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OPINION REVIEW

Use of cognitive event-related potentials in the management of psychiatric disorders: Towards an individual follow-up and multi-component clinical approach

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Abstract

Relapse prevention remains a major challenge in psychiatry, thus indicating that the established treatment methods combining psychotherapy with neuropharmacological interventions are not entirely effective. In recent years, several intervention strategies have been devised that are aimed at improving psychiatric treatment by providing a complementary set of add-on tools that can be used by clinicians to improve current patient assessment. Among these, cognitive event-related potentials (ERPs) have been indexed as valuable biomarkers of the pathophysiological mechanisms of various mental illnesses. However, despite decades of research, their clinical utility is still controversial and a matter of debate. In this opinion review, I present the main arguments supporting the use of cognitive ERPs in the management of psychiatric disorders, stressing why it is currently still not the case despite the vast number of ERP studies to date. I also propose a clinically-oriented suitable way in which this technique could — in my opinion — be effectively incorporated into individual patient care by promotion of the use of individual ERP test-retest sessions and the use of a multi-component approach.

Key Words: Event-related potentials; Psychiatry; Cognitive disorders; Follow-up; Multi-component approach; Personalized medicine

Core Tip: Despite decades of intense research and many promising results, cognitive

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event-related potentials (ERPs) have yet to be implemented in daily psychiatric care units as an add-on tool to psychotherapy and medication. I present here the main arguments supporting the notion that ERPs represent a highly suitable tool for performing individual "neuro-cognitive" assessments in psychiatric patients. Such ERP data could help clinicians to specify individual cognitive interventions that will target each patient's specific needs, thus promoting an "individualized" or "personalized" medicine.

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INTRODUCTION

The 1990s have been referred to as the "Decade of the Brain", with developments such as brain imaging tools allowing patterns of distributed neural activity associated with both normal and pathological behaviors to be identified[1]. On this basis, major mental illnesses, such as schizophrenia, autism, major depression, anxiety disorders, and addictions, were redefined as brain diseases[2], with a deep impact of the environment at both the social and physical levels[1]. Nowadays, the separation of neurology and psychiatry appears arbitrary, and in the framework of modern neuroscience, psychiatrists and neurologists could be called "clinical neuroscientists" who apply neuroscientific discoveries to the care of patients with brain disorders[3]. Clearly, the management of a mentally ill patient necessarily requires consideration (mainly through psychotherapy) of a single individual embedded in a specific social-cultural context in order to encompass the social and psychogenic aspects of individual clinical symptoms[4]. However, mapping the live brain activity of a patient, by—for instance—the use of positron emission tomography (PET), magnetic resonance imaging (MRI), or electroencephalography (EEG), has demonstrated that all normal or dysfunctional mental processes are ultimately biological[2]. It is, therefore, also important to consider these cognitive, emotional, and social processes, subtended by specific choreographed patterns of brain activity that — when dysfunctional — can mediate the onset and persistence of specific clinical symptoms[5]. For instance, an alteration of mental state attribution, the ability to infer mental states of others in order to guide social interactions, is classically observed in schizophrenic patients[6]. This deficit, mainly subtended by neural alterations in the prefrontal cortex and the superior temporal sulcus[7], is associated with a poor outcome, social functioning, and social competence in schizophrenia[8]. As antipsychotic medication has been shown to have a limited impact on recovery and social cognition[9], the challenge is to develop new therapeutic strategies to specifically improve social cognition in schizophrenia. Promising results, revealing improvement of social functioning and reduction of psychotic symptoms, have been achieved through social cognition training programs and psychosocial interventions[10] as well as by brain stimulation through transcranial direct-current stimulation (tDCS)[11] or transcranial magnetic stimulation[12]. Similarly, in major depressive disorder, deficits in cognitive inhibition, subtended by a hyperactivated amygdala insufficiently controlled by a hypoactivated prefrontal region[13] appear to be a main causal factor for ruminations[14]. Sessions of training to inhibit negative thoughts[15] as well as a combined tDCS-mindfulness program resulted in a decrease in ruminations and lower depressive scores[16], while medication only has been reported to provide modest improvements[17]. In alcohol dependence, an increased salience of alcohol-related cues grasping drinkers' attention (hyperactivated mesolimbic activity[18]) combined with a lack of inhibitory resources (anterior cingulate and frontal hypoactivity[19]) defines the main neurocognitive mechanisms triggering relapse[20]. In light of the modest effect of anti-craving medications[21], cognitive bias modification training alone[22] or combined with tDCS[23] has shown promising trend on treatment outcomes by reducing craving and by improving early abstinence. Overall, convergent empirical data illustrating alterations in brain networks that underlie cognitive impairments have provided

foundational information about transdiagnostic circuits and promising targets for intervention[24]. Indeed, numerous studies have provided consistent evidence that mental illness involves significant cognitive impairments that represent valid therapeutic targets, as enhancing cognitive functioning leads to a reduction of clinical symptoms and a better quality of life. One of the main challenges at present consists of developing new ways to use neurocognitive mechanisms as an add-on tool in the clinical and conventional management of psychiatric patients.

Due to their high anatomical resolution, PET and functional MRI (fMRI) clearly constitute the most suitable tools to assess the distributed brain networks involved in diverse cognitive functions[25]. However, their coarse temporal resolution (1-2 s) does not allow definition of the temporal activation sequence, thus preventing isolation of the series of individual sensory, cognitive, affective, and motor processes that occur between a stimulus and a response[26,27]. Electrophysiological tools, by recording spontaneous electrical brain activity from multiple electrodes placed over the scalp[28], are more suitable for this purpose due to their optimal temporal resolution on the order of milliseconds[29]. EEG is an inexpensive and non-invasive tool defining a valuable clinical first-line method to exclude a diagnosis of epilepsy, drug intoxication, or sleep disorders in psychiatric patients[30]. A derivative of the EEG technique refers to event-related potentials (ERPs), *i.e.*, averaged EEG responses that are time-locked to the cognitive processing of stimuli. The past several decades have witnessed a vast number of task-dependent ERP components being described and studied among healthy people. While studies on healthy participants have helped to define the various cognitive steps needed throughout the entire information processing stream to achieve a cognitive function, such data also have great relevance in pathology. Indeed, by accessing the various cognitive steps needed to achieve a cognitive function, cognitive ERPs may then also allow definition of where a dysfunctional behavior originates at the cognitive level. This has great clinical relevance, as a similar altered behavior may be subtended by various cognitive disorders[31]. Therefore, by indexing the specific neurocognitive functions that are dysfunctional in a patient, ERPs pinpoint cognitive functions that should be rehabilitated in each patient through specific and individualized cognitive remediation procedures[26]. However, despite a solid theoretical basis[29] and decades of research showing alterations of these components in various psychiatric diseases[32], their relevance in clinical settings is still a matter of debate[33]. The scope of this paper is not to provide an exhaustive review of the literature regarding ERPs in various psychiatric diseases. Rather, my aim is to present relevant arguments supporting the notion that it is important to incorporate the use of cognitive ERPs in the management of psychiatric disorders, by also stressing why it is still not the case nowadays despite thousands of ERP studies to date. I then propose a clinically-oriented suitable way in which this technique could—in my opinion—be effectively incorporated into individual patient care.

DECADES OF ERP STUDIES IN PSYCHIATRY: WHY SO MANY HOPES AND PROMISING RESULTS FOR SUCH A MINOR CLINICAL IMPACT TO DATE?

Depending on the cognitive task one is confronted with and the cognitive processes one is focusing on, several ERP components have been described in recent decades in the literature. The P50, the contingent negative variation (CNV), the mismatch negativity (MMN), the P300 with its P3a and P3b subcomponents, the No-go N2 and No-go P3, the error-related negativity (ERN), and the N400 are some of the most studied ERPs. When elicited through a specific task in healthy subjects, such ERPs are the neural correlates that assess the efficiency of diverse cognitive processes, such as sensory gating[34], arousal and motor preparation[35], auditory discrimination[36], novelty processing *vs* decision making[37], cognitive and motor inhibition[38], insight[39], and semantic congruency[40]. As ERP amplitudes reflect differences in the intensity of responses whereas measurements of latency inform regarding the processing time duration[40,41], several anomalies in amplitude and/or latency of these components have been reported in various psychiatric disorders[32,42]. In such a view, ERPs could characterize biological markers of pathophysiological mechanisms[43]. Such biological markers can be state (only present during the acutely ill state but stabilized after remission) or trait (always present, during and after the disease) markers[44,45]. On the one hand, by reflecting pathophysiological processes

that are active during the disease, state markers could provide clinicians important input to assist with choosing the most appropriate treatment. For instance, a decreased amplitude of the P3b component is considered to be a state marker of depression[46]: The P3b amplitude has been shown to be increased after four weeks of antidepressant treatment[47] as well as following recovery from electroconvulsive therapy[48]. Similarly, chronic schizophrenic patients exhibit reduced MMN amplitudes compared to healthy controls[49], and antipsychotics such as aripiprazole[50] or drugs acting on the NMDA (N-Methyl-D-aspartate) receptor[51] appear to induce its recovery, while the CNV is reduced in amplitude in children[52] and adults[53] with ADHD but has been shown to exhibit an amplitude recovery with even just a single dose of stimulant medication[54]. Such instances clearly highlight how ERP state markers could be particularly useful in monitoring the efficiency of a treatment. On the other hand, trait markers can also be particularly useful, mainly as indicators of vulnerability[45]. Indeed, the amplitude reduction of the P3b as well as the absence of P50 suppression in schizophrenia[55], an enhanced ERN in child and adult anxiety disorders[56], and an altered P3 component in cocaine users[57] are examples of trait markers, indexing during and after the disease, of impaired cognitive functions that play a pivotal role in the onset and persistence of these mental diseases. But importantly, such alterations can also define a risk marker for healthy people with, for instance, a positive family history to further develop it[58-60]. Therefore, such markers, if present, can improve early detection of illness, and, as such, facilitate more effective and targeted interventions[44].

Overall, state and trait ERP markers can serve to aid diagnosis (as prognostic elements[61]), assist in choosing the most appropriate treatment for psychiatric disorders[62], and help with detecting illness at an early phase[63]. However, although such empirical data, even in meta-analyses[64-68], may appear convincing and useful, the reality is quite different as, up to now, the utility of cognitive ERPs in daily clinical care settings remains (very) modest[30]. Several explanations may account for this situation. First, at a technical level, the worldwide current ERP screening procedure favours the huge number of ERP studies, despite the heterogeneity of the data. For instance, an amplitude reduction and/or a delayed latency of the P3b and the MMN is usually considered to be a state marker of depression[69] and early psychosis[70], respectively. However, contradictory data have also been reported, suggesting no P3b and MMN differences between depressive[48] and psychotic[71] patients, respectively, with controls. Such heterogeneity has understandably led to a degree of scepticism among clinicians as it raises questions regarding reliability. The main factors accounting for these discrepancies are the clinical subtypes of patients included in these studies, with comorbidities inducing particular responses[72], higher artifact contamination in clinical patients than in typical subjects[27], a potential influence of medication[27], and differences in ERP recording protocols leading to data misinterpretations[73]. In this respect, a very interesting initiative, called "ERP CORE" (Compendium of Open Resources and Experiments)[74], has recently been launched in order to provide standardized ERP paradigms for seven widely used ERP components (N170, MMN, N2pc, N400, P3, lateralized readiness potential, and ERN). By providing researchers with a useful tool and guidelines for selected tasks to record specific ERP components, this will notably promote the possibility of comparing ERP data sets from different laboratories. At a clinical level, such guidelines already exist[75]; however, their use in studies around the world is still by no means ensured, and this could notably lead to a degree of misinterpretation of the data[73]. It is, therefore, urgent to again underscore that using such guidelines accepted by the field would clearly help with clinical implementation[76] by providing access to normative data gathered on large samples in order to follow the progression of patients as a function of the treatment, but also to control for potential confounding factors, such as gender, age, medication, and comorbid symptoms. Secondly, at a conceptual level, the potential role of ERP components in the management of mental disorders has also suffered from the predominance in psychiatry of the official nosological systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD)[77]. In such a categorical view, patients either do or do not meet the criteria to be diagnosed with a mental illness, thus suggesting that the presence of a specific cluster of symptoms will necessarily correspond to a specific mental disease (*e.g.*, borderline personality disorder). On this basis, the psychiatrist will select what they consider the best option of treatment among the range of those appropriate for that specific diagnosis (*e.g.*, selective serotonin reuptake inhibitors; SSRIs). If this treatment proves to be ineffective, they will then have to choose another option (*e.g.*, combination of SSRIs and quetiapine[78]) or reconsider the former diagnosis[79]. A main and crucial point that makes this categorical approach still

dominant in psychiatry is that it greatly facilitates clinical communication among mental health practitioners, as all textbooks and practice guidelines have been developed based on these categories[80]. In such a categorical view, mental illnesses are discontinuous entities with distinct symptoms, etiologies, and biomarkers[81]. However, inter-individual variability in the severity of symptoms among patients receiving a similar diagnosis, common symptoms across different disorders, and an extremely usual comorbidity factor are well-documented facts in clinical experience[77]. In other words, common liabilities across these "categories"[81,82] are more suggestive of a dimensional underlying cross-cutting transdiagnostic structure for mental disorders[77]. This still ongoing debate regarding the transdiagnostic *vs* the categorical frameworks to guide psychopathology assessments[83] is not the scope of this paper. However, it clearly appears that, due to the dominance of the nosological approach in psychiatry, the imprecision of categorical psychiatric diagnoses[84] has been a limiting factor in understanding the pathophysiological mechanisms of human behavioral abnormalities. Indeed, although decades of research have provided evidence of the relevance of various ERP components as biological markers of mental illnesses[32,43], their clinical sensitivity has been hampered by the fact that their parameters (*e.g.*, amplitude and latency) are diagnostically unspecific[33]. In other words, ERP deficits are a common feature of several psychiatric afflictions, but they will not assist clinicians in deciding whether a given patient is depressed, paranoid, or an alcoholic (high sensitivity but low specificity). Moreover, cognition is not considered as a primary treatment target, being still envisaged as a particular category of symptoms (among others), and not as a core phenomenon triggering the onset and/or the persistence of the disease. Many psychiatrists still then focused on finding the best suited drugs combination in order to contain symptoms et minimize side effects. Therefore, the approach using ERPs to classify patients according to DSM categories was entirely inappropriate, and, in the next section, I will specify how I think ERPs may be genuinely useful in clinical settings, mainly as predictive biomarkers, *i.e.*, as measured indices that may be used to predict clinical responses to treatment[85]. Finally, at a clinical level, a major practical issue is that the majority of ERP-based studies compare their results with matched controls using grand-averaged data. While such "group results" have ample merit at a fundamental "research" level, there is now a need for more "individualized", "personalized" medicine[86], *i.e.*, individual data that helps with devising interventions that are specifically targeted based on each patient's needs[26]. In the next section, I will try to provide some insights on how ERPs may be used effectively in clinical settings as an individual monitoring tool to reveal (or not) expected changes in brain function in response to a treatment[87].

USING ERPS IN PSYCHIATRY: WHAT PERSPECTIVES?

In an influential paper published in 1991 arguing for the use of PET in clinical care[88], Wagner[88] stated that: "…Today's medical practice is yesterday's research. The bridge linking the two is technology assessment, which makes possible the acceptance or rejection of new technologies in the practice of medicine. Experience is the key determinant of effectiveness. If the information provided is not useful to the physician caring for the patient, the procedure will eventually fall by the wayside...". The notion that ERPs are useful for managing psychiatric diseases, such as, for instance, depression[89], alcohol disorders[90], or schizophrenia[91], is not novel at all. However, despite decades of research, ERPs have yet to be implemented in the clinical management of mental illnesses[27]. It clearly appears at present that the clinical value of ERP components as a diagnostic index is low[33], merely reflecting a common measure of brain dysfunction[92]. With this in mind, it is, therefore, now urgent to precisely define what constitutes be the best use of ERPs in the management of psychiatric disorders. In order words, there is a need to find out which properties of ERPs as a tool could be the best-suited ones to help with managing a currently still unsolved clinical question.

A prominent issue in the treatment of mental illnesses relates to the relapse rate[93], which is approximately 50% at 1 year and 70% at 5 years for manic episodes in bipolar disorders[94]; approximately 35% at 18 mo and 74% at 5 years following a first episode of schizophrenia[95]; and approximately 50% at 3 mo and 85% at 1 year for recently detoxified alcoholic patients[96]. Despite the beneficial impact of psychotherapy and neuropharmacological interventions, as well as the positive effect of more recent intervention strategies such as multisystemic[97], cognitive behavioral[98], or mindful-

ness[99] therapies, the relapse rate is still extraordinarily high. Clearly, the idea is not at all to discredit the existing treatment methods, but providing a complementary set of add-on tools to be used by clinicians to improve current patient assessments is still a major challenge. Starting with the fact that mental diseases are also brain disorders, a neurocognitive approach has emerged[100]. This can be summarized as follows: (1) Mental illness involves significant cognitive impairment[101]; (2) These cognitive alterations, subtended by perturbed brain networks, may trigger the onset and/or persistence of clinical symptoms, thereby defining valid therapeutic targets[24]; and (3) Retraining these cognitive functions (through the use of cognitive retraining programs and/or neuromodulation tools) has been reported to reduce clinical symptoms and to enhance patient quality of life[11,16,22,23]. Overall, once admitted to a psychiatric care unit, there is still a huge difficulty with assessing "partial recovery", which allows patients to leave the hospital to return home, and achievement of long-term "complete clinical recovery", defined as the reduction of psychiatric symptoms and functional disabilities[102].

In my opinion, it is in this regard that ERPs may have an important clinical role in the management of psychiatric patients, as a monitoring and a predictive biomarker tool. Indeed, psychiatric evaluations are made almost entirely on the basis of clinical symptoms, and the longitudinal course is determined by a clinician speaking with the patient and informants (as well as sometimes by the use of clinical scales), but diagnostic frameworks do not usually incorporate biomarkers[103]. However, once the notion that mental illnesses are subtended by impaired neural functioning is acknowledged, a main assumption is to consider that this dysfunctional brain should undergo significant and enduring neural changes in order to be reflected in medium-to-long-term real-world behavioral modifications[104]. Indeed, test-retest ERP studies on healthy participants have, for instance, shown that subjects exhibiting improvements in inhibitory performance in a Go/No-go task had a similar residual gain in inhibition one week after post-training, albeit only when this effect was neurophysiologically indexed by faster Nogo-N2 latencies[105]. Accordingly, in neuropsychiatric conditions, several studies found that specific cognitive gains induced specific brain changes that were positively associated with decreased symptoms and better quality of life, even 6 mo later[106-108]. Taking these neural modifications into account would, therefore, be of the greatest clinical relevance, as their absence would suggest a high vulnerability to relapse. In this view, state ERP markers provide the possibility (1) to monitor the change, triggered spontaneously or by a specific treatment, in neurocognitive mechanisms that are involved in the onset and maintenance of clinical symptoms in an individual patient; and (2) to verify whether these neural changes induced by the treatment are predictive of the clinical trajectory. By fostering a longitudinal follow-up and intra-individual ERP approach, recent works have tried to verify the clinical utility of such designs, in which ERP measurements are included just as one would include measurements of symptoms. In a study by our laboratory of alcohol-dependent patients undergoing a four-week detoxification program[109], we showed that monitoring the changes in dual-processes that are well-known to trigger addictions (No-go P3 for inhibition[110] and P3 for cue reactivity[111]), at the start and at the end of the program, can provide clues about the mechanisms involved in abstinence or relapse. Indeed, specific changes in cognitive ERP markers during detoxification (a preserved oddball P3 and an enhanced No-go P3) indexed complete abstinence (over a 3-mo period) in alcoholic patients. The main clinical relevance of such test-retest ERP data is the possibility of pinpointing the change in specific neurocognitive functions (cue reactivity, inhibition) during the detoxification program that can predict further abstinence. Such a procedure necessarily implied: (1) Specification of the various cognitive mechanisms that should be considered as the primary targets subtending the clinical symptoms of interest; and (2) Selection of the appropriate cognitive tasks that will generate specific and reliable ERPs related to these specific processes at an individual level.

A crucial step, therefore, concerns the identification of the various cognitive processes of interest. As such, transdiagnostic (as opposed to disorder-specific) factors appear uniquely suited to bridge psychiatric phenomena and biological substrates of behavior[77]. Transdiagnostic impairment of cognitive control[82], self-referential processes[112], working memory[113], decision making[114], and attention[115] largely contribute to the real-world socio-occupational impairment common across disorders. Decades of research have validated reliable ERP markers for such processes (No-go P3, ERN, P300, MMN, and P50, respectively). Indeed, an altered No-go P3 response inhibition, as well as a deficit in P300 (in tasks tagging updating in working memory or decision making), are neurophysiological disorders present in psychotic[116,117], bipolar[118,119], unipolar[48,120] depressive disorders as well as

in anxiety[121,122] and substance use disorders[123,124]. Studies also commonly reported an altered ERN in anxiety disorders and in obsessive-compulsive disorders[125]; an altered MMN (indexing preattentive auditory memory processing) in major depression, schizophrenia, psychosis, and substance use disorders[36]; and a deficit in P50 sensory gating in stable schizophrenic patients and euthymic bipolar patients[58]. In such a dimensional transdiagnostic view, the lack of specificity reported for these various ERP components tagging specific cognitive functions will vanish and allow monitoring of the change in these processes during a treatment, independently of a categorical disorder. Such a proposition relies on two main "technical" recommendations for future ERP screening methods: (1) The use of individual ERP test-retest sessions; and (2) The use of a multi-component approach[126].

ERP serial recordings may be used in clinical contexts for the assessment of changes in cortical function during follow-up programs[33]. Indeed, although slight differences in the wave shape, size, and timing of ERPs between individuals are usually observed, these tend to be highly stable within an individual across recordings, as high internal consistency and high test-retest reliability have been reported[127-130]. A high degree of reliability is a key factor that makes state ERP markers highly suitable for examining changes in brain activity resulting from treatment intervention or disease progression in a single patient[12]. This could provide ERPs a novel and particularly useful role in the management of psychiatric disorders. Indeed, assessing that neural changes have been induced spontaneously and/or by a treatment is a necessary outcome to envisage medium to long-term positive behavioral changes[104]. For instance, recovering a normalized MMN amplitude or P50 suppression appears to be a good indicator of abstinence in alcohol and cocaine users, respectively[131]. In such a view, it is also particularly important to always merge ERP data obtained through "active" tasks with behavioral results. To illustrate this crucial point, we can focus on contradictory data showing that excessive alcohol users compared to controls exhibited decreased No-go P3 amplitudes[38,123], probably reflecting poor neural resources indexing a poor performance; while other studies have reported increased No-go P3 amplitudes[132], probably reflecting compensatory neuro-functional mechanisms that allow drinkers to achieve a similar performance level as controls. In other words, an increased amplitude should not necessarily be interpreted as a recovered activity, and a decreased amplitude should not necessarily be interpreted as a disrupted function. Therefore, merging test-retest ERP data with behavioral performances would allow identification of patients who need to recover more neural resources to achieve better performance (*e.g.*, an increase of inhibitory No-go P3 resources to maintain abstinence in alcoholic patients[109]), while patients exhibiting compensatory or exacerbated mechanisms may need to reduce the activity allocated to the task (*e.g.*, decreased ERN in anxiety disorders to assess better emotional regulation[56]). These types of individual assessments would help clinicians specify individual interventions that will target each patient's needs, thus providing "individualized" or "personalized" medicine[26]. For instance, a recently detoxified alcoholic patient who does not exhibit improvements on the No-go P3 component could be redirected to post-cure specific inhibitory boosting programs[109], while a patient with a severe anxiety disorder who does not exhibit a reduced ERN due to a drug treatment could be directed to therapies that address emotional regulation such as mindfulness[133]. Naturally, it is important at this point to outline that, on the basis of DSM or ICD psychiatric categories, some ERP trait markers have also been described. For instance, obsessive-compulsive disorder has been characterized by an increased ERN both before and after therapy[68] as well as for the altered P3 component in cocaine users[57]: Such trait markers, *i.e.*, neurophysiological mechanisms persisting during and after the disease, suggest that such ERP markers could be related to the risk for the disorder but not the expression of its phenotype. Even in a dimensional perspective, such trait markers, if present, can improve early detection of illness (*e.g.*, in healthy people with a positive family history), and, as such, facilitate more effective and targeted interventions[44]. Moreover, this also highlights a main challenge of future "ERP research applied to the clinic" to develop novel interventions/manipulations that could modify an ERP of interest. As such, it was found for instance that performing a secondary dual-task resulted in a reduced ERN, and this reduction was larger in patients with obsessive-compulsive disorder than in the group of healthy participants[134], as well as a single session of attention bias modification[135] or expressive writing[136], thus suggesting that increased ERNs in clinical anxiety disorders can be normalized, at least temporarily[137]. Increased sensitivity of the P3a and the P3b amplitudes to depression severity are also now observable thanks to the development of adapted new ERP protocols, such as the three-stimulus oddball design[138,139] and bimodal

oddball protocols[140,141], respectively. Research assessing the efficiency of a procedure or a treatment to impact an ERP of interest, even in healthy participants, will, therefore, remain of fundamental relevance in the ERP research area.

Many ERP studies have focused on "a single ERP component" (*i.e.*, P50, MMN, P3a, P3b, *etc.*), comparing it in a pathological population *vs* healthy matched control. However, at the clinical level, it has been suggested that although ERPs clearly exhibit high sensitivity and predictive power, they suffer from poor specificity[26,33]. The idea that a "multivariate endophenotype", based on a weighted combination of diverse electrophysiological features, may provide more information than any single endophenotype, is not novel[142]. Price and colleagues compared and contrasted four electrophysiological endophenotypes — MMN, P50, P300, and antisaccades — and showed that this combination of features decreased the impact of group heterogeneity. In the same vein, at an individual level, a prominent idea is that a psychiatric patient will exhibit various cognitive disorders, of varying severities, that will subtend their own clinical symptoms. In a dimensional view, such disturbances may evolve differentially, so that some ERP measurements that index a specific cognitive function may recover during a disorder, while others will exhibit long-lasting damage. As an example, we recently showed that a post-cure 3-mo abstinence period in alcoholic patients can be neurophysiologically indexed by an increased No-go P3 yet similar oddball P3 components between the start and the end of a detoxification program[109]. Future studies should hence adopt a multi-component approach in order to potentially increase the sensitivity of ERP recordings, as the change in the patterns of ERPs could be specific (*e.g.*, which components recover, and which remain disturbed) from one psychiatric patient to another. In my opinion, such patterns indexing the changes of various ERP components through test-retest sessions appear to be the best way for ERPs to provide clinicians with relevant information regarding change in the disease (due to a treatment) in a single patient and the residual cognitive impairments that still need to be addressed. Indeed, once cognitive disturbances have been characterized through ERP screening of individual patients, psychiatrists will be able to orient the "cognitive" treatment (individually or in groups that present homogeneous patterns of cognitive deficits). More precisely, specific cognitive retraining procedures could be used to target deficits and to increase cognitive efficiency, as both cognitive training and neuromodulation boosting methods have already been shown to reduce clinical symptoms[143,144].

CONCLUSION

The main aim of this opinion review was to present the main arguments in favour of the clinical utility of ERP components to help in the management of psychiatric disorders. ERPs may be of great value to psychiatrists for the identification and monitoring of cognitive processes that should be rehabilitated on a patient-by-patient basis[126]. Such a proposition is limited per se, as, naturally, the complexity of dealing with a mental illness encompasses a large variety of stakeholders, such as psychologists, psychiatrists, nurses, and social workers, as well as neuropsychologists and neurophysiologists. I am, therefore, fully aware that the ERP contribution would be minimal, as moreover, many other EEG tools (*e.g.*, event-related oscillations[145] or microstates[146]) could also be of interest. Also, combining ERPs data with more structural and functional information (through for instance fMRI studies[147,148]) would be of the greatest relevance in order to better capture the pathophysiological mechanisms underlying specific clinical symptoms and orient treatment. I am also fully aware that there is still a long way to go before such a proposition could be widely implemented in clinical care units: If such a procedure could be quite easy to install at a technical level for inpatients in psychiatric clinics in highly developed countries, the situation could be more problematic for lower-income countries, and even more for outpatients visiting on a punctual daily basis a psychiatric office. If such a procedure would reveal high efficiency in the future, economical discussions will have to be undertaken to furnish full access of such a material to all countries in order to (1) manage, monitor and orient treatment for inpatients; and (2) allow straight collaborations between research centers and outpatients' psychiatric office in order to deliver information to clinicians that could be of help in orienting treatment. In such a view, lack of normative data, technical artefacts linked to the recordings with patients, adoption of clear multisite guidelines, as well as a constructive dialogue between researchers and clinicians in the assessment of a suitable cognitive-ERP battery are still some of the main issues that warrant our full attention. A major issue with such a

proposal indeed relates to the fact that clinicians and researchers have to agree on a cognitive ERP-battery that could be used across centres (in terms of its content, but also, naturally, its multisite technical guidelines) and across disorders. Such a battery should be as complete as possible, but not too time-consuming in order for it to be adapted to all types of psychiatric patients (probably approximately a maximum of 45 min for a session recording?). It is nowadays well-accepted that transdiagnostic impairment of cognitive control[83], self-referential processes[112], working memory[113], decision making[114], and attention[115] largely contribute to the real-world socio-occupational impairment common across disorders. Therefore, I am inclined to suggest that such a cognitive ERP-battery should at least include two active and two passive tasks: (1) A Go/No-go task, which appears to be the best-suited task to assess cognitive control[143], and to record the No-go N2, the No-go P3, and the ERN as the main ERPs of interest; (2) A bimodal (visual-auditory) three-stimulus oddball task, in order to probe for updating memory and decision-making processes through the recording of P3a and P3b components[87,140]; (3) A passive auditory paired-stimulus paradigm, classically used to record sensory gating through the P50[149]; and (4) A passive auditory oddball design in order to access the MMN component[150]. Monitoring the changes in these components in a single patient during treatment would be of the greatest clinical interest for identifying neural changes that are positive predictors of the clinical trajectory as well as cognitive functions that still warrant being trained. Clearly, much work is still needed to achieve this aim, such as reaching an agreement regarding the battery content as well as establishing multicenter large sample recordings to obtain normative data and to test the efficiency of the procedure at a clinical level. Nevertheless, as EEG is a cheap method that can be readily implemented in any type of psychiatric care unit, and because ERPs can provide invaluable information regarding the neurocognitive status of a patient as a monitoring and a predictive biomarker tool, I very much think this method deserves attention and should be given more consideration for further development. The challenge for future studies will be to establish whether this procedure, driven by serial follow-up recordings of various ERP components in a singular patient, is efficient enough to be incorporated into novel psychiatric treatment methods.

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OPINION REVIEW

Implications from translational cross-validation of clinical assessment tools for diagnosis and treatment in psychiatry

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Abstract

Traditional therapeutic methods in psychiatry, such as psychopharmacology and psychotherapy help many people suffering from mental disorders, but in the long-term prove to be effective in a relatively small proportion of those affected. Therapeutically, resistant forms of mental disorders such as schizophrenia, major depressive disorder, and bipolar disorder lead to persistent distress and dysfunction in personal, social, and professional aspects. In an effort to address these problems, the translational approach in neuroscience has initiated the inclusion of novel or modified unconventional diagnostic and therapeutic techniques with promising results. For instance, neuroimaging data sets from multiple modalities provide insight into the nature of pathophysiological mechanisms such as disruptions of connectivity, integration, and segregation of neural networks, focusing on the treatment of mental disorders through instrumental biomedical methods such as electro-convulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS). These methodologies have yielded promising results that have yet to be understood and improved to enhance the prognosis of the severe and persistent psychotic and affective disorders. The current review is focused on the translational approach in the management of schizophrenia and mood disorders, as well as the adaptation of new transdisciplinary diagnostic tools such as neuroimaging with concurrently administered psychopathological questionnaires and integration of the results into the therapeutic framework using various advanced instrumental biomedical tools such as ECT, TMS, tDCS and DBS.

Key Words: Translational neuroscience; Evidence-based psychiatry; Schizophrenia; Affective disorders; Psychopharmacology; Electro-convulsive therapy; Transcranial magnetic stimulation; Transcranial direct current stimulation; Deep brain stimulation

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Core Tip: The current review is focused on the translational approach in the management of schizophrenia and mood disorders, as well as the adaptation of new transdisciplinary diagnostic tools such as neuroimaging with concurrently administered psychopathological questionnaires and integration of the results into the therapeutic framework using various advanced instrumental biomedical tools such as electro-convulsive therapy, transcranial magnetic stimulation, transcranial direct current stimulation and deep brain stimulation.

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INTRODUCTION

Behavioral disorders are amongst the leading causes of disability and their characteristic features including early age of onset as well as high prevalence among the working-age population are an influential determinant of their negative socio-economic impact[1,2]. The severe mental illnesses, such as schizophrenia and mood disorders demonstrate a high comorbidity rate with somatic diseases as well as with other psychiatric conditions, which in addition to the significant risk for self-inflicted death, marks a high mortality rate[3].

Unlike other branches of medicine, where the clinician can rely on objective measures (blood tests, imaging methods, *etc.*), in psychiatry, diagnosis is mediated by subjectivism, which affects the reliability of the assessment methods used. Consequently, there is a frequent change in psychotropic drugs which leads to increased risk of drug-resistant disorders and relapse[4]. The integration of neuroimaging evidence with comprehension of the role of brain networks and their abnormal interactions as a pathogenic mechanism for the development of certain behavioral deviance is an important step toward a systematic biological understanding of mental disorders.

Establishing a diagnosis and treating these disorders is challenging. Numerous molecules are assumed to have the appropriate characteristics to induce improvement; however, therapeutic outcome and adverse side effects differ significantly among patients[5]. With conventional treatments (psychopharmacology and psychotherapy), a large percentage of patients report inadequate symptom resolution, and relapse rates remain high[6,7]. A growing amount of interest has been centered on focal neuromodulation in the search for better treatments. The interest in this field is driven by the latest data considering neuroanatomical models of modulation of mood, thought, perception, and behavior, as well as more sophisticated techniques for direct and focal modification of the neural function.

In the current review we will discuss new perspectives of the translational approach in the diagnosis and treatment of severe mental disorders, namely schizophrenia and mood disorders. Although genetic risk factors and pharmacogenomics in the field of psychiatry are promising strategies to predict or mitigate the therapeutic response of medication, and thus to inform medication selection and dosing decisions, the focus in this review will be on the adaptation of new transdisciplinary diagnostic methods such as neuroimaging and concurrently administered psychopathological questionnaires and the implementation of the results into treatment using various advanced biomedical treatment methods like electro-convulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS).

PSYCHIATRIC DIAGNOSTICS IN THE 21ST CENTURY

One of the most widely discussed problems in psychiatry seems to be the fact that the diagnostic process is primarily focused on patients' reports, behavioral observation and the capacity to draw conclusions about the real inner nature of patients' experiences, rather than on accurate objective biomarkers[8].

The primary diagnostic tools in contemporary psychiatry are the International Classification of Diseases[9] and the Diagnostic and Statistical Manual of Mental Disorders[10], yet their foundational criterial categorization lacks biological validity[11,12]. This phenomenon is illustrated by existing barriers, such as heterogeneity, comorbidity, and ambiguous distinctions between healthy and abnormal behavior, which impede the diagnostic process. Another significant concern is that mental illnesses are categorized purely on clinical manifestations, without consideration for their etiology. When the conventional diagnostic labels themselves are not absolutely accurate, it is difficult to recognize a biological marker for a specific disorder. For this purpose, the National Institute of Mental Health has introduced the Research Domain Criteria Project[13,14], which seeks to extend the understanding of brain-behavior correlations and eventually incorporate this knowledge into clinical practice and enhance the development of more successful treatments. Innovative brain imaging technology provides the possibility to discover disease-specific anatomical and functional neural impairments.

Neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography, single-photon emission computed tomography, magnetoencephalography and electroencephalography provide resources for a non-invasive analysis of the brain structure and function associated with mental diseases with excellent precision[15]. Understanding the complex mechanisms of communication between different brain regions at rest and in the conditional performance of tasks is a promising field for studying the etiological mechanisms of severe mental illnesses that lead to personal and social decline. For example, functional MRI (fMRI) used in schizophrenia research was able to detect anatomical and functional aberrations of brain plasticity and connectivity, which clinically manifest as cognitive disturbances[16]. Another example of an accessible translational method is pharmacological fMRI[17], which facilitates the study of the effects of different pharmacological agents on the central nervous system (CNS) and the search for accurate neuroimaging biomarkers[18].

TRANSLATIONAL APPROACH

The concept of translation can be defined as a mechanism for improving health status, thus reducing mortality and morbidity rates among patients by incorporating scientific findings from research into clinical applications[19]. The translational approach in psychiatry encompasses a wide range of scientific disciplines and innovative techniques. MRI techniques such as quantitative structural imaging, voxel-based neuromorphometry, functional neuroimaging and spectroscopy are widely used in psychiatric research. These imaging tools, together with the knowledge gained regarding the underlying neurochemical dysfunctions have the potential to change the current state of "crisis" in psychiatry[20,21] through the use of evidence-based biomarkers and insight into the etiology of mental disorders.

Disruptions in communication within and between brain networks and the pathological processes involving their nodes are a promising discovery of translational neuroscience towards gaining a biological understanding of mental disorders and defining them as impaired connectivity disorders. Low-frequency variations in random brain functions can be localized by resting state fMRI (rs-fMRI), representing a common instrument for macro-scale functional connectomics to characterize inter-individual discrepancies in brain activity and mind-brain interactions observed in various mental disorders[22]. These metrics have a tremendous potential for accelerating the discovery of biomarkers for different mental disorders, which need first and foremost reliability and reproducibility to be addressed.

In this sense, critical questions are whether the progress in this field has succeeded in contributing to the development of more effective therapeutic methods, and whether biomarkers could be incorporated into everyday practice. However, despite years of efforts in this area, the results remain inconsistent[23]. Over the past decades, substantial advancement has been made in recognizing and understanding the fundamental neurobiological correlations of psychiatric disorders, such as schizo-

phrenia spectrum disorders and mood disorders, but the effects of these advancements have not yet been established in clinical practice[24-26]. This may be partly due to the specificity of the design of the methods used. A common practice in fMRI studies is to conduct a clinical assessment before and after the scanning. Yet, in cases such as examining patients with bipolar disorder with rapid cycling, which presents with mood shifts from depression to mania within hours for example, this could affect the accuracy of the findings. To address this issue, fMRI gathered neuroimaging data, together with the parallel implementation of a self-assessment scale[27], could construct a scientifically valid instrument that can be used by clinicians in daily practice with trust in the reliability of the method. This initiative might positively affect the diagnostics, prevention, treatment, as well as facilitate the decision regarding the choice of the appropriate therapeutic method.

With the aim of implementing the translational model in psychiatry, our research group is concentrating on developing a new paradigm that combines a clinical self-assessment scale (von Zerssen and Koeller[28]'s paranoid-depressive scale) applied simultaneously with the acquisition of fMRI in two groups of patients—with a paranoid syndrome in the context of schizophrenia and with a depressive syndrome in the context of recurrent depressive disorder or bipolar disorder[29-33]. The goal is to compare the differences in brain activation during the task-related fMRI (tr-fMRI) with structural and functional changes in connectivity at rest with the hypothesis that the zones which demonstrate differential activation may have aberrant effective connectivity patterns and structural abnormalities. The results of the study can be summarized as follows: (1) In terms of grey matter (GM) volume alterations, the comparison at a whole brain level, voxel by voxel, yielded no significant structural differences between the two groups; (2) The paranoid group was associated with significantly more robust activations in the default mode network (DMN) structures—left precuneus (PreCu), left posterior cingulate cortex (PCC), and angular gyrus (AngG) during the processing of paranoid items from the scale (Figure 1); and (3) There was an aberrant connectivity pattern in the paranoid group—abnormal inhibitory connection from the prefrontal cortex (PFC) to the anterior insula (aI) (Figure 2).

We suggest that the observed activations of the PreCu, PCC, and AngG (DMN components) may be indirect evidence of the inhibitory influence from PFC⇒aI, which interferes with the balancing function of the insula as a dynamic switch in the DMN and fronto-parietal network (FPN)[32]. Impaired aI⇒DMN and aI⇒FPN connections lead to hyperactivity of DMN[34], which could explain social withdrawal and autistic behavior observed in patients with schizophrenia. In addition, the identified inhibitory effective connectivity from PFC⇒aI offers new insights into how the PFC dysfunction may contribute to cognitive impairment[35-37], behavioral disorganization[38], and functional decline observed in patients with schizophrenia. We propose a pathophysiological model in which cognitive deficits are due to the inability of the CNS to initiate and maintain an organized fronto-insular network[36].

On the other hand, we raise the question of whether and to what extent the prediction of clinical diagnostic classes can be improved by superimposing different dimensions of MRI (structural, tr-fMRI and rs-fMRI) compared to a single modality by application of a multivariate linear model (MLM)[36]. Using MLM and principal component analysis, we have made progress towards distinguishing the two psychiatric populations. The dopamine-ergic and noradrenaline-ergic pathways with DMN nodes were reported to be significant. The regions involved [planum polare (PP), inferior frontal gyrus (IFG), insula, nucleus accumbens, *etc.*] have both structural and functional characteristics that can distinguish the two groups. When focusing on the discriminatory power of the functional modalities, the predominant regions are a part of the effort mode network, DMN, and subcortical areas with mainly glutamate-ergic and GABA-ergic neurotransmission. The most significant structure in our MLM study is PP, which is a part of the superior temporal gyrus (STG) and is not only involved in auditory and linguistic processing but is also a critical construct for cognitive processes. Neuroimaging studies show that subjects with schizophrenia have structural abnormalities in the STG[39], suggesting that it plays a key role in the etiology of auditory perceptual disturbances and disorganization of thoughts[40]. There is evidence that auditory hallucinations are associated with a functional network of brain areas, namely the auditory and linguistic areas of the STG and IPG, as well as speech motor areas in the IFG[41-43], which are also significant regions in our study. Those findings support the abovementioned aim to develop a translationally valid instrument in the diagnostic process of schizophrenia and depression.

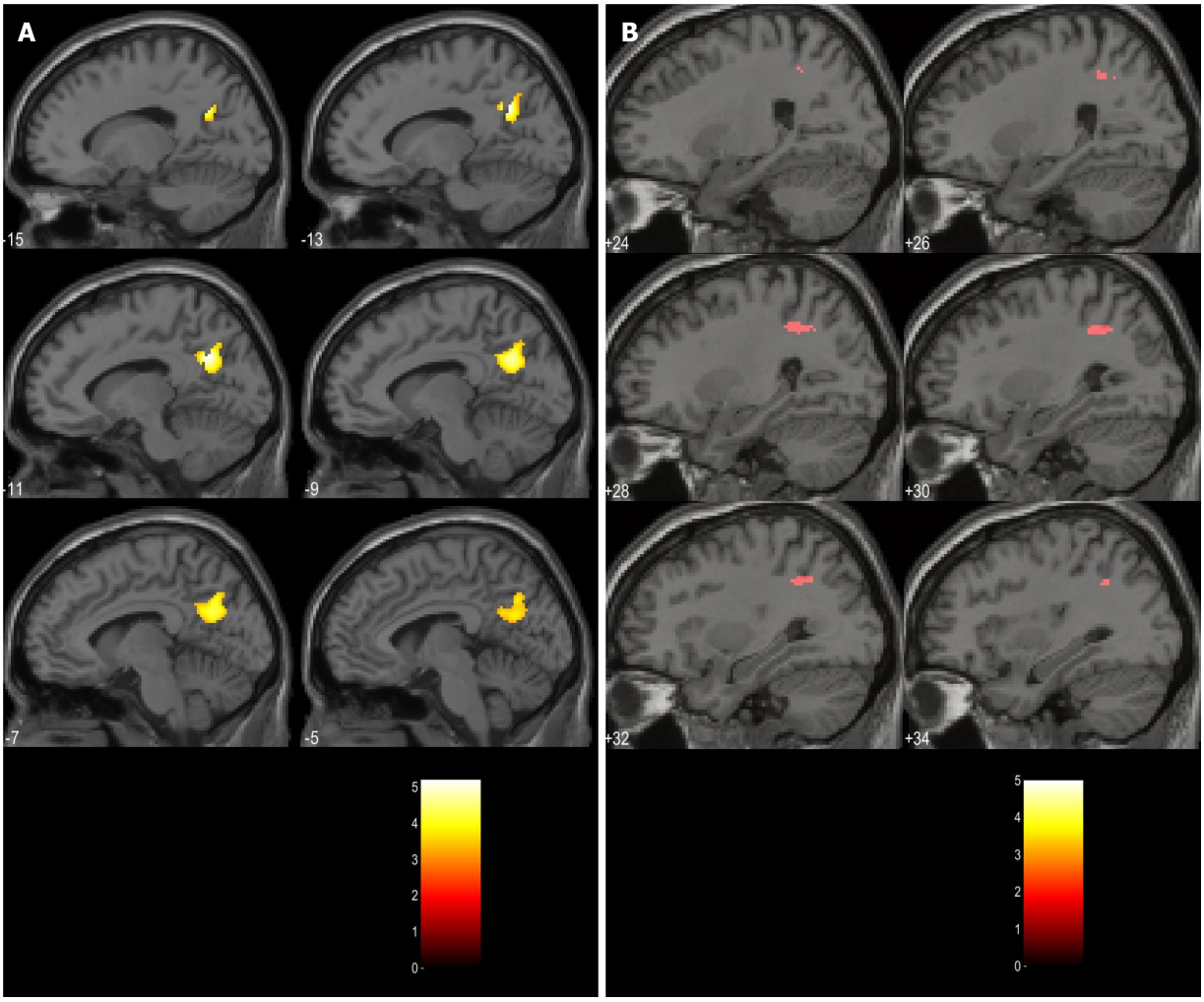

Figure 1 Clusters of activations significantly higher in schizophrenia. A: Left precuneus; B: Right posterior parietal lobule. Citation: Stoyanov D, Aryutova K, Kandilarova S, Paunova R, Arabadzhiev Z, Todeva-Radneva A, Kostianev S, Borgwardt S. Diagnostic Task Specific Activations in Functional MRI and Aberrant Connectivity of Insula with Middle Frontal Gyrus Can Inform the Differential Diagnosis of Psychosis. *Diagnostics (Basel)* 2021; 11(1): 95. Copyright ©The Author(s) 2021. Published by MDPI[32].

TREATMENT IMPLICATION OF THE TRANSLATIONAL APPROACH

Considering the controversial efficacy of the conventional treatments (psychopharmacology and psychotherapy), a large percentage of patients do not achieve complete remission (*i.e.*, become asymptomatic) or retain symptomatic improvement. This lack of efficacy has led to the quest for alternative solutions, which involve the utilization of more invasive interventions for treatment-resistant patients with psychiatric illnesses[44]. Therefore, the focus has been on neuromodulation, *i.e.*, modulation of the connections between various pathways and neurotransmitter systems in the brain. This emphasis has been driven by enhanced neuroanatomical concepts of mood, thought, and behavioral control, as well as more techniques to modify neural activity directly and focally.

ECT

ECT was first performed by a team of physicians led by Ugo Cerletti and Lucio Bini in 1938[45,46], along with Accornero[47] who contributed to the development of what they called electroshock[48] leading to the replacement of less effective biological interventions such as deep sleep therapy[49] and insulin shock therapy[50]. ECT has come a long way in refining the method and is still used today in cases of severe major depressive disorder (MDD), mania, and catatonia as a safe and effective treatment, despite the numerous critiques. ECT is an ideal example of translational neuroscience, involving the application of an instrumental method that generates electricity acting at a neurobiological level and modulating neuronal plasticity and brain connectivity. In the macro- and micro-environment of the brain, ECT induces numerous

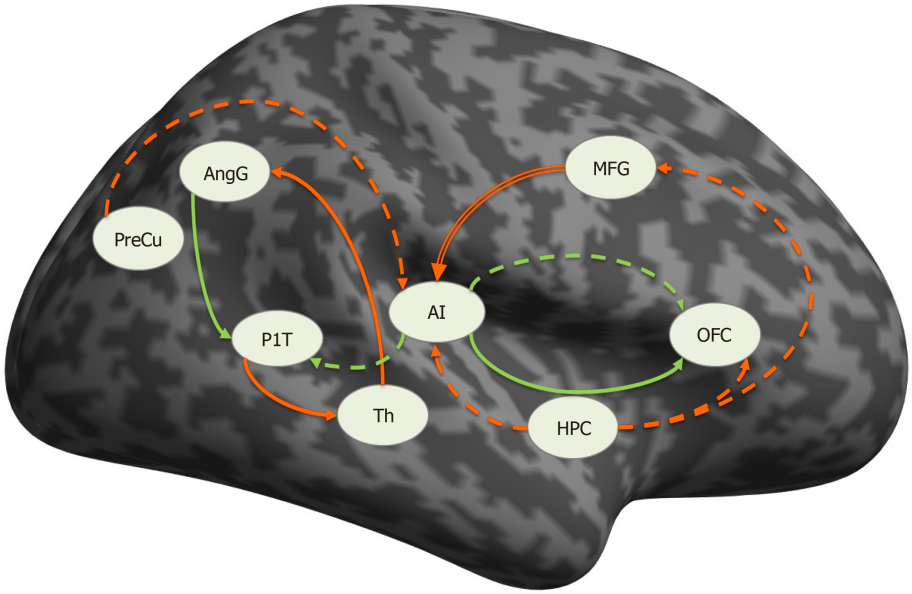

Figure 2 Connections significantly different from zero. Solid line: schizophrenia, dashed line: in depression, green: excitatory, red: inhibitory, double red line: significantly different between the groups. PreCu: Precuneus; HPC: Hippocampus; AI: Anterior insula; AngG: Angular gyrus; OFC: Orbitofrontal cortex; PIT: Planum temporale; Th: Thalamus; MFG: Middle frontal gyrus. Citation: Stoyanov D, Aryutova K, Kandilarova S, Paunova R, Arabadzhiev Z, Todeva-Radneva A, Kostianev S, Borgwardt S. Diagnostic Task Specific Activations in Functional MRI and Aberrant Connectivity of Insula with Middle Frontal Gyrus Can Inform the Differential Diagnosis of Psychosis. *Diagnostics (Basel)* 2021; 11(1): 95. Copyright ©The Author(s) 2021. Published by MDPI[32].

neurophysiological as well as neurochemical changes. It has been suggested that changes in gene expression, functional connectivity, neurotransmission, membrane permeability, and immune system function are responsible for the therapeutic effects of ECT[51]. Neuroimaging studies show that the GM volume of key regions like the amygdala, hippocampus, and anterior cingulate cortex (ACC) is decreased in patients with depression and increases following administration of ECT[52]. It remains an unresolved issue as to whether ECT efficacy in various psychiatric conditions (depression, mania, catatonia, delirium, and psychosis) is due to common neurobiological features shared by those disorders or to a single mechanism of action[53]. A mechanism that has recently been suggested is that the seizures triggered by ECT may induce a significant alteration in the sleep structure[54].

We suggest that this and other hypotheses concerning neuroplasticity can be tested by our paradigm as it can be used as a tool to monitor the therapeutic effect of ECT by comparing the results before and after the procedure, considering the fact that the von Zerssen and Koeller[28]'s self-assessment scale was primarily designed for monitoring the treatment response.

TMS

TMS was developed in 1985 as a non-invasive method to stimulate the cerebral cortex[55]. A strong magnetic field is produced by a TMS device, which induces an electrical current in a specific area. This is a method based on the principle of electromagnetic induction, which can have a different effect on the targeted areas depending on the stimulation parameters and the physiological activity of the areas. Low frequencies around and below 1 Hz (low frequency TMS) have been found to suppress the excitability of the stimulated cortical zone and functionally related structures, while those above 1-3 Hz (high frequency TMS) lead to its activation[56].

Unlike ECT, the administration of TMS requires no anesthesia and therefore patients are awake and alert during the procedure and it is often performed in an outpatient setting[57]. The short-term effect of the procedure is prolonged by applying a series of stimuli with a certain frequency, the so-called repetitive TMS (rTMS). TMS affects the underlying brain structures by altering the regional activity in the underlying cortical structures. Such changes have also been found in brain areas distant from the site of stimulation, proving that the effect of rTMS propagates in other remote parts of the brain, and these changes are functionally significant and take place on existing neural networks[58].

Depressive disorders are the most studied area of therapeutic use of TMS. Recently there has been an increasing interest in the management of schizophrenia as research results indicate that the negative symptoms of schizophrenia appear to be attributed to PFC hypoactivity, whereas positive symptoms appear to be correlated with left temporo-parietal cortex hyperactivity[59]. It has also been hypothesized that auditory hallucinations may be attributed to aberrant activation of language perception zones (*i.e.*, Wernicke's area) in the left temporo-parietal cortex[60]. It is therefore proposed that the use of high frequency TMS in the left PFC may reduce negative symptoms of schizophrenia, whereas the application of low-frequency TMS to the left temporo-parietal cortex may reduce the positive symptoms[60,61].

Considering the fact that all of those structures appear to be significant in our MLM study, we support the abovementioned model for applying rTMS in individuals suffering from schizophrenia. Moreover, our finding of the effective connectivity aberration between the PFC and the insula provides further insight on the etiopathophysiology of schizophrenia and the role of the disruption of the salience and executive systems processing due to the insular dysfunction because of its failure as a dynamic switch between the DMN, FPN and salience network (SN). Due to its deep location, the insula is considered to be beyond the reach of rTMS. However, we suggest that the insula may still be indirectly modulated by the identified abnormal connectivity from PFC to aI by focusing on PFC, the localization of which makes it accessible for stimulation.

Despite the promising applications of TMS, in about 30% of cases the standard procedure misses the target area, as it only allows stimulation of focal areas just below the skull[62,63]. Deep TMS (dTMS) has been implemented to overcome these drawbacks. dTMS offers all the advantages of conventional TMS with the benefit of stimulating deeper brain zones with lower focal distribution of the electric field[64]. Some studies have been conducted on the use of conventional TMS for the treatment of auditory hallucinations in drug-resistant patients with schizophrenia, which have shown that the method is moderately effective[65,66]. In this sense, we propose inhibitory dTMS as a therapeutic intervention targeting temporal, frontal, and parietal areas, taking into account data from functional neuroimaging which established that hallucinations are accompanied by transient hyperactivity in specific zones—STG, PFC, ACC, inferior parietal cortex, *etc.*[67] and dTMS may be even more effective than conventional TMS due to greater stimulus depth. In addition, dTMS can even be used as a method to modulate the function of the insula directly, unlike standard TMS, in which this area is inaccessible and can only be reached indirectly. Restoring the function of the insula and the networks in which it participates will further improve the function of the SN as a dynamic switch between DMN and FPN. Finally, our paradigm in tr-fMRI can also be applied as a tool for monitoring TMS, with good enough accuracy and reliability of the method.

tDCS

TDCS is a neuromodulatory procedure that facilitates or inhibits spontaneous neuronal activity by delivering low-intensity direct current to cortical areas *via* scalp electrodes. Over the past decade, the physiological mechanisms of action of tDCS have been studied to support the investigation of its clinical neuropsychiatry applications. TDCS was developed as a treatment method for brain injuries and neuropsychiatric disorders, especially MDD. Given the absence of a triggered seizure, it is hypothesized that this technique operates by plastic effects exerted by endogenous firing potentiation[68].

A variety of studies have found that in healthy individuals, anodal tDCS to dorsolateral PFC (DLPFC) leads to increased cognitive performance[69]. In the treatment of MDD, the anode is located over the left DLPFC, which is hypoactive, helping to improve local activation and regain regular functioning[70]. The cathode is located either over the right DLPFC or the right supraorbital or frontotemporal area, leading to distinct current distributions. In addition, after anodal DLPFC tDCS in patients with schizophrenia, enhanced results on working memory tasks[71], probabilistic learning tasks[72], adaptive control tasks[73], and attention-vigilance tasks[74] have been demonstrated. A consistent feature of these diverse tasks is that they all depend, in part, on cognitive control mechanisms such as goal maintenance mediated by DLPFC.

We suggest a model in which the tDCS, instead of focusing on a single cortical area, could simultaneously target several zones that are part of a common network. Considering the results of our imaging studies, they point to the hypothesis that in schizophrenic patients the DMN is incorrectly activated in conditions that are not typical for such activation (tr-fMRI), while based on the study of connectivity we note

that the DMN is deactivated in rest conditions, which is the normal condition of its activation.

Our views are that tDCS can be useful for restoring the normal connectivity of the different components of the DMN if the electrodes are placed simultaneously in several areas of the parietal cortex, namely the PreCu, PCC and AngG, which can potentially regulate the disrupted connection between the individual components of DMN and thus lead to improved symptoms such as cognitive impairment in schizophrenia.

DBS

DBS is the most invasive focal neuromodulation tool for mental disorders available. This technique allows us to deliver electrical stimulation of GM or white matter in a therapeutic attempt to improve the dysfunctional activity of the brain. DBS is probably the most elegant and complex perfect example of the translational approach – integration of instrumental, neurobiological, neurosurgical, and psychopathological knowledge in performing this precise and innovative psychosurgical procedure. It involves a high-frequency deep-brain stimulation by stereotactic inserted electrodes. It is known to act primarily by functional inhibition around the electrode, but it may also have excitatory effects on local axons and far-reaching excitatory effects[75].

DBS has proven to be beneficial in the treatment of severe mental illnesses like major depression[76], obsessive-compulsive disorder (OCD)[77], Tourette's syndrome[78] and addiction[79]. The use of DBS in patients suffering from schizophrenia is still in its early stages and at present has not been officially approved. There seems to be no consensus regarding the particular brain structures, networks, and circuits which could be clinically beneficial for DBS treatment of schizophrenia. Studies have reported DBS of the habenula[80], nucleus accumbens and ACC[81]. These early experiments indicate the capacity of DBS to have beneficial effects in schizophrenic patients who do not respond to any other treatment. In order to assess the magnitude of the advantages and whether they can be accomplished without psychiatric side-effects, further studies would be needed with thoughtful consideration.

We suggest that the future research on the therapeutic effect of DBS in schizophrenia should focus extensively on two important areas, namely the insula and the PreCu, as they are the key nodes of the SN and DMN — the two brain networks that appear to be disconnected in the paranoid group in our study. We speculate that the enhancement of the altered function of the DMN and SN could ultimately restore the cognitive deficits and the disorganized thought and behavior observed in schizophrenic patients.

CONCLUSION

Psychotic and mood disorders affect a large number of people all over the world and have significant effects for individuals, their loved ones and society. To improve the prognosis and outcome of these disorders, it is crucial to make changes in their management. Unconventional instrumental biomedical methods have proven effectiveness for different psychiatric conditions (*e.g.*, ECT for depression, mania, and catatonia; TMS for drug-resistant depression; tDCS for cognitive enhancement in schizophrenia; DBS for OCD, addiction and severe MDD). However, their usage is still limited, and these tools remain in the shadow of psychopharmacology and psychotherapy.

Results from our studies on cross-validation of tr-fMRI, effective connectivity at rest and the MLM point to some interesting and new therapeutic applications that can modulate the SN and thereby the DMN and FPN function that are impaired in people suffering from schizophrenia. Moreover, these findings could be translated in the protocols of methods like ECT, TMS, tDCS and DBS that have the potential to modulate the network plasticity of the brain. The comprehensive approach towards modifying dysfunctional SN and DMN found in patients with schizophrenia is likely to require a combination of pharmacogenomic testing to inform pharmacotherapy selection and dosing decisions in order to restore the aberrant plasticity of brain networks, together with targeted neurostimulation to trigger network reorganization. However, this approach and the specific mechanisms that influence the complex abnormal interactions between the SN and the DMN are not fully understood and need further investigation.

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ORIGINAL ARTICLE

Basic Study

COVID-19 knowledge, risk perception, and information sources among Chinese population

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Abstract

BACKGROUND

Measures for effective control of the coronavirus disease 2019 (COVID-19) pandemic include identifying the causal organisms, applying appropriate therapies, and developing vaccines, as well as improving understanding among the general public.

AIM

To evaluate the knowledge, awareness, perception, and response of the general public to COVID-19 in China.

METHODS

A detailed questionnaire comprising 47 questions designed in both English and Chinese was developed. The survey was conducted *via* WeChat, a multipurpose messaging, social media, and mobile payment app that is widely used by the Chinese population. In total, 1006 participants responded, and most of them were from different provinces of mainland China.

RESULTS

Overall, this comprehensive survey revealed that the general public in China is highly aware of the basic information concerning COVID-19 and its precautions. Interestingly, more respondents (99.3%) were aware of the term severe acute respiratory syndrome (SARS) than COVID-19 (97.2%) and Middle East respiratory syndrome (MERS) (73.4%). Among them, 2.4%, 1.6%, and 0.9% said that they or their family members or friends were affected by COVID-19, SARS, and MERS,

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respectively. The majority of the respondents (91.2%) indicated that knowledge about COVID-19 was received mainly from WeChat, followed by TV (89%), friends (76.1%), and QQ (a Chinese instant messaging software service) (57.7%).

CONCLUSION

The general public in China is highly aware of COVID-19 and the necessary precautions. Unexpectedly, 2.8% of the participants were unaware of the current epidemic. The remaining information gaps highlight the necessity of further enhancing awareness and preparedness.

Key Words: COVID-19; Knowledge; WeChat; China; Pandemic; Knowledge

Core Tip: This study comprehensively evaluated the knowledge, awareness, and perceptions about coronavirus disease 2019 (COVID-19) among the general Chinese population. Overall, the general public is well aware of the COVID-19 epidemic, knows what COVID-19 is, and is familiar with the precautionary measures. Strikingly, this survey indicated that 2.8% of the participants in China were unaware of the current COVID-19 epidemic.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is now affecting the global population[1]. In addition to significant losses in terms of morbidity and mortality, COVID-19 has imposed major negative impacts on society and the economy in various aspects. COVID-19 was initially sparked in Wuhan, the capital of Hubei Province, and subsequently spread to the entire province and other parts of China, and eventually to the rest of the world[2]. Measures for effective control of outbreaks include identifying the causal organisms, applying appropriate therapies, and developing vaccines, as well as promoting understanding among the general public.

Syndemics is a group of interlinked health issues associated with two or more conditions that interact synergistically and cause an increased disease burden in the population. At this moment, COVID-19 and an array of noncommunicable diseases interact on a social and economic background, which exacerbates its adverse effects[3]. Strict guidelines with specific emphasis on protective measures such as city lockdowns, travel bans, and within-population quarantines were developed by the authorities for controlling the pandemic. As these measures lead to physical inactivity, they also had an adverse impact on health, such as promoting obesity, premature ageing, cardiovascular vulnerability, bone loss, muscle atrophy, decreased aerobic capacity[4], and psychological issues[5-8]. Physical activity is vital for public health[6], as it acts on the cardiovascular and respiratory systems[7].

Furthermore, the effectiveness of epidemic control implementations relies substantially on the support and cooperation of the public. Thus, awareness and knowledge about the epidemic are essential[9-11]. Despite the experience of the SARS outbreak in 2003 in China, the early response to the COVID-19 outbreak was inadequate from both the Chinese authorities and the general public[12]. Subsequent implementation of strict control measures by the authorities with strong support and cooperation from the public finally resulted in the control of COVID-19 in China. However, COVID-19 has grown into a pandemic and may become endemic[13]. Knowledge gaps always exist about disease epidemics, their potential risks, and the clinical spectrum[13]. Thus, we designed and conducted this survey to evaluate the knowledge, awareness, perception, and response of the general public to COVID-19 in China.

MATERIALS AND METHODS

Study design and participants

A detailed questionnaire comprising 47 questions related to COVID-19 with some questions about SARS and Middle East respiratory syndrome (MERS)[14-16] was designed in both English and Chinese. The survey was conducted *via* WeChat, a Chinese multipurpose messaging, social media, and mobile payment app. It is widely used in China, with monthly active users estimated at one billion.

Knowledge about COVID-19, MERS, and SARS was assessed with questions about whether they had heard about these infections, whether they or their family members or friends had been infected, whether they knew what COVID-19 is and knew its causes, whether they knew the zoonotic origin of the infection, whether they ever ate civet or other wild animals, and whether they knew about the death rate from COVID-19. The participants were assessed regarding COVID-19 risks and associated factors along with their knowledge of possible control measures to avoid the infection. The participants were also asked about general signs and symptoms of the disease and from where they obtained information regarding this infection.

Statistical analysis

Descriptive and inferential statistics were calculated using SPSS version 20.0 for Windows (SPSS Inc., Chicago IL, United States). Awareness and knowledge about COVID-19, SARS, MERS, and related factors are shown as percentage values. All independent variables were divided into two or more categories. Variables that were statistically significant in the univariate analyses were included in the final multivariate logistic regression analysis using SPSS. All statistical tests were two-sided, with a P value < 0.05 considered statistically significant.

RESULTS

The questionnaire was completed from March 11 to 14, 2020. In total, 1006 individuals (aged 18-71 years) from all over China participated in the survey by filling out the questionnaires. The majority of our participants (99.3%) were distributed across 29 provinces of China, with 8.7% from Hubei Province and 0.7% residing outside of China (Supplementary Table 1). Among the respondents, 99.1% were Chinese and 0.9% were foreigners residing in China. Based on ethnicity, 65.4% were Hans and 34.6% were from other Chinese ethnic groups or foreigners. Approximately 63% of participants were female. The detailed sociodemographic characteristics of the participants are presented in Table 1.

Interestingly, more respondents (99.3%) were aware of the term SARS than COVID-19 (97.2%) and MERS (73.4%). Among them, 2.4%, 1.6%, and 0.9% said that they or their family members or friends were affected by COVID-19, SARS, and MERS, respectively. Most of the participants (87.4%) believed that COVID-19 is more dangerous than SARS and MERS, while 47.9% of participants answered that the death rate for COVID-19 patients is less than that of SARS and MERS (Table 2). Approximately 81% of respondents answered that SARS-CoV-2 infection could be transmitted through oral, nasal, and eye routes. Up to 69.7% of people believed that the virus has been transferred from animals to humans and that bats (82.4%) are the reservoir for SARS-CoV-2. The proportion of respondents who had recently consumed wildlife meat was found to be 1.4%. A total of 62.4% of individuals thought that a treatment is available for COVID-19 (Table 2).

This study further revealed that the majority of respondents (46.4%) were experiencing psychological pressure along with economic (19.1%) losses due to the current COVID-19 epidemic in China. A total of 69.4% indicated that they still had not resumed their normal life due to the ongoing epidemic. Unfortunately, 1.5% of people replied that they had lost a loved one due to COVID-19. Furthermore, most of the participants (78%) preferred going in private cars for treatment to hospitals in cases of infection, while 2.2% refused to go to hospitals (Table 2).

Knowledge about the signs and symptoms of COVID-19, such as fever, chills, cough, shortness of breath, and flu, was known by 86.3%, 36.9%, 83.4, 79.0%, and 53.3% of the participants, respectively. However, knowledge about other questions related to the disease incubation period was poor (Table 2). Pearson correlation analysis indicated that the risk of acquiring COVID-19 was negatively associated with general information/knowledge and knowledge about precautionary measures (Supplementary Table 2).

Table 1 Demographic characteristics of participants

Variable	Respondents	Percentage (%)
Sex		
Male	373	37.1
Female	633	62.9
Age, yr		
< 30	524	52.1
31-39	170	16.9
40-49	150	14.9
50-59	98	9.7
> 60	64	6.4
Ethnicity		
Han	658	65.4
Others	348	34.6
Residence		
Rural	372	37.0
Urban	634	63.0
Education		
Middle or less	146	14.5
Undergraduate	724	72.0
Master	88	8.7
PhD	48	4.8
Profession		
Farmer	85	8.4
Teacher	134	13.3
Doctor	73	7.3
Nurse	14	1.4
Government	129	12.8
Private	114	11.3
Students	412	41.0
Business	45	4.5
Marital status		
Married	499	49.6
Unmarried	507	50.4
Monthly income (RMB)		
< 3000	498	49.5
3001-5000	265	26.3
5001-10000	179	17.8
> 10000	64	6.4

Multivariate logistic models indicated that urban-background participants turned out to be significantly (P = 0.006) more informed regarding the death rate due to COVID-19 *vs* SARS and MERS (P = 0.006) (Supplementary Table 3). Knowledge about high death rates in patients with comorbidities was significantly associated with sex (P = 0.012), age (P = 0.001), and ethnicity (P = 0.007) (Supplementary Table 2). On the

Table 2 Positive responses on different questions related to epidemiological and clinical knowledge (total *n* = 1006)

	Numbers (*n*)	Percentage (%)
Do you know about COVID-19	978	97.2
Do you know SARS	999	99.3
Do you know MERS	738	73.4
Have you, your family members, or friends got infected with SARS-CoV-2	24	2.4
Did you or your family or friends got infected with SARS-CoV	16	1.6
Did you or your family or friend got infected MERS-CoV	9	0.9
Is COVID-19 more serious/dangerous than SARS and MERS	879	87.4
Do you know deaths due to COVID-19 are less as compared to SARS and MERS	482	47.9
Do you know SARS-CoV-2 transmitted from animals into humans	827	82.2
Have you eaten Civet ever in your life	12	1.2
Have you and your family members consumed meat of wild animals recently	14	1.4
Do you think early detection and treatment will help COVID-19 patient to recover	962	95.6
Comorbidity increases the risk of death due to SARS-CoV-2 infection	862	85.7
Wearing mask and washing hand with soap and water can minimize the risk of SARS-CoV-2 infection	946	94
Is there a cure for COVID-19	628	62.4
If you are feeling unwell, will you disclose it	993	98.7
Is your community center well furnished with basic medical facilities	610	60.6
Are you back to your routine after COVID-19 outbreak	308	30.6
DO you know SARS-CoV-2 can enter to healthy person *via* all (mouth, nose, and eye)	819	81.4
Source/origin of SARS-CoV-2 infection is animal	701	69.7
Bat is source SARS-CoV-2 infection	829	82.4
COVID-19 affected you psychologically	467	46.4
COVID-19 affected you economically	192	19.1
Are you back to your routine after COVID-19 outbreak (no)	698	69.4
Have you lost family member or friend in COVID-19 outbreak	15	1.5
If you are feeling unwell how will you go to hospital (own car)	785	78.0
If you are feeling unwell you will not go hospital	22	2.2
Signs and symptoms		
Fever	868	86.3
Cough	839	83.4
Chills	371	36.9
Breathing difficulty	795	79.0
Flue like symptoms	538	53.5
All above	480	47.7
Do not know	8	0.8

COVID-19: Coronavirus disease 2019; SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

other hand, information about the protective effects of wearing masks and washing hands with soap for at least 30 s was significantly higher among women (P = 0.007) and rural residents (P = 0.007) (Supplementary Table 3). Chinese people, compared to foreigners (P = 0.024), and farmers, compared to other professions (P = 0.001), were

significantly more satisfied with their community health centre facilities (Supplementary Table 4).

The majority of respondents (91.2%) indicated that information about COVID-19 was received mainly from WeChat, followed by TV (89%), friends (76.1%), and QQ (a Chinese instant messaging software service) (57.7%). Some participants said that they received information related to COVID-19 from newspapers (35.5%), magazines (29.2%), WhatsApp (24.9), and Facebook (24.0%), as shown in Figure 1.

DISCUSSION

Preparing the general population for epidemics or pandemics of infectious diseases is not a static or binary exercise but a dynamic state that is continuously changing[16,17]. Therefore, different states prepare their populations with different methods built on their interpretation of disease outbreak threats and global contracts, such as the International Health Regulations[18].

This study represents a comprehensive survey report about the knowledge, awareness, perception, and response of the general public in China regarding COVID-19. Our results indicate that knowledge and awareness of COVID-19 are high among the general Chinese population. Interestingly, the majority of participants said that WeChat was their main source of information, indicating that valuable information about diseases can be effectively communicated among the general public *via* WeChat in mainland China[19]. Moreover, information dissemination through health departments was surprisingly low (48.1%). As 37% of the participants live in rural areas, these people do not regularly engage with doctors, practitioners, or healthcare officials. This might be the possible cause of their low level of knowledge and awareness about different aspects of COVID-19. Interestingly, WhatsApp and Facebook were not the main sources of information for respondents in mainland China; therefore, information and recommendations regarding COVID-19 and other diseases from international stakeholders such as the World Health Organization should use all possible resources to increase knowledge and awareness among the public.

This study was based on an online questionnaire method; hence, limitations such as recall and social desirability biases cannot be excluded. However, the impact of these biases in this study is difficult to assess, as other similar studies have not been conducted so far. The inclusion of innovative interventional methods with informative evaluation plans to monitor the level of knowledge among the community, respond to their needs, and fill the gaps with better preventive methods would be helpful in prospective research.

CONCLUSION

In summary, this study comprehensively evaluated knowledge, awareness, and perceptions about COVID-19 among the general Chinese population. The overall knowledge, awareness, and attitudes about the disease are at a high level, but strikingly, 2.8% of the participants in China were unaware of the current COVID-19 pandemic, which is unexpected. Therefore, we emphasize the importance of initiating health promotion programs to educate the public and healthcare workers about infectious diseases in general for better preparedness for future epidemics and pandemics.

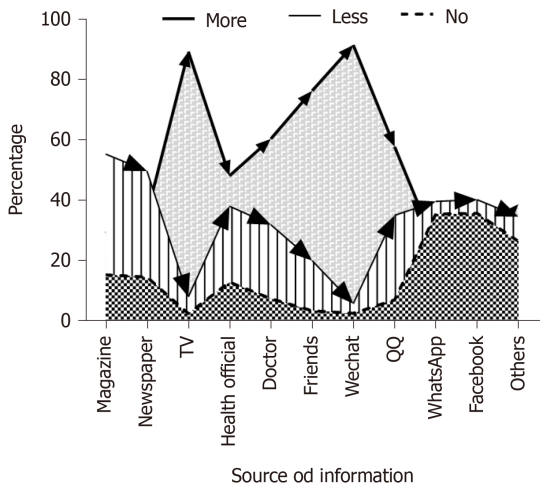

Figure 1 Source of information (little, much, and no) about coronavirus disease 2019. WeChat is a Chinese multi-purpose messaging, social media and mobile payment app. QQ is a Chinese instant messaging software service and web portal. WhatsApp is an American freeware, cross-platform messaging and voice service. Users can send text and voice messages, make voice and video calls, and share images, documents and other media. Facebook is an American online social media and social networking service.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) was initially sparked in Wuhan, the capital of Hubei Province, and subsequently spread to the entire province and other parts of China, and then around the globe. Measures for effective control of outbreaks include identifying the causal organisms, applying appropriate therapies, and developing vaccines, as well as improving understanding among the general public.

Research motivation

COVID-19 has grown into a pandemic and may become endemic. Knowledge gaps always exist about disease epidemics, their potential risks, and the clinical spectrum.

Research objectives

We designed and conducted this survey to evaluate the knowledge, awareness, perception, and response of the general public to COVID-19 in China.

Research methods

A detailed questionnaire comprising 47 questions designed in both English and Chinese was developed. The survey was conducted *via* WeChat, a multipurpose messaging, social media, and mobile payment app that is widely used by the Chinese population. In total, 1006 participants responded from different provinces in mainland China.

Research results

Overall, this comprehensive survey revealed that the general public in China is highly aware of the basic information concerning COVID-19 and the necessary precautions. Interestingly, more respondents were aware of the term severe acute respiratory syndrome than COVID-19 and Middle East respiratory syndrome. The majority of the respondents indicated that knowledge about COVID-19 was received mainly from WeChat, followed by TV, friends, and QQ (a Chinese instant messaging software service).

Research conclusions

We comprehensively evaluated the knowledge, awareness, and perceptions about COVID-19 among the general Chinese population. The overall knowledge, awareness, and attitudes about the disease are at a high level, but strikingly, 2.8% of the participants in China were unaware of the current COVID-19 pandemic, which is unexpected.

Research perspectives

We emphasize the importance of initiating health promotion programs to educate the public and healthcare workers about infectious diseases in general for better preparedness for future epidemics and pandemics.

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SYSTEMATIC REVIEWS

Uncertainty following an inconclusive result from the BRCA1/2 genetic test: A review about psychological outcomes

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Abstract

BACKGROUND

An inconclusive result from BRCA1/2 genetic testing indicates that a genetic variant of uncertain significance is detected. This case constitutes the majority of genetic test results, but studies specifically addressing the psychological adjustment of people with inconclusive results are scarce.

AIM

To examine psychological outcomes of receiving an uninformative BRCA1/2 test result.

METHODS

PubMed, PsychInfo, and Cochrane Central Register of Controlled Trials were screened for studies focusing on distress, anxiety, and depression levels in individuals with inconclusive genetic test results. This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method.

RESULTS

Studies on psychological outcomes of inconclusive BRCA1/2 focused on general and specific distress, anxiety, and depression. Overall, they produced mixed results. These inconsistent findings are probably due to the uncertainty caused by this type of result, that may also influence the decisions of individuals about surveillance and prophylactic options, reducing their compliance. In addition, this review highlights specific risk and protective factors that affect psychological adjustment in individuals with an inconclusive genetic testing result.

CONCLUSION

Individuals with inconclusive genetic test results need specific educational programs and support to better understand the meaning of their results in order

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to be able to make decisions about surveillance and prophylactic options.

Key Words: Genetic testing; BRCA1/2 mutation; Inconclusive result; Psychological distress; Depression; Anxiety; Review

Core Tip: Undergoing BRCA1/2 genetic testing can produce a significant psycho-social impact. The possible test results are positive (increased risk of developing cancer), negative (the same probability of developing cancer as the general population), or inconclusive. This last outcome produces a more complex situation, as it means that a deleterious mutation is neither identified nor definitively excluded. Though the inconclusive case constitutes most genetic test results, studies specifically addressing psychological adjustment of people with such a result are scarce. The current review aims to address this gap, highlighting psychological outcomes following this kind of result and highlighting specific risk and protective factors.

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INTRODUCTION

In the context of breast and ovarian cancer surveillance, genetic screening for the detection of mutations in *BRCA1* (chromosome 13) and *BRCA2* (chromosome 17) genes is a significant advance in cancer care. Each individual carries these two genes, which are responsible for the control and repair of DNA alterations; however, in their mutated form, they are linked to an increased risk of tumor development[1]. These genes are characterized by autosomal dominant inheritance, so one parent has a 50% chance of transmitting them to their children[1,2]. The lifetime risk of developing breast cancer in the general population ranges from 10%-14%, and this risk rises to 85% in women who carry a mutation in the *BRCA1* and *BRCA2* genes[2,3].

For individuals with high cancer history, genetic counselling is proposed. Medical and family histories are collected, and if there is at least 10% likelihood, a buccal smear or a blood sample is taken. The possible test results are positive, negative, or inconclusive[4]. The first one implies that the individual is a carrier of a mutation with an increased risk of developing cancer during his life. A negative result means that the individual is not a carrier of mutation, so he has the same probability of developing cancer as the general population. An inconclusive result produces a more complex situation, as it means that a deleterious mutation is neither identified nor definitively excluded. This may be due to two main reasons: (1) No known BRCA1/2 mutations were found, but a genetic variant of uncertain significance is detected; and (2) Not detecting a mutation in a cancer-affected person who is the first member tested (proband) in a high-risk family[5,6]. In the current review we indistinctly use the terms "inconclusive" and "uninformative" to refer to both the aforementioned situations. Though the inconclusive case constitutes the majority of genetic test results[1,7], research and clinical attention is lacking in this topic, as stated by several authors[5,8].

Undergoing genetic testing and its results can produce a significant psycho-social impact[2,9]. Generally, individual who receives a positive test result reports higher levels of distress, anxiety, and depression[10] while who receives a negative test result reports a decrease in distress levels following the discovery of test results[11]. A recent review of existing literature[12] highlighted that a positive genetic testing results can be traumatic, although not all individuals with such a result experience increased distress. The high distress levels experienced by individuals who receive a positive test results may depend by an increased risk of future diseases and the implications for their whole family[12]. A study highlighted that a possible factor that influences affective states is the perceived risk of developing cancer, regardless of test result[13].

Overall, higher levels of distress, anxiety and depression could depend by some risk factors as having a cancer diagnosis, having a greater history of breast/ovarian cancer, being younger than 40 years old, being unmarried and having high pre-test levels of anxiety and depression[12].

As for those who receive an inconclusive result, the literature is conflictual; some studies identify higher levels of distress in those with an inconclusive result[14] while other studies found that individuals who receive an inconclusive result seem reassured[15]. However, as stated by several authors[12,16], studies specifically addressing psychological adjustment of people with inconclusive genetic test results are scarce. According to Vadaparampil *et al*[8], this gap should be filled, as the topic of inconclusive test results is a key topic deserving clinical and research attention.

Starting from these premises, the main purpose of the current review was to investigate short-, intermediate-, and long-term consequences of receiving uninformative BRCA1/2 test results. To pursue this aim, we analyzed cross-sectional and longitudinal studies which examined anxiety, depression and distress in individuals who receive inconclusive results compared to positive and negative results. In addition, we aimed to highlight risk and protective factors that affect psychological adjustment in individuals with an inconclusive genetic testing result, also considering differences associated with being or not affected by a cancer diagnosis.

MATERIALS AND METHODS

Identification and selection of studies

This systematic review followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analyses[17].

We conducted a comprehensive literature search in PubMed, PsychInfo, and Cochrane Central Register of Controlled Trials. All search results were limited to the last 21 years (1999-2020).

We combined search terms related to genetic counselling and its result [(Genetic*, Familial*, OR Mutation*) and (Inconclusive OR Uncertain) and (Breast* OR BRCA*)] with terms relating to psychological outcomes (Psycho*, Distress, Emot*, Anxiety, OR Depression). The reference sections of previous reviews were also checked to ensure that all relevant studies for this review were included.

Selection of eligible articles

Studies were included if they: Analyzed psychological outcomes of receiving an uncertain result; included adult, human subjects; and were written in the English language.

Exclusion criteria were: Articles not specific to BRCA mutation; articles not reporting psychological outcomes; articles that assessed the impacts of genetic counselling before subjects received genetic test results; and literature reviews, qualitative studies, commentaries, letters to the editor, unpublished articles and doctoral theses, abstracts of conferences, congresses, books, and case-reports.

Following the review by Hamilton *et al*[18], we defined short-term as within 1 mo of genetic testing results, intermediate term between 1 and 6 mo, and long-term over 6 mo.

The eligibility criteria were evaluated according to the following aspects: Participants, intervention, comparison, outcome, and study design. (1) Participants: Human adult participants receiving an uncertain result from genetic testing about the presence of BRCA mutation; (2) Intervention: The focus was not limited on a specific intervention; (3) Comparison: Studies comparing people with inconclusive genetic test results to positive and negative results; (4) Outcomes: We analyzed studies that considered short- (1 mo), intermediate- (1-6 mo), and long- (6+ mo) term psychological outcomes (*i.e.*, general and specific distress, anxiety, and depression); and (5) Study design: We included observational and/or quantitative studies.

Anxiety, depression, and distress (both general and specific) have been the focus of the review as they were the outcome measures most frequently evaluated.

RESULTS

A total of 341 studies were identified; of those, 174 were removed as duplicates. The

titles of the selected studies were double screened by two authors independently, 66 studies were excluded because they were not consistent with the eligibility criteria. The abstract of 101 selected studies and the full text of all potentially relevant articles were double screened and evaluated by two authors independently; discrepancies were resolved by discussion; the following were excluded: 11 were reviews, 46 did not focus on psychological variables, 23 studies involved a sample with a different genetic mutation from BRCA or did not focus on inconclusive results, and 11 had an inadequate study design (qualitative studies, unpublished articles, case-reports, books or abstracts of congresses). A total of 10 articles met our inclusion criteria and were, therefore, considered in this systematic review (Figure 1). Included studies were published between 2002-2017 and were most commonly conducted in the United States, followed by Canada and the United Kingdom. Eight studies were longitudinal (80%) and two were cross-sectional (20%). All the included studies were classified on the basis of the timing of questionnaire administration; most studies (n = 7) assessed also baseline levels of psychological measures before the blood test or buccal smear test.

Only one study considered exclusively short-term psychological outcomes, four studies only intermediate-term, and three studies long-term (Table 1). Sample sizes from the reviewed studies ranged from 48 to 465 (mean = 193.30, standard deviation = 135.14), resulting in a total of 1933 participants. Of these, 38% (n = 730) received inconclusive test results, 32% (n = 620) received negative results, 21% (n = 408) received positive results, 7% (n = 126) decided not to undergo genetic testing, and 2% (n = 49) were still waiting for their test results. Only two studies included male participants; the sample was predominantly female (98%).

Of the reviewed articles, six studies compared people with and without a cancer history. The majority of the sample (73%) had a cancer diagnosis. Only four studies reported the type of cancer diagnosis; of these, 94% had breast cancer, 4% had ovarian cancer, and 2% had both.

Outcome measures of the included studies

The findings were divided into four categories: (1) General distress; (2) Anxiety; (3) Depression; and (4) Genetic testing-specific distress. The tools used for the evaluation of each construct are synthesised in Table 2.

The Brief Symptoms Inventory (BSI)[19-22], the Symptom Checklist 90 Revised (SCL-90)[23-25], the Impact of Event Scale[26,27], the General Health Questionnaire[28,29], and the Hopkins Symptom Checklist[30,31] were used to assess general distress symptoms. Depressive symptoms were assessed using the BSI[6,19,20], the SCL-90[23,24], the Hospital Anxiety and Depression Scale (HADS)[29,32], and the Center for Epidemiologic Studies Depression Scale[25,33].

The BSI[6,19,20], the SCL-90[23,24], the HADS[29,32], and the State Trait Anxiety Invento-ry[25,34] evaluated anxiety symptoms.

Finally, genetic testing-specific distress was evaluated by means of the Multidimensional Impact of Cancer Risk Assessment[6,20,27,35,36].

General distress

The majority of the reviewed studies did not find significant differences in psychological adjustment among individuals who received inconclusive, positive and negative results[22,24,25,29,31]. One study observed higher levels of distress, especially on the somatization scale, in those who received inconclusive results compared with positive and negative results, and people deciding not to undergo genetic testing[21]. Instead, a recent study of Lumish *et al*[27] highlighted that individuals receiving an inconclusive result reported intermediate levels of general distress, higher than negative but lower than positive result.

Schwartz *et al*[31] did not find increased levels of distress in people with inconclusive results compared to positive and negative results, but they did not identify a decrease in distress levels in the intermediate-term (*i.e.*, 1-6 mo) in individuals with inconclusive results, which occurs in those who receive negative results. Two studies found that general distress decreased slightly over time, from pre-test to 6 mo post-test[20,25]. Other studies reported that there were no differences in distress levels from pre-test levels up to 6 mo after genetic test disclosure[22,29].

Regarding differences between cancer affected patients and unaffected patients, overall, unaffected patients with positive or inconclusive results reported higher levels of distress compared to both affected patients and unaffected patients with negative results[27]. Other studies highlighted that having had a cancer diagnosis did not influence distress levels; in fact, they did not detect differences between affected and unaffected patients[21,22,25].

Table 1 Time of psychological outcome measures after genetic test disclosure

Ref.	Average months after genetic test disclosure		
	≤ 1 m	Between 1 and 6 mo	More than 6 mo
Bish *et al*[29], 2002[1]	Y	Y	
Claes *et al*[24], 2004[1]			Y
Graves *et al*[36], 2012[1]			Y
Lumish *et al*[27], 2017			Y
Manne *et al*[22], 2004[1]		Y	
O'Neill *et al*[20], 2006[1]		Y	
O'Neill *et al*[6], 2009		Y	Y
Power *et al*[21], 2011	Y		
Schwartz *et al*[31], 2002[1]		Y	
Smith *et al*[25], 2008[1]	Y	Y	

[1]Studies that assessed also baseline levels of general distress, anxiety, depression and genetic test specific distress (*i.e.*, before genetic test disclosure).
Y: Yes.

In addition to genetic test results, other factors which could increase distress levels in those who receive an inconclusive result may be a cancer diagnosis[27], higher distress levels before genetic testing[25], the intolerance of uncertainty[20], and cancer-related distress[20].

However, there are also some protective factors that could mitigate or decrease distress levels such as marital status[20], partner support, and protective buffering[21].

Anxiety

None of the reviewed studies found differences in anxiety levels among individuals with inconclusive, positive and negative results[24,25,29] except for one study that found that patients with inconclusive results reported higher levels of anxious symptoms after test result disclosure than negative ones[6].

Some studies observed anxious symptoms in the intermediate-term[25] and long-term[6,29]. Two studies of these did not find changes in anxiety levels in the intermediate-term[25,29], while O'Neill *et al*[6] detected a decrease in anxiety over time for individuals who received negative test result and stable levels of anxiety in those who received inconclusive results from the discovery of the test result up to 6 mo later, with a subsequent decrease.

Only one of the reviewed articles that focused on anxiety investigated whether there were differences among affected and unaffected patients and found that there were no differences between them[25].

Overall, some factors that could influence anxiety levels in individuals who receive an inconclusive test results, might be: Higher distress levels before genetic testing[25], higher pre-testing anxiety[6], correctly interpreting the meaning of the genetic test result[24,29], primary appraisal, namely the way people evaluate the importance of a stressful situation[6], and ethnicity[6].

Depression

Four of the included studies focused on depression[6,24,25,29]. The majority of the reviewed studies did not identify differences between those receiving inconclusive, positive and negative results[24,25,29].

Two studies did not identify effects of time on depression in the intermediate-term[25,29]. Only one study analyzed long-term outcomes (6 mo), highlighting that depressive levels were significantly higher in individuals receiving inconclusive results compared to negative[6].

Having received a cancer diagnosis did not influence depressive levels, regardless of the test results[25]. Other factors could influence depressive levels among individuals who receive an inconclusive test result: Misinterpretation of test results[24,29], pre-test depressive levels[6,25], primary appraisal[6], and ethnicity[6].

Table 2 Characteristics of included studies

Ref.	C country	AAim	Study design	Psychological measurements	Sample size and gene mutation status	Personal cancer history
Bish *et al* [29], 2002	United Kingdom	Examine the effects of an uncertain test results affects mood and behavior	Longitudinal	HADS; IES; GHQ-28; Cancer Worry Scale	Total sample = 48. Positive = 0. Negative = 0. Inconclusive = 48	History = 48. No history = 0
Claes *et al*[24], 2004	United States	Evaluate the impact of a genetic test result	Retrospective	IES; STAI; SCL-90; UCL; Semi structured-interview	Total sample = 48. Positive = 18. Negative = 6. Inconclusive = 24	History = 48. No history = 0
Graves *et al*[36], 2012	United States	Evaluate the long-term psychosocial impact of the genetic test result	Longitudinal	IES; STAI; BSI; PSS; MICRA	Total sample = 465. Positive = 144. Negative = 60. Inconclusive = 261	History = 390. No history = 75
Lumish *et al*[27], 2017	United States	Investigate the psychological outcomes of people who undergoing genetic test	Cross-sectional	IES; MICRA; SWD; AT-20	Total sample = 232. Positive = 25. Negative = 173. Inconclusive = 34	History = 129. No history = 103
Manne *et al*[22], 2004	United States	Evaluate the distress related to undergoing the genetic test	Longitudinal	IES; BSI; Discussion about testing; Sharing of concerns; Comfort sharing concerns; Protective Buffering; Relationship strain; Support/encouragement for testing; Perceived negative partner behaviors.	Total sample = 144. Positive = 38. Negative = 15. Inconclusive = 91	History = 115. No history = 29
O'Neill *et al*[20], 2006	United States	Explore psychological consequence and the tolerance of uncertain in women who receive an inconclusive test result	Longitudinal	IES; BSI; MICRA; IUS	Total sample = 64. Positive = 0. Negative = 0. Inconclusive = 64	History = 64. No history = 0
O'Neill *et al*[6], 2009	United States	Assess differences in distress levels over time	Longitudinal	IES; BSI; MICRA	Total sample = 209. Positive = 0. Negative = 190. Inconclusive = 19	History = 209. No history = 0
Power *et al*[21], 2011	Canada	Examine levels of distress in people undergoing genetic test	Cross-sectional	History Questionnaire; Feelings about Test Results Measure; Psychosocial Needs Questions; BSI-18	Total sample = 318. Positive = 85. Negative = 51. Inconclusive = 33. Attending result = 49. Not undergo genetic test = 100	History =160. No history = 158
Schwartz *et al*[31], 2002	United States	Examine the long-term psychological impact of receiving BRCA 1/2 test result	Longitudinal	IES; HSCL-25	Total sample = 279. Positive = 78. Negative = 58. Inconclusive = 143	History = 186. No history = 93
Smith *et al*[25], 2008	United States	Evaluate psychological consequences of genetic test results	Longitudinal	GSI; IES; PSS; STAI; CES-D; QoLS	Total sample = 126. Positive = 20. Negative = 67. Inconclusive = 13. Not undergo genetic test = 26	History = 58. No history = 68

HADS: Hospital Anxiety and Depression Scale; QoLS: Quality of Life Scale; CES-D: Center for Epidemiologic Studies Depression Scale; STAI: State-Trait Anxiety Inventory; IES: Impact of Event Scale; MICRA: Multidimensional Impact of Cancer Risk Assessment; UCL: Utrecht Coping List; SCL-90: Symptom Checklist-90; BSI: Brief Symptom Inventory; BSI-18: Brief Symptom Inventory-18; GSI: Global Severity Index; PSS: Perceived Stress Scale; SWD: Satisfaction with Decision Instrument; AT-20: Revised Scale for Ambiguity Tolerance; IUS: Intolerance of Uncertain; HSCL-25: Hopkins Symptom Checklist-25; GHQ-28: General Health Questionnaire-28.

Genetic testing-specific distress

Four of the included studies focused on genetic testing-specific distress[6,20,27,36], which was assessed only after genetic test disclosure. All the reviewed studies measured specific distress in the long-term[6,27,36] except for one study that assessed it in the intermediate-term[20].

Two studies found that inconclusive results were associated with lower levels of genetic testing-specific distress than positive test results[27,36] but higher than negative results[27,36].

Higher levels of genetic testing-specific distress were observed from 1-6 mo and 1 year after genetic test disclosure[6,20,36]; specifically, individuals with inconclusive

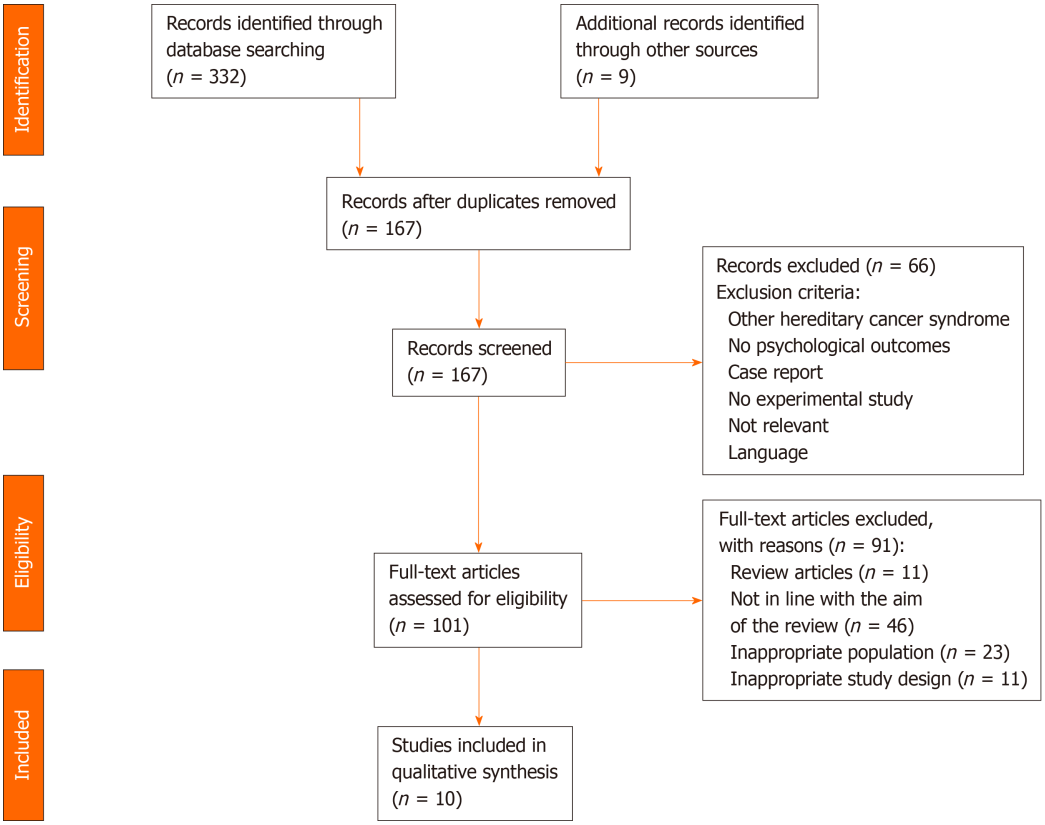

Figure 1 Flow chart of selection and inclusion process, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

results reported higher levels of specific distress persisting even 1 year after test disclosure[6]. O'Neill *et al*[6] detected that distress levels among inconclusive results stayed stable over time and decreased among negative results.

Individuals affected by cancer who receive inconclusive results showed higher levels of distress related to genetic testing than unaffected individuals with inconclusive results, affected carriers, and both affected and unaffected non-carriers[27]. On the contrary, Graves *et al*[36] identified that mutation carriers with a cancer diagnosis had higher levels of distress than affected individuals with uncertain results.

In general, some potential risk factors that could influence genetic testing-specific distress in individuals who receive an inconclusive result are higher pre-test perceived risk[6,20], lower education level[27,36], younger age[27,36], ethnicity[6,36], lower genetic knowledge[27], coping with uncertainty[20], confusion regarding the interpretation of test results[27], pre-test distress[6,36], pre-test anxiety[36], and stronger levels of primary appraisal[6]. Some protective factors, such as being married[36] and stronger secondary appraisal[6], can reduce distress related to genetic testing.

DISCUSSION

The main purpose of the current review was to investigate the consequences of receiving inconclusive results from BRCA1/2 genetic testing on psychological outcomes such as general distress, anxiety, depression, and genetic testing-specific distress. To our knowledge, our review is the first to explore the short-, intermediate-, and long-term psychological effects of receiving inconclusive results in both affected and unaffected patients, as previous reviews were mainly based on individuals who receive a positive or a negative result[12,13,37]. From the analysis of the selected articles, overall different results were found.

Most studies (five of the ten considered) did not report differences in levels of general distress, anxiety, and depression among individuals with inconclusive results, as compared with both positive and negative results[22,24,25,29,31]. Other studies

have found that those who receive inconclusive results experience higher levels of general and specific distress, anxiety, and depression than who have a negative result[6,27,36], but lower than positive ones[27,36]; and finally, a study identified that the inconclusive results caused greater levels of general distress when compared with both positive and negative results[21].

The differences detected from the reviewed studies might depend on the different tools used to assess distress, anxiety, and depression, which might not be sufficiently sensitive in this field[12]. As evidenced by a study by Power *et al*[21], individuals with an uninformative BRCA1/2 test result reported higher levels of distress, specifically in the somatization scale, so it could be that this subgroup of patients experienced distress through the body. Hence, it could be useful to develop more sensible tools, specifically addressing this field.

Although no differences were found between negative and inconclusive results, there was no decrease over time in the levels of distress, anxiety, or depression, which instead occurred in individuals with a negative result[6,31]. A possible explanation for these results might be the lack of relief from this type of test result[16] and having to copy with the uncertainty[21,24,29,38,39]. Indeed, individuals who have difficulty in coping with uncertainty have higher levels of ongoing distress[20]. The uncertainty related to this type of result also influences the decisions of individuals about surveillance and prophylactic options; only a fraction of patients who receive this type of result decides to increase cancer screening[27]. Moreover, some patients determine not to carry out preventive surgery, as they need a more certain result before deciding on this irreversible option[24], from which psychological benefits might be derived due to the cancer risk decrease[40], or it can also lead to adverse psychological impacts and dissatisfaction[41-43]. Graves *et al*[36] identified that having prophylactic surgery does not reduce distress levels but only the perceived risk of developing cancer.

Two studies showed that individuals with a cancer diagnosis have greater levels of distress, anxiety, and depression than those without a previous cancer diagnosis[27,36]; in the group of affected people, being mutation carriers[36] or having received an inconclusive result[27] were associated with a worse psychological adjustment. Patients with a recent cancer diagnosis could represent a population more vulnerable to higher levels of distress, anxiety, and depression due to the impact of the diagnosis and its treatment[44,45]. Other studies did not find differences between affected and unaffected patients[20,25,31]. A possible explanation for these inconsistent results could be the psychological benefit that affected patients derived from genetic testing[12,37], because medical surveillance protocols make the process predictable and understandable[37]. Due to this, affected patients and individuals who receive a positive test result might be better able to cope with this situation than individuals who have to cope with the uncertainty[20,46,47].

Apart from having had a cancer diagnosis[27,36], other factors that influence the psychological outcomes related to genetic test disclosure also emerged from the current review. Among the major risk factors are: Higher pre-test levels of distress and anxiety[6,24,25,31], younger age[6,22,27,36], correctly interpreting the meaning of the test result[24,29], intolerance of uncertainty[20], use of the primary appraisal[6], higher perceived risk before genetic testing[6,20], having a family history of cancer[25,36], lower education level[27,36], lower genetic knowledge[27], having children[36], lower income[36], and belonging to a minority ethnicity[6]. Regarding appraisal, it consists in the evaluation of the relevance of a stressful event such as genetic testing and/or cancer diagnosis[48,49]. Some studies have shown that different coping and evaluation strategies influence distress and stress levels; using a higher primary appraisal and emotional suppression are associated with higher levels[50,51], while increased use of secondary appraisal and cognitive reappraisal are associated with better psychological outcomes[50,52].

In addition to secondary appraisal and cognitive reappraisal, other factors could decrease distress levels such as being married[20,36], having partner support[22], having a bilateral salpingo-oophorectomy[36], and protective buffering[22].

This review revealed that those who receive inconclusive results are a subgroup of patients who need educational programs and more pre-test information to better understand the meaning of their test so they can make decisions about surveillance and prophylactic options.

This literature review has some limitations. First, only a few studies were included in this review because the majority of studies focus on the psychological outcomes of those who receive positive or negative results, although inconclusive results are the most common[1,7]. Another limitation is that the studies we analyzed included different standardized measures concerning distress, anxiety, and depression. It could be that these standardized tools are not sufficiently sensitive in this field and that those

who receive positive, negative, and inconclusive results experience emotional distress differently. Moreover, the sample is unbalanced, as some studies exclusively include patients affected by a cancer diagnosis, a factor that contributes to experiencing higher levels of distress, anxiety, and depression. Finally, there was high variability between the time elapsed from the genetic test to the administration of the psychological questionnaires among the reviewed articles, and not all the reviewed studies administered the questionnaires at the same time to all patients. These limitations lead us not to generalize our results.

CONCLUSION

The results of this systematic review give a fuller picture of the psychological impact of receiving inconclusive results and can help genetic counsellors, health professionals, and researchers to provide more support to this subgroup of patients, by providing adequate information about the meaning of inconclusive genetic test result and its implications in terms of risk to develop cancer. The present review could also be able to improve the knowledge of experiences related to coping with uncertainty, suggesting which are the psychological aspects to consider when working with this type of patients. There is still much to understand in this difficult context, and it is necessary to take into greater consideration those who receive inconclusive results in the research and pre-test and post-test educational program to fully explain to people that inconclusive results do not exclude the possibility that they still might face a higher risk of developing ovarian or breast cancer. These considerations are required in health care contexts to provide adequate psychosocial support for people undergoing genetic testing.

ARTICLE HIGHLIGHTS

Research background

The majority of BRCA1/2 genetic test consists of an inconclusive result, which produces a complex situation, as it means that a deleterious mutation is neither identified nor definitively excluded.

Research motivation

Studies specifically focusing on the psychological adjustment of people with inconclusive results are scarce and a systematic review on this topic is missing.

Research objectives

The principal purpose of this review was to examine short-, intermediate-, and long-term psychological outcomes of receiving an uninformative BRCA1/2 test result, with regard to distress (both general and genetic testing-specific), anxiety, and depressive levels. A further purpose was to highlight risk and protective factors affecting psychological adjustment in individuals with an inconclusive genetic testing result, also considering differences associated with being or not affected by a cancer diagnosis.

Research methods

The guidelines of Preferred Reporting Items for Systematic Review and Meta-Analyses were followed in the current review. A comprehensive literature search in PubMed, PsychInfo, and Cochrane Central Register of Controlled Trials was carried out. Search results referred to the last 21 years (1999-2020).

Research results

Studies on psychological outcomes of inconclusive BRCA1/2 focused on general and specific distress, anxiety, and depression. Overall, they produced mixed results. These inconsistent findings are probably due to the uncertainty caused by this type of result, that may also influence the decisions of individuals about surveillance and prophylactic options, reducing their compliance. In addition, this review highlights specific risk and protective factors that affect psychological adjustment in individuals with an inconclusive genetic testing result.

Research conclusions

This review highlights that individuals who receive an inconclusive result are a subgroup of patients who need educational programs and more pre-test information to better understand the meaning of their test in order to make adequate decisions about surveillance and prophylactic options.

Research perspectives

Overall, the current review highlights the importance to address two main issues in this field: From a research perspective, it is recommended the development of tools more sensible to detect the psychological outcomes of inconclusive BRCA1/2 genetic test results; from a clinical perspective, health professionals and genetic counsellors should provide more psychoeducational support to this subgroup of patients about the meaning and the management of the uncertainty associated with their condition.

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