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Neuroinflammation and cytokine abnormality in major depression: Cause or consequence in that illness?

Sang Won Jeon, Yong Ku Kim

Sang Won Jeon, Yong Ku Kim, Department of Psychiatry, College of Medicine, Korea University, Ansan Hospital, Seoul 02841, South Korea

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 Telephone: +82-31-4125140
 Fax: +82-31-4124930

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Abstract

Depression results from changes in the central nervous system (CNS) that may result from immunological abnor-

malities. The immune system affects the CNS through cytokines, which regulate brain activities and emotions. Cytokines affect two biological systems that are most associated with the pathophysiology of depression: The hypothalamic-pituitary-adrenal axis and the catecholamine/sympathetic nervous system. Neuroinflammation and cytokines affect the brain signal patterns involved in the psychopathology of depression and the mechanisms of antidepressants, and they are associated with neurogenesis and neural plasticity. These observations suggest that neuroinflammation and cytokines might cause and/or maintain depression, and that they might be useful in the diagnosis and prognosis of depression. This psychoneuroimmunologic perspective might compensate for some of the limitations of the monoamine theory by suggesting that depression is a result of a failure to adapt to stress and that inflammatory responses and cytokines are involved in this process. In this review, the interactions of cytokines with the CNS, neuroendocrine system, neurotransmitters, neurodegeneration/neurogenesis, and antidepressants are discussed. The roles of cytokines in the etiology and psychopathology of depression are examined. The use of cytokine inhibitors or anti-inflammatory drugs in depression treatment is explored. Finally, the significance and limitations of the cytokine hypothesis are discussed.

Key words: Depression; Neurogenesis; Antidepressant; Cytokine; Neuroinflammation; Psychoneuroimmunology; Neuroendocrine; Neurotransmitter

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Core tip: We investigated the etiology and the pathogenesis of depression regarding the cytokine network. It was concluded that depression may be caused by neuroinflammation and cytokine imbalances, which are closely connected with the central nerve system, hypothalamic-pituitary-adrenal axis, neurotransmitter, autonomic nerve system, neural plasticity, and antidepressants.

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INTRODUCTION

Severe psychological and/or physical stress can result in homeostatic imbalances and abnormal immune responses. Several hypotheses have proposed that immunologic imbalances affect the central nervous system (CNS) and result in psychopathology. Depression is a disease that is associated with changes in the CNS that might be caused by immunological abnormalities. Recent clinical and experimental studies have confirmed that internal and external stress significantly affects the expression of depressive symptoms and their persistence in vulnerable individuals with immunological abnormalities^[1]. Moreover, cytokines affect the activity of the two biological systems that are most associated with the pathophysiology of depression: The hypothalamic-pituitary-adrenal (HPA) axis and the catecholamine/sympathetic nervous system^[2].

The CNS affects the immune system through the autonomic nervous system and the neuroendocrine system. Reciprocally, the immune system affects the CNS through cytokines secreted by immune cells that regulate brain activities and emotions^[3]. Thus, the immune system can be regarded as a sensory organ that recognizes internal or external stress. Stress can trigger overall changes in the immune system, neurotransmitters, neuroendocrine system, and CNS, and their interactions contribute to the expression, continuation, and termination of depressive symptoms.

This psychoneuroimmunologic perspective suggests that depression is mediated by inflammatory responses and cytokines, and that the disease results from a failure to adapt to stress. This view might compensate for some of the limitations of the monoamine theory, which is an important psychopathologic model of depression.

In this review, the interactions of cytokines with the CNS, neuroendocrine system, neurotransmitters, neurogenesis, and antidepressants are investigated. The roles of cytokines in the etiology and psychopathology of depression are examined. In addition, the use of cytokine inhibitors and anti-inflammatory drugs in the treatment of depression are explored, and the significance and limitations of the cytokine hypothesis are discussed.

CYTOKINE SYSTEM

Peripheral and central cytokines and neuroimmune circuits

Cytokines mediate signaling among immune cells. They activate or inhibit other immune cells, which results in a complicated circuit. Cytokines act on cell membrane

receptors like neurotransmitters or on intracellular receptors like hormones to transmit information to cells. They are mainly secreted from monocytes (or macrophages) or lymphocytes as well as from brain cells, such as neurons, endothelial cells, astrocytes, and microglia. Cytokines are divided into various types, including interleukins (ILs), chemokines, tumor necrosis factors (TNFs), interferons (IFNs), and transforming growth factors (TGFs).

Proinflammatory cytokines include IL-1, IL-2, IL-6, IFN- γ , and TNF- α . Anti-inflammatory cytokines include IL-4, IL-10, IL-11, IL-13, and TGF- β ^[4]. The proinflammatory cytokines activate cyclo-oxygenase-2 (COX-2), increase the levels of prostaglandin E2 (PGE2), activate inflammatory cells, and induce inflammatory reactions. They interact with each other to maintain balance. For example, IL-10 reduces TNF production, and the IL-1 receptor antagonist (IL-1ra) antagonizes the IL-1 receptor. In chronic inflammation, the proinflammatory cytokines are increased and the anti-inflammatory cytokines are decreased, which results in the onset of various diseases^[5].

The production of the peripheral cytokines that are secreted from monocytes or macrophages is determined by the level of immune activity. In pathologic states, such as acute or chronic inflammation or tissue damage, immune function and macrophages are activated to increase the levels of proinflammatory cytokines. Cortisol secreted from the adrenal cortex as a result of HPA-axis activation is most important in peripheral cytokine production. When cortisol levels are low, the production of proinflammatory cytokines increases, while their production is inhibited when cortisol levels are high^[6]. Neurotransmitters regulate peripheral cytokines through cortisol levels. For example, acetylcholine (ACh), dopamine (DA), and noradrenaline (NA) promote the secretion of corticotropin-releasing hormone (CRH) in the hypothalamus, and serotonin (5-HT) inhibits the secretion of CRH in the hypothalamus and adrenocorticotrophic hormone (ACTH) in the pituitary^[7]. In addition, the autonomic nervous system regulates peripheral cytokine production. Parasympathetic nerves directly affect the immune system, while sympathetic nerves affect the immune system through NA secretion from the peripheral sympathetic ganglia. The vagus nucleus, which is located in the pons, inhibits immune functions and cytokine production through the secretion of ACh from the vagus nerve^[8] (Figure 1).

Because peripheral cytokines are hydrophilic and have large molecular weights, they are unable to pass through the blood-brain barrier (BBB) in their normal state. However, they can pass through the BBB in pathological states that involve increased BBB permeability. Moreover, cytokines are also able to affect the CNS through mediators, such as nitric oxide or prostaglandins released in response to cytokines^[9,10]. IL-1 receptors are densely distributed in glial cells near arterioles or the plexus choroideus^[11]. This suggests that the IL-1 receptors in the CNS and IL-1 in the peripheral blood actively communicate with each other. Additional channels through which peripheral cytokines

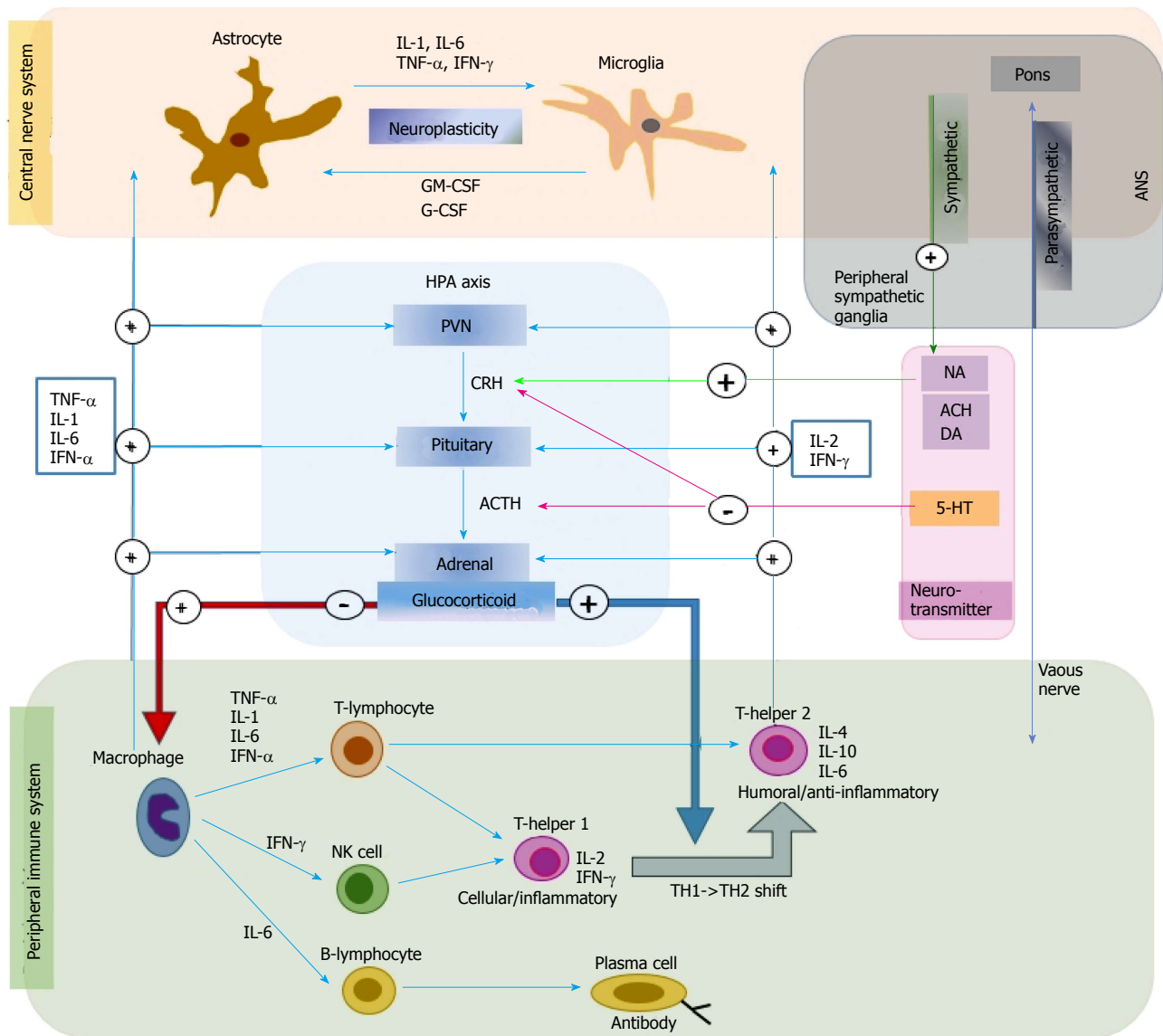


Figure 1 The role of cytokine network in depression in connection with immune system, hypothalamic-pituitary-adrenal axis, neurotransmitter, and autonomic nerve system. The figure shows communication between peripheral and central cytokine system. Early innate proinflammatory cytokines released by macrophage (TNF- α , IL-1, IL-6 and INF- α), and late acquired T cell cytokines (IL-2 and INF- γ) stimulate glucocorticoid secretion by acting at all three levels of the HPA axis. Glucocorticoids are negatively feedback on the peripheral immune system to suppress the production of proinflammatory cytokines. Glucocorticoids also play an important role in causing a shift from cellular (T-helper 1) to humoral (T-helper 2) immune responses. The central cytokines are usually secreted from the astrocyte or microglia. Central cytokines (IL-1, IL-6, TNF- α , and INF- γ) are considered to be involved in neuroplasticity in brain. The neurotransmitters (NA, ACH, and 5-HT) regulate the peripheral cytokines by changing the cortisol concentration level. The Ach, DA, and NA promote the secretion of the CRH in hypothalamus, and 5-HT inhibits the secretion of the CRH in hypothalamus and the ACTH in pituitary. The ANS also regulates the peripheral cytokine production. The parasympathetic nerve directly reaches the immune system while the sympathetic nerve affects the immune system through the NA secretion from the peripheral sympathetic ganglia. 5-HT: Serotonin; ACH: Acetylcholine; ACTH: Adrenocorticotropic hormone; ANS: Autonomic nerve system; CRH: Corticotropin-releasing factor; DA: Dopamine; HPA: Hypothalamic-pituitary-adrenal; NA: Noradrenalin; PVN: Paraventricular nucleus of the hypothalamus; TH: Helper T cell; IL: Interleukins; TNF: Tumor necrosis factor; INF: Interferons.

transmit immune signals to the CNS include passive diffusion through the circumventricular organs (brain regions that do not have a BBB), active transport to the CNS, and nerve conduction pathways through the vagus nerve^[6].

Central cytokines are usually secreted from astrocytes or microglia, but neurons can secrete them in certain conditions^[12]. Central cytokines are produced in a number of brain regions, including the circumventricular region, hypothalamus, hippocampus, cerebellum, forebrain,

basal ganglia, and brain stem nuclei^[13]. IL-1, which is secreted from the brain, is found in the hypothalamus and hippocampus^[14]. The roles of central cytokines in the brain are not fully understood. However, the proinflammatory cytokines IL-1, IL-6, TNF- α , and IFN- γ have been implicated in neuronal development, neuroplasticity, synaptogenesis, and tissue repair^[15]. Proinflammatory cytokines promote neuronal necrosis after traumatic brain injuries^[16].

Cytokine receptors are located in the immune

system and various tissues, including the peripheral nervous system and CNS. For example, IL-1, IL-2, IL-6, and TNF- α receptors are densely distributed in the hippocampus and hypothalamus^[17]. IL-1 has two receptor types: Type I and type II. The nuclear transcription factor nuclear factor kappa B (NF κ B) is activated and intracellular signals can be transmitted through the type I receptor. A role of cytokines in specific mental functions and/or mental diseases has been suggested because of the locations of their receptors in the CNS and not because of the specific functions of the cytokines. The important CNS structures that are affected by central cytokines include the locus coeruleus, hippocampus, prefrontal cortex, and hypothalamus. These CNS structures are associated with the biological processes that underlie psychological changes^[18].

THE CYTOKINE HYPOTHESIS OF DEPRESSION

Stress-cytokine-inflammation-depression

According to the cytokine hypothesis (Figure 2), internal or external stress induces cytokine imbalances that play important roles in the expression and continuity of depressive symptoms in vulnerable individuals^[19]. A number of major research findings support the cytokine hypothesis.

First, the injection of cytokines into animals and humans induces depression-like symptoms. Depression occurs frequently in patients with hepatitis C undergoing INF treatment. Of note in one study, 23% of patients during INF treatment satisfied the diagnostic criteria for major depressive disorders; in 74% of them depression occurred within 2 mo after the start of INF treatment^[20]. The levels of IL-6 and TNF- α , which increase after IFN- α administration, are significantly associated with the severity of depression^[21]. Polymorphisms in the 5-hydroxytryptamine (5-HT) transporter and *IL-6* genes contribute to the fatigue and depressive symptoms that are observed after IFN- α administration^[22].

Second, increases in the levels of proinflammatory cytokines, such as IL-1, IL-6, IL-12, TNF- α , prostaglandin E2 (PGE2), and negative immunoregulatory cytokines have been observed in patients with depression^[23,24].

Third, cytokines trigger activity in the HPA axis and the catecholamine/sympathetic nervous system, two biological systems that are closely associated with the pathophysiology of depression^[2]. Cytokines stimulate corticotrophin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH), and activate the HPA axis^[25]. In addition, cytokines activate indoleamine-2,3-dioxygenase (IDO), which catalyzes the metabolism of the 5-HT precursor tryptophan to kynurenine, and inhibits 5-HT synthesis in the brain^[26]. The proinflammatory cytokine, NA, and DA promote CRF secretion, activate the sympathetic nerve system, and promote immune reactions. During this process, the temperature of the CNS increases and sickness behaviors may be induced^[27].

Sickness behaviors refer to behavioral changes that are observed during an infection period. These include feelings of helplessness, depressive mood, anxiety, hypersomnia, loss of appetite, and inattention. Based on findings that patients with depression exhibit increased levels of proinflammatory cytokines in the plasma^[23,24], decreased levels of anti-inflammatory cytokines^[28], and increased levels of PGE2 in the cerebrospinal fluid^[29], depression is considered a sickness behavior.

Fourth, antidepressants improve depressive symptoms by inhibiting cytokine secretion from immune cells or by acting as an antagonist of cytokine receptors. Antidepressants inhibit proinflammatory cytokine secretion from monocytes or macrophages, act as chemotaxis inhibitors, and increase the production of anti-inflammatory cytokines^[30]. An *in vitro* study reported anti-inflammatory reactions with therapeutic doses of antidepressants that involved the inhibition of IFN- γ and increased IL-10^[31]. In addition, antidepressants significantly inhibit the lipopolysaccharide-induced production of IL-1 β , IL-6, and TNF- α , as well as the secretion of IL-2 and IFN- γ in T cells^[32].

In summary, neuroinflammation and cytokines, which affect patterns of brain signal transmission, are important in the psychopathology of depression and mechanism of antidepressants. Furthermore, they are associated with neurogenesis and neural plasticity in the brain. Thus, neuroinflammation and cytokines appear to cause or continue depression and might be useful for determining the diagnosis and prognosis of depression. Epidemiological studies support the view that increased levels of IL-6, IL-1ra, and C-reactive protein (CRP) can be harnessed to predict the occurrence of depression^[33]. A recent meta-analysis demonstrated that the markers of inflammation with relatively consistent increases in patients with depression are IL-6, TNF- α , TNF- β 1, IFN, and CRP^[34].

ARE CYTOKINES A CAUSE OF DEPRESSION?

Cytokine, HPA-axis activation, and glucocorticoid receptor resistance

HPA-axis activation is one of the most important biological findings in depression research. The activation results in increased cortisol concentrations in the plasma, urine, and cerebrospinal fluid, and exaggerated cortisol responses against ACTH^[35]. HPA-axis activation has been suggested to result from excessive secretion of CRF, which triggers depressive mood, loss of appetite, and sleep disturbance^[36]. These suggestions are supported by findings of increased CRF levels in the cerebrospinal fluid, increased levels of CRF mRNA in the paraventricular nucleus of the hypothalamus, blunted ACTH responses in CRH tests due to the down-regulation of CRF receptors in the pituitary gland in patients with depression, and also by the down-regulation of CRF receptors in the frontal cortex to compensate for CRF oversecretion in patients

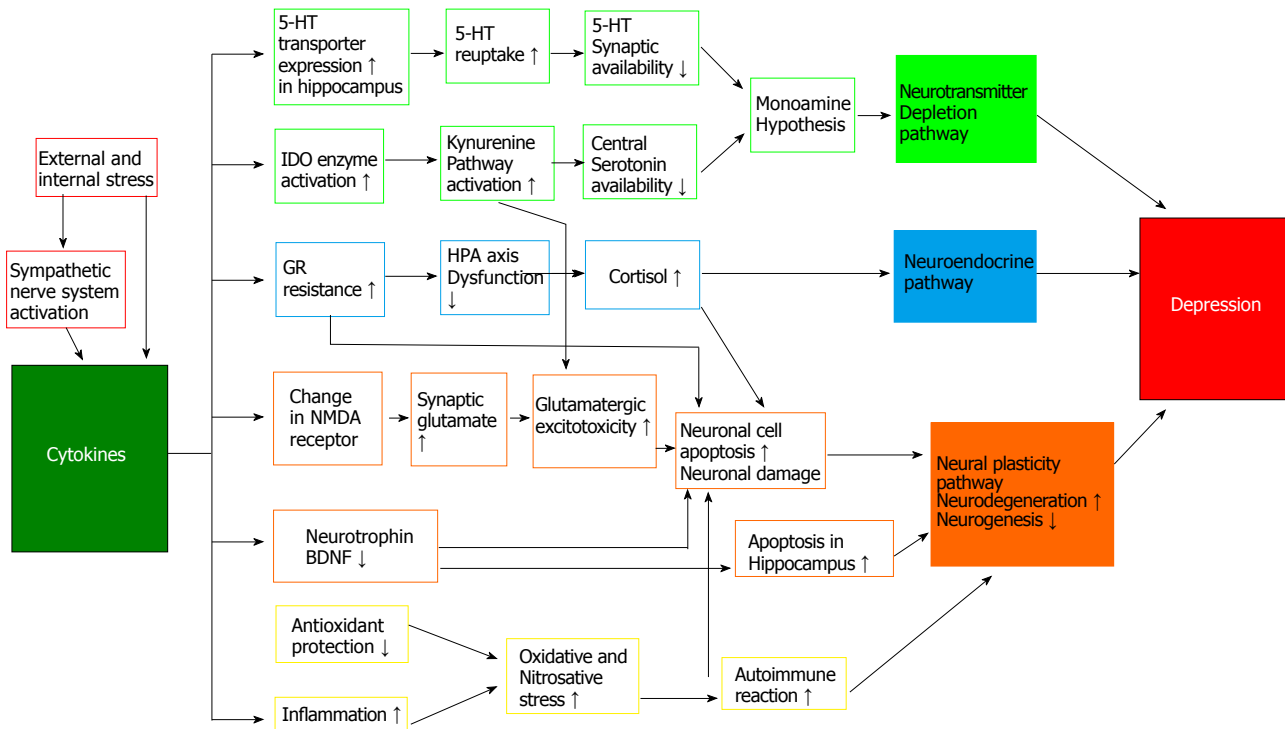


Figure 2 Schematic representation of neuroinflammatory pathways in the pathogenesis of depression. Cytokine production is initially activated by stress and sympathetic nerve system activation. In turn, cytokines have an important role by acting via neurotransmitter depletion pathway, neuroendocrine pathway, and neural plasticity pathway. There are multiple interactions between these pathways suggesting existence of a complex model for pathogenesis of depression. 5-HT: Serotonin; BDNF: Brain derived neurotrophic factor; GR: Glucocorticoid receptor; HPA: Hypothalamic-pituitary-adrenal; IDO: Indoleamine-2,3-dioxygenase; NMDA: N-methyl-D-aspartate.

who committed suicide^[35,36]. In patients with depression, CRF oversecretion can appear due to dysfunction of the negative feedback of glucocorticoids. Accordingly, cortisol is not inhibited in dexamethasone suppression tests in these patients. This might be due to deterioration in glucocorticoid receptor (GR) sensitivity. Glucocorticoid resistance results in absence of inhibition in the dexamethasone suppression test and CRF oversecretion.

Cytokines can cause HPA-axis activation, increased CRF, and glucocorticoid resistance. Proinflammatory cytokines, such as IL-1 β and IL-6, stimulate CRH secretion from the paraventricular nucleus of the hypothalamus, activate the HPA axis, and promote ACTH and glucocorticoid secretion^[37] (Figure 1). In early depression research, the cortisol oversecretion from HPA-axis activation was thought to inhibit immune function^[32]. However, more recently, immune cells are thought to be unaffected by cortisol in chronic stress and depression because of the inhibition of GR function in immune cells^[38]. This may be a result of the oversecretion of proinflammatory cytokines from increased cell-mediated immunity^[38]. In support of this, IL-1 inhibits the translocation of the GR from the cytoplasm into the cell nucleus and GR-mediated gene transcription^[39]. These findings suggest that cytokines directly affect GR function and induce glucocorticoid resistance. Moreover, antidepressants like desipramine stimulate GR translocation from the cytoplasm to the nucleus and increase GR-mediated gene transcription, which eventually promotes the feedback inhibition that

is mediated by glucocorticoids in the HPA axis^[40].

Theoretically, the glucocorticoid increase that is induced by HPA-axis activation and the cytokine increase that results from immune activation are not likely to occur at the same time in depression, but an inverse correlation should be observed because the synthetic glucocorticoids that are used to treat inflammatory diseases inhibit the release of proinflammatory cytokines and their synthesis, which results in anti-inflammatory effects^[41]. However, no inverse correlations between the concentrations of plasma glucocorticoids and cytokines have been observed in patients with depression. Because the negative inhibitory mechanism of cortisol that prevents increased levels of CRF is impaired in patients with depression, the negative inhibitory mechanism of cytokine secretion in immune cells against increased levels of cortisol is also impaired in these patients. In other words, depression is characterized as a dysfunction of the cortisol feedback inhibitory mechanism to the GR, which is the mechanism for inhibiting CRF oversecretion, and to immune cell receptors, which is the mechanism for inhibiting cytokine oversecretion. These impairments may be directly related to the etiology of depression.

Cytokines and central neurotransmission

Stress simultaneously activates the HPA axis and the sympathoadrenal system (sympathetic nervous system and adrenal medulla). The most important stress response is activation of the noradrenergic (NA) neurons,

which show stress responses through pathways from the locus coeruleus to the cortex, hippocampus, and cerebellum, and from the nucleus tractus solitarius to the hypothalamus. Dopaminergic (DA) neurons display stress responses through the nigrostriatal, mesolimbic, and mesocortical pathways. The mesocortical system, which connects the prefrontal cortex and cingulate, is the most important. The stress responses of the serotonergic (5-HT) system result in significant increases in tryptophan in all brain regions. These increases are not localized to the specific brain areas where 5-HT neurons are present. During stress responses, changes in the metabolism and secretion of neurotransmitters, such as Ach and γ -aminobutyric acid (GABA), are observed. Neuropeptides of the peptidergic system, which include CRF, are also involved in the stress response.

According to the monoamine depletion hypothesis, depression develops as a result of decreased availability of monoamine neurotransmitters, especially 5-HT and NA, in the synapse. Proinflammatory cytokines significantly affect the peripheral and central 5-HT systems. Peripheral injections of IL-1 β and TNF- α increase the extracellular levels of 5-hydroxyindoleacetic acid (5-HIAA) in the nucleus raphe dorsalis, and central injection (intracerebroventricular application) of IL-1 β , IFN- γ , and TNF- α stimulates the 5-HT transmission in the nucleus raphe dorsalis^[42]. Peripheral injections of IL-1 increase NA turnover in the hypothalamus and hippocampus, 5-HT turnover in the hippocampus and prefrontal cortex, and DA turnover in the prefrontal cortex^[43]. In an *in vitro* study, IL-1 β increased the activity of the 5-HT transporter^[44], which has a critical role in 5-HT transmission because it facilitates 5-HT reuptake. If the 5-HT transporter is activated in central 5-HT neurons, the amount of 5-HT removed from the synapses increases, which results in a deterioration of 5-HT-mediated functions. In addition, IL-1 β receptors are expressed in 5-HT neurons and IL-1 β is synthesized in neurons and glia^[45]. IL-1 and IFN- γ increase the activity of IDO, which promotes the metabolism of tryptophan and decreases 5-HT synthesis in the brain^[26]. IL-1 β acts on 5-HT transporters to increase 5-HT reuptake in the synapse, and the decreased concentrations of serum tryptophan decrease the usefulness of the 5-HT system, which eventually induces depression (Figure 2).

The neurodegeneration hypothesis of depression: Cytokine-5-HT interaction

According to the monoamine hypothesis, patients with depression have a vulnerable 5-HT system. Their 5-HT turnover is increased and then becomes depleted, inducing 5-HT₂ receptor up-regulation. The levels of tryptophan, a precursor of 5-HT, in the blood of patients with depression are decreased compared with those of healthy people^[46]. Eating tryptophan-deficient foods worsens mood, while the administration of tryptophan improves depressive symptoms^[47].

Depression is significantly associated with old age, chronic medical diseases (e.g., coronary heart diseases,

diabetes, Parkinson's disease, stroke, and cancer), and chronic stress. Nevertheless, not all elderly or chronically ill people experience depression. How can these individual differences be explained? One hypothesis that can explain these differences is the neurodegeneration hypothesis: Cytokine-5-HT interaction^[47,48].

According to this hypothesis, acute psychological stress triggers tryptophan defects and mood swings. To correct the 5-HT imbalance, 5-HT synthesis and receptor expression are modified. This is the first stage of coping with psychological stress. If the psychological stress is chronic, the levels of proinflammatory cytokines increase. The levels of proinflammatory cytokines also increase in cases of physical stress or chronic diseases. These increases in proinflammatory cytokines trigger an increase in the levels of anti-inflammatory cytokines as a compensatory mechanism in order to maintain balance. This is the second stage. If the balance is not maintained and the levels of proinflammatory cytokines increase excessively, animals show sickness behaviors, while humans show depressive symptoms. The increased levels of proinflammatory cytokines activate the IDO enzyme and accelerate the metabolism of tryptophan to kynurenine. The level of 5-HT in the brain decreases, which further aggravates the symptoms of depression in individuals vulnerable to depression. Through the complicated tryptophan metabolism process, the neurodegenerative quinolinate and the neuroprotective kynurenate are formed in the brain. This is the third stage, which is important for maintaining balance between neurodegeneration and neuroprotection (Figure 2).

Minor neurodegeneration can occur in all people. However, in the elderly population or in individuals with severe stress or chronic diseases, the balance between the proinflammatory cytokines and anti-inflammatory cytokines is lost, and the process of metabolizing tryptophan to kynurenine is accelerated, which lowers the concentration of 5-HT in the brain. If the balance between neurodegeneration and neuroprotection is also lost, neurodegeneration begins. Neurodegeneration in brain regions including the hippocampus and frontal lobe results in cognitive and memory impairments. As a result, the neurodegeneration process inhibits all of the brain strategies that might cope with the stress, which induces depression or treatment-resistant depression. The neurodegeneration process is further deteriorated due to neurotoxicity from cortisol oversecretion from stress-induced HPA-axis activation^[49].

The neurodegeneration hypothesis of depression can explain the development of depression in the elderly and chronically ill. In addition, it suggests methods for coping with various stresses in various stages according to the stress intensity and period. In a recent study^[49], patients with depression showed a significantly higher tryptophan breakdown index and lower kynurenic acid concentration level compared with those in the normal population. These findings imply that patients with depression exhibit decreased levels of neuroprotection markers, which

supports the neurodegeneration hypothesis.

Cytokines, microglia, and neurogenesis

Cytokines have been reported to promote neuronal differentiation and remodeling in the brain. Accordingly, their roles in neurodegenerative diseases are of interest. The brains of patients with chronic depression show increased cell apoptosis with decreased volumes of the hippocampus, prefrontal cortex, and amygdala and increased ventricular volume. The chances for developing dementia increase accordingly in these patients, and chronic inflammatory responses are thought to be involved in this process^[50]. Proinflammatory cytokines reduce neuroplasticity by increasing the levels of quinolinic acid, which is a strong agonist of the N-methyl-D-aspartate (NMDA) receptor^[51] (Figure 2).

Stress induces inflammatory responses through cytokine secretion. Cytokines are secreted from peripheral immune cells and central immune cells. Chronic stress activates brain microglia, which secrete cytokines and in turn affect neurogenesis. Neurogenesis is either inhibited or stimulated according to the level of microglia activation^[52]. This means that various microglia perform various functions, such as stimulating or inhibiting neurons^[52]. Inflammation and cytokines usually directly inhibit neurogenesis. Proinflammatory cytokines, such as TNF- α and INF- α , inhibit neurogenesis through IL-1 regulation^[53]. The decline of neurogenesis is prevented by inhibiting IL-1 β activity^[54], confirming the important role of cytokines in inhibiting neurogenesis in the brain. In contrast, the administration of drugs that inhibit inflammation recovered or increased neurogenesis^[55]. In summary, chronic stress promotes cytokine secretion in the peripheral blood and brain microglia, and cytokines affect neurogenesis.

CYTOKINES AND ANTIDEPRESSANTS

The mechanisms of antidepressants relative to cytokines

Stress induces proinflammatory cytokine oversecretion, which results in depressive symptoms. Antidepressants may inhibit the production and function of peripheral and brain cytokines. As mentioned above, the use of antidepressants decreases the levels of proinflammatory cytokines and increases the levels of anti-inflammatory cytokines^[30]. These findings imply that antidepressants inhibit cytokine secretion in immune cells and/or antagonize cytokine receptors to improve the depressive symptoms.

How do antidepressants regulate cytokine secretion and improve depressive symptoms? Several hypotheses have been suggested^[19,56-58]. First, the changes in peripheral and central cytokines after antidepressant treatment might be secondary results of the neurotransmitter changes that are induced by antidepressants. Stress-induced increases in IL-6 levels are inhibited by pretreatment with propranolol, a β -adrenoceptor antagonist, which

suggests that the IL-6 increases could be mediated by the sympathetic nervous system and increased adrenalin in the adrenal medulla. Immune cells have neurotransmitter receptors, and antidepressants act on these receptors to regulate immune cell activity. T lymphocytes express 5-HT receptors (5-HT1A and 5-HT2A/2C) and high-affinity 5-HT transporters. Macrophages have a 5-HT uptake system that is similar to the system in platelets. Antidepressants can have negative immunoregulatory effects by causing deficiencies in intracellular 5-HT storage, increases in extracellular 5-HT, and blocking 5-HT2A/2C receptors; second, antidepressants restore the cytokine-induced GR resistance. In addition, they restore the inhibition of the negative feedback of the HPA axis and normalize HPA axis function; third, antidepressants inhibit the nitric oxide and PGE2 production that is increased by the cytokines; fourth, antidepressants inhibit IDO activity; fifth, antidepressants directly act on macrophages and lymphocytes to stimulate the production of anti-inflammatory cytokines.

In meta-analyses of 22 types of antidepressants, treatments with antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), result in decreased levels of IL-1 β and IL-6^[58]. Inflammation increases the activities of the microglial cells and induce astroglial loss, which consequently induces glutamate release and an upregulation of NMDA receptors^[59]. The anti-inflammatory effects of riluzole and ketamine, which are glutamatergic modulators, are being studied. Riluzole and ketamine prevent neurotoxicity and relieve inflammation by inhibiting glutamate secretion and modulating NMDA receptors^[60].

Promising cytokine-related antidepressants

If cytokines are associated with the pathophysiology of depression, then receptor antagonists that can regulate inflammatory cytokines, anti-cytokine antibodies, and anti-inflammatory cytokines might improve depressive symptoms. Although the therapeutic usefulness of cytokine inhibitors in depression treatment has not been fully investigated, the possibility has been suggested by the results of experimental studies.

The long-term administration of antidepressants in mice results in significant increases in the mRNA levels of IL-1ra in the hypothalamus, hippocampus, frontal lobe, and diencephalon. The learned helplessness that is induced by inescapable shocks is inhibited in mice that were pretreated with IL-1ra^[61]. These results suggest that stress-induced IL-1 secretion is a primary cause of the behavioral disturbances shown in the learned helplessness model of depression. CRF receptor antagonists could prevent learned helplessness^[62] because the behavioral changes induced by IL-1 occur through central CRF secretion. The cytokine antagonists with a broad action range, such as IL-4 and IL-10, might be more effective than cytokine antagonists, such as IL-1ra, which inhibit specific cytokines, in the treatment of depression. In one study, seven severely depressed patients given low-dose lipopolysaccharide showed

improved symptoms the next day, when the levels of anti-inflammatory cytokines were expected to peak^[63]. These mood changes were transient, and the patients' previous conditions returned after several days. TNF- α has most recently drawn attention as a treatment that can change the course of bipolar disorder (disease-modifying treatment)^[64]. Current evidence suggests that TNF- α regulates apoptotic cascades that may be associated with neuronal and glial loss in bipolar disorder. TNF- α antagonists, such as adalimumab, etanercept, and infliximab, have been used as therapeutic agents for rheumatic diseases, and are currently being used in clinical trials to treat the depressive episodes of patients with bipolar disorder^[64].

The antidepressant effects of anti-inflammatory drugs

If inflammatory responses contribute to the pathogenesis of depression, anti-inflammatory agents are expected to be effective for treating depression. The use of celecoxib, a COX-2 inhibitor, to augment SSRI treatment resulted in better treatment effects compared with the use of the SSRI alone^[65]. Celecoxib augmentation therapy can accelerate the treatment responses in depressive episodes of patients with bipolar disorder^[66]. In addition, acetylsalicylic acid (aspirin) improves the effects of SSRIs^[67]. However, the combination of SSRIs and non-steroidal anti-inflammatory drugs inhibits the effects of the antidepressant. The effects of citalopram, which regulates TNF- α and IFN- γ in mouse frontal lobe, are inhibited by ibuprofen^[68]. These laboratory results have been confirmed in clinical trials; the combined use of citalopram and anti-inflammatory drugs resulted in more treatment failures than the use of citalopram alone. These results were not found in subsequent studies^[69]. These discrepancies suggest that inflammatory drug reactions vary according to depression subtype.

Eicosapentaenoic acid and docosahexaenoic acid, which are omega-3 fatty acids, can be used to treat rheumatoid arthritis, psoriasis, asthma, and inflammatory bowel diseases because they reduce proinflammatory cytokines. In addition, they can be used as a supplemental agent of antidepressants^[70]. Angiotensin receptor blockers, which are hypertension agents, are thought to have anti-inflammatory effects in the CNS. When their mechanism is fully understood, they can be used in depression treatment.

LIMITATIONS

Limitations of the cytokine hypothesis of depression

Many clinical studies have suggested that the neuro-immune activation that results from the production of proinflammatory cytokines is significantly involved in the etiology and pathogenesis of depression. However, the cytokine hypothesis of depression is still controversial due to the following limitations.

First, the cytokine hypothesis states that increased levels of proinflammatory cytokines cause secondary

changes, such as neurotransmitter depletion, HPA-axis activation, and the expression of depressive symptoms. Nevertheless, it has not been clarified if the increased levels of proinflammatory cytokines are the cause of depression or are a concomitant phenomenon that maintains the depressive symptoms regardless of the depression etiology. When IFN- α was used in cancer patients as an immunotherapy, the patients developed depression. When the immunotherapy was discontinued or antidepressants were administered, the depressive symptoms improved^[20,21]. Accordingly, the proinflammatory cytokines probably function as a causative factor in patients with depression from medical diseases or immunotherapies. However, it is still unclear how the proinflammatory cytokines function as a causative factor in patients with depression that is caused by etiologies other than diseases or immunotherapies^[71].

Second, the effects of antidepressant treatments are not always associated with decreased levels of proinflammatory cytokines^[72,73]. The effects of antidepressant treatment may not be caused by decreased cytokine release or synthesis but rather by disturbance of the actions of peripheral-released cytokines on the CNS regardless of the concentration of released cytokines. Thus, antidepressants may not directly inhibit immune activation but, rather, indirectly regulate immune functions.

Third, previous studies have shown that the increased levels of cytokines in depression are within a low range compared with those in systemic infection and inflammation. In acute infection, the huge amounts of cytokines are produced and act on the brain functions, which often results in the progression of depression. However, in most clinical conditions, such as chronic infection and inflammation, only low amounts of cytokines circulate. Thus, there is a question whether and how low amounts of peripheral cytokines act on the brain and develop depression, even under baseline conditions. The difference in brain function affected by low and high levels of cytokines is another issue. Low levels of peripheral cytokines have a similar effect on sleep-awake behaviors compared with a high dose of peripheral cytokines^[74]. On the other hand, low levels of cytokines promote non-REM sleep, but this stage of sleep is suppressed by high level of cytokines^[75]. It is still unclear, if the doses have similar effects on depression^[74]. Because insufficient research for depression and brain functions in various levels of cytokines, the answer to these questions depend on further experimental studies.

It is unclear whether depression is caused by increased neuroinflammation or vice versa because depression diagnoses are made by examining patients' histories of perceptible symptoms and the intrinsic heterogeneity and various environmental factors of the patients are not controlled. We may consider various aspects of the cytokine hypothesis of depression. These include genetic aspects, role of early life stress and trauma, information on modulators of cytokine activity in depression (diet, obesity, gut health, physical condition, sleep deprivation,

vitamin D deficiency), medical illness, differences of cytokine activities between animal models and human, inflammatory markers in suicide, and the influence of treatments like antidepressant drugs, psychotherapy, and electroconvulsive therapy.

CONCLUSION

Depression is considered a syndrome that includes diverse symptoms and a mental disorder with various causes. No single mechanism that explains every aspect of depression exists. Some depressive symptoms appear in association with the cell proteins that are produced by the complicated intracellular signal transmission of neurotransmitters, such as 5-HT and NE. However, in some cases, childhood stress sustains CRF hyperactivity and increases stress responses in adulthood, which then results in the oversecretion of cerebral CRF and eventually leads to depression^[75,76]. In other cases, increases in the levels of cytokines from immune system activation activate the HPA axis and increase neurotransmitter turnover, thus leading to depression. These findings suggest that either various etiologies can be observed at the same time in a single patient with depression or that a specific etiology can be dominant.

From a psychoneuroimmunological point of view, the immune, endocrine, and neurotransmission systems closely interact with each other, and inflammation acts as an allostatic load to disconnect them. Depression can be caused by these functional impairments. The sickness behaviors that are observed under inflammatory conditions are similar to depressive symptoms, and some cytokine treatments lead to depression. These results confirm the association between inflammation and depression. Cytokines including IL-1, IL-2, IL-6, IFN- γ , and TNF- α , and hormones like CRF and glucocorticoid have been suggested as inflammation markers. Inflammatory responses that are thought to affect the synthesis and transmission of neurotransmitters, glucocorticoid resistance, and neurodegeneration/neurogenesis contribute to the onset of depression and inhibit recovery. Although no definitive markers of inflammation have been established, they could at least be used in vulnerable patients with depression. Future studies on the mechanisms of neuroinflammation are expected to help overcome the limitations of the monoamine theory and contribute to finding new solutions for the diagnosis and treatment of depression.

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Gene environment interaction in periphery and brain converge to modulate behavioral outcomes: Insights from the SP1 transient early in life interference rat model

Eyal Asor, Dorit Ben-Shachar

Eyal Asor, Dorit Ben-Shachar, Laboratory of Psychobiology, Department of Psychiatry, Rambam Medical Center and B. Rappaport Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Haifa 31096, Israel

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Correspondence to: Dorit Ben-Shachar, Professor, Laboratory of Psychobiology, Department of Psychiatry, Rambam Medical Center and B. Rappaport Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Technion, PO Box 9649, Haifa 31096, Israel. shachar@tx.technion.ac.il
Telephone: +972-4-8295224
Fax: +972-4-8295220

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Abstract

It is generally assumed that behavior results from an

interaction between susceptible genes and environmental stimuli during critical life stages. The present article reviews the main theoretical and practical concepts in the research of gene environment interaction, emphasizing the need for models simulating real life complexity. We review a novel approach to study gene environment interaction in which a brief post-natal interference with the expression of multiple genes, by hindering the activity of the ubiquitous transcription factor specificity protein 1 (Sp1) is followed by later-in-life exposure of rats to stress. Finally, this review discusses the role of peripheral processes in behavioral responses, with the Sp1 model as one example demonstrating how specific behavioral patterns are linked to modulations in both peripheral and central physiological processes. We suggest that models, which take into account the tripartite reciprocal interaction between the central nervous system, peripheral systems and environmental stimuli will advance our understanding of the complexity of behavior.

Key words: Gene-environmental interaction; Specificity protein 1; Mithramycin; Stress; Animal-model; Essential amino acids; Tryptophan; Insulin

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Core tip: We review the main theoretical and practical concepts in the research of gene environment interaction. We present a novel approach to study gene environment interaction in which a brief post-natal interference with the expression of multiple genes by inhibiting the activity of the ubiquitous transcription factor specificity protein 1 is followed by later-in-life exposure of rats to stress. Finally, we discuss the role of peripheral processes in behavioral responses, demonstrating how specific behavioral patterns are linked to modulations in interwoven brain and body physiological processes due to gene and environmental changes.

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INTRODUCTION

The role of nature vs nurture in shaping complex behavior and in mental disorders is a matter of long running dispute and creates a split between psychobiology, which emphasizes the dominancy of the being's innate predispositions and psychotherapy supporters, which point out the surrounding influence. Evidence from decades of heredity research has suggested that complex behaviors and psychiatric disorders have a solid genetic basis^[1,2]. It has been reported by many studies that consistent differences in behavioral traits between subjects, such as stress responsivity and temperament, show a familial pattern^[3]. On the other hand, the impact of environmental factors on physical illness is well established^[4,5] and well recognized in behavioral disturbance^[6,7]. Numerous studies reported a correlation between candidate genes, and behavioral phenotype^[8,9], yet with significantly lower rate of replication and a clear tendency toward positive results^[10]. Environmental aspects are formulated in the vast psychoanalytical literature and in models that use a scientific platform, such as the impact of different nursing abilities of female rats, on stress responsivity of their pups^[11]. Environmental physical factors such as intrauterine inflammatory reaction induced by Lipopolysaccharide, which simulates the impact of prenatal infection on behavior^[12,13] were studied as well.

The stress diathesis theory, which suggests that disorders induced by the combination of varying degrees of predisposition with invers degrees of stressful stimuli, has become an accepted conceptual research framework for studying complex behaviors. Following this hypothesis numerous studies over the last decade assessed the relationship between candidate genes and behavior in the form of genome-wide association studies (GWAS)^[14], most of them focusing on the pathologic consequences of genetic alteration. Despite the remarkable advances in genetic tools and techniques, very few direct genetic effects on mental health have been identified and replicated^[10].

An alternative paradigm to the stress diathesis theory is the differential susceptibility theory, which assumes that individuals react differently to environmental stimulus depending on the plasticity of gene rather than their susceptibility. Thus showing higher responsiveness to both positive and negative external cues, frequently with opposing outcomes^[15,16]. For example, high frequency of antisocial behavior was correlated with childhood maltreatment the in low activity MAO-A allele carriers^[17]. Interestingly, low activity MAO-A allele carriers, who

were not exposed to childhood maltreatment showed the lowest anti-social behavior scores compared with normal activity MAO-A carriers^[16]. An additional extensively studied genetic variant in psychiatry is the short allelic form of the serotonin transporter-linked polymorphic region (5-HTTLPR), which is associated with a reduction in the transporter activity^[18] and with high risk for major depression in individuals exposed to stressful life events^[19]. Yet, 5HTT s-allele carriers were shown to be more responsive to the Attention Bias Modification training than long-allele carriers, supporting Belsky's hypothesis that the s-allele may be considered as a plasticity gene rather than a susceptible gene^[20]. Taken together, these examples support the differential responsiveness theory of sensitive genes in the etiology of complex behaviors^[16].

Unfortunately, the current gene environment interaction models have substantial limitations, ranging from weak validation to poor predictive power and although genome studies have expanded our understanding of complex phenotypes and many human diseases, they hardly explain a small proportion of their heritability in the population^[21]. Genetic variants are usually considered as having additive, suppressive or neutral effects on the phenotype, but the effect size for a single genetic variant is minor^[22]. A more comprehensive model of real life interaction between multiple genes that influence the expression of each other and thereby the manifestation of a particular phenotype, is needed.

One possible gate for modelling real life gene environment interaction are through manipulation of key point genes, genes that are essential for the modulation of multiple genes' activity, such as the ubiquitous transcription factor specificity protein 1 (Sp1). Sp1 is a member of the SP proteins family, which constitutes a group of highly conserved transcription factors present in a wide range of organisms. Their structure is defined by the presence of three highly conserved DNA-binding zinc finger domains which bind to similar, yet distinct, GC-rich target sequences. Members of the SP family function either as activators or repressors in cell *via* a promoter-dependent manner^[23]. Sp1 is essential for the regulation of various physiological functions, maintains organ homeostasis, regulates tissue repair, and possibly serves as an anti-inflammatory mechanism that protects against organ inflammation and injury^[24]. Sp1 regulates the expression of numerous genes in early developmental stages^[25] and the expression of most growth factors and their receptors depend on Sp1^[26-28]. Sp1 activity can be modulated by various environment-dependent factors including metabolic factors such as glucose and insulin, immunologic factors such as tumor necrosis factor-alpha (TNF- α), glucocorticoid receptors and several major kinases including CDK2 and ERK1/2^[29-32]. Sp1 also modulates the expression of many genes implicated in psychiatry research, including neuregulin-1^[33], reelin^[34], GAD67^[35], MAO A and B^[36,37], NMDA receptor subunits (NR1 and NR2)^[38,39], GABA A receptor^[40], DA receptors^[41] and genes of the oxidative phosphorylation

system (OXPHOS)^[42]. In this article we will describe how simulating real life by minor manipulation of multiple gene expression, based on Sp1 unique characteristics, models more accurately gene environment interaction in behavioral sciences.

SP1 IN SCHIZOPHRENIA AND OTHER NEUROPSYCHIATRIC DISORDERS

The alterations in different genetic trajectories in schizophrenia reported by numerous studies^[43], can result from transcriptional dysregulation in the disorder^[44]. Our group showed that the expression of Sp1 is disrupted in brain samples and peripheral blood lymphocytes of schizophrenia patients as compared with those of healthy subjects. Specifically, downregulation in Sp1 mRNA expression was prominent in the prefrontal cortex and the striatum, while upregulation was observed in the parieto-occipital cortex and in blood lymphocytes of schizophrenic patients. Sp1 levels were highly and significantly correlated with two subunits (NDUFV2 and NDUFV1) of the first complex of the OXPHOS in lymphocytes and brain specimens of normal subjects, while abolished in schizophrenic patients^[45]. We have shown that Sp1 is a transcription factor of both subunits, which have been repeatedly implicated in schizophrenia^[46,47]. A defect in Sp1 transcriptional activity, which leads to abnormal expression of complex I subunits, can be one of the causes for reduced complex I activity associated with mitochondrial dysfunction and reduced energy metabolism observed in schizophrenia brains by numerous imaging studies^[48]. Such distortion in brain energy production can affect synaptic plasticity and connectivity of neuronal networks and thereby cognitive and emotional behaviors^[49]. Additional studies by other groups substantiated the role of Sp1 in mental and neurological disorders by showing a reduction of Sp1 protein and mRNA in the postmortem prefrontal cortex brain of chronic schizophrenia patients^[50], increased Sp1 mRNA levels in the hippocampus^[51] and a reduction in Sp1 and Sp4 protein levels in lymphocytes of first-episode psychosis patient^[52]. These reports are in line with other studies demonstrating a role of Sp1 in the regulation of many genes associated with neuropsychiatric psychiatric disorders. Thus, elevation in Sp1 protein levels was observed in autistic brains, which was associated with altered expression of autism candidate genes such as OXTR and PTEN^[53]. Sp1 mRNA and protein was also found to be up-regulated in Alzheimer's disease (AD) brains and in a transgenic mice model of the disease^[54]. In Huntington disease, Sp1-regulated huntingtin transcription is dysregulated. In adrenal medulla-derived PC12 cell cultures it was shown that Sp1 is involved in the regulation of epinephrine biosynthesis in response to acute and chronic stress^[55]. The dual characteristic of Sp1, having specific environmental and internal signal regulated transcriptional activities, together with its role in the regulation of multiple genes, coincide with the multi-gene alteration and the heterogeneous symptomatology of

mental disorders.

SP1 MANIPULATION MODELS

Complete inhibition of Sp1 is incompatible with life and Sp1 knockout mice die *in utero* with multiple phenotypic aberrations^[56]. However, Sp1 transcriptional activity can be inhibited by Mithramycin (MTR)^[57]. MTR is an antineoplastic antibiotic, which binds to GC-rich regions on the DNA displacing the Sp family transcription proteins from their binding sites^[58]. MTR is a clinically approved antibiotic that is effective for the treatment of many cancers such as testicular cancer^[59] and also for cancer induced hypercalcemia^[60]. Our group has reported that MTR induced a time dependent decrease in the expression levels of complex I subunits NDUFV1, NDUFV2 and NDUFV1, as well as of reelin, all regulated by Sp1 and implicated in schizophrenia^[45]. The availability of a simple pharmacologic agent that modulates the transcription of different genes, turns it into an attractive tool for modelling multiple gene dysregulation. Indeed, neonatal rats treated for a few days (7-10 postnatal days) with MTR, showed three months later cognitive and behavioral deficits such as spatial working memory impairment and anxious behavior, without any impact on their bodily well-being^[61]. The effect of MTR treatment was also studied in AD experimental models. Thus, MTR injections to AD transgenic adult mice for several months, resulted in greater memory impairment in these mice and increased amyloid β peptide levels^[62], with no additional behavioral differences. These data suggest that manipulation of Sp1 transcriptional activity at adulthood has long lasting effects on behavior depending on predisposing genetic aberration earlier in life. In contrast to these results chronic MTR administration to AD transgenic mice by another group resulted in cognitive improvement^[63], emphasizing the need for better understanding the role of Sp1 transcriptional activity in the pathophysiology of AD. In a mouse model for Huntington disease chronic MTR treatment from PND 20 throughout life extended survival, enhanced motor performance, and improved brain histopathology^[64]. The neuroprotective effect of MTR was also demonstrated in adult rats exposed to repeated administration of methamphetamine^[65], an accepted model for schizophrenia^[66].

STRESS EXPOSURE MODEL

Studying the additive effect of environmental variables on top of the predisposing susceptibility is complex and may have many bias pitfalls. Stress is commonly used to mimic environmental insults in models of mental disorders and complex behaviors. We have used peripubertal mild unpredictable stress protocol. One major parameter in modeling environmental effects is the timing of exposure to insult. However, timing and duration of exposure to stress differ between studies. There are early in-life stress models, mainly maternal separation, which increase

stress reactivity in the offspring^[67], while there are adult stress models, including the unpredictable chronic mild stress model, which differ in chronicity, protocol elements and actual age of stress exposure, adolescence or adulthood^[68-70]. Both prenatal period and postnatal mid to late adolescence were shown to be particularly vulnerable to stress in rats^[61]. Chronic adolescence stress was repeatedly shown to be associated with HPA dysfunction^[71], hippocampal volume reduction and impairments in spatial learning^[72] later in life. To elaborate our view on the impact of environment we compared two stress regimens differing only in duration, chronic and sub-chronic regimens, in adolescence. Interestingly, high serum corticosterone levels and higher anxiety index were related to the sub-chronic stress regimen, while rats exposed to chronic stress did not differ significantly from the controls, which implies adaptation to stress^[61]. Although chronic mild stress is an accepted paradigm for induction of depressive-like symptoms in rats^[73], several studies show resilience effects of long-term stress^[74,75] which is in line with the adaptation to the chronic stress regimen.

MANIPULATION OF GENE EXPRESSION AND THE ENVIRONMENT

Studies modeling genetic predisposition for behavioral alterations, induce predisposition in one or more of the four following paradigms: Manipulation of a candidate gene, interference with a candidate system/pathway, intrauterine insults or exposure to early post-natal stressors that induce epigenetic changes.

Numerous studies using candidate gene knockout mice and chronic stress were published. Candidate system interference studies mostly involve HPA axis manipulation either pharmacologically by glucocorticoids administration^[76] or induced by early life stress^[77]. Examples for intrauterine insult models include the prenatal protein malnutrition, which affects development of the brain in utero and induces cognitive impairment and severe widespread morphological abnormalities similar to schizophrenia^[78,79]. Other models are based on the intrauterine infection theory for schizophrenia^[80]. These models include prenatal exposure of mice to viruses, such as the influenza virus^[81] which cause brain developmental damages similar to those observed in schizophrenia brain, or maternal immune activation by lipopolysaccharide or polyinosinic:polycytidylic acid (Poly I:C) during pregnancy, which model schizophrenia and autism in the offspring^[82,83]. The best studied model for epigenetic changes induced by early life stressors is the maternal separation model, which enhances behavioral changes^[84,85], and causes epigenetic modifications that can be transmitted through generations^[11]. We hypothesize that a transient interference with the expression of many various genes, by MTR for example, at a critical developmental stage of the brain together with an exposure of the animal to stressful environment later

in life, will provide an animal model to study the role of gene environment interaction in long lasting complex behavior relevant to mental disorders. Although it may be argued that modification of the expression of numerous genes is inaccurate and difficult to monitor, we believe that it is a closer model to real life complexity. Indeed, we found that MTR treated rats exposed to sub-chronic stress demonstrated higher anxiety index, anhedonia and indifference to novel objects. However, MTR treated rats exposed to the chronic stress paradigm demonstrated normal sucrose preference, low anxiety index and high novelty seeking behavior. These findings support the differential sensitivity theory, claiming increased reactivity to environmental stimuli in genetically sensitive individuals, with differential responses to various stimuli^[16].

INTERTWINED PERIPHERAL AND BRAIN INTERACTION

The molecular and biochemical pathways that contribute to behavioral phenotypes are still a mystery and it is almost impossible to differentiate between genetic and environmental impacts. The currently common dominant hypothesis is that changes in brain cellular pathways are responsible for alterations in behavioral responses. We and others suggest that peripheral factors are essential for formulating behavioral responses. In our rat model for example, we showed that exposing MTR treated rats to chronic stress (MTR + stress) caused a significant reduction in tryptophan brain levels, which in part stems from peripheral changes. Alteration in peripheral tryptophan levels was found to be associated with behavioral and cognitive phenotypes. For example, aggression tendencies associated with a low serum tryptophan levels^[86] and impulsivity^[87] was observed in the course of manic episodes^[88], while increased serum tryptophan levels were observed during the recovery periods in bipolar manic patients^[89]. Tryptophan depletion studies have reported association with worsening of depressive symptoms in human, yet the data are inconclusive^[90,91]. In addition, it was reported that a reduction in tryptophan levels interrupts memory consolidation yet improves attention^[92]. Dietary tryptophan depletion is also used in modeling major depression in rats^[93] and dietary prenatal protein deprivation is used to model cognitive impairment observed in schizophrenia^[78]. In our model, the reduction in brain tryptophan in the MTR + stress rats was probably not due to its extensive metabolism in brain, as no change was observed in its two major metabolic pathways the serotonin and kynurenine pathways^[94]. However, being an essential amino acid tryptophan level in brain depends also on its availability, which can be modulated by several variables including its serum level and its BBB transporter (LAT1) activity^[95]. Serum level of amino acids, which compete with tryptophan on its transporter, the branched chain amino acids (BCAA) for example^[96,97], can affect tryptophan availability to the brain. Indeed, serum tryptophan/BCAA ratio is an established measure to

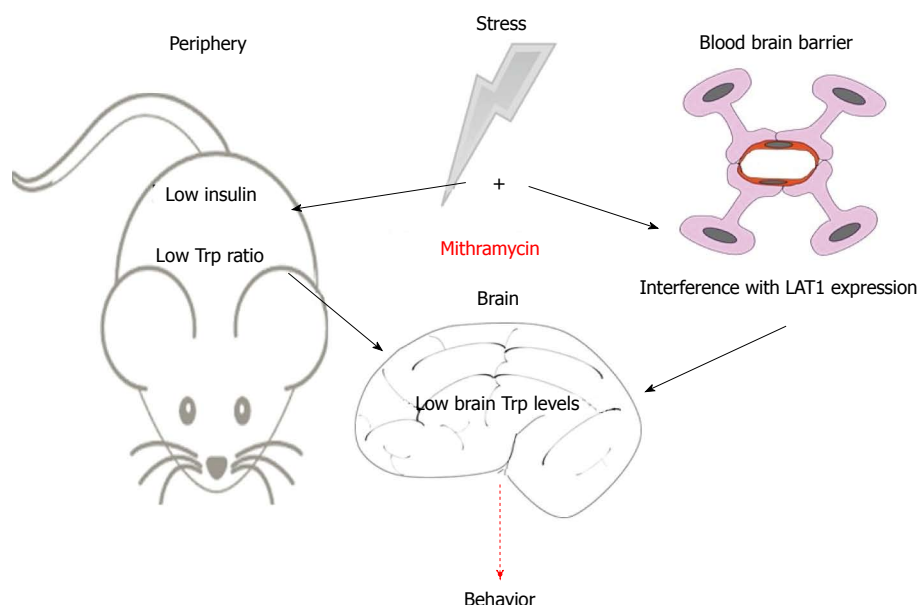


Figure 1 Brain and periphery combined effects modulate behavior in the specificity protein 1 rat model. Early in life transient interference with specificity protein 1 activity by mithramycin and later in life exposure to chronic stress, affect availability of tryptophan (Trp) to the brain, both by reducing serum Trp ratio and brain LAT1 expression. Deficits in brain Trp levels may affect behavior. LAT1: BBB transporter.

estimate brain tryptophan levels^[98]. In the MTR + Stress rats, reduced tryptophan brain levels were associated with reduced LAT1 protein levels and its light chain SLC3A2 transcript levels. In addition, we observed a reduction in serum tryptophan/BCCA ratio, implying a peripheral contribution to reduced brain tryptophan levels. We further suggest that tryptophan/BCCA reduction is due to a failure of these MTR treated rats to respond to stress by increasing serum glucose and insulin, a known regulator of serum BCAA^[99], as did rats exposed to chronic stress only. Taken together, these data suggest that interference with brain tryptophan homeostasis is due to joint brain and peripheral physiological processes. In line with the latter is the finding that brain tryptophan levels were only affected in rats receiving the combined treatment of MTR + stress, while serum tryptophan/BCCA ratio or brain LAT1 were affected by either Stress or MTR, respectively^[94]. Our data suggest that a mild modulation of both peripheral and central processes, which converge and mutually interact, can influence behavioral phenotype. A similar interaction can be seen in circuits of energy balance regulation in the body. Thus, adipose tissues secrete leptin as an afferent signal, which influences the activity of the hypothalamus. The hypothalamus signals decrease food intake by inhibiting anabolic circuits, and enhance energy expenditure through the activation of catabolic circuits^[100]. It is quite intuitive, but sometimes neglected, that the brain collects both central and peripheral internal inputs, as well as external inputs and executes reaction based on the sum of predisposition and experience. The recent increasing interest in the link between microbiome and brain function and its role in mental disorders^[101] further substantiates a role for peripheral inputs in behavior.

CONCLUSION

The ubiquitous transcription factor Sp1 plays a role in the regulation of many genes in response to internal and environmental signals and is suggested to have implication in neuropsychiatric disorders and complex behaviors. Using simple manipulation of Sp1 we showed that a wide and transient interference with gene expression in inbred rats at a critical developmental stage, can induce a long lasting impact on metabolic and behavioral response to environmental stimuli, with different and even opposite outcomes, depending on the characteristics of the environmental stimuli/insult. Already at 1963, Bleuler^[102] wrote that "unfavourable nature and environment develop together and influence each other. They are interwoven from babyhood. The environment influencing the manifestation of the hereditary disposition is already a reflected image of this disposition"^[102]. Peripheral and central physiological processes, which are both subjected to genetic and environmental changes, interact reciprocally to induce specific behavioral patterns (Figure 1). Further studies could shed light on the importance of these brain-periphery reciprocal interactions for whole body homeostasis and its influence on behavior. In addition, new targets may emerge from such a perspective of behavioral modulators for future clinical intervention.

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Basic Study

Ecological Momentary Assessment with smartphones for measuring mental health problems in adolescents

Ernesto Magallón-Neri, Teresa Kirchner-Nebot, Maria Forns-Santacana, Caterina Calderón, Irina Planellas

Ernesto Magallón-Neri, Teresa Kirchner-Nebot, Maria Forns-Santacana, Institute of Research in Brain, Cognition and Behavior (IR3c), 08036 Barcelona, Spain

Ernesto Magallón-Neri, Teresa Kirchner-Nebot, Maria Forns-Santacana, Caterina Calderón, Research Group on Measure Invariance and Analysis of Change (GEIMAC), 08036 Barcelona, Spain

Ernesto Magallón-Neri, Teresa Kirchner-Nebot, Maria Forns-Santacana, Caterina Calderón, Irina Planellas, Department of Clinical Psychology and Psychobiology, Personality, Assessment and Psychological Treatment Section, University of Barcelona, 08036 Barcelona, Spain

Author contributions: Magallón-Neri E designed and coordinated the research, acquired the data, wrote the paper, analyzed and interpreted the data; Kirchner-Nebot T and Forns-Santacana M designed and coordinated the research, revised made critical revisions of the paper and acquired the data; Calderón C and Planellas I acquired the data.

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Correspondence to: Ernesto Magallón-Neri, PhD, Professor, Department of Clinical Psychology and Psychobiology, Personality, Assessment and Psychological Treatment Section, University of Barcelona, Pg. Vall d'Hebron, 171, 08036 Barcelona, Spain. emagallonneri@ub.edu
Telephone: +34-93-3125096
Fax: +34-93-4021362

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Abstract

AIM

To analyze the viability of Ecological Momentary Assessment (EMA) for measuring the mental states associated with psychopathological problems in adolescents.

METHODS

In a sample of 110 adolescents, a sociodemographic data survey and an EMA Smartphone application over a one-week period (five times each day), was developed to explore symptom profiles, everyday problems, coping strategies, and the contexts in which the events take place.

RESULTS

The positive response was 68.6%. Over 2250 prompts about mental states were recorded. In 53% of situations the smartphone was answered at home, 25.5% of cases

they were with their parents or with peers (20.3%). Associations were found with attention, affective and anxiety problems ($P < 0.001$) in the participants who took longer to respond to the EMA app. Anxious and depressive states were highly interrelated ($\rho = 0.51$, $P < 0.001$), as well as oppositional defiant problems and conduct problems ($\rho = 0.56$, $P < 0.001$). Only in 6.2% of the situations the subjects perceived they had problems, mainly associated with inter-relational aspects with family, peers, boyfriends or girlfriends (31.2%). We also found moderate-high reliability on scales of satisfaction level on the context, on positive emotionality, and on the discomfort index associated with mental health problems.

CONCLUSION

EMA methodology using smartphones is a useful tool for understanding adolescents' daily dynamics. It achieved moderate-high reliability and accurately identified psychopathological manifestations experienced by community adolescents in their natural context.

Key words: Ecological Momentary Assessment; Mental health problems; Smartphone; Coping; Adolescents

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Core tip: Adolescence is a stage of life characterized by a great many changes. If they are not coped with effectively, these changes may trigger mental health problems. Among the range of methodologies used to assess the impact of daily problems, Ecological Momentary Assessment allows the recording of mental microprocesses and fluctuations as they happen. We found anxious and depressive states were highly interrelated, as well as oppositional defiant problems and conduct problems in daily life. This methodology based on mobile technology using smartphones is a useful tool with high viability for measuring psychopathological mental states in adolescents in their natural context.

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INTRODUCTION

Adolescence is a stage of life characterized by a great many changes which, if not addressed effectively, may trigger problems of mental health^[1-5]. There is a substantial body of literature assessing the possible impact of individual everyday problems on the development of mental health disorders^[6].

One of the formats used to assess the impact of everyday problems is Ecological Momentary Assessment

(EMA). This methodology allows the recording of the expression of mental microprocesses and their fluctuations in several situational contexts as they happen^[7]. Its applicability has been demonstrated in a variety of populations in studies of general health^[8].

Specifically, in adolescent samples, EMA has been used to assess or predict health needs^[9], mental status^[10] emotional instability^[11], drug use^[12], stress associated with traumatic events^[13], and anxiety problems^[14].

In fact EMA has been used for decades^[7], but reports of its use in the field of mental health are relatively recent. At present there is no evidence of its use in adolescent community populations to measure broad areas of psychopathological symptoms (sadness, anxiety, somatic, thought, behavioral and attentional problems) in real time in their natural setting, focusing on the coping strategies used and their relation to their situational and personal contexts.

The aim of this study is to explore the viability of EMA for measuring the mental states associated with psychopathological problems in adolescents, taking into account the situational context and the coping strategies they apply.

MATERIALS AND METHODS

Participants

The sample was constituted initially by 110 adolescents from the province of Barcelona, of whom 101 successfully completed the EMA study. Following the recommendations of previous researchers regarding the quality of information^[6,15], only subjects who completed at least 12 of the 35 possible recordings (roughly 33%) were considered.

Instruments

Sociodemographic data: A survey sheet was created *ad hoc* to gather basic data on age, gender, school year, citizenship, family and employment status.

EMA

Each participant received a smartphone with an Android-based EMA application already installed. This application was programmed to give a series of alarms associated with the task of answering mini-questionnaires at five semi-random moments over the course of the day between 9 am and 9 pm for a complete week. The mini-questionnaires comprised 21 items (five with multiple choice answers, two with yes/no answers, 14 to be rated on a 5-point Likert scale) which participants were required to answer within three minutes of hearing the first alarm. If the user did not start to answer within this period of time the application stopped the smartphone alarm and blocked the unit.

Users could not delay their answers beyond five minutes after their last interaction with the application, or take longer than ten minutes to answer the entire mini-questionnaire, in order to ensure that the information was instantaneous and not retrospective. If users were unable to answer within these time limits the application

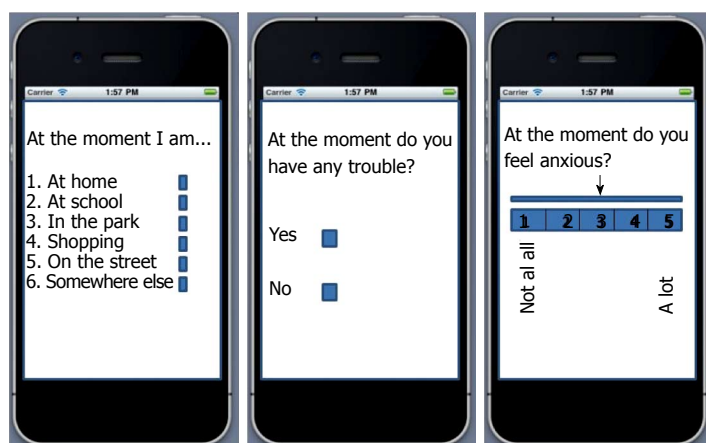


Figure 1 Example of questions asked within Ecological Momentary Assessment app in this study.

blocked the smartphone and they were told to wait until the next random alarm; this reply attempt was considered empty.

These mini-questionnaires comprised questions regarding situational context and broad areas associated with psychopathological problems such as behavior problems, anxiety, sadness, lack of concentration, and so on. It also covered everyday problems and how to cope with them. Figure 1 shows an example of the questions asked.

The application stored the data collected for a week (7 d). Once the evaluation period finished, the data were downloaded by the research team. As a result, a maximum of 35 moments of semi-random evaluation were obtained from each subject. Figure 2 displays the EMA cycle used in this study.

Procedure

Several social service centers and schools in the metropolitan Barcelona area and its surroundings were contacted. Two centers agreed to participate after a full explanation of the project and its logistic implications with regard to the distribution and application of EMA methodology with smartphones. After obtaining the centers' approval, 30-min information sessions were arranged for students from eighth to eleventh grade. In these sessions, students received explanations of their role in the study and the implications of their participation. Informed consent forms were then distributed among the participants for authorization, either by the participants themselves or by their parents and/or tutors. All the procedure and assessment protocols had been previously authorized by the research ethical committee of the University, and complied with the guidelines of the Declaration of Helsinki and legislation regarding confidential data protection.

After obtaining written consent, meetings were arranged for explaining the instruments and the workings of the smartphone devices and EMA app functioning. On receiving the smartphone, participants were assigned an individual alphanumeric code to protect their identity in case of loss or theft of the device. They were informed that they would have the phone for a whole week and that it would ring five times a day at semi-random times,

and that they should answer as often as possible. They were also asked as well to sign a commitment to take good care of the smartphone and received an information sheet explaining how the smartphone functioned and how to answer and containing contact data in case of any technical problem during the experiment.

Statistical analysis

The χ^2 test was used to calculate differences between proportions in frequencies, the *t*-student test to calculate differences of means between two groups, ANOVA for comparisons between several subgroups with Bonferroni correction, and Spearman correlations to calculate associations between variables.

RESULTS

Socio-demographic data

The sample comprised 101 adolescents (age $M = 14.68 \pm 1.64$; 61% women). Sixty percent were Spanish natives and 40% were foreigners (28% were Latin Americans). Regarding family structure, between 67% and 71% of participants' parents were married and between 21% and 23% separated or divorced. As for parents' employment, 77% of fathers were employed and 70% of mothers.

EMA answer rates

In all, 68.6% of questionnaires were completed, while in 31.4% data were missing: Ignored alarms accounted for 23.9% of the missing data (due to a lack of time to answer or not paying attention), rejected answer attempts for 4.5%, and incomplete records not quantified in the analysis for 3.0%. The difference between the types of answer was significant ($\chi^2 = 3712.60$; $P < 0.001$). The mean time taken to answer the questionnaires was $80.6 \text{ s} \pm 56.5 \text{ s}$. These data suggest a mean answer time of between one and three minutes.

Contextual variables

Variables about the context (Where, who with, and what were they doing?). In 53% of situations the smartphone was answered at home, followed by 24.3% at school and 15.5% outside in the street. There were

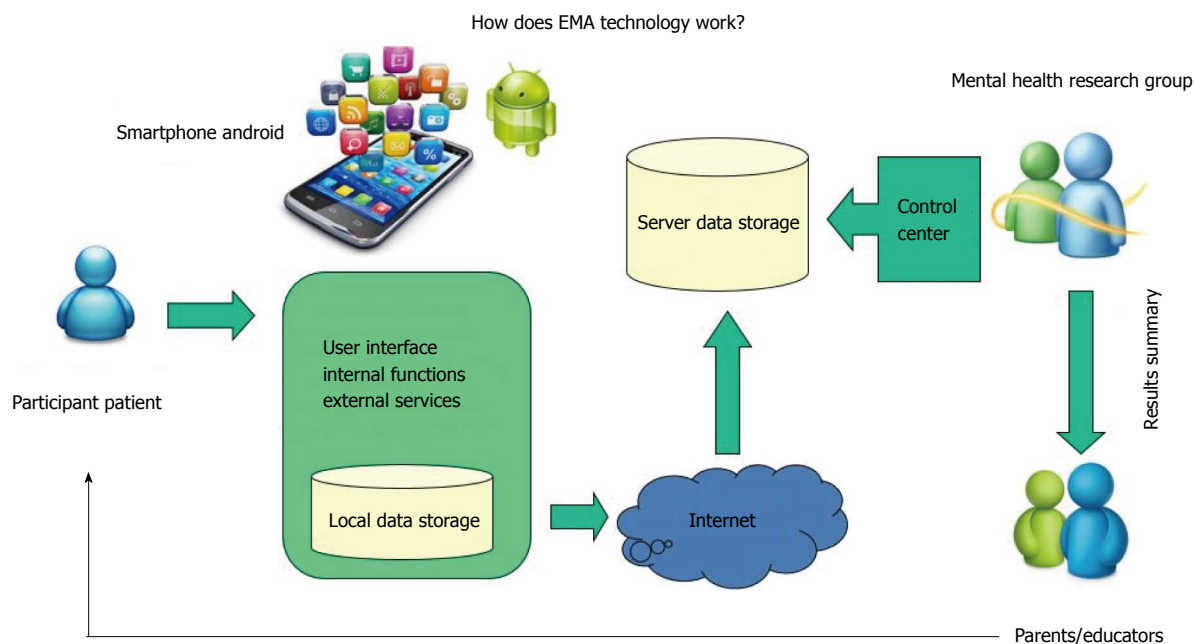


Figure 2 Assessment cycle used in this study with Ecological Momentary Assessment methodology.

significant differences between these three response contexts ($\chi^2 = 1072.38$; $df = 2$; $P < 0.001$). On a 1-5 point Likert scale, in 69% of cases the situational context was assessed as pleasant (a score of 4) or very pleasant (a score of 5). Only in 11.2% of the situations was the context unpleasant or very unpleasant (scores of 1 or 2).

Regarding the people being with the adolescents at the time of assessments, in 25.5% of cases they were with their parents, in 20.3% with peers and in 19.1% alone. There were significant differences between these three groups ($\chi^2 = 25.28$; $df = 2$; $P < 0.001$). The company was regarded as pleasant or very pleasant in 77.9% of situations and unpleasant or very unpleasant in only 7.1%.

The three activities that participants were most frequently engaged in at the time of answering the EMA questionnaires were school tasks or activities (26.7%), talking to somebody (19.7%), and watching TV or the computer (16.8%). There were significant differences between these three activities ($\chi^2 = 58.11$; $df = 2$; $P < 0.001$). The adolescents regarded the activities they were engaged in when they answered the smartphone as pleasant or very pleasant in 64% of cases and as unpleasant or very unpleasant in only 8.9% ($\chi^2 = 113.49$; $df = 3$; $P < 0.001$). The momentary level of satisfaction associated with the context (physical, relational and activity-related) composed by three items, obtained a Cronbach's alpha of 0.75.

Momentary emotional status and behaviors

In a collection of around 2250 responses obtained from the participants during the week, it was found that in most of situations, these people reported the absence of problems associated with the following

symptoms: Affective (79%), anxious (78.2%), somatic (84.3%), inattentive (81%), oppositional (93.7%), aggressive (95%), obsessive-compulsive (82.6%) or traumatic (93.6%). All these situational problems were significantly absent ($P < 0.001$). Regarding the intensity of problems according to gender, girls presented more affective ($t = -9.077$; $P < 0.001$), anxious ($t = -4.808$; $P < 0.001$), somatic ($t = -6.603$; $P < 0.001$) and post-traumatic symptoms ($t = -4.040$; $P < 0.001$) than boys. Boys presented slightly more inattentive-hyperactive problems ($t = 2.046$; $P = 0.041$), but there were no significant differences in other disruptive behaviors or obsessive-compulsive problems in daily life. All eight items constituting the general discomfort index associated with momentary mental health problems obtained a Cronbach's alpha of 0.76.

It was also observed that subjects who presented strong situational problems of inattention, sadness or anxiety, they also took longer to respond (120 s \pm 78 s for inattention; 111 s \pm 57 s for sadness; and 122 s \pm 79 s for anxiety) than subjects who did not present these problems (75 s \pm 52 s in absence of inattention, 76 \pm 53 s in absence of sadness and 75 s \pm 53 s in absence of anxiety). The difference was significant ($F = 37.15$; $df = 4$; $P < 0.001$ for inattention; $F = 28.31$; $df = 4$; $P < 0.001$ for sadness; and $F = 31.33$; $df = 4$; $P < 0.001$ for anxiety). Bonferroni's post-hoc results showed that significant differences appeared essentially between subjects who did not have these problems and subjects who had them with a certain degree of intensity.

With regard to situations associated with positive emotionality, in particular to feeling happy or loved, subjects reported being happy or very happy (64.2% of cases) and feeling loved or loved very much (66% of cases). There were significant differences in comparison

Table 1 Mental health symptomatology areas measured by Ecological Momentary Assessment in boys and girls

Variables	1	2	3	4	5	6	7	8
Affective problems	--	0.38	0.26	0.33	0.15	0.11	0.2	0.32
Anxiety problems	0.57	--	0.23	0.35	0.18	0.14	0.27	0.18
Somatic problems	0.22	0.23	--	0.14	0.12	0.09	0.20	0.10
Hyperactivity-Inattention problems	0.39	0.38	0.18	--	0.22	0.21	0.34	0.28
Oppositional-defiant problems	0.27	0.30	0.19	0.29	--	0.58	0.29	0.31
Conduct Behavior problems	0.27	0.31	0.20	0.27	0.56	--	0.16	0.30
Obsessive compulsive problems	0.25	0.34	0.22	0.31	0.31	0.32	--	0.31
Posttraumatic stress problems	0.34	0.36	0.19	0.34	0.47	0.46	0.39	--

Above the diagonal, boys' results, below the diagonal, girls' results. All the results are significant ($P < 0.001$). In bold-face, the correlations with high-moderate index.

with unhappy situations ($\chi^2 = 978.15$; $df = 4$; $P < 0.001$) or situations in which one does not feel loved ($\chi^2 = 1101.58$; $df = 4$; $P < 0.001$). The intensity of positive emotionality of these two items obtained a Cronbach's alpha of 0.81 in this study.

Anxious and depressive states were interrelated in the whole sample ($\rho = 0.51$; $P < 0.001$), and oppositional/defiant problems were associated with conduct problems ($\rho = 0.56$; $P < 0.001$). Table 1 displays the relationship between problems associated with mental health symptoms by gender. Specifically, girls presented strong relationships between anxiety and affective problems, oppositional/defiant problems and conduct problems, posttraumatic stress problems and disruptive behaviors, while in boys the only strong relationship observed was between oppositional/defiant problems and conduct problems.

Everyday problems and coping strategies

Only in 6.2% of the situations in which they were asked to answer the mini-questionnaire with the smartphone did the subjects perceive they had a problem. The most common problems, in order of frequency, were those associated with inter-relational aspects with family, peers, boyfriends or girlfriends (31.2%), followed by schoolwork or worrying about exams (29.1%), and arguments or behavior problems (9.9%). Significant differences were found between these three types of everyday problems in adolescents ($\chi^2 = 14.80$; $df = 2$; $P = 0.001$).

The most frequently used kind of coping strategy when a problem appeared was seeking relaxing diversions (21.5%), followed by trying to see the positive side of the situation (20.1%) and then seeking help from peers (16%). The least used strategies were looking for help in the family (6.3%) and seeking spiritual support (1.4%). Significant differences were found in the types of coping ($\chi^2 = 38.23$; $df = 7$; $P < 0.001$).

Regarding their satisfaction with their coping strategies, on more than a third of occasions (35%) adolescents felt neither happy nor unhappy with the strategy chosen to face a specific problem. In 11.2% of cases the subjects were discontent with their choice

of strategy, but in 28% they felt very satisfied. There were differences in the appreciation of the application of coping strategies ($\chi^2 = 35.92$; $df = 4$; $P < 0.001$), in that case the majority believed them to be effective.

DISCUSSION

The most relevant result in this study is the finding that in most situations in daily life (between 78% and 93%) adolescents do not present problems that trigger mental health symptoms. When these problems appear, they tend to be closely related to states of sadness or anxiety. Similarly, oppositional defiant behaviors were associated with conduct problems, a finding that corroborates the syndromic daily patterns associated with the two broad areas of symptoms (internalizing/externalizing) regularly found in the field of child and teenager psychopathology^[16-18]. It was also observed that the positive response rate of the EMA app (68.6%), and the time taken (about 1-2 min) reflect an accurate measurement of associated context, the broad areas of clinical symptomatology and coping strategies in real time. We also found moderate-high reliability on scales of satisfaction level on the context, on positive emotionality, and on the discomfort index associated with mental health problems. These results show that EMA methodology based on mobile technology offers high viability for measuring mental health states in adolescents.

Among the contextual variables, we stress that during the week-long EMA, the adolescents were regularly at home when answering the smartphone application. This result should be borne in mind, due to the contextual relation of family dynamics in the promotion and development of symptomatology or solutions to everyday problems.

For their part, the results regarding satisfaction in the immediate context show that in most cases adolescents feel satisfied with the surrounding environment (in this case their home). Moreover, in relation to variables of interpersonal contact, it is interesting that the people with whom they have the most contact are their parents, followed by their colleagues or peers: This finding may challenge the concept of adolescence as a stage in which

subjects prefer to be with their peers or alone^[4,5].

Nevertheless, this does not mean that they prefer to be with their parents, because the adolescents can share a great deal of time together. Perhaps this result reflects the fact that our adolescents regularly answered the application at home (53%), where they are more likely to record direct contact with their parents. However, this shows us that the parents may play a significant role in their children's development of functional patterns of psychological adaptation *via* this continuous contact during the adolescent stage, as stated previously by other authors^[19]. In adolescent-parent relationships related to parenting styles, it is highlighted the importance of authoritative homes (where parents are both demanding and responsive) with more psychosocial and academic competence^[5], that prevent some potential risk situations such as a problematic drug use^[3], internalizing/externalizing symptoms^[4] or victimization problems^[1].

When studying daily patterns it is important to bear in mind that the context and the people with whom we are in contact have a strong effect on the activities we perform. Being in tune with the evolutive stage and the main function to be developed by adolescents at these ages. The adolescents reported that when they were had to answer the questionnaire, in more than a quarter of the cases they were doing school homework, followed by talking and leisure activities (TV-PC). Here the level of pleasure was influenced considerably by their interaction with the place and the people present^[4]. Being the homework an activity regularly imposed, they reflect their perception of not being completely satisfied with this activity development, not necessarily meaning extreme dissatisfaction level, in this contextual activity.

In relation to emotional states, momentary symptomatology was broadly absent in the different areas studied (affective, anxious, somatic, inattentive, oppositionist, aggressive behavior, obsessive-compulsive problems, and trauma situations).

In general, the low results for impairment obtained reflect the type of population studied (*i.e.*, a community population). Higher reports of impairment would be likely if the assessment had been applied in a clinical sample^[6,20]. The intensity of impairments may also depend on the level of clinical assistance received (out-patient, day hospital or inpatient). These hypotheses should be verified in further studies of clinical samples of adolescents with psychiatric disorders.

The perception of everyday problems and the use of coping strategies is an interesting result. Only rarely did the adolescents record the presence of problems in the assessment, the most frequent being inter-relational and academic performance problems. This reflects the main worries of adolescents at this development stage, characterized by openness to new experiences in the field of social relations^[5] and an increase in academic pressure prior to entry to university or to a vocational training center. Similar results has been obtained by other others using traditional methodology^[21]. On the

other hand, it is important to promote a high parental self-efficacy, which would be highly related to ecological variables and parenting competence, in such a way that environmental conditions and ecological contexts may influence and undermine parent's confidence and parenting competence^[22].

This study has a number of limitations that may affect the interpretation of the results. The first is the sample size. The application of the EMA methodology for seven consecutive days raises a series of logistical issues that complicate the recruitment and maintenance of participants. Compared with the pencil-paper assessment at a specific moment, EMA offers a considerable number of benefits (assessment in real time, decrease in memory bias, contextual association) and drawbacks (time-limited evaluation, sampling, loss of important events and overload) as noted by Shiffman *et al.*^[7] 2008, van Os *et al.*^[20] 2014, and Stone^[23] 2007. All these points should be taken into account when applying EMA. In fact, the sample size in this study is within the range of most other studies in clinical^[12-14,24] or community^[9-11,25] adolescent populations.

Another issue to be considered is the type of population studied. As our data are from a community sample, they cannot be directly extrapolated to the clinical population or to a specific subgroup with psychiatric disorders. Nevertheless, one should bear in mind that the clinical population is a particular and acute subgroup of the community population. This study may represent a first step in the advancement of knowledge of daily patterns associated with mental health problems in adolescence and the assessment of contextual variables and coping strategies. Third, as this assessment study was carried out over a week, it would be interesting to compare these results with those from wider populations with specific psychiatric disorders, over different time periods, and with a longitudinal design. Despite these limitations, this is, to our knowledge, the first study in adolescents to apply the smartphone-based EMA methodology to measure the triad of contextual variables, symptoms associated with mental health problems and coping strategies.

EMA methodology using smartphones is a useful tool for assessing daily dynamics. It provides a sufficiently accurate measure of the psychopathological manifestations experienced by community adolescents in their natural context. In the study of momentary states associated with mental health symptomatology over a one-week period, we found that in most cases adolescents do not present emotional alterations or problems in their daily life. Girls were slightly more affected in their momentary emotional status and behaviors in daily life than boys. And among the situations in which a conflict is generated - on the one hand, anxious-depressed states, and on the other the oppositional-aggressive behavior are closely inter-related. Our results show that the family and home context could be crucial for the potential development of training interactions, both positive and negative, in the

mental health field, and they also stress the importance of individuals' coping resources in relation with their formative, relational, and physical context.

COMMENTS

Background

Adolescence is a stage of life characterized by a great many changes which, if not addressed effectively, may trigger problems of mental health. There is a substantial body of literature assessing the possible impact of individual everyday problems on the development of mental health disorders.

Research frontiers

Ecological Momentary Assessment (EMA) is a methodology allows to assess the impact of everyday problems in several situational contexts as they happen. Its applicability has been demonstrated in a variety of populations in studies of general health.

Innovations and breakthroughs

This study may represent a first step in the advancement of knowledge of daily patterns associated with mental health problems in adolescence and the assessment of contextual variables and coping strategies. The results show that EMA methodology based on mobile technology offers high viability for measuring mental health states in adolescents.

Applications

EMA methodology using smartphones is a useful tool for assessing daily dynamics. It provides a sufficiently accurate measure of the psychopathological manifestations experienced by community adolescents in their natural context.

Terminology

EMA is a methodology that allows the recording of the expression of mental microprocesses and their fluctuations in several situational contexts as they happen. Compared with the pencil-paper assessment at a specific moment, EMA offers a considerable number of benefits (assessment in real time, decrease in memory bias, contextual association) and also drawbacks (time-limited evaluation, sampling, loss of important events and overload).

Peer-review

The authors have reported their findings based on EMA with Smartphones for measuring mental health problems in adolescents. The study was well taken and the results indicate that such an evaluation is helpful to assess whether using smartphones is a useful tool for assessing daily dynamics or sufficiently accurate measure of the psychopathological manifestations experienced by community adolescents.

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Case Control Study

Voxel-based magnetic resonance imaging investigation of poor and preserved clinical insight in people with schizophrenia

Adegboyega Sapara, Dominic H Ffytche, Michael A Cooke, Steven CR Williams, Veena Kumari

Adegboyega Sapara, Michael A Cooke, Veena Kumari, Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, United Kingdom

Dominic H Ffytche, Department of Old Age Psychiatry and Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, United Kingdom

Steven CR Williams, Department of Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, United Kingdom

Veena Kumari, NIHR Biomedical Research Centre for Mental Health, South London and Maudsley NHS Foundation Trust, London SE5 8AF, United Kingdom

Author contributions: Sapara A, Ffytche DH and Kumari V designed the study; Cooke MA carried out the neuropsychological assessments; Williams SCR assisted with neuroimaging data acquisition; Sapara A performed all analyses and wrote the manuscript under Ffytche DH and Kumari V's joint supervision.

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Correspondence to: Veena Kumari, PhD, Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London SE5 8AF, United Kingdom. veena.kumari@kcl.ac.uk
Telephone: +44-207-8480233

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Abstract

AIM

To define regional grey-matter abnormalities in schizophrenia patients with poor insight (Insight⁻), relative to patients with preserved clinical insight (Insight⁺), and healthy controls.

METHODS

Forty stable schizophrenia outpatients (20 Insight⁻ and 20 Insight⁺) and 20 healthy controls underwent whole brain magnetic resonance imaging (MRI). Insight in all patients was assessed using the Birchwood Insight Scale (BIS; a self-report measure). The two patient groups were pre-selected to match on most clinical and demographic parameters but, by design, they had markedly distinct BIS scores. Voxel-based morphometry employed in SPM8 was used to examine group differences in grey matter volumes across the whole brain.

RESULTS

The three participant groups were comparable in age [$F(2,57) = 0.34, P = 0.71$] and the patient groups did not differ in age at illness onset [$t(38) = 0.87, P = 0.39$]. Insight⁻ and Insight⁺ patient groups also did not differ in symptoms on the Positive and Negative Syndromes scale (PANSS): Positive symptoms [$t(38) = 0.58, P = 0.57$], negative symptoms [$t(38) = 0.61, P = 0.55$], general psychopathology [$t(38) = 1.30, P = 0.20$] and total PANSS scores [$t(38) = 0.21, P = 0.84$]. The two patient groups, as expected, varied significantly in the level of BIS-assessed insight [$t(38) = 12.11, P < 0.001$]. MRI results revealed lower fronto-temporal, parahippocampal, occipital and cerebellar grey matter volumes in Insight⁻ patients, relative to Insight⁺ patients and healthy controls (for all clusters, family-wise error corrected $P < 0.05$). Insight⁺ patient and healthy controls did not differ significantly ($P > 0.20$) from each other.

CONCLUSION

Our findings demonstrate a clear association between poor clinical insight and smaller fronto-temporal, occipital and cerebellar grey matter volumes in stable long-term schizophrenia patients.

Key words: Psychosis; Insight; Grey matter volumes; Fronto-temporal; Neural networks; Birchwood insight scale

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Core tip: Poor clinical insight is the most prevalent symptom in patients with schizophrenia and is of growing importance due to its direct association with poor clinical outcomes, such as frequent relapses and hospital admissions. This study identified significantly reduced fronto-temporal, parahippocampal, occipital and cerebellar grey matter volumes in Insight⁻ patients relative to both Insight⁺ patients and healthy controls. The involvement of multiple brain areas and corresponding neural networks supports the theory that clinical insight, as a neurological function, is not confined to specific neuroanatomical regions but probably a function of a complex neurocognitive interplay with contributions from multiple neural networks.

Sapara A, Ffytche DH, Cooke MA, Williams SCR, Kumari V.

Voxel-based magnetic resonance imaging investigation of poor and preserved clinical insight in people with schizophrenia. *World J Psychiatr* 2016; 6(3): 311-321 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v6/i3/311.htm> DOI: <http://dx.doi.org/10.5498/wjp.v6.i3.311>

INTRODUCTION

Nearly a century ago, Kraepelin (1919) observed that schizophrenia patients often had "no real understanding of the gravity of their disorder" and regularly disputed that they suffer from a mental illness^[1]. In the 1930s, Lewis described clinical insight as having "a correct attitude to a morbid change in one's self"^[2,3] and low clinical insight is the most prevalent symptom occurring in about 97% of schizophrenia patients^[2,4]. Impaired insight in schizophrenia is of growing importance due to its direct correlation with poor clinical outcomes, such as frequent relapses and hospital admissions^[5], poor compliance with medication and treatment plans^[6-8], severe psychopathology^[9], greater suicidal tendencies and self-injurious behaviour^[9-12]. Some studies reporting positive correlations between improvement in clinical insight and better global clinical impression and clinical outcome scores^[13] have further suggested the adoption of clinical insight as a possible therapeutic target in schizophrenia patients^[14].

Similarities between impaired insight in schizophrenia and unawareness of neurological deficits such as anosognosia, first described in patients with acute brain lesions with left-sided hemiplegia who were unaware of the impairments in their paralysed limbs^[15,16], led to the notion that both phenomena share a common neurological basis^[17-19] and prompted investigations of neuroanatomical abnormalities in relation to impaired clinical insight in schizophrenia. Earliest studies, using computerized tomography (CT) scan, reported significant and direct associations between impaired clinical insight and ventricular enlargement^[20], total insight scores and total brain volumes^[21] and a linear relationship between global cortical atrophy and impaired clinical insight^[22]. These studies all concluded that there is a significant association between whole brain volume loss and impaired clinical insight in schizophrenia. Structural magnetic resonance imaging (MRI) studies also reported correlations between impaired clinical insight and smaller regional grey matter volumes, including the frontal lobe, anterior cingulate cortex (ACC), posterior cingulate, temporal and parietal lobes^[23-28]. More recently, correlations have been reported between impaired insight and smaller right posterior insula volumes^[29], smaller grey matter volumes of the right ventro-lateral prefrontal cortex (PFC)^[30], left ventrolateral PFC, right dorsolateral PFC, insula, bilateral premotor area and the putamen; and reduced white matter volumes of the right superior longitudinal fasciculum, left corona radiata, left forceps minor and bilateral cingulum^[31].

Although most studies have reported a correlation between brain volume loss and impaired insight, some studies failed to find any correlation between clinical insight and either ventricular or total/regional brain volumes^[3,32,33], while others reported associations between impaired clinical insight and increased (rather than decreased) right medial orbitofrontal cortex grey matter volumes^[28], and between symptom misattribution and increased grey matter volumes in bilateral caudate regions, right thalamus, left insula, putamen and cerebellum^[34]. Bassitt *et al.*^[35] found no significant inverse correlation between total or regional grey matter volumes and clinical insight but, contrary to their expectations, observed a positive correlation between degree of insight impairment and the left medial PFC and ACC grey matter volumes, which they attributed to higher doses of antipsychotics given to patients with impaired clinical insight in their sample. The marked variation in findings may be due to the use of different brain volumetric assessment techniques, the heterogeneity of clinical insight measures and varying clinical characteristics of schizophrenia patients studied^[25,35,36].

The aim of the present study was to characterise grey matter alterations in stable long-term schizophrenia outpatients with impaired clinical insight by directly comparing them, for the first time to our knowledge, with schizophrenia outpatients with preserved clinical insight, matched on average for age, sex and relevant demographic and clinical characteristics. Our approach of utilising the two extremes of the insight distribution should yield the largest structural difference in relation to insight. We also compared how these distinct groups of patients might differ from healthy controls, matched on average on age and sex of the patient groups. Based on the findings (where positive) of existing studies involving solely or predominantly chronic patient samples, we hypothesised that, patients with impaired insight (Insight⁻) will show smaller frontal and temporal regional grey matter volumes compared to patients with preserved insight (Insight⁺) and healthy controls. This hypothesis also has support from previous studies showing, on average, poor cognitive function in patients with impaired insight^[25,37,38] and a positive association between grey matter volumes of these regions and a range of cognitive functions in schizophrenia^[39].

MATERIALS AND METHODS

Participants and study design

This study included 60 right-handed participants. Forty of these were patients with a diagnosis of schizophrenia, confirmed using the Structured Clinical Interview for DSM-IV (SCID)^[40]. The patients formed two groups of 20 patients each, pre-selected to have preserved and impaired insight, out of a larger pool of 70 stable community patients. The assessment of insight and differentiating criteria are described in detail under "clinical assessment". All included patients were required to be: (1) on well established antipsychotic medication

doses for ≥ 3 mo; (2) in the stable (chronic) phase of the illness; and (3) ≥ 2 years from illness onset. Twenty healthy controls screened to exclude neuropsychiatric conditions and matched, on average, for age and sex of the patients were studied for comparison purposes. Ethics approval was granted by the ethics committee of the Institute of Psychiatry and South London and Maudsley Foundation NHS Trust, London. All participants provided written informed consent.

Clinical assessment

Birchwood Insight Scale (BIS)^[41], a self-rated questionnaire, was used to assess insight in all patients. The BIS measures three different aspects of clinical insight^[2]: (1) the awareness of the presence of a mental disorder (2nd and 7th statement); (2) the awareness of the need for treatment (3rd, 6th statement); and (3) the ability to label symptoms as abnormal (1st and 8th statement). Each individual BIS statement (8 in total) is rated and given a score of one for unsure, and either 0 or 2 for agree and disagree, depending on whether agreeing with the statement depicts preserved clinical insight (all statements are corrected for response valence). As we did not include any inpatients, Item 4 "My stay in hospital is necessary" was deleted, thus yielding a maximum possible score of 14, compared with a maximum possible score of 16 in the full scale BIS. In operationalising the BIS, Birchwood *et al.*^[41] classified preserved insight as having a minimum score of 9 (out of 14). In this study, we defined "preserved insight" as a minimum score of 13 (out of 14) and "impaired insight" as a score of 8 or below. This rather conservative method was designed to ensure that the two groups had distinct levels of insight and also to eliminate those with partial clinical insight levels. All patients were supervised during the completion of the BIS. The BIS has acceptable internal consistency ($\alpha = 0.75$) and one week test-retest reliability ($r = 0.90$ for the total score^[41]), and insight assessed on the BIS correlates positively with scores on other measures of insight^[10,26,42]. For sample characterization purposes, symptoms in patients were assessed using the Positive and Negative Syndrome Scales (PANSS^[43]). In addition, predicted IQ of all study participants was measured using the National Adult Reading Test (NART^[44]).

Image acquisition and processing

Whole brain MRI scans were acquired for all study participants using a 1.5 Tesla GE NV/I Signa system (General Electric, Milwaukee WI, United States) at the Maudsley Hospital, London. A series of sagittal fast gradient echo scout images were obtained to correct for head tilt and to orient subsequent images relative to the anterior-commissure/posterior-commissure line and the interhemispheric fissure. A 3-D inversion recovery prepared fast spoiled GRASS sequence was applied to acquire T1-weighted images in the axial plane with 1.5 mm contiguous sections (TR = 18 ms, T1 = 450 ms, TE = 5.1 ms, flip angle = 20° with one data average and a 256 × 256 × 128 voxel matrix). Acquisition

parameters were selected employing a sophisticated image simulation^[45]. All MRI images were converted into ANALYZE format (ANALYZE software, BRU, Mayo Foundation, Rochester, MN) and pre-processed using Statistical Parametric Mapping (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) running in MATLAB 2006a (MathWorks, Natick, MA). Customised T1-weighted templates of the whole brain, grey matter, white matter and cerebrospinal fluid (CSF) were created for patient and healthy participant groups separately, and also for the whole study sample combined.

Statistical analysis

Demographic and clinical measures: Possible group differences in age, education and NART IQ were examined using analyses of variance (ANOVAs), and significant Group effects were followed by independent sample *t*-tests. Possible differences between the two patient groups in clinical variables (age at illness onset, PANSS symptom scores and medication) were examined using independent sample *t*-tests. All statistical analyses were conducted using SPSS 22, with alpha level for significance testing maintained at $P \leq 0.05$ (two-tailed), unless stated otherwise.

MRI: Group differences (healthy controls vs Insight⁻ patients, healthy controls vs Insight⁺ patients, and Insight⁻ vs Insight⁺ patients) in grey matter volumes, across the whole brain, were examined using ANOVA in SPM8 (height threshold $P < 0.005$; familywise-error (FWE)-corrected at the cluster level $P < 0.05$). To rule out the possibility that any observed group differences were due to trend-level Group differences in education and IQ (see RESULTS, demographic and clinical measures), group differences in grey matter volumes were re-evaluated using analysis of co-variance, with education and IQ entered as co-variables.

RESULTS

Demographic and clinical characteristics

The three participant groups did not differ in age [$F(2,57) = 0.34$, $P = 0.71$]. There were trend level effects of Group in years of education [$F(2,57) = 2.60$, $P = 0.08$] and NART IQ [$F(2,57) = 2.67$, $P = 0.08$]. Healthy controls spent more years in education than Insight⁻ patients [$t(38) = 2.11$, $P = 0.04$] but differed only at a trend level when compared with Insight⁺ patients [$t(38) = 1.77$, $P = 0.08$]. Healthy controls also had higher NART IQ than Insight⁻ patients [$t(38) = 2.47$, $P = 0.02$] but did not differ from Insight⁺ patients [$t(38) = 1.19$, $P = 0.24$]. There were no significant differences between the Insight⁻ and Insight⁺ patient groups in education [$t(38) = 0.06$, $P = 0.95$] and NART IQ [$t(38) = 1.04$, $P = 0.31$] (Table 1). The two patient groups were similar in age at illness onset [$t(38) = 0.87$, $P = 0.39$], positive symptoms [$t(38) = 0.58$, $P = 0.57$], negative symptoms [$t(38) = 0.61$, $P = 0.55$], general

psychopathology [$t(38) = 1.30$, $P = 0.20$] and total PANSS symptoms [$t(38) = 0.21$, $P = 0.84$]. Patients in the two groups were on a range of typical and atypical antipsychotics (Table 1) but received, on average, similar doses of antipsychotic medication [$t(38) = 0.86$, $P = 0.40$]. The Insight⁺ patient group, confirming our insight-based pre-selection, had significantly higher BIS score than the Insight⁻ group [$t(38) = 12.11$, $P < 0.001$].

MRI: Group effects in regional grey matter volumes

Group differences in brain MRI grey matter volumes are presented in Table 2, and described below.

Insight⁻ vs Insight⁺ patients: Compared to Insight⁻ patients, Insight⁺ patients had larger grey matter volumes in the inferior frontal and precentral gyri, superior and middle temporal gyri, parahippocampus, cuneus and cerebellum of both cerebral hemispheres (Figure 1).

Healthy controls vs Insight⁻ patients: Compared to Insight⁻ patients, healthy controls had larger grey matter volumes in the left inferior and middle frontal gyri, left superior, middle and inferior temporal gyri, left parahippocampus, right cerebellum, and bilateral superior, middle and inferior occipital gyri (Figure 1).

Healthy controls vs Insight⁺ patients: There were no significant differences between healthy controls and Insight⁺ patients.

Group differences after co-varying for education and predicted IQ

Differences in grey matter volumes (noted earlier) between healthy controls and Insight⁻ patients remained present but with reduced significance when we co-varied for education and IQ (Table 3). Group differences between Insight⁻ and Insight⁺ patients, however, were not affected.

DISCUSSION

In this study, we directly compared two matched groups of schizophrenia patients but with distinct levels of clinical insight (Insight⁻ vs Insight⁺) and investigated how they differ from each other and also from healthy controls in regional grey matter volumes examined using voxel-based morphometry (VBM) technique. We tested the hypothesis that Insight⁻ patients will show smaller frontal and temporal grey matter volumes compared to Insight⁺ patients. All three participant groups were comparable in age and the two patient groups were similar in all demographic and clinical parameters, including age at illness onset, years of education, NART IQ, symptoms (PANSS scores) and doses of medication prescribed. Insight⁻ patients, however, had lower IQ and fewer years in education than healthy controls. Although, on average, lower IQ as well as deficits in many specific cognitive

Table 1 Demographics and clinical characteristics of the study groups

	Healthy controls (<i>n</i> = 20; 15 male, 5 female)		Patients insight ⁺ group (<i>n</i> = 20; 16 male, 4 female)		Patients insight ⁻ group (<i>n</i> = 20; 16 male, 4 female)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Demographics						
Age (yr)	35.25 (10.93)	20-59	36.15 (10.54)	19-54	37.80 (7.85)	22-49
Education (yr)	15.05 (2.86)	10-20	13.45 (2.86)	9-20	13.40 (2.01)	11-19
Predicted IQ (NART)	113.10 (9.91)	91-128	109.20 (10.80)	86-122	106.10 (7.87)	90-119
Clinical characteristics						
BIS			11.65 (0.57)	13-14	5.88 (2.05)	1-8
Age at illness onset (yr)			25.90 (8.72)	13-48	23.85 (5.84)	10-37
PANSS positive symptoms			16.15 (5.38)	8-25	17.05 (4.43)	8-23
PANSS negative symptoms			17.20 (4.38)	7-27	18.15 (5.46)	8-27
PANSS general psychopathology			34.35 (7.36)	24-56	31.55 (6.27)	21-40
PANSS total symptoms			67.70 (14.90)	43-108	66.75 (14.02)	37-86
Medication (chlorpromazine equivalent in mg)			461.21 (333.95)	100-1600	556.63 (366.49)	200-1367
Medication type						
Atypical antipsychotics			18 (9 olanzapine, 5 risperidone, 3 clozapine, 1 quetiapine)		13 (7 olanzapine, 3 clozapine, 1 aripiprazole, 1 amisulpride, 1 risperidone)	
Typical antipsychotics			2 (1 sulpiride, 1 haloperidol)		5 (2 flupenthixol, 1 fluphenazine, 1 sulpiride, 1 haloperidol)	
Both			--		2 (1 on clozapine + levomepromazine, 1 zuclopenthixol + aripiprazole)	

NART: National Adult Reading Test^[44]; BIS: Birchwood insight scale^[41]; PANSS: Positive and negative syndrome scale^[43].

domains in patients with schizophrenia, relative to the healthy population, are commonly reported^[46], our study suggests that this may be particularly true for those with impaired insight^[37] and in turn may also explain the finding of significantly fewer years in education in the Insight⁻ (but not Insight⁺) patient group, compared with the healthy controls. The patient groups scored at opposing ends of the BIS scale; this allows for the interpretation of observed neuroanatomical differences in relation to clinical insight levels of the respective patient group.

As hypothesized, we found that Insight⁻ patients had smaller grey matter volumes than Insight⁺ patients, bilaterally in the frontal and temporal lobes (mainly in the inferior frontal and precentral gyri and superior and middle temporal gyri), as well as in the parahippocampal gyrus, occipital lobes (including the cuneus) and the cerebellum. Insight⁻ patients also showed similar grey matter deficits, particularly on the left, when compared to healthy controls (Figure 1).

Our findings of smaller fronto-temporal regional grey matter volumes are in accordance with previous imaging studies, that used the "Region of Interest" (ROI) approach and found a significant and direct correlation between smaller frontal areas, including the dorsolateral PFC, inferior frontal and middle frontal gyri^[22,26-28,47,48] and impaired clinical insight. Early reports of poor executive functioning in schizophrenia patients with impaired insight, similar to those with frontal lobe lesions, initiated the interest in the integrity of the frontal lobe in schizophrenia. Since then, several studies^[26,30,31,47],

including this one, have reported frontal neuroanatomical abnormalities in relation to impaired clinical insight in schizophrenia. Some functional imaging studies have further associated aberrant frontal functional MRI activity with impaired clinical insight during working memory^[49], self-reflection^[50], self-monitoring^[51] and self-awareness tasks^[52] in schizophrenia. In addition, earlier correlational VBM studies have also reported associations between smaller superior and middle temporal lobe grey matter volumes and impaired clinical insight^[23,48].

Our other finding of smaller cuneus and occipital grey matter volumes in Insight⁻ patients is also broadly in agreement with the earlier reported association between poor symptom relabelling dimension of clinical insight and smaller grey matter volumes of the precuneus, cuneus and medial occipital gyrus by Morgan *et al.*^[25]. Unlike Morgan *et al.*^[25], we did not investigate preferential or predominant contribution of particular insight dimensions because the BIS subscale scores in our sample were highly positively correlated with each other ($\rho = 0.50-0.882$; $P < 0.001$). This might be due to our sampling methods that ensured that our Insight⁻ and Insight⁺ patient groups had markedly different insight levels, possibly in all domains. Other VBM studies have also reported an association between the smaller precuneus grey matter volumes and lower insight in schizophrenia^[23]. The role of the precuneus has been described in the facilitation of increased awareness into one's mental states^[23,53] and has also been implicated, in conjunction with other midline structures, in the self-appraisal processes^[54,55]. Compared to anterior cortical

Table 2 Group differences in grey matter volumes (height threshold $P < 0.005$)

Groups	BA	Size	Side	MNI			<i>T</i> value	Cluster <i>P</i>	FWE-corrected unless in <i>italics</i>	Voxel <i>P</i>	FWE-corrected
				X	Y	Z					
Insight ⁺ > Insight ⁻ patients											
Superior temporal gyrus	22	46555	R	63	-3	5	4.91		0.001		0.020
				45	20	-33	4.74				0.034
				66	-8	4	4.68				0.040
Precentral gyrus	4			66	-5	22	4.55				0.057
Inferior frontal gyrus	47			54	19	0	4.52				0.063
Precentral gyrus	6			64	0	26	4.40				0.088
Postcentral gyrus	43			66	-8	16	4.33				0.106
parahippocampus	28			14	0	-27	4.07				0.406
Inferior frontal gyrus	47	103898	L	-41	15	-6	4.81		< 0.001		0.027
Middle frontal gyrus	9			-37	19	35	4.74				0.034
Inferior frontal gyrus	47			-37	15	-10	4.73				0.035
				-35	20	-10	4.54				0.059
Precentral gyrus	44			-59	8	7	4.39				0.091
Superior temporal gyrus	22			-62	-4	8	4.36				0.097
Precentral gyrus	6			-60	4	6	4.33				0.107
Middle temporal gyrus	21			-35	-3	-23	4.27				0.126
parahippocampal gyrus	20			-34	-5	-28	4.16				0.166
Cuneus	18	35993	L	-5	-83	5	4.43		0.003		0.082
Cerebellum	-		R	35	-90	-17	4.26				0.129
Cuneus	18		R	26	-93	-18	3.90				0.305
Cerebellum	-		R	4	-61	2	3.88				0.317
Cuneus	18		R	5	-98	10	3.50				0.630
			R	5	-96	3	3.44				0.674
Cerebellum	-		L	-36	-82	-15	3.38				0.730
Insight ⁺ > Insight ⁻ patients											
Nil significant											
Healthy controls > Insight ⁻ patients											
Inferior frontal gyrus	47	35300	L	-49	19	-3	4.63		0.004		0.046
Superior temporal gyrus	22			-60	1	3	4.30				0.115
Inferior frontal gyrus	47			-41	18	-5	4.21				0.144
				-38	22	-8	4.19				0.153
				-36	-1	-14	3.86				0.333
Inferior temporal gyrus	20			-28	-14	-41	3.61				0.530
Parahippocampal gyrus	34			-13	4	-23	3.58				0.552
Middle frontal gyrus	11			-42	40	-19	3.39				0.722
Inferior occipital gyrus	18	11168	L	-38	-92	-2	4.51		0.034		0.065
Middle occipital gyrus	19			-52	-76	-10	4.29				0.117
				-48	-80	-14	3.96				0.266
				-49	-81	7	3.90				0.302
Middle temporal gyrus	39/ 19			-53	-72	22	3.37				0.740
				-52	-74	18	3.33				0.768
				-49	-76	20	3.29				0.797
Cerebellum	-	25235	R	35	-90	-17	4.46		0.016		0.074
(posterior lobe)				11	-90	-37	4.21				0.146
Occipital lobe	18			23	-94	-18	4.01				0.238
Cerebellum				34	-85	-40	3.93				0.355
(posterior lobe)				38	-82	-41	3.91				0.489
Insight ⁻ patients > healthy controls											
Nil significant											
Healthy control > Insight ⁺ patients											
Nil significant											
Insight ⁺ patients > healthy controls											
Nil significant											

BA: Brodmann area; L: Left; R: Right; MNI: Montreal Neurological Institute.

regions, much less is known about the involvement of posterior medial cortices due to the dearth of research into the contributions of these brain regions to various aspects of psychotic disorders^[25]. In our recent study, we found further evidence of functional contributions from the precuneus, as well as the cerebellum, in supporting

neural activities sub-serving the preservation of insight in schizophrenia patients^[49].

There have been previous reports of cerebellar atrophy, on average, in schizophrenia patients^[56]. A previous study^[48] also observed a significant association between impaired clinical insight and reduced bilateral

Table 3 Group differences in grey matter volumes after co-varying for education and National Adult Reading Test IQ (height threshold $P < 0.005$)

Groups	BA	Size	Side	MNI			T value	Cluster P	FWE-corrected unless shown in <i>italics</i>	Voxel P	FWE-corrected
				X	Y	Z					
Insight ⁺ > Insight ⁻ patients											
Superior Temporal gyrus	22	37261	R	63	-3	5	4.70		0.002		0.044
				45	20	-33	4.56				0.066
				66	-8	4	4.45				0.088
Precentral gyrus	4			66	-5	22	4.44				0.092
Inferior frontal gyrus	47			54	19	0	4.39				0.103
Precentral gyrus	6			64	0	26	4.28				0.137
Postcentral gyrus	43			66	-8	16	4.15				0.192
Inferior frontal gyrus	47	65047	L	-42	16	-4	4.65		< 0.001		0.050
				-38	14	-8	4.65				0.052
				-36	18	-10	4.52				0.073
Middle frontal gyrus	9			-37	19	35	4.52				0.073
Superior temporal gyrus	22			-61	-2	7	4.28				0.139
Precentral gyrus	44			-59	9	9	4.17				0.184
Parahippocampal gyrus	21			-34	-3	-36	4.10				0.213
Cuneus	18	24291	L	-5	-83	5	4.32		0.014		0.125
Cerebellum	-		R	35	-90	-17	4.17				0.181
Cuneus	18		R	26	-93	-18	3.73				0.466
Cerebellum	-		R	4	-61	2	3.80				0.409
Cuneus	18		R	5	-98	10	3.35				0.787
Medial frontal gyrus	10	16854	L	0	60	3	3.98		0.050		0.285
Superior frontal gyrus	9			0	51	26	3.64				0.544
Insight ⁻ > Insight ⁺ patients											
Nil significant											
Healthy controls > Insight ⁻ patients											
Inferior frontal gyrus	47	9770	L	-51	19	-2	3.68		0.036		0.511
Superior temporal gyrus	38			-21	5	-24	3.35				0.786
Inferior frontal gyrus	47			-26	18	-7	3.34				0.796
Parahippocampal gyrus	34			-16	4	-23	3.29				0.827
Inferior occipital gyrus	18	4935	L	-38	-92	-2	3.92		0.122		0.323
Middle occipital gyrus	19			-52	-76	-10	3.70				0.494
				-44	-83	8	3.37				0.775
Middle temporal gyrus	18			-43	-81	13	3.22				0.873
Cerebellum (posterior lobe)	-	6085	R	35	-90	-17	3.68		0.089		0.304
				11	-90	-37	3.60				0.378
Occipital lobe	18			28	-94	-16	3.32				0.656
				23	-94	-18	3.26				0.713
Insight ⁻ patients > healthy controls											
Nil significant											
Healthy controls > Insight ⁺ patients											
Nil significant											
Insight ⁺ patients > healthy controls											
Nil significant											

BA: Brodmann area; L: Left; R: Right; MNI: Montreal Neurological Institute.

cerebellar grey matter volumes in schizophrenia, and that this relationship was not associated with any specific dimension of clinical insight. Other studies have described the involvement of the cerebellum in higher cognitive functioning, with its extensive connectivity with limbic structures, including the parahippocampal gyrus, and associated cortical areas involved in cognition and executive function^[57,58], and this has been implicated in the neuropathology of schizophrenia and poor clinical insight^[48,59]. Our recent finding of increased cerebellar activity, detected using fMRI, in Insight⁺ patients compared to Insight⁻ patients, during a working memory task, also indicated cerebellar involvement in the preservation of clinical insight in schizophrenia^[49].

In accordance with the observations made by other studies, we also found grey matter reductions in many areas in Insight⁻ patients, compared to healthy controls^[48]. These differences remained, but became less significant, after we co-varied for education and NART IQ. Co-varying for education and NART IQ had no effects on grey matter volume differences between preserved and Insight⁻ patient groups, most likely because these two groups were comparable on these parameters.

Strengths and limitations

We employed a direct comparison method between distinct groups of schizophrenia patients (Insight⁻ and Insight⁺) with closely matched demographic and clinical

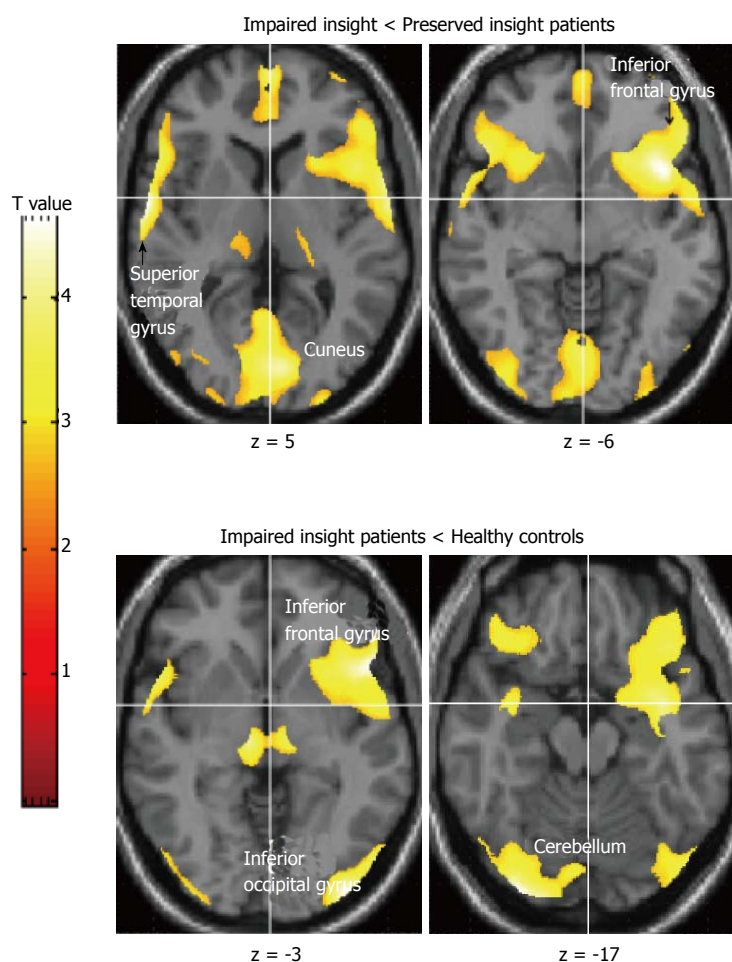


Figure 1 Images showing regions of decreased grey matter volume in the impaired insight patient group, relative to the preserved insight patient and healthy controls (maps thresholded at $P = 0.005$; left = right).

qualities, thereby facilitating valid comparisons and inferences. The study also had 60 participants ($n = 20$ per group) and thus was adequately powered for the observations made. We were, however, limited in our ability to explore the effects of sex on brain volumes and in the observed group differences, as our sample was predominantly male. Nonetheless, male:female ratios were similar and any possible effect is expected to be uniform in all groups. Also, although the patient groups were comparable in all relevant areas, our healthy controls had more education than our patient groups, and had higher IQ scores than Insight⁺ patient group, although co-varying for these differences did not change the pattern of observed group differences. By adopting a direct comparison method between matched patient groups at the extremes of insight measures, we minimised confounding effects of partial insight levels and were able to exclude overall effects of schizophrenia on brain volumes. However, in as much as we endeavoured that our two patient groups are highly comparable but for their insight levels, there are possibilities of other differential properties, such as brain functional properties, which could possibly contribute to our findings. Lastly, patients in both the Insight⁺ and Insight⁻ groups were on a range of atypical and typical antipsychotics (Table 1) which vary in their pharmacological profiles^[60,61] as well as in their effects on brain volumes^[62]. This may have

influenced the results we observed in this study.

In conclusion, schizophrenia patients with impaired insight patients have smaller fronto-temporal, parahippocampal, occipital and cerebellar grey matter volumes, compared with preserved insight schizophrenia patients and healthy controls. The involvement of multiple brain areas and corresponding neural networks supports the theory that clinical insight, as a neurological function, is not confined to specific neuroanatomical regions in the brain but probably a function of a complex neurocognitive interplay with contributions from neural networks, including working memory and executive functioning, self-monitoring and awareness and others^[19,23,49,63,64].

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We are grateful to the MRI unit, Maudsley Hospital for their help with data acquisition.

COMMENTS

Background

Impaired insight in schizophrenia is found to have a direct correlation with poor clinical outcomes, such as frequent relapses and hospital admissions, poor compliance with medication, greater suicidal tendencies and self-injurious behaviour. Some studies reporting positive correlations between improvement in clinical insight and better clinical outcomes have further suggested the adoption of clinical insight as a possible therapeutic target in schizophrenia

patients.

Research frontiers

The ability to target insight therapeutically is highly complex and remains elusive to most methods trialled so far. The identification of the underpinning neural correlates of clinical insight will aid the development of specific treatment strategies aimed at improving insight in schizophrenia.

Innovations and breakthroughs

The study reported in this manuscript is distinct from all previous studies in this area (mostly correlational) in that it identifies regional grey matter abnormalities in stable schizophrenia outpatients with impaired clinical insight, relative to those with preserved clinical insight (impaired and preserved insight groups scoring at extreme ends of a multidimensional insight scale but matched on age, sex and other symptoms) as well healthy controls, using a categorical approach. The authors found a clear association between impaired clinical insight and smaller fronto-temporal, occipital and cerebellar grey matter volumes in stable long-term schizophrenia patients.

Applications

Clinical insight, as a neurological function, is likely to be dependent on complex neurocognitive interplay with contributions from multiple neural networks.

Terminology

Voxel-based-morphometry is a neuroimaging analysis technique in which structural brain properties are examined on a voxel-by-voxel basis and reported in standardized coordinates. Clinical insight refers to a patient's complex state of awareness of his or her own mental disorder.

Peer-review

The study is well designed and the manuscript is clearly written and easy to read all throughout.

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Case Control Study

Stressful life events and psychosocial correlates of pediatric inflammatory bowel disease activity

George Giannakopoulos, George Chouliaras, Daphne Margoni, Sophia Korlou, Vassiliki Hantzara, Ioanna Panayotou, Eleftheria Roma, Magda Liakopoulou, Dimitris C Anagnostopoulos

George Giannakopoulos, Sophia Korlou, Vassiliki Hantzara, Magda Liakopoulou, Dimitris C Anagnostopoulos, Department of Child Psychiatry, National and Kapodistrian University of Athens, School of Medicine, Aghia Sophia Children's Hospital, 11527 Athens, Greece

George Chouliaras, Daphne Margoni, Ioanna Panayotou, Eleftheria Roma, 1st Department of Pediatrics, National and Kapodistrian University of Athens, School of Medicine, Aghia Sophia Children's Hospital, 11527 Athens, Greece

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Correspondence to: Dr. George Giannakopoulos, Department of Child Psychiatry, National and Kapodistrian University of Athens, School of Medicine, Aghia Sophia Children's Hospital, Thivon and Papadiamantopoulou, 11527 Athens, Greece. giannakopoulos.med@gmail.com
Telephone: +30-21-32013258
Fax: +30-21-32013669

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Abstract

AIM

To investigate the association of psychiatric and psychosocial correlates with inflammatory bowel disease (IBD) activity in children and adolescents.

METHODS

A total of 85 pediatric IBD patients (in remission or active state of the disease) and their parents completed a series of questionnaires and semi-structured interviews measuring life events, depression, anxiety, family dysfunction, and parent mental health. Differences between the remission and the IBD active group and the association of any significant variable with the disease activity state were examined.

RESULTS

Parents of children being in active state of the disease reported more life events ($P = 0.005$) and stressful life events ($P = 0.048$) during the past year and more mental health symptoms ($P < 0.001$), while the children

themselves reported higher levels of anxiety symptoms ($P = 0.017$) compared to the remission group. In the logistic regression multivariate analysis, the only predictor which had a significant positive effect on the probability of the patients being in active state was parent mental health symptoms (OR = 4.8; 95%CI: 1.2-25.8).

CONCLUSION

Life events, child anxiety and parent mental health symptoms may be important correlates of pediatric IBD activity and targets of thorough assessment and treatment.

Key words: Inflammatory bowel disease; Children and adolescents; Stressful events; Anxiety; Depression

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Core tip: The present study examined the associations of several psychosocial factors and outcomes with pediatric inflammatory bowel disease (IBD) activity. Second, it shed some light on the relationship of the disease activity (*i.e.*, IBD remission or active state) with preceding life events. Addressing simultaneously psychosocial needs of both children and parents in the course of pediatric IBD seem to be of importance in any effective preventive and therapeutic intervention. Moreover, the role of stressful events in the course of pediatric IBD although being mediated or moderated by individual factors seem to be a possible target for future research and psychosocial treatment modalities.

Giannakopoulos G, Chouliaras G, Margoni D, Korlou S, Hantzara V, Panayotou I, Roma E, Liakopoulou M, Anagnostopoulos DC. Stressful life events and psychosocial correlates of pediatric inflammatory bowel disease activity. *World J Psychiatr* 2016; 6(3): 322-328 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v6/i3/322.htm> DOI: <http://dx.doi.org/10.5498/wjp.v6.i3.322>

INTRODUCTION

Epidemiological studies indicate that the incidence of pediatric inflammatory bowel disease (IBD), consisting of Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU), has been increasing over time^[1]. Elevated levels of depression, anxiety, low self-esteem, disrupted social functioning, family dysfunction, and parental distress are among the most common findings from studies comparing pediatric IBD patients with other chronic disease patients or healthy controls^[2,3].

However, only few studies have investigated the association of psychiatric and psychosocial correlates with IBD activity in children and adolescents. Specific depressive symptoms (*e.g.*, lack of interest and energy, decreased appetite) have been shown to be related with moderate/severe disease activity^[4]. Higher levels of depressive symptoms have been also related to poorer subjective health in IBD pediatric patients^[5]. A recent

study^[6] found that the disease activity was associated with adolescents' general well-being, emotional functioning, social functioning, and body image. In another sample of young adults with IBD, poor college adjustment and physical quality of life were correlated with increased disease activity^[7]. However, no significant correlations were reported elsewhere^[5,8-11].

Moreover, impaired parent mental health and physical functioning have been correlated significantly with pediatric IBD symptom exacerbation^[12]. Similarly, family general dysfunction has been related with more symptomatic IBD among adolescents, and maternal positive affect (*e.g.*, mothers describing themselves as more active, and interested) has been related with less IBD symptoms^[13]. Finally, although the role of stressful life events has been studied in adult IBD patients with mixed findings^[14], there are no published reports examining the relationship of stressful events with the disease activity in pediatric populations. Only two studies comparing IBD patients to healthy and clinical controls^[15,16] and one study comparing depressed to non-depressed IBD pediatric patients^[17] supported the association of retrospectively reported stressful life events with the onset of pediatric IBD.

The present study investigates the relationship of several psychosocial factors and outcomes with pediatric IBD activity. More specifically, we try to provide a more comprehensive examination than currently available evidence by assessing differences in the often neglected life events among other possibly significant psychosocial problems, such as depressive and anxiety symptoms, family dysfunction, and parent mental health between an IBD remission group and an IBD active group of children and adolescents. It was hypothesized that the active group would show more stressful life events the year prior the present assessment and higher levels of psychosocial problems. Furthermore, we examine the association of any psychosocial variable that is shown to be correlated with the disease activity state by entering these variables in the same model as covariates. The aim of the latter examination is to clarify interactions and the possible moderating role of any of the abovementioned psychosocial correlates in their association with pediatric IBD activity.

MATERIALS AND METHODS

The study was reviewed and approved by the Aghia Sophia Children's Hospital Institutional Review Board. All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Participants

This cross-sectional study was conducted at the Gastroenterology Unit of the First Department of Pediatrics in collaboration with the Department of Child Psychiatry of the National and Kapodistrian University of Athens, School of Medicine, Aghia Sophia Children's Hospital. Eligible for inclusion were all children and their parents,

Table 1 Demographic information by inflammatory bowel disease activity and type of disease

	IBD active group (<i>n</i> = 43)		Remission group (<i>n</i> = 42)	
	CD (<i>n</i> = 30)	UC (<i>n</i> = 13)	CD (<i>n</i> = 27)	UC (<i>n</i> = 15)
Age, mean (yr)	12.8 ± 2.2	12.9 ± 2.0	13.9 ± 2.0	13.1 ± 1.4
Child gender (female), %	56.7	61.5	66.7	46.7
Parent gender (female) ¹ , %	80.8	77.8	86.9	75

¹Gender of the parent who was present during the assessment. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis.

diagnosed with IBD according to the ESPGHAN Porto-criteria^[18,19] who were either admitted in the First Department of Pediatrics or followed as outpatients. The period of recruitment lasted for 24 mo. Inclusion criteria were age between 8-18 years and the ability to read Greek and complete the questionnaires themselves. Exclusion criteria were diagnosis of developmental pervasive disorder or mental retardation, and a comorbid chronic illness. No patient was on psychiatric medication. One hundred subjects fulfilling the inclusion criteria were asked to participate. A total of 85 children and adolescents (50 females) with a mean age of 13.2 years ± 2.4 years and their parents agreed to participate in the study (85% response rate) and they were included in the analysis. The cases that refused to participate did not differ from the study group according to age, sex and disease activity. The characteristics of the study sample are shown in Table 1. Regarding steroid medication, 44.9% (*n* = 38) of the study population was on steroids at the time of evaluation, 14.7% (*n* = 6) of those in remission and 74.9% (*n* = 32) of those with a relapse. Three participants were of non-Greek ethnicity.

Materials and procedures

All patients were classified at the time of the evaluation, as being in remission or in active state of IBD according to the Pediatric Crohn's Disease Activity Index (PCDAI)^[20] or the Pediatric Ulcerative Colitis Activity Index (PUCAI)^[21] depending on the diagnosis. For both scales, remission is defined by a total score < 10 and active state if the total score was ≥ 10. Disease activity was assessed both as activity index and as disease state (remission or relapse). Both children and their parents completed the questionnaires in the outpatient or inpatient clinics. Socio-demographic details and past medical and psychiatric history were recorded.

The parents completed a semi-structured psychosocial interview evaluating recent life events for their children^[22,23], which is based on Coddington's Life Events Questionnaire^[24]. The onset of each event that had occurred over the previous 12 mo was dated to within 4 wk. Life events that are measured through this interview include: (1) danger to self (child's illness or accidents, involvement in a household or community disaster or being the subject of a personal attack; (2) danger to others (expectation or occurrence of physical threat where the person exposed is a parent, sibling, friend or

significant other; (3) disappointments (e.g., to the self includes breakdown of boyfriend/ girlfriend relationship, examination failure; to another includes loss of job, new financial difficulties, extramarital affair); and (4) loss (includes only death and permanent separations). Life events data were collected only from parents in order not to cause survey fatigue to the patients. Both the stressful events (those carrying a moderate to severe degree of negative impact on the child according to parents' subjective perception) and the total number of events (the objective number of reported events) were computed in the present analysis, so as to take into consideration the possible impact of events that parents may underestimate.

Child and adolescent anxiety symptoms were measured by the Revised Children's Manifest Anxiety Scale (RCMAS)^[25]. The RCMAS is a widely used self-report 37-item questionnaire, with higher values corresponding to higher levels of anxiety. The psychometric properties of the RCMAS have been found acceptable in previous research^[26].

The Children's Depression Inventory (CDI)^[27], a self-report 27-item scale, was used to screen for depressive symptoms. The total score ranges from 0 to 54, with higher values corresponding to higher levels of depression. Previous research has shown that the CDI is adequately reliable and valid with respect to depressive symptoms^[28].

In order to assess parent mental health symptoms, the Symptom Checklist-90-Revised (SCL-90-R) was administered^[29]. The SCL-90-R is a 90-item multidimensional questionnaire designed to screen for a broad range of psychological problems. Each of the 90 items is rated on a five-point Likert scale of distress. The Global Severity Index (GSI), the mean rating across all items, was used for assessing parent mental health symptoms. The psychometric properties of the SCL-90-R GSI have been found acceptable in previous research^[30] and support its use as a self-report measure.

Family dysfunction was assessed through the McMaster Family Assessment Device (FAD)^[31]. It is a 60-item instrument that assesses 6 domains of family functioning as well as general family dysfunction. The 12-item General Functioning scale, which assesses overall family pathology or dysfunction, was analyzed in the present study. Higher mean values indicate greater general dysfunction. The reliability and validity of the FAD General Functioning scale have been demonstrated in clinical and non-clinical samples^[32].

Table 2 Comparisons of self-reported child emotional problems, parent mental health symptoms, family dysfunction and life events by inflammatory bowel disease activity group

Variable	IBD active group (<i>n</i> = 43)	IBD remission group (<i>n</i> = 42)	<i>P</i>
Life events	3.8 ± 2.5	2.4 ± 2.8	0.005 ²
Stressful life events	2.9 ± 2.1	2.0 ± 2.3	0.048 ²
FAD GFS family dysfunction	22.6 ± 5.5	20.1 ± 4.9	0.061 ¹
SCL-90-R parent mental health symptoms	1.11 ± 0.72	0.52 ± 0.39	< 0.001 ¹
RCMAS anxiety symptoms	54.3 ± 12.7	46.9 ± 13.1	0.017 ¹
CDI depression symptoms	8.9 ± 5.6	7.2 ± 5.5	0.2 ¹

¹Student's *t* test; ²Mann-Whitney test. IBD: Inflammatory bowel disease; FAD GFS: Family Assessment Device General Functioning Scale; SCL90-R: Symptom Checklist-90-Revised; RCMAS: Revised Children's Manifest Anxiety Scale; CDI: Children's Depression Inventory.

Statistical analysis

Continuous variables are presented using mean ± standard deviation (SD) while categorical variables are presented by absolute (*n*) and relative (%) frequencies. In order to test our hypothesis, Student's *t*-test was used for comparisons of means between IBD remission group and IBD active group, with the exception of continuous variables with a small number of distinct values in the dataset where the non-parametric Mann-Whitney statistic was used. Categorical variables were compared between the two groups by Fisher's exact test. Exact logistic regression analysis was applied in order to evaluate to what extent the explanatory variables that were already found to be associated with IBD activity in univariate analysis had a multivariate effect on the latter. The estimate of the relative risks of being in IBD active state was performed by calculating the odds ratios (OR) and the corresponding 95%CI. All tests were two-sided and a level of ≤ 0.05 was considered statistically significant. Data were analyzed using STATA 11.0 (Stata Corporation, College Station, TX 77845, United States).

RESULTS

Disease state was not related to age or gender ($P = 0.17$ and $P = 0.55$ respectively).

Comparisons of psychosocial variables by IBD activity group

The results of the univariate analysis, that is the differences in each psychosocial factor tested individually by IBD activity group, are presented in Table 2. Parents of children being in active state of the disease reported more life events ($P = 0.005$) and stressful life events ($P = 0.048$) during the past year, and more mental health symptoms ($P < 0.001$), while the children themselves reported higher levels of anxiety symptoms ($P = 0.017$), compared to the remission group. Similarly, when the disease activity was assessed through activity index, it was positively associated with life events ($P = 0.04$) during the past year, parent mental health symptoms ($P = 0.0081$) and children's anxiety symptoms ($P = 0.0028$). Evaluation of the abovementioned differences

after stratifying according to the diagnosis (CD or UC) had not sufficient statistical power.

Multivariate effects of psychosocial variables on IBD activity in the logistic regression analysis

Since no change in the direction of the observed relations was detected in the stratified analysis, data were combined for all the subsequent analyses. When the factors which were proven to be significant in the univariate analysis (*i.e.*, life events and stressful life events during the past year, self-reported anxiety symptoms, and parent mental health symptoms) were included in the logistic regression multivariate analysis, the only predictor variable which had a significant positive effect on the probability of the patients being in IBD active state was parent mental health symptoms (OR = 4.8; 95%CI: 1.2-25.8). Since steroid medication was related to self-reported anxiety symptoms ($P = 0.006$) and parent gender was related to parent mental health symptoms ($P = 0.038$), were both considered confounding variables and included in the final model. Steroid medication had a significant association with disease state with patients on steroids being more likely to be in relapse (OR = 19.8; 95%CI: 3.2-120.8), whereas parent gender was statistically not significant and therefore removed from the regression equation.

DISCUSSION

This study was an effort to examine differences in the often neglected life events among other possibly significant psychosocial variables, such as depression and anxiety symptoms, family dysfunction, and parent mental health between an IBD remission group and an IBD active group of children and adolescents. Results indicate that parent-reported life events during the past year, self-reported anxiety symptoms, and parent mental health symptoms are related with the disease activity. Moreover, parent mental health symptoms seem to be a strong correlate of IBD activity when all significant variables are entered into a model simultaneously.

Self-reported emotional problems (*i.e.*, depressive and anxiety symptoms) tended to be higher in the IBD active group than in the remission group, with self-reported

anxiety symptoms, in particular, differing significantly between the 2 groups. This finding agrees with previous research showing that internalizing problems are correlated with IBD symptom exacerbations^[4]. Family dysfunction also did not differ between children and adolescents with or without active state of the disease, although the difference was close to statistical significance.

Parents reported significantly more mental health symptoms in the IBD active state than in the remission group, consistent with previous studies^[12,13]. Interestingly, they also reported significantly more life events during the year prior the present assessment. This finding is the first to our knowledge to support the relationship of preceding life stress with IBD activity in pediatric populations, although 2 previous studies have supported the association of stressful life events with the onset of pediatric IBD^[15,16]. Moreover, in the present study, while the parents in the active group compared to the remission group reported significantly more life events in total, this difference between the two groups was not significant regarding the events that the parents perceived as stressful for their children. It could be hypothesized that this discrepancy might suggest that parents could underestimate the potential negative impact of some life events on their children wellbeing and functioning and consequently not report them as stressful. In general, parents could ignore some aspects of the life of the patients, and underestimate or overestimate other known stressors. At the same time, one could argue that young patients couldn't estimate correctly the power of different events when using a questionnaire to detect them. The combination of reports from multiple informants (*i.e.*, parents and children) could possibly yield more reliable estimations.

Parent mental health symptoms were shown to be the only strong independent psychosocial correlate of IBD activity when all significant variables were entered into the same model of regression analysis. It is interesting that the associations of childrens' anxiety symptoms and life events with the disease activity were not significant anymore in the final model. These findings could be interpreted in different ways. With regard to anxiety symptoms, although some of the effect seen at the univariate analysis was probably due to the confounding effect of steroid medication (which was strongly related to the probability of relapse, as most patients experiencing a flare of the disease receive steroids) there is a possibility that anxiety symptoms may have an important impact on disease activity and a larger sample would provide enough power to detect it. With regard to life events, the significant relationship with disease activity that was initially found in the univariate analysis may have been subsequently moderated by the effect of parent mental health symptoms in the model of regression analysis since parents themselves reported the events and this reporting may have been possibly influenced by their mental health state. Alternatively, there may be a mediating factor such as parent coping strategies that was not examined in the present analysis

and was related to parent mental health symptoms on the one hand and the effect of life events on the other hand. This unexamined factor could have weakened the effect of life events on IBD activity in the final model, although it did not manage to weaken the relative effect of parent symptomatology. Moreover, the disease activity is a momentary state that can change within days or weeks, so that it may be difficult to detect any associations with the number of life events. In any case, these preliminary findings deserve further examination in future research.

The present study extends previous research mainly in two ways. First, it examined the associations of several psychosocial factors and outcomes with pediatric IBD activity both in univariate and regression analyses providing a more comprehensive picture of these complex relations; second, it shed some light on the relationship of the disease activity (*i.e.*, IBD remission or active state) with preceding life events, an issue that was missing in pediatric IBD literature. The findings reported here can offer some useful implications. Addressing simultaneously psychosocial needs of both children and parents in the course of pediatric IBD seem to be of importance in any effective preventive and therapeutic intervention; moreover, the role of stressful events in the course of pediatric IBD although being mediated or moderated by individual factors seem to be a possible target for future research and psychosocial treatment modalities.

The present findings should be interpreted in the context of some limitations. First, to diminish the burden of the examination on the patients we did not use adequate diagnostic interviews to screen for comorbid psychiatric disorders; second, the study was based only on parent-reported life events that limit the interpretation of the results; moreover, the study did not examine the effect of socioeconomic status on the reported differences, although this limitation is common in pediatric IBD studies, with high socioeconomic status threatening generalizability of results. Similarly, factors such as hospital stay and parent perceived social support that have been found to be associated with impaired mental health outcomes in children and parents, respectively, were not examined in the present analysis. In addition, the sample size was rather small, leading to a low statistical power. The deviance from normality of the continuous variables of our sample led to the use of non-parametric statistics that had less statistical power than parametric ones if there was a normal distribution. The cross-sectional design of the study did not allow us to examine variations over time or make causal inferences; last, it would be interesting to include a control group not affected by IBD, since even inactive IBD patients may have a higher rate of self-reported psychosocial problems than age-matched controls. Regardless of these limitations, the present study clearly suggests that several psychosocial factors and outcomes (*i.e.*, life events, child anxiety and parent mental health symptoms) may be important correlates of pediatric IBD

activity and they may be targets of thorough assessment and treatment.

COMMENTS

Background

Epidemiological studies indicate that the incidence of pediatric inflammatory bowel disease (IBD) has been increasing over time. Elevated levels of depression, anxiety, low self-esteem, disrupted social functioning, family dysfunction, and parental distress are among the most common findings from studies comparing pediatric IBD patients with other chronic disease patients or healthy controls.

Research frontiers

Only few studies have investigated the association of psychiatric and psychosocial correlates with IBD activity in children and adolescents. Moreover, although the role of stressful life events has been studied in adult IBD patients with mixed findings, there are no published reports examining the relationship of stressful events with the disease activity in pediatric populations.

Innovations and breakthroughs

The authors provide a more comprehensive examination than currently available evidence by assessing differences in the often neglected life events among other possibly significant psychosocial problems, such as depressive and anxiety symptoms, family dysfunction, and parent mental health between an IBD remission group and an IBD active group of children and adolescents. Furthermore, they examine the association of any psychosocial variable that is shown to be correlated with the disease activity state by entering these variables in the same model as covariates.

Applications

Several psychosocial factors and outcomes (*i.e.*, life events, child anxiety and parent mental health symptoms) may be important correlates of pediatric IBD activity and they may be targets of thorough assessment and treatment.

Peer-review

The paper is well-written, easy to read and give some new considerations on the treated issue. The authors indicate correctly all the limitations.

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Case Control Study

Self-worth and psychological adjustment of obese children: An analysis through the Draw-A-Person

Giuseppe Scimeca, Amelia Alborghetti, Antonio Bruno, Giulia Maria Troili, Gianluca Pandolfo,
Maria Rosaria Anna Muscatello, Rocco Antonio Zoccali

Giuseppe Scimeca, Antonio Bruno, Giulia Maria Troili, Gianluca Pandolfo, Maria Rosaria Anna Muscatello, Rocco Antonio Zoccali, Psychiatric Unit, Department of Biomedical, Dental Sciences and Morpho-functional Imaging, University of Messina, 98125 Messina, Italy

Amelia Alborghetti, "Don Carlo Gnocchi" Foundation, 00135 Rome, Italy

Author contributions: Scimeca G designed the study and contributed to the manuscript writing and final revision; Alborghetti A performed the majority of experiments and contributed to the writing of the manuscript; Bruno A performed data analysis and contributed to the writing of the manuscript; Troili GM contributed to the literature search and writing of the manuscript; Pandolfo G performed part of experiments and contributed to the writing of the manuscript; Muscatello MRA contributed to the literature search, manuscript writing, and final revision; Zoccali RA contributed to the study idea, manuscript writing and final revision of the article.

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Correspondence to: Antonio Bruno, MD, PhD, Psychiatric Unit, Department of Biomedical, Dental Sciences and Morpho-functional Imaging, University of Messina, Via Consolare Valeria n. 1, 98125 Messina, Italy. antonio.bruno@unime.it
Telephone: +39-090-2212092
Fax: +39-090-695136

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Abstract

AIM

To investigate psychopathological correlates of child obesity *via* the Draw-A-Person test (DAP).

METHODS

The participants were 50 children with a mean age of 9.74 years. Body mass index (BMI) was used as a measure of body fat. Children were divided into normal ($n = 17$), overweight ($n = 14$) and obese ($n = 19$). Two qualitative methods of scoring the DAP based on an integrative approach were used to assess self-concept (ESW) and overall level of children's adjustment (EAC). A procedure for judging interpretative skills of clinicians was implemented before they evaluated children's drawings.

RESULTS

As predicted by our hypothesis, BMI was negatively correlated with ESW, $r(50) = -0.29$, $P < 0.05$, but not with EAC, $r(50) = -0.08$, $P = ns$. To evaluate the effect of gender, Pearson correlations were re-computed

regrouping the sample accordingly: BMI and EAC reached a significant negative correlation in female subjects, $r(24) = -0.36, P < 0.05$, and a positive correlation in male subjects, $r(26) = 0.37, P = < 0.05$; negative correlation between BMI and ESW became stronger in females, $r(24) = -0.51, P < 0.01$ but not in males, whose correlation disappeared resulting not-significant, $r(26) = -0.06, P = ns$. No effect of age was found. Results indicate that obesity has a negative correlation exclusively on overall adjustment and self-concept in female children.

CONCLUSION

It was concluded that there is a negative bias toward females that reveals how the stigma of obesity is widespread in Western society.

Key words: Obesity; Draw a person; Draw-A-Person test; Projective techniques; Psychopathology

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Core tip: This study was executed to investigate psychopathological correlates of child obesity *via* the Draw-A-Person test (DAP). A new procedure for using the DAP was suggested. Results indicate that obesity has a negative correlation exclusively on overall adjustment and self-concept in female children. It is consequently concluded that there is a negative bias toward females that reveals how the stigma of obesity is widespread in Western society. The "intuitive reading" of figure drawings can be considered a valid tool of assessment, even though interpreters' skills should always be assessed before executing each single studies in order to guarantee sound methodological praxis.

Scimeca G, Alborghetti A, Bruno A, Troili GM, Pandolfo G, Muscatello MRA, Zoccali RA. Self-worth and psychological adjustment of obese children: An analysis through the Draw-A-Person. *World J Psychiatr* 2016; 6(3): 329-338 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v6/i3/329.htm> DOI: <http://dx.doi.org/10.5498/wjp.v6.i3.329>

INTRODUCTION

Obesity is a serious problem all over the world, both in developing and industrialized countries. It is associated with severe emotional, medical and economical difficulties. According to the World Health Organization (WHO) "in many countries more than half of the adult population is above the overweight threshold, with 20%-30% of adults categorized as clinically obese"^[1]. The increasing prevalence of this disorder has led the WHO to declare obesity a global epidemic^[2]. The prevalence of childhood obesity has doubled over the last three decades^[3], forecasts for the future are not good: Wang *et al*^[4] (2006) have predicted, for the coming years, that almost 50%

of children in North America and 38% of children in the European Union will become overweight. Being obese during adolescence or childhood increases the probability and the severity of long-term health complications^[5]; early obesity also enhances the likelihood of being obese as an adult^[6] and, furthermore, it is a strong predictor of expected mortality^[7].

Though no doubt exists about the medical consequences of obesity, the same can't be said about psychopathological correlates. Reviews addressing this association, indeed, have led to contradictory findings, so that some authors have concluded that there is no link between these two conditions^[8,9]. Friedman *et al*^[10] (1995) have instead maintained that the absence of overall significant results contradict clinical experience and can be explained by specific theoretical or methodological limitations in reviewed studies (*e.g.*, sampling errors and narrow measurement). They maintain that obesity will determine psychopathological consequences only in individuals carrying definite risk factors and that it prevalently affects specific domains of psychological functions (like self-concept, pessimistic attributions or body image disturbance) rather than overall psychopathology or personality (obesity has thus been defined as a "syndrome of subclinical suffering"). They propose a second generation of studies addressing factors likely to place overweight individuals at psychopathology risk and a third generation of studies to comprehend the relationship between obesity and psychopathological correlates.

Following Friedman *et al*^[10]'s (1995) considerations, the present research was conducted to investigate, utilizing the Draw-A-Person test (DAP), two possible psychopathological correlates of childhood obesity: Self-concept, a specific domain of psychological function, and general psychopathology. We also considered the effect of developmental age and gender on these correlations.

There are some reasons why obesity and child psychopathology are expected to be correlated. The stigma of obesity is widespread in Western society: Obese people are easily blamed and condemned for their condition since our culture favours aesthetic models characterized by thinness^[11,12]. Staffieri^[13] found that obese individuals are easily labelled with negative attributions such as "stupid" or "cheats" compared to normal weight individuals. Negative attributions by others can easily affect self-concept as this schema also evolves by feedbacks from the perceptions of others^[14,15]. The habit of being negatively addressed as obese can thus determine the development of a negative perception of oneself as worthless, inadequate, inferior or inept. Some research has in fact found a negative correlation between body image dissatisfaction and self-esteem^[16-18]; other studies have found this relation to be mediated by childhood teasing^[19,20].

Another hypothesis worth considering is the opposite one: Excessive eating may develop to reduce emotional suffering stemming from an aversive self-concept. This so-called "psychosomatic" hypothesis maintains that

food consumption is an attempt to cope with negative emotions like depression and anxiety^[21,22]. The ability of self-esteem to affect eating habits is evident if we consider that the manipulation of self-esteem (e.g., by telling subjects they have failed on a problem solving task) has been shown to provoke disinhibited eating^[23]. Furthermore, studies tracking mood and eating by periodic self-monitoring have shown that binge eating is preceded by greater negative moods and followed by emotional relief^[24-26]. Heatherton *et al.*^[27] (1991), in an extensive review, have proposed the so-called "escape model" according to which binge eating arises as a way to narrow a person's attention to immediate food sensations and consequently to avoid broadly and threatening thoughts concerning the self.

In spite of this, research addressing self-concept in obese children has led to contradictory findings, some indicating an association between negative self-worth and excessive weight^[28,29] and others which do not evidence this relationship^[30-34]. A meta-analysis of Miller *et al.*^[35] (1999) showed a moderate negative effect size was present as a measure of the relation between self-esteem and weight; they also found this relation to be higher for high school and college students than for children.

We think that obesity and children's self-worth are correlated and that, at least in part, contradictory findings can be explained by two kinds of factors.

The first is question of methodology. Studies of the psychopathological functioning of obese patients have prevalently employed assessment instruments like diagnostic interview schedules, self-made measurements, questionnaires, scales and inventories^[10]. The problem here is that children usually have significant difficulties in comprehending and correctly expressing inner feelings and, in general, all subjective states (especially those related to discomforting emotions). Consequently, projective measures have been expressly developed with the aim of capturing unconscious personality dynamics and functioning utilizing samples of behaviours which go beyond self description or clinical observations. It has been demonstrated that they can provide useful and valid information concerning personality and psychopathology (inner conflicts, perception of self and others, fears, relationships with family members or other relevant emotional figures) missed by self-report measures^[36,37]. This is one of the reasons why draw a person and other projective techniques are routinely applied for the assessment of children's psychopathology: They are among the first ten most used assessment tools in clinical practice^[38,39]. The assumption underlying the DAP is that when a person draws a human figure, he represents the way he views himself^[40]. According to this so-called "body image" hypothesis, the representation of one's body becomes a way to express inner emotions and beliefs related to the "self": "The general style and content of a drawing should give an interpreter a sense of how the respondent experiences him- or her-self in the world"^[41]. Given the low effect that obesity seems

to have on psychopathology and the methodological difficulties associated with the psychological assessment of children, a projective evaluation of adjustment level and self-concept through the DAP could be particularly effective. Most of all, we think that a projective evaluation of self-worth in obese children could be useful since negative self-attributions are seldom far from an almost tacit level of self-awareness^[42].

The 2nd factor which can shed light on the contradictory findings concerning self-worth in obese children is the effect of certain moderator variables like gender and age.

As far as the effect of gender is concerned, though the prevalence of obesity is about the same for both sexes, a number of results and clinical observations indicate that female subjects are at higher risk of developing emotional suffering than male subjects^[35,43,44]. Given the importance that body self-esteem plays in the development of female self-concept, women are surely stigmatized more than men^[45,46]. It's not a coincidence that treatment for obesity is predominantly requested by women rather than men and this could be explained by corresponding emotional suffering^[10]. We consequently hypothesize that obese female children should show higher levels of negative self-attributions than male ones.

As regards the effect of age, Friedman *et al.*^[10] (1995) maintained that the absence of a clear relationship between self-worth and obesity can be explained if we consider that the link between body esteem and self-esteem during childhood is weak and becomes stronger approaching adolescence. They maintain that this can explain why older obese individuals (adolescents and college-age women) show clearer evidence of negative self-attributions. We agree that this link is more evident during adolescence, but we think it slowly develops during childhood, becoming stronger as adolescence approaches.

These two factors can affect the correlation between obesity and psychopathology whatever the direction of the causal link between them. If we take into consideration the "psychosomatic" model, we can hypothesize that, once it develops in order to reduce emotional suffering, obesity might, in turn, have a worse effect on females and on adolescents for the same reason.

These are, consequently, the hypotheses of this study: (1) obesity has no clear correlation with children's overall level of adjustment; (2) obesity has a specific negative correlation with self-worth; and (3) being female and older in age have an effect on the psychopathological correlates of obesity.

Traditionally, two methods of scoring have been developed for DAP evaluation: A quantitative approach based on the aggregation of multiple variables and a qualitative approach based on holistic clinical evaluation^[41]. We used this last method to evaluate drawings since qualitative methods have shown to be sounder than quantitative ones^[47,48]. Holistic evaluation scales have been developed on the assumption that the intuitive judgement of clinical psychologists can be a valid and reliable assessment tool^[49]. Overall adjustment was assessed through the so-called "Estimated Adjustment of the

Client" (EAC)^[50], while we tried a new procedure we called "Estimated Self-Worth" (ESW) to evaluate self-concept of obese children.

Before evaluating children's drawings, it was decided to ascertain the interpretative skills of the two clinicians who were instructed to evaluate adjustment and self-worth through the DAP. Hammer^[51] stressed how human figure drawing can be a sensitive tool in the hands of some evaluators while it could be a misleading instrument in the hands of others. Hunt^[52] and Fowler^[53] maintained that the same clinician should be considered as an assessment instrument and that interpretative performance should be evaluated just like we ordinarily do for tests. Personality characteristics like empathy, intuition, creativity and "affiliative" interpersonal orientations have been underlined as factors predicting good interpretive skills^[54]. Above all, we found this evaluation essential since we decided to use a holistic approach which - differently from quantitative scales - relies almost entirely on the clinician's emotional and cognitive reactions to the observation of drawings. We validated interpretative skills using two drawing samples of patients with two different personality disorders and a control group made by subjects with no history of psychopathological problems. The assignment of a patient to a group was decided according to the specific self-concept associated with the correspondent personality disorder (low self-worth vs overvalued self-worth). We expected patients belonging to low-self worth personality to have the lower mean score on the ESW measure, patients belonging to the overvalued self-worth personality to reach the higher mean score and subjects with no history of psychopathological problems to have the middle mean score. As regards the evaluation of adjustment, we expected both groups with personality disorders to have lower levels of psychological adjustment than the control group.

MATERIALS AND METHODS

Preliminary analyses regarding interpreters judges

Raters were two experienced clinical psychologists with a formal education and at least five years of clinical practice in the field of assessment through projective techniques and psychotherapy.

DAP scoring

EAC: Following the instructions of Albee *et al.*^[49,55] judges were first introduced to a definition of adjustment as the capacity for emotional investment in relationships and as the ability to translate reality in a way that is compatible with conventional perceptions of others. No specific DAP indicators were recommended to them: They were instructed to feel free to choose any sign they thought helpful in making a conclusion concerning children's well being. They were also told to rely on clinical experience, empathy and intuition. Adjustment was rated on a 5-point scale ranging from very maladjusted (1) to extremely

well-adjusted (5); the midpoint (3) was labelled as normally adjusted. Intuitive adjustment evaluation has already been successfully applied to evaluate the presence of psychopathology^[55,56], to predict psychiatric hospital admission^[57] and foster-care placements^[50] and to differentiate children with mood and mood/anxiety disorders from control group children^[48].

ESW: As regards the measurement of self-esteem, judges were first introduced to a definition of self-esteem as a global judgement of self-worth^[58]; it was rated on a 5-point scale ranging from viewing oneself as worthless (1) to viewing oneself as special (5); the midpoint (3) was labelled as balanced view of self-worth. Judges were instructed to choose level 1 when they thought children had a negative view of themselves as worthless; this adjective was further explained using terms referring to personality characteristics like feeling inadequate, fragile, weak, lacking in self-confidence and self-esteem, inept, inferior. Level 5 was defined as feeling special: This term was further explained with other words like superior, admirable, unique, grandiose. Level 3 was labelled as balanced self-worth: Judges were told to select this midpoint level when they thought children were characterised by a balanced self-confidence and self-esteem. As with EAC, no specific DAP indicators were suggested to judges who were left free to choose any indicator they thought helpful in making a conclusion concerning children's self-concept.

Reliability of interpretative skill

Training was carried out to reach at least 80% agreement of all DAP measures on two samples of drawings before working on the experimental ones. A first training sample of twenty-five human figure drawings was randomly selected from the files of a neuropsychiatry service; a second training sample of twenty-five drawings was taken from a local primary school. These drawings were selected to assure that the training could be reliable both with psychopathological and normal subject evaluations; the random selection of training drawings was realized controlling the participants in the main study for age and sex. The choice of experienced clinical psychologists and a period of training were preferred since it has been proved that experience can improve both the interpretative ability and reliability rates of skilled interpreters^[59]. Pearson correlations between the two judges were computed for continuous variables: Interrater reliability for EAC was 0.79, for ESW it was 0.81.

Validity of interpretative skill

The overall sample of participants used for the validation of interpreters consisted of 45 individuals, 30 of whom had been seen for psychological testing and psychotherapy at a public psychiatric health service; 15 more participants with no history of psychological counselling or intervention were selected as a control group, controlling for age and sex. A diagnosis of personality disorders was carried out

Table 1 Evaluation of interpretative skill: Mean scores by group membership

Measure	DPD group (<i>n</i> = 15)		NPD group (<i>n</i> = 15)		<i>n</i> (<i>n</i> = 15)	
	M	SD	M	SD	M	SD
EAC	1.86	0.65	1.8	0.96	3.93	0.79
ESW	2.13	1.06	4.27	0.88	3.13	1.12

EAC: Estimated adjustment of the client; ESW: Estimated self-worth; DPD: Dependent personality disorder; NPD: Narcissistic personality disorder; *n*: Subjects with no history of psychopathological problems.

through the SCID-II, the Structured Clinical Interview for DSM-IV Personality Disorders^[60]. Since all the patients involved in the study entered psychotherapy soon after the assessment procedure, initial SCID diagnoses were confirmed by subsequent clinical observations. Two groups of 15 patients were formed: The first one who received a diagnosis of "dependent personality disorder" and the second one received a diagnosis of "narcissistic personality disorder". It was not possible to assess self-esteem through questionnaires or other measures, since we used randomly selected archival data which were collected before planning and executing this study. However both experimental and clinical research have widely demonstrated the association between low self-esteem and dependency^[61-63] while high self-esteem and narcissism are obviously linked. We essentially relied on a clinical diagnosis of the whole personality to assess self-worth, the single domain of psychopathological functioning we were interested in. Drawings were scored on a blind basis: Scorers were unaware of diagnoses of personality disorders (they only knew sex and age).

In accordance with our predictions, mean scores on EAC resulted significantly lower for both groups with personality disorders and higher for the group with no history of psychopathological problems (Table 1); the ANOVA test yielded significant differences between groups on the mean total score, $F(44, 2) = 34.24$, $P < 0.0001$. Planned contrasts indicated that the two groups with personality disorders did not differ on mean EAC score, but they all had significant lower mean scores than the group without psychopathological problems. To examine the validity of ESW, an ANOVA test was computed yielding significant differences between groups on the mean total score, $F(44, 2) = 16.16$, $P < 0.0001$. As predicted, the sample with dependent personality disorder had the lowest ESW mean score while the sample with narcissistic personality disorder had the highest ESW value; balanced self-worth personalities had the middle mean score (Table 1).

Evaluation of obese psychopathology

Subjects and procedure: The participants were 78 Italian children from two Roman schools. To assure generalizability of data, the two schools were randomly selected from the whole sample Roman public schools. Eight children refused to participate in the study, data

coming from 20 children had to be dropped from the sample because of missing information. Thirty-three children were signalled by their teachers due to their excessive weight, thus suggesting the possible risk of obesity. The remaining 17 were taken from the same schools as a control group (controlling for age and sex). Body mass index [BMI; weight (kg)/height (m²)] was used as a measure of body fat. Height was measured to the nearest millimeter with a portable stadiometer while weight was assessed to the nearest 0.1 kg using digital scales. Children did not dress shoes and wore light clothing. Heightbar^[10] was fixed on the wall, and children were standing with back and heels pressed to the wall. Measurements were performed by three trained examiners according to standard procedures (Lohman *et al.*^[64], 1992). Children were subdivided into normal (*n* = 17), overweight (*n* = 14) and obese (*n* = 19) using the standard definition established by Cole *et al.*^[65] (2000). Participants had a mean (\pm SD) age of 9.74 ± 1.84 years and a mean BMI of 22.01 ± 2.81 ; mean BMI were 18.87 (normal), 22.25 (overweight) and 24.65 (obese).

Human figure drawings were obtained by providing children with a pencil and instructing them to simply "draw a person" on a sheet of white typing paper. They were scored on a blind basis: Scorers were unaware of the child's weight, they only knew their sex and age. Pearson correlations between the two judges were computed for continuous variables: Interrater reliability for EAC was 0.81, for ESW it was 0.82. Disagreements were solved by computing the mean for each of the two divergent scores. The research project was described to the parents of obese children as a study of the psychological functioning of obese and overweight children. Parental consensus was requested and obtained for each subject before starting assessment procedures. All of the children's parents gave their assents.

Statistical analysis

A one-sample Kolmogorov-Smirnov test was conducted beforehand to detect excessively skewed data; data which were not normally distributed were subjected to natural log transformations. Analysis of variance (ANOVA) was used to compare the dependent variables across the three groups. Pearson correlation test was used to search for possible association between the different variables under investigation. χ^2 test was used to investigate for possible differences whenever qualitative variables were involved. Statistical analyses were performed in SPSS for Windows 16.0 (SPSS, 2007).

RESULTS

Before testing experimental hypotheses, it was verified that EAC and ESW were not correlated through the Pearson correlation test ($r = -0.034$; $P = \text{ns}$). Nor were differences found regarding distribution of sex, χ^2 (2, $n = 50$) = 0.31, $p = \text{ns}$ and mean age, $F(47, 2) = 2.81$,

Table 2 Evaluation of anthropometrical outcomes and Draw-A-Person test measures by gender

Measure	Male (<i>n</i> = 24)		Female (<i>n</i> = 26)	
	M	SD	M	SD
BMI	21.47	0.24	23.56	0.34
EAC	3.32	0.28	2.91	0.32
ESW	3.12	0.36	2.93	0.37

BMI: Body mass index; EAC: Estimated adjustment of the client; ESW: Estimated self-worth.

$P = ns$; mean BMI across the groups gave significantly different results, $F(47, 2) = 84.43$, $P < 0.0001$ (means and standard deviations for BMI, EAC and ESW are shown in Tables 2 and 3).

Two univariate ANOVA tests were computed to examine possible differences on EAC and ESW among children subdivided into groups according to weight; analyses yielded negative results both for EAC, $F(47, 2) = 0.92$, $P = ns$, and for ESW, $F(47, 2) = 2.88$, $P = ns$. Since ESW means showed the trend we expected on the basis of our hypothesis, diminishing from normal to obese children, we decided to run a Pearson correlation test to verify our hypothesis: It was thought to be a more sensible measure of the association between DAP scores and BMI. As predicted by our hypothesis, BMI was negatively correlated with ESW, $r(50) = -0.29$, $P < 0.05$, but not with EAC, $r(50) = -0.08$, $P = ns$.

To evaluate the effect of gender, Pearson correlations were re-computed regrouping the sample accordingly: BMI and EAC reached a significant negative correlation in female subjects, $r(24) = -0.36$, $P < 0.05$, and a positive correlation in male subjects, $r(26) = 0.37$, $P \leq 0.05$; negative correlation between BMI and ESW became stronger in females, $r(24) = -0.51$, $P < 0.01$ but not in males, whose correlation disappeared resulting not-significant, $r(26) = -0.06$, $P = ns$.

These data strongly suggest that gaining weight is associated both with an overall level of psychopathology and negative self-worth but only in female children, not in males; better still, males show a positive association between weight and adjustment. The effect of BMI is stronger on the specific domain of self-worth rather than on the general level of psychopathology. If we consider the most obese children ($BMI > 24$; $n = 15$) we find further confirmation of our conclusions, since nine of them have the lowest level of ESW ($ESW = 1$).

To calculate the effect of age on EAC and ESW, a possible correlation between them was first verified. Age resulted associated with ESW, $r(50) = 0.36$, $P < 0.005$ while EAC had a near-significant correlation with age, $r(50) = 0.23$, $P = 0.06$. Further analysis was performed to test the possible interaction between age and BMI on EAC and ESW. It was found that controlling for BMI, both the correlation between age and ESW, $r(47) = 0.37$, $P < 0.004$, and between age and EAC, $r(47) = 0.23$, $P = 0.053$, showed no substantial change.

Table 3 Evaluation of obesity: Mean scores by group membership

Measure	Normal weight group (<i>n</i> = 17)		Over weight group (<i>n</i> = 14)		Obese (<i>n</i> = 19)	
	M	SD	M	SD	M	SD
BMI	18.87	0.37	22.25	0.31	24.66	0.32
EAC	3.18	0.32	3.43	0.27	2.89	0.23
ESW	3.24	0.36	2.79	0.37	2.11	0.32

BMI: Body mass index; EAC: Estimated adjustment of the client; ESW: Estimated self-worth.

Contrary to our predictions, we consequently found no effect of age on the level of self-worth and on the overall level of adjustment of obese children.

DISCUSSION

Obesity

The results of the present study suggest that obesity is associated with low self-worth and lower levels of overall adjustment exclusively in female subjects. Obese female children dislike themselves and show a tendency to feel worthless, inadequate and lacking in self-esteem. Male children do not seem to suffer because they are overweight: Our data even suggest that in male children, weight may be associated with higher levels of adjustment.

Our data are consistent with Friedman *et al.*^[10]'s idea of obesity as a "syndrome of subclinical suffering". It can be hypothesized that being an obese female child is a risk factor for the development of a negative self-concept (self-worth) and for the development of low levels of adjustment. This negative bias toward females supports the hypothesis that obesity is a cultural problem: It may be that aesthetic models characterised by thinness have negative consequences on self-concept.

The other explanation worthy of consideration is that obesity develops as a consequence of emotional suffering coming from low self-worth: Once developed, overeating could be enhanced by the negative affect caused by social stigma, especially for female children for whom cultural models are particularly demanding. According to this different explanation, it is possible that the negative self-image associated with obesity reinforces pre-existent self-deprecating processes which usually affect self-worth.

In any case, whatever the direction of this link, the management of obesity should focus on self-worth since obese young females are prone to emotional distress and negative mood: Working on self-esteem is of primary importance in facilitating mental health and adjustment to body fat. Some non-dietary approaches to obesity have in fact successfully attempted to improve self-esteem and body image through self-acceptance^[66-69]. Nevertheless, it is also important to consider the role that sex hormones, and maturity of the hypothalamic, pituitary gonad axes in the psychological symptoms and

self-esteem of adolescent girls. Some researchers have shown that there is a negative relationship between self-esteem and sexual development of girls and adolescents. Specifically, Huerta *et al.*^[70] showed that girls who are older and achieve highest sexual development had lower self-esteem, more anxiety and depression than girls younger and with less sexual development, independent of the girls' body weight. Consequently, it may be important to consider sexual development of obese female adolescents in the assessment of their possible emotional problems, as it may take an important role in the development of their psychological troubles.

Clinical judgement of DAP made by experienced clinical psychologists can be successfully used to evaluate self-worth and overall adjustment level in obese children. Indeed, the self-defeating and often unconscious convictions concerning the self found in female subjects, may be observed through some specific DAP signs produced by our sample. For instance, insecurity and low self-esteem may have brought participants to draw human figures with light lines, line discontinuity or erasures. Some DAP indicators may be used to evaluate these psychopathological correlates. According to our judges, the most frequent signs influencing their evaluation might have been small human figures, light lines, line discontinuity, erasures, body simplification, sad or frightened posture/facial expression. These signs are usually associated with anxiety^[71] and depression^[40,72-74]. This is consistent with research findings that show how obese female adolescents spend significantly fewer months at high school^[75] and with other studies which have found an association between obesity and depression^[76,77]. Both of these conditions - depression and low scholastic achievement - are indeed associated with low self-esteem and low self-efficacy. Since DAP can be administered in a short period of time and is easily complied by patient, it could be used as a preliminary screening test for the selection of children needing therapeutic intervention.

We also found that age does not mediate the relationship between weight and psychopathology. The absence of the effect of age can be related to the typology of measure used in this study. It may be that an implicit negative self-perception develops during childhood and that it does not change during adolescence, while overt emotional suffering concerning the self, may start during adolescence or later during adulthood. Further research is needed to solve this question: Longitudinal studies with different kinds of assessment instruments should be used to distinguish between low self-esteem and emotional suffering.

Methodological considerations concerning the DAP

The "intuitive reading" of figure drawings can be considered a valid and reliable tool of assessment both from a scientific and clinical point of view. The DAP "feeling approaches" consist of using the cognitive and emotional reactions of a clinician when the drawings are

examined to obtain information concerning the drawer's personality: They probably rely on primitive layers of "knowing" far beyond an individual's awareness^[54,78] because, while evaluating drawings, judges describe empathising as an involuntary and automatic mental activity. When evaluating drawings characterised by low self-worth our judges said they had the "impressions" of feeling sad or frightened, or imagining a weak child lacking in self-confidence. Sometimes they said they didn't know exactly why they attributed specific scores to drawings: They said they intuitively felt the child had a negative view of himself or a grandiose one even when signs didn't suggest anything clear.

Riethmiller *et al.*^[41] stressed the importance of multivariable scales when discussing quantitative evaluations of DAP. They maintained that the same construct can find expression through different signs: Evaluating a single sign could consequently be misleading since a single item has a low correlation with the associated construct^[79]. Qualitative evaluation of DAP could be useful since clinical intuition may produce a deeper and sounder evaluation of single signs whose meaning may vary in relation to the remaining characteristics of the figure. In other words, holistic evaluation of the figure, through clinical intuition, could give the correct importance and meaning to the varying individual signs of the drawing, thus making possible a more valid overall interpretation.

The problem here is that it is not clear what kind of personality factors or experiences are responsible for the development of interpretative skill: This is the reason why assessment is sometimes considered an art rather than a scientific discipline. From a methodological point of view the problem is the correspondence between subjective involuntary mental activity and objective external reality: Subjective impressions could simply be wrong. The reliability of certain indicators is not enough: Joiner *et al.*^[80] found that size, detail and line heaviness had high rates of reliability but they were not significantly associated with external measures of depression and anxiety. We used the evaluation of personality disorders as a measure of validity by sorting subjects with different levels of self-worth and adjustment. This choice was made on the assumption that DAP is particularly suitable for the assessment of stable personality tendencies rather than for transient behavioural or mood alterations^[81]. The evaluator's personality should consequently be considered as an assessment tool to be validated^[53], just like tests, before starting an empirical and holistic evaluation of DAP research data^[82]. Even when evaluators have good interpretative skills, countertransference problems could bias interpretations of the drawings. Hammer *et al.*^[83] found a correlation between the degree of evaluators' hostility and their inclination to perceive aggressive tendencies when evaluating drawings. We consequently think that all research involving holistic DAP measures should require an evaluation of the judges' skills, specifically those relating to the variables to be measured.

The validation procedure which discriminates between the different personality disorders here tested can be thus considered a way to scientifically ascertain the intuitive and empathic skills of evaluators, rather than a way of validating EAC or ESW. It is indeed simply impossible to use traditional tests to evaluate clinical skills like empathy or affiliative tendencies. It would be sounder to validate the accuracy of judges' evaluations by using categories of patients which share the same characteristics of the experimental group. To evaluate disordered thinking for instance, it would be useful to test interpretative skills by comparing drawings by subjects with a diagnosis of schizophrenia with other drawings made by subjects with different psychopathological problems and samples from individuals without any kind of psychiatric diagnosis.

DAP research has been characterised by lack of coherent findings and severe methodological criticism, just like other research involving projective techniques. One of the reasons why DAP research has produced contradictory findings is that the interpreters who evaluate the drawings have different skills. Consequently, interpreters' skills should always be assessed and measured before executing each single studies in order to guarantee sound methodological praxis: "...focus should instead be on good interpreters, who demonstrate outstanding ability to interpret the DAP"⁽⁷⁸⁾.

This study has different limitations. First of all, it was not considered the possible effect of socioeconomic strata on the relationship between obesity and the EAC and ESW variables; however, random selection of the two samples probably reduced the possible effect of socioeconomic factors on the results of this study. Also, sexual development that children and the antecedent of age at menarche had at the moment of the study were not considered; this is a limitation as these variables are related with different personality characteristics of children. Future research may address this question.

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COMMENTS

Background

Obesity is a serious problem all over the world. Reviews addressing the association between obesity and psychopathology have led to contradictory findings. It has been proposed that obesity will determine psychopathological consequences only in individuals carrying definite risk factors and that it prevalently affects specific domains of psychological functions. Thus, the present research was conducted to investigate two possible psychopathological correlates of childhood obesity (self-concept and general psychopathology) via the Draw-A-Person test (DAP). The authors also considered the effect of developmental age and gender on these correlations.

Research frontiers

Current research suggests that clinical judgement of DAP made by experienced clinical psychologists can be successfully used to evaluate self-worth and

overall adjustment level in obese children.

Innovations and breakthroughs

This study is, to the authors' knowledge, the first to investigate psychopathological correlates of child obesity via DAP.

Applications

Clinical judgement of DAP made by experienced clinical psychologists can be successfully used to evaluate self-worth and overall adjustment level in obese children. Since DAP can be administered in a short period of time and is easily complied by patient, it could be used as a preliminary screening test for the selection of children needing therapeutic intervention.

Terminology

Obesity: Excessive accumulation of body fat that may impair health; **Draw-A-Person test:** An implicit measure of personality consisting of drawing a person on a sheet of white typing paper.

Peer-review

This is an interesting and methodologically well developed study.

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Case Control Study

Chronic pelvic pain, psychiatric disorders and early emotional traumas: Results of a cross sectional case-control study

Flávia L Osório, Ana Carolina F Carvalho, Mariana F Donadon, André L Moreno, Omero Polli-Neto

Flávia L Osório, Ana Carolina F Carvalho, Mariana F Donadon, André L Moreno, Omero Polli-Neto, Medical School of Ribeirão Preto, São Paulo University, Ribeirão Preto 14048-900, Brazil

Author contributions: Osório FL and Poli-Neto O designed research; Carvalho ACF and Donadon MF collected material and clinical data from patients; Osório FL and Carvalho ACF analysed data; Osório FL, Poli-Neto and Moreno AL wrote the paper.

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Correspondence to: Flávia L Osório, Professor, Medical School of Ribeirão Preto, São Paulo University, Avenida dos Bandeirantes 3900, Ribeirão Preto 14048-900, Brazil. flaliosorio@gmail.com
Telephone: +51-16-36022530
Fax: +51-16-36022703

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Abstract

AIM

To compare the prevalence of psychiatric disorders and early emotional traumas between women with chronic pelvic pain (CPP) and healthy women.

METHODS

One hundred women in reproductive age, 50 of them had CPP (according to the criteria set by the International Association for Study of Pain), and 50 were considered healthy after the gynecological evaluation. The eligibility criteria were defined as follows: chronic or persistent pain perceived in the pelvis-related structures (digestive, urinary, genital, myofascial or neurological systems). Only women in reproductive age with acyclic pain for 6 mo, or more, were included in the present study. Menopause was the exclusion criterion. The participants were grouped according to age, school level and socio-economic status and were individually assessed through DSM-IV Structured Clinical Interview (SCID-I) and Early Trauma Inventory Self-report - short form (ETISR-SF Brazilian version). Descriptive statistics, group comparison tests and multivariate logistics regression were used in the data analysis.

RESULTS

The early emotional traumas are highly prevalent, but their prevalence did not differ between the two groups. The current Major Depressive Disorder was more prevalent in women with CPP. The CPP was associated

with endometriosis in 48% of the women. There was no difference in the prevalence of disorders when endometriosis was taken into account (endometriosis *vs* other diseases: $P > 0.29$). The current Major Depressive Disorder and the Bipolar Disorder had greater occurrence likelihood in the group of women with CPP (ODDS = 5.25 and 9.0).

CONCLUSION

The data reinforce the link between mood disorders and CPP. The previous evidences about the association between CPP and early traumas tended not to be significant after a stronger methodological control was implemented.

Key words: Pelvic pain; Psychiatric disorder; Early trauma; Emotional; Depression

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Core tip: There is also evidence about the association between depressive and anxious symptoms and the presence of chronic pelvic pain (CPP). The weakest points in these data refer to the quality of the studies; as most of them are descriptive and assess symptoms, instead of confirming the disorder symptoms, which may affect the understanding of the link between conditions. The current study used "gold standard" psychiatric diagnostic instruments to assess the presence or absence of Axis I mental disorders. The results showed associations between mood disorders and CPP, but the association between CPP and early trauma tends not to be significant after increased methodological control.

Osório FL, Carvalho ACF, Donadon MF, Moreno AL, Polli-Neto O. Chronic pelvic pain, psychiatric disorders and early emotional traumas: Results of a cross sectional case-control study. *World J Psychiatr* 2016; 6(3): 339-344 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v6/i3/339.htm> DOI: <http://dx.doi.org/10.5498/wjp.v6.i3.339>

INTRODUCTION

The chronic pelvic pain (CPP) is a prevalent condition in women, mainly in those who are in reproductive age. The CPP occurrence is estimated in approximately 4%^[1] but, in Brazil, it is close to 10%^[2,3]. According to the International Association for Study of Pain (IASP), CPP is featured as a chronic or persistent pain in pelvis-related structures; it is often associated with negative emotional, sexual, behavioral and cognitive consequences, as well as with symptoms that suggest dysfunctions in such systems. Its symptoms include either cyclic or acyclic pain; however, it is not necessary to show the symptoms for more than six months if the patient presents evident signs of central sensitization. The central sensitization is an important event in

patients with chronic pain. There are no pathognomonic clinically signals or symptoms. Nevertheless, primary or secondary hyperalgesia, dynamic tactile allodynia, the temporal summation of pain are some of them. When these conditions were presented, the chronicity can be considered before six months^[4].

Factors related to the etiology and maintenance of CPP remain unclear. So far, it is known that CPP is a complex condition influenced by, or resulting from, the interaction between many systems, for instance: the gastrointestinal, urinary and genital ones; it is also associated with neurological and psychological aspects^[5,6]. There are many studies pointing towards the role played by the emotional factors, mainly towards the presence of Early Emotional Traumas (EET)^[7] and mental disorders^[1,8-10] in the psychological aspects associated with CPP.

A meta-analysis conducted by Latthe *et al.*^[11] pinpointed that sexual and physical EETs increase in approximately 1.5-2.1 times the chances of developing CPP. However, these authors state that the associations between sexual abuse and CPP are more prevalent in low methodological quality studies; thus, it is worth being careful at the time to interpret the results. There are also evidences about the association between depression and anxiety symptoms, and CPP^[11]. Nevertheless, one of the weakest points to these evidences is the quality of the studies, most of them are descriptive and just assess the symptoms rather than confirming the disorder. Thus, it may compromise the understanding about the link between different conditions.

The current study was based on the aforementioned panorama, which evidenced the lack of cross sectional case-control studies that use psychiatric "gold standard" diagnostic instruments to assess the presence or absence of axis I mental disorders, as well as the lack of studies focused on etiological factors associated with CPP.

Thus, the main aims of the current study are: (1) to assess the prevalence of psychiatric disorders and EETs in women with CPP; and (2) to verify the hypothesis that these disorders and traumas had greater occurrence likelihood in the group of women with CPP.

MATERIALS AND METHODS

The present research is a cross sectional study and its convenience sample was composed of 100 women in reproductive age, 50 of them had CPP (according to the criteria set by IASP), and 50 were considered healthy after the gynecological evaluation. The eligibility criteria were defined as follows: Chronic or persistent pain perceived in the pelvis-related structures (digestive, urinary, genital, myofascial or neurological systems). Only women in reproductive age with acyclic pain for six months, or more, were included in the present study. Menopause was the exclusion criterion. Women with CPP were recruited in the Chronic Pelvic Pain Center of a university hospital and the healthy women were

Table 1 Sociodemographic features of the samples according to the chronic pelvic pain and control groups

Variable		CPP (<i>n</i> = 50)		C (<i>n</i> = 50)		Statistics
		<i>n</i>	%	<i>n</i>	%	
Age	Mean (SD)	37.44 (8.12)		37.9 (8.72)		<i>U</i> = 1218.00 <i>P</i> = 0.82
School level	Up to 8 yr	19	38	19	38	$\chi^2 = 0.45$
	From 9 to 11 yr	26	52	26	52	<i>P</i> = 0.98
	Over 12 yr	5	10	5	10	
Marital status	Single/widow/divorced	15	30	24	48	$\chi^2 = 3.40$
	Married/law marriage	35	70	26	52	<i>P</i> = 0.07
Number of kids	Mean (SD)	1.72 (1.67)		2.08 (1.61)		<i>U</i> = 1055.50 <i>P</i> = 0.17
Professional status	Non-active	24	48	4	8	$\chi^2 = 19.84$
	Active	26	52	46	92	<i>P</i> < 0.001 ¹

¹Statistically significant difference; CPP: Chronic pelvic pain group; C: Control group; U: Mann-Whitney test.

recruited among the employees and outpatients of the primary care center in the same institution. The participants were grouped according to age, school level and socio-economic status. The recruiting process took place in 2014.

The following instruments were used for data collection: (1) Structured Clinical Interview for DSM-IV - clinical version (SCID-I/CV): Which is used to diagnose different axis I mental disorders, it was translated into Portuguese and validated by Del-Ben *et al.*^[12], its inter-appraiser reliability score was 0.83; (2) Early Trauma Inventory Self-report - short form (ETISR-SF): Which is a self-report instrument used to investigate traumatic experience history before the age of 18. It is composed of 27 items, divided in four dimensions (general trauma, physical abuse, emotional abuse and sexual abuse) and scored in dichotomous scale (Yes/No). The total score and the score of each sub-scale are given by summing the items. The larger the sum is, the larger the number of experienced traumatic events. The version translated into Portuguese and validated by Osório *et al.*^[13] was used. It presented internal consistency 0.83 and test-retest reliability 0.78-0.90; (3) Socio-demographic Questionnaire: which is composed of items linked to the socio-demographic features of the sample; and (4) Medical records: Were used to get clinical information associated with CPP.

The SCID-I-CV was applied in person, during individual sections, by an appraiser trained and experienced in using this instrument. Subsequently, the participants filled out the self-report instruments. The study was approved by the Local Ethics Committee (Process No. 11798/2012) and conducted according to the ethical principles of research involving human beings. We got the written consent from the participants.

Data were analyzed in the SPSS statistical software. The descriptive statistics (mean and standard deviation), and the χ^2 and Mann-Whitney tests were used to compare the groups. Cohen statistic was used to estimate the magnitude of the differences between groups. The parameters adopted for the interpretation

of this parameter will be: < 0.20 = small, 0.2-0.8 = medium; > 0.80 = large^[14].

The prediction analysis was performed through multivariate logistics regression (the backward method). The presence or absence of CPP was the endpoint. The independent variables (psychiatric disorders), whose *P* values were lower than 0.20 in the group comparison analysis, were included in the initial regression model and tested as possible predictors^[15,16]. The *P* < 0.05 was adopted as significance value in all the analyses.

RESULTS

The socio-demographic feature is shown in Table 1, which shows differences in the professional status and higher percentage of inactive women in the CPP group. The list of diagnoses comprised endometriosis (*n* = 24), myofascial and neuralgia (*n* = 6), irritable bowel syndrome (*n* = 5); other diagnosis (adhesions, pelvic inflammatory disease, pelvic congestion syndrome, interstitial cystitis, *n* = 13); undetermined symptom (*n* = 2).

The prevalence of EETs is high (Table 2), but it did not differ between groups.

The specific analysis of each traumatic situation assessed through ETIS-SR also did not show statistic differences between the groups (*P* > 0.11).

There was significantly higher prevalence of current Major Depressive Disorder in women with CPP than in the healthy controls, in cases of Axis I psychiatric disorders (Table 3).

There was the general trend of Mood Disorder prevalence in the CPP group. There was no statistical difference in the prevalence of different disorders when the clinical group and the causes were taken into account (endometriosis vs other diseases: *P* > 0.29).

The variables tested in the initial model (*P* > 0.20) of the multivariate regression analysis were: Major Depressive Disorder, Bipolar Disorder, Panic Disorder, Hypochondria and Anorexia. However, the model appeared to be inappropriate. New models were tested, and

Table 2 Scores of the early trauma inventory - short form - and their sub-scales according to the chronic pelvic pain and control groups

Type of early trauma		CPP (n = 50)	C (n = 50)	Statistics	Effect Size
General traumas	Mean ¹	2.56	2.16	U = 1159.00	0.20
	(SD)	(2.26)	(1.81)	P = 0.52	
	% Yes ²	84	82		
Physical punishment	Mean	2.04	1.51	U = 1011.00	0.36
	(SD)	(1.66)	(1.28)	P = 0.12	
	% Yes	72	70		
Emotional abuse	Mean	2	1.92	U = 1204.00	0.04
	(SD)	(1.93)	(1.87)	P = 0.88	
	% Yes	64	68		
Sexual events	Mean	1.14	0.98	U = 1169.00	0.11
	(SD)	(1.5)	(1.36)	P = 0.54	
	% Yes	50	42		
Total	Mean	7.8	6.54	U = 1091.50	0.24
	(SD)	(5.84)	(4.5)	P = 0.44	
	% Sim	94	98		

¹Mean of traumatic situation sexperienced in each category; ²Percentage of subjects with at least one type of trauma within the category. CPP: Chronic pelvic pain group; C: Control group; U: Mann-Whitney test.

Table 3 The prevalence of different Axis I Psychiatric disorders according to the chronic pelvic pain and control groups

Psychiatric disorders ¹		CPP (n = 50)		C (n = 50)		Statistics
		n	%	n	%	
Mood	Current major depressive	14	28	4	8	P < 0.011
	Bipolar disorder	6	12	1	2	P = 0.11
	Dysthymia	1	2	–	–	P = 1.00
	Any mood disorder	24	48	15	30	P = 0.06
Use substances anxiety	Abuse/dependence Substance	10	20	12	24	P = 0.63
	Panic	8	16	3	6	P = 0.11
	Obsessive-compulsive	12	24	9	18	P = 0.46
	Post-traumatic stress	3	6	2	4	P = 0.65
	Social anxiety	10	20	6	12	P = 0.28
	Specific phobias	12	24	11	22	P = 0.81
	Any anxiety disorder	27	34	26	52	P = 0.84
	Somatization	7	14	5	10	P = 0.54
Somatoforms	Hypochondria	4	8	1	2	P = 0.17
	Eating disorders	4	8	–	–	P = 0.12
	Bulimia	5	10	5	10	P = 1.00

¹According to the DSM-IV criteria. CPP: Chronic pelvic pain group; C: Control group.

the variables with lower statistical significance level were individually suppressed, until the final model presented in Table 4 was reached.

This table shows that the current Major Depressive Disorder and the Bipolar Disorder emerged with higher occurrence likelihood in women with CPP. Thus, women with current Major Depressive Disorder and Bipolar Disorder have 5.25 and 9.0 more chances of having CPP than women without the referred disorders, respectively.

DISCUSSION

The main results in the current study pointed out significant differences in the prevalence of current Major Depressive Episodes between women with and without CPP. The recent review conducted by Carvalho *et al.*^[11] highlighted the link between depressive symptomatology

and CPP. However, the present study advanced in the knowledge about this association since it used the gold standard diagnostic interview and a control group paired by age, school level and economic status to assess the presence of depressive disorders. Thus, based on the current results, it is possible stating that the depressive disorder is more prevalent in women with CPP, as well as that the occurrence rate in this group is about five times higher than that in the group of women without CPP (OR = 5.25).

Such finding may be associated with the presence of comorbid conditions often found in depressive states such as pain experience and somatization^[17]. On the other hand, it is worth highlighting that most of the studies related to such association point towards a two-way relation between these two conditions. The pain and the limitations linked to these conditions may favor

Table 4 Final logistics regression model showing chronic pelvic pain as endpoint variable

Disorder		OR	95%CI	P value
Current depressive episode	No	1 ¹	(1.57-17.49)	0.007
	Yes	5.25		
Bipolar disorder	No	1 ¹	(1.03-18.57)	0.047
	Yes	9		

¹The reference variable. OR: Odds ratio; P value: Significance level.

the depressive symptoms and disorders^[18-20]. Hence, by taking the current findings into consideration, as well as the design of the present study, it is more reasonable to state that the presence of current Major Depressive Episodes is an independent factor associated with CPP.

However, when it comes to the association with Bipolar Disorder, it was observed that such disorder also are more likely to occur in the group of women with CPP, although the analysis between groups did not show statistical significance. Prevalence differences were also not observed in the analyses that have considered the presence or absence of endometriosis. Such finding is interesting because the previously conducted studies disagree on the presence of such association, mainly when the presence of endometriosis, as etiologic risk factor, is taken into account. Kumar *et al*^[21] compared 27 women who had endometriosis and other 12 endometriosis-free women with CPP, and found that 45% of the women in the first group presented Bipolar Disorder, whereas no woman in the CPP group presented such condition. Before that, Lewis *et al*^[22] had assessed 16 women with endometriosis in an observational study and found that 75% of them presented mood disorder, mainly the affective Bipolar disorder ($n = 10$). On the other hand, just as in the current study, Walker *et al*^[23] assessed women with and without endometriosis and found different prevalence of Bipolar disorder.

According to the aforementioned authors, the reason for such association among CPP, endometriosis and Bipolar Disorder remains unknown due to lack of studies on the topic. However, they stand for the hypothesis that the gonadotropin-releasing hormone agonist (GnRH) used to treat endometriosis may also favor emotional instability and other affective disorder conditions in the group of women with CPP and endometriosis; thus it may favor the development of such disorder^[22]. Due to such contradictory findings, the methodologically refined studies and those that consider the possible association between medication and affective symptoms, mainly regarding the Bipolar disorder, are timely. These studies may help minimizing the impacts of these disorders and favor the correct approach and treatment applied to different conditions in order to diminish comorbidity risks.

Hence, we may conclude that the current study helped overcoming some of the methodological gaps found in previous studies on this topic and was an attempt to better elucidate the link between CPP and

psychosocial conditions. The present study evidenced the association between CPP and mood disorders that need deeper investigation, mainly with regard to their specificities. On the other hand, it reinforced the items highlighted in the meta-analysis conducted by Latthe *et al*^[1], who found that the association between CPP and EET tend to be insignificant if strict methodological control is taken.

COMMENTS

Background

The chronic pelvic pain (CPP) is a prevalent condition in women, mainly in those who are in reproductive age. CPP is featured as a chronic or persistent pain in pelvis-related structures; it is often associated with negative emotional, sexual, behavioral and cognitive consequences, as well as with symptoms that suggest dysfunctions in such systems. Factors related to the etiology and maintenance of CPP remain unclear. There are many studies pointing towards the role played by the emotional factors, mainly towards the presence of early emotional traumas and mental disorders in the psychological aspects associated with CPP. There is evidence about the association between depressive and anxious symptoms and the presence of CPP.

Research frontiers

The weakest points in these data refer to the quality of the studies; as most of them are descriptive and assess symptoms, instead of confirming the disorder symptoms, which may affect the understanding of the link between conditions.

Innovations and breakthroughs

The data reinforce the link between mood disorders and CPP. The knowledge about this link is improved by the use of the "gold standard" diagnostic interview and of the group control paired according to the socio-demographic variables.

Applications

Hence, they may conclude that the current study helped overcoming some of the methodological gaps found in previous studies on this topic and was an attempt to better elucidate the link between CPP and psychosocial conditions.

Peer-review

The authors did a very well designed and analyzed study about the presence of chronic pelvic pain and affective disorders. It could be better if the authors take one position or other and explain their reasons clearly in the conclusion section.

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Case Control Study

Self-reported and behavioural impulsivity in anorexia nervosa

Andrea Phillipou, Larry Allen Abel, David Jonathan Castle, Caroline Gurvich, Matthew Edward Hughes, Susan Lee Rossell

Andrea Phillipou, Larry Allen Abel, Department of Optometry and Vision Sciences, the University of Melbourne, Melbourne, VIC 3010, Australia

Andrea Phillipou, David Jonathan Castle, Department of Psychiatry, the University of Melbourne, Melbourne, VIC 3010, Australia

Andrea Phillipou, Department of Mental Health, the Austin Hospital, Melbourne, VIC 3084, Australia

Andrea Phillipou, David Jonathan Castle, Susan Lee Rossell, Department of Psychiatry, St Vincent's Hospital, Melbourne, VIC 3065, Australia

David Jonathan Castle, Faculty of Health Sciences, Australian Catholic University, Melbourne, 3065 VIC, Australia

Caroline Gurvich, Susan Lee Rossell, Monash Alfred Psychiatry Research Centre, Melbourne, VIC 3004, Australia

Matthew Edward Hughes, Susan Lee Rossell, Brain and Psychological Sciences Research Centre, Swinburne University of Technology, Melbourne, VIC 3122, Australia

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Institutional review board statement: The study was granted independent ethics approval by the Human Research Ethics committees at St Vincent's Hospital [(Human Research Ethics Committee A (HREC-A)) (057/12), Austin Health [(Non Drug Study Advisory Committee (NDSAC)) (H2012/04646) and The Melbourne Clinic [(The Melbourne Clinic Research Ethics Committee (TMC REC)) (235). In addition, the study received expedited ethics approval from Swinburne's Human Research Ethics Committee (SUHREC) (2012/277) and was registered with The University of Melbourne Health Sciences Human Ethics Sub-Committee (HESC) (1239068), on the basis of the prior St Vincent's Hospital review.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the lead author at ap@unimelb.edu.au. No additional data are available.

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Correspondence to: David Jonathan Castle, MD, Professor of Psychiatry, Department of Psychiatry, St Vincent's Hospital, Level 2, 46 Nicholson St, Fitzroy, 3065 VIC, Australia. david.castle@svha.org.au
Telephone: +61-3-92314751
Fax: +61-3-92314802

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Abstract

AIM

To examine how self-reported and behavioural impulsivity are related in anorexia nervosa (AN).

METHODS

Twenty-four females with AN and 25 healthy controls (HC) participant in the study. Self-reported impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11). The scale yields three second-order factors: Attentional, motor and non-planning. Behavioural impulsivity was investigated with the continuous performance test (CPT), a computer-based task of sustained attention in which numbers are flashed briefly on screen and participants are required to click the mouse when the same number appears consecutively. The rate of commission and omission errors can be used as a measure of behavioural impulsivity.

RESULTS

AN participants self-reported increased attentional [AN: 20.67 (3.64), HC: 13.88 (2.91), $P = 0.001$] and reduced motor impulsivity [AN: 11.55 (2.28), HC: 14.08 (2.78), $P = 0.002$]. The rate of omission or commission errors on the CPT did not differ between groups ($P > 0.05$). BIS-11 and CPT measures did not significantly correlate, but attentional impulsivity was related to negative mood states in AN (depression: $r = 0.52$, $P = 0.010$, anxiety: $r = 0.55$, $P = 0.006$, stress: $r = 0.57$, $P = 0.004$).

CONCLUSION

The discrepancy between self-reported and behavioural impulsivity are discussed in terms of perfectionism in AN. Furthermore, it is suggested that improving negative mood states may resolve this inconsistency in AN.

Key words: Eating disorder; Continuous performance; Anorexia nervosa; Attention; Inhibition

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Core tip: The findings of the study suggest a discrepancy between self-reported and behavioural impulsivity in anorexia nervosa (AN). Although AN patients did not demonstrate differences from healthy controls in behavioural impulsivity, they self-reported reduced motor impulsivity and greater attentional impulsivity. Attentional impulsivity was associated with negative mood states in AN, suggesting that improving these symptoms may improve patients' perceptions of their attentional impulsivity.

Phillipou A, Abel LA, Castle DJ, Gurvich C, Hughes ME, Rossell SL. Self-reported and behavioural impulsivity in anorexia nervosa. *World J Psychiatr* 2016; 6(3): 345-350 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v6/i3/345.htm> DOI: <http://dx.doi.org/10.5498/wjpv6.i3.345>

INTRODUCTION

Anorexia nervosa (AN) is a psychiatric illness whose core characteristics include significantly low body weight, a fear of weight gain and disturbed perception of one's own body shape or weight. AN is also frequently associated with obsessive behaviours and perfectionistic tendencies^[1,2]. In particular, individuals with AN display elevated concerns over making mistakes^[3], and relatedly, often self-report lower rates of impulsivity^[4]. However, it is unclear whether self-reported rates of impulsivity are influenced by eating disorder symptomatology or are stable traits exhibited by these individuals. It is also unclear whether these self-reported rates of impulsivity translate to behavioural performance on cognitive tasks of inhibition.

For example, Pieters *et al*^[5] reported reduced impulsivity on a speeded choice-reaction task in AN; whereas, Butler, Montgomery^[4] found increased errors of commission and shorter response times in AN on a continuous performance task (CPT), but lower rates of self-reported impulsivity.

The CPT is typically utilised as a broad measure of sustained attention and vigilance. However, by examining different components of task performance, researchers have also used it to examine impulsivity. In the visual variant of this task, numbers of letters are typically flashed briefly on screen to participants. The task requires a response (usually a mouse click) when the same number appears twice in a row. Errors of omission describe when the same number appears twice consecutively in sequence, but the participant fails to respond (*i.e.*, inattention); whereas errors of commission involve responding when two consecutive numbers do not match (*i.e.*, impulsivity)^[6]. The CPT has been utilised to assess both sustained attention and impulsivity in a variety of conditions associated with these features; predominantly attention deficit hyperactivity disorder (ADHD) which is characterised by both inattention and increased impulsivity^[7].

The aim of this study was to investigate the relationship between self-reported impulsivity and behavioural impulsivity in AN, assessed through neuropsychological task performance. It was hypothesised that participants with AN would self-report lower levels of impulsivity than healthy controls, and would similarly demonstrate reduced behavioural impulsivity (*i.e.*, fewer commission errors on the CPT). A further aim was to examine whether differences in impulsivity between AN and healthy control groups were related to eating disorder-related factors, including eating disorder symptomatology, negative mood states, illness duration and body mass index (BMI).

MATERIALS AND METHODS

This study was approved by the human research ethics departments at The University of Melbourne, Swinburne University of Technology, The Melbourne Clinic, The Austin Hospital and St Vincent's Hospital; all in Melbourne,

Australia. Informed written consent was obtained from all participants. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants

Participants were 24 right-handed females with AN and 25 healthy controls (HC) matched for age and premorbid intelligence quotient (IQ). HCs were recruited through public advertisements, whereas AN participants were recruited through public advertisements; the Body Image and Eating Disorders Treatment and Recovery Service at the Austin and St Vincent's Hospitals; and The Melbourne Clinic; all in Melbourne, Australia.

All participants were English speaking and had no history of significant brain injury or neurological condition. Controls were required to have no history of an eating disorder or other mental illness. The Mini International Neuropsychiatric Interview, 5.0.0 (MINI)^[8] was used to screen all participants for major Axis I psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). It was also used to confirm diagnoses of AN, with the exception of the amenorrhea criterion which is no longer included in the current DSM-5. AN was required to be the primary diagnosis of the AN group. AN participants with comorbid psychiatric conditions, other than psychotic conditions, were not excluded as this would not have represented a typical AN sample.

Assessments

Premorbid intelligence was estimated using the Wechsler Test of Adult Reading (WTAR)^[9]. Eating disorder symptomatology was investigated with the Eating Disorders Examination Questionnaire (EDE-Q)^[10], and negative emotional states with the Depression Anxiety Stress Scale (DASS)^[11]. Self-reported impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11)^[12]. The scale yields three second-order factors: attentional (consisting of the first-order factors attention and cognitive instability), motor (consisting of the first-order factors motor and perseverance) and non-planning (comprised of the first-order factors self-control and cognitive complexity).

Behavioural impulsivity was assessed with the Continuous Performance Test - Identical Pairs (CPT-IP), a computer-based task of sustained attention in which numbers are flashed on the screen for 50 ms and participants are required to click the mouse when the same number appears consecutively. The task consists of two-, three- and four-digit conditions, each consisting of 150 trials in which the total number of possible hits is 30 (*i.e.*, the inverse of omission errors), the total number of possible false alarms is also 30 (*i.e.*, commission errors), and total number of possible random responses is 90 (detailed findings of this task which contained the current

sample and additional participants are presented in^[13]). Response times (*i.e.*, the time taken to click the mouse from the presentation of the stimulus) are also recorded for omission and commission errors.

Statistical analysis

Following normality checking and the removal of outliers, group differences in BIS-11, EDE-Q, DASS and CPT-IP scores were examined with analyses of variance (ANOVAs). Group differences in BIS-11 subscale scores and CPT-IP scores were further explored with Pearson's correlations between these measures and illness duration, BMI, and EDE-Q and DASS scores. Due to the large number of correlations, alpha was set to 0.01 to account for multiple comparisons.

RESULTS

Table 1 presents the group comparisons in BIS-11, EDE-Q and DASS scores. AN participants had significantly higher EDE-Q and DASS scores, relative to controls. BIS-11 scores significantly differed in the second order factor "attentional", and its two first-order factors "attention" and "cognitive instability", with AN participants reporting higher impulsivity. AN participants also reported significantly lower impulsivity in the first-order factor "motor".

Table 2 describes the CPT-IP findings. Groups were not found to differ in the proportion of hits (inverse of omission errors), false alarms (commission errors) or random responses. AN participants were, however, found to have increased false alarm response times, and greater intra-individual variability in this response.

Pearson's correlation analyses did not reveal any significant correlations between measures for the HC group. A number of significant correlations were revealed in the AN group. The first-order factor, "attention" of the BIS-11 was positively correlated with state depression ($r = 0.53$, $P = 0.007$), anxiety ($r = 0.58$, $P = 0.003$) and stress ($r = 0.65$, $P = 0.001$) as measured by the DASS. The second-order factor, "attentional" was also positively correlated with depression ($r = 0.52$, $P = 0.010$), anxiety ($r = 0.55$, $P = 0.006$) and stress ($r = 0.57$, $P = 0.004$).

DISCUSSION

The findings of the current study suggest that individuals with AN self-report different levels of impulsivity relative to healthy individuals, but do not display behavioural impulsivity (*i.e.*, increased commission errors on the CPT).

AN patients reported lower levels of motor impulsivity, compared to the healthy control group. This subscale relates to acting without thinking^[13,14], and suggests that individuals with AN regard themselves as controlled individuals who think before they act. Although the AN group reported lower impulsivity on this subscale, they reported increased impulsivity in terms of attention and cognitive instability - *i.e.*, an

Table 1 Participant information

	AN		HC		P
	M	SD	M	SD	
Age	23.07	6.88	22.67	3.19	0.798
Premorbid IQ	104.67	8.19	105.6	7.00	0.670
BMI	16.52	1.14	22.4	3.59	0.001
Illness duration	6.67	7.66	-	-	-
Age of illness onset	16.04	3.50	-	-	-
EDE-Q restraint	3.93	1.42	0.43	0.40	0.001
EDE-Q eating concern	3.78	1.24	0.20	0.20	0.001
EDE-Q shape concern	5.01	0.90	0.99	0.59	0.001
EDE-Q weight concern	4.5	1.41	0.42	0.47	0.001
EDE-Q global score	4.3	1.12	0.60	0.43	0.001
DASS depression	25.08	12.41	1.08	1.29	0.001
DASS anxiety	16.00	9.48	1.88	2.13	0.001
DASS stress	24.92	10.23	3.78	2.78	0.001
BIS-11 attentional	20.67	3.64	13.88	2.91	0.001
BIS-11 attention	13.67	2.99	8.48	2.12	0.001
BIS-11 cognitive instability	7.00	1.44	5.40	1.44	0.001
BIS-11 motor	19.67	3.61	21.28	4.02	0.146
BIS-11 motor	11.55	2.28	14.08	2.78	0.002
BIS-11 perseverance	7.54	1.74	6.92	1.96	0.247
BIS-11 nonplanning	23.21	4.33	22.16	5.71	0.474
BIS-11 self-control	11.75	3.98	11.32	3.87	0.703
BIS-11 cognitive complexity	11.46	2.54	10.84	3.04	0.444
BIS-11 total score	61.88	8.48	57.32	10.98	0.112

AN: Anorexia nervosa; HC: Healthy controls; Premorbid IQ: Standardised Wechsler Test of Adult Reading Score; BMI: Body mass index; EDE-Q: Eating Disorders Examination Questionnaire; DASS: Depression, Anxiety, Stress Scale; BIS-11: Barratt Impulsiveness scale; Age: Age of illness onset and duration illness are reported in years.

inability to focus attention or concentrate^[14]. Rosval *et al.*^[15] similarly reported increased rates of attentional impulsivity in AN. However, attentional impulsivity was not related to eating disorder symptomatology, nor was it related to indicators of potential malnutrition (*i.e.*, BMI and illness duration), or to behavioural impulsivity in the current study. It was, however, significantly correlated with all three measures of negative mood state, *i.e.*, depression, anxiety and stress. This findings suggests that attentional impulsivity in AN may not be related to starvation or to the severity of the eating disorder, but the associated negative mood states. Though, this conclusion remains speculative as the findings are based on statistical association, and also do not take into account longitudinal data. Unlike attentional impulsivity, though, motor impulsivity was not correlated with any measure suggesting that a perceived decrease in motor impulsivity is unrelated to eating disorder symptoms, mood state or behavioural impulsivity.

Groups were also found to not differ in behavioural performance on the majority of measures of the CPT-IP. Groups did not significantly differ in the proportion of correct hits, false alarms or random responses. Groups also did not significantly differ in response times of correct hits, but showed similar response times to a large sample of healthy female participants, who had significantly longer response times than male participants^[16]. Groups in the current study did, however, differ in the mean and intraindividual variability (IIV) of response times of

false alarms, with the AN group demonstrating increased response times and IIV of false alarms. However, this finding is somewhat limited as only a very small proportion of false alarms were elicited in each group (*i.e.*, 11% and 10% for AN and HC, respectively, of 90 potential responses). Similarly to the current findings, a lack of significant group differences in performance on the CPT-IP has also been reported in a small number of other studies in AN^[17,18]. Furthermore, the same group of participants were not found to differ on typical saccadic eye movement measures of impulsivity (*i.e.*, antisaccade or no-go saccade error rates), further supporting the lack of behavioural impulsivity in AN (saccadic eye movement findings are to be reported elsewhere).

The findings of the study, however, are subject to a number of potential limitations. First, given the conservative sample size and the number of statistical comparisons, the statistical power of the study is limited. The DASS and BIS-11 are also restricted in their divergent validity, and further, the conclusions based on these measures are based on statistical association and do not take into account longitudinal validity. The findings of the current study do, however, provide preliminary evidence for divergent self-reported and behavioural impulsivity in AN, which requires replication in a larger sample.

The findings of this study have a number of important implications. Firstly, they suggest that self-reported impulsivity in AN may be unrelated to behavioural

Table 2 Continuous performance test - identical pairs results

	AN		HC		P
	M	SD	M	SD	
Proportion of hits	0.83	0.97	0.86	0.9	0.319
Hits RT	547.34	59.41	533.94	53.06	0.409
Hits RT IIV	123.35	28.91	115.38	26.31	0.318
Proportion of false alarms	0.11	0.06	0.09	0.06	0.314
False alarms RT	504.65	151.18	365.41	137.89	0.002
False alarms RT IIV	68.38	32.98	46.48	29.28	0.039
Proportion of random responses	0.01	0.01	0.01	0.01	0.278

AN: Anorexia nervosa; HC: Healthy control; RT: Response time; IIV: Intraindividual variability (a comparison of individual's standard deviations).

performance. This finding may be related to the “control paradox” often reported in AN, in which individuals seek to control their surrounding environment as much as possible but report feeling like they are out of control^[19]. Furthermore, this may be related to perfectionistic tendencies reported in AN; thus, further research in this area utilising measures of control and perfectionism would be advantageous to further elucidate this inconsistency in AN. The findings also suggest increased reports of attentional impulsivity in AN is related to negative mood state. Thus, addressing negative mood symptoms may be beneficial in resolving the inconsistency and potential distress in how individuals with AN think they behave and how they actually behave.

In conclusion, overall, the findings of the study suggest that individuals with AN report lower rates of motor impulsivity, and higher rates of attentional impulsivity than HCs; the latter of which is associated with increases in negative mood state symptoms. Reported rates of impulsivity were, however, unrelated to behavioural performance. Therefore, the findings suggest an inconsistency between self-reported impulsivity and behaviour in AN, which may be resolved by improving negative mood states in these individuals.

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COMMENTS

Background

Anorexia nervosa (AN) is associated perfectionistic tendencies, particularly displaying increased concerns over making mistakes. Relatedly, patients often

self-report lower rates of impulsivity. However, it is unclear whether self-reported rates of impulsivity are influenced by eating disorder symptoms or are stable traits in AN. It is also unclear whether these self-reported rates of impulsivity translate to behavioural performance on cognitive tasks of inhibition in AN.

Research frontiers

Self-reported and behavioural impulsivity appear to be discrepant in AN.

Innovations and breakthroughs

This study found inconsistencies between self-reported and behavioural impulsivity in AN. The results also indicated that self-reported attentional impulsivity in AN was related to negative mood states.

Applications

Improving negative mood symptoms may improve perceived attentional impulsivity in AN.

Peer-review

In this article, the authors claim that there is a discrepancy between self-reported and behavioural impulsivity in patients with AN. The study appears to have been carefully planned with appropriate tests and adequate controls. The results are interesting and can lead to novel therapeutic approaches in AN.

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Retrospective Study

Oral but not written test anxiety is related to social anxiety

Lisa Laurin-Barantke, Jürgen Hoyer, Lydia Fehm, Susanne Knappe

Lisa Laurin-Barantke, Jürgen Hoyer, Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, 01187 Dresden, Germany

Lydia Fehm, Center for Psychotherapy (ZPHU), Humboldt-Universität zu Berlin, 10179 Berlin, Germany

Susanne Knappe, Institute of Clinical Psychology and Psychotherapy, Center for Preventive Intervention Studies, Technische Universität Dresden, 01187 Dresden, Germany

Author contributions: Laurin-Barantke L and Knappe S conceptualized and designed the study; Laurin-Barantke L was responsible for data collection; Laurin-Barantke L and Knappe analyzed the data and interpreted the results; Laurin-Barantke L, Hoyer J, Fehm L and Knappe S helped to draft the manuscript; Hoyer J and Fehm L critically revised the manuscript related to important intellectual consent; all authors approved the manuscript for submission and publication.

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Correspondence to: Dr. Susanne Knappe, PD, Dipl. Psych, Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Chemnitz Str. 46, 01187 Dresden, Germany. susanne.knappe@tu-dresden.de
Telephone: +49-351-46339727
Fax: +49-351-46336984

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Abstract

AIM

To examine the associations of test anxiety (TA) in written *vs* oral exam situations with social anxiety (SA).

METHODS

A convenience sample of 204 students was recruited at the Technische Universität Dresden (TU Dresden, Germany) and contacted *via* e-mail asking to complete a cross-sectional online survey based on established questionnaires. The study protocol was approved by the ethics committee of the TU Dresden. Full data of $n = 96$ students were available for dependent *t*-tests and correlation analyses on the associations of SA and TA respectively with trigger events, cognitions, safety behaviors, physical symptoms and depersonalization. Analyses were run using SPSS.

RESULTS

Levels of TA were higher for fear in oral exams than for fear in written exams ($M = 48.1$, $SD = 11.5$ *vs* $M = 43.7$, $SD = 10.1$ $P < 0.001$). Oral TA and SA were positively correlated (Spearman's $r = 0.343$, $P < 0.001$; Pearson's $r = 0.38$, $P < 0.001$) contrasting written TA and SA (Spearman's $r = 0.17$, $P > 0.05$; Pearson's $r = 0.223$, $P > 0.05$). Compared to written TA, trigger

events were more often reported for oral TA (18.2% *vs* 30.3%, $P = 0.007$); which was also accompanied more often by test-anxious cognitions (7.9% *vs* 8.5%, $P = 0.001$), safety behavior (8.9% *vs* 10.3%, $P < 0.001$) and physical symptoms (for all, $P < 0.001$).

CONCLUSION

Written, but not oral TA emerged being unrelated to SA and may rather not be considered as a typical facet of SA disorder.

Key words: Social anxiety; Derealization; Test anxiety; Depersonalization; Safety behavior

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Core tip: In a convenience student sample, levels of test anxiety (TA) were higher for fear in oral exams than for fear in written exams. Oral TA and social anxiety (SA) were positively correlated, contrasting written TA and SA. Compared to written TA, trigger events were more often reported for oral TA; which was also accompanied more often by test-anxious cognitions, safety behavior and physical symptoms. Results point to overlaps between oral TA and SA. Since written TA appeared unrelated to SA, it may rather not be considered as a typical facet of SA.

Laurin-Barantke L, Hoyer J, Fehm L, Knappe S. Oral but not written test anxiety is related to social anxiety. *World J Psychiatr* 2016; 6(3): 351-357 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v6/i3/351.htm> DOI: <http://dx.doi.org/10.5498/wjpv6.i3.351>

INTRODUCTION

The aim of a deepened understanding of social anxiety (SA) disorder, its putative subtypes and differentiation from other mental disorders has stimulated research in the last decade, *e.g.*, on the relationship of public speaking anxiety with other facets of SA disorder^[1,2]. Broadly, the diagnostic category of SA disorder represents a multi-faceted phenomenon, that spans from more or less isolated social fears to severe anxiety in social situations related to interactions with others and performance in public^[1,3,4]. Results of Hall^[5] and Knappe *et al.*^[6] pointed to notable differences between fear of public speaking and test anxiety (TA) on the one hand, and other social fears and SA disorder on the other, namely in terms of age of onset, social anxious cognitions, physical symptoms and increase of self-reported anxiety levels over time. For example, in a community sample of adolescents and young adults, isolated social fears in test situations were unrelated to catastrophic social anxious cognitions, but associated with significant avoidance (though not with moderate/severe impairment), lower comorbidity, behavioral inhibition, and

parental psychopathology as compared to respondents with other performance or interaction related social fears^[6]. Findings suggest that TA might be meaningfully distinguished from SA, and question whether TA is in fact part of the SA spectrum or if it should be better classified as a specific fear or phobia^[3,5,6].

Despite efforts to better understand the relationship of TA and SA disorder, little attention has been paid to the fact that TA can occur in oral and written exams and that these two types of situations imply differing cues for anxiety reactions: A convenience sample of college students preferred written exams over oral exams^[7,8], probably because social interaction is limited in written exams, whereas oral exams demand both performance and social interaction skills.

To better understand the relationship of TA and SA, this study aims to explore similarities and differences in written and oral exams, as well as similarities and differences between both forms of TA and SA.

Some facets of TA and SA have been explored so far: Sarason^[9] hypothesized, that some type of TA is triggered by "quite specific unfortunate experiences, *e.g.*, a traumatizing teacher in the third grade". Accordingly, trigger events may be particularly relevant for TA, whereas for SA, only few of those affected recall a specific event as origin of their fear^[10]. With regard to cognitions, Knappe *et al.*^[6] found that fear of taking tests was negatively associated with socially phobic cognitions like "something embarrassing or shameful could happen", "to be ashamed" and "to blush", whereas there was a positive association between catastrophic anxiety cognitions and the majority of social fears. Bögels *et al.*^[3] concluded that blushing is a physical, maybe even unique, sign of SA disorder compared with other anxieties. However, they did not differentiate for specific social fears or social situations. Hoyer *et al.*^[11] found that symptoms of depersonalization were more frequent in social phobia patients (92%) than in controls (52%).

Overall, based on however limited findings on clinical features, it is suggested that: (1) TA in oral exams is associated with higher levels of SA as compared to written exams; that (2) oral TA is more similar to SA in terms of safety behaviors, cognitions and physical symptoms than written TA; and (3) similar to SA, symptoms of depersonalization/derealization are expected to occur more frequently in oral exams than in written exams.

MATERIALS AND METHODS

Procedure and participants

A convenience sample of 204 students was recruited at the Technische Universität Dresden (TU Dresden), Germany, and contacted *via* email asking to complete an online survey. Students received course credits and/or randomly drawn cinema and bowling vouchers for participation. The ethics committee of the TU Dresden approved the study protocol.

Data from 105 students were not available for

Table 1 Description of full and partial responders

	Complete responders (<i>n</i> = 99) ¹		Partial responders (<i>n</i> = 22) ²		χ^2 test
	<i>n</i>	%	<i>n</i>	%	
Sex					0.290
Males	25	26	8	36.4	
Females	74	74	14	63.6	
Age (M, SD)	22.9 (3.6)		23.0 (2.6)		0.573
Branch of study					0.297
Mechanical engineering	9	9.4	2	9.1	
Psychology	32	33.3	6	27.3	
Sociology	5	5.2	4	18.2	
Medicine	34	35.4	6	27.3	
Architecture	6	6.3	1	4.5	
Biology	7	7.3	1	4.5	
Other	6	6.3	2	9.1	
Degree of study					0.814
Diploma	31	32.3	7	31.8	
Bachelor	33	34.4	9	40.9	
Master	2	2.1	0	0.0	
State exam	33	34.4	6	27.3	
Number of days since last exam					
Written exam (M, SD)	51.1 (69.0)		51.3 (63.5)		0.920
Oral exam (M, SD)	253.7 (342.8)		406.1 (518.5)		0.468
Probable social anxiety disorder					
SSQ	14	14.1	5	22.7	0.317
LSAS-anxiety (M, SD)	15.6 (10.5)		13.0 (10.0)		0.366
LSAS-avoidance (M, SD)	13.6 (10.2)		11.9 (12.1)		0.574
Probable test-anxiety					
Written exam LSAS-anxiety (M, SD)	1.1 (0.8)		0.9 (0.8)		0.804
Written exam LSAS-avoidance (M, SD)	0.2 (0.6)		0.3 (0.6)		0.550
Oral exam LSAS-anxiety (M, SD)	1.8 (1.0)		1.5 (1.1)		0.566
Oral exam LSAS-avoidance (M, SD)	0.2 (0.6)		0.3 (0.9)		0.619

¹Data of additional 3 participants were not used since they did not report any fear or avoidance of social situations and thus were not asked about trigger events, test anxiety, cognitions, behavior, depersonalization and physical symptoms due to skip rules; ²Data of additional 14 participants were not used since they did not give written informed consent. M: Mean; SD: Standard deviation; SSQ: Symptom screening questionnaire; LSAS: Liebowitz Social Anxiety Scale (subscales for severity of social anxiety and avoidance of social situations).

analyses, since e-mail addresses were incorrect (*n* = 14), students did not respond (*n* = 55), or filled in less than 50% of the questionnaire (*n* = 36, 18.9%). There were no systematic differences between participants responding only partly (*n* = 22) and those who responded completely (*n* = 99) (Table 1). Via skip rule, only participants who reported anxiety in or avoidance of at least one social situation listed in the Liebowitz Social Anxiety Scale (LSAS) (see below) were asked about trigger events, TA, cognitions, behavior, depersonalization and physical symptoms. Indication of TA based on the PAF [Prüfungsangstfragebogen, (TA Questionnaire), see below] was not required as a necessary condition (*i.e.*, no skip rule when no TA was reported) because Knappe *et al.*^[6] observed that fear of taking tests occurred independently from SA but not vice versa. Three subjects were excluded because they skipped the survey after indicating no fear or avoidance of social situations. Accordingly, analyses were based on *n* = 96 subjects with complete data sets. The sample consisted of 23 males (24%) and 73 females (76%), aged 19 to 46 years (*M* = 22.9 years, *SD* = 3.6). Additional information was collected on the target degree (*n* = 32 state examination, *n* = 32 bachelor, *n*

= 2 master, *n* = 30 diploma) and branch of study (*n* = 33 medicine, *n* = 31 psychology, *n* = 8 mechanical engineering, *n* = 7 biology, *n* = 6 architecture, *n* = 5 sociology, *n* = 6 other). Students were also asked to recall any event as a trigger for their anxiety in social situations, oral or written exams.

Measures

SA: The 24-item German self-report Version of the "LSAS"^[12] was administered. Item 17 ("taking a test") was splitted for detailed assessment of anxiety and avoidance during written or oral exam situations (namely: Taking a written test, taking an oral examination). The 27-item German "Fragebogen zu sozialphobischem Verhalten" [SPV (Questionnaire for Social Phobic Behavior)]^[13] was used to assess social anxious motivated safety behavior, *e.g.*, "I try to behave as normal as possible". Ratings were shown in inversed order for comprehensiveness with other measures.

TA: The German questionnaire "Prüfungsangstfragebogen" [PAF (TA Questionnaire), 20 items]^[14] was used to assess severity of TA. In addition, generic items asked for trigger events for fear of written and oral exams

Table 2 Reliability of scales and measures ($n = 96$)

		α
Social anxiety	LSAS anxiety subscale	0.914
	LSAS avoidance subscale	0.897
	SPK	0.926
	SPV	0.821
	BSPS-G physical subscale	0.737
Written test anxiety	CDS-9 frequency subscale	0.848
	PAF	0.897
	TAC	0.884
	TAB	0.780
	BSPS-G, physical subscale	0.775
Oral test anxiety	CDS-9 frequency subscale	0.911
	PAF	0.906
	TAC	0.888
	TAB	0.811
	BSPS-G, physical subscale	0.756
	CDS-9 frequency subscale	0.919

α : Cronbach's α ; LSAS: Liebowitz Social Anxiety Scale; SPV: FragebogenzusozialphobischemVerhalten (Questionnaire for Social Phobic Behavior); BSPS-G: Brief Social Phobia Scale, German Version; CDS-9: Cambridge Depersonalisation Scale; PAF: Prüfungsangstfragebogen (test anxiety questionnaire); TAC: Test anxious cognitions (generic questionnaire); TAB: Test anxious coping and safety behavior (generic questionnaire).

separately, as well as for test-anxious cognitions (TAC, 10 items) and test-anxious coping and safety behavior (TAB, 17 items). The subscale "physical symptoms" of the German "Brief Social Phobia Scale" (BSPS-G, 4 items)^[15] was used to assess bodily symptoms of TA. All instructions were slightly modified to allow for separate self-assessment in written and oral exams.

Symptoms of depersonalization/derealization:

The German version of the "Cambridge Depersonalisation Scale 9" (CDS-9, 9 items)^[16] was used to assess symptoms of depersonalization/derealization. The instruction was slightly modified for separate assessment with regard to social situations, as well as written and oral exams. The items were presented following the numerical order of the full CDS (in contrast to Michal *et al.*^[16]). To increase reasonableness of the questionnaire, the duration scale of the CDS-9 was omitted.

The PAF, TAB, TAC, BSPS-G und CDS-9 were administered twice for separate assessments in oral and written TA situations. Internal consistencies (Cronbach's α) for scores of all modified scales ranged between 0.737 and 0.919 (Table 2). Convergent and discriminant validity of all modified scales were explored based on their correlation patterns, indicating sufficient validity (Table 3).

Statistical analysis

Dependent *t*-tests for paired samples were used to compare mean values of the number of trigger events, TA, test-anxious cognitions, test-anxious coping and safety behavior, symptoms of depersonalization/derealization and physiological symptoms (blushing, palpitation, tremor and sweating) in written exams to

oral exams. Associations of SA (based on LSAS) with TA during written exams and TA during oral exams (based on PAF) were compared using Steiger's Z ^[17], which allows to compare overlapping correlations. In absence of normally distributed data, Spearman correlations were computed. Pearson correlations were additionally computed since they are necessary for the computation of Steiger's Z . The correlations were similar and therefore the Pearson correlations were compared within a sample using Steiger's Z . Analyses were run using SPSS^[18]. A Bonferroni correction ($\alpha_{\text{corr}} = 0.025$) was applied for analyses on safety behaviors to account for multiple testing (*i.e.*, comparison between SA and oral TA; comparison between SA and written TA). It was not applied for explorative analyses, where a higher α error can rather be tolerated than an increase of the β error^[19].

RESULTS

Frequencies and associations of SA and written or oral TA

Isolated oral and written TA was reported in 14.6% ($n = 14$) and 2.1% ($n = 2$), respectively, of the sample. More than one third of the sample reported at least one condition out of SA, written TA or oral TA (36.5%, $n = 35$). Symptoms of depersonalization/derealization occurred most often in social situations ($n = 13$; 13.5%), followed by oral exams ($n = 11$; 11.5%) and written exams ($n = 8$; 8.3%) (Table 4).

As expected, SA was unrelated to written TA (Spearman's $r = 0.17$, $P > 0.05$; Pearson's $r = 0.22$, $P > 0.05$), but positively related to oral TA (Spearman's $r = 0.34$, $P < 0.001$; Pearson's $r = 0.38$, $P < 0.001$). Correlations of SA with written vs oral TA however did not differ (Steiger's $Z = -1.18$, $P > 0.05$).

Comparisons between written and oral TA

Analyses revealed substantial differences between oral and written TA in terms of trigger events, clinical characteristics and physiological symptoms (Table 5). Specifically, trigger events were more often reported for oral TA (30.3%) than written TA (18.2%) [$t(95) = 2.78$, $P = 0.007$]. As expected, the level of TA was higher among those reporting fear of oral exams than in those with fear of written exams (Table 5) [$t(95) = -4.86$, $P < 0.001$]. Further, TAC and TAB were reported more often for oral TA than for written TA. For symptoms of depersonalization/derealization, no differences between oral and written TA were observed. Physical symptoms were reported more often for oral TA than for written TA.

Comparison between SA, and written and oral TA

SA, based on the LSAS, was positively related to safety behaviors (Spearman's $r = 0.64$, $P < 0.001$; Pearson's $r = 0.70$, $P < 0.001$). Both forms of TA were moderately associated with safety behaviors (written: Spearman's r

Table 3 Convergent and discriminant validity of scales and measures

	LSAS anxiety subscale	LSAS avoidance subscale	PAF written	PAF oral	TAC written	TAC oral	TAB written	TAB oral
Oral PAF	0.379 ^d	0.304 ^d	0.663 ^d	1	0.625 ^d	0.806 ^d	0.332 ^d	0.442 ^d
Written PAF	0.223 ^b	0.167	1	0.663 ^d	0.770 ^d	0.650 ^d	0.467 ^d	0.236 ^b
SPK	0.673 ^d	0.592 ^d	0.283 ^d	0.453 ^d	0.425 ^d	0.562 ^d	NE	NE
SPV	0.701 ^d	0.678 ^d	0.425 ^d	0.524 ^d	NE	NE	0.301 ^d	0.412 ^d
CDS-9 frequency subscale social	0.338 ^d	0.320 ^d	0.323 ^d	0.311 ^d	NE	NE	NE	NE
CDS-9 frequency subscale written	0.274 ^d	0.306 ^d	0.398 ^d	0.383 ^d	NE	NE	NE	NE
CDS-9 frequency subscale oral	0.390 ^d	0.341 ^d	0.337 ^d	0.488 ^d	NE	NE	NE	NE
Tremor social	0.322 ^d	0.352 ^d	0.258 ^b	0.223 ^b	NE	NE	NE	NE
Sweating social	0.351 ^d	0.298 ^d	0.200	0.311 ^d	NE	NE	NE	NE
Blushing social	0.242 ^b	0.115	0.218 ^b	0.278 ^d	NE	NE	NE	NE
Palpitation social	0.379 ^d	0.351 ^d	0.206 ^b	0.313 ^d	NE	NE	NE	NE
Tremor written	0.294 ^d	0.141	0.640 ^d	0.452 ^d	NE	NE	NE	NE
Sweating written	0.096	0.028	0.484 ^d	0.361 ^d	NE	NE	NE	NE
Blushing written	-0.099	-0.094	0.137	0.201 ^b	NE	NE	NE	NE
Palpitation written	0.168	0.050	0.657 ^d	0.488 ^d	NE	NE	NE	NE
Tremor oral	0.289 ^d	0.151	0.488 ^d	0.608 ^d	NE	NE	NE	NE
Sweating oral	0.182	0.048	0.291 ^d	0.434 ^d	NE	NE	NE	NE
Blushing oral	0.120	-0.060	0.189	0.332 ^d	NE	NE	NE	NE
Palpitation oral	0.172	0.054	0.499 ^d	0.612 ^d	NE	NE	NE	NE

Pearson's correlation coefficient ^b $P < 0.005$, two-tailed ^d $P < 0.001$, two-tailed. NE: Not estimated; CSD-9: Cambridge Depersonalisation Scale-9 items; LSAS: Liebowitz Social Anxiety Scale; PAF: Prüfungsangstfragebogen. SPK Fragebogen zu sozialphobischen Kognitionen; SPV Fragebogen zu sozialphobischem Verhalten.

Table 4 Frequencies of social anxiety, written or oral test anxiety and depersonalization ($n = 96$)

Social anxiety disorder and test anxiety	<i>n</i>	%
Overall		
Social anxiety disorder	12	12.5
Written test anxiety	13	13.5
Oral test anxiety	28	29.2
Isolated conditions		
Social anxiety disorder	4	4.2
Written test anxiety	2	2.1
Oral test anxiety	14	14.6
Co-occurrence of conditions		
Written and oral test anxiety	7	7.3
Social anxiety disorder and written test anxiety	1	1
Social anxiety disorder and oral test anxiety	4	4.2
Social anxiety disorder, written and oral test anxiety	3	3.1
Symptoms of depersonalization/derealization		
Social situations	13	13.5
Written exams	8	8.3
Oral exams	11	11.5

Social anxiety disorder was assessed using the anxiety subscale of the LSAS and test anxiety was assessed using the PAF. Symptoms of depersonalization/derealization were measured using the CDS-9. LSAS: Liebowitz social anxiety scale; PAF: Prüfungsangstfragebogen.

= 0.31, $P < 0.001$; Pearson's $r = 0.28$, $P < 0.001$; oral: Spearman's $r = 0.42$, $P < 0.001$; Pearson's $r = 0.45$, $P < 0.001$; these correlations were however lower than the correlation between LSAS and safety behaviors and did not differ (written TA: Steiger's $Z = 3.22$, $P < 0.001$; oral TA: Steiger's $Z = 2.23$, $P < 0.005$; written compared to oral TA: Steiger's $Z = -0.93$, $P > 0.05$).

Symptoms of depersonalization/derealization were similarly frequent across all conditions (scale: 0 = never

to 4 = constantly; SA: $M = 3.7$, $SD = 2.7$, oral TA: $M = 3.2$, $SD = 5.2$, written TA: $M = 2.7$, $SD = 1.9$), and only the difference between SA and written TA was statistically significant [$t(95) = 2.95$, $P = 0.004$].

DISCUSSION

Compared to written TA, SA was more closely related to oral TA and oral TA was triggered more often by an event and accompanied more often by test-anxious cognitions, safety behavior and physical symptoms. In terms of safety behaviors and symptoms of depersonalization/derealization, TA conditions and SA were quite similar. Hence, both the differences between TA conditions and associations between oral TA with SA indicate that SA and oral TA are overlapping entities.

Notably, TA in oral exams was associated with SA, unlike with TA in written exams. Hence, TA seems to be a heterogeneous phenomenon that comprises of different types of exam situations which are more or less social in nature. In fact, oral test situations could be presumed as social situations that require social skills, interaction and communication with others and that may elicit fear of negative evaluation. Further, oral exams are difficult to predict and to control, similar to social situations in general. In contrast, written test situations do not necessarily include interacting with others, and often follow familiar structures or schedules. Written exams may thus elicit lower levels or even no SA. Accordingly, Fehm *et al.*^[20] reported higher levels of prolonged rumination about past social situations (*i.e.*, post-event processing) in interaction-related social situations as compared to performance-related social situations. When written exams are

Table 5 Clinical correlates of test anxiety in written and oral exams (*n* = 96)

	Test anxiety		Δ (SD)	95%CI	df	<i>t</i>	<i>P</i>
	Written	Oral					
	M (SD)	M (SD)					
Test anxiety	43.66 (10.12)	48.12 (11.52)	-4.46 (8.98)	(-6.28, -2.64)	95	-4.86	< 0.001
Test-anxious cognitions	20.02 (7.89)	21.72 (8.49)	-1.69 (4.71)	(-2.65, -0.74)	95	-3.53	0.001
Test-anxious behavior	39.00 (8.99)	44.57 (10.34)	-5.57 (6.74)	(-6.94, -4.21)	95	-8.11	< 0.001
Any trigger event (<i>n</i> , %)	18 (18.2%)	30 (30.3%)	-12 (-)	(0.036, 0.214)	95	2.775	0.007
Symptoms of DP/DR	2.71 (4.71)	3.167 (5.22)	-.46 (2.85)	(-1.04, 0.12)	95	-1.58	0.118
Blushing	0.27 (0.62)	1.17 (1.19)	-0.90 (1.00)	(-1.10, -0.69)	95	-8.78	< 0.001
Palpitation	1.47 (1.05)	2.11 (1.11)	-0.65 (0.78)	(-0.80, -0.49)	95	-8.1	< 0.001
Tremor	0.70 (0.95)	1.33 (1.26)	-0.64 (0.94)	(-0.83, -0.45)	95	-6.61	< 0.001
Sweating	1.22 (1.05)	1.81 (1.14)	-0.59 (0.87)	(-0.77, -0.42)	95	-6.72	< 0.001

All values represent raw, non-standardized scores. Test anxiety was measured using the PAF. Test-anxious cognitions were assessed using a generic questionnaire. Test-anxious coping and safety behavior was assessed using a generic questionnaire. Symptoms of depersonalization/derealization were measured with the CDS-9. Blushing, palpitation, tremor and sweating were assessed using the respective item of the BSPS-G. *P* two-tailed at *P* < 0.05; CI: Confidence interval; df: Degrees of freedom; *t*: *t*-value; DP/DR: Symptoms of depersonalization/derealization; PAF: Prüfungsangstfragebogen; BSPS-G: German "Brief Social Phobia Scale".

perceived as aversive, this may be related to other factors than to SA, such as inefficient study skills and/or test-taking skills, intolerance of uncertainty^[21], avoidance temperament^[22], perfectionism^[23] or low self-efficacy. Nonetheless, cognitive interference may affect performance in both written and oral exams^[24].

Findings need to be considered in light of some limitations: The limited convenience sample (*n* = 96) with overrepresentations of students of psychology and medicine did not allow for analyses on isolated conditions. Though standardized or structured measures are preferred for a more comprehensive evaluation, indications of SA and TA were deduced from established self-report questionnaires (LSAS and PAF) which were modified for separate evaluations of anxiety in oral vs written exams. Rates for SA were however in line with population-based data in similar age ranges^[6]. Given the limited sample size and the absence of normally distributed data for some variables, multivariate statistics were not applied. Statistical analyses based on correlation analyses and dependent *t*-tests for paired samples were sufficient for testing hypotheses and for the exploration of similarities and differences in written and oral exams, as well as of similarities and differences between both forms of TA and SA. For larger samples with independent assessments for written and oral tests, ANOVA models may be more adequate. All questionnaires were conceptualized as paper-pencil-measures but administered in a web-based format. Internal consistencies for the modified scales were however medium to high. In addition, putative influences on TA like stereotype threat or language difficulties, perceived difficulty or relevance of the exams, or indicators of performance (*i.e.*, grades, results of previous exams) were not assessed.

The similarities and differences of oral and written TA with SA again support the conceptualization of SA as a multi-faceted phenomenon. Because of the notable differences between oral and written TA in terms of

trigger events, test-anxious cognitions, safety behavior and physical symptoms, it may be concluded that TA could be rather used to describe anxiety in oral exams than in written exams, similar to the recently introduced DSM-5 "performance only" specifier for SAD where SA is limited to speaking or performing in public^[1]. Further differentiation of situation-specific types of TA would allow clarifying the facets of TA and their relationships to SA.

COMMENTS

The diagnostic category of social anxiety (SA) disorder spans from more or less isolated social fears to severe anxiety in social situations related to interactions with others and performance in public. Studies so far pointed to notable differences between fear of public speaking and test anxiety (TA) on the one hand, and other social fears and SA disorder on the other. Findings suggest that TA might be meaningfully distinguished from SA. Some suggest even an alternative diagnostic classification of TA apart from the SA spectrum, for example as a specific fear or phobia.

Research frontiers

Little attention has been paid to the fact that TA can occur in oral and written exams and that these two types of situations imply differing cues for anxiety reactions. More details on the clinical features may help to inform the diagnostic classification of TA.

Innovations and breakthroughs

Compared to written TA, SA was more closely related to oral TA and oral TA was triggered more often by an event and accompanied more often by test-anxious cognitions, safety behavior and physical symptoms. In terms of safety behaviors and symptoms of depersonalization/derealization, TA conditions and SA were quite similar.

Applications

Because of the notable differences between oral and written TA, it may be concluded that TA could be rather used to describe anxiety in oral exams than in written exams, similar to the recently introduced DSM-5 "performance only" specifier for SA disorder.

Terminology

TA refers to excessive stress, marked anxiety or fear and discomfort during

and/or before taking a test or examination. Associated symptoms include physiological over-arousal, tension and somatic symptoms, cognitive symptoms such as worry, dread, fear of failure, and catastrophizing of anticipated consequences of the test situation.

Peer-review

Nice little study with a defined focus.

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Prospective Study

Agreement and conversion formula between mini-mental state examination and montreal cognitive assessment in an outpatient sample

Luqman Helmi, David Meagher, Edmond O'Mahony, Donagh O'Neill, Owen Mulligan, Sutha Murthy, Geraldine McCarthy, Dimitrios Adamis

Luqman Helmi, Geraldine McCarthy, Dimitrios Adamis, Sligo Medical Academy, NUI Galway and Sligo/Leitrim Mental Health Services, F91 CD34 Sligo, Ireland

David Meagher, Dimitrios Adamis, Cognitive Impairment Research Group, Graduate Entry Medical School, University of Limerick, V94 F858 Limerick, Ireland

David Meagher, Department of Psychiatry, University Hospital Limerick, V94 F858 Limerick, Ireland

Edmond O'Mahony, Donagh O'Neill, Owen Mulligan, Sutha Murthy, Geraldine McCarthy, Dimitrios Adamis, Sligo/Leitrim Mental Health Services, F91 CD34 Sligo, Ireland

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Correspondence to: Dimitrios Adamis, Consultant Psychiatrist,

Sligo/Leitrim Mental Health Services, Clarion Rd Sligo, F91 CD34 Sligo, Ireland. dimaadamis@yahoo.com
Telephone: +353-71-9144829
Fax: +353-71-9144177

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Abstract

AIM

To explore the agreement between the mini-mental state examination (MMSE) and montreal cognitive assessment (MoCA) within community dwelling older patients attending an old age psychiatry service and to derive and test a conversion formula between the two scales.

METHODS

Prospective study of consecutive patients attending outpatient services. Both tests were administered by the same researcher on the same day in random order.

RESULTS

The total sample ($n = 135$) was randomly divided into two groups. One to derive a conversion rule ($n = 70$), and a second ($n = 65$) in which this rule was tested. The agreement (Pearson's r) of MMSE and MoCA was 0.86 ($P < 0.001$), and Lin's concordance correlation coefficient (CCC) was 0.57 (95%CI: 0.45-0.66). In the second sample MoCA scores were converted to MMSE scores according to a conversion rule from the first sample which achieved agreement with the original MMSE scores

of 0.89 (Pearson's r , $P < 0.001$) and CCC of 0.88 (95%CI: 0.82-0.92).

CONCLUSION

Although the two scales overlap considerably, the agreement is modest. The conversion rule derived herein demonstrated promising accuracy and warrants further testing in other populations.

Key words: Mini mental state examination; Montreal cognitive assessment; Cognition; Equation; Assessment; Old age psychiatry

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Core tip: In this study we examined the agreement between mini-mental state examination and montreal cognitive assessment in an older population attending mental health service outpatients. Although both scales assess the same construct (cognition) the agreement between them was modest. Further we delivered a conversion rule which can allow conversion of scores between these scales. The converted scores had a high agreement with original ratings. Finally, this new conversion rule was superior to three previously suggested equating rules.

Helmi L, Meagher D, O'Mahony E, O'Neill D, Mulligan O, Murthy S, McCarthy G, Adamis D. Agreement and conversion formula between mini-mental state examination and montreal cognitive assessment in an outpatient sample. *World J Psychiatr* 2016; 6(3): 358-364 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v6/i3/358.htm> DOI: <http://dx.doi.org/10.5498/wjp.v6.i3.358>

INTRODUCTION

The mini-mental state examination (MMSE)^[1] and montreal cognitive assessment (MoCA)^[2] are cognitive screening tests that are widely used in both everyday clinical practice and research. However, some evidence suggests that the MMSE is less sensitive for detecting milder cognitive deficits compared to the MoCA, while other studies indicate that it's relative insensitivity to visuospatial and executive deficits impact limit it's suitability in particular populations, e.g., vascular cognitive impairment or Parkinson's disease^[3-6]. Comparison of these two tests in specific populations such as patients with Parkinson's disease^[7,8] brain metastases^[9] or sub-arachnoid haemorrhage^[10] indicate that the MoCA is more suitable because it can detect mild forms of cognitive impairment and especially where this includes executive dysfunction. Similarly, population based studies of mild cognitive impairment (MCI) indicate that the MoCA is more sensitive than the MMSE in detecting mild forms of cognitive impairment^[11]. However, to our knowledge no specific

comparison of those two tests has been conducted in a general psychogeriatric population where cognitive testing is routine practice.

Furthermore, clinical trials vary in their use of these two scales which makes comparisons between studies and meta-analyses difficult. Equating methodologies can facilitate comparison between studies using different scales to measure the same construct. Previous studies have developed conversion rules for the MMSE and MoCA using either equipercetile equating and/or log-linear smoothing methods. These studies relate to specific populations; Roalf *et al*^[12] studied a selected population with Alzheimer's disease (AD), MCI and cognitively intact participants, van Steenoven *et al*^[8] studied a population with Parkinson's disease, and Trzepacz *et al*^[13] studied a selected population of AD, MCI and participants deemed cognitively intact. However, given that these studies used specific and biased populations there is a lack of data in general elderly psychiatric patients. In addition, only one of these conversion rules (van Steenoven *et al*^[8]) has been subject to further examination^[7] which although conducted in a similar population only found moderate agreement [Pearson correlation coefficient 0.66 (95%CI: 0.56-0.75)].

Given that both scales are widely used in clinical settings, as well as in clinical trials and cohort studies, a rule to facilitate conversions and comparison of data from different centres and different clinical trials which have used these instruments would have utility.

Therefore, the aims of the present study were threefold (1) to estimate the level of agreement between MMSE and MoCA within an old age psychiatry population; (2) to derive a conversion formula for the two scales and test it in a random population of similar setting; and (3) to compare the new conversion formula with those described in previous studies.

MATERIALS AND METHODS

Subjects and design

This is an observational cross sectional study of performance using two screening cognitive scales in consecutive patients attending an old age psychiatry outpatient clinic and Day Hospital. The "single group design" method was used in this study reflecting that the same population was assessed with the two cognitive tests (MoCA and MMSE).

Procedures

All assessments were conducted by the same psychiatrist who was trained in the use of MoCA and MMSE (McCarthy G). Both tests were administered on the same day with a maximum of 3 h time gap to avoid boredom and/or learning effects. The tests were administered with no particular order (randomly).

Clinical assessments

Demographics: Demographic data (gender, age) were collected from medical records (files and hospital com-

puterised database). In addition, information about years of education was collected from patients and relatives.

Diagnosis: ICD-10 psychiatric diagnoses were collected from the files and collapsed to main ICD-10 F categories. Where multiple diagnoses were evident the most predominant was chosen.

Cognitive assessments: (1) MoCA^[2]. The MoCA assesses visuospatial/executive function, naming, memory, attention, concentration, language, abstract thinking, recall memory and orientation. It is scored on a 30-point scale. Higher scores indicate better cognitive performance. Administration typically takes about 12-15 min. Its psychometric properties have been investigated in many studies and it has been found to be superior to the MMSE for the detection of MCI^[14]. In addition unlikely to MMSE it takes to account the education level; and (2) MMSE^[1]. The MMSE comprises 11 questions assessing orientation to time and place, attention, immediate and short-term recall, language and visuospatial abilities. It is a brief cognitive screening instrument that takes less than ten minutes for administration. Over the past 40 years it has been the most widely used tool in clinical and research settings for brief assessment of cognitive status in elderly individuals. Its psychometric properties have been thoroughly reviewed and indicate moderate-to-high levels of reliability and good evidence of criterion and construct validity^[15]. It has a total score of 30, with higher scores indicating better cognitive performance. Disadvantages of the MMSE include a ceiling effect, the influence of education especially for the serials sevens component^[15,16], and a documented learning effect^[17].

Ethics

The procedures and rationale for the study were explained to all patients but because many patients had cognitive impairment at entry into the study it was presumed that many might not be capable of giving informed written consent. Because of the non-invasive nature of the study, Sligo Regional Ethics Committee approved an approach to establishing consent by virtue of augmenting patient assent with proxy consent from next of kin (where possible) or a responsible caregiver for all participants in accordance with the Helsinki Guidelines for Medical research involving human subjects.

Statistical analysis

Statistical analyses were conducted using the R "equate" package^[18]. Z scores were used to compare MMSE and MoCA scores because although they are from the same sample they follow different distributions. The overall agreement between the two scales was assessed using Pearson's product-moment correlation coefficient (r). However this estimation has been criticised by Bland *et al*^[19] as misleading and therefore the concordance correlation coefficient (CCC) was also calculated^[20]. The CCC measures agreement by assessing how well the

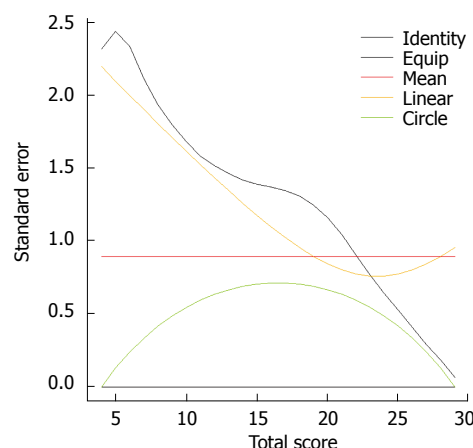


Figure 1 Graphical representation of standard errors after bootstrapping of different equating methods.

relationship between the measurements is represented by a line through the origin at an angle of 45 degrees (as would be generated if the two measurements generated identical results).

To convert MoCA scores to MMSE (and *vice versa*), we generated an equating table to link the two scales. The conversions were extracted from a random population of the studied group and then tested in the remaining sub-population. Given that both scales have the same lower and higher scores but with different difficulty we used the Circle - Arc Method^[21]. However, we also applied other methods of equating models (linear, mean and equipercentile) and compared the standard errors of each model after bootstrapping (Figure 1).

By doing this we made the following assumptions: (1) that both scales measure the same latent construct (cognition); (2) that the two scales are not free of errors but the errors are small (both scales must have high reliability); and (3) that the ratings have been conducted by experts and the conversion rule will apply again in measurements that have been performed by experts.

Although both scales are continuous they are discretized continuous meaning that for a person A the score in MoCa (or MMSE) will be for example 11 and never 11.2 and thus the delivered score in MMSE was converted to the nearest integer. Finally, in the second sample we evaluated the conversion methods suggested by (1) Roalf *et al*^[12]; (2) van Steenoven *et al*^[8]; and (3) Trzepacz *et al*^[13] using Pearson's r and CCC to measure the agreement between the original scores and the converted scores.

RESULTS

The total sample ($n = 135$) was randomly divided in two groups; one which was used to derive the equating table (called experimental sample, $n = 70$) and a second evaluation sample ($n = 65$) in which the derived conversion rule was tested.

Table 1 Demographic characteristics and cognitive test scores of the two samples

	Experimental <i>n</i> = 70 range (min-max)		Evaluation <i>n</i> = 65 range (min-max)	
Males	21 (30%)		21 (32.3%)	
Age	77.36 (SD: 7.06)	62-89	78.83 (SD: 6.6)	66-91
MoCA	19.03 (SD: 6.35)	4-29	18.57 (SD: 6.78)	4-30
MMSE	24.47 (SD: 4.87)	9-30	24.45 (SD: 4.71)	8-30
Years of education	10.71 (SD: 2.47)	6-18	10.20 (SD: 2.15)	7-17

MoCA: Montreal cognitive assessment; MMSE: Mini-mental state examination.

Descriptive statistics

Table 1 shows demographic data as well as the MoCA and MMSE scores in the two samples. The two samples did not significantly differ regarding gender distribution ($\chi^2 = 0.084$, df: 1, $P = 0.772$), age ($t = 1.25$, df: 133, $P = 0.214$), MoCA scores ($t = 0.406$, df: 133, $P = 0.686$), MMSE scores ($t = 0.31$, df: 133, $P = 0.976$) and years of education ($t = 1.29$, df: 133, $P = 0.200$). In addition, Table 2 shows the principal diagnoses in the two samples in percentages. A comparison of the two samples in terms of diagnoses did not identify significant difference ($\chi^2 = 0.644$, df: 3, $P = 0.886$). However, as shown in Table 1 the total MoCA scores were significantly lower than the total MMSE scores in both samples (For experimental sample: $n = 70$, z scores: -4.77, -8.19 respectively for MMSE and MoCA; $P < 0.001$; for the evaluation sample, $n = 65$, z -scores: -4.35, -7.88; $P < 0.001$).

Agreement of the two scales in the experimental sample

The Pearson's product-moment correlation coefficient for MoCA and MMSE was 0.86 ($P < 0.001$) which indicates very good agreement. However, the more conservative CCC was 0.57 (95%CI: 0.45-0.66), indicating a lower agreement between the two scales. Figure 2 depicts a scatterplot including a fitted linear line and a cubic. As evident from the scatterplot, the scores do not fit well to a linear model.

Linking the two scales (MoCA and MMSE)

The "circle-arc" method was used. Table 3 shows the conversion table. Also other equating methods were used but as expected the "circle-arc" had the least standard errors and less biases compared to the others. Figure 1 shows the standard error of the different methods after bootstrapping.

Evaluation of the derived conversion

In the 2nd sample (evaluation sample) we converted MoCA scores to MMSE scores according to the above table and then examined the agreement between the converted MMSE scores and the originals. The Pearson's product-moment correlation coefficient was 0.89 ($n = 65$, $P < 0.001$) and the Lin's CCC was 0.88 (95%CI: 0.82-0.92).

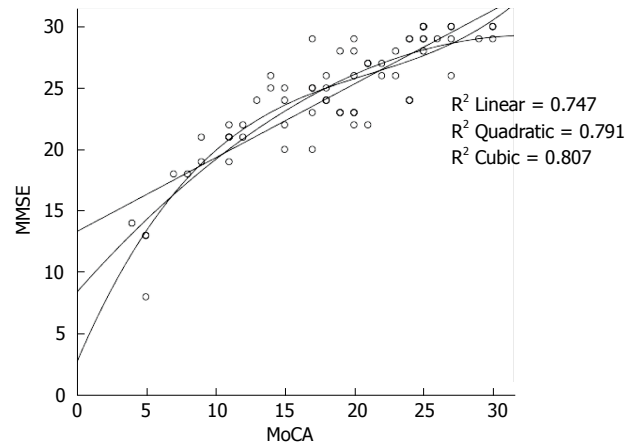


Figure 2 Linear Quadratic and Cubic relationship of montreal cognitive assessment and mini-mental state examination scores.

Thus the converted MMSE scores from MoCA have a high level of agreement with the actual MMSE scores.

Evaluation of the other methods suggested

With the Roalf *et al*^[12]'s method, the Pearson's product-moment correlation coefficient was equal to 0.88 ($n = 65$, $P < 0.001$) and the CCC equal to 0.86 (CI: 0.79-0.81). With the van Steenoven *et al*^[8]'s method the agreement between the converted and the actual MMSE scores was high with the Pearson's product-moment correlation coefficient of 0.86 ($n = 65$, $P < 0.001$) and the CCC of 0.84 (CI: 0.76-0.90). Finally, using the method suggested by Trzepacz *et al*^[13] the Pearson's product-moment correlation coefficient was 0.85 ($n = 65$, $P < 0.001$) and the CCC was 0.82 (CI: 0.72-0.88). All three previously described conversion rules were inferior to that derived herein.

DISCUSSION

It is often assumed that because the MoCA and MMSE measure the same general construct (cognition) that they can be used interchangeably. However, they each emphasise different aspects of cognition and, as our results demonstrate, their agreement is modest. For instance, the MMSE allocates more points for orientation (10 out of 30) compared to only 6 out of 30 in the MoCA, while the MoCA places greater emphasis on visuospatial domains (5 out of 30) compared to only 1 point out of 30 with the MMSE. As a consequence, it is not surprising that these two tests do not have a linear relationship (Figure 2). Furthermore because performance is more difficult in visuospatial and executive domains than orientation, scores in MoCA were significantly lower compared to scores in MMSE. In addition, although both tests are used as continuous scales (ranging from 0 to 30) in fact neither is a true ratio scale such that a score of 10 does not indicate half the cognitive ability of a score of 20. Similarly, both scales include arbitrary anchor points (e.g., a score of 0 does not mean that someone has no

Table 2 Main diagnoses in the two samples

Diagnoses	Experimental sample			Evaluation sample			Total
	<i>n</i> (%)	MMSE mean (SD)	MoCA mean (SD)	<i>n</i> (%)	MMSE mean (SD)	MoCA mean (SD)	
Organic, including symptomatic, mental disorders (F00-F09)	32 (45.7)	22.31 (4.95)	15.93 (5.68)	32 (49.2)	21.75 (4.61)	13.91 (5.11)	64
Schizophrenia, schizotypal and delusional disorders (F20-F29)	4 (5.7)	23.5 (3.7)	18.25 (4.43)	2 (3.1)	26 (5.66)	20 (7.07)	6
Mood (affective) disorders (F30-F39)	18 (25.7)	26.06 (4.42)	21.61 (6.29)	17 (26.2)	26.17 (3.46)	22.29 (5.47)	35
Neurotic, stress-related and somatoform disorders (F40-F48)	16 (22.9)	27.25 (3.49)	22.5 (5.33)	14 (21.5)	28.28 (1.85)	24.5 (3.69)	30

MoCA: Montreal cognitive assessment; MMSE: Mini-mental state examination.

Table 3 Conversion table

MoCA scores	MMSE scores
1	3
2	6
3	8
4	10
5	11
6	13
7	14
8	15
9	16
10	17
11	19
12	19
13	20
14	21
15	22
16	23
17	24
18	25
19	25
20	26
21	27
22	27
23	28
24	28
25	29
26	29
27	30
28	30
29	30
30	30

MoCA: Montreal cognitive assessment; MMSE: Mini-mental state examination.

cognitive function at all).

Our second aim was to derive an equating rule to allow for accurate conversion of scores between the two scales. This has important utility for standardising multiple assessments of patients who are assessed using different scales over time. However, most importantly this conversion rule can allow for comparisons between multiple centers in clinical trials which use MoCA or MMSE alternately and can be used for pooling data from different studies to facilitate meta-analyses. Our conversion rule compared very favourably with those described in previous studies in terms of a better

(higher agreement). We examined this issue using both Pearson's correlation coefficients as well as the CCC which provides a more conservative method as, in comparison to Pearson's correlation coefficient, it emphasises level of actual agreement over the general pattern of relationship^[19]. Of note, the new method described herein performed better than previous methods by both measures of agreement (Pearson's *r* or CCC). One explanation for these findings is that our sample is more representative of a general old age population in comparison to the three previous studies in which the samples were more restricted. However, one of the assumptions for equating methods is that the equating relationship is group invariant and as such does not change across the groups^[22], if the sample or sampling method influenced the converted scores the conversion rule is not valid.

Although the sample can influence some psychometric values, the most likely explanation for the higher agreement is the equating method that we used as it provides a better fit for our data. The circle-arc which we used does not require the estimated equating transformation to be linear. It constrains the end points in the two pre-specified end points and a middle point determined from the data and it is thus robust even for small samples^[21]. In addition, the circle-arc method produces the most accurate results for different sample sizes compared to other methods like equipercenile with smoothing, linear equating, and mean equating^[23]. Therefore, it is likely that the greater accuracy of the conversion rule described herein relates substantially to the methods that were used in its development rather than to the sampling method. These observations are further supported by Armstrong *et al*^[7] who found a moderate agreement between the converted and actual scores when they applied the conversion rule suggested by van Steenoven *et al*^[8], even though they tested the rule in a similar sample to that in which the rule was originally derived (*i.e.*, patients with Parkinson's disease). However, when the two scales or tests are different in content, reliability, or intended population, it is expected that the scales will be less equivalent to some degree^[24], but this is not the case for the MoCA and MMSE as they both have high reliability, assumes that measure the

same construct, (cognition) and are used in populations with possible cognitive deficits.

In conclusion, we found that the MMSE and MoCA have moderate agreement when used to assess general cognitive function reflecting their different emphasis into particular neuropsychological domains. Further, we found that their relationship is non-linear such that non-linear methods of equating should be used to compare performance on these scales. Finally, we derived a conversion rule which performed well in comparison to previously suggested methods and which merits further assessment in other larger and clinically diverse samples.

COMMENTS

Background

Mini-mental state examination (MMSE) and montreal cognitive assessment (MoCA) are widely used assessments of cognition in older people populations.

Research frontiers

Given the different tests of cognition the challenge is how to interpret them to a common "language".

Innovations and breakthroughs

This study applies advance and robust techniques to overcome the above challenges.

Applications

The authors have derived an equation rule to convert the scores from MoCA to MMSE which can be used to pull together data from different studies.

Terminology

Equation models can be used to transform the scores from one scale or instruments to another.

Peer-review

The manuscript is a generally well-written and interesting paper. The topic is important because the rate of dementias increases around the world.

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Randomized Controlled Trial

Comparative effectiveness of quetiapine and haloperidol in delirium: A single blind randomized controlled study

Sandeep Grover, Sudhir Mahajan, Subho Chakrabarti, Ajit Avasthi

Sandeep Grover, Sudhir Mahajan, Subho Chakrabarti, Ajit Avasthi, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Author contributions: All authors contributed to this paper.

Institutional review board statement: The study was approved by the Institute Ethics Committee.

Informed consent statement: Proxy written informed consent was obtained from the primary caregivers of the patients who were staying with the patient during the hospitalization prior to randomization. The purpose of the study was explained to the caregivers. The caregivers were told about the currently available pharmacotherapy for management of delirium. The caregivers were explained about the commonly used pharmacological agents along with their efficacy and side effect profile. They were informed about the evidence available for quetiapine for management of delirium. The primary caregivers were informed that they could withdraw consent at any stage.

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Correspondence to: Dr. Sandeep Grover, MD, Additional Professor, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Cobalt Block, Nehru Hospital, Chandigarh 160012, India. drsandeepg2002@yahoo.com
Telephone: +91-172-2756807
Fax: +91-172-2744401

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Abstract

AIM

To evaluate the effectiveness of quetiapine and haloperidol in patients of delirium referred to psychiatry consultation liaison services.

METHODS

The study followed a single blind randomised controlled trial design. Thirty-two patients in the haloperidol group and 31 patients in the quetiapine group were assessed at the baseline and 6 consecutive days. Flexible dosing regimen (haloperidol: 0.25-1.25 mg; quetiapine 12.5-75 mg/d) was used. Delirium Rating Scale-Revised-98 (DRS-R-98) and mini mental status examination (MMSE) were the primary and secondary efficacy measures respectively.

RESULTS

Baseline DRS-R-98 severity score and MMSE scores did not differ between the 2 study groups. From baseline to day 6, there was significant reduction in the total DRS-R-98 scores, DRS-R-98 cognitive domain scores, DRS-R-98 non-cognitive domain scores and significant increase in the MMSE scores in both the groups. Both the groups did not differ on any of the assessments in terms of DRS-R-98 and MMSE scores. The effectiveness of both the medications was similar in adult and elderly (≥ 60 years) patients. At the end of the trial, 68.75% and 67.74% of subjects in the haloperidol and quetiapine group respectively had mean DRS-R-98 scores below 10. By 6th day, 12 (37.5%) patients in haloperidol group and 9 (29.03%) patients in the quetiapine group had

DRS-R98 score of "0" with no significant difference between the two groups ($P = 0.47$).

CONCLUSION

Quetiapine is as effective as haloperidol in the management of delirium.

Key words: Delirium; Quetiapine; Effectiveness; Atypical antipsychotics

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Core tip: This Comparative study showed that quetiapine when used in the doses of 12.5-75 mg/d is as effective as haloperidol in the doses of 0.25-1.25 mg in management of delirium. The effectiveness of both the medications was similar in adult and elderly (≥ 60 years) patients. By 6th day, 37.5% patients in haloperidol group and 29.03% patients in the quetiapine group had Delirium Rating Scale-Revised-98 score of "0" with no significant difference between the two groups. Accordingly, this study suggests that quetiapine is as effective as haloperidol in the management of delirium.

Grover S, Mahajan S, Chakrabarti S, Avasthi A. Comparative effectiveness of quetiapine and haloperidol in delirium: A single blind randomized controlled study. *World J Psychiatr* 2016; 6(3): 365-371 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v6/i3/365.htm> DOI: <http://dx.doi.org/10.5498/wjp.v6.i3.365>

INTRODUCTION

Delirium is considered to be a psychiatric emergency seen among medically compromised patients. Management of delirium involves addressing the underlying etiology, providing reorientation cues, ensuring safety of the patients along with improvement in the patient's functioning. Over the years haloperidol has been the main antipsychotic, which has been recommended for management of delirium. However, in view of the extrapyramidal side effects associated with haloperidol, over the last 15 years or so, many researchers have evaluated atypical antipsychotic in the management of delirium^[1].

Quetiapine is an atypical antipsychotic considered to have very low extrapyramidal side effect potential and good sedating effect. Due to these, over the years this has been evaluated in the management of delirium in few case reports^[2-5], retrospective studies^[6], open label trials^[7-13] and randomised controlled trials with some following open label design and others followed blinded assessments^[14-16]. These studies suggest that quetiapine is better than placebo^[15,16] in the management of delirium and as effective as amisulpride^[9] and haloperidol^[14]. Data also suggests that compared to placebo, quetiapine is associated with shorter time to first resolution of

delirium, shorter duration of delirium and had lower level of agitation among the intensive care unit patients^[15]. In further analysis of the data authors also showed that compared to placebo, quetiapine is associated with faster first resolution of symptoms of fluctuation, inattention and disorientation. However, it took longer time to first resolution of symptoms of agitation and hyperactivity^[17].

However, it is important to note that the data with regard to usefulness of quetiapine in management of delirium is limited with total number of patients treated with quetiapine in all the studies less than 200 patients, with none of the studies having more than 25 patients in the quetiapine arm. Hence, there is a need to expand this data. This led to the present single blind randomized, controlled trial, which assessed the effectiveness of quetiapine and haloperidol in patients of delirium, admitted in medical and surgical wards and referred to psychiatry consultation-liaison services.

MATERIALS AND METHODS

This study was conducted in multispecialty tertiary care hospital. Institute Ethics Committee approved the study. The trial was submitted to Clinical trial registry of India. Proxy written informed consent was obtained from the primary caregivers of the patients who were staying with the patient during the hospitalization prior to randomization. The purpose of the study was explained to the caregivers. The caregivers were told about the currently available pharmacotherapy for management of delirium. The caregivers were explained about the commonly used pharmacological agents along with their efficacy and side effect profile. They were informed about the evidence available for quetiapine for management of delirium. The primary caregivers were informed that they could withdraw consent at any stage.

The study was an equivalence trial which followed a single blind randomised controlled trial design. Randomization was done based on the computer generated randomization table, which was done prior to starting of the study. Consecutive patients diagnosed with delirium by the consultation liaison psychiatry team were considered for this research.

Only those patients who fulfilled a diagnosis of delirium (based on the Diagnostic and Statistical Manual, 4th Revision)^[18] and were aged more than 18 years were included into the study. Patients with delirium associated with alcohol or benzodiazepine withdrawal, poisoning due to overdose and delirium associated with dementia (based on clinical history) were excluded. Patients who were unresponsive to any verbal or physical stimulus, those with history of aphasia, profound hearing or visual loss, those with prolonged QTc interval (> 500 ms) and past history of hypersensitivity to any of the drugs were also excluded. Patients who had developed neuroleptic malignant syndrome were also not considered for this study. Those with comorbid Parkinson's disease, psychotic or mood disorders and terminal illnesses were also excluded.

For this study, 101 patients were assessed initially. Twenty-seven patients were excluded because they did not fulfil the selection criteria for the study, *i.e.*, 4 patients had comorbid psychiatric illness, drug withdrawal state was present in 5 cases, prolonged QTc interval (> 500 ms) in electrocardiogram (ECG) was seen in 4 patients, 1 patient had Parkinson's disease, 3 patients had terminal illness, in 5 cases the delirium was associated with organophosphorous poisoning and 2 patients were younger than 18 years of age. According only 77 out of 104 patients were eligible for the study and their primary caregivers were approached for the study, out of which written informed consent was given by 70 caregivers. These patients were allocated to receive haloperidol ($n = 35$) or quetiapine ($n = 35$) based on predetermined random number generated prior to recruitment.

Four patients (2 in the quetiapine and 2 in the haloperidol group) were not available for assessment after the initial assessments of 1-2 d as they left the hospital against the medical advice (LAMA). One patient in quetiapine group, the primary treating team used Inj. Haloperidol for management on the second day and as a result the patient was excluded. Two patients (one from each group) could not be started on the assigned medication, due to deterioration in the clinical status [1 subjects went into coma and 1 was transferred to intensive care unit (ICU)] on the same day.

Accordingly out of 70 patients only 63 completed the trials with 32 in the haloperidol group and 31 in the quetiapine group.

The dose of medication was adjusted as per the clinical judgement. Flexible dosing regimen (haloperidol: 0.25-10 mg and quetiapine: 12.5-75 mg/d) was used. At our consultation-liaison psychiatry practice setup, haloperidol is usually administered in the dose of 0.25 mg two to three times a day and titrated as per the requirement and majority of the patients are managed with 0.75 to 2.5 mg of haloperidol per day. In case of agitation, a dose of 1.25 to 2.5 mg is given intravenously and same is repeated as per need. For quetiapine a regiment of 12.5 mg/d OD dose was started and depending on the need the dose was increased to 75 mg/d.

Based on the daily clinical assessment, dose titration was done; however, in case the patient was agitated, dose titration was done as per the requirement. In case the delirium improved, the dose used on the previous day was continued till the end of the trial.

One of the investigators (SG) was responsible for the randomization and dose adjustments and another investigator (SM) who was blinded for the medication being administered carried out the clinical assessments.

Besides use of haloperidol or quetiapine, patients were continued on medications for their medico-surgical ailments. However, any medication (like benzodiazepines, steroids, *etc.*) that could possibly contribute to delirium or those medications which were not essential were discontinued. The underlying etiologies for delirium were managed with appropriate measures. The primary

caregivers of all the patients were advised to provide optimal level of environmental stimulation, avoid sensory impairments of the patient and make the environment familiar to the patient by ensuring proper environmental cues that could facilitate orientation.

Primary efficacy measure

Delirium Rating Scale-Revised-98 (DRS-R-98)^[19] was used as the primary outcome measure. The DRS-R-98 is a 16-item scale with 13 severity and 3 diagnostic items that rate the preceding 24-h period. Each item is rated 0 (absent/normal) to 2/3 (severe impairment). Higher severity scores (0-39) indicating more severe delirium. The scale has high interrater reliability, sensitivity and specificity for detecting delirium in mixed neuropsychiatric and other hospital populations^[19]. Both, the severity scale (13 items) and the total scale (16 items) have been validated for repeated measures.

Secondary efficacy measure

Additionally the patients were assessed on Mini mental status examination (MMSE)^[20] and this was used as a secondary outcome measure for the study. It is a 30 point scale widely used in delirium and dementia research.

Assessments

Patients were initially evaluated at the baseline and 6 subsequent consecutive 6 d, at a particular time of the day (6-8 PM) on DRS-R-98 and MMSE.

Additionally, at the baseline, patients were assessed on Amended Delirium Motor Checklist^[21,22], Short IQCODE^[23] and etiology checklist.

Amended Delirium Motor Checklist (Amended DMC)^[21,22] comprises of 13 items (5 hyperactive features and 8 Hypoactive features) of activity patterns that can be rated by both physicians and nurses. Each item is evaluated in absolute manner, *i.e.*, there is some evidence of the particular behaviour in last 24 h or not. Based on the number of criteria met for hyperactive and hypoactive checklists, the patients are categorized into hyperactive, hypoactive, mixed or no subtypes.

Short IQCODE^[23] was used to evaluate the cognitive functions in the last 6 mo. It is a 16-item instrument that allows for the assessment of cognitive status for a defined period prior to the interview point, *e.g.*, six months previously. It is rated based on an interview with a key relative. Each item is rated on a 5 point scale with a score of 3 indicating no change (higher scores denote worsening while lower denote improved cognition). The scale is scored by adding all items and then dividing the total score by 16 to get a mean score per item. The suggested cutoff for suspected dementia is a score > 3.31 -3.38.

The etiology checklist was designed for this study and included 47 commonly associated factors which are known to be associated with delirium. Each item was rated as present or absent. For the laboratory parameters, if any of the values was out of the laboratory

range of the hospital it was considered as present.

Statistical analysis

SPSS-14 was used to analyse the data. Mean and standard deviation were calculated for the continuous variables and frequency and percentages were calculated for the ordinal or nominal variable. Comparisons between the groups were done by using students *t* test/ χ^2 test. If the DRS-R-98 data had non-normal distribution, then these were compared by using non-parametric tests. For the same, instead of paired *t* test, Mann-Whitney *U* test and Wilcoxon sign rank test were used. Repeat measure ANOVA was used to evaluate the effectiveness of medications on the primary and secondary outcome measure.

RESULTS

The mean age of the participants was 46.42 (SD: 18.26) and slightly less than one-third of the study sample was ≥ 60 years. The mean duration of education in years for the participants was 9.60 (SD: 4.22). Majority of the patients were male, from urban locality and had hospital emergent delirium. The average duration of delirium was 2.61 (SD: 2.08) d prior to enrollment into the trial. The mean IQCODE score was 3.07 (SD: 0.29) with only 3 patients scoring above 3.31, however, clinically these patients were never diagnosed with dementia. In terms of motor subtype, majority of the patients had hyperactive delirium and the mean number of etiologies associated with delirium was 6.82 (SD: 3.60). The mean baseline DRS-R-98 total score for the study sample was 31.52 (SD: 3.34). There was no statistically significant difference between the groups on any of the above variables (Table 1). Two patients with short IQCODE score were in the quetiapine group and 1 patient was in the haloperidol group.

The average dose of haloperidol was 0.67 mg (SD: 0.35; range 0.25-1.25) and that of quetiapine was 31.83 mg (SD: 4.10; range 12.5-75).

For the haloperidol group the average baseline DRS-R98 severity score and MMSE scores were 24.81 (SD: 2.19) and 7.50 (SD: 3.83) respectively and those for quetiapine group were 25.48 (SD: 3.60) and 6.83 (SD: 4.45) respectively with no significant difference between the two groups. As shown in Table 1 there was no significant difference in the DRS-R98 scores and MMSE scores from day 1 to day 6 between the two groups.

Effectiveness of haloperidol and quetiapine

In terms of both DRS-R-98 and MMSE, there was significant improvement in both the study groups from day 1 through day 6 (Table 2). Additionally, repeat measure ANOVA was used to evaluate the effectiveness for both the groups. As there was significant difference in the Mauchly's test of Sphericity, Green-House Geissier within subject effect was considered while interpreting the "F"

and "P" values in the repeat measure ANOVA. Accordingly, ANOVA with repeated measures with a Greenhouse-Geisser correction, showed significant reduction in the mean scores for DRS-R-98 for haloperidol group (*F* value = 134.25, corrected DF = 82.44; *P* < 0.0005) and also in the quetiapine group (*F* value = 118.78, corrected DF = 91.23; *P* < 0.0005). Repeat measure ANOVA for MMSE scores with a Greenhouse-Geisser correction for haloperidol group (*F* value = 73.86, corrected DF = 74.84; *P* < 0.0005) and quetiapine group (*F* value = 69.62, corrected DF = 77.83; *P* < 0.0005) were also significant.

For both the groups, there was significant difference between the DRS-R-98 scores for each day except for lack of significant difference between day 5 and 6, indicating that with each subsequent day, there was significant improvement from baseline to day 5. As with DRS-R-98, in both the groups, there was significant difference between the MMSE scores for each day except for lack of significant difference between day 5 and 6 in the haloperidol group and 4 and 5, day 4 and 6 and day 5 and 6, indicating that with each subsequent day, there was significant improvement in MMSE from baseline to day 5 in haloperidol group and baseline to day 4 in the quetiapine group.

No significant difference was seen between the two groups, in terms of percentage of patients whose DRS-R-98 score dropped down below 10 (Table 1). Overall by using a cutoff of DRS-R98 severity score of < 10, haloperidol was found to be efficacious in 68.75% and quetiapine was found to be efficacious in 67.74% of cases, with no significant difference between the two groups. As is evident from Table 1, with each passing day there was increase in proportion of patients achieving the DRS-R-98 score of < 10, from baseline to day-5.

At the end of the trial, 12 (37.5%) patients in haloperidol group and 9 (29.03%) patients in the quetiapine group had DRS-R98 score of "0" with no significant difference between the two groups (χ^2 value: 0.508; *P* = 0.47).

Further analysis was done for each day to evaluate the effect of both the medications on the cognitive and non-cognitive domains of DRSR-98 and no significant difference emerged between both the groups for assessment on any given day. In terms of efficacy measure when the repeat measure ANOVA was used, scores on the non-cognitive domain in the haloperidol group showed significant reduction for each day except for lack of significant difference between day 4-5, day 4-6 and day 5 and 6. Similarly in the quetiapine group, there was significant difference between the scores for each day except for lack of significant difference between day 3-4, day 3-5, day 3-6, day 4-5, day 4-6 and day 5 and 6. In terms of cognitive symptoms there was significant difference between the scores for each day in the haloperidol and quetiapine groups except for lack of significant improvement between day 5 and 6 in the quetiapine group.

Data was also analysed separately for young and

Table 1 Sociodemographic, clinical profile, delirium subtype, Delirium Rating Scale-Revised-98 and mini mental status examination ratings for both the study groups

Variables	Haloperidol <i>n</i> = 32 mean (SD)	Quetiapine <i>n</i> = 31 mean (SD)	χ^2/t -test
Age (yr)	44.40 ± 16.76 (range 18-76)	48.51 ± 19.75 (range 18-85)	0.89 (<i>P</i> = 0.37)
Age ≥ 60 yr	7 (32%)	12 (38.7%)	2.11 (0.146)
Education (No. of years)	9.81 ± 4.46 (range 0-15)	9.38 ± 4.03 (range 0-17)	0.396 (<i>P</i> = 0.693)
Male	28 (87.5%)	21 (67.74%)	3.55 (<i>P</i> = 0.06)
Locality- Urban	21 (65.6%)	24 (77.4%)	1.073 (<i>P</i> = 0.300)
Type of onset - hospital emergent	23 (71.87%)	25 (80.64%)	0.668 (<i>P</i> = 0.414)
Duration of delirium prior to assessment (d)	2.38 ± 1.81	2.83 ± 2.32	0.85 (<i>P</i> = 0.398)
Total IQCODE	3.01 ± 0.053	3.13 ± 0.40	1.57 (0.12)
Delirium subtype as per amended DMSS			
Hyperactive	28 (87.5%)	27 (87.09%)	
Hypoactive			5.36 (<i>P</i> = 0.76)
Mixed	3 (9.37%)	2 (6.45%)	
	1 (3.12%)	2 (6.45%)	
Mean dose (mg/d)	0.67 ± 0.35 (range 0.25-1.25)	26.63 ± 15.61 (range 12.5-75)	
Mean number of etiologies	7.06 ± 3.31	6.58 ± 3.92	0.52 (<i>P</i> = 0.60)
DRS-R-98 total score at baseline	31.21 ± 2.40	31.83 ± 4.10	0.73 (<i>P</i> = 0.46)
DRS-R-98 scores (severity items only)			
Day 0	24.81 ± 2.19	25.48 ± 3.60	0.89 (<i>P</i> = 0.37)
Day 1	20.46 ± 3.93	19.54 ± 6.40	0.68 (<i>P</i> = 0.49)
Day 2	15.43 ± 6.19	13.54 ± 7.67	1.07 (<i>P</i> = 0.28)
Day 3	11.46 ± 6.58	9.51 ± 7.29	1.11 (<i>P</i> = 0.26)
Day 4	8.65 ± 6.73	7.83 ± 7.42	0.45 (<i>P</i> = 0.64)
Day 5	6.46 ± 6.06	6.48 ± 6.84	473 (<i>P</i> = 0.749) ¹
Day 6	5.43 ± 5.84	5.58 ± 5.84	466.5 (<i>P</i> = 0.679) ¹
DRS-R-98 < 10 on day 0	0	0	-
DRS-R-98 < 10 on day 1	0	3 (9.67%)	FE = 0.11
DRS-R-98 < 10 on day 2	5 (15.62%)	8 (25.80%)	0.99 (<i>P</i> = 0.31)
DRS-R-98 < 10 on day 3	14 (43.75%)	16 (51.61%)	0.39 (<i>P</i> = 0.53)
DRS-R-98 < 10 on day 4	21 (65.62%)	20 (64.51%)	0.009 (<i>P</i> = 0.92)
DRS-R-98 < 10 on day 5	23 (71.85%)	22 (70.96%)	0.006 (<i>P</i> = 0.93)
DRS-R-98 < 10 on day 6	22 (68.75%)	21 (67.74%)	0.007 (<i>P</i> = 0.93)
MMSE scores			
Day 0	7.50 ± 3.83	6.83 ± 4.45	0.63 (<i>P</i> = 0.53)
Day 1	11.31 ± 5.91	11.80 ± 6.02	0.328 (<i>P</i> = 0.74)
Day 2	15.50 ± 5.16	16.00 ± 6.37	0.343 (<i>P</i> = 0.73)
Day 3	18.28 ± 0.73	18.38 ± 6.26	0.070 (<i>P</i> = 0.94)
Day 4	20.34 ± 5.72	20.67 ± 6.41	0.218 (<i>P</i> = 0.828)
Day 5	21.93 ± 5.01	21.58 ± 5.74	0.263 (<i>P</i> = 0.794)
Day 6	23.00 ± 4.75	22.54 ± 5.34	0.354 (<i>P</i> = 0.724)

¹Mann-Whitney *U* value. DRS-R98: Delirium Rating Scale-Revised-98; MMSE: Mini mental status examination; FE: Fisher Exact test.

elderly patients (≥ 60 years). No significant difference was noted in the DRS-R-98 and MMSE scores on any of the assessments between the haloperidol and quetiapine groups among the elderly (≥ 60 years) and the young adults.

DISCUSSION

In 2 decades or so some data has emerged for the efficacy of atypical antipsychotic medications in management of delirium. Present study was also a step in the same direction. Most of the earlier studies which have evaluated efficacy of quetiapine have done so in sample sizes less than 25 in quetiapine arm. Most of the previous studies have been open label studies^[7-14], with only few studies following randomization and blinding^[15,16].

Like our previous study^[24], the present study too followed a single blind randomised controlled trial design, included patients with delirium with different etiologies in

a sample which predominantly comprised of young adult subjects (< 60 years) admitted to medico-surgical wards. Outcome was assessed by using DRS-R-98 and MMSE, which are considered to be useful for serial evaluation of delirium. However, unlike the previous study^[24], in the present study, besides analysing the data for the whole group, separate analysis was done for adult and elderly groups. Further, the DRS-R-98 data was evaluated separately for cognitive and non-cognitive symptoms. Motor subtypes were assessed by using validated scales, and besides ruling out dementia on the basis of clinical history cognitive functions in the last 6 mo were assessed by using short-IQCODE.

The demographic profile (age and gender distribution) of the participants included in the present study is characteristics of patients with delirium seen in psychiatry consultation liaison services at our centre^[25,26] and those included in a previous antipsychotic trial from this centre^[24]. The dose of quetiapine in the present

Table 2 Efficacy of haloperidol and quetiapine

	Haloperidol group	Quetiapine group
	Paired “t” test/ Wilcoxon sign rank test	Paired “t” test/ Wilcoxon sign rank test
DRS-R98 severity scores		
Day 0 and day 1	7.10 ($P < 0.001$)	5.12 ($P < 0.001$)
Day 0 and day 2	9.48 ($P < 0.001$)	8.60 ($P < 0.001$)
Day 0 and day 3	11.69 ($P < 0.001$)	11.68 ($P < 0.001$)
Day 0 and day 4	14.08 ($P < 0.001$)	12.90 ($P < 0.001$)
Day 0 and day 5	17.63 ($P < 0.001$)	4.86 ($P < 0.001$) ¹
Day 0 and day 6	4.94 ($P < 0.001$) ¹	4.86 ($P < 0.001$) ¹
Day 3 and day 6	4.70 ($P < 0.001$) ¹	3.98 ($P < 0.001$) ¹
MMSE		
Day 0 and day 1	3.83 ($P = 0.001$)	4.81 ($P < 0.001$)
Day 0 and day 2	8.53 ($P < 0.001$)	7.40 ($P < 0.001$)
Day 0 and day 3	9.00 ($P < 0.001$)	8.66 ($P < 0.001$)
Day 0 and day 4	10.07 ($P < 0.001$)	9.45 ($P < 0.001$)
Day 0 and day 5	11.68 ($P < 0.001$)	10.55 ($P < 0.001$)
Day 0 and day 6	12.38 ($P < 0.001$)	12.23 ($P < 0.001$)
Day 3 and day 6	6.50 ($P < 0.001$)	5.66 ($P < 0.001$)

¹Wilcoxon Sign Rank test. DRS-R98: Delirium Rating Scale-Revised-98.

study is lower than the mean dose used in most of the previous studies (42.2 to 93.7 mg/d)^[6,8,11,14,16], evaluating quetiapine in delirium. This can be understood from the Pharmacogenomic evidence, which suggests that compared to people from West, patients from countries like India require lower doses of psychotropics^[27].

The present study suggests that quetiapine in low dose is as beneficial as haloperidol in management of delirium. This finding supports the available literature which suggests that quetiapine is efficacious in management of delirium^[7-16]. Present study also provides credence to the available evidence that quetiapine is as efficacious as haloperidol in management of delirium^[14]. This research also suggests that quetiapine is equally efficacious in adults and elderly population. Usefulness in elderly provides support to the previous studies^[11]. Accordingly it can be said that quetiapine can be considered as another option in the management of delirium.

There are few limitations of the present study. The sample size for the study was small and due to the same the possibility of a type I error cannot be ruled out. No power calculation was done for estimation of sample size for the study. We did not include a placebo control arm and the side effects of both the study medications were not evaluated. As the rater was aware that all the patients were receiving active treatment and hence this could have affected the ratings. The study was limited to referred patients. Due to very few patients in the hypoactive group and those with short IQCODE score above the cut-offs, efficacy could not be compared in different motoric subtypes and those with possible dementia and without dementia. The treating psychiatrist was not blinded to the medication and this would have some bearing on the dose used. Hence, these limitations

must be considered while interpreting the results of this study. This study suggests that quetiapine is as effective as haloperidol in the management of delirium in adult and elderly patients.

COMMENTS

Background

There is limited data on use of quetiapine in management of delirium.

Research frontiers

Very few studies have evaluated the effectiveness of atypical antipsychotics in delirium.

Innovations and breakthroughs

Few studies have evaluated the usefulness of quetiapine in management of delirium.

Applications

Quetiapine can be considered as an alternative to haloperidol in management of delirium.

Peer-review

This is an interesting randomized controlled trial comparing haloperidol and quetiapine in delirium not related to substance withdrawal. The study has been adequately performed and is well presented.

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Cognitive behavioural therapy for auditory hallucinations in schizophrenia: A review

Maria Pontillo, Franco De Crescenzo, Stefano Vicari, Maria Laura Pucciarini, Roberto Averna, Ornella Santonastaso, Marco Armando

Maria Pontillo, Stefano Vicari, Maria Laura Pucciarini, Roberto Averna, Ornella Santonastaso, Marco Armando, Child and Adolescence Neuropsychiatry Unit, Department of Neuroscience, Children Hospital Bambino Gesù, 00165 Rome, Italy

Franco De Crescenzo, Department of Psychiatry and Psychology, Catholic University of Sacred Heart, 00168 Rome, Italy

Marco Armando, Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, 1211 Geneva, Switzerland

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Correspondence to: Dr. Maria Pontillo, PhD, Child and Adolescence Neuropsychiatry Unit, Department of Neuroscience, Children Hospital Bambino Gesù, Piazza Sant'Onofrio 4, 00165 Rome, Italy. maria.pontillo@opbg.net
Telephone: +39-06-685927030
Fax: +39-06-68592450

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Abstract

AIM

To provide an updated of recent findings about efficacy of cognitive-behavior therapy (CBT) in reduction of command hallucinations.

METHODS

PubMed/MEDLINE, Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature, PsycINFO, ClinicalTrial.gov searches were performed using the keywords "hallucinations", "behavioural therapy" and "cognitive therapy" in order to identify relevant articles published during the years of 2011 to 2016. No language limits were used. Studies conducted within control group, reviews, editorials, were excluded. Data on efficacy, acceptability and tolerability were extracted by three authors independently. Disagreements were resolved in a consensus meeting or by another reviewer.

RESULTS

A total of eight articles were eligible for inclusion. Two are randomized clinical trials (RCTs) and six are observational studies. The two RCTs included showed a greater efficacy of CBT compared to standard care on auditory hallucinations (AHs). Nevertheless, they considered different CBT models, particularly Treatment of Resistant Command Hallucinations and Cognitive Therapy for Command Hallucinations. As regards non RCT-studies, all papers included showed reduction on frequency and severity of AHs and distress related to them. However, the lack of content details within non-RCTs studies decreased their comparability. In terms of predictive variables,

our findings show that negative symptoms at baseline appeared to be the strongest predictor of the treatment efficacy. Indeed, negative symptoms showed a significant negative correlation on outcome.

CONCLUSION

Although more conclusive studies are still needed, we found some preliminary evidence for the efficacy of CBT in the treatment of command hallucinations.

Key words: Auditory hallucinations; Cognitive-behavior therapy; Schizophrenia; Psychotic disorder; Treatment; Distress; Functional impairment

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Core tip: Auditory hallucinations (AHs), especially command hallucinations, represent a special problem for the clinical management of schizophrenia and contribute significantly to distress and disability related to this disorder. The aim of this article is to review the current knowledge and evidence on the efficacy of cognitive-behavior therapy interventions in AHs.

Pontillo M, De Crescenzo F, Vicari S, Pucciarini ML, Averna R, Santonastaso O, Armando M. Cognitive behavioural therapy for auditory hallucinations in schizophrenia: A review. *World J Psychiatr* 2016; 6(3): 372-380 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v6/i3/372.htm> DOI: <http://dx.doi.org/10.5498/wjp.v6.i3.372>

INTRODUCTION

Hallucinations can be defined as sensory experiences in any sensory modality, occurring in the absence of a corresponding external stimulation whilst in a fully conscious state, and resembling veridical perceptions^[1-3]. In schizophrenia, hallucinations occur with a high frequency of up to 50%-80%^[4]. Among hallucinations, auditory hallucinations (AHs) are considered the highest, with prevalence estimates in schizophrenia ranging between 40% and 80%^[5-7].

AHs, especially command hallucinations, are also associated with an increased risk of harmful or dangerous actions^[8-13]. Shawyer *et al*^[8] reported a median 53% prevalence of command hallucinations in adult participants with psychiatric disorders, 48% of these participants said the commands stipulated harmful or dangerous actions, rising to 69% for participants in medium secure unit. However, the link between the presence of command hallucinations and harm to self or others is not straightforward. In the MaCarthur study^[14], no association was reported between the presence of delusions or command hallucinations and violence. Thoughts about violence, however, were a strong predictor of violence 6 mo later^[14].

Besides the high prevalence, AHs experienced in psychotic illness contribute significantly to distress and disability^[8]. Indeed, several clinical studies show that AHs appraised as malevolent are significantly and positively associated with distress^[9-11]. These findings were confirmed in a recent systematic review by Mawson *et al*^[12].

Antipsychotic agents are considered to be the first choice for the treatment of psychotic symptoms^[15], but at least one third of patients exhibit persistent psychotic symptoms, despite drug treatment^[16]. Treatment of drug-resistant patients can be complicated by adverse effects, due to the use of second-line drugs such as Clozapine^[17] or combination therapy with multiple antipsychotic agents^[18]. Moreover, there are many concerns regarding patients' refusal to adhere with drug regimes^[19] and long-term compliance to therapy^[20]. Consequently, there is a growing interest on psychological interventions, which are now recognized as important components of a comprehensive therapeutic approach in the treatment of schizophrenia. AHs are some of the most prominent and distressing of the treatment-resistant symptoms, and command hallucinations are the most high risk of these^[21]. Command hallucinations represent a special problem for the clinical management of psychosis. Previous research suggests cognitive-behavior therapy (CBT) to be a useful treatment for reducing compliance with harmful command hallucinations^[8,22].

Specifically, CBT applied to the treatment of command hallucinations does not focus on reducing the experience of voices, but on reducing the perceived power of voices to harm the individual and to motivate compliance^[8,22]. Indeed, the main rationale is that by challenging key beliefs about the power of commanding voices, the patients would show a lower level of compliance and appeasement behavior and an increase in resistance to the same voices. In a recent meta-analysis, van der Gaag *et al*^[23] showed that CBT is effective in the treatment of AHs and delusions. Specifically, individually tailored case formulation CBT showed larger effect-size than broad CBT including standard training programs. However, in this study van der Gaag *et al*^[23] have considered both the AHs that delusions.

The aim of our review is to provide an updated overview on the efficacy of CBT interventions in AHs. Specifically, we focus on the efficacy of CBT in reducing command hallucinations.

MATERIALS AND METHODS

This is a review of the literature published between 2011 and 2016 on trials using CBT targeted on AHs in schizophrenia and related psychotic disorders.

A comprehensive literature search of the PubMed/MEDLINE, Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature (CINHAL), PsycINFO, ClinicalTrial.gov databases were conducted. A search algorithm based on a combination of the terms: (hallucinations) AND (behavioral therapy OR cognitive

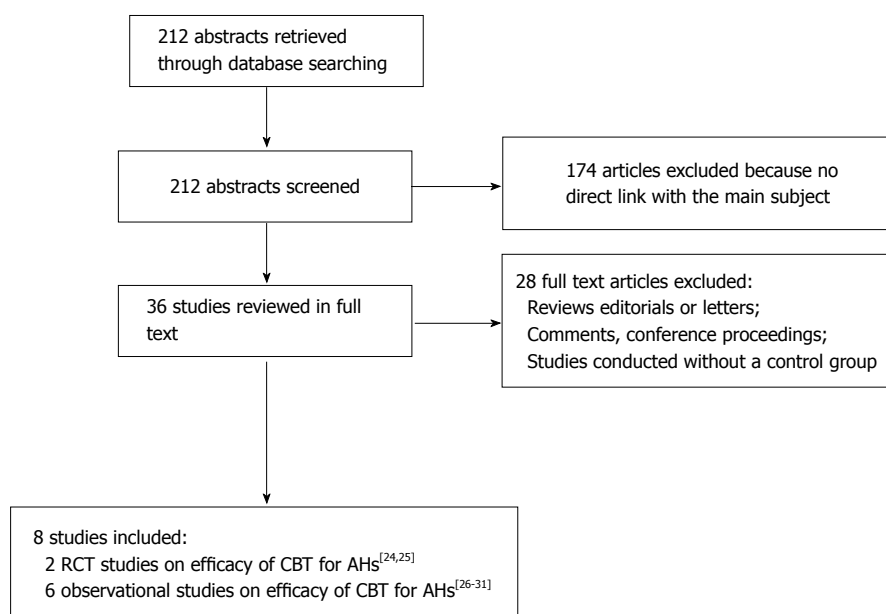


Figure 1 Flow chart of literature review. AHs: Auditory hallucinations; CBT: Cognitive-behavior therapy; RCT: Randomized clinical trial.

therapy) was used. Moreover the bibliographies of the most relevant published articles in the field were screened. The last update of the search was on March 2016. Data on efficacy, acceptability and tolerability were extracted by three authors independently (Franco De Crescenzo, Maria Laura Pucciarini, Maria Pontillo). Disagreements were resolved in a consensus meeting or by another reviewer (Marco Armando). No language limits were used.

The search algorithm resulted in 212 articles, of which 38 referred to potentially eligible studies. Of these, 30 articles were non-empirical studies, reviews and commentaries. We found a total pool of eight studies on CBT for the treatment of AHs.

Two randomized clinical trials (RCTs)^[21,24] and six observational studies^[25-30] fulfilled the inclusion criteria. In terms of evidence-based medicine, the quality of these studies was moderate.

We decided to focus on the past five years (2011-2016) because this is the period in which CBT models specifically targeted on AHs were developed. In fact, for the previous period, van der Gaag *et al.*^[23] (2014) had already published a meta-analysis. However, this meta-analysis does not focus specifically on AHs.

In Figure 1 are represented the search strategy with inclusion/exclusion criteria for the papers.

RESULTS

RCTs

During the last four years two RCTs have been conducted, proving the efficacy of CBT for the treatment of AHs, both were specifically on Command Hallucinations. Details on the methodologies and results of the studies are shown in Table 1.

Shawyer *et al.*^[24] evaluated the efficacy of a cognitive behavioural intervention model called Treatment of Resistant Command Hallucinations (TORCH) compared

with befriending, which is a fully manualised control intervention^[31] that provides the patients with the same amount of therapist engagement and expectancy as CBT. The treatment program was conducted for 15 weekly sessions lasting approximately 50 min and with a follow up at six months. Despite TORCH participants subjectively reporting greater improvement in command hallucinations compared to Befriending participants, the study found no significant group differences in the primary outcome (*e.g.*, degree of compliance with harmful command hallucinations), nor in the secondary outcomes (*e.g.*, severity illness, global functioning, level of distress related to command hallucinations, quality of life), based on blinded assessment data.

Birchwood *et al.*^[21] performed a multi-centre RCT of Cognitive Therapy for Command Hallucinations (CTCH)^[32] which is a subtype of CBT specifically targeted on AHs, compared to usual treatment, on 197 participants with command hallucinations, to prevent harmful compliance. This RCT was programmed to follow the patients for 19 sessions, delivered steadily over the 9 mo post-randomisation. The results showed a better efficacy of CTCH respect to treatment as usual.

Both the studies^[21,24] were powered on the compliance behavior to voices. In Shawyer *et al.*^[24] the Voices Acceptance and Action Scale (VAAS)^[33] was used, while in Birchwood *et al.*^[21] the Voice Compliance Scale (VCS)^[34] was preferred.

The two RCTs differed in many ways. First of all, Shawyer *et al.*^[24] did not find any statistical difference between the treatments considered (TORCH vs befriending). Birchwood *et al.*^[21] is a much larger trial which found a significant difference between the treatments considered (CBT vs treatment as usual) and which was based and powered on a previous pilot study^[22]. The comparisons used for the two RCTs were different as well. In Shawyer *et al.*^[24] the intervention "befriending" was used. It has a similar amount of therapist engagement and expectancy as CBT,

Table 1 Randomized clinical trials of cognitive behavioral therapy for auditory hallucinations

Ref.	Sample	Methods	Criteria for diagnosis	Criteria for outcome	Focused treatment	Results	Follow-up
Shawyer <i>et al</i> ^[14]	<i>n</i> = 44 Mean age: 39	RCT	(1) diagnosis of schizophrenia or related condition based on DSM-IV criteria (2) command hallucinations within the previous 6 mo that caused distress or dysfunction despite treatment with antipsychotic medication at therapeutic doses	Assessor-rated degree of compliance with harmful command hallucinations on a scale of 0-7 Self-rated confidence to resist obeying harmful commands and confidence in coping with general commands on a scale of 0-100 PANSS Modified GAF PSYRATS Quality of Life Enjoyment and Satisfaction Questionnaire Client Satisfaction Questionnaire VAAS BAVQ-R 8-item self-report Insight Scale RSQ	Randomized to 15 sessions of the intervention "TORCH" or the control, "Befriending". A sub-sample of 17 participants was randomized to a waitlist control before being allocated to TORCH or Befriending Pharmacological treatment: Chlorpromazine equivalent dose (mg) Mean = 742.9 SD = 388.7	Confidence to resist harmful CHs (<i>P</i> = n.s.) Confidence in coping with CHs (<i>P</i> < 0.01) PANSS total (<i>P</i> < 0.05) Modified GAF (<i>P</i> = n.s.) Distress PSYRATS (<i>P</i> < 0.01) Disruption PSYRATS (<i>P</i> < 0.01) Quality of Life (<i>P</i> < 0.05) VAAS (<i>P</i> = n.s.) BAVQ-R (<i>P</i> = n.s.)	6-mo
Birchwood <i>et al</i> ^[15]	<i>n</i> = 197 Mean age: 37.4	RCT	(1) ICD-10 schizophrenia, schizoaffective, or mood disorders, under care of a clinical team (2) history of harmful command hallucinations of at least 6 mo duration with recent (< 9 mo) history of harm to self, others or major social transgressions as a result of the commands (full or partial compliance); or harmful command hallucinations where the individual is distressed and appeasing the powerful voice	VCS VPD Personal knowledge questionnaire/omniscience scale BAVQ-R PSYRATS Calgary Depression Rating Scale for Schizophrenia Beck Hopelessness Scale Beck Scale for Suicidal Ideation PANSS	Randomized to cognitive Therapy for command Hallucinations + treatment as usual or treatment as usual alone Adherence to cognitive therapy was excellent: only 12 (12%) of 98 participants not attending any sessions, and 79 (81%) completing the therapy (all manualised elements) Pharmacological treatment: Olanzapine equivalents dose (mg) 25.79 (SD: 21.73).	RSQ (<i>P</i> = n.s.) VCS experimental group: 41; control group: 49 VPD total, experimental group: 21.31; control group: 23.98 Personal knowledge questionnaire (<i>P</i> = 0.09) BAVQ-R (<i>P</i> = n.s.) PSYRATS total (<i>P</i> = n.s.) Calgary Depression Rating Scale for Schizophrenia (<i>P</i> = n.s.) Beck Scale for Suicidal Ideation (<i>P</i> = n.s.) PANSS total (<i>P</i> = n.s.)	18-mo

AHs: Auditory hallucinations; BAVQ-R: Beliefs about the voices questionnaire-revised; CHs: Command hallucinations; GAF: Global assessment of functioning scale; n.s.: Not significant; PANSS: Positive and negative syndrome scale; RCT: Randomized clinical trial; PSYRATS: Psychotic symptom rating scale; RSQ: Recovery style questionnaire; VAAS: Voices acceptance and action scale; VCS: Voice compliance scale; VPD: Voice power differential scale.

with similar drop-out rates^[35]. Befriending involves a series of conversations that resemble conversations with a friendly social acquaintance. In Birchwood *et al*^[21] the treatment as usual^[15] was used as comparison.

On the one hand, in Shawyer *et al*^[24] no differences were found between or within the TORCH and befriending

groups on confidence to resist harmful commands at endpoint or follow up. On the other hand in Birchwood *et al*^[21] the CTCH intervention showed to be significantly superior to the usual treatment and the efficacy interpreted as the effect that is common to the 9 and 18 mo follow-up points, was calculated as an odds ratio of

0.574 (95%CI: 0.33-0.98, $P = 0.042$). Both the trials had high quality and a low risk of bias (Table 1).

Non-RCT clinical studies

We found six non-RCT studies examining the efficacy of CBT for AHs in patients with psychosis. Details on the methodologies and results of the studies are shown in Table 2.

In the latest study, Zanello *et al.*^[30] investigated the effectiveness of a group cognitive behavioural therapy for AHs, the Voices Group, in 41 patients with schizophrenia or schizoaffective disorders. The program Voices Group was conducted for seven specific sessions. The results showed a significant reduction in the severity of AHs ($P < 0.005$) and in total symptoms severity score of BPRS 4.0 [Brief Psychiatric Rating Scale^[36]; without hallucination ($P < 0.01$)]. This result remained stable after the 6-mo follow-up.

Thomas *et al.*^[25] conducted an open label trial on the efficacy of CBT in reducing AHs in 33 subjects with schizophrenia. They also investigated the role of insight, beliefs about the origin of hallucinations, negative symptoms and cognitive disorganization as predictors of the outcome. The study observed post-treatment improvements in hallucination severity when AHs were considered a specific target of psychological treatment. Only overall negative symptoms showed a significant negative correlation on (rpb = -0.60, $P = 0.001$) with outcome. This effect appeared to be independent of length of illness, drop-out and number of sessions.

Mortan *et al.*^[26] evaluated the effectiveness of a group-based CBT program for AHs on 7 inpatients with schizophrenia and other psychotic disorders compared to 5 in patients treated with treatment as usual. The CBT treatment program was conducted for 9-10 sessions twice/wk. The results showed a significant reduction ($P < 0.005$) in the severity and frequency of hallucinations, delusions, negative symptoms, distress and anxiety after group-based CBT.

A case study by Hutton and Morrison^[27] described the effectiveness of brief CBT (12 wk) in an 18-year-old male with psychotic disorder and AHs who refused antipsychotic medication. By week 12, the frequency and duration of AHs had reduced to zero.

Dannahy *et al.*^[28] examined the impact of group person-based cognitive therapy (PBCT) for distressing voices in a sample of 62 participants with treatment-resistance and subjectively distressing voices. Participants were divided in nine groups and PBCT was conducted over 8-12 sessions. Results demonstrated significant improvements in the outcomes measure of general well-being ($P < 0.001$), voice-distress ($P < 0.001$), control ($P < 0.01$) and dependence upon voice ($P < 0.05$).

Gottlieb *et al.*^[29] tested the feasibility and effects of a 10 session web-based CBT for AHs in a sample of 17 individuals with schizophrenia spectrum disorder. Results showed a significant reduction of AHs, including the perception of voices as an outside entity and intensity

of negative commentary. Interestingly, participants improved in depression and delusion severity, although these symptoms were not directly targeted in the program.

DISCUSSION

The present review describes the efficacy of CBT in patients with AHs. In summary, the two RCTs included showed a greater efficacy of CBT compared to standard care on AHs. However, in Shawyer *et al.*^[24], TORCH participants subjectively reporting greater improvement in command hallucinations compared to Befriending but no significant group differences on primary outcome measure that was level of compliance with harmful command hallucination. In Birchwood *et al.*^[21] instead, CTCH participants showed an improvement in this measure.

One possible explanation of the discrepancy between the two RCTs in term of efficacy on reducing level of compliance with harmful command hallucinations is that, within the general framework of CBT, different theoretical approach can play a different role on the efficacy of the intervention. Indeed, the two RCTs were built on different theoretical frameworks. The TORCH framework is based on the "acceptance" of voices by "cultivating the capacity to just notice voices and associated thoughts rather than believing and acting on them". The CTCH focuses on targeting individuals' appraisals, behavior and affect, and not necessarily symptoms. It is based on the nature of the relationship with the personified voice. Therefore, if the voice hearer believes the voice to have malevolent intent, and crucially to have the power to deliver the threat, this can motivate compliance or appeasement behavior. In addition, in Shawyer *et al.*^[24] the intervention "befriending" was used as the control condition and it has a similar amount of therapist engagement and expectancy as CBT. This is likely to have resulted in smaller between-group effect sizes respect to Birchwood *et al.*^[21].

As regards non RCT-studies, all papers included showed reduction on frequency and severity of AHs and distress related to them. However, the lack of content details and on rationales within non-RCTs studies decreases their comparability and therefore the chance to draw final conclusions.

In terms of predictive variables, negative symptoms appeared to be the strongest predictor of the treatment efficacy. It may be that negative symptoms are a barrier to treatment specific to hallucinations, although it would be important to verify this association in other studies. However, based on this finding, it is possible to propose that negative symptoms interfere with engagement in therapy, in rapport with the therapist, and completion to homework. This might lead to modifications of CBT to treatment for the presence of negative symptoms, such as the use of more behavioral methods.

Some limitations and strenghts should be con-

Table 2 Non randomized clinical trials of cognitive behavioral therapy for auditory hallucinations

Ref.	Sample	Methods	Criteria for diagnosis	Criteria for outcome	Focused treatment	Results	Follow-up
Zanello <i>et al</i> ^[21]	<i>n</i> = 41 age-range: 18-65	Naturalistic Study	(1) Diagnosis of a schizophrenia or schizoaffective disorder (2) Current AHs in the form of voices, occurring at least once per week	Reduction of AHs: BPRS Total symptom severity without AHs: BPRS	7 sessions of CBT based upon the program "Voice Group" of Wikes <i>et al</i> 1999 Pharmacological treatment: New antipsychotic Combined antipsychotic Anxiolytic, mood stabilizer, hypnotic or antidepressant medication Dosage: Changed when clinically required	Decrease in the hallucinations item score of Bprs ($P < 0.05$) Decrease in the total symptoms severity score of BPRS ($P < 0.01$)	6-mo
Thomas <i>et al</i> ^[16]	<i>n</i> = 33 Mean age: 36.4	Non-RCT Open trial	1) Diagnosis of a schizophrenia or schizoaffective disorder (2) Current AHs in the form of voices, occurring at least once per week (3) Voices associated with significant subjective distress (4) History of voices for at least one year; and (5) currently prescribed antipsychotic medication	Correlation between PSYRATS, PANSS, SAI and Outcome Main Outcome measure: Improvement of five points of more on the PSYSTRATS	24 sessions of CBT based upon the manual of Fowler <i>et al</i> (1995) Pharmacological treatment: Chlorpromazine-equivalent pre-treatment: <i>M</i> = 793.1 mg, <i>SD</i> = 468.6 mg; post-treatment: <i>M</i> = 768.1 mg, <i>SD</i> = 473.8 mg	Only negative symptoms showed a statistically correlation with outcome (<i>rpb</i> = -0.60; $P \leq 0.001$)	None
Mortan <i>et al</i> ^[17]	<i>n</i> = 12 age range: 18-55	Pilot study	(1) Criteria for schizophrenia or schizoaffective based on DSM-IV-R (SCID I) (2) At least 1 psychotic attack with hospitalization (3) Ongoing AHs (4) Use of oral and injectable antipsychotic	Presence of Positive Symptoms: SAPS Presence of Negative Symptoms: SANS Comorbid symptoms: BDI HDI	9-10 sessions of CBT upon the manual of Morrison, 2002, Goldberg, 2007) Pharmacological treatment: Oral and injectable antipsychotic medication	Difference between pre-treatment and post-treatment Treatment group: SAPS hallucination subscale score ($P = 0.027$) SAPS delusion subscale score ($P = 0.028$) SANS total scored ($P = 0.046$) KSQ ($P = n.s.$) BDI ($P = n.s.$) Control group: SAPS hallucination subscale score ($P = n.s.$) SAPS delusion subscale score ($P = n.s.$) SANS total scored ($P = n.s.$) BDI ($P = 0.043$) HDI ($P = n.s.$)	1-yr post-treatment follow-up
Hutton <i>et al</i> ^[18]	Single case, An 18-year-old man	Case report	Criteria for schizophrenia spectrum disorder based on DSM-IV Symptoms and psychosocial functioning: GAF; BPRS; Clinical questionnaire	Positive Symptoms: PSYRATS/CAARMS Beliefs about control of AHs: IVI	Brief CBT upon the mindfulness approach Pharmacological treatment: None	Pre-treatment: IVI score: 62 Post treatment: IVI score 2 The frequency and duration of AHs had reduced to zero	1, 3, 4, 9 mo post therapy
Dannahy <i>et al</i> ^[19]	<i>n</i> = 62 divided in nine groups	Pilot study	The individual had been experiencing treatment-resistant and subjectively distressing voices for at least the preceding	Primary outcome measure: Improve general psychosocial well-being (CORE-OM); Secondary measures:	Group person-based cognitive Therapy (PBCT) conducted over 8-12 sessions based upon the manual of Chadwick <i>et al</i> (2006) Pharmacological treatment: Standard psychiatric care	CORE-OM Total score: Post-group: 1.90 ^b (0.70) VOICE-DISTRESS Total score:	1 mo

	Mean age: 41.1 SD: 9.2	2 yr, with the voice- distress rated at 3 or greater on at least one of the two PSYRATS voice-distress items	Reduce distress and perceived voice- control; Evaluate the relationship with voice (VAY)	Group person-based cognitive Therapy (PBCT) conducted over 8-12 sessions based upon the manual of Chadwick <i>et al</i> (2006) Pharmacological treatment: Standard psychiatric care	Post-group: 3.57 ^b (0.83) VOICE-CONTROL total score: Post-group: 53.47 ^b (23.59) VAY Voice Dependence total score: Post group: 6.76 (5.69) VAY Voice Intrusiveness total score: Post group: 9.03 (4.32) VAY Voice Dominance total score: - Post group: 14.46 (6.37) VAY Hearer distance total score: Post group: 12.93 (5.93)	
Gottlieb <i>et al</i> ^[20]	<i>n</i> = 17 Pilot study Mean age: 40.10 SD: 13.63	(1) Criteria for schizophrenia, schizoaffective disorder, or psychosis, NOS based on DSM- IV (2) At least “moderate” level of AHs severity over the past week (BPRS Hallucinations item 4 or higher); (3) Between the ages of 18-65; (4) No exposure to CBTp within the past 3 yr (5) No current suicidal ideation or hospitalization within the past month (6) Taking a stable dose of an antipsychotic medication for at least one month; (7) No active substance abuse/ dependence (8) MMSE score \geq 24)	Primary outcomes: Reduce the frequency, intensity, loudness, associated distress, perceived degree of controllability of, and interference from AHs (PSYRATS) Secondary outcomes: Evaluate beliefs about AHs (BAVQ-R); Evaluate overall psychopathology (BPRS), and depression (BDI-II)	Web-based cognitive-behavioral therapy for AHs: - 10 session: - psychoeducational video tutorials - games - interactive exercises - social network to examine the coping strategies of other users. Pharmacological treatment: stable dose of antipsychotic medication for at least one month	Significant reductions from baseline to post- treatment in several measures of AHs and in overall psychopathology on the BPRS: PSYRATS AHs subscale total: <i>P</i> = 0.007 PSYRATS AHs Subscale: Voices location: <i>P</i> = 0.029 Voices intensity of negative statements: <i>P</i> = 0.049 PSYRATS delusions subscale total: <i>P</i> = 0.101 BPRS total score: <i>P</i> = 0.001 BPRS Subscale: BPRS Psychosis: <i>P</i> = 0.002 - BPRS Depression: <i>P</i> = 0.004 BPRS Activation: <i>P</i> = 0.001 BAVQ-R total score: <i>P</i> = 0.902 (n.s.) BDI-II-total score: <i>P</i> = 0.085 (n.s.)	None

^b*P* < 0.001. BPRS: Brief psychiatric rating scale; PSYRATS: Psychotic symptom rating scale; PANSS: The positive and negative syndrome scale for schizophrenia; SAI: The Schedule for the Assessment of Insight; SCID-I: Structured Clinical Interview for DSM; SAPS: Scale for the assessment of positive symptoms; SANS: Scale for the assessment of negative symptoms; BDI-II: The Beck Depression Inventory II; HDI: Hamilton depression inventory; CAARMS: Comprehensive Assessment of At-Risk Mental States; GAF: Global Assessment of functioning; IVI: Interpretation Voices of Inventory; CORE-OM: Clinical outcomes in routine evaluation-outcome measure; VAY: Voice and You; BAVQ-R: The Belief about Voices Questionnaire-Revised; MMSE: Mini Mental State Examination; AHs: Auditory hallucinations.

sidered in our review. Firstly, the role and the possible interference of antipsychotic medications with psychotherapy should be further assessed in the primary studies. Secondly, there is a discrepancy of study design and outcome measures between studies, which did not allow a quantitative analysis of the results. Thirdly, most studies are only preliminary and underpowered. Among strenghts, we have two RCTs with 241 individuals randomized in total and both of them conclude that CBT may be an alternative for individuals with schizophrenia who experience AHs despite antipsychotic treatment.

Overall, several CBT models were tested in the studies included. Apart TORCH and CTCH, Mindfulness approach, PBCT or web-based CBT were used.

We propose that further RCTs are needed. In particular, based on our findings, future studies should be drawn with reference to validated theoretical framework that predicts individuals' compliance with voices and the associated distress, rather than the presence of psychotic symptoms *per se*. This validated theoretical framework should also consider the role of negative symptoms in predicting the effectiveness of the intervention on AHs.

Finally, due to the efficacy and high tolerability and acceptability of RCT-studies, we believe that the treatment with CBT should be integrated into standard care for AHs, taking into account that individuals with AHs and command hallucinations especially, and more in general with psychotic disorders, show often a poor compliance to pharmacological treatments.

COMMENTS

Backgrounds

In schizophrenia, auditory hallucinations (AHs) occur with a high frequency ranging between 40% and 80%. AHs, especially command hallucinations, are also associated with an increased risk of harmful or dangerous actions and are some of the most prominent of the pharmacological treatment-resistant symptoms. Consequently, there is a growing interest on psychological interventions. The aim of this review is to provide an updated of recent findings about efficacy of cognitive-behavior therapy (CBT) in reduction of command hallucinations.

Research frontiers

Previous research suggests CBT to be a useful treatment for reducing compliance with harmful command hallucinations. Specifically, CBT applied to the treatment of command hallucinations does not focus on reducing the experience of voices, but on reducing the perceived power of voices to harm the individual and to motivate compliance. Indeed, the main rationale is that by challenging key beliefs about the power of commanding voices, the patients would show a lower level of compliance and appeasement behavior and an increase in resistance to the same voices.

Innovations and breakthroughs

In literature evidence on efficacy of CBT in reduction of command hallucinations are still few. Only in recent years CBT models specifically targeted on AHs were developed. Studies published in the last five years were critically reviewed by the authors who make a comparison between the current existing CBT models for AHs and data to support each.

Applications

This review suggests that the treatment with CBT should be integrated into standard care for AHs, taking into account that individuals with AHs and command hallucinations especially show often a poor compliance to

pharmacological treatments.

Terminology

AHs can be defined as sensory experiences in auditory modality, occurring in the absence of a corresponding external stimulation whilst in a fully conscious state, and resembling veridical perceptions. CBT is a psychosocial intervention that is the most widely used evidence-based practice for treating mental disorders. CBT focuses on the development of personal coping strategies that target solving current symptoms and changing unhelpful patterns in cognitions (e.g., thoughts, beliefs, and attitudes), behaviors, and emotional regulation.

Peer-review

The topic is interesting, informative and useful for a clinician. The paper is clearly written.

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Understanding the paranoid psychosis of James: Use of the repertory grid technique for case conceptualization

Helena García-Mieres, Susana Ochoa, Marta Salla, Raquel López-Carrilero, Guillem Feixas

Helena García-Mieres, Susana Ochoa, Raquel López-Carrilero, Development Unit of Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, 08330 Barcelona, Spain

Helena García-Mieres, Marta Salla, Guillem Feixas, Department of Personality, Assessment and Psychological Treatments, Faculty of Psychology, University of Barcelona, 08035 Barcelona, Spain

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Correspondence to: Helena García-Mieres, MD, Department of Personality, Assessment and Psychological Treatments, Faculty of Psychology, University of Barcelona, Passeig de Valld'Hebrón

171, 08035 Barcelona, Spain. helenagarcia@ub.edu
Telephone: +34-93-3125100

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Abstract

In this paper we illustrate the potential of the repertory grid technique as an instrument for case formulation and understanding of the personal perception and meanings of people with a diagnosis of psychotic disorders. For this purpose, the case of James is presented: A young man diagnosed with schizophrenia and personality disorder, with severe persecutory delusions and other positive symptoms that have not responded to antipsychotic medication, as well with depressive symptomatology. His case was selected because of the way his symptoms are reflected in his personal perception of self and others, including his main persecutory figure, in the different measures that result from the analysis of his repertory grid. Some key clinical hypotheses and possible targets for therapy are discussed.

Key words: Persecutory delusions; Personal constructs; Schizophrenia; Repertory grid technique; Case formulation

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Core tip: The repertory grid measures indicated that the patient's meaning system was strongly articulated around a very negative view of self, and by symptomatic constructs related to fear, anxiety, sense of loneliness, and perceived aggressiveness in others. Furthermore, constructs related

to hostility dominated his perception of his persecutory figure and also of his parental figures. Based on this appraisal, the case formulation was suggested as a focus for psychotherapy to enhance his self-esteem and deal with family conflicts.

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INTRODUCTION

Psychotic disorders are complex conditions with a wide range of clinical symptoms. One of the central psychotic experiences is persecutory delusions, which are present in over 70% of early psychotic patients^[1], and which are accompanied by many clinically important symptoms such as anxiety and depression^[2]. Despite the common administration of antipsychotic medication, more than half of patients still have persistent positive symptoms that interfere with their daily functioning^[3,4]. In this context of drug-resistant cases, the use of psychotherapy, with cognitive-behavioral therapy (CBT) the most widely studied, is of increasing interest and importance, and is recommended either as an adjuvant or even an alternative treatment. To this effect, a recent meta-analysis demonstrated the efficacy of CBT in reducing symptom severity in these cases^[5]. In addition, one randomized controlled trial demonstrated similar results for cases not taking antipsychotic drugs^[6].

In cognitive models of psychosis and other mental disorders, an essential element for planning psychological therapy is the use of case conceptualization. From a person-based approach to psychosis^[7], paranoid psychotic symptoms cannot be studied in isolation because the distress experienced by these patients is not a direct consequence of psychotic symptoms. Rather, it is mediated by the meaning patients ascribe to them. With this approach more attention is paid to personal meanings than to symptoms when developing each patient's case conceptualization.

From a more general perspective, this focus on the subjective construction of the symptoms and problems experienced by the client was previously highlighted by personal construct theory (PCT)^[8]. This theory sees psychological activity as a subjective meaning-making process for the events people encounter in life^[9]. Thus, the person's cognitive system is formed by a complex network of bipolar dimensions of meaning, interdependent and hierarchically organized, denominated personal constructs (as opposed to theoretical constructs), such as "friendly-hostile". This system of constructs is used to interpret the person's

experience and to organize his or her actions.

In PCT, case conceptualization is understood as a way to see the world through the patient's eyes^[10]. To study personal views of the world, the most widely used method is the Repertory grid technique (RGT). It allows us to access the idiosyncratic meanings of the person about self and others, in his or her interpersonal world. Also, it yields some measures regarding the cognitive structure of the subject. Both sources of information have interesting clinical implications: They allow the therapist to formulate clinical hypotheses and identify possible targets for therapy^[11]. In addition, in a review by Freeman *et al.*^[2], perceptions of self and others have been linked to the development and maintenance of persecutory delusions, as well as being proposed as important targets for therapy.

Despite its possibilities as an instrument for the detailed exploration of the individual's belief system to be employed for case conceptualization, little use is made of the RGT in common psychiatric practice and psychotherapy, and no recent studies have been found involving cases with paranoid psychotic symptoms. This is even more surprising given the line of research led by Bannister in the 1960s and 1970s^[12] (although they were using another type of grid with provided rather than elicited personal constructs).

In this article, we present the possibilities for the application of the RGT toward the understanding of paranoid psychosis, showing the sense that symptoms can have for the person with schizophrenia. To this end, we have selected the case of James (fictitious name), a man diagnosed with schizophrenia and personality disorder, who presents severe persecutory delusions that have not improved with medication. He was one of the first patients to participate in a Spanish clinical trial based in Metacognitive Training (MCT+) for psychosis by Moritz *et al.*^[13]; in the initial evaluation, a battery of instruments was administered, including instruments that assess psychopathology and the RGT. The main indices obtained from the RGT are described and used to understand his personal meanings about himself and others at the delicate moment when his persecutory delusions are very intrusive. Possible clinical hypotheses derived from this analysis, and targets for the therapeutic process of James, are discussed.

CASE REPORT

James is a Spanish man 25 years of age who lives with his parents and is unable to study or work although he completed high school studies. He reports a relationship with a girl, Ana, at the current moment, who lives in a distant part of Spain. He refers to her as his girlfriend but their only contact has been by internet and telephone.

He has a diagnosis of schizophrenia and personality disorder not otherwise specified. The disturbances started 2 years ago, and the last psychotic episode occurred 10 mo before the present assessment, for which he had

Table 1 Assessment of psychopathology

	Raw scores
PANSS positive	23
P1: Delusions	6
P6: Suspiciousness/persecution	6
PANSS negative	17
PANSS general psychopathology	37
PSYRATS delusions	21
PSYRATS hallucinations	33
BDI-II	32

to be hospitalized. Since this last hospitalization, he has been experiencing persecutory delusions and auditory hallucinations that have not been reduced, despite taking antipsychotic medication, olanzapine 20 mg/d and aripiprazole 15 mg/d, last one administered monthly as depo.

As relevant background to the psychotic symptoms, James had a relationship two years ago with another girl, Mary, which lasted eighteen months. During the assessment, he told us that it was a good relationship most of the time. He also stressed that both of them felt the lack of support from other people ("We were both alone, we had in common that we had no one else, and we relied on each other"). At the end of the relationship, James uploaded a song on line in which he talked about Mary and their relationship, and he also made comments on social networks about the girl, resulting in conflict with Mary and her family and friends, and turning all of them against him. In this context, James developed intense fears of the girl and her relatives, which culminated in a psychotic crisis experienced 10 mo before this assessment.

Since then, James says that he lives in fear every day, convinced that his ex-girlfriend and her relatives seek to harm or even kill him, even when he recognizes not having had any contact with them for months. He has a general feeling of being threatened and persecuted, being very alert to signs in the environment, which makes him afraid to go outside. His psychotic experiences seem to increase at night when he hears noises at his window. He is afraid that they could be caused by his persecutors, so most nights he has problems falling asleep. From time to time, he also presents auditory hallucinations of which he is unaware, hearing voices on the street, which always have threatening content, referring to hurting or killing him.

Regarding the relationship with his parents, he says that the family atmosphere is not good, there having been severe conflicts since adolescence, when James had episodes of aggression toward his parents. James maintains a discourse greatly focused on his paranoid ideas, and when he talks about his fears at home he says he feels unheard and slighted, and that he has received aggressive and dismissive responses. He experiences family life as hostile, and describes having suffered episodes of aggression from his father not only in the past but also recently. He also notes that since

the psychotic crisis, he has lost the few friends he had, feeling very alone and with little support.

Assessment of psychopathology

In the Metacognitive Training study in which James is enrolled, a battery of instruments was administered in two sessions before the beginning of the therapy.

The instruments assessing psychopathology, shown in Table 1, were administered in the first session. James's scores on the Positive and Negative Syndrome Scale (PANSS), Spanish adaptation of Peralta *et al.*^[14], and the Psychotic Symptom Rating Scales (PSYRATS), Spanish adaptation by González *et al.*^[15], showed a high severity for the positive symptoms. In addition, on PANSS items related to passive social withdrawal and active social avoidance the scores indicate moderate-severe social isolation, which is associated with his suspiciousness and persecutory fears. He also presented severe depressive symptomatology, as measured with the Beck Depression Inventory (BDI-II), Spanish adaptation by Sanz, Perdigón *et al.*^[16].

The severity of his psychopathology could also be observed during the second interview, when the repertory grid was administered. He was very cooperative and talkative, but he was also invaded by his delusions and made repeated verbalizations about them and the suffering that they brought him ("I'm scared. Before coming here I heard a man in a bar talking about killing me").

The administration of the repertory grid technique

The RGT is a structured interview exploring the patient's personal meanings. The first phase is the selection of elements, which represent a sample of the most significant people for the patient. In the case of James, 17 elements were chosen. Four of them were provided by the clinician according to their possible clinical implications: "self now", "ideal self" (which represents how he would like to be), "self before the psychotic crisis", and the "non-grata person", which represents a person he does not like (for James, this was his ex-girlfriend, his main persecutory figure). The remaining elements, elicited by James, were his parents, six members of the extended family who live far away but for whom he felt much appreciation (maternal grandparents, two uncles, and two cousins), two good friends from the time before the psychotic crisis, Ana, identified by him as his current partner, and a friend of his partner's with whom he often talks. The selected items are recorded in the upper part of the protocol of the grid (Figure 1) defining the columns, the first column for the "self now" and the last for the "ideal self".

In the second phase, constructs are not provided by the clinician (like items in nomothetic research); rather, they are elicited directly from the person evaluated as a way to express his or her personal meanings. Personal constructs are elicited using the dyadic method, which consists of asking the subject about similarities and then differences in each pair of elements in terms of their

Date :		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Name: James		Self	Father	Mother	Grand-	Grand-	Aunt	Uncle	Cousin	Cousin	Friend	Friend	Current	Friend	Self-	Mary	Ideal
Grid number: PRE-THERAPY		now			father	mother			-1	-2	-1	-2	partner	-3	before		self
1. Harsh	1. Tolerant	3	2	3	7	7	6	7	5	6	6	6	7	7	7	2	7
2. Worrier	2. Careless	2	5	1	1	1	1	1	1	2	7	2	1	1	1	6	5
3. Attentive	3. Non-attentive	1	3	3	1	1	1	3	2	5	3	3	1	1	7	2	1
4. Calm	4. Nervous	7	5	7	1	1	2	5	5	5	2	1	1	1	6	6	1
5. Argumentative	5. Assertive	6	1	1	7	7	7	3	3	3	5	7	7	7	2	2	7
6. Empathetic	6. Egocentric	4	6	2	1	1	1	1	1	5	4	2	1	1	1	2	1
7. Friendly	7. Unfriendly	4	5	5	1	1	1	1	1	2	2	1	1	1	6	2	1
8. Hysterical	8. Relaxed	4	3	2	7	7	6	6	3	3	5	7	7	7	1	6	6
9. Tidy	9. Untidy	6	1	3	1	1	1	1	1	5	2	2	1	2	7	1	1
10. Happy	10. Sad	5	3	3	1	1	1	1	2	1	2	1	1	1	5	5	1
11. Funny	11. Boring	5	3	2	2	1	1	6	6	2	2	2	2	5	2	2	1
12. Capable of loving	12. Incapable of loving	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1
13. Fighter	13. Coward	7	1	1	1	1	1	1	1	1	3	1	1	1	7	3	1
14. Generous	14. Mean	1	3	3	1	1	1	1	1	1	3	3	1	1	5	5	1
15. Respects-family	15. Detached	6	1	1	1	1	1	1	1	1	1	1	1	1	6	1	1
16. Tires easily	16. Even-tempered	3	1	1	3	7	6	5	3	3	3	7	7	7	1	3	7
17. Altruist	17. Selfish	4	2	1	1	1	1	1	1	1	5	1	1	1	6	5	2
18. Goodperson	18. Badperson	2	2	1	1	1	1	1	1	1	2	1	1	1	6	2	1
19. Aggressive	19. Non-aggressive	6	2	2	6	7	7	7	7	7	3	7	7	7	2	3	7

1 Very 4 Middle point 5 Slightly
2 Quite 6 Quite
3 Slightly 7 Very

Figure 1 The repertory grid of James.

perceived personality or character traits. For example, the first question for James was: "In terms of their personality, in which way would you say your mother and father are alike?" James answered, "Both of them are harsh". This answer constitutes one pole of the first construct, so to obtain the other pole we asked "What would be the opposite of harsh for you?" and the answer was "tolerant". Thereby, the first construct ("harsh vs tolerant") was obtained and more similarity and difference questions were made for this and other pairs of elements. Elicited constructs were written down by the interviewer in the horizontal entries of the grid (Figure 1). After 19 constructs were obtained from James he started to repeat many constructs and showed fatigue. This is usually the time to end the elicitation process, which is known as the "saturation point".

The last phase is the rating of the elements. Each element is assigned a value in a seven-point Likert-type scale for each construct. Taking as an example the cited construct, 1 means "very harsh", 2 "quite harsh", 3 "slightly harsh", 4 "middle point", 5 "slightly tolerant", 6 "quite tolerant", and 7 "very tolerant".

Once the grid data matrix was filled (see James's grid in Figure 1), the administration process ended, and the data were ready to be analyzed qualitatively or quantitatively, for which there is software available, the GRIDCOR, with a manual to guide interpretation of the data^[17]. This software allows synthesizing and analyzing the great amount of information reflected in the grid using different

statistical methods.

Qualitative analysis of the repertory grid: How does James define himself in his own words?

From the data of the grid we may grasp the personal views of James about himself. To do so, we should focus on the constructs in which James rates himself with extreme values (scores of 1-2 and 6-7). Once obtained, we can narratively formulate his self-definition: "I am a very attentive, generous person, with a great capacity to love. But I'm also very nervous and very cowardly. I also consider myself quite a good person, concerned and assertive, but I am also quite messy and detached from my family, for whom I feel I have little respect".

We identify what James values about himself by finding congruent constructs in his grid. These are the constructs where the elements "self now" and "ideal self" are rated in the same pole, dimensions for which James does not wish any change. We found six such constructs: Attentive, assertive, capable of loving, generous, good person, and non-aggressive.

In contrast, discrepant constructs reveal aspects that James does not like about himself and which he would like to change. These are constructs in which the "ideal self" is rated at the opposite pole to the "self now". These discrepant constructs can be also expressed narratively: "Contrary to what I am (harsh, nervous, messy, sad, boring, cowardly, detached, and someone who tires easily), I would like to be tolerant, quiet, happy, funny, a

Table 2 Main significant measures of the repertory grid of James

Self-construing		Cognitive structure	
Self-ideal distance	0.5	PVAFF	54.11%
Self-others distance	0.4	Polarization	60.53%
Ideal-others distance	0.25		

fighter, and even-tempered”.

James’s congruent constructs are his “strong points”, those which might be central to his identity. Additionally, they may be seen as resources to validate and protect during the therapy process. However, James presents more discrepant than congruent constructs (eight to six), which could be a reflection of his current life moment in which he lives dominated by fears that stem from his persecutory delusions (“I would like to be a fighter, but I am a coward”), in a state of suffering and dissatisfaction with himself (“I would like to be happy and quiet, but instead I am sad and nervous”).

Main cognitive measures derived from the repertory grid technique

The GRIDCOR program outputs many quantitative measures that explain different aspects of how the patient construes himself and others, and also about the structure of his cognitive system. In the case of James, the most significant indices are shown in Table 2.

Construing self and others: Various aspects of the self can be evaluated taking the Euclidean distances between the elements “self now”, “ideal self” and “others” (an artificially generated element taking into account the average of the scores of all elements but “self now” and “ideal self”).

Self-ideal differentiation: The discrepancy in the ratings of the elements “self now” and “ideal self” can be considered as a measure of self-esteem, since by comparing these two elements the patient is evaluating himself on his own terms. High differentiation (*e.g.*, $d > 0.32$) is usually taken as indicative of low self-esteem. This is the case with James: He feels very far away from the way he would like to be and he therefore feels great dissatisfaction with himself and serious distress. This finding matches with the self-definition of James, with many discrepant constructs, and with the clinical observations made during the assessment process.

Self-others differentiation: The discrepancy between self and others becomes an index of how people see themselves as different (or similar) with respect to the other elements in the grid. This differentiation is considered as a measure of perceived social isolation. High differentiation (*e.g.*, $d > 0.35$) is an indication that a person experiences himself or herself as different from others, feeling that he or she shares few features with other people.

James presented high perceived social isolation,

viewing himself as very different, which is compatible with feeling like “the weird guy”, accompanied by notable feelings of loneliness.

Ideal-others differentiation: The discrepancy between the ideal self and others is considered as an index of the degree of perceived adequacy of others. High dissimilarity (*e.g.*, $d > 0.28$) means that the person has great dissatisfaction with others, while a lower score suggests a positive perception of them, as was the case with James. For a wider perspective, we can take into account his self-esteem, which is very low and negative, with others being closer to his ideal self than his current self; they are the “good ones”.

Self-construction profile: Five different self-construction profiles can be identified taking into account the joint interpretation of the three differentiation indices explored: Positivity, superiority, negativity, depressive isolation, and resentment profiles.

The conjoint interpretation of the three indices of James suggests a depressive isolation profile. This profile represents the combination of having a negative view of oneself, high perceived social isolation, and a positive perceived adequacy of others. This combination suggests that James views himself in negative terms and different from others, as if he was saying: “The others are great, but not me. I am the only one who is weird”. This profile usually applies to depressive patients and people with other psychiatric categories who manifest hopelessness, which is congruent with James’s depressive symptoms.

The structure of the cognitive system

Interpersonal cognitive differentiation: Interpersonal cognitive differentiation refers to the extent to which a person can construe his or her social experiences from different points of view. The more differentiated a cognitive structure is, the more meaningful dimensions are available to the person to perceive and understand the behavior of others.

Several measures have been proposed to assess cognitive differentiation, but the percentage of variance accounted for by the first factor (PVAFF) resulting from the factor analysis is the one with the strongest reputation. This percentage indicates the importance or weight of the main dimension of meaning. It is estimated that a low PVAFF indicates a differentiated cognitive structure, favoring multidimensional thinking and allowing other dimensions to play relevant roles in the way the subject construes, while a high PVAFF indicates low cognitive differentiation, with a tendency to one-dimensional thinking. James’s score indicates a cognitive structure with low differentiation, with one dimension which plays the main role for the construction of himself and the others.

Polarized thinking: Polarization refers to the extent to which a person construes reality in an extreme

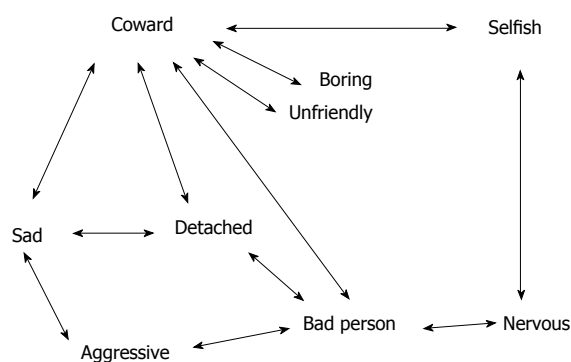


Figure 2 Main construct correlations for "coward".

way, and it is considered as a measure of cognitive rigidity. It is computed as the percentage of extreme scores in the grid. High percentages are indicative of a polarized structure. This score is very high in the case of James, suggesting a very rigid cognitive structure, with a tendency to construe himself and others in a dichotomous way.

Centrality of symptomatic constructs: The variance accounted for by each construct in the grid data matrix is calculated with Bannister's^[18] Intensity score, which is based on the strength of the correlations with the other constructs. Thus, those constructs with the highest intensity scores tend to be the ones with greater weight or importance in the cognitive system. When these constructs express aspects which can be considered as symptomatic, then potential difficulties for change in the therapeutic process may appear. For James, five constructs are the most intense or central to his cognitive system: "coward vs fighter", "aggressive vs non-aggressive", "unfriendly vs friendly", "tires easily vs even-tempered" and "nervous vs calm". Analyzing their content, most of these core constructs could be considered as symptomatic, reflecting his emotional experience of fear and anxiety, and his perception of threat in others, both in the context of the persecutory delusions. The construct "coward vs fighter" is central to the sense of identity of James. Additionally, it does have a very high percentage of polarization (87.50%). Checking his grid raw data matrix (Figure 1), we observe that he considers himself as the only element who is a "coward", while all the others are perceived as "fighters" (as he would like to be). Clinically, this construct might be related to the suffering and permanent sense of fear and alertness that invades his personal life.

To analyze the identity implications of this construct, the correlation matrix among constructs can be used to explore its personal meaning in the context of his cognitive system. In Figure 2, the network of constructs associated with the pole "coward" is represented. All the constructs that are associated with it have negative connotations. The construct pole "coward" is strongly associated, by this order, with the poles "detached" ($r =$

0.94), "boring" ($r = 0.90$), "selfish" ($r = 0.83$), "sad" ($r = 0.81$), "bad person" ($r = 0.79$) and "unfriendly" ($r = 0.61$). Therefore, this highly interrelated meaning configuration articulated around the core construct "coward vs fighter" helps us to understand how invalidating it must have been for James to experience intense fears (such as those caused by the perceived threat of others). We may infer here a massive invalidation of his most central aspirations (becoming "fighter", "funny", "altruist", "happy", a "good person", "friendly", and someone who "respects his family"). In PCT, this invalidation of core constructs is linked to intense negative emotions.

A graphic display of the main axes of construction:

The GRIDCOR program employs Correspondence Analysis, a multivariate statistical technique similar to principal component analysis, in order to simultaneously compute both constructs and elements expressed in the grid data matrix. It aims to represent the main dimensions of meaning employed by the subject in order to understand his interpersonal world. Each axis or dimension is composed of both elements and constructs with their corresponding loads (which varies across axes).

In the case of James, as mentioned before, the first factor explained 54.11% of variance while the second one accounted for 16.54%. Taken together, these two axes are responsible for 70.66% of the variance in the grid data. The GRIDCOR software yields a graph placing both axes orthogonally, creating a two-dimensional space, which allows us to get an approximate picture of how James perceives himself and others from his main dimensions of meaning (Figure 3). As explained before, each axis represents a dimension of meaning, comprising a particular combination of specific constructs and elements, which are arranged along the axis, being allocated the ones that account for major weight in each axis at the extremes, and around the central area the ones with less weight in that dimension of meaning. In this graph, the final allocation of both constructs and elements results from the combination of the dimensions of meaning of both axes, the first axis represented in the horizontal (abscissa) plane and the second axis in the vertical (ordinate). In this case, for instance, the extremes of the first axe are delimited by the elements "self before" and the "ideal self" or "current partner", whereas the extremes of the second axis are represented by "father" and "self now". The selected constructs and elements that appear in the graph account for the major weight in both axes, and, therefore, it represents the meanings that James gives the most importance to in his view of his interpersonal world, according to grid data. From the distribution of people and meanings in this graph we may derive three different groupings with which James categorizes and interprets his interpersonal world.

James's group, the lonely guy: Me and my "self before the crisis". According to his grid, James perceived

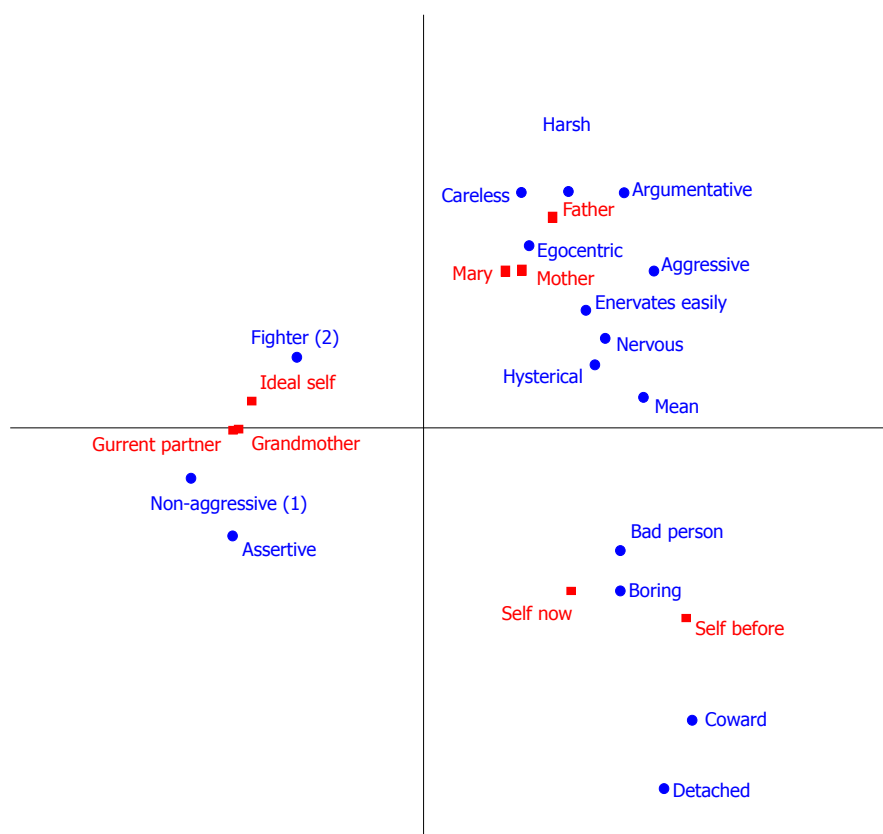


Figure 3 Graph output for the main axes of James. Note: (1) The construct poles “even-tempered”, “quiet” and “calm” are also allocated here; (2) The construct poles “happy”, “respects family” and “good person” are also allocated here.

his current and past selves in negative terms (“coward”, “detached”, and “boring”), different and far from other people, reflecting his experience of self-isolation. Looking at the direct ratings in the grid, the only notable difference is that his current self is now seen as quite a “good person” while the self before the crisis is rated as quite a “bad person”. This could be an important aspect to explore in the therapy process to understand the meanings of this change for James.

The group of the good ones: Where James wants to belong. The ideal self of James is situated in an opposite quadrant, with his current partner and his grandmother. Although they do not appear in the graph due to lack of space and lesser variance loading, most of the other elements are located there as well. All the constructs with positive connotations appear there; James would like to be a “fighter”, which would imply also being “happy” and “respectful of family”, as others are perceived. Another constellation of constructs in this area is related to a desired change in the anxiety of James: He would like to become “even-tempered”, “quiet” and “calm”, like the others.

The threatening group: The parents and the persecutory figure. In this group we find Mary, his ex-girlfriend, whom he identifies as one of his main persecutors. His parents, with whom he has had many severe conflicts and from whom he feels little support, are there as well. Unexpectedly, these three people are located very close to each other. It may be seen that James gives meaning to them mainly in terms of a constellation of constructs with hostile content (“harsh”,

“argumentative”, “aggressive”, and as people who “tire easily”).

DISCUSSION

In this article, the main objective was to illustrate how the RGT can provide clinicians with a systematic portrayal of the personal views of a patient with paranoid psychotic symptoms. This approximation might help in uncovering a patient’s personal meanings, and their relationship with symptoms, in order to enhance case formulation and identify therapy targets. We can also focus on the repertory grid indices found for James and contrast them with the current literature about psychosis. His self-definition and self-construction profile denote low self-esteem, with many negative evaluations about the self, which correspond to a set of discrepant constructs (“I am harsh, nervous, messy, sad, boring, a coward...”). Both low self-esteem and negative self-evaluations have been associated with the development and maintenance of positive symptoms^[19,20]. More specifically, paranoid delusions have been linked to reflections of specific negative evaluations about the self^[21]. Similarly, the high perceived social isolation reflected in James’s grid seems to be common in people with early psychosis, along with depressive symptoms^[22]. Effectively, depression is common in psychotic patients, and following acute psychosis it may be a psychological response to the apparently uncontrollable life event that psychosis episodes represent for patients^[23]. Furthermore, depression can be a contributing factor in

the maintenance of persecutory delusions^[24].

A first clinical hypotheses derived from these findings is that the negative self-concept and depressive isolation profile of James play a significant role in his paranoid symptoms. He would benefit from therapy having as a target the enhancement of his self-esteem, reconstructing his discrepant constructs and protecting his congruent constructs from further invalidation, which could be expected to have a positive effect on his paranoid delusions as well as on his depressive symptoms. Another important target would be ways to help James feel integrated with others, which might also have a positive effect on his depressive symptomatology.

At this point some of the results derived from the analysis of the relationships among James's personal constructs must be taken into consideration. First, we have to remember that some of these discrepant and symptomatic constructs for James constitute part of his identity, and being a "coward" and "detached" has many negative implications in his cognitive system. From the perspective of PCT, to the extent that symptomatic constructs define the patient's self-identity we may foresee difficulties for change in therapy. On the other hand, it may be observed that all the positive construct poles are located together, close to the ideal self and far from the self now (which could be expressed like this: "If only I was fighter and respectful with family... everything would change"). For James, the change in one construct implies a change in many others, which renders the objective of change too large and difficult to achieve, as it becomes overly idealized and magnified.

Another feature of James's grid is the low differentiation and high polarization of his construct system. Actually, cognitive rigidity has been associated with delusions^[25,26] and with severity of the course of depression^[27-29]. Polarization could be considered as a measure of cognitive rigidity as it reflects dichotomous thinking, the "all-or-nothing" style^[17]. Also, the high PVAFF of James's grid indicates a tendency to one-dimensional thinking. Therefore, reducing the tendency to making extreme judgments and increasing his cognitive differentiation would be reasonable targets for his therapeutic process, which is one of the lines of the MCT + work, introducing doubt into reasoning^[30].

Another issue of the case conceptualization of James is the perceived relationship of his parents and his main persecutory figure. Constructs related to malevolence and hostile content have been associated with the perceived main persecutors in paranoid psychotic patients in a repertory grid study^[31]. Within the constructs employed by James, those with a hostile intent reflect both his paranoid thoughts (about his ex-girlfriend) and the bad atmosphere experienced at home. These constructs employed by James might be related with the tradition of Expressed Emotion, conceptualized for the first time by Brown *et al.*^[32]. We do not have any direct assessment of James's parents but his perception of them is based on hostility and criticism, which has been

related with higher severity of positive symptoms^[33] and risk for relapse in early psychosis populations^[34]. Many studies have demonstrated the efficacy and importance of working with families with high expressed emotion in psychosis^[35], so this would be another therapy focus.

We may also focus on the perceived similarity within the hostility constructs for the parents and the persecutory figure. Is there any possible explanation for this phenomenon? From a constructivist perspective, Gara^[36] developed a set-theory model of person perception. Following this model, there are some main people in an individual's life, called "supersets", who provide the perceptual categories for the construing of other people, so the personality characteristics attributed to them would probably be first observed in these supersets. Usually supersets are found to be significant people in the subject's life, very often his or her parental figures. Following this line of thought, it would be possible to consider as a clinical hypotheses that James's supersets would be his mother and his father, and that he might be construing his persecutory figure in line with them in terms of hostility constructs, probably developed within the context of many years of conflict at home. This hypothesis reinforces the previous suggestion of including a family intervention in James's therapeutic process. The intervention would focus on increasing the understanding of James disorder for the parents and on easing their supposedly conflictive family interactions. According to this clinical hypothesis, these improvements should facilitate changes in the tendency of James to perceive others in terms of threat and hostility, thereby also changing the structure of these core constructs for his identity and becoming less central. Thus, the intervention would also be expected to have a positive effect on his positive symptoms.

In conclusion, the use of the RGT in exploring the case of James has made it possible to understand how he construes his personal world at such a delicate moment, when his persecutory delusions are so severe. Furthermore, some possible key clinical hypotheses have been constructed with this information, signaling important areas such as self-concept and family relationships, as possible targets for therapy. However, the measures and clinical hypotheses derived from the repertory grid analysis must not be the only ones to consider in the implementation of therapy. RGT furnishes detailed information about the self and personal identity of patients, which is only one factor to consider in case formulation and therapy planning. The RGT is an assessment technique that provides the clinician with relevant systematic information about the personal meanings, self-concept, and cognitive structure of patients, which can also be applied to psychotic patients. This instrument has already demonstrated its utility in case formulation and research in psychology and psychotherapy^[37,38], but its clinical and research potential for psychotic disorders has not been sufficiently exploited to date.

COMMENTS

Case characteristics

A 25-year-old man with severe persecutory delusions and hallucinations with threatening content without improvement following antipsychotic medication.

Clinical diagnosis

Psychiatric diagnosis of schizophrenia and personality disorder not otherwise specified. The onset of the disorder was 2 years ago.

Treatment

Olanzapine 20 mg/d and Aripiprazole 400 mg/mo as depo. The case is going to start metacognitive individual training for psychosis.

Experiences and lessons

The authors highlight the possibilities of the repertory grid technique to understand the personal meanings behind the symptoms and to identify targets for psychotherapy.

Peer-review

The article is very good as of its scientific.

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