ST studies (23) and most LT studies (9) were observational. The mean follow-up period in the ST studies was 1.5 years and in the LT studies 5.3 years, and the mean sample sizes were 7.9 and 14 respectively. No significant differences were detected in gender distribution, mean age at inclusion, mean Y-BOCS scores at baseline and last observation, or the percentage of reduction in Y-BOCS scores. However, the mean percentage of responders (patients with a > 35% reduction in Y-BOCS scores) rose from 60.6% in the ST studies to 70.7% in the LT studies. There was considerable

Table 1 Risk of bias for randomized controlled trials

Ref.	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Abelson *et al* [67], 2005			-	-	+		
Barcia *et al* [32], 2019		+	-	-	-		
Goodman *et al* [16], 2010			-	-	+		
Huff *et al*[31], 2010					+		
Luyten *et al* [20], 2016	+		-	-			
Tyagi *et al* [17], 2019		+			+	+	
Welter *et al* [39], 2020		+	-	-	-		

+: High risk of bias; -: Low risk of bias. If there is no sign, the risk of bias is uncertain.

variability in the programming parameters reported in the studies: both monopolar and bipolar stimulation were used, and the average frequency of stimulation ranged from 100-130 Hz, average pulse width from 60-450 μs, and average voltage from 2-7.4 V.

The level of depression, as assessed by different scales, was reported more frequently in LT than in ST studies. However, depressive symptoms improved regardless of the follow-up duration. The characteristics and results for the ST and LT studies, grouped into RCT and non-RCT designs, are presented in Tables 4-7.

Primary outcomes: Obsessive symptoms

The minimum Y-BOCS score required for DBS implantation was 30-32 in most studies, a score range consistent with severe illness; some studies applied less restrictive inclusion criteria (scores > 24)[28-32]. The mean changes in Y-BOCS scores from pre- to post-treatment were similar in the ST studies (change from 33.0 to 17.2) and the LT studies (change from 34.4 to 18.0). Thus, the percentage reduction in Y-BOCS scores remained stable when comparing ST and LT responses to DBS (47.4% *vs* 47.2%), but significantly more patients in the LT reports met the criteria for response (ST: 60.6%, *vs* LT: 70.7%). These results are consistent with those of previous meta-analyses[9-11].

Given that DBS has only been authorized for the treatment of OCD for 20 years, the evidence available on the LT clinical course remains limited. Our systematic review includes information on 155 patients from different parts of the world treated for a mean follow-up period of 5.3 years. Those responding to DBS, either completely or partially, tended to achieve the maximum symptom reduction in the first 12-14 mo after implantation[19,21]. Graat *et al*[19] followed the largest sample to date (50 patients) from 3 years to 13 years and found that most responders at LT follow-up had responded in the first year. This initial period of improvement coincided with a time when more stimulator adjustments were performed and the patient engaged in simultaneous behavioral therapy. Holland *et al*[21] reported that their nine patients needed > 1 year to achieve maximum improvement, but their mean results of 32.5 mo were seriously affected by an outlier with a significantly prolonged response time. After excluding this subject, the mean response time fell to 14.6 mo, again suggesting that response in the first year significantly predicts the extent to which an OCD patient will benefit from DBS.

Reports indicate a consistent tendency for the improvement to be maintained to the mid-term for most patients[19,22,33-38], but it is controversial whether this improvement persists, increases or decreases in the LT. Winter *et al*[28], Holland *et al*[21] and Mallet *et al*[22] found progressive decreases in obsessive symptoms over time. For example, while Mallet *et al*[22] reported that the mean Y-BOCS score decreased by one point per year up to 46 mo, Graat *et al*[19] reported a slight increase of 1.8 points at the end of their follow-up period. Luyten *et al*[20] also reported a 66% reduction in Y-

Table 2 Risk of bias for non-randomized controlled trials

Ref.	Selection	Comparability	Outcome
Anderson and Ahmed[74], 2003	++	+	++
Aouizerate *et al*[75], 2009	++	+	+++
Azriel *et al*[76], 2020	++	+	+++
Chabardes *et al*[29], 2020	++	+	++
Chang *et al*[77], 2017	++	+	+++
Choudhury *et al*[78], 2017	++	+	+++
Coenen *et al*[79], 2017	++	+	+++
Denys *et al*[44], 2020	++	+	++
Doshi *et al*[80], 2019	++	+	+++
Farrand *et al*[42], 2018	++	+	+++
Fayad *et al*[33], 2016	++	+	+++
Franzini *et al*[81], 2010	+++	+	+++
Gabriëls *et al*[53], 2003	++	+	+++
Graat *et al*[19], 2020	++	+	+++
Grant *et al*[34], 2016	++	+	+++
Greenberg *et al*[36], 2010	++	+	+++
Gupta *et al*[35], 2019	++	+	+++
Holland *et al*[21], 2020	++	+	+
Huys *et al*[30], 2019	++	+	+++
Islam *et al*[40], 2015	++	+	+++
Jiménez *et al*[55], 2013	++	+	+++
Lee *et al*[37], 2019	++	+	+++
Maarouf *et al*[45], 2016	+++	+	++
Mallet *et al*[22], 2019	++	+	+++
Menchón *et al*[13], 2021	++	+	++
Mulders *et al*[82], 2017	++	+	+++
Plewnia *et al*[83], 2008	++	+	+++
Polosan *et al*[38], 2019	++	+	+++
Roh *et al*[61], 2012	++	+	+++
Sachdev *et al*[84], 2012	++	+	++
Senova *et al*[85], 2020	++	+	+++
Tsai *et al*[49], 2012	++	+	++
Winter *et al*[28], 2021	++	+	+++

Each "+" symbol indicates lower risk of bias.

BOCS scores 4 years after DBS implantation, which had become a 45% reduction by 14 years. The percentage of responders (67%) remained significant at the end of follow-up.

The lack of individual data from the studies analyzed rules out a statistical classification of the LT evolution of OCD after treatment with DBS. Nevertheless, the data available suggest at least three patterns of LT response. First, 26.6% of subjects in all the studies were non responders, in whom the clinical effect was negligible despite all attempts to adjust the stimulation parameters for months or years[21,28,29,33,39,40]. Second, 49.5% of patients were responders who showed a maximum improvement in

Table 3 Differences in mean characteristics between the short-term and long-term studies

Characteristic	Short-term		Long-term	
	mean ± SD	Range	mean ± SD	Range
Sample size, *n*	7.9 ± 13.6	1-70	14 ± 14.4	1-50
Female, %	54 ± 36.9	0-100	61.5 ± 22	33-100
Average age, yr	41.7 ± 9.9	28-72	40.5 ± 4.3	32-45
Average duration of illness, yr	24 ± 16.4	5-52	20.4 ± 3.2	16-25
Follow-up since DBS, mo	18.5 ± 8	7-36	63.7 ± 20.7	38-96
Follow-up since DBS, yr	1.5 ± 0.6	1-2.7	5.3 ± 1.7	3-7.7
Baseline Y-BOCS, mean score	33 ± 3.7	19-39	34.4 ± 1.7	32-38
Last Y-BOCS, mean score	17.2 ± 7.4	1-31	18 ± 3.2	11-21
Y-BOCS improvement, %	47.4 ± 21	10-97	47.2 ± 9.9	36-71
Responders, %	60.6 ± 36.2	0-100	70.7 ± 24.8	22-100
	Yes/no		**Yes/no**	
RCT	6/23		1/10	
Depression assessment	21/6		9/11	
Depression improvement	15/4		8/1	
Functionality assessment	16/13		7/4	
Functionality improvement	14/1		7/0	

DBS: Deep brain stimulation; NR: Not reported; RCT: Randomized controlled trial; Y-BOCS: Yale-Brown Obsessive Compulsive scale.

the first 12-24 mo and remained in stable remission for years. A third group of partial responders (22.5% of patients) improved at some point during treatment, but then experienced relapses during follow-up. Although some of the relapses among partial responders were linked to external stressors, such as the loss of a family member[19], device-related events (*e.g.*, battery depletion[41]), or comorbid conditions (*e.g.*, depression or generalized anxiety[42]), no clear external stressors have been associated with relapses in other patients with fluctuating courses[33]. Thus, some patients will be expected to show an oscillating response to DBS that we still cannot explain. Virtually all studies agree that battery depletion is accompanied by severe symptom deterioration, which may be very abrupt[22]. While this finding reinforces the therapeutic benefit of DBS for OCD, it also highlights the need to monitor patients closely for this risk.

Secondary outcomes: Depression and global function

Depressive symptoms: Depressive disorders are the most frequent comorbidity among patients with OCD treated by DBS[10,41,43], with 63.3% being diagnosed with any mood disorder and 40.7% meeting the diagnostic criteria for a major depressive disorder[2]. Twenty-nine of the 40 studies assessed changes in depressive symptoms after DBS implantation, but the use of seven different scales (HDRS, MADRS, BDI, DASS, QIDS, IDS-30, POMS) makes direct comparisons difficult. In most studies, maximum improvement of depressive symptoms was observed in the first year after DBS therapy, regardless of the follow-up period. These improvements tended to parallel those for obsessive symptoms and tended to endure over time[20,21,36] (Table 2), but there was not always a clear correlation. Winter *et al*[28], for example, found a greater decrease in the MADRS score in patients who responded to DBS, whereas both Denys *et al*[44] and Graat *et al*[19] described a significant improvement in depressive symptoms in patients who experienced no change in their OCD symptomatology. In fact, these patients requested continued stimulation despite an improvement in obsessive symptoms. The same research group has previously described the improvement process as a sequence that begins with the amelioration of affective symptoms (in seconds), followed by anxious symptoms (in minutes), obsessive symptoms (in days), and compulsions (in weeks or months)[43]. Unfortunately, a significant worsening of mood symptoms in some patients who respond to

Table 4 Participant characteristics in the short-term studies

	Ref.	*n*	Female %	Average age (yr)	Average duration of illness (yr)	Average follow-up since DBS implantation (mo)	Target site
RCT	Abelson *et al*[67], 2005	4	50	40.2	22.5	12.8	ALIC
	Barcia *et al*[32], 2019	7	57.1	35.2	25.3	21	NAcc/CN
	Goodman *et al*[16], 2010	6	66	36.2	24	12	VC/VS
	Huff *et al*[31], 2010	10	40	36.3	22.2	12	NAcc
	Tyagi *et al*[17], 2019	6	16.6	45.5	24.1	12	VC/VS, STN, VC/VS/STN
	Welter *et al*[39], 2020	8	12.5	42.5	NR	22	STN, CN, NAcc
Non-RCT	Anderson and Ahmed[74], 2003	1	100	35	10	10	ALIC
	Aouizerate *et al*[75], 2009	2	0	51	33.5	15	NAcc/CN
	Azriel *et al*[76], 2020	1	100	67	44	16	amGPI
	Chabardes *et al*[29], 2020	19	63.1	39	20.7	24	STN
	Chang *et al*[77], 2017	1	100	28	8	12	VC/VS
	Coenen *et al*[79], 2017	2	0	41.5	29	12	MFB
	Denys *et al*[44], 2020	70	69	41.7	25	12	ALIC
	Doshi *et al*[80], 2019	1	100	42	NR	12	NAcc
	Farrand *et al*[42], 2018	7	57.1	46	25	31	NAcc or BNST
	Franzini *et al*[81], 2010	2	0	37	21.5	25.5	NAcc
	Gabriëls *et al*[53], 2003	3	67	41.7	24.3	27	NAcc/ALIC
	Grant *et al*[34], 2016	1	0	30	5	36	NAcc
	Huys *et al*[30], 2019	20	50	40.1	26.1	12	ALIC-NAcc
	Islam *et al*[40], 2015	8	17	45.8	30.2	25	BNST, NAcc
	Jiménez *et al*[55], 2013	6	50	34.7	16.2	24	ITP
	Maarouf *et al*[45], 2016	4	75	39.3	23.5	11.5	MD/VA
	Menchón *et al*[13], 2021	29	52	41	24.5	12	ALIC
	Mulders *et al*[82], 2017	1	100	49	34	24	VC/VS
	Plewnia *et al*[83], 2008	1	100	51	NR	24	ALIC/NAcc
	Roh *et al*[61], 2012	4	25	45.5	24.2	24	VC/VS
	Sachdev *et al*[84], 2012	1	100	32	28	7	NAcc
	Senova *et al*[85], 2020	1	100	72	52	36	STN
	Tsai *et al*[49], 2012	4	0	25.5	8.3	15	VC/VS

ALIC: Anterior limb on internal capsule; amGPI: Anteromedial globus pallidus internus; BNST: Bed nucleus of stria terminalis; CN: Caudate nucleus; ITP: Inferior thalamic peduncle; MD/VA: Medial dorsal and the ventral anterior nucleus of the thalamus; MFB: Medial forebrain bundle; NAcc: Nucleus

accumbens; NR: Not reported; RCT: Randomized controlled trial; VC/VS: Ventral caudate/ventral striatum.

Table 5 Participant characteristics in the long-term studies

	Ref.	*n*	Female %	Average age (yr)	Average duration of illness (yr)	Average follow-up since DBS implantation (mo)	Target site
RCT	Luyten *et al*[20], 2016	24	50	39	NR	77	ALIC/BST
Non-RCT	Choudhury *et al*[78], 2017	1	100	45	21	51	ALIC
	Fayad *et al*[33], 2016	6	66	44.5	NR	92.5	VC/VS
	Graat *et al*[19], 2020	50	68	41.6	25.2	81.6	ALIC
	Gupta *et al*[35], 2019	2	100	46.5	23	42	VC/VS/ ALIC
	Greenberg *et al*[36], 2010	26	46	35.3	22	96	VC/VS
	Holland *et al*[21], 2020	9	44.4	40.2	NR	54.8	VC/VS
	Lee *et al*[37], 2019	5	60	32.4	16.2	49.8	ITP
	Mallet *et al*[22], 2019	14	42.8	43.8	NA	46	STN
	Polosan *et al*[38], 2019	12	67	38.3	18	38	STN
	Winter *et al*[28], 2021	6	33.3	39.6	18	72	ALIC/BNST

The study sample conducted by Fayad *et al*[33] corresponds to the follow-up of Goodman *et al*[16]'s study sample. Greenberg *et al*[36] conducted a multicenter study in which some patients from Fayad *et al*[33]'s study were included. The patients in the studies by Mallet *et al*[22] and Chabardes *et al*[29] are included in the STOC study. ALIC: Anterior limb on internal capsule; BNST: Bed nucleus of stria terminalis; ITP: Inferior thalamic peduncle; NR: Not reported; RCT: Randomized controlled trial; VC/VS: Ventral caudate/ventral striatum.

DBS has also been observed, which supports the relative independence of the antidepressant and antiobsessive effects[33,42].

Global functioning: Consideration of DBS for OCD presupposes the presence of extremely severe obsessive symptoms that severely impair patient function in all areas of life. The GAF was the most frequently used scale of functionality in the studies included, with median baseline scores of 40 indicating impairment in work or school, family relations, judgment, thinking, or mood[41]. Of the 40 studies analyzed, 23 included an assessment of global functioning as a secondary outcome, using the GAF scale, the Instrumental Activities of Daily Living scale, the Clinical Global Impressions Severity Scale, or the Social and Occupational Functioning Assessment Scale. All but one study reported a progressive and significant improvement in the functionality of patients with OCD after DBS treatment, which was maintained in parallel to their obsessive symptoms in the LT follow-up studies. However, the improvement was not always universal; some studies described the persistence of social difficulties despite an abrupt increase in the GAF scale in the first 24 mo[29]. In the only article to report no functional improvement, stimulation of the medial dorsal and ventral anterior nucleus of the thalamus did not produce any improvement in obsessive symptoms [45].

Adverse effects

The side effects of DBS can also be divided into surgical or hardware-related complications, stimulation-induced side effects, and others[46]. The first observable side effects are those related to the device implant; they are associated with the surgery or the presence of the electrodes in the brain, and are usually temporary. Some patients needed reoperation due to poor electrode positioning[19,44,45] or intracranial infection [36,39] enforcing removal and reimplantation[19,36], a situation that significantly increased the surgical risks. Intracranial hemorrhage was the most severe secondary

Table 6 Summary of results for the short-term studies

	Ref.	Average baseline Y-BOCS	Average Y-BOCS at LFU	Average Y-BOCS improvement (%)	Average responders (%)	Depression (HDRS, BDI, MADRS, DASS, POMS)	Depression scale improvement	Global functionality (GAF, CGIS, SOFAS)	Functionality improvement
RCT	Abelson *et al* [67], 2005	32.7	23	30	50	Yes, HDRS	Yes	NR	NR
	Barcia *et al* [32], 2019	32.2	15.4	51	85.7	Yes, HDRS and BDI	No	NR	NR
	Goodman *et al*[16], 2010	33.7	18	46	67	Yes, HDRS	Yes	Yes, CGISS	Yes
	Abelson *et al* [67], 2005	32.3	25.4	21	8.3	Yes, HDRS and BDI	Yes	Yes, GAF	Yes
	Barcia *et al* [32], 2019	36.1	14.1	61	NR	Yes, MADRS	Yes	NR	NR
	Goodman *et al*[16], 2010	33.5	23.2	30	37.5	Yes, MADRS	No	NR	NR
Non-RCT	Anderson and Ahmed [74], 2003	34	1	97	100	NR	NR	Yes, GAF	Yes
	Aouizerate *et al*[75], 2009	25	11	56	100	Yes, HDRS	Yes	NR	NR
	Azriel *et al* [76], 2020	33	16	48	100	NR	NR	NR	NR
	Chabardes *et al*[29], 2020	33.3	15.8	53	73	NR	NR	Yes, GAF	Yes
	Chang *et al* [77], 2017	36	25	30	0	Yes, HDRS	NR	Yes, GAF	Yes
	Coenen *et al* [79], 2017	30	20.5	31	50	Yes, BDI	Yes	Yes, GAF	NR
	Denys *et al* [44], 2020	33.7	20.2	40	52	Yes, HDRS	Yes	NR	NR
	Doshi *et al* [80], 2019	19	5	73.7	100	Yes, HDRS	Yes	NR	NR
	Farrand *et al* [42], 2018	32.8	24	26	42.8	Yes, DASS-D	Yes	Yes, SOFAS	Yes
	Franzini *et al* [81], 2010	34	20	41	50	Yes, HDRS	Yes	Yes, GAF	Yes
	Gabriëls *et al* [53], 2003	33.6	21	37.5	66.6	Yes, POMS	No	NR	NR
	Grant *et al* [34], 2016	32	9	71	100	NR	NR	NR	NR
	Huys *et al* [30], 2019	30.9	20.7	33	40	Yes, BDI	No	Yes, GAF	Yes
	Islam *et al* [40], 2015	35.3	20.8	41	50	Yes, HDRS	NR	Yes, GAF	NR
	Jiménez *et al* [55], 2013	35.8	15.5	56	100	NR	NR	Yes, GAF	Yes
	Maarouf *et al*[45], 2016	34.7	31	10	0	Yes, BDI	NR	Yes, GAF	No
	Menchón *et al*[13], 2021	34.7	20	42	60	Yes, MADRS	Yes	Yes, GAF	Yes
	Mulders *et al*[82], 2017	34	17	48	100	NR	NR	NR	NR

	Plewnia *et al* [83], 2008	31	24	25	0	NR	NR	Yes, GAF	Yes
	Roh *et al* [61], 2012	38	14.8	59.7	100	Yes, HDRS	NR	Yes, GAF	Yes
	Sachdev *et al* [84], 2012	39	5	87.1	100	NR	NR	NR	NR
	Senova *et al* [85], 2020	31	1	96	100	Yes, MADRS	Yes	NR	NR
	Tsai *et al* [49], 2012	36.3	24	33.8	25	Yes, HDRS	Yes	Yes, GAF	Yes

BDI: Beck depression inventory; CGISS: Clinical global impression severity scale; DASS-D: Depression anxiety stress scale-depression; GAF: Global Assessment of Functioning; HDRS: Hamilton depressive rating scale; LFU: Last follow-up; MADRS: Montgomery Asberg Depression rating scale; NR: Not reported; POMS: Profile of mood states; RCT: Randomized controlled trial; SOFAS: Social and Occupational Functioning Assessment scale; Y-BOCS: Yale-Brown Obsessive Compulsive scale.

Table 7 Summary of results for the long-term studies

	Ref.	Average baseline Y-BOCS	Average Y-BOCS at LFU	Average Y-BOCS improvement (%)	Average responders (%)	Depression (HDRS, BDI, MADRS, QIDS, IDS-30)	Depression scale improvement	Global buncionality (GAF, IADL, SF-36)	Functionality improvement
RCT	Luyten *et al* [20], 2016	35	19.3	45	67	Yes, HDRS	Yes	Yes, GAF	Yes
Non-RCT	Choudhury *et al*[78], 2017	37	21	43	100	Yes, BDI	Yes	Yes, IADL	Yes
	Fayad *et al* [33], 2016	33.6	15.1	55	66	Yes, HDRS	No	Yes, SF-36	Yes
	Graat *et al* [19], 2020	33.3	20.5	39	50	Yes, HDRS	Yes	Yes, GAF	Yes
	Gupta *et al* [35], 2019	38	11	71	100	Yes, BDI	Yes	NR	NR
	Greenberg *et al*[36], 2010	34	21.5	36	61	Yes, HDRS	Yes	Yes, GAF	Yes
	Holland *et al* [21], 2020	34.5	20.7	40.3	22	Yes, HDRS, MADRS, QIDS, IDS-30 and BDI	Yes	Yes, GAF	NR
	Lee *et al*[37], 2019	35	16	54	100	Yes, HDRS	Yes	NR	NR
	Mallet *et al* [22], 2019	32.4	15.4	50	75	Yes, BDI	Yes	Yes, GAF	Yes
	Polosan *et al* [38], 2019	34.3	20	41	NR	NR	NR	NR	NR
	Winter *et al* [28], 2021	32.1	17.7	45	66	Yes, BDI	Yes	NR	NR

BDI: Beck depression inventory; GAF: Global Assessment of Functioning; HDRS: Hamilton depressive rating scale; IADL: Lawton instrumental activities of daily living scale; IDS-30: Inventory of depressive symptomatology; LFU: Last follow-up; MADRS: Montgomery Asberg Depression rating scale; NR: Not reported; QIDS: Quick inventory of depressive symptomatology; RCT: Randomized controlled trial; SF-36: Short form survey; Y-BOCS: Yale-Brown Obsessive Compulsive scale.

effect related to surgery. Although its frequency was very low in most studies[13,22], in others[20,36] rates were as high as 4.8% or 7.7%. Seizures have been described during both ST follow-up[13,36,40] and LT follow-up after 2-5 years[20], with poor electrode positioning[13], intracranial infection[40], somatic complications (*e.g.*, hypoglycemia), and abrupt changes in the stimulation parameters cited as risk factors [40].

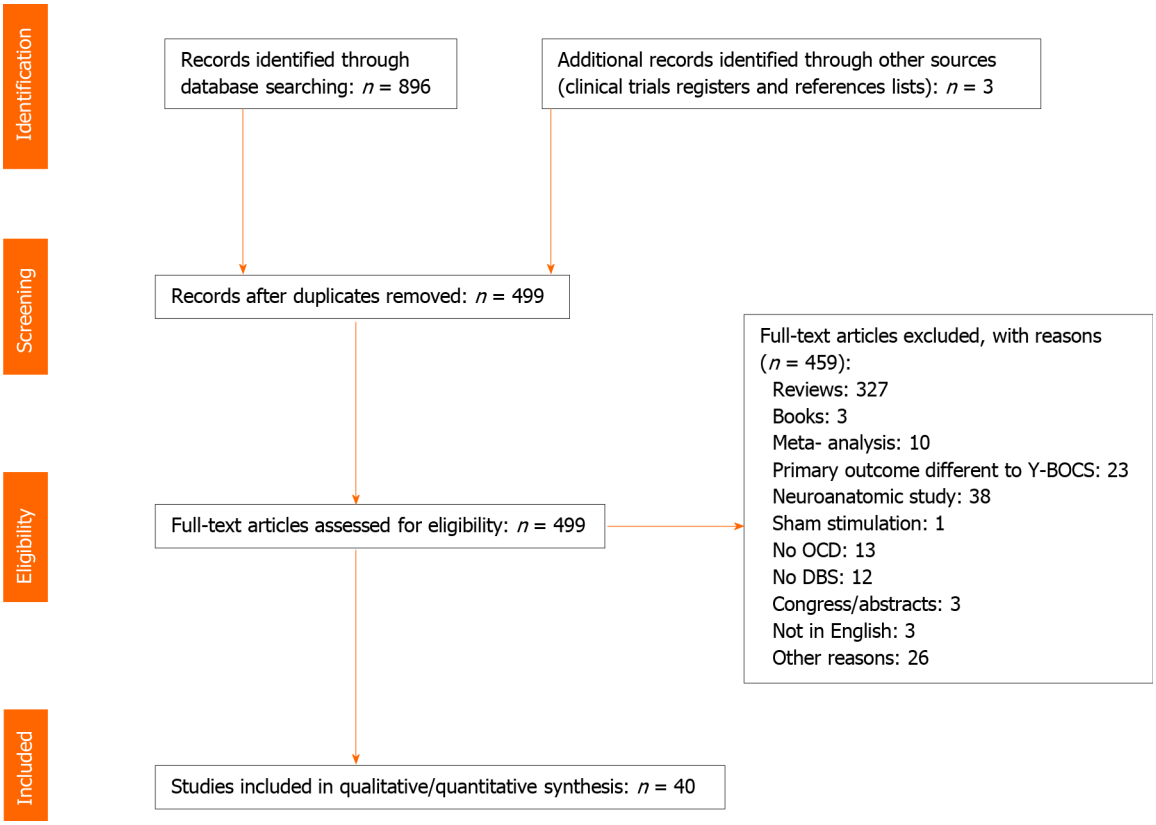

Figure 1 PRISMA flow diagram for add-on deep brain stimulation and obsessive-compulsive disorder in PubMed, Cochrane, Scopus databases and ClinicalTrials.gov databases. DBS: Deep brain stimulation; OCD: Obsessive-compulsive disorder; Y-BOCS: Yale-Brown Obsessive-Compulsive scale.

The most frequent side effect of stimulation is hypomania[21,22,43], although this usually resolves after adjusting the stimulation parameters[16,47,48]. Hypomania has been reported to be a predictor of good response to DBS in other studies, and this has confused the perceptions of its relevance as a side effect[48,49]. Denys *et al*[44] attributes the occurrence of hypomanic symptoms to the stimulation of the anterior limb of the internal capsule (ALIC) and argues that they should be considered not as an adverse effect but as a sign of effective treatment. However, the predictive utility of hypomania is controversial, because other authors have reported that it occurs equally in DBS responders and non-responders[44]. Indeed, the risk of manic and hypomanic symptoms may be modulated by clinical factors, with right monopolar stimulation and female sex predicting manic symptoms during DBS[50,51]. Other adverse effects related to stimulation include insomnia or sleep disturbances[16,33], weight gain[19], fatigue, subjective cognitive problems[19,52], and increased anxiety. Despite subjective reports of cognitive complaints, studies specifically addressing neuropsychological performance have detected no significant impact of DBS[16,20,53].

The relationship between DBS and the risk of suicide attempts or suicide is also controversial. Suicide may be related to the disease itself, to the DBS, or to the ineffectiveness of the treatment. Fernández de la Cruz *et al*[54] reported that patients with severe OCD symptoms were more likely to present suicide attempts (odds ratio = 5.45) and die from suicide (odds ratio = 9.83), and that a history of prior suicide attempt was the strongest predictor. Most studies associate suicide attempts or suicide after DBS in patients with OCD to a comorbid diagnosis of major depressive disorder[19,28,29] or to a lack of response to DBS and the persistence of disabling symptoms[19,20,29]. Comorbidities, including drug use and personality disorders, also appear to increase the risk of death by suicide during DBS among patients with OCD[22,55]. Finally, Graat *et al*[19] reported death by euthanasia in two nonresponding patients with no history of suicide attempts and an average of 4.5 years from DBS implantation to death.

We found no significant differences in these adverse effects between the ST and LT studies.

Predictors of response

DBS is not only expensive but also poses the risk of severe side effects. Given the risks involved, the significant consumption of human and clinical resources, and the need for lifelong follow-up, establishing reliable predictors of response would help to improve patient selection, guide DBS implantation, and optimize stimulation parameters. To date, however, no clinical variables or biomarkers have been clearly defined, probably because of the heterogeneity of the neuroanatomical targeting, the electrodes used, and the stimulation protocols.

Clinical variables: Few published studies have addressed the existence of clinical predictors of response to DBS. Among those that have, most have failed to uncover any clear predictive factors. In the study by Huys *et al*[30], gender, age, preoperative severity (Y-BOCS score), and personality traits did not predict patient improvement after DBS. Similarly, Chabardes *et al*[29] detected no significant differences by age at OCD onset, age at surgery, disease duration, or obsession and compulsion types between responders and nonresponders after 24 mo of subthalamic nucleus (STN)-DBS; however, they detected a significantly higher female-to-male ratio in the responder group, with all females meeting the response criteria. Nevertheless, contradictory results have been reported for age at OCD onset. In a meta-analysis of 16 studies Alonso *et al*[9] reported that patients with later onset OCD exhibited higher response rates and greater Y-BOCS reductions, whereas Mallet *et al*[22] found that patients with early onset OCD showed better LT outcomes after 46 mo of STN-DBS. In another meta-analysis, Martinho *et al*[10] observed that illness duration positively predicted ST response in RCTs, but not LT response in the open phases of those studies. Illness severity at baseline did not predict ST response, but it negatively predicted response at the last follow-up.

Differences in response to DBS between specific symptom profiles have also been hypothesized, as occurs with selective serotonin reuptake inhibitors and CBT. Intuitively, this is highly probable in a focal neuromodulating tool like DBS in which the different symptom dimensions of OCD are reported to have partially distinct neural substrates[56]. Nevertheless, the data on this topic are scarce and often contradictory. Many published trials lack detailed descriptions of symptom profiles and no single study has used a specific psychometric tool to assess OCD symptom dimensions. Two of the ten patients in the study by Greenberg *et al*[57] who had the poorest response to ventral caudate (VC)/ventral striatum (VS) DBS suffered OCD symptoms motivated principally by a feeling of incompleteness and a need to repeat actions until they felt that everything was "just right". Nevertheless, four other patients who also reported "just right" experiences significantly improved with DBS. Patients with contamination and washing symptoms showed lower response to DBS (45.5%) than those who suffered doubts and checking compulsions (100%).

According to Denys *et al*[43], patients needing perfection, symmetry, or reassurance, as well as those with hoarding, showed poor response to nucleus accumbens (NAcc) stimulation. In other series[49,58-61], patients with symmetry or ordering obsessions and compulsions have been reported to respond to DBS. Results for hoarding symptoms are also controversial. Welter *et al*[39] described that hoarding was the main symptom in one of two patients resistant to DBS of the STN, NAcc, and caudate nucleus; by contrast, Fontaine *et al*[62] reported that prominent hoarding symptoms almost disappeared after STN stimulation in a patient with Parkinson's disease, while Guehl *et al*[60] described a woman with hoarding, contamination/cleaning, and symmetry/ordering symptoms who improved significantly with caudate nucleus stimulation. Similarly, some authors have reported that somatic obsessions improve with DBS[59], but others have not[53]. In the meta-analysis by Alonso *et al*[9], it was notable that the presence of sexual or religious obsessions and compulsions was associated with a better response.

Interestingly, two recent studies by Barcia *et al*[32,63] raise the possibility of personalizing the targets in DBS in patients with OCD depending on the obsessional focus. They stimulated seven patients with OCD by placing a tetrapolar electrode along the striatum and observed that those with mainly washing obsessions and compulsions responded better to the more ventral contacts, while those presenting checking, ordering, and incompleteness symptoms responded better to activation of the more dorsal contacts. The authors concluded that the most effective neuroanatomical target structure for each patient could be calculated by combining a preoperative index derived from functional MRI symptom provocation and probabilistic tractography.

Electrode location, intraoperative changes and electrophysiological data: Haq *et al*[48] first reported that patients who showed higher percentages of laughing conditions

(smiling or laughter with euphoria) during intraoperative DBS testing for electrodes placed at the ALIC and NAcc showed the greatest reduction in Y-BOCS scores in the LT. Similarly, Tsai *et al*[49] reported that the appearance of smiling/Laughter on postoperative test stimulations performed two weeks after implantation at the VC/VS also significantly predicted good response in the LT (at 15 mo). Goodman *et al*[16] reported that experiencing hypomania as an early stimulation-induced side effect made clinical response more likely. Hypomania is the most frequent side effect of DBS programming in OCD and is reported to affect 40%-45% of subjects[44,50], but it remains unclear whether it necessarily predicts a good response to DBS in OCD.

Optimal electrode location is an anatomical factor that markedly affects response to DBS. Current targets in OCD include the ALIC, the VS, the anteromedial limbic STN, and midbrain. These four targets affect orbitofrontal cortex (OFC) or anterior cingulate cortex (ACC) connections passing through, entering, or leaving the internal capsule. This explains why stimulation at different brain locations can target different components of the same circuit. To optimize outcomes, the initial electrode position within the ALIC has changed over the years; several studies have concluded that more posteriorly targeted stimulation at the bilateral bed nucleus of the stria terminalis and the VC/VS near the ACC appears to improve outcomes, producing greater symptom reduction than more dorsal or anterior stimulation of the ALIC[13,20,36] or NAcc[40]. Although most studies indicate that differences between targets in relation to the antiobsessive effect of DBS are not significant, the different electrode locations do produce specific effects: For example, DBS of the anteromedial STN, but not the VC/VS, improves cognitive flexibility, while DBS of the VC/VS achieves greater mood improvement than STN stimulation[17].

Regarding electrophysiological measures, Welter *et al*[64] reported a correlation between presurgical STN neuronal activity and response to bilateral high-frequency STN stimulation. Good response was associated with higher mean presurgical neuronal discharges, bursts, and intraburst frequencies, but with lower mean presurgical interburst intervals. van Westen *et al*[65] replicated these findings and reported that patients with lower interburst intervals and higher intraburst frequencies had the best Y-BOCS outcome.

Neuroimaging data: With respect to neuroimaging data, in a small sample (six patients) Van Laere *et al*[66] found that higher preoperative activity in the subgenual ACC assessed by positron emission tomography with fluorodeoxyglucose integrated with computed tomography (^{18}F-FDG PET/CT) correlated with greater response to DBS. Abelson *et al*[67] reported that such scans detected decreased OFC activity in only two of four patients who responded to bilateral ALIC stimulation, suggesting that DBS improves OCD symptoms only when it restores the inhibitory function of the ventral cortico-striato-thalamo-cortical pathway. Le Jeune *et al*[68] similarly reported a reduction in Y-BOCS after DBS that correlated with decreased metabolic activity in the ventro-medial prefrontal region of the OFC. Regarding connectivity, Figee *et al*[69] detected that clinical improvement after DBS correlated with a normalization of functional connectivity in the NAcc prefrontal cortex, and Baldermann *et al*[70] recently showed that response to DBS could be predicted by analyzing the effects of stimulation on structural connectivity to prefrontal and frontal regions. Modulation of structural connectivity to the right middle frontal gyrus with DBS was associated with a better clinical response in a sample of six patients, whereas changes in connectivity to the OFC were associated with nonresponse. The same group has recently reported that response to ALIC and STN in four OCD cohorts predicted whether electrodes could or could not stimulate a fiber bundle connecting medial prefrontal regions to the STN[71].

DISCUSSION

In this study we aimed to summarize the efficacy and tolerability of DBS for treatment-resistant severe OCD, comparing ST and LT response to stimulation, and assessing whether different patterns and predictors of response emerged from the data available from 40 studies including a total of 344 patients. Of these, 29 studies (with 230 patients) covered ST response over an average of 18.5 mo, and 11 studies (with 155 patients) covered LT response over an average of 63.7 mo. The mean decreases in Y-BOCS scores from baseline to final follow-up were 47.4% in the ST studies (Y-BOCS fell from 33 to 17.2) and 47.7% in the LT studies (Y-BOCS fell from 34.4 to 18). The percentage of responders increased from 60.6% in the ST studies to 70.7% in the LT

studies, indicating that DBS provided effective therapy for severe resistant OCD in at least two-thirds of subjects in the long term, comparable with data published in previous meta-analyses[9-11]. Our results suggest that the first year of stimulation is critical to obtaining benefit from DBS. Three patient groups could be described according to their pattern of LT response to DBS: sustained good responders (49.5%), persistent non responders (resistant patients with no or almost no improvement) despite treatment adjustments (28.1%), and fluctuating responders who presented relapses of their symptoms irrespective of environmental factors (22.5%). At this point no clear predictors of response can be established, in terms of either clinical features or biomarkers.

Although DBS in OCD is far less effective than in neurological disorders such as essential tremor, its therapeutic potential should not be overlooked if we consider that candidates for DBS have typically proven treatment-resistant. Indeed, they usually show no improvement with multiple pharmacological approaches, including all selective serotonin reuptake inhibitors, clomipramine, and various antipsychotics, as well as prolonged and intensive CBT. The fact that two-thirds of these severely disabled and highly resistant patients improve on DBS supports the efficacy of direct electrical modulation of hypothesized dysfunctional circuits in OCD. Along these lines, recent proposals to individualize anatomical targets by brain connectivity findings or symptoms hold out promise for future improvements[32].

The results of published studies are limited to adult patients with OCD. Candidates for DBS must meet strict criteria in order to be considered for electrode implantation: their Y-BOCS scores must indicate severe to extreme OCD and they must present serious impairment in daily functioning lasting more than five years despite a minimum of three adequate pharmacological trials and cognitive-behavioral therapy. Even for patients with early-onset OCD in childhood or adolescence, it takes years to meet these criteria. In fact, in the studies assessed here mean illness duration before DBS implantation was around 24 years. It is unknown at this time if younger patients or patients with shorter disease progression might be better candidates for DBS.

What can be offered to patients with treatment resistance or limited/fluctuating response to DBS? Several studies indicate the usefulness of retrying CBT after implanting electrodes in order to target rituals that persist even though patients experience fewer intrusive thoughts or less associated emotional distress[19]. In these cases, the rituals may have been a part of their lives for years and may have become habitual. For subjects resistant to DBS, especially those in whom suboptimal electrode placement is confirmed, reimplantation of the electrodes at different targets may be appropriate. There are some reports of cases that have been successfully managed in this way, in spite of the surgical risks [19]. Studies in which more than two electrodes are implanted in the same patient, allowing the stimulation of limbic and non-limbic areas, suggest that some subjects respond to the stimulation of certain anatomical targets but not others, even though these features share the cortico-striato-thalamo-cortical pathway. Finally, subjects who exhaust all DBS options should still be considered for stereotactic surgery. Neuroablative surgical techniques have improved dramatically in recent years, showing optimized results and reduced side effects[72]. In a recent meta-analysis, ablative neurosurgery for OCD obtained a greater reduction in Y-BOCS scores than DBS (50.4% *vs* 40.9% reductions) and also produced fewer adverse effects (in 43.6% *vs* 64.6% of patients)[73].

DBS is not without adverse effects. Although most are mild and transient, and can usually be resolved by modifying the stimulation parameters, some serious adverse effects are possible. Among the psychiatric effects, hypomania was the most commonly identified in the present review, but it remains unclear whether this is a predictor of DBS response or an inevitable consequence of the treatment's mechanism of action. Another topic that deserves special attention is the risk of suicide and death by suicide among patients with OCD who are treated with DBS. Most studies relate this risk to the presence of comorbid major depressive disorder or the absence of an adequate response to DBS[19,29]. The presence of excessive and unrealistic expectations of improvement after stimulation also seems to increase the risk of suicidality [13]. It is therefore essential that patients receive clear and realistic information about their expected response to DBS and are aware that several months of treatment and multiple adjustments are often necessary before an adequate response is achieved. Careful ongoing assessment of suicide risk is required, especially in the presence of comorbid major depressive disorder and nonresponse.

To date, it has not been possible to establish clear predictors of response to DBS that might help to improve patient selection or treatment application. In fact, the significant heterogeneity in the targets proposed for stimulation and the absence of standardized programming settings have meant that DBS has remained an experimental therapeutic

option for OCD, with limited scientific proof of its efficacy. Recent efforts to develop measurable biomarkers using fMRI, tractography, or electroencephalography may help to develop a more personalized approach to DBS, and thus identify more accurately the patients most likely to benefit from a treatment with a very high economic cost and significant risks.

Our review has several limitations. We decided not to restrict our search to RCTs and included open studies, series, and published clinical cases, which represented 79% of ST studies and 91% of LT studies. Although this makes our results more representative, it also limits their methodological validity because we were unable to adequately control for biases and for the risk of a placebo response. The marked heterogeneity among the studies reviewed, including sample size, study design, stimulation parameters, anatomical targets, and psychometric tools for defining primary and secondary outcomes, also makes any meaningful comparison difficult. Finally, many groups use other therapeutic approaches (*e.g.*, CBT) concurrently with DBS or do not define whether pharmacological treatments are interrupted after DBS implantation. Therefore, we cannot be sure that the beneficial effects attributed to DBS were not in fact due to a multimodal treatment approach.

CONCLUSION

In conclusion, the present review confirms that DBS is a promising therapy for patients with severe resistant OCD, with evidence of efficacy in the short and long term. There remain many unknowns, including the optimal anatomical targets, the criteria for standardized stimulation protocols, and the identification of biomarkers or factors that predict outcomes and allow treatment individualization. To achieve a progressive improvement of DBS outcomes, we strongly recommend that this approach be applied only at centers that can guarantee access to multidisciplinary teams comprising not just neurosurgeons with experience in functional surgery but also psychiatrists and behavioral therapists with adequate expertise in the pharmacological and psychotherapeutic management of severe OCD. This strategy will ensure the selection of suitable potential candidates, the timely implementation of advances in surgical techniques, improved postoperative management, optimization of stimulation parameters, and the concomitant use of other therapies like CBT. The development of an international registry with clinical, programming, and neuroimaging data on all patients undergoing DBS for treatment-resistant OCD would also contribute to expanding our knowledge of this technique, which constitutes the last therapeutic option for many patients with severe OCD.

ARTICLE HIGHLIGHTS

Research background

Twenty years after the first deep brain stimulation (DBS) implantation in a patient with obsessive-compulsive disorder (OCD), we review all the information published to date regarding the efficacy and tolerability of this therapeutic option for severe obsessive patients resistant to pharmacological approaches and behavioral therapy.

Research motivation

There are still many unknowns regarding the benefits and risks of using DBS in OCD. The main ones are the optimal anatomical targets, the best stimulation parameters, the long-term effects of the therapy or the possibility of establishing clinical or biological factors associated with response. Responding to them would allow optimizing the results of this therapeutic alternative, with a high economic and human resources cost, and not without potentially serious risks.

Research objectives

The main objectives of this systematic review were to summarize existing knowledge regarding efficacy and tolerability of DBS in treatment-resistant OCD as well as to analyze the possible existence of response predictors that allow improving the selection of candidates. We confirmed that DBS proved to be an effective and safe alternative for two out of three severe and resistant OCD patients who received it. Although we did not detect any clear predictor of response, there are promising proposals based on the use of neuroimaging tools to individualize treatment that

should be analyzed in depth in future research.

Research methods

We performed a comprehensive search in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020 with "(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS)" as searching strategy. Inclusion criteria were a main diagnosis of OCD, DBS conducted for therapeutic purposes in humans and variation in symptoms of OCD measured by the Yale-Brown Obsessive-Compulsive scale (Y-BOCS) as primary outcome. Data was recorded using a standardized collection tool and analyzed with descriptive statistics. Risk of bias was assessed using the Cochrane Handbook for Systematic Reviews of Interventions for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies.

Research results

Our systematic review detected 40 studies fulfilling inclusion criteria. 29 of them reported results on short-term response to DBS in 230 patients (follow-up: 18.5 ± 8 mo, range: 7-36) and eleven on long-term response in 155 subjects (63.7 ± 20.7 mo, range: 38-96). Mean Y-BOCS reduction reported on short-term studies was 47.4% ± 21% and on long-term studies 47.2% ± 9.9%, confirming the long-term stability of the response. A significantly greater number of patients fulfilled criteria for response (Y-BOCS reduction > 35%) on the long-term studies (70.7%) than in the short-term ones (60.6%), although the maximum symptom reduction was achieved in general in the first 12-14 mo after DBS implantation. Comorbid depressive symptoms tend to improve in parallel to obsessive symptoms, although this correlation was not observed in all patients. DBS was well-tolerated by most OCD patients, with reversible hypomania as the most frequently reported side effect associated to stimulation. No clear clinical or biological predictors of response emerged from our data, probably due to the high heterogeneity on DBS application conditions in OCD patients.

Research conclusions

Our results underscore the importance of exploring new strategies that allow individualizing the conditions of application of DBS in OCD, combining neuroimaging data and a detailed analysis of the patient's symptoms.

Research perspectives

Future directions on research on DBS application in OCD should focus on establishing which individual factors at the clinical and/or neuroimaging level can allow us to establish which will be the target and the optimal stimulation conditions for each patient, since the results show that although the standard application of the technique is effective and safe for 2 out of 3 operated patients, there are still patients who do not benefit from the treatment.

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REFERENCES

1 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders 5th ed. (DSM-5®). American Psychiatric Pub, 2013 [DOI: 10.1176/appi.books.9780890425596]

2 **Ruscio AM**, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry* 2010; **15**: 53-63 [PMID: 18725912 DOI: 10.1038/mp.2008.94]

3 **Pérez-Vigil A**, Fernández de la Cruz L, Brander G, Isomura K, Jangmo A, Feldman I, Hesselmark E, Serlachius E, Lázaro L, Rück C, Kuja-Halkola R, D'Onofrio BM, Larsson H, Mataix-Cols D. Association of Obsessive-Compulsive Disorder With Objective Indicators of Educational Attainment: A Nationwide Register-Based Sibling Control Study. *JAMA Psychiatry* 2018; **75**: 47-55 [PMID: 29141084 DOI: 10.1001/jamapsychiatry.2017.3523]

4 **Pallanti S**, Quercioli L. Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; **30**: 400-412 [PMID: 16503369 DOI: 10.1016/j.pnpbp.2005.11.028]

5 **Brock H**, Hany M. Obsessive-Compulsive Disorder. In: Stat Pearls. Treasure Island (FL): Stat Pearls Publishing, 2020

6 **Bais M**, Figee M, Denys D. Neuromodulation in obsessive-compulsive disorder. *Psychiatr Clin North Am* 2014; **37**: 393-413 [PMID: 25150569 DOI: 10.1016/j.psc.2014.06.003]

7 **Nuttin B**, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet* 1999; **354**: 1526 [PMID: 10551504 DOI: 10.1016/S0140-6736(99)02376-4]

8 **U.S. Food and Drug Administration**. Food and Drug Administration. Humanitarian Device Exemption (HDE). [cited 27 Feb 2021]. In: U.S. Food and Drug Administration [Internet]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H050003

9 **Alonso P**, Cuadras D, Gabriëls L, Denys D, Goodman W, Greenberg BD, Jimenez-Ponce F, Kuhn J, Lenartz D, Mallet L, Nuttin B, Real E, Segalas C, Schuurman R, du Montcel ST, Menchon JM. Deep Brain Stimulation for Obsessive-Compulsive Disorder: A Meta-Analysis of Treatment Outcome and Predictors of Response. *PLoS One* 2015; **10**: e0133591 [PMID: 26208305 DOI: 10.1371/journal.pone.0133591]

10 **Martinho FP**, Duarte GS, Couto FSD. Efficacy, Effect on Mood Symptoms, and Safety of Deep Brain Stimulation in Refractory Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis. *J Clin Psychiatry* 2020; **81** [PMID: 32459406 DOI: 10.4088/JCP.19r12821]

11 **Kisely S**, Hall K, Siskind D, Frater J, Olson S, Crompton D. Deep brain stimulation for obsessive-compulsive disorder: a systematic review and meta-analysis. *Psychol Med* 2014; **44**: 3533-3542 [PMID: 25066053 DOI: 10.1017/S0033291714000981]

12 **Tastevin M**, Spatola G, Régis J, Lançon C, Richieri R. Deep brain stimulation in the treatment of obsessive-compulsive disorder: current perspectives. *Neuropsychiatr Dis Treat* 2019; **15**: 1259-1272 [PMID: 31190832 DOI: 10.2147/NDT.S178207]

13 **Menchón JM**, Real E, Alonso P, Aparicio MA, Segalas C, Plans G, Luyten L, Brunfaut E, Matthijs L, Raymakers S, Bervoets C, Higueras A, Katati M, Guerrero J, Hurtado M, Prieto M, Stieglitz LH, Löffelholz G, Walther S, Pollo C, Zurowski B, Tronnier V, Kordon A, Gambini O, Ranieri R, Franzini A, Messina G, Radu-Djurfeldt D, Schechtmann G, Chen LL, Eitan R, Israel Z, Bergman H, Brelje T, Brionne TC, Conseil A, Gielen F, Schuepbach M, Nuttin B, Gabriëls L. A prospective international multi-center study on safety and efficacy of deep brain stimulation for resistant obsessive-compulsive disorder. *Mol Psychiatry* 2021; **26**: 1234-1247 [PMID: 31664175 DOI: 10.1038/s41380-019-0562-6]

14 **Goodman WK**, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 1989; **46**: 1006-1011 [PMID: 2684084 DOI: 10.1001/archpsyc.1989.01810110048007]

15 **Goodman WK**, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale. II. Validity. *Arch Gen Psychiatry* 1989; **46**: 1012-1016 [PMID: 2510699 DOI: 10.1001/archpsyc.1989.01810110054008]

16 **Goodman WK**, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H, Shapira NA, Wu SS, Hill CL, Rasmussen SA, Okun MS. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biol Psychiatry* 2010; **67**: 535-542 [PMID: 20116047 DOI: 10.1016/j.biopsych.2009.11.028]

17 **Tyagi H**, Apergis-Schoute AM, Akram H, Foltynie T, Limousin P, Drummond LM, Fineberg NA, Matthews K, Jahanshahi M, Robbins TW, Sahakian BJ, Zrinzo L, Hariz M, Joyce EM. A Randomized Trial Directly Comparing Ventral Capsule and Anteromedial Subthalamic Nucleus Stimulation in Obsessive-Compulsive Disorder: Clinical and Imaging Evidence for Dissociable Effects. *Biol Psychiatry* 2019; **85**: 726-734 [PMID: 30853111 DOI: 10.1016/j.biopsych.2019.01.017]

18 **De Vloo P**, Raymaekers S, van Kuyck K, Luyten L, Gabriëls L, Nuttin B. Rechargeable Stimulators in Deep Brain Stimulation for Obsessive-Compulsive Disorder: A Prospective Interventional Cohort Study. *Neuromodulation* 2018; **21**: 203-210 [PMID: 28256778 DOI: 10.1111/ner.12577]

19 **Graat I**, Mocking R, Figee M, Vulink N, de Koning P, Ooms P, Mantione M, van den Munckhof P, Schuurman R, Denys D. Long-term Outcome of Deep Brain Stimulation of the Ventral Part of the Anterior Limb of the Internal Capsule in a Cohort of 50 Patients With Treatment-Refractory Obsessive-Compulsive Disorder. *Biol Psychiatry* 2020 [PMID: 33131717 DOI: 10.1016/j.biopsych.2020.08.018]

20 **Luyten L**, Hendrickx S, Raymaekers S, Gabriëls L, Nuttin B. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. *Mol Psychiatry* 2016; **21**: 1272-1280 [PMID: 26303665 DOI: 10.1038/mp.2015.124]

21 **Holland MT**, Trapp NT, McCormick LM, Jareczek FJ, Zanaty M, Close LN, Beeghly J, Greenlee JDW. Deep Brain Stimulation for Obsessive-Compulsive Disorder: A Long Term Naturalistic Follow Up Study in a Single Institution. *Front Psychiatry* 2020; **11**: 55 [PMID: 32184741 DOI: 10.3389/fpsyt.2020.00055]

22 **Mallet L**, Du Montcel ST, Clair AH, Arbus C, Bardinet E, Baup N, Chabardès S, Chéreau I, Czernecki V, Fontaine D, Harika-Germaneau G, Haynes WI, Houeto JL, Jaafari N, Krack P, Millet B, Navarro S, Polosan M, Pelissolo A, Welter ML; STOC Long-term Study Group. Long-term effects of subthalamic stimulation in Obsessive-Compulsive Disorder: Follow-up of a randomized controlled trial. *Brain Stimul* 2019; **12**: 1080-1082 [PMID: 30992192 DOI: 10.1016/j.brs.2019.04.004]

23 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ,

Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]

24 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

25 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR). American Psychiatric Association, 2000

26 **Higgins JP**, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]

27 **Stang A**. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]

28 **Winter L**, Saryyeva A, Schwabe K, Heissler HE, Runge J, Alam M, Heitland I, Kahl KG, Krauss JK. Long-Term Deep Brain Stimulation in Treatment-Resistant Obsessive-Compulsive Disorder: Outcome and Quality of Life at Four to Eight Years Follow-Up. *Neuromodulation* 2021; **24**: 324-330 [PMID: 32667114 DOI: 10.1111/ner.13232]

29 **Chabardes S**, Krack P, Piallat B, Bougerol T, Seigneuret E, Yelnik J, Fernandez Vidal S, David O, Mallet L, Benabid AL, Polosan M. Deep brain stimulation of the subthalamic nucleus in obsessive-compulsives disorders: long-term follow-up of an open, prospective, observational cohort. *J Neurol Neurosurg Psychiatry* 2020; **91**: 1349-1356 [PMID: 33033168 DOI: 10.1136/jnnp-2020-323421]

30 **Huys D**, Kohl S, Baldermann JC, Timmermann L, Sturm V, Visser-Vandewalle V, Kuhn J. Open-label trial of anterior limb of internal capsule-nucleus accumbens deep brain stimulation for obsessive-compulsive disorder: insights gained. *J Neurol Neurosurg Psychiatry* 2019; **90**: 805-812 [PMID: 30770458 DOI: 10.1136/jnnp-2018-318996]

31 **Huff W**, Lenartz D, Schormann M, Lee SH, Kuhn J, Koulousakis A, Mai J, Daumann J, Maarouf M, Klosterkötter J, Sturm V. Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: Outcomes after one year. *Clin Neurol Neurosurg* 2010; **112**: 137-143 [PMID: 20006424 DOI: 10.1016/j.clineuro.2009.11.006]

32 **Barcia JA**, Avecillas-Chasín JM, Nombela C, Arza R, García-Albea J, Pineda-Pardo JA, Reneses B, Strange BA. Personalized striatal targets for deep brain stimulation in obsessive-compulsive disorder. *Brain Stimul* 2019; **12**: 724-734 [PMID: 30670359 DOI: 10.1016/j.brs.2018.12.226]

33 **Fayad SM**, Guzick AG, Reid AM, Mason DM, Bertone A, Foote KD, Okun MS, Goodman WK, Ward HE. Six-Nine Year Follow-Up of Deep Brain Stimulation for Obsessive-Compulsive Disorder. *PLoS One* 2016; **11**: e0167875 [PMID: 27930748 DOI: 10.1371/journal.pone.0167875]

34 **Grant JE**, Odlaug BL, Chamberlain SR. Long-term deep-brain stimulation treatment for obsessive-compulsive disorder. *J Clin Psychiatry* 2016; **77**: 132-133 [PMID: 26845271 DOI: 10.4088/JCP.15cr09931]

35 **Gupta A**, Khanna S, Jain R. Deep brain stimulation of ventral internal capsule for refractory obsessive-compulsive disorder. *Indian J Psychiatry* 2019; **61**: 532-536 [PMID: 31579146 DOI: 10.4103/psychiatry.IndianJPsychiatry_222_16]

36 **Greenberg BD**, Gabriels LA, Malone DA Jr, Rezai AR, Friehs GM, Okun MS, Shapira NA, Foote KD, Cosyns PR, Kubu CS, Malloy PF, Salloway SP, Giftakis JE, Rise MT, Machado AG, Baker KB, Stypulkowski PH, Goodman WK, Rasmussen SA, Nuttin BJ. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatry* 2010; **15**: 64-79 [PMID: 18490925 DOI: 10.1038/mp.2008.55]

37 **Lee DJ**, Dallapiazza RF, De Vloo P, Elias GJB, Fomenko A, Boutet A, Giacobbe P, Lozano AM. Inferior thalamic peduncle deep brain stimulation for treatment-refractory obsessive-compulsive disorder: A phase 1 pilot trial. *Brain Stimul* 2019; **12**: 344-352 [PMID: 30514614 DOI: 10.1016/j.brs.2018.11.012]

38 **Polosan M**, Droux F, Kibleur A, Chabardes S, Bougerol T, David O, Krack P, Voon V. Affective modulation of the associative-limbic subthalamic nucleus: deep brain stimulation in obsessive-compulsive disorder. *Transl Psychiatry* 2019; **9**: 73 [PMID: 30718450 DOI: 10.1038/s41398-019-0404-y]

39 **Welter ML**, Alves Dos Santos JF, Clair AH, Lau B, Diallo HM, Fernandez-Vidal S, Belaid H, Pelissolo A, Domenech P, Karachi C, Mallet L. Deep Brain Stimulation of the Subthalamic, Accumbens, or Caudate Nuclei for Patients With Severe Obsessive-Compulsive Disorder: A Randomized Crossover Controlled Study. *Biol Psychiatry* 2020 [PMID: 33012521 DOI: 10.1016/j.biopsych.2020.07.013]

40 **Islam L**, Franzini A, Messina G, Scarone S, Gambini O. Deep brain stimulation of the nucleus accumbens and bed nucleus of stria terminalis for obsessive-compulsive disorder: a case series. *World Neurosurg* 2015; **83**: 657-663 [PMID: 25527882 DOI: 10.1016/j.wneu.2014.12.024]

41 **Guzick A**, Hunt PJ, Bijanki KR, Schneider SC, Sheth SA, Goodman WK, Storch EA. Improving long term patient outcomes from deep brain stimulation for treatment-refractory obsessive-compulsive disorder. *Expert Rev Neurother* 2020; **20**: 95-107 [PMID: 31730752 DOI: 10.1080/14737175.2020.1694409]

42 **Farrand S**, Evans AH, Mangelsdorf S, Loi SM, Mocellin R, Borham A, Bevilacqua J, Blair-West S,

Walterfang MA, Bittar RG, Velakoulis D. Deep brain stimulation for severe treatment-resistant obsessive-compulsive disorder: An open-label case series. *Aust N Z J Psychiatry* 2018; **52**: 699-708 [PMID: 28965430 DOI: 10.1177/0004867417731819]

43 **Denys D**, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, Bosch A, Schuurman R. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* 2010; **67**: 1061-1068 [PMID: 20921122 DOI: 10.1001/archgenpsychiatry.2010.122]

44 **Denys D**, Graat I, Mocking R, de Koning P, Vulink N, Figee M, Ooms P, Mantione M, van den Munckhof P, Schuurman R. Efficacy of Deep Brain Stimulation of the Ventral Anterior Limb of the Internal Capsule for Refractory Obsessive-Compulsive Disorder: A Clinical Cohort of 70 Patients. *Am J Psychiatry* 2020; **177**: 265-271 [PMID: 31906709 DOI: 10.1176/appi.ajp.2019.19060656]

45 **Maarouf M**, Neudorfer C, El Majdoub F, Lenartz D, Kuhn J, Sturm V. Deep Brain Stimulation of Medial Dorsal and Ventral Anterior Nucleus of the Thalamus in OCD: A Retrospective Case Series. *PLoS One* 2016; **11**: e0160750 [PMID: 27504631 DOI: 10.1371/journal.pone.0160750]

46 **Beric A**, Kelly PJ, Rezai A, Sterio D, Mogilner A, Zonenshayn M, Kopell B. Complications of deep brain stimulation surgery. *Stereotact Funct Neurosurg* 2001; **77**: 73-78 [PMID: 12378060 DOI: 10.1159/000064600]

47 **Zarzycki MZ**, Domitrz I. Stimulation-induced side effects after deep brain stimulation - a systematic review. *Acta Neuropsychiatr* 2020; **32**: 57-64 [PMID: 31452489 DOI: 10.1017/neu.2019.35]

48 **Haq IU**, Foote KD, Goodman WK, Ricciuti N, Ward H, Sudhyadhom A, Jacobson CE, Siddiqui MS, Okun MS. A case of mania following deep brain stimulation for obsessive compulsive disorder. *Stereotact Funct Neurosurg* 2010; **88**: 322-328 [PMID: 20714212 DOI: 10.1159/000319960]

49 **Tsai HC**, Chang CH, Pan JI, Hsieh HJ, Tsai ST, Hung HY, Chen SY. Pilot study of deep brain stimulation in refractory obsessive-compulsive disorder ethnic Chinese patients. *Psychiatry Clin Neurosci* 2012; **66**: 303-312 [PMID: 22624735 DOI: 10.1111/j.1440-1819.2012.02352.x]

50 **Widge AS**, Licon E, Zorowitz S, Corse A, Arulpragasam AR, Camprodon JA, Cusin C, Eskandar EN, Deckersbach T, Dougherty DD. Predictors of Hypomania During Ventral Capsule/Ventral Striatum Deep Brain Stimulation. *J Neuropsychiatry Clin Neurosci* 2016; **28**: 38-44 [PMID: 26404172 DOI: 10.1176/appi.neuropsych.15040089]

51 **Diflorio A**, Jones I. Is sex important? *Int Rev Psychiatry* 2010; **22**: 437-452 [PMID: 21047158 DOI: 10.3109/09540261.2010.514601]

52 **Senova S**, Clair AH, Palfi S, Yelnik J, Domenech P, Mallet L. Deep Brain Stimulation for Refractory Obsessive-Compulsive Disorder: Towards an Individualized Approach. *Front Psychiatry* 2019; **10**: 905 [PMID: 31920754 DOI: 10.3389/fpsyt.2019.00905]

53 **Gabriëls L**, Cosyns P, Nuttin B, Demeulemeester H, Gybels J. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: psychopathological and neuropsychological outcome in three cases. *Acta Psychiatr Scand* 2003; **107**: 275-282 [PMID: 12662250]

54 **Fernández de la Cruz L**, Rydell M, Runeson B, D'Onofrio BM, Brander G, Rück C, Lichtenstein P, Larsson H, Mataix-Cols D. Suicide in obsessive-compulsive disorder: a population-based study of 36 788 Swedish patients. *Mol Psychiatry* 2017; **22**: 1626-1632 [PMID: 27431293 DOI: 10.1038/mp.2016.115]

55 **Jiménez F**, Nicolini H, Lozano AM, Piedimonte F, Salín R, Velasco F. Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. *World Neurosurg* 2013; **80**: S30.e17-S30.e25 [PMID: 22824558 DOI: 10.1016/j.wneu.2012.07.010]

56 **van den Heuvel OA**, Remijnse PL, Mataix-Cols D, Vrenken H, Groenewegen HJ, Uylings HB, van Balkom AJ, Veltman DJ. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain* 2009; **132**: 853-868 [PMID: 18952675 DOI: 10.1093/brain/awn267]

57 **Greenberg BD**, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, Rasmussen SA. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology* 2006; **31**: 2384-2393 [PMID: 16855529 DOI: 10.1038/sj.npp.1301165]

58 **Mallet L**, Mesnage V, Houeto JL, Pelissolo A, Yelnik J, Behar C, Gargiulo M, Welter ML, Bonnet AM, Pillon B, Cornu P, Dormont D, Pidoux B, Allilaire JF, Agid Y. Compulsions, Parkinson's disease, and stimulation. *Lancet* 2002; **360**: 1302-1304 [PMID: 12414208 DOI: 10.1016/S0140-6736(02)11339-0]

59 **Aouizerate B**, Cuny E, Martin-Guehl C, Guehl D, Amieva H, Benazzouz A, Fabrigoule C, Allard M, Rougier A, Bioulac B, Tignol J, Burbaud P. Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. *J Neurosurg* 2004; **101**: 682-686 [PMID: 15481726 DOI: 10.3171/jns.2004.101.4.0682]

60 **Guehl D**, Benazzouz A, Aouizerate B, Cuny E, Rotgé JY, Rougier A, Tignol J, Bioulac B, Burbaud P. Neuronal correlates of obsessions in the caudate nucleus. *Biol Psychiatry* 2008; **63**: 557-562 [PMID: 17945196 DOI: 10.1016/j.biopsych.2007.06.023]

61 **Roh D**, Chang WS, Chang JW, Kim CH. Long-term follow-up of deep brain stimulation for refractory obsessive-compulsive disorder. *Psychiatry Res* 2012; **200**: 1067-1070 [PMID: 22784468 DOI: 10.1016/j.psychres.2012.06.018]

62 **Fontaine D**, Mattei V, Borg M, von Langsdorff D, Magnie MN, Chanalet S, Robert P, Paquis P. Effect of subthalamic nucleus stimulation on obsessive-compulsive disorder in a patient with Parkinson disease. Case report. *J Neurosurg* 2004; **100**: 1084-1086 [PMID: 15200126 DOI:

10.3171/jns.2004.100.6.1084]
63 **Barcia JA**, Reneses B, Nombela C. Precision surgery for obsessive compulsive disorder-which is the proper target? *Ann Transl Med* 2019; **7**: S184 [PMID: 31656763 DOI: 10.21037/atm.2019.07.65]
64 **Welter ML**, Burbaud P, Fernandez-Vidal S, Bardinet E, Coste J, Piallat B, Borg M, Besnard S, Sauleau P, Devaux B, Pidoux B, Chaynes P, Tézenas du Montcel S, Bastian A, Langbour N, Teillant A, Haynes W, Yelnik J, Karachi C, Mallet L; French Stimulation dans Trouble Obsessionnel Compulsif (STOC) Study Group. Basal ganglia dysfunction in OCD: subthalamic neuronal activity correlates with symptoms severity and predicts high-frequency stimulation efficacy. *Transl Psychiatry* 2011; **1**: e5 [PMID: 22832400 DOI: 10.1038/tp.2011.5]
65 **van Westen M**, Rietveld E, Figee M, Denys D. Clinical Outcome and Mechanisms of Deep Brain Stimulation for Obsessive-Compulsive Disorder. *Curr Behav Neurosci Rep* 2015; **2**: 41-48 [PMID: 26317062 DOI: 10.1007/s40473-015-0036-3]
66 **Van Laere K**, Nuttin B, Gabriels L, Dupont P, Rasmussen S, Greenberg BD, Cosyns P. Metabolic imaging of anterior capsular stimulation in refractory obsessive-compulsive disorder: a key role for the subgenual anterior cingulate and ventral striatum. *J Nucl Med* 2006; **47**: 740-747 [PMID: 16644742]
67 **Abelson JL**, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor SF, Martis B, Giordani B. Deep brain stimulation for refractory obsessive-compulsive disorder. *Biol Psychiatry* 2005; **57**: 510-516 [PMID: 15737666 DOI: 10.1016/j.biopsych.2004.11.042]
68 **Le Jeune F**, Vérin M, N'Diaye K, Drapier D, Leray E, Du Montcel ST, Baup N, Pelissolo A, Polosan M, Mallet L, Yelnik J, Devaux B, Fontaine D, Chereau I, Bourguignon A, Peron J, Sauleau P, Raoul S, Garin E, Krebs MO, Jaafari N, Millet B; French Stimulation dans le trouble obsessionnel compulsif (STOC) study group. Decrease of prefrontal metabolism after subthalamic stimulation in obsessive-compulsive disorder: a positron emission tomography study. *Biol Psychiatry* 2010; **68**: 1016-1022 [PMID: 20951978 DOI: 10.1016/j.biopsych.2010.06.033]
69 **Figee M**, Luigjes J, Smolders R, Valencia-Alfonso CE, van Wingen G, de Kwaasteniet B, Mantione M, Ooms P, de Koning P, Vulink N, Levar N, Droge L, van den Munckhof P, Schuurman PR, Nederveen A, van den Brink W, Mazaheri A, Vink M, Denys D. Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. *Nat Neurosci* 2013; **16**: 386-387 [PMID: 23434914 DOI: 10.1038/nn.3344]
70 **Baldermann JC**, Melzer C, Zapf A, Kohl S, Timmermann L, Tittgemeyer M, Huys D, Visser-Vandewalle V, Kühn AA, Horn A, Kuhn J. Connectivity Profile Predictive of Effective Deep Brain Stimulation in Obsessive-Compulsive Disorder. *Biol Psychiatry* 2019; **85**: 735-743 [PMID: 30777287 DOI: 10.1016/j.biopsych.2018.12.019]
71 **Li N**, Baldermann JC, Kibleur A, Treu S, Akram H, Elias GJB, Boutet A, Lozano AM, Al-Fatly B, Strange B, Barcia JA, Zrinzo L, Joyce E, Chabardes S, Visser-Vandewalle V, Polosan M, Kuhn J, Kühn AA, Horn A. A unified connectomic target for deep brain stimulation in obsessive-compulsive disorder. *Nat Commun* 2020; **11**: 3364 [PMID: 32620886 DOI: 10.1038/s41467-020-16734-3]
72 **Hageman SB**, van Rooijen G, Bergfeld IO, Schirmbeck F, de Koning P, Schuurman PR, Denys D. Deep brain stimulation *vs* ablative surgery for treatment-refractory obsessive-compulsive disorder: A meta-analysis. *Acta Psychiatr Scand* 2021; **143**: 307-318 [PMID: 33492682 DOI: 10.1111/acps.13276]
73 **Kumar KK**, Appelboom G, Lamsam L, Caplan AL, Williams NR, Bhati MT, Stein SC, Halpern CH. Comparative effectiveness of neuroablation and deep brain stimulation for treatment-resistant obsessive-compulsive disorder: a meta-analytic study. *J Neurol Neurosurg Psychiatry* 2019; **90**: 469-473 [PMID: 30679237 DOI: 10.1136/jnnp-2018-319318]
74 **Anderson D**, Ahmed A. Treatment of patients with intractable obsessive-compulsive disorder with anterior capsular stimulation. Case report. *J Neurosurg* 2003; **98**: 1104-1108 [PMID: 12744372 DOI: 10.3171/jns.2003.98.5.1104]
75 **Aouizerate B**, Cuny E, Bardinet E, Yelnik J, Martin-Guehl C, Rotge JY, Rougier A, Bioulac B, Tignol J, Mallet L, Burbaud P, Guehl D. Distinct striatal targets in treating obsessive-compulsive disorder and major depression. *J Neurosurg* 2009; **111**: 775-779 [PMID: 19284243 DOI: 10.3171/2009.2.JNS0881]
76 **Azriel A**, Farrand S, Di Biase M, Zalesky A, Lui E, Desmond P, Evans A, Awad M, Moscovici S, Velakoulis D, Bittar RG. Tractography-Guided Deep Brain Stimulation of the Anteromedial Globus Pallidus Internus for Refractory Obsessive-Compulsive Disorder: Case Report. *Neurosurgery* 2020; **86**: E558-E563 [PMID: 31313803 DOI: 10.1093/neuros/nyz285]
77 **Chang CH**, Chen SY, Tsai ST, Tsai HC. Compulsive skin-picking behavior after deep brain stimulation in a patient with refractory obsessive-compulsive disorder: A case report. *Medicine (Baltimore)* 2017; **96**: e8012 [PMID: 28885367 DOI: 10.1097/MD.0000000000008012]
78 **Choudhury TK**, Davidson JE, Viswanathan A, Strutt AM. Deep brain stimulation of the anterior limb of the internal capsule for treatment of therapy-refractory obsessive compulsive disorder (OCD): a case study highlighting neurocognitive and psychiatric changes. *Neurocase* 2017; **23**: 138-145 [PMID: 28457185 DOI: 10.1080/13554794.2017.1319958]
79 **Coenen VA**, Schlaepfer TE, Goll P, Reinacher PC, Voderholzer U, Tebartz van Elst L, Urbach H, Freyer T. The medial forebrain bundle as a target for deep brain stimulation for obsessive-compulsive disorder. *CNS Spectr* 2017; **22**: 282-289 [PMID: 27268576 DOI: 10.1017/S1092852916000286]
80 **Doshi PK**, Hegde A, Desai A. Nucleus Accumbens Deep Brain Stimulation for Obsessive-Compulsive Disorder and Aggression in an Autistic Patient: A Case Report and Hypothesis of the

Role of Nucleus Accumbens in Autism and Comorbid Symptoms. *World Neurosurg* 2019; **125**: 387-391 [PMID: 30797934 DOI: 10.1016/j.wneu.2019.02.021]

81 **Franzini A**, Messina G, Gambini O, Muffatti R, Scarone S, Cordella R, Broggi G. Deep-brain stimulation of the nucleus accumbens in obsessive compulsive disorder: clinical, surgical and electrophysiological considerations in two consecutive patients. *Neurol Sci* 2010; **31**: 353-359 [PMID: 20127500 DOI: 10.1007/s10072-009-0214-8]

82 **Mulders AEP**, Leentjens AFG, Schruers K, Duits A, Ackermans L, Temel Y. Choreatic Side Effects of Deep Brain Stimulation of the Anteromedial Subthalamic Nucleus for Treatment-Resistant Obsessive-Compulsive disorder. *World Neurosurg* 2017; **104**: 1048.e9-1048.e13 [PMID: 28532905 DOI: 10.1016/j.wneu.2017.05.067]

83 **Plewnia C**, Schober F, Rilk A, Buchkremer G, Reimold M, Wächter T, Breit S, Weiss D, Krüger R, Freudenstein D. Sustained improvement of obsessive-compulsive disorder by deep brain stimulation in a woman with residual schizophrenia. *Int J Neuropsychopharmacol* 2008; **11**: 1181-1183 [PMID: 18700054 DOI: 10.1017/S1461145708009188]

84 **Sachdev PS**, Cannon E, Coyne TJ, Silburn P. Bilateral deep brain stimulation of the nucleus accumbens for comorbid obsessive compulsive disorder and Tourette's syndrome. *BMJ Case Rep* 2012; **2012** [PMID: 22977057 DOI: 10.1136/bcr-2012-006579]

85 **Senova S**, Mallet L, Gurruchaga JM, Rabu C, Derosin M, Yelnik J, Brugieres P, Pelissolo A, Palfi S, Domenech P. Severe Obsessive-Compulsive Disorder Secondary to Neurodegeneration With Brain Iron Accumulation: Complete Remission After Subthalamic Nuclei Deep Brain Stimulation. *Biol Psychiatry* 2020; **87**: e39-e41 [PMID: 31472980 DOI: 10.1016/j.biopsych.2019.07.006]

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