

# World Journal of *Psychiatry*

*World J Psychiatr* 2013 September 22; 3(3): 50-84





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**NAME OF JOURNAL**  
*World Journal of Psychiatry*

**ISSN**  
ISSN 2220-3206 (online)

**LAUNCH DATE**  
December 31, 2011

**FREQUENCY**  
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Telephone: +852-3177-9906  
E-mail: [bpgooffice@wjgnet.com](mailto:bpgooffice@wjgnet.com)  
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**PUBLICATION DATE**  
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## Differential diagnosis of obsessive-compulsive symptoms from delusions in schizophrenia: A phenomenological approach

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Received: April 17, 2013 Revised: May 31, 2013

Accepted: June 8, 2013

Published online: September 22, 2013

### Abstract

Several studies suggest increased prevalence-rates of obsessive-compulsive symptoms (OCS) and even of obsessive-compulsive disorder (OCD) in patients with schizophrenic disorders. Moreover, it has been recently proposed the existence of a distinct diagnostic subgroup of schizo-obsessive disorder. However, the further investigation of the OCS or OCD-schizophrenia diagnostic comorbidity presupposes the accurate clinical differential diagnosis of obsessions and compulsions from delusions and repetitive delusional behaviours, respectively. In turn, this could be facilitated by a careful comparative examination of the phenomenological features of typical obsessions/compulsions and delusions/repetitive delusional behaviours, respectively. This

was precisely the primary aim of the present investigation. Our examination included seven features of obsessions/delusions (source of origin and sense of ownership of the thought, conviction, consistency with one's belief-system, awareness of its inaccuracy, awareness of its symptomatic nature, resistance, and emotional impact) and five features of repetitive behaviours (aim of repetitive behaviours, awareness of their inappropriateness, awareness of their symptomatic nature, and their immediate effect on underlying thought, and their emotional impact). Several of these clinical features, if properly and empathically investigated, can help discriminate obsessions and compulsive rituals from delusions and delusional repetitive behaviours, respectively, in patients with schizophrenic disorders. We comment on the results of our examination as well as on those of another recent similar investigation. Moreover, we also address several still controversial issues, such as the nature of insight, the diagnostic status of poor insight in OCD, the conceptualization and differential diagnosis of compulsions from other categories of repetitive behaviours, as well as the diagnostic weight assigned to compulsions in contemporary psychiatric diagnostic systems. We stress the importance of the feature of mental reflexivity for understanding the nature of insight and the ambiguous diagnostic status of poor insight in OCD which may be either a marker of the chronicity of obsessions, or a marker of their delusional quality. Furthermore, we criticize two major shortcomings of contemporary psychiatric diagnostic systems (DSM-IV, DSM-V, ICD-10) in their criteria or guidelines for the diagnosis of OCD or OCS: first, the diagnostic parity between obsessions and compulsions and, second, the inadequate conceptualization of compulsions. We argue that these shortcomings might artificially inflate the clinical prevalence of OC symptoms in the course of schizophrenic disorders. Still, contrary to a recent proposal, we do not exclude on purely a priori grounds the possibility of a concurrence of genuine obsessions along with delu-



sions in patients with schizophrenia.

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**Key words:** Schizophrenia; Obsessive-compulsive symptoms; Obsessions; Compulsions; Delusions; Clinical features; Phenomenological approach; Differential diagnosis

**Core tip:** Obsessive-compulsive symptoms are commonly diagnosed in patients with schizophrenia and a distinct diagnostic sub-group of schizo-obsessive schizophrenia has been proposed. However, further research presupposes the accurate differential diagnosis of obsessions from delusions and of compulsions from repetitive behaviours motivated by delusions. We provide here a comparative examination of twelve clinical features of typical obsessions and delusions and, correlatively, of compulsions and delusional repetitive behaviours. We also discuss several still open or controversial issues, such as the nature of insight, the diagnostic status of poor insight into obsessions, the conceptualization of compulsions, as well as the diagnostic weight accorded to them.

Oulis P, Konstantakopoulos G, Lykouras L, Michalopoulou PG. Differential diagnosis of obsessive-compulsive symptoms from delusions in schizophrenia: A phenomenological approach. *World J Psychiatr* 2013; 3(3): 50-56 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v3/i3/50.htm> DOI: <http://dx.doi.org/10.5498/wjp.v3.i3.50>

## INTRODUCTION

Obsessive-compulsive disorder (OCD) or obsessive-compulsive symptoms (OCS) are commonly diagnosed in patients with schizophrenic disorders, with weighted average rates of 12.6% and 25%, respectively (see for recent reviews<sup>[1,2]</sup>). These high prevalence-rates contrast with the much lower rates reported in the past, when, under the dominant influence of Freudian psychoanalysis, OCS or even OCD were considered as clinical expressions of defence mechanisms against psychosis. In turn, contemporary epidemiological findings led to a wealth of studies investigating the etiological, clinical and therapeutic significance of obsessive-compulsive symptoms in schizophrenia. In a recent review of these studies, Poyurovsky and co-workers formulated explicit diagnostic criteria for a distinct clinical sub-group of schizophrenia, namely “schizo-obsessive” psychotic disorder<sup>[3]</sup>. However, they acknowledged that “the definition of obsessions and compulsions in the nosological context of schizophrenia and the differential diagnosis distinguishing these symptoms from delusions and delusionally motivated behaviours are essential for the study of schizo-obsessive schizophrenia”<sup>[3]</sup>. Accordingly, our aim in this paper is to examine in a comparative manner the relevant clinical phenomenological features involved in the differential

diagnosis between obsessions and delusions, as well as between compulsions driven by obsessions and repetitive behaviours driven by delusions in patients with schizophrenic disorders. Moreover, we also deal with the related issues of the nature of insight, the diagnostic status of poor insight, the conceptualization of compulsions and the diagnostic weight accorded to them in current psychiatric diagnostic systems. Finally, we stress the relevance of these issues to the investigation of OCS symptoms in the course of schizophrenia.

## CLINICAL FEATURES OF OBSESSIONS/COMPULSIONS VERSUS DELUSIONS/DELUSIONAL BEHAVIOURS

According to the canonical definition provided in the DSM-IV, delusions are false beliefs based on incorrect inference about external reality that are firmly sustained despite what almost everyone else believes and despite what constitutes incontrovertible evidence to the contrary. Likewise, obsessions are defined as recurrent and persistent thoughts, impulses or images that are experienced as intrusive and inappropriate and that cause marked anxiety or distress<sup>[4]</sup>. These definitions imply a major difference between delusions and obsessions. On the one hand, delusions are beliefs, *i.e.*, thoughts which patients entertain and to which they give their full assent as being true. On the other hand, obsessions are thoughts, images or impulses invading patients’ consciousness, without however being believed by them as true. In other words, obsessions are not, at least typically, beliefs. To be sure, patients’ attitude of pathological doubt towards their obsessions renders them apprehensive and makes them behave as if the content of their obsessions might come true. Thus, obsessions of contamination lead to compulsive rituals of hand-washing, and obsessions of doubt lead to compulsive checking rituals. However, patients’ insight into the excessiveness and unreasonableness of their obsessions is typically preserved.

Moreover, the definition of delusions implies that delusional beliefs are recognized by psychotic patients as products of their own mental activity, *i.e.*, as self-generated and self-owned beliefs or inferences, with the sole exception of delusions of inserted thoughts into their minds by alien agents. Likewise, the definition of obsessions states that they are invariably recognized by patients as products of their own mental activity. Thus, the features of source of origin and self-ownership fail to discriminate delusions from obsessions. Furthermore, the definition of delusions implies that, at least at the height of a psychotic episode, they are invariably held with firm conviction about their accuracy. Patients consider their delusions as fully reasonable to entertain and even as self-evident. As a result, they see no reason to entertain doubts about their validity, let alone to oppose or resist them. This holds even for delusions of thought-insertion and, more generally, for delusional explanations of other

primary psychotic experiences such as hallucinations. By contrast, obsessions, as intrusive thoughts, images or impulses, are experienced as excessive, unreasonable and thus distressful. The features of intrusiveness, inappropriateness and distress of obsessions, jointly, constitute their “ego-dystonicity”. Whereas patients conceive of their delusions as totally justified true beliefs, their obsessive counterparts realize immediately that their obsessive thoughts, images or impulses are excessive and rationally unwarranted.

Delusional beliefs are typically integrated into patients’ total belief-system. This integration may require the revision of some of their remaining beliefs in order to preserve their systemic coherence. Moreover, delusions are expressed in patients’ attitudes and possibly their manifest behaviour as well. For example, patients become suspicious towards their presumed persecutors, or, alternatively, they may try to avoid or challenge them. However, patients may not express their delusions in their overt behaviour as attested by the well-known phenomenon of “double book-keeping”. Be that as it may, patients experiencing typical obsessions try to drive them out from their consciousness, albeit unsuccessfully. Delusions of the most common thematic content, namely delusions of persecution, are also accompanied by anxiety and distress. However, deluded patients’ distress stems from their firm conviction that they are mortally threatened by their persecutors, against which they have to defend themselves. Their persecutory delusions are never questioned or resisted against. By contrast, patients with obsessions experience great distress and anxiety, owing to their “ego-dystonicity” and the failed efforts to repress them. The primarily internal source of anxiety and distress in obsessions contrasts with the merely external source of anxiety and distress that delusions might bring about. At any rate, the mere experience of distress fails to discriminate obsessions from delusions. Only the precise identification of its internal or external source of origin can help in this respect<sup>[5]</sup>.

Compulsions, according to the DSM-IV-TR<sup>[4]</sup>, are defined as repetitive behaviours or mental acts that the patient feels driven to perform in response to an obsession or according to rules that must be applied rigidly. It is often clinically difficult, especially in chronic OCD or OCS, to trace patients’ compulsions to underlying obsessions. Patients report that they perform their compulsive rituals because they “inexplicably feel” that they “have to”. In such cases, an accurate history of the initial stage of patients’ symptoms is mandatory. Compulsions aim at neutralizing intrusive thoughts, mental images or feared impulses, which are invariably experienced as unwanted and anxiety-generating. Delusions also may lead to the performance of repetitive acts. For example, a patient with the bizarre delusion that the world will end soon unless he/she repeatedly washes his/her hands, engages in this repetitive behaviour, or, another patient with delusions of persecution may check repeatedly whether her persecutors are after him/her. Thus, repetitive delusional

behaviours in patients with schizophrenia originate from their delusional beliefs and are congruent with them. Compulsions are behaviours recognized as lacking rational justification, whereas repetitive delusional behaviours are deemed fully justified. The recognized irrationality of compulsions may even generate further distress and anxiety. By contrast, repetitive delusional behaviours, by themselves, do not increase distress or anxiety. Compulsions make obsessive thoughts temporarily less intrusive and thus reduce somewhat patients’ internally generated distress. By contrast, lacking the feature of intrusiveness, repetitive delusional behaviours exhibited by patients with schizophrenia do not affect patients’ possible concomitant anxiety or distress. Table 1 summarizes the previous contrasts.

## COMMENTARY

We provided in the foregoing a comparative examination of the major clinical phenomenological features involved in the differential diagnosis of obsessions and compulsions from delusions and repetitive delusional behaviours, respectively. This comparative examination could facilitate the differential diagnosis of obsessions from delusions in the course of schizophrenia. Both obsessions and delusions are typically recognized as originating in patients’ own mind, with the exception of inserted or made-thoughts. However, typical delusions are firmly held beliefs, usually integrated into patients’ overall belief system. As a result, they are never resisted against and are not experienced as distressful. By contrast, typical obsessions are unwanted excessive and unreasonable thoughts, images or impulses, experienced as distressful. As a result, obsessions are promptly resisted against and the failed attempts to resist them generate further distress and anxiety. Furthermore, compulsive rituals aim to neutralize patients’ underlying obsessions, by contrast to repetitive delusional behaviours which lack completely this feature. These differences are also reflected in patients’ differential appraisal of the appropriateness of their repetitive behaviours, as well as in the differential impact of the latter on patients’ beliefs and emotional state.

The foregoing considerations are consistent with those of another recent comparative investigation, whereby the clinical features of lower levels of conviction and fixity and greater levels of fluctuation, resistance and insight were proposed as discriminating obsessions from delusions<sup>[6]</sup>. More precisely, the authors of this study distinguished the following six features of abnormal beliefs: (1) conviction: degree to which the person is convinced that his/her belief is true; (2) fixity: un-corrigibility or stability of the belief when the person is presented with recalcitrant evidence; (3) fluctuation: spontaneous changes in the level of conviction, that is, when the person is not being presented with evidence contrary to his/her belief; (4) resistance: the effort the person makes to reject his/her belief; (5) awareness of the inaccuracy of belief: the degree to which the person is aware that his/her belief is

**Table 1 Clinical features of obsessions/compulsions versus delusions/delusional repetitive behaviours**

Clinical features	Obsessions/compulsions	Delusions/delusional repetitive behaviours
Source of origin and sense of ownership of the thought(s)	Internal origin, assumed ownership	Internal origin, assumed ownership (with the exception of passivity-experiences of thought-insertion)
Conviction	Absent, though patient fears that they might come true	Absolute
Consistency with one's belief-system	Inconsistent	Integrated into patients' belief-system
Awareness of inaccuracy	Recognized as excessive and unreasonable to hold	Recognized as totally justified or even as self-evident
Awareness of their symptomatic nature	Very strong or at least medium strong	Virtually absent
Resistance	Very strong though unsuccessful	None
Emotional impact	Experience of marked distress/anxiety as a joint effect of obsessions' intrusiveness, doubts that their contents may come true along with the failure to resist them successfully	Possible experience of distress and anxiety as an effect of one's conviction about incurred imminent dangers
Aim of repetitive behaviours	Temporary neutralization of intrusive thoughts, images or impulses	Harmonization of behaviour with delusional beliefs
Awareness of their inappropriateness	Recognized as inappropriate, excessive and unreasonable	Recognized as appropriate and even reasonable, given their motivating delusional beliefs
Awareness of their symptomatic nature	Strong	Virtually absent
Immediate effect of repetitive behaviours on thoughts	Behaviours make thoughts temporarily less intrusive	Behaviours per se do not affect underlying delusional beliefs
Emotional impact of repetitive behaviours	Temporarily distress-reducing, but eventually sources of further distress/anxiety	Behaviours per se do not affect level of distress or anxiety

inaccurate, unreasonable and/or senseless; and (6) ability to attribute the belief to an illness: the extent to which the person is able to acknowledge that his/her belief is due to OCD<sup>[6]</sup>.

Strictly speaking, these features apply only to delusions, since obsessions are not beliefs. Thus, their application to obsessions requires the substitution of "thoughts, images or impulses" for "beliefs": the features of conviction, fixity and fluctuation which qualify only beliefs cannot apply to obsessions. Instead of conviction, the distinguishing feature of obsessions is patients' pathological doubt that the content of their thoughts, images or impulses might come true, however with preserved insight into the excessiveness of their doubts. Besides, the same excessive doubt and even disbelief may also attach to the "correct" execution of their compulsive rituals. As a result, patients may not "believe their eyes" that their cleaning or checking rituals have been effectively completed.

## DIAGNOSTIC SIGNIFICANCE AND NATURE OF INSIGHT

According to the DSM-IV-TR diagnostic criteria of OCD<sup>[4]</sup>, the recognition that the obsessions or compulsions are excessive or unreasonable is by definition one of the distinguishing features of the disorder. However, DSM-IV-TR acknowledges also that insight into the unreasonableness of the obsessions or compulsions can vary from good to poor in the course of the disorder. Accordingly, a diagnostic specifier of OCD with good versus poor insight has been provided. The "poor insight" specifier introduces a dimensional approach to obsessions. This approach posits a continuum between

obsessions and delusions and has been adopted by several authors<sup>[7-9]</sup>. The continuum in question ranges from typical obsessions, through overvalued ideas, to typical delusions. However, the concept of overvalued ideas remains still imprecise. According to DSM-IV-TR, overvalued ideas are abnormal beliefs not held with clearly delusional conviction, but not ego-dystonic either<sup>[4]</sup>. Thus, overvalued ideas lack any positive characterization. This is the main reason why we have avoided the use of this concept in our comparative examination. At any rate, overvalued ideas, as beliefs, are much closer to delusions than to obsessions. This is not to deny that the features of conviction and ego-dystonicity may come in degrees. Typically, the strength of delusional conviction diminishes in the course of appropriate biological or psychological successful treatments. Moreover, according to DSM-IV-TR, OCD patients with preserved insight ("good insight") attempt initially to ignore or suppress their obsessions. This attempt usually results in mounting anxiety or distress, which patients try to reduce by compulsive rituals. However, in the course of OCD, after repeated failures to resist obsessions and/or compulsions, patients may give up any resistance to them. As a result, obsessions and/or compulsions are then incorporated into patients' daily routine<sup>[4]</sup>. We consider this feature as a marker of OCD chronicity. Moreover, the feature of lack of resistance to OCS has to be clearly distinguished from the feature of poor insight. Although poor insight may be also a marker of chronicity, when ever lacking from the very beginning of the illness, this feature should be considered as a strong diagnostic marker of delusionality.

A particularly valuable analysis of the precise nature of insight in OCD has been proposed by Jaspers<sup>[10]</sup> in

his classic textbook “General Psychopathology”. Jaspers’ analysis has been recently applied by German psychopathologist B r gy<sup>[11,12]</sup> to the problem of the differential diagnosis of obsessions from delusions. Following Jaspers, B r gy stressed the feature of reflexivity as the distinguishing feature of pure obsessions or “obsessions in the strict sense” from delusions and claimed that “obsessions in the strict sense” are impossible in the course of schizophrenia. More precisely, B r gy<sup>[11,12]</sup> argued that normal mental life is in principle reflective, in the sense that human subjects normally have the capacity to reflect on the experiential contents of their own consciousness (their thoughts, feelings, memories, volitions, motivations *etc.*). This capacity is fully preserved in patients with “pure” obsessions or obsessions “in the strict sense”: patients are aware of the intrusion of their obsessive thoughts, images or impulses into their consciousness. Thus, they experience a conflict between the content of their consciousness and its recognition as excessive and unreasonable in their reflective self-consciousness. Moreover, this conflict between patients’ “first order” obsessive thoughts, images or impulses and their “second order” assessment of them as “crazy” is the primary source of patients’ experienced anxiety and distress. This anxiety is even independent from the anxiety generated by the specific content of patients’ obsessions, *e.g.*, their fear of contamination by microbes. By contrast, the formation of delusional beliefs implies the, at least temporary, abolition of the capacity of critical reflection on the contents of one’s consciousness: patients entertain firmly their delusional beliefs without any awareness or critical reflection on their possible irrationality. To be sure, delusions of persecution may be also a source of anxiety and distress, however secondary to the perceived threats emanating from patients’ presumed persecutors. Thus, whereas “obsessions in the strict sense”, whenever experienced, are simultaneously evaluated as nonsensical, such evaluation of delusional experiences becomes possible, if at all, only retrospectively, after their (spontaneous or treatment-induced) remission. The preservation of the feature of reflexivity captures the core aspect of “insight”, that is, the awareness of having abnormal mental experiences or even symptoms of mental illness. By the same token, this capacity for mental reflexivity underlies normal “reality testing” the loss of which is the hallmark of psychotic disorders.

The same author has argued that obsessions in the “strict sense” - as defined by the reflective experience of their senselessness - are specific to obsessive-compulsive disorder and, as such, cannot occur in the course of schizophrenia<sup>[11,12]</sup>. The rationale of this radical thesis seems to be that the principle of mental reflexivity cannot simultaneously operate selectively on some contents (obsessions) of patients’ consciousness, but not on others (delusions). To be sure, several cases of *prima-facie* obsessions in patients with schizophrenia may prove delusional. Perhaps the smooth transition from obsessions to delusions is impossible, although this is still in need of

clinical corroboration. However, this does not exclude *a priori* the possibility of a sudden transformation of obsessions into delusions. At least one study suggests the real possibility of a reversible transition from obsessions to delusions<sup>[7]</sup>. Moreover, as already mentioned, numerous studies reported consistently elevated rates of OCS or even OCD in the course of schizophrenic disorders<sup>[1,2]</sup>. The crucial issue here is whether “obsessions in the strict sense” occur in schizophrenic patients only when in full remission from their delusions or also concurrently with them. If the former were the case, B r gy’s claim would be vindicated. By contrast, if active delusions were entertained along with the experience of genuine obsessions B r gy’s account would have to be revised. At any rate, only carefully designed clinical studies probing simultaneously patients’ levels of insight in both psychotic and OC symptoms could help address conclusively this issue. In the meantime, clinical experience suggests that obsessions may co-exist along with active delusions. After all, the principle of reflexivity is still operative in psychotic patients on the non-psychotic contents of their consciousness. Accordingly, the *a priori* exclusion of the very possibility of co-existence of obsessions in the strict sense along with delusions in patients with schizophrenic disorders seems clearly exaggerated. Relatedly, treatment of schizophrenia with atypical antipsychotics has been associated with the *de novo* formation of OCS<sup>[13]</sup>. However, with the possible exception of clozapine, this association might also be attributed to illness characteristics<sup>[14]</sup>.

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## ON THE DIAGNOSTIC WEIGHT AND CONCEPTUALIZATION OF COMPULSIONS

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A further major complication for the differential diagnosis of OC symptoms in the course of schizophrenia, also stressed by B r gy<sup>[11,12]</sup>, is the diagnostic parity accorded to obsessions and compulsions for the diagnosis of OCD or OCS in the diagnostic criteria and diagnostic guidelines of DSM-IV and ICD-10, respectively<sup>[4,15]</sup>. This diagnostic parity of obsessions and compulsions is also maintained in the new revision of the DSM, namely DSM-V ([dsm5.org](http://dsm5.org), Updated May 1, 2012, accessed November 6, 2012). The relevant passage in Criterion A reads thus: “Presence of obsessions, compulsions or both”. Thus, OCD may be diagnosed in patients with compulsions only, without obsessions. However, this contradicts DSM-IV claim that compulsions are motivated by underlying obsessions. Furthermore, compulsions can remain un-manifested in patients’ overt behaviour. These are the well-known covert compulsions whereby patients are engaged in further repetitive mental activities, such as, *e.g.*, counting or praying, in order to neutralize their primary obsessions. However, without underlying obsessions, the diagnosis of repetitive behaviours as compulsive is unwarranted: repetitive



behavioural patterns *per se* are diagnostically non-specific, since they may occur in various and quite heterogeneous psychopathological conditions, such as tics, stereotypic movements, delusions, command hallucinations, passivity experiences or even impulses in the context of impulse-control disorders. In other words, whereas obsessions without compulsions, though unlikely, are possible, the reverse does not hold. Moreover, recent clinical research findings suggest that OCD patients display both obsessions and compulsions<sup>[16]</sup>. Thus, for both conceptual and empirical reasons, the diagnosis of OCS in OCD and in the course of schizophrenic disorders should require the presence of both obsessions and compulsions, at least at the time of their initial manifestation.

To be sure, the full definition of compulsions in the DSM-IV-TR<sup>[4]</sup> runs thus: repetitive behaviours or mental acts that the patient feels driven to perform in response to an obsession or according to rules that must be applied rigidly. However, the expression “according to rules that must be applied rigidly” is ambiguous: it might denote either deeply entrenched personal or cultural habits without pathological significance, or repetitive behaviours in response to an obsession. In the first sense it would be dispensable, whereas in the second sense it would be redundant.

Overall, the current diagnostic parity of obsessions and compulsions and the inadequate conceptualization of the nature and differential diagnosis of compulsions might inflate artificially the diagnosis of OCD or OCS in the course of schizophrenia. Indeed, virtually all available studies investigating OCD or OCS in the course of schizophrenia have been carried out according to the DSM-diagnostic criteria<sup>[1,2]</sup>. However, DSM-IV criteria, even when applied through the Structured Clinical Interview for DSM-IV diagnoses<sup>[17]</sup>, might still misdiagnose as compulsions merely compulsive-like repetitive behaviours in schizophrenia. This misdiagnosis, along with the diagnostic parity between obsessions and compulsions in DSM-IV, would then allow the additional diagnosis of comorbid OCD or OCS. Several of these studies have also used concurrently the Yale-Brown Obsessive Compulsive Scale (YBOCS). However, the YBOCS has been designed for the assessment of OCD or OCS severity, not for their diagnosis<sup>[18]</sup>. Therefore, we concur with the proposal of Bürgy<sup>[11,12]</sup> that future revisions of the psychiatric diagnostic systems, should consecrate the diagnostic primacy of obsessions “in the strict sense” over compulsions along with the provision of a more strict conceptualization of the latter. However, contrary to him, we do not deny the real possibility of coexistence of genuine OCS and delusions in the course of schizophrenia.

Finally, we have also stressed that clinicians should take seriously into account the duration of OC symptoms in their clinical assessment of the features of poor insight and lack of resistance, in order to discriminate chronic obsessions and compulsions from delusions and repetitive delusional behaviours, respectively.

## LIMITATIONS

The major limitation of our paper consists in its exclusively descriptive-phenomenological approach. Thus, we have not taken into account findings from clinical, neurobiological or pharmacological studies of potential relevance to the investigation of OCS or OCD in patients with schizophrenia. For instance, a meta-analysis of 18 clinical studies showed that the presence of OCS in patients with schizophrenia, though not of OCD, was significantly associated with greater severity of global psychotic symptoms, positive psychotic symptoms and negative psychotic symptoms<sup>[19]</sup>. Moreover, in schizotypal patients, it has been found that OC symptoms emerge earlier than schizophrenic symptoms<sup>[20]</sup>. Furthermore, differential activation of brain networks underlies the clinical symptomatology of OCD and schizophrenia. More precisely, increased functional activity of the orbito-frontal cortex and the right dorso-lateral prefrontal cortex, along with decreased activity of the right anterior cingulate cortex and the insula have been reported in drug-naïve OCD patients<sup>[21]</sup>, as well as abnormally heightened functional connectivity of ventro-limbic corticostriatal regions<sup>[22]</sup>. By contrast, reduced frontocingulate and frontoparietal and increased frontotemporal and frontostriatal functional connectivity have been reported consistently in schizophrenia<sup>[23]</sup>.

## CONCLUSION

Although preliminary, the results of our phenomenological approach suggest that the comparative assessment of major features of obsessions versus delusions, as well as of compulsions versus delusional repetitive behaviours could facilitate their accurate differential diagnosis in patients with schizophrenic disorders. In turn, this would provide a more solid ground for the investigation of their epidemiology and aetiology, as well as their clinical, prognostic and therapeutic import. Moreover, we have also discussed several conceptual and clinical diagnostic issues that remain still controversial: the nature of insight, the diagnostic status of poor-insight, as well as the conceptualization, differential diagnosis and the diagnostic weight of compulsions. Better conceptually informed future empirical studies in order to address these controversial or open issues are thus fully warranted.

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**P- Reviewers:** Hosak L, Müller MJ, Orellana AF **S- Editor:** Gou SX **L- Editor:** A **E- Editor:** Wang CH



## New findings in the genetics of schizophrenia

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Author contributions: Hosak L solely contributed to this paper. Supported by The Research Grant NT14504/2013 from the Internal Grant Agency of the Ministry of Health of the Czech Republic  
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Received: April 5, 2013 Revised: June 5, 2013

Accepted: July 18, 2013

Published online: September 22, 2013

### Abstract

New findings in schizophrenia genetics are based on genome-wide association studies (GWAS), research into DNA copy number variations (CNVs), and endophenotypes. More than 70 genes have recently been suspected to be involved in the genetic background of schizophrenia based on the GWAS's results. They are typically related to neurodevelopment/neuroplasticity, immunology and neuroendocrinology. Nevertheless, for many detected genes their possible relationship to schizophrenia etiopathogenesis is still unknown. The CNVs at genome loci 1q21.1 (candidate gene *e.g.*, *PRKAB2*), 2p16.3 (candidate gene *e.g.*, *NRXN1*), 3q29 (candidate genes *e.g.*, *BDH1*, *DLG1*, *PAK2* or *TFRC*), 15q11.2 (candidate gene *e.g.*, *CYFIP1*), 15q13.3 (candidate gene *e.g.*, *CHRNA7*), 16p13.1 (candidate genes *e.g.*, *NTAN1* or *NDE1*) and 22q11.2 (candidate genes *e.g.*, *COMT*, *GSTT2* or *PRODH*) were associated with schizophrenia most frequently. Genetic research of schizophrenia endophenotypes, usually neurophysiological, neuromotoric, neurocognitive, neuroanatomical, neurological or

personality-related, will help us to discover the role of relevant genes in the pathogenesis of schizophrenia. It is also necessary to integrate knowledge from other research platforms in schizophrenia, like epigenetics, studies of gene-environment interactions, transcriptomics, proteomics, metabolomics, neuroimaging and psychopathology. A better knowledge of the genetic background of schizophrenia can lead to changes in the treatment, prevention and genetic counselling. It may also reduce stigma in this severe mental disorder.

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**Key words:** Schizophrenia; Genetics; Genome-wide association study; Copy number variations; Endophenotypes

**Core tip:** New findings in schizophrenia genetics are based on genome-wide association studies (GWAS), research into DNA copy number variations (CNVs), and endophenotypes. More than 70 genes have been recently suspected to be involved in the genetic background of schizophrenia based on the GWAS's results. The CNVs at genome loci 1q21.1, 2p16.3, 3q29, 15q11.2, 15q13.3, 16p13.1 and 22q11.2 were associated with schizophrenia most frequently. Genetic research of schizophrenia endophenotypes helps us to discover the role of relevant genes in the pathogenesis of schizophrenia. A better knowledge of the genetic background of schizophrenia can lead to changes in the treatment, prevention and genetic counselling.

Hosak L. New findings in the genetics of schizophrenia. *World J Psychiatr* 2013; 3(3): 57-61 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v3/i3/57.htm> DOI: <http://dx.doi.org/10.5498/wjp.v3.i3.57>

### INTRODUCTION

Schizophrenia (SZ) is a chronic disabling disease of the

brain. SZ affects 0.5%-1% of the adult population worldwide. It is commonly manifested by auditory hallucinations, paranoid or bizarre delusions, and disorganized speech and thinking. Schizophrenia results in a significant social or occupational dysfunction. The causes of SZ consist of genetic and environmental factors<sup>[1]</sup>. Heritability of schizophrenia is mentioned to be up to 80%<sup>[2]</sup>. Even although we already have certain empirical data about the genetic basis of schizophrenia that implicate specific DNA loci, our recent knowledge on the genetics of schizophrenia is still nascent<sup>[3]</sup>.

Genome-wide association studies, studies on DNA microdeletions/microduplications (genomic copy number variations), and genetic studies on schizophrenia endophenotypes represent three attitudes recently applied in the genetic research of schizophrenia.

## GENOME-WIDE ASSOCIATION STUDIES

A genome-wide association study (GWAS), also known as a whole genome association study, is an examination of frequencies of single nucleotide polymorphisms (SNPs) in most of the genes of different individuals with or without a certain disease. The aim of the GWAS is to see how much the polymorphisms in genes vary among the affected (cases) compared to the unaffected subjects (controls)<sup>[4]</sup>. GWASs incorporate the power to detect small effects with the advantage of the positional genetics design, which requires no specific knowledge of pathogenesis. Published GWASs related to human diseases, including schizophrenia, are included in the National Human Genome Research Institute (NHGRI) GWAS Catalog<sup>[5]</sup>. The NHGRI is one of the 27 National Institutes of Health in the United States. GWAS is the most comprehensive procedure to discover a genetic background of complex diseases.

The NHGRI GWAS Catalog has recently covered 26 GWASs of schizophrenia. Their results have been summed up, e.g., by Doherty *et al*<sup>[6]</sup> or Hosak *et al*<sup>[7]</sup>. More than 70 genes are suspected to be involved in the genetic background of schizophrenia based on the GWAS's results. They are typically related to neurodevelopment/neuroplasticity (e.g., *AMBR1*, *ANK3*, *DOCK4*, *LNX2*, *NRGN*, *NRG1*, *PRODH*, *RELN*, *SHISA9* or *TCF4*), immunology (e.g., *CSF2RA*, *HLA-DQA1*, *HLA-DRB1*, *IL3RA*, *PLA4*, *PRSS16*, *PTGS2*, *SPA17* or *TLR4*) and neuroendocrinology (e.g., *NRGN* or *PAM*). Nevertheless, for many detected genes (e.g., *ACSM1*, *AGBL1*, *DBC1*, *DGKZ*, *LRRFIP1*, *MDK*, *NOTCH4*, *PDC*, *PGBD1*, *PTBP2*, *SLCO6A1* or *UGT1*), their possible relationship to schizophrenia etiopathogenesis is still unknown. The data proceeding from GWAS studies provide evidence for suggesting that a number of chromosomal regions with common polymorphisms show genome-wide association with schizophrenia; however, they present only small odds ratios<sup>[8]</sup>. Past experiences suggest that for some disorders, as many as 20000 to 30000 case subjects and a similar number of comparison subjects are required

to obtain highly robust findings<sup>[9]</sup>. This may be the arrangement in future SZ GWASs.

## GENOMIC COPY NUMBER VARIATIONS

Recent genomic microarray technology has allowed genome-wide discovery of small deletions or duplications, known as copy number variations/variants (CNVs). The term "copy number variant" denotes a DNA sequence with a magnitude of 1 kb at least (by current convention), which is differently represented among individuals based on its deletion or duplication. CNVs are too small to be identified by standard karyotype. Most of the CNVs can be detected by the same technology which is used in genome-wide association studies<sup>[10]</sup>. CNVs are generated by diverse mutational mechanisms, including meiotic recombination, homology-directed and non-homologous repair of double-strand breaks, and errors in replications<sup>[11]</sup>.

Copy number variations account roughly for 12% of human genomic DNA and each variation may range from one kilobase to several megabases in size. CNVs contrast with single nucleotide polymorphisms which affect only one single nucleotide base. CNVs may be inherited or caused by de novo mutation. CNVs can be limited to a single gene or include a contiguous set of genes. If a complete gene is affected by a duplication, the expression of the relevant protein can be increased. On the other hand, if a complete gene is lacking, the relevant protein is not synthesized at all<sup>[12]</sup>. The significance of microdeletions in schizophrenia etiopathogenesis was signalled long ago, when the 22q11.2 deletion syndrome (Velo-Cardio-Facial Syndrome) brings in a 20-fold increase in risk for schizophrenia<sup>[13]</sup>.

According to a recent review, the CNVs at genome loci 1q21.1 (candidate gene e.g., *PRKAB2*), 2p16.3 (candidate gene e.g., *NRXN1*), 3q29 (candidate genes e.g., *BDH1*, *DLG1*, *PAK2* or *TFRC*), 15q11.2 (candidate gene e.g., *CYFIP1*), 15q13.3 (candidate gene e.g., *CHRNA7*), 16p13.1 (candidate genes e.g., *NTAN1* or *NDE1*) and 22q11.2 (candidate genes e.g., *COMT*, *GSTT2* or *PRODH*) were associated with schizophrenia most frequently<sup>[14]</sup>. The data provide evidence for low prevalent (< 1%) but high penetrant CNVs associated with schizophrenia. CNVs may involve multiple genes and/or regulatory regions. CNV deletions show higher penetrance than duplications. Larger CNVs (> 100 kb) often have higher penetrance than smaller CNVs<sup>[15]</sup>. Although the vast majority of CNVs are inherited, CNVs that have newly occurred as de novo (spontaneous) mutations have more readily been implicated in diseases. *De novo* CNVs may be responsible for the presence of schizophrenia in only one of two monozygotic twins, who otherwise have identical genomes<sup>[16]</sup>. The explanation of the biological significance of CNVs, whether a deletion or a duplication, could be that the "dosage" of gene expression is tightly controlled during neurodevelopment and that the abnormalities of levels of gene expression, too much or too little transcription of a given gene, can perturb brain

development and lead to neurodevelopmental disorders. The increases in gene dosage may be less deleterious than the decreases<sup>[17]</sup>.

## ENDOPHENOTYPES IN GENETIC STUDIES OF SCHIZOPHRENIA

GWASs and studies of DNA microdeletions/microduplications help us to find genes and their polymorphisms that are important in schizophrenia etiology, yet the findings do not clarify schizophrenia pathogenesis. That is why genetic research of schizophrenia endophenotypes has recently been emphasized. The useful criteria for the identification of endophenotypes in psychiatric genetics has been postulated by Gottesman and Gould and supplemented by Gottesman *et al*<sup>[18]</sup> and Leboyer *et al*<sup>[19]</sup>: (1) The endophenotype is associated with illness in the population; (2) The endophenotype is heritable; (3) The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active); (4) Within families, endophenotype and illness co-segregate; and (5) The endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population.

Neurophysiological (prepulse inhibition of the startle response, P50 suppression, P300 event-related potential, mismatch negativity), neuromotoric (smooth-pursuit eye movement, antisaccade task), neurocognitive (continuous performance task, span of apprehension, visual backward masking, Wisconsin card sorting test, verbal declarative memory), neuroanatomical (gyrus frontalis interior, gyrus temporalis superior, total brain volume, white brain matter connectivity), neurological (neurological soft signs) and personality (schizotypy, openness to experience) endophenotypes are studied in schizophrenia most frequently<sup>[20]</sup>.

Imaging genetics of schizophrenia, as recently reviewed by Meyer-Lindenberg<sup>[21]</sup>, represents a progressive approach to discovery of genetic background of neuroanatomical endophenotypes<sup>1</sup>. The catechol-O-methyltransferase (*COMT*) gene has been the most-studied gene in schizophrenia imaging. The effects of genetic variation in *COMT* (rs4680 val/met polymorphism) are more consistent in functional findings compared to brain structure assessments. *e.g.*, de Frias *et al*<sup>[22]</sup> tested the tonic-phasic dopamine hypothesis by dissociating sustained and transient brain activity during performance on a 2-back working memory test using mixed blocked/event-related functional magnetic resonance imaging in 11 met/met and 11 val/val male carriers recruited from a random sample of the population. No differences in 2-back performance between genotype groups were found, but the met carriers displayed a greater transient medial temporal lobe response in the updating phase of working memory, whereas val carriers showed a greater sustained activation of the prefrontal cortex in the maintenance phase. These results support the tonic-phasic theory of dopamine function in the phenotypic influence of the *COMT* val(158)met polymorphism on different components of working memory,

which is frequently impaired in schizophrenia<sup>[22]</sup>. *DRD2*, *DRD4*, *DAT1*, *RGS4* or *PPP1R1B* are other dopaminergic genes investigated in schizophrenia imaging. These studies provide strong support for the prefronto-neostriatal system as a core circuit for dopaminergic variation related to schizophrenia risk<sup>[21]</sup>. Interactions between genes (epistasis), CNVs and discovery science using imaging genetics are three of the research frontiers in imaging genetics of schizophrenia. In summary, the results especially related to lateral prefrontal cortex and subcortical structures (striatum, hippocampus) highlight a core neural system for genetic risk for schizophrenia.

According to Braff *et al*<sup>[23]</sup> researchers still face many problems related to genetic investigation of schizophrenia endophenotypes. Almost none of the recently described endophenotypes completely fulfils general criteria for endophenotypes. Genetic background of some endophenotypes may be complex and thus less attainable for research. Endophenotypes and their occurrence may be different in individual schizophrenia subtypes, especially in deficit vs non-deficit schizophrenia.

On the other hand, research of schizophrenia endophenotypes and their genetic background allows us to dissect complex clinical and etiopathogenetical characteristics of schizophrenia into simpler and better understandable sub-units and so reveal schizophrenia pathogenesis step by step.

## DISCUSSION

A major limitation in genetic research is that clinical heterogeneity is typical in schizophrenia. Schizophrenia is not a disease but a cluster of clinical symptoms. No biological marker is involved in schizophrenia diagnostics at present. This means that very few schizophrenia patients probably share identical genomic causation.

The complex genetic architecture of the phenotype is another problem. Some genes may be disease-causing, whilst others only disease-modifying and thus less significant<sup>[24]</sup>.

Many genetic findings are non-specific. Similar predisposing genes can be found across a number of psychiatric disorders. A notable finding is the overlap of susceptibility between schizophrenia and bipolar disorder for several individual risk alleles<sup>[25]</sup>. Population studies support this, *e.g.*, the association of polymorphisms in the genes for calcium and potassium channels in the central nervous system with the genetic risk for bipolar disorder as well as schizophrenia<sup>[26]</sup>. From this point of view, a quantitative dimensional approach to the assessment of individual clinical symptoms of mental disorders seems to be more valuable than the use of current psychiatric diagnoses. In schizophrenia, negative, delusional, depressive, manic, hallucinatory and disorganisation factor dimensions can be applied<sup>[27]</sup>.

Further limitation is that rare variants with a large effect have a very low frequency in the general population and therefore will not be detected by the population-based GWAS strategy. This may be overcome by studying



families and ethnically homogenous populations<sup>[28]</sup>.

Susceptibility for schizophrenia involves a complex interplay of both common (SNPs) and rare (CNVs) genetic risk variants. Because the common risk alleles individually have small effects on risk, collectively more than 70 identified common risk loci from GWAS may explain < 5% of the total genetic variance in schizophrenia susceptibility. The CNVs have much larger effects (odds ratio = 2-30) but are individually rare and are likely to make an even smaller contribution to the total risk. Genetic etiology of schizophrenia is complex and recently only partially resolved<sup>[29]</sup>.

Genes themselves are not sufficient to induce schizophrenia; they also interplay with the environment (maternal pregnancy complications, prenatal maternal infection, abuse during childhood, urban environment, cannabis use, stressful life events *etc.*). This means that it is also necessary to study gene-environment interactions. As for the effect of cannabis in first episode schizophrenia, COMT, CNR1, BDNF, AKT1 and NRG1 are the most promising genetic variants interacting with cannabis exposure<sup>[30,31]</sup>. Nevertheless, not all these findings have been replicated.

On the other hand, the advantage of GWAS and studies of CNVs is that they may be based on a hypothesis-free genome-wide approach. GWAS, studies of CNVs and genetic research into schizophrenia endophenotypes do not compete but rather complement each other. The genes relevant for schizophrenia etiology may be discovered by GWAS and CNVs studies at first. Subsequently, the researchers will be able to find the matching neurobiological pathways in schizophrenia pathogenesis by the genetic research of endophenotypes.

Last but not least, there is a pressing need for better integration of the multiple research platforms in schizophrenia genetics, including biology computational models, epigenetics, transcriptomics, proteomics, metabolomics, neuroimaging and clinical correlations<sup>[32]</sup>.

## CONCLUSION

Looking for causes of schizophrenia, including the genetic ones, belongs to the most ambitious goals in modern psychiatry and will still probably continue to be so in the following decades. A better knowledge of the genetic background of schizophrenia can lead to changes in the treatment, prevention and genetic counselling helpful to the patient, family and clinicians. It may also reduce stigma in this severe mental disorder.

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**P- Reviewers:** Castle DJ, Heiser P   **S- Editor:** Zhai HH

**L- Editor:** Roemmele A   **E- Editor:** Wang CH



## Acetylcholinesterase inhibitors in cognitive impairment in Huntington's disease: A brief review

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Received: June 29, 2013 Revised: August 24, 2013

Accepted: September 3, 2013

Published online: September 22, 2013

### Abstract

Huntington's disease (HD) is a neurodegenerative disease associated with cognitive deficits. Cognitive dysfunction may be present in the early stages of the disease, even before the onset of motor symptoms. The cognitive dysfunction includes executive dysfunction, psychomotor symptoms, visuospatial deficits, perceptual deficits, memory loss and difficulty learning new skills. Acetylcholinesterase inhibitors have shown good effect in the treatment of other types of dementia and it is postulated that it might delay cognitive decline in HD. We reviewed the evidence for Acetylcholinesterase inhibitors in the treatment of cognitive decline and dementia associated with Huntington's disease. We identified 6 articles that investigated the role of Acetylcholinesterase inhibitors for treatment of cognitive deficits in Huntington's disease. Following the review, the authors concluded that there is limited evidence for the use of Acetylcholinesterase inhibitors for cognitive impairment in HD.

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**Key words:** Huntington's disease; Huntington's dementia; Cognitive deficits; Acetylcholinesterase inhibitors; Donepezil; Rivastigmine; Galantamine

**Core tip:** The evidence for Acetylcholinesterase inhibitors in the treatment of cognitive decline and dementia associated with Huntington's disease is reviewed in this article. Six articles were identified that investigated the role of Acetylcholinesterase inhibitors for treatment of cognitive deficits in Huntington's disease (HD). We concluded that there is limited evidence for the use of Acetylcholinesterase inhibitors for cognitive impairment in HD.

Vattakatuchery JJ, Kurien R. Acetylcholinesterase inhibitors in cognitive impairment in Huntington's disease: A brief review. *World J Psychiatr* 2013; 3(3): 62-64 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v3/i3/62.htm> DOI: <http://dx.doi.org/10.5498/wjp.v3.i3.62>

### INTRODUCTION

The clinical description of Huntington's disease (HD) was reported by George Huntington in 1872 and led to increased recognition of the condition<sup>[1]</sup>. The prevalence of the illness is about 5.70 per 100000 births<sup>[2]</sup>. HD is characterised by movement disorder, cognitive deficits and psychiatric symptoms. HD is a progressive neurodegenerative autosomal dominant disorder caused by a single defective gene on chromosome 4. In HD, mutation of *HTT* gene leads to abnormal CAG trinucleotide repeat<sup>[3]</sup>. A larger number of repeat is associated with earlier onset of the illness<sup>[4]</sup>.

The clinical features of HD frequently include cognitive dysfunction<sup>[5]</sup>. Cognitive dysfunction may be present in the early stages of the disease, even before the onset of motor symptoms<sup>[6]</sup>. Cognitive dysfunction includes executive dysfunction, psychomotor symptoms, visuospatial deficits, perceptual deficits, memory loss and difficulty learning new skills. Cognitive dysfunction lead to frontal and subcortical dementia<sup>[7]</sup>. There are structural and

**Table 1** Trials and reports of Acetylcholinesterase use in Huntington's disease

Ref.	Design	Medication used	Outcome measures	Result
Fernandes <i>et al</i> <sup>[11]</sup>	Open labelled study	Donepezil	UHDRS, MMSE, Wechsler memory scale-III, Symbol Digit, Odd Man Out test, Hopkins Verbal Learning test	No statistical significance between mean scores at baseline and 6 wk on all neuropsychological tests.
Rot <i>et al</i> <sup>[12]</sup>	Longitudinal study	Rivastigmine	UHDRS, MMSE, Trail making test	Improvement on cognitive tests and behavioural part of UHDRS
Petrikis <i>et al</i> <sup>[13]</sup>	Case report	Galantamine	PANSS ESRS MMSE	Improvement on PANSS and ESRS but no improvement on MMSE
de Tommaso <i>et al</i> <sup>[14]</sup>	Prospective, open labelled randomized controlled trial	Rivastigmine	MMSE, Marsden and Quinn Chorea Severity Scale, Total Functional Capacity score, Abnormal Involuntary Movement scale	Improvement on MMSE compared to baseline
Cubo <i>et al</i> <sup>[15]</sup>	Randomized controlled trial	Donepezil	UHDRS, Alzheimers Disease Assessment Scale, Sickness Impact Profile	No significant improvement except for improvement on UHDRS-FAS (Verbal Fluency test)
de Tommaso <i>et al</i> <sup>[16]</sup>	Randomized, blinded, controlled, open labelled prospective	Rivastigmine	MMSE, Marsden and Quinn Chorea Severity scale, Total Functional Capacity score, Abnormal Involuntary Movement scale	Slight increase in MMSE but not statistically significant

UHDRS: Unified Huntington's Disease Rating Scale; MMSE: Mini Mental State Examination; PANSS: Positive and negative syndrome scale; ESRS: Extrapyramidal symptom rating scale.

functional brain changes in HD that correlate to cognitive deficits<sup>[8]</sup>. Decreased Acetyl Choline levels have been noted in HD patients<sup>[9,10]</sup>.

## REVIEW OF LITERATURE

### Search strategy

We used Medline, EMBASE and PsychINFO databases and used key terms such as Acetylcholinesterase inhibitors, HD, Huntington's dementia, Donepezil, Galantamine and Rivastigmine. The bibliographies of all identified articles and previously published reviews were scanned for additional studies.

### Description of identified studies

Six studies were identified that investigated the effect of Acetylcholinesterase inhibitors in HD.

Fernandez *et al*<sup>[11]</sup> conducted an open label trial of 8 patients with HD and prescribed Donepezil. Two patients had slight improvement in memory and concentration at 5 mg/d. There was no statistically significant improvement at 6 wk from baseline scores on all neuropsychological tests. Due to 4 patients dropping out, analysis at 12 wk was not done due to lack of statistical power.

Rot *et al*<sup>[12]</sup> investigated the effect of Rivastigmine on four symptomatic HD patients (3 females, 1 male). Unified Huntington's Disease Rating Scale (UHDRS), Mini Mental State Examination (MMSE) and Trail making test were used to assess change in cognitive function. They were evaluated at baseline and 26 wk of therapy. The results showed an improvement in cognitive and behavioral parts of UHDRS, MMSE and Trail making test. There was no improvement in motor and functional subscales of UHDRS. As the study had only four subjects (only 3 completed the trial) and did not have a control group, it is difficult to make any worthwhile conclusions about

the efficacy of Acetylcholinesterase inhibitors from this study.

Petrikis *et al*<sup>[13]</sup> report a case of a 35-year-old male patient with HD who presented with symptoms of an acute psychotic episode. He was evaluated using Positive and Negative Syndrome Scale, Extrapyramidal Symptom Rating Scale and MMSE. He was initially treated with Haloperidol Decanoate and after a month this was changed to Galantamine. The authors report good improvement of psychotic symptoms and chorea on Galantamine but there was no improvement in his cognitive functioning (Table 1).

de Tommaso *et al*<sup>[14]</sup> conducted a single centre; short term randomised open labelled controlled study in twenty one patients affected by HD. Patients received Rivastigmine as an add-on therapy for 8 mo. Fourteen patients were allocated to Rivastigmine group and 7 to control group. Patients were evaluated using MMSE, Marsden and Quinn Chorea Severity Scale and Abnormal Involuntary Movements Scale. Patients on Rivastigmine approached statistically significant improvement ( $P = 0.06$ ) in MMSE score compared to their basal score. Statistical significance was not achieved when intervention group was compared to control group during repeated measures of other clinical features in the 8 mo of the study. Rivastigmine did not appear to reduce hyperkinesia in the intervention group. This study has several drawbacks. The study had only 21 patients and the lack of statistically significant results may be due to the lack of power. Secondly, MMSE was used to assess cognitive function. This may not be an appropriate tool because MMSE fails to capture frontal lobe dysfunction, which is typically impaired in HD.

Cubo *et al*<sup>[15]</sup> investigated the effect of Donepezil on motor and cognitive function in HD. Thirty patients were randomly allocated to active or placebo groups. Drug and placebo were administered for 6 wk (Donepezil 5 mg) and donepezil was increased to 10 mg at 6 wk for further 6 wk. Patients were evaluated at baseline, 6 and 12 wk.

Unified Huntington's Disease Rating Scale (UHDRS) was used to evaluate motor performance. Cognitive function was assessed using cognitive section of Alzheimer's Disease Assessment Scale and UHDRS. Chorea change was used as primary outcome measure and cognitive function change was used as a secondary outcome measure. There was no significant improvement in chorea measure between the two groups. There was no significant improvement in any measure of cognition except of a trend towards improvement on UHDRS-FAS (Verbal Fluency test). The study was not designed to evaluate change in cognitive function on donepezil as chorea change was used as primary outcome measure. One of the exclusion criteria was dementia with HD.

de Thommaso *et al*<sup>[16]</sup> reported the results of two-year follow up of HD patients on Rivastigmine therapy previously evaluated in a short-term study. This was a long term, open-label, blinded, controlled study. The evaluation was carried out in a final group of 11 treated patients and 6 non-treated patients. The results showed a slight increase in MMSE scores in patients Rivastigmine compared to non-treated group who exhibited a mild decline in MMSE scores. However, these differences were not statistically significant. This study has similar drawbacks as those raised about their original study.

## CONCLUSION

Cognitive deficits due to Huntington's disease are common and cause significant morbidity. Cubo *et al*<sup>[15]</sup> postulates that the role of cholinergic system in cognitive deficits may be less relevant than previously thought and cholinergic stimulation may not be beneficial. There are no adequately powered well-designed trials to support the use of Acetylcholinesterase inhibitors in treating cognitive impairment in HD<sup>[17]</sup>. Review of existing studies suggests that there is limited evidence for the use of Acetylcholinesterase inhibitors in the treatment of cognitive deficits associated with HD. Large randomised controlled trials with adequate follow up are needed to investigate the efficacy of Acetylcholinesterase inhibitors in HD.

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P- Reviewer: Orlacchio A S- Editor: Song XX L- Editor: A  
E- Editor: Wang CH





## Improving caregiving competence, stress coping, and mental well-being in informal dementia carers

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Supported by Social Development Partnerships Program, Human Resources and Skills Development Canada, No. 8470775

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Received: May 7, 2013 Revised: September 14, 2013

Accepted: September 16, 2013

Published online: September 22, 2013

### Abstract

**AIM:** To study the effectiveness of Reitman Centre "Coaching, Advocacy, Respite, Education, Relationship, and Simulation" (CARERS) program, which uses problem-solving techniques and simulation to train informal dementia carers.

**METHODS:** Seventy-three carers for family members with dementia were included in the pilot study. Pre- and post-intervention data were collected from carers using validated measures of depression, mastery, role captivity and overload, caregiving competence and burden, and coping styles. To assess program effective-

ness, mean differences for these measures were calculated. One-way ANOVA was used to determine if change in scores is dependent on the respective baseline scores. Clinical effects for measures were expressed as Cohen's *D* values.

**RESULTS:** Data from 73 carers were analyzed. The majority of these participants were female (79.5%). A total of 69.9% were spouses and 30.1% were children of the care recipient. Participants had an overall mean age of  $68.34 \pm 12.01$  years. About 31.5% of participating carers had a past history of psychiatric illness (*e.g.*, depression), and 34.2% sustained strained relationships with their respective care recipients. Results from carers demonstrated improvement in carers' self-perception of competence ( $1.26 \pm 1.92$ ,  $P < 0.0001$ ), and significant reduction in emotion-focused coping (measured by the Coping Inventory of Stressful Situations,  $-2.37 \pm 6.73$ ,  $P < 0.01$ ), Geriatric Depression scale ( $-0.67 \pm 2.63$ ,  $P < 0.05$ ) and Pearlin's overload scale ( $-0.55 \pm 2.07$ ,  $P < 0.05$ ), upon completion of the Program. Secondly, it was found that carers with more compromised baseline scores benefited most from the intervention, as they experienced statistically significant improvement in the following constructs: competence, stress-coping style (less emotion-oriented), sense of mastery, burden, overload.

**CONCLUSION:** Study results supported the effectiveness of the CARERS Program in improving caregiving competence, stress coping ability and mental well-being in carers caring for family members with dementia.

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**Key words:** Informal carers; Dementia; Problem solving techniques; Competence; Stress coping; Skills-training; Simulated patients

**Core tip:** The "Coaching, Advocacy, Respite, Education, Relationship, and Simulation" (CARERS) Program is a



comprehensive package of evidence-based interventions for informal carers comprised of 3 integrated components: group psychotherapy, Problem-Solving Techniques and skill acquisition for specific current challenging interactions in caregiving. The demonstrated outcomes are reduction of emotion-based coping, enhanced mastery, and reduced burden. The Program is structured, and requires active participation of carers as they acquire knowledge and develop caregiving competence. It is the first carer intervention to make systematic use of standardized patients to role play the spouse or parent with dementia, which allows for real-time coaching in managing current, specific, emotionally difficult interpersonal interactions.

Chiu M, Wesson V, Sadavoy J. Improving caregiving competence, stress coping, and mental well-being in informal dementia carers. *World J Psychiatr* 2013; 3(3): 65-73 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v3/i3/65.htm> DOI: <http://dx.doi.org/10.5498/wjp.v3.i3.65>

## INTRODUCTION

Informal family carers provide most of the care given to individuals with dementia. In Canada, it has been estimated ninety-seven percent of persons with dementia have at least one carer, the majority being members of their families<sup>[1,2]</sup>. The value of care they provide has been estimated to be about \$26 billion per year<sup>[3]</sup>. Carers often express satisfaction with their caregiving role<sup>[4,5]</sup> and their efforts can allow those with dementia to remain at home rather than rely on institutional care<sup>[6-9]</sup>. However, carers enter the caregiving role generally unprepared with little knowledge of and few skills to deal with dementia. In particular, they often know very little about the behavioural and psychological symptoms of dementia (BPSD) that almost inevitably emerge during the course of the disease. This knowledge gap is especially significant because many studies report that BPSD are the most challenging feature of dementia for carers and that BPSD contributes most to caregiver burden, which is comprised of the physical, psychological, social and financial hardships experienced by those caring for individuals with dementia<sup>[8,10-14]</sup>. Caregiver burden, in turn, impairs carers' problem-solving ability and reduces their caregiving capacity.

Numerous interventions have been proposed to support carers and address caregiver burden. Recent meta-analyses of carer intervention studies suggest that the most effective interventions integrate a variety of techniques which are: structured and intensive; require active participation of carers; include education, support, and respite; promote knowledge transfer, skill building and competency; and take place in both group and individual settings<sup>[15-17]</sup>. In particular, interventions derived from cognitive-behavioural theory (CBT) appear to have positive effect<sup>[18]</sup>.

Problem-solving therapy (PST) is a structured intervention that is derived from CBT principles and teaches individuals to address problems by systematically examining and finding solutions to problems, without directly focusing on the emotion inherent in challenging situations. PST has been proven effective in reducing negative emotions and moderating distress in family caregivers of persons with severe physical disabilities, in hospice settings and with oncology patients<sup>[19-21]</sup>.

This paper describes the Reitman Centre "Coaching, Advocacy, Respite, Education, Relationship, and Simulation" (CARERS) Program which emphasizes the acquisition and honing of problem-solving skills and the management of emotion-based coping as a method of ameliorating the stress and burden of family caregivers. The theoretical basis and foundation for the CARERS Program is built upon the recognition of the intense emotional challenge of caregiving, the susceptibility of carers to caregiver burden, and the intention to guide them in dealing with impairments in problem-solving and skills deficits in interaction and communication with care recipients. Successful dementia assessment and management requires that the target of care be broadened to include both partners in the carer-care recipient dyad<sup>[22]</sup>. The CARERS program addresses the needs of carers as a primary focus with comprehensive services designed specifically to address their needs. Integrating formal group psychotherapy principles, formal problem-solving techniques and experiential learning through the novel use of guided simulation, program clinicians aim to address the complex mix of factors that affect carers' ability to cope with and adapt to the role of carer. Caregiving problems are explicitly defined and targeted with one or both of PST-based intervention and simulations. Program clinicians concurrently attend carefully to carers often intense emotional experiences grounded in loss and grief, acknowledge their efforts, and help normalize the burden inherent in caregiving. At the same time, carers are provided with education regarding dementia as an illness and are assisted in the development of emotional self awareness. Ultimately, the CARERS program aims to minimize emotional and functional impairment of vulnerable carers and to maintain their ability to look after their family members with dementia.

While hospital-based, the program is targeted to community-dwelling family carers and members of their families with dementia. The program is grounded in inter-professional collaboration between psychiatrists, social workers, occupational therapists, educators and researchers at Mount Sinai Hospital (MSH), the Simulated Patient Program at the University of Toronto, and an array of community organizations. The CARERS Program makes use of standardized patients (SPs) to provide carers with a novel learning experience using simulations. It is a vehicle for change in understanding, emotions, and behaviours of individuals who are in conflicted interpersonal situations. Simulation-based coaching is a validated and powerful experiential learning tool traditionally in-

**Table 1** Reitman Centre “Coaching, Advocacy, Respite, Education, Relationship, and Simulation” Program session outline

Session	Objective	Description
1	Building group cohesion and trust Education about dementia	Participants are introduced to the group process and encouraged to connect directly with the facilitators and other group members. They are also introduced to the SP, who will be more actively involved in the therapeutic process beginning in Session 5. In response to their specific questions, participants gain a better understanding of dementia: overview, symptoms and effects on the care-recipients, the carers, and the family.
2-4	Introduction and elucidation of Problem-solving techniques Objective analysis of individual caregiving problems, and identifying solutions	The key goal of these sessions is to teach the PST method and help carers adopt a problem focused approach rather than less-effective, emotion-focused coping. Facilitator weaves the understanding of emotions described by the carers into the discussions of the PST process to help carers recognize how their emotions may interfere with identifying problems and solving them objectively. Carers are encouraged to implement the solutions at home and report the outcomes of implementation.
5-9	Skills training Simulations	Through role playing with a SP, carers can practice approaching caregiving challenges differently, focusing in points of interactional conflict and communication.
10	Skills training, simulation Summing up and termination	Review and recognition of gains made, and acknowledgement of the transition into a new and different phase of supportive care. First maintenance group is scheduled during this session.

PST: Problem solving therapy; SP: Simulated patient.

corporated in health professional educational curricula<sup>[23]</sup> but has not been commonly used in the therapeutic setting. To our knowledge, the CARERS Program is the first intervention for carers to make systematic use of SPs trained to play the role of persons with dementia for hands-on training of informal carers in behavioural techniques and new ways to approach interpersonal interactions.

The primary aim of this study was to evaluate the effectiveness of the CARERS intervention on specific measures of change in participating carers, namely: depression<sup>[24]</sup>, mastery, role overload, role captivity, caregiving competence<sup>[25]</sup>, caregiver burden<sup>[26]</sup>, and stress coping style<sup>[27,28]</sup>.

## MATERIALS AND METHODS

### Participants

Carers entered the program through self-referral or through referral by hospital or community-based physicians or other health professionals and a wide range of community organizations throughout the Greater Toronto Area, including memory clinics, and social agencies. To be included in the study, the carer had to be a relative of a care recipient who had been usually but not always formally diagnosed with dementia. The care recipient had to be living in a community setting, not necessarily with the carer, but not in a long-term care facility.

### Intervention

The Reitman Centre CARERS program is delivered in 10 weekly small group sessions, each lasting 2.5 h. The small, intensive format group is co-led by two facilitators, both of whom are mental health professionals. Facilitators coach carers through problem-solving and simulation tailored to their personal challenges as well as presenting information in an interactive didactic format when appropriate. Group psychotherapy principles guide management of the often intense emotions which arise in the process. Thus, the method integrates proven

group-based psychotherapeutic and educational clinical techniques<sup>[29]</sup> with an innovative hands-on experiential method employing professional SPs. Carers, guided by the expert clinical coaches, learn how to deal with challenging situations they are encountering at home. The program addresses the need for respite by providing a concurrent interactive arts-based group for the family members with dementia. Carers are further supported through seamless access for both carers and care recipients to state-of-the-art outpatient psychiatric services. Table 1 provides an outline of the objectives and curriculum of the CARERS Program.

In weeks 1-4, PST and education are the predominant intervention methods. Caregiving problems are explicitly defined and they are taught PST as a method of containing emotions, understanding their problems and finding solutions. As appropriate, carers are educated about brain function and the effect of dementia on behaviour. Throughout the 10-wk intervention, less structured focal psychotherapeutic interventions address significant emotional issues when they arise in the group.

### Study design

A quasi-experimental pre-post treatment design was used. A control group was not included in this demonstration program.

### Assessments

Prior to the first group session, an intake assessment of the carer and care recipient was conducted by program clinicians. At this meeting, in addition to gathering demographic data and developing an understanding of the specific caregiving challenges faced, the clinician administered a baseline series of standardized outcome measures to the carer. The same series of outcome measures were repeated in a post-intervention interview within 1 mo of the last session of the program.

The standardized assessment tools used to evaluate outcomes have been widely used and their properties are well-established. These assessments were depression

**Table 2 Psychometric details of outcome measures**

Instrument	Descriptions	Ref.
15-item geriatric depression scale	Validated and widely applied in older populations in community, acute and long-term care settings. Fifteen questions from the Long Form GDS which had the highest correlation with depressive symptoms in validation studies were selected for the Short Form GDS. Scores of 0-4 are considered normal; 5-8 indicate mild depression; 9-11 indicate moderate depression; and 12-15 indicate severe depression.	[35,36]
Self-mastery scale	Self-mastery is a perception that reflects one's personal mastery or control over life outcomes. Seven items are scored on a 4-point (agree-disagree format) scale with two items recoded in the opposite direction to produce scores ranging from 7 to 28. In the current study, Mastery score was calculated using a negative-oriented scale ( <i>i.e.</i> , response to positively phrased questions were reverse-coded). Thus, lower scores indicate higher self-mastery.	[26]
Role captivity scale	Three-items scale assesses degree of entrapment which carers perceive in their caregiving role. A 4-point Likert scale is used to document the extent to which carers may feel constrained in their caregiving role during the past week. Scores may range from 3 to 12, with higher scores indicating more role captivity.	[26]
Role overload scale	Four-item scale that reflects how carers may be overwhelmed as their time and energy level are being exhausted by the demands of caregiving. A 4-point Likert scale reports extent to which carers may feel overloaded in the past week. Scores may range from 4 to 16, with higher scores indicating more overload.	[26]
Caregiving competence scale	Four-item scale measures carers' self-perception of his/her ability to carry out carer role properly. A 4-point Likert scale reports the level of competence.	[26]
12-item zarit burden interview	Covers multiple domains: financial difficulties, social life, physical and psychological health, and the relationship between the persons with dementia and the carer. A 5-point Likert scale assesses level of burden experienced by carers. Total burden scores range from 0 to 60, with higher scores reflecting greater caregiver burden.	[14]
Coping inventory for stressful situations	48-item measure describes the manner in which an individual responds to stressful situations. It measures three forms of coping style: emotion-focused, task-oriented, avoidance-oriented. For each coping strategy, respondents rate the usage frequency on a 5-point Likert scale ranging from 1 (not at all) to 5 (very much).	[28,29]

GDS: Geriatric depression scale.

(15-item Geriatric Depression scale)<sup>[25]</sup>, mastery, role overload, role captivity, caregiving competence<sup>[26]</sup>, caregiver burden (12-item Zarit Burden Interview)<sup>[27]</sup>, and stress coping style (The Coping Inventory for Stressful Situations)<sup>[28,29]</sup>. Details of outcome measures are presented in Table 2.

History of past psychiatric illness and pre-morbid relationship between the carer and the care recipients were also routinely inquired about during the intake assessment, and included in each carer's clinical record. These records were reviewed and information regarding psychiatric history were extracted and included in data analysis for the current study.

### Ethics

Research ethics approval for this study was obtained from the Mount Sinai Hospital Research Ethics Board, a member of the Toronto Academic Health Sciences Network. All participants provided informed consent to data collection and publications of data.

### Statistical analysis

To assess the effectiveness of the CARERS program, mean  $\pm$  SD for the assessment tools listed above were calculated. The unit of analysis was the family carer. Simple descriptive analysis was performed for the baseline demographics. Paired *t*-tests were used to compare baseline scores and follow-up scores upon completion of the program. The change in scores was calculated as

the post-program score minus the baseline score.  $P < 0.05$  indicates a clinically significant change in the score.

In order to determine if the change in scores for each of these outcome measures is dependent on the baseline score, one-way ANOVA was performed for each outcome measure with score difference as dependent variable and baseline score as the independent variable. For outcome measures without established standard clinical cut-off scores, the mean score for the outcome measure was calculated and used as the arbitrary cut-off for the corresponding baseline score. For example, the mean Competence score was calculated to be 11.9, and arbitrary cut-off for the measure was set at 12 for the purpose of the current study (*i.e.*, 0-12 low sense of competence;  $> 12$  high sense of competence).

To determine the clinical relevance of the changes, outcomes measures were stratified by their respective baseline scores, and the clinical effects for the stratified groups were calculated for each outcome measure and expressed as Cohen's *D* values. From a clinical perspective, an effect size of 0.56-1.2 can be interpreted as a large effect, while effect sizes of 0.33-0.55 are moderate, and effect sizes of 0-0.32 are small<sup>[30]</sup>. Data were analyzed using SPSS, Version 19, IBM Corporation.

## RESULTS

### Characteristics of carers

Data from 73 carers from the first 22 groups to com-

**Table 3** *t*-Test comparison of outcome measures taken before and after participation in the “Coaching, Advocacy, Respite, Education, Relationship, and Simulation” program (mean  $\pm$  SD)

Measures	<i>n</i>	Mean scores pre- and post-intervention		Change from baseline	
		Baseline	Post	mean $\pm$ SD	<i>P</i> value
CISS A (-) <sup>1</sup>	68	40.59 $\pm$ 9.70	40.49 $\pm$ 10.26	-1.03 $\pm$ 5.97	0.887
CISS E (-)	68	39.65 $\pm$ 11.21	37.28 $\pm$ 10.49	-2.37 $\pm$ 6.73	0.005
CISS T (+)	68	57.72 $\pm$ 9.02	56.76 $\pm$ 8.94	-0.96 $\pm$ 7.99	0.327
Competence (+)	70	12.14 $\pm$ 2.12	13.40 $\pm$ 2.07	1.26 $\pm$ 1.92	< 0.0001
Geriatric depression scale	64	4.70 $\pm$ 3.89	4.03 $\pm$ 3.70	-0.67 $\pm$ 2.63	0.045
Mastery (-) <sup>2</sup>	70	14.76 $\pm$ 3.69	14.51 $\pm$ 3.32	-0.24 $\pm$ 2.54	0.426
Overload (-)	67	9.93 $\pm$ 2.67	9.37 $\pm$ 2.71	-0.55 $\pm$ 2.07	0.032
Role captivity (-)	69	7.42 $\pm$ 2.68	7.29 $\pm$ 3.23	-0.13 $\pm$ 2.20	0.623
Zarit burden (-)	67	19.87 $\pm$ 10.61	19.04 $\pm$ 9.54	-0.82 $\pm$ 6.87	0.332

<sup>1</sup>The plus or minus sign following each measure indicates the direction of change sought through the intervention. For example, a decrease in Emotion-focused coping style or an increase in the Competence score would indicate good outcomes; <sup>2</sup>Mastery score was calculated using a negative-oriented scale (*i.e.*, response to positively phrased questions were reverse-coded). Thus, a decrease in Mastery score indicates improvement. CISS A: Coping inventory of stressful situations (Avoidance-Oriented); CISS E: Coping inventory of stressful situations (Emotion-Oriented); CISS T: Coping inventory of stressful situations (Task-Oriented); Competence: Pearlin's competence scale; GDS: Geriatric depression scale (GDS-15); Mastery: Pearlin's mastery scale; Overload: Pearlin's overload scale; Role Captivity: Pearlin's role captivity scale.

plete the Program have been analyzed. All of these participants attended at least 8 of the 10 sessions. Reasons for absence included conflicts in scheduling and health problems of the carers or the care recipients. The majority of these participants were female (79.5%). A total of 69.9% were spouses and 30.1% were children of the care recipient. Participants had an overall mean age of 68.34  $\pm$  12.01 years (mean age of adult children is 55.09  $\pm$  11.51 years and mean age of spouses is 72.87  $\pm$  8.41 years). According to carers' clinical records obtained during intake assessment, 31.5% of participating carers had a past history of psychiatric illness (*e.g.*, depression), and 34.2% reported strained relationships with their respective care recipients.

### Pre-intervention vs Post-intervention Findings

Table 3 reports the results of a pre-intervention versus post-intervention *t*-test analysis on the carers' outcome measures, taken prior to and within one month of the last session. Mean differences between pre- and post-scores for competence (1.26  $\pm$  1.92,  $P$  < 0.0001), emotion-focused coping style (-2.37  $\pm$  6.73,  $P$  < 0.01), geriatric depression score (-0.67  $\pm$  2.63,  $P$  < 0.05) and Pearlin's overload (-0.55  $\pm$  2.07,  $P$  < 0.05) were statistically significant.

Carers who entered the Program faring worse (*i.e.*, those with worse baseline scores based on the standard or arbitrary cut-off scores) in certain constructs appeared to benefit most from the intervention. Upon completion of the 10-wk program, carers who had worse baseline scores in the following constructs experienced statistically significant improvement: competence, stress-coping style (less emotion-oriented), sense of mastery, burden, overload. These treatment effects are represented in separate graphs in Figure 1. To quantify these treatment effects, outcomes measures were stratified by their respective baseline scores, and the clinical effects for the two stratified groups were calculated for each outcome measure and expressed as Cohen's *D* values, which are shown in Table 4. The *D* values of the aforementioned constructs

(competence, emotion-oriented coping, sense of mastery, burden, overload) all fall in the moderate to large clinical effect range (0.33-1.2) in their respective “more compromised” strata.

## DISCUSSION

This paper describes the CARERS Program, a carer intervention designed to emphasize the acquisition and honing of problem-solving, interpersonal and communication skills and the reduction of emotion-based coping in order to ameliorate the stress and burden of caregiving. Based on the data it appears that equipping informal carers with the necessary coping skills, knowledge and techniques can increase caregiving capacity.

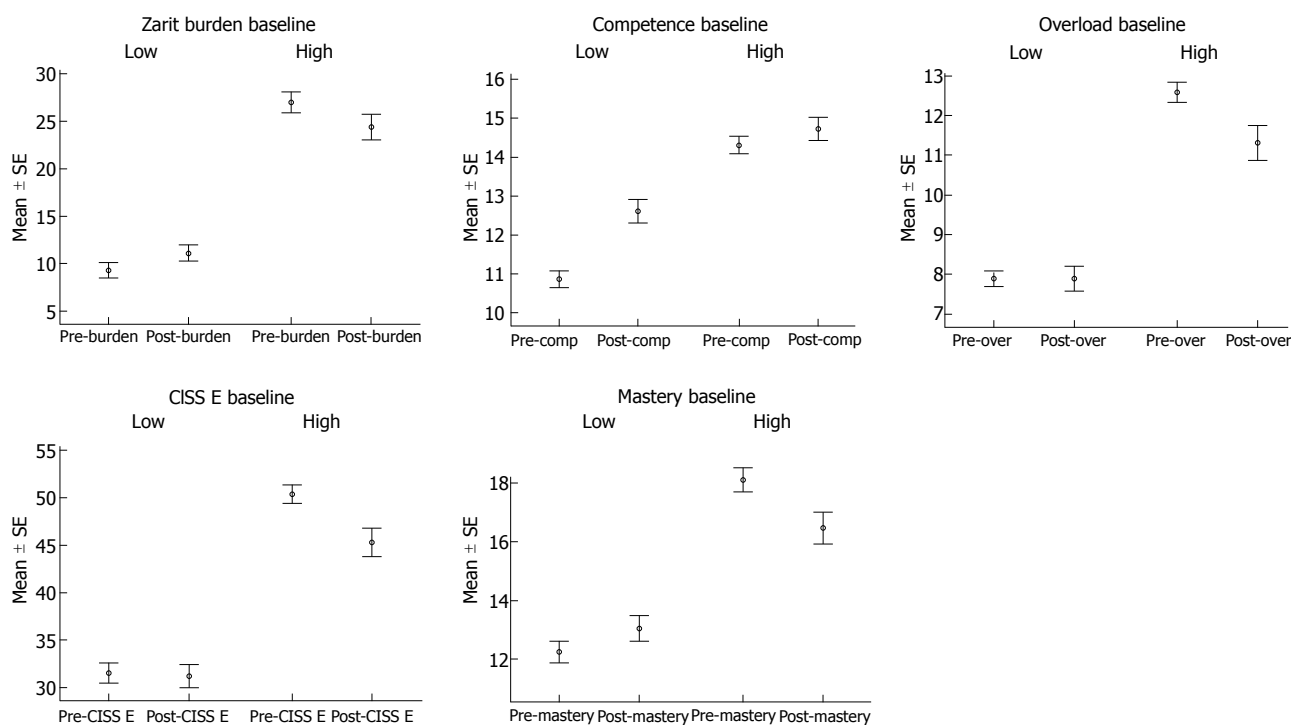
The CARERS Program was able to produce a statistically significant reduction in carers' emotion-focused stress coping (-2.37  $\pm$  6.73,  $P$  < 0.01). Emotions impair carers' ability to understand and manage problems, diminish their ability to seek social support and reduce their sense of mastery and control. Hence, emotion focused coping, which uses emotional reactions to reduce the stress caused by problems, is often maladaptive and produces a downward spiral: poor problem-solving skills may lead to a more negative perception of a stressful situation which can compromise caregiving capacity, increase emotional distress and further impair problem-solving skills. The CARERS Program trains carers to apply problem-solving techniques in the identification of specific caregiving challenges and development of effective, adaptive solutions for them. Thus, carers may depend less on emotions when coping with stress, adopt a more effective task-focused stress coping style and learn to solve problems directly through cognitive re-conceptualization, management of their impact and generation of realistic, practical solutions. As might be predicted by the underlying premise of problem-solving techniques that feelings of stress, burden, depression and anxiety are linked, this proactive approach seems to have a posi-



**Table 4** Participants with more compromised baseline scores may experience more significant improvement in some outcome measures upon completion of the 10-wk “Coaching, Advocacy, Respite, Education, Relationship, and Simulation” intervention

	<i>n</i>	Standard/arbitrary cut-off	<i>P</i> value	Clinical effect (Cohen's <i>D</i> )	
				More “Compromised” baseline; (mean score; Cohen's <i>D</i> )	Less “Compromised” baseline; (mean score; Cohen's <i>D</i> )
Measures with standard cut-off					
Geriatric depression scale	64	5 <sup>[37]</sup>	0.074	9.00 ± 2.42; <i>D</i> = -0.58	2.14 ± 1.60; <i>D</i> = -0.022
zarit burden	67	15 <sup>[38]</sup>	0.015	27.00 ± 6.93; <i>D</i> = -0.34	14.30 ± 1.10; <i>D</i> = 0.42
Measures with arbitrary cut-off					
CISS A	68	40	0.40	49.74 ± 5.95; <i>D</i> = -0.15	33.00 ± 4.55; <i>D</i> = 0.077
CISS E	68	40	0.003	50.26 ± 5.10; <i>D</i> = -0.74	31.55 ± 6.58; <i>D</i> = -0.045
CISS T	68	55	0.004	48.52 ± 5.83; <i>D</i> = 0.38	63.38 ± 6.37; <i>D</i> = -0.47
Competence	70	12	0.012	10.82 ± 1.40; <i>D</i> = 1.06	14.30 ± 1.10; <i>D</i> = 0.33
Mastery (negative-oriented scale)	70	15	0.022	18.10 ± 2.30; <i>D</i> = -0.62	12.21 ± 2.23; <i>D</i> = 0.34
Overload	67	10	0.011	12.59 ± 1.35; <i>D</i> = -0.69	7.98 ± 1.20; <i>D</i> = -0.058
Role captivity	69	7	0.332	9.74 ± 1.48; <i>D</i> = -0.22	5.32 ± 1.42; <i>D</i> = 0.10

Cohen's *D* values of each intervention effect stratified by baseline scores of respective outcome measure were also shown. CISS A: Coping inventory of stressful situations (Avoidance-Oriented); CISS E: Coping inventory of stressful situations (Emotion-Oriented); CISS T: Coping inventory of stressful situations (Task-Oriented); Competence: Pearlin's competence scale; Mastery: Pearlin's mastery scale; Overload: Pearlin's overload scale; Role Captivity: Pearlin's role captivity scale.

**Figure 1** Graphs showing significant treatment effects on individuals with more compromised baseline scores. CISS E: Coping Inventory of Stressful Situations.

tive impact on carers' mental well-being, causing carers to feel less depressed and overloaded<sup>[31,32]</sup>.

Carers who participated in the Program also experienced a robust improvement in self-perceived level of caregiving competence ( $1.26 \pm 1.92$ ,  $P < 0.0001$ ). Competence is a measure of the efficacy of the simulation component of the Program. The use of simulations in the CARERS Program arises from the foundational evidence that demonstrates that the most effective interventions for teaching caregiving skills combine direct observation and coaching of carers as they respond to

challenging situations while simultaneously using the group process to integrate the exploration and understanding of individual carer's emotional reactions<sup>[23]</sup>. A related core principle of the Program is that the stress of caregiving can be ameliorated by attending to specific challenges as perceived by the individual carer. Simulations allow each carer to receive real time coaching in the management of the challenges unique to them. Factors that impede effective caregiving and communication with the person with dementia can then be modified by education, interpretation, coaching and practice<sup>[33]</sup>.



Through repeated practice, skills are developed, polished and retained. Simulation also encourages application in real life situation.

This study did not demonstrate a statistically significant reduction in caregiver burden in the study sample as a whole, perhaps because the mean baseline level of burden was low (mean of 19.87 on a scale of 0 to 60, Table 3). However, carers whose baseline level of burden was higher (mean score of  $27.00 \pm 6.93$ ) had a significant drop in their burden scores (Cohen's  $D = -0.34$ ). Also, as indicated by the Cohen's  $D$  values, it appeared that the Program was particularly effective in helping the most distressed carers since those who entered the Program faring worse also experienced statistically significant improvement in sense of mastery and levels of caregiver burden and overload in addition to improved caregiving competence and reduced emotion focused coping. These preliminary data suggest that screening for severity of the above constructs might provide valuable information to guide subsequent therapeutic interventions.

The study has a number of limitations. It lacked a control group thus making it impossible to rule out the possibility that other factors, such as the passage of time or regression to the mean, contributed to the improvements noted over the course of the Program. Future plans include the implementation of a time-rolling control group of carers assessed and accepted for the Program who are waiting to begin. A second difficulty lies in the fact that carers found the number of outcome measures and the emotions they evoked to be difficult to tolerate. The results of the current work will allow the evaluation of which measures capture the salient changes in participants. This will allow the development of a more streamlined package of outcome measures. A third limitation is that the care recipients were not evaluated either before or after participation in the Program. Thus, it is not possible to state whether the development of carers' problem-solving and other caregiving capacities translated into meaningful improvement in care recipient outcomes.

This was a proof of concept pilot delivered in a single location by professionals who were also integral to the Program's conceptualization and development. In such situations, it might be difficult or impossible to replicate the intervention and its success in other sites. However, it can be reported that the program has been successfully disseminated in various other settings. Professionals in other organizations in other locations have been taught the skills of the CARERS method to develop and deliver the Program and have been successful in setting up programs for carers at their sites. Further, the Program has been successfully replicated in another language (Cantonese) in two institutions providing care to Chinese carers and their family members with dementia. Broader dissemination is planned in populations of more vulnerable carers such as those belonging to a different ethnic group with unique cultural needs or those living in remote or rural areas without direct access to tertiary care<sup>[34]</sup>.

The principal and predominant approach of the Reitman Centre CARERS Program is to train carers for the unfamiliar role into which they have been thrust. The theoretical rationale is that insufficient skills and knowledge, emotion-focused coping and distress, and breakdown in problem-solving ability with loss of sense of control and feeling trapped are at the core of caregiver burden. To address these complex factors a comprehensive integrated package of evidence-informed interventions were developed which are structured and intensive, require active participation of carers; include education, support, and respite; promote knowledge transfer, skill building and competency; and delivered in a group therapy setting.

Evaluation results provide support for the effectiveness of the CARERS Program in improving competence, stress coping ability and mental well-being in carers taking care of family members with dementia. The intervention was shown to be well-received by carers. To refine validity of outcome data, the next phase of program evaluation is underway with the inclusion of a control group. Broader dissemination is planned in populations of more vulnerable carers such as those belonging to a different ethnic group with unique cultural needs or those living in remote or rural areas without direct access to tertiary care.

## COMMENTS

### Background

Informal family carers provide most of the care given to individuals with dementia. Health care systems for dementia could not function without effective family carers. However, family carers are a vulnerable group at disproportionate risk of developing psychological and physical problems associated with providing care and are in need of services designed specifically for them. It has been demonstrated that interventions for carers are effective in increasing their caregiving capacities and resilience and improving their lives and those of their loved ones. While carers have not previously been considered to be a group with legitimate health-care needs, it is clear that the care of carers is a necessary component of the system of care of individuals with dementia. Sustaining carers and improving their effectiveness by maximizing their abilities and minimizing their burden will ensure that they can continue to look after their family members with dementia.

### Research frontiers

Many interventions have been developed and shown to be effective in supporting carers. The research hotspot is how to develop an new intervention that incorporates and integrates efficacious elements of past programs to help carers deal with the emotional consequences of caregiving for a loved-one with dementia, improve their problem solving skills and minimize emotion-focused coping and distress, enhance their skills in managing the behavioural and psychological symptoms of dementia, teach them about dementia, and, in so doing, increase carer competence and coping capacity, sense of mastery and control and overall psychological well being.

### Innovations and breakthroughs

The Reitman Centre "Coaching, Advocacy, Respite, Education, Relationship, and Simulation" (CARERS) Program is a unique, therapeutic-skills-training program. It is a comprehensive integrated package of evidence informed interventions for vulnerable family carers designed to emphasize the acquisition and honing of problem-solving, interpersonal and communication skills and the reduction of emotion-based coping with the goal of reducing caregiver burden. It is structured, intensive and requires active participation of carers as they acquire knowledge and develop caregiving skills and competence. The Program is built on three foundational principles: one, that caregiving is an intensely

emotionally challenging process for family carers, two, that the stress of caregiving can be ameliorated by attending to specific challenges encountered by the individual carer; and three, that the most effective interventions for teaching caregiving skills combine direct observation and coaching of carers as they respond to challenging situations. The Program is the first carer intervention to make systematic use of standardized patients to play the role of persons with dementia for hands-on, real time coaching in managing specific, difficult interpersonal interactions. Formal problem solving therapy techniques are also used to define and address each carer's unique challenges. At the same time, therapeutic group process is used to assist carers in developing emotional self-awareness and normalizing the burden inherent in caregiving.

### Applications

Broader dissemination of the program is underway in other populations of carers at risk in diverse cultures and geographical locations. The Reitman Centre also serves as a centre for the education of health professionals interested in learning the CARERS methods.

### Terminology

Caregiver burden is the combination of the physical, psychological, social and financial hardships experienced by those caring for someone with dementia. Problem solving therapy (PST) is a structured intervention derived from Cognitive Behavioural Therapy principles that teaches individuals to address problems by systematically examining and finding solutions, without directly focusing on the emotion inherent in challenging situations. PST has been proven effective in reducing negative emotions and moderating distress in family caregivers in a variety of caregiving situations. Standardized patients are healthy individuals trained to portray the personal history, physical symptoms, emotional characteristics and every day concerns of an actual patient. Simulation based coaching is a validated and powerful experiential learning tool traditionally incorporated in health professional education curricula. It is a vehicle for change in understanding, emotions and behaviours of individuals who are in conflicted interpersonal situations.

### Peer review

The authors described the pilot research of the Reitman Centre CARERS Program, which uses problem-solving techniques and simulation for hands on skills training in informal caregivers. They concluded that their results supported the effectiveness of the Program in improving caregiving competence, stress coping ability and mental well-being in carers caring for family members with dementia.

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**P- Reviewer:** Shinagawa S

**S- Editor:** Zhai HH **L- Editor:** A **E- Editor:** Liu XM



## Interpersonal distances, coping strategies and psychopathology in patients with depression and schizophrenia

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**Supported by** The Ministry of Immigrant Absorption to Professor Ponizovsky AM

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Received: June 23, 2013 Revised: July 30, 2013

Accepted: August 4, 2013

Published online: September 22, 2013

### Abstract

**AIM:** To explore (1) intergroup differences in comfortable interpersonal distances (CIDs) and the use of coping strategies; (2) the association of these parameters with individual symptomatology; and (3) the interplay between CIDs and coping styles in patients with depression and schizophrenia.

**METHODS:** The parameters of interest were assessed by means of standardized questionnaires: CID and Coping Inventory for Stressful Situations. Psychopathology was evaluated with the Beck Depression Inventory and Positive and Negative Syndromes Scale. ANOVA, Pearson's correlations and multiple regression analyses were used to examine relationships among the variables.

**RESULTS:** Compared with controls, depressed patients were more distanced from family members, significant others and self-images, whereas patients with schizophrenia were less distanced from neutral and threat-related stimuli. Distancing from self-images was mostly associated with depression severity in depressed patients, whereas distancing from hostile and threat-related stimuli with the severity of psychotic and affective symptoms in patients with schizophrenia. Both patient groups used more emotion-oriented than task-oriented and avoidance-oriented coping strategies. Self-distancing among patients with schizophrenia was positively associated with the use of the social diversion coping, implying social support seeking.

**CONCLUSION:** Patients with depression and schizophrenia use different maladaptive emotion - regulation strategies to cope with their symptoms and related distress. Training in stress management might provide these patients with skills for more effective emotion regulation.

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**Key words:** Interpersonal distance; Coping strategies; Psychopathology; Depression; Schizophrenia

**Core tip:** This paper takes a unique approach by investigating two emotion-regulation strategies, interpersonal distancing and coping with stress, in patients diagnosed with both adjustment disorder with depression and schizophrenia, and the relationships of these strategies to symptomatology of the disorders. The findings generally supported the hypotheses that the patient groups would display greater interpersonal distances from both positively and negatively valenced stimuli, and greater use of emotion-focused coping than controls. The findings suggest that patients with depression and schizophrenia use different maladaptive emotion-regulation



strategies to cope with their symptoms and related distress. Training in stress management might provide patients with skills for more effective emotion regulation.

Ponizovsky AM, Finkelstein I, Poliakova I, Mostovoy D, Goldberger N, Rosca P. Interpersonal distances, coping strategies and psychopathology in patients with depression and schizophrenia. *World J Psychiatr* 2013; 3(3): 74-84 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v3/i3/74.htm> DOI: <http://dx.doi.org/10.5498/wjp.v3.i3.74>

## INTRODUCTION

Despite accumulating evidence of the important role of emotional regulation and coping with stress in the development and maintenance of psychopathology, little is known about the interplay between distinct emotion-regulation strategies and individual clinical symptoms in different mental disorders. Based on the models of emotional regulation<sup>[1]</sup>, coping with stress<sup>[2]</sup> and personal space<sup>[3]</sup> in the frameworks of the stress-vulnerability model of psychopathology<sup>[4,5]</sup>, this study will explore the relationships among interpersonal distancing, coping styles, psychopathology and associated emotional distress in patients diagnosed with adjustment disorder (AJD) with depressed mood (as a model of stress-induced depression) and schizophrenia. We assume that this integrative approach will enable the identification of findings that can have useful implications for treatment.

### Conceptual foundation

**Emotion regulation:** In recent decades there has been increased interest in affective phenomena in psychopathology and emotion-regulatory strategies incorporated into psychopathology models<sup>[6-10]</sup>. Emotion regulation is defined as a mixture of conscious and unconscious processes by which individuals modulate their emotions to appropriately respond to environmental stress<sup>[1,11-15]</sup>. Regulatory strategies modify either the magnitude or the type of individual emotional response to the emotion-inducing event<sup>[1,16]</sup>.

The well known stress-vulnerability model of aetiological impact in psychiatry suggests that due to genetic or psychological predispositions individuals who are selectively vulnerable to environmental risks respond to stressors with increasing levels of emotional distress and by mobilizing psychosocial resources<sup>[4,5,17,18]</sup>. From the stress-process perspective, the distress-related disorders are viewed as the outcome of emotion dysregulation<sup>[9,11,14]</sup>. Several researchers have also empirically demonstrated that individuals who are unable to effectively manage their emotional responses to external or internal stresses, experience more severe and protracted periods of emotional distress that may evolve into diagnosable depression or anxiety disorders<sup>[5,9,19,20]</sup>. The stress-vulnerability models also suggest that training in specific stress management techniques could provide benefits to

patients with schizophrenia and affective disorders<sup>[21,22]</sup>.

Different emotion-regulation strategies have been hypothesized to function as either risk factors or protective factors against a defined type of psychopathology. For example, in their recent meta-analytic review, examining the relationships between emotion-regulation strategies (acceptance, avoidance, problem solving, reappraisal, rumination, and suppression) and symptoms of mental disorders, Aldao *et al*<sup>[10]</sup> demonstrated that mood-related disorders (anxiety and depression) were more consistently associated with regulatory strategies than behavioral disorders (eating and substance-related disorders).

Regarding schizophrenia research, there are conflicting results on widely used emotion-regulation strategies and their association with specific psychopathology. For instance, van der Meer *et al*<sup>[23]</sup> reported increased use of suppression and less use of reappraisal strategies by patients with schizophrenia than by healthy controls, and found that it was associated with depressive symptoms. Conversely, Henry *et al*<sup>[24]</sup> found neither such differences nor an association between the use of suppression and reappraisal strategies and blunted affect ratings. There are also studies that show specific differences in stress-reactivity among different psychopathologies, *e.g.*, relative to normal controls, patients with schizophrenia show significantly more frequent and higher levels of trait emotional reactivity<sup>[25]</sup>, whereas depressive patients significantly more often report an impaired tolerance to certain stresses<sup>[26]</sup>.

**Coping strategies:** According to the Folkman *et al*<sup>[2]</sup> stress-coping transactional model, coping strategies are used to change the person-environment relationship either by using strategies regulating emotional distress (emotion-oriented coping) or by using strategies directed to reframe the problem precipitating the distress (problem-oriented coping). In either way, the coping strategies function as emotion modulators and in this sense they are similar to the above concept of emotion regulation. Research on coping with stress has indicated that individuals with schizophrenia are inflexible in their use of coping strategies<sup>[27]</sup>, tend to use maladaptive emotion-oriented coping styles<sup>[28-30]</sup>, and rely more on passive avoidant strategies and less on active problem solving<sup>[31,32]</sup>. Maladaptive coping patterns in people with schizophrenia have been associated with higher levels of negative symptoms, depression, and anxiety<sup>[33]</sup>. A previous study found a significant relationship between different coping strategies and both severity of symptoms and emotional distress<sup>[34]</sup>: particularly avoidance-oriented coping strategies (*e.g.*, distraction) were negatively correlated with paranoid symptoms. Another study of the same researchers reported that patients with schizophrenia used emotion-oriented coping significantly more frequently, and task-oriented and combined task-avoidance oriented coping patterns significantly less often than healthy controls<sup>[35]</sup>. Obviously, the vulnerable patients with high levels of trait emotional reactivity who use maladaptive emotion-oriented coping

strategies are at an increased risk of psychotic relapse under stress conditions.

**Approach-avoidance distress regulation:** Another mechanism providing affect regulation when faced with environmental stress operates through approach-avoidance behavior responses that maintain comfortable interpersonal distance (CID) in social interactions<sup>[36,37]</sup>. In some sense, this mechanism resembles Gross' strategy of "situation selection"<sup>[1]</sup>, which comprises approaching or avoiding people, places or objects in order to regulate emotions. The boundaries of personal space, with underlying interpersonal distances outlining an invisible circle surrounding oneself, known as comfort, buffer, safe or security zone, if violated, cause a person to become vulnerable or defensively aggressive to protect him/herself<sup>[3]</sup>. These boundaries develop during infancy through interpersonal interactions, when a child develops his/her self-concept and becomes unique and distinct from others<sup>[38]</sup>. During adult life, keeping a distance from strangers, potentially dangerous or threatening figures<sup>[39]</sup>, as well as proximity seeking to attachment figures<sup>[40]</sup>, become important defensive mechanisms, the normal functioning of which may be considerably disturbed in psychopathological states.

The relation between symptomatology of mental disorders and approach-avoidance responses to environmental stress are thought to play an important role in individual defensive reactions to stress. Unfortunately, the psychiatric literature rarely refers to personal space, although closeness and distance, as well as the relative position of the patient and therapist, are intuitively used and modulated in psychotherapy<sup>[41]</sup>. The relationship between CIDs and psychopathology has been explored by only few studies<sup>[42-45]</sup>. These found that compared with normal controls, people with schizophrenia maintained significantly larger distances from generally close persons and themselves and smaller distances from neutral and threatening people<sup>[44]</sup>, and that this inversion was related to the negative syndrome severity. We are aware of no research investigating interpersonal distances in relation to symptomatology and coping abilities among patients diagnosed with depression and schizophrenia.

Given the importance of a multi-sample approach to the study of psychopathology<sup>[10]</sup>, in the present study we decided to compare patients diagnosed with depression and schizophrenia versus non-patient controls in order to explore (1) between-group differences in CIDs from word stimuli distinguished by emotional valences, and coping strategies used in stressful situations, (2) associations between CIDs and the severity of specific symptoms, and (3) the relationships between the CIDs and coping strategies used by patients with both disorders. Based mostly on our clinical observation and the relevant literature, we hypothesized that comfortable interpersonal distance would be specifically associated with (1) psychiatric diagnosis (schizophrenia *vs* depression *vs* normal); (2) clinical symptoms (positive *vs* negative *vs* affective); and (3) coping strategies (task- *vs* emotion- *vs* avoidance-oriented coping).

## MATERIALS AND METHODS

### Participants

**Depressive group:** Seventy patients (29 men and 41 women) aged 18-50 years were recruited, who consecutively attended a community outpatient clinic (Talbieh Mental Health Center, Jerusalem, Israel) in 2006, and had a Diagnostic Statistical Manual, Fourth edition (DSM-IV) diagnosis of adjustment disorder with depressed mood (AJD, 309.0). This diagnosis was used as a model of stress-induced depression, because in psychiatric practice AJD is very often subsumed under the label of "reactive" or "situational" depression. For reasonable homogeneity of the sample we evaluated and excluded competing diagnoses of other stress-related and mood disorders, such as posttraumatic stress disorder (309.81), generalized anxiety disorder (300.02), dysthymia (300.4), and major depressive disorder (296.2).

**Schizophrenia group:** Fifty-one patients (36 men and 15 women) aged 18-50 years, with DSM-IV diagnosis of schizophrenia (295.0-9) and who had been stabilized on antipsychotic medication, were recruited during 2007 in an open ward of the Kfar Shaul Mental Health Center, Jerusalem, Israel. Patients with other comorbid Axis-I disorders, personality disorders and those with comorbid medical illness were not included.

**Comparison group:** Sixty-one subjects (30 men and 31 women) age-matched to the patient groups and without known history of mental disorders were enrolled from staff members of the same centers as a comparison group.

**Ethical considerations:** After explanation of the study aims and procedure all participants provided written informed consent for participating in the study as approved by the Institutional Review Boards for Human Studies.

### Clinical assessment

**Depressed group:** In the extended clinical interview performed by an experienced psychiatrist, all patients were diagnosed as fulfilling the DSM-IV criteria for AJD with depressed mood (309.0). A senior psychiatrist was consulted for all unclear cases requiring differential diagnosis. Depending on the case complexity, the interview lasted from 1 to 1.5 h.

**Schizophrenia group:** Diagnoses were made by two senior psychiatrists using the Structured Clinical Interview for DSM-IV<sup>[46]</sup>. The schizophrenia group included 27 patients with paranoid type (295.30), 10 with undifferentiated type (295.90), 7 with disorganized type (295.10), and 7 with residual type (295.60) of the disorder. All patients were stabilized on antipsychotic drugs: 35 were receiving typical antipsychotics (*e.g.*, haloperidol, perphenazine) and 16 atypical ones (*e.g.*, risperidone, olanzapine).

**Comparison group:** In order to exclude any psychiatric

disorder among non-clinical participants, a short clinical interview was conducted with each of them. In addition, to exclude sub-threshold depressive symptoms, controls completed the Beck Depression Inventory (BDI)<sup>[47]</sup>.

### Measures

Severity of current depressive symptoms was evaluated with the Beck Depression Inventory (BDI-abridged form)<sup>[47]</sup>. The BDI is an extensively validated self-report measure of depressive symptoms (sadness, pessimism, past failure, loss of pleasure, guilt feelings, self-dislike, suicidal thoughts or wishes, loss of interest, indecisiveness, change in appearance, loss of energy, fatigue, and changes in appetite). Each of its 13 symptom and attitude categories score from 0 (absence of the symptom) to 3 (extreme severity of the symptom). Total scores range from 0-4, none or minimal, to 5-7, mild, 8-15, moderate; and 16 and over, severe depressive symptoms. The Cronbach's  $\alpha$  for the present study is 0.93.

The Positive and Negative Syndromes Scale (PANSS)<sup>[48]</sup> was administered as a Structured Clinical Interview<sup>[49]</sup> for assessing the severity of psychopathology in the schizophrenia group. This instrument assesses the symptomatology in three subscales reflecting positive, negative and general psychopathological symptoms, as well as a total score. The 30 items are scored from absent (1) to extreme problem (7). The Cronbach's  $\alpha$  for the present study was 0.70 for the positive scale, 0.92 for the negative scale, and 0.87 for both general psychopathology scale and PANSS as a total.

To evaluate the parameters of interest, all participants were asked to complete two standardized questionnaires, the Comfortable Interpersonal Distance scale (CID)<sup>[50]</sup> and the Coping Inventory for Stressful Situations (CISS)<sup>[51]</sup>. The time-frame for all the instruments was the 10 days preceding the interview.

The CID determines safe interpersonal distance. The original instrument displays a plane with 8 radii emanating from a common point, each 90 mm of the radius being associated with a randomly numbered "entrance" to what is described as an imaginary "round room". Subjects are instructed to imagine themselves at the center-point of the diagram (room) and to respond to imaginary persons (stimuli) approaching them along a particular radius by marking on the radius the person's preferred closeness to themselves (stop-distance procedure<sup>[39]</sup>). Responses are scored as the distance in millimeters between the mark and the center of the CID. Psychological distance, as measured by this projective technique, has been found to be highly correlated with physical distances in "real life" interactions<sup>[52,53]</sup>. In this study, we used the CID to measure 20 distances between the subject and emotionally-valenced stimuli grouped in 5 subscales: (1) close family members (mother, father, sibling, child); (2) significant others (friend, doctor, neighbor, boss); (3) self-images (myself in the childhood, recent past, present and future); (4) neutral persons (builder, salesman, shoemaker, tailor); and (5) threat-related/hostile images (murderer,

robber, gangster, monster)<sup>[44]</sup>. The Cronbach's  $\alpha$  for the present study ranged from 0.87 for the family member scale to 0.78 for the neutral person scale.

The CISS consists of 48 statements describing ways people can cope with various difficult, stressful, or upsetting situations. The statements represent three 16-item orthogonal factors - task-oriented coping (*e.g.*, "Schedule my time better" or "Analyze the problem before reacting"), emotion-oriented coping (*e.g.*, "Blame myself for not knowing what to do" or "Worry about what I am going to do"), avoidance-oriented coping, including social diversion ("Try to be with other people" or "Phone a friend") and distraction ("Go out for a snack or meal" or "Watch TV") subscales. In the present study, the patients were asked to indicate how often they currently used each of the 48 coping devices, on a 5-point Likert scale ranging from 1 ("not at all") to 5 ("very much"). The CISS has demonstrated high reliability, as well as convergent and concurrent validity<sup>[5,35]</sup>. The Cronbach's  $\alpha$  for the present study ranged from 0.84 for the task-oriented coping scale to 0.77 for the avoidance-oriented coping scale.

### Statistical analysis

Statistical analyses were performed with SAS-9.1 software package (SAS Institute Inc, Cary, NC). We computed frequency distributions and mean scores for the participants' sociodemographic and clinical characteristics. Yates' chi-squared tests were used for intergroup comparisons of categorical variables. Mean scores and standard deviations were computed for the parameters of interest. To test our hypotheses, first, univariate analyses comparing intergroup measures were performed using ANOVA with post-hoc Tukey single comparisons, and Pearson correlations among the measures were computed. In addition, we calculated correlations between each interpersonal distance and the PANSS individual items for the schizophrenia group, as well as between each distance and the BDI items for the depression group. Then, multiple regression analysis was performed on four linear models to predict PANSS general psychopathology and BDI scores (the outcome variable) from both CID domains' and CISS dimensions' scores (the outcome variables) in patients with schizophrenia and depression, separately. Only five and three predictor variables were included in the respective models to keep the variable-to-patient ratio large enough to prevent multicollinearity. For all analyses, the level of statistical significance was set at  $P < 0.05$ .

## RESULTS

### Participants' characteristics

Table 1 presents and compares participants' demographic and selected clinical characteristics. All groups were comparable by age, but they differed significantly by gender, marital status and years of education. The depression group had more females and the schizophrenia group more males, while both patient groups, in particular schizophrenia had more singles than the con-

**Table 1 Basic characteristics of patients and controls**

Characteristics	Depression group ( <i>n</i> = 70)	Schizophrenia group ( <i>n</i> = 51)	Control group ( <i>n</i> = 61)	Significance test
Gender				
Male	29 (41.4)	36 (70.6)	30 (49.2)	$\chi^2 = 9.1, df = 2, P = 0.01$
Female	41 (58.6)	15 (29.4)	31 (50.8)	
Age (yr)	37.4 ± 13.4	33.8 ± 10.5	35.7 ± 11.3	$F = 1.09, df = 129, P = 0.27$
Marital status				
Single	34 (48.6)	40 (78.4)	24 (39.3)	$\chi^2 = 19.1, df = 4, P < 0.001$
Married	26 (37.1)	6 (11.8)	31 (50.8)	
Divorced/separated/widowed	10 (14.3)	5 (9.8)	6 (9.8)	
Schooling (yr)	13.4 ± 1.7	11.2 ± 3.0	14.1 ± 2.3	$F = 1.96, df = 129, P < 0.05$
Age at onset (yr, range)	35.5 ± 13.6 (15-39)	25.3 ± 9.4 (14-29)	--	$t = 4.61, df = 119, P < 0.01$
Duration of disorder (mo, range)	12.8 ± 7.7 (1-36)	28.0 ± 13.4 (6-131)	--	--
Depressive symptoms <sup>1</sup>	13.3 ± 5.7	--	1.2 ± 1.9	$t = 15.82, df = 129, P < 0.001$
PANSS <sup>2</sup> total score	--	54.5 ± 18.5	--	--
Positive syndrome	--	11.0 ± 5.5	--	--
Negative syndrome	--	15.8 ± 7.9	--	--
General psychopathology	--	27.6 ± 9.6	--	--

<sup>1</sup>Beck depression inventory- short form (Beck *et al.*<sup>[47]</sup>); <sup>2</sup>Positive and negative syndrome scale (Kay *et al.*<sup>[48]</sup>). Data are expressed as *n* (%) and mean ± SD.

**Table 2 Comfortable interpersonal distance from stimuli with different emotional valence and coping patterns (coping inventory for stressful situations) across the study groups**

Variable	Depression group ( <i>n</i> = 70)	Schizophrenia group ( <i>n</i> = 51)	Nonpatient group ( <i>n</i> = 61)	ANOVA <sup>F</sup>	<i>P</i> value	Tukey post-hoc single comparisons <sup>1</sup>
Interpersonal distance (from)						
Family members	115.5 ± 80.6	99.2 ± 57.5	80.4 ± 48.8	3	0.05	D > N
Self-images	129.1 ± 83.6	103.7 ± 75.9	59.5 ± 56.0	9.02	0.001	D > N < S
Significant others	192.5 ± 68.1	178.0 ± 68.3	158.8 ± 63.9	3.76	0.03	D > N
Neutral people	270.5 ± 63.1	219.2 ± 73.7	268.8 ± 76.6	9.02	0.001	D > S < N
Hostile images	336.2 ± 44.6	312.1 ± 75.9	348.0 ± 20.9	4.92	0.01	D > S < N
Coping pattern						
Task-oriented	3.5 ± 0.8	3.1 ± 0.9	3.8 ± 0.7	7.45	0.001	D > S < N
Emotion-oriented	3.2 ± 0.9	3.0 ± 0.8	2.3 ± 0.8	14.01	0.0001	D > N < S
Avoidance-oriented	2.8 ± 1.0	3.0 ± 1.0	3.0 ± 0.9	0.82	0.44	D = S = N
Distraction	2.6 ± 1.2	2.7 ± 1.2	2.4 ± 1.1	0.53	0.59	D = S = N
Social diversion	3.0 ± 1.2	3.3 ± 1.2	3.6 ± 1.1	2.99	0.05	D < N

Mean score ± SD are shown. <sup>1</sup>All comparisons are significant at the 0.05 level.

trol group, and the depression and control groups were more educated than the schizophrenia group ( $P < 0.05$ ). The patient groups differed in mean age at onset of the disorder, with earlier onset in patients with schizophrenia ( $P < 0.01$ ). Likewise, in comparison with the depressed patients, those with schizophrenia had a longer duration of the disorder ( $P < 0.001$ ). There was also a significant between-group difference in depression severity, with moderate depression for the depressed group (BDI score > 8 but < 15) versus no depression (BDI score < 4) for the control group ( $t = 15.82, df = 129, P < 0.001$ ).

### Comfortable interpersonal distance

Table 2 presents inter-group comparisons of CID sub-scale mean scores. As can be seen, distances from stimuli with different emotional valences significantly differed between the study groups. Distances from family members ( $P < 0.05$ ), self-images ( $P < 0.001$ ), and significant others ( $P < 0.02$ ) were significantly larger in depressed

individuals, compared with controls. Distances from neutral people ( $P < 0.001$ ) and hostile images ( $P < 0.01$ ) were also significantly larger for depressed individuals than for patients with schizophrenia. Compared with the controls, patients with schizophrenia were less distanced from neutral people ( $P < 0.001$ ) and hostile images ( $P < 0.01$ ) but more distanced from themselves ( $P < 0.001$ ).

Despite the between-group differences in the relative size of interpersonal distances, rank order (hierarchy) of preferable interpersonal distances was similar within each group, except that compared to the control group, both patient groups maintained a larger distance from their self image than from family members, the opposite of the control group. All groups maintained the largest distance from threat-related stimuli, with distances from emotionally neutral and significant others following in descending order.

### Coping strategies

Table 2 also compares the study groups by the coping



**Table 3** Significant Pearson correlations between comfortable interpersonal distance and specific symptoms measures

Symptoms	Distance from				
	Family members	Significant others	Self-images	Neutral persons	Threat-related persons
Schizophrenia sample ( <i>n</i> = 51)					
PANSS items:					
Conceptual disorganization		-0.32 <sup>a</sup>		-0.30 <sup>a</sup>	
Excitement					0.35 <sup>b</sup>
Suspiciousness/persecution					0.26 <sup>a</sup>
Anxiety					0.27 <sup>a</sup>
Guilt feelings			0.28 <sup>a</sup>		
Tension					0.33 <sup>a</sup>
Motor retardation					0.34 <sup>a</sup>
Lack of judgment and insight					-0.34 <sup>b</sup>
Depression sample ( <i>n</i> = 70)					
BDI items:					
Sadness		0.28 <sup>a</sup>	0.40 <sup>b</sup>		
Guilt		0.26 <sup>a</sup>	0.28 <sup>a</sup>	0.29 <sup>a</sup>	
Self-dislike		0.44 <sup>d</sup>	0.32 <sup>b</sup>	0.30 <sup>b</sup>	0.30 <sup>b</sup>
Self-harm			0.28 <sup>a</sup>		
Social withdrawal	0.26 <sup>a</sup>	0.40 <sup>b</sup>		0.41 <sup>b</sup>	
Indecisiveness			0.23 <sup>a</sup>		
Self-image change		0.28 <sup>a</sup>	0.24 <sup>a</sup>	0.32 <sup>b</sup>	
Work difficulty			0.23 <sup>a</sup>		
Fatigability			0.23 <sup>a</sup>		

PANSS: Positive and negative syndrome scale (Kay *et al.*<sup>[47]</sup>); BDI: Beck depression inventory (Beck *et al.*<sup>[48]</sup>). Comfortable interpersonal distance *vs* specific symptoms measures: <sup>a</sup>*P* < 0.05, <sup>b</sup>*P* < 0.01.

strategies used to overcome stressful situations. Compared with healthy individuals, both patient groups used significantly more emotion-oriented coping (*P* < 0.0001), while depressed patients used less avoidance-oriented coping in its social diversion form (*P* < 0.05). Patients with depression exceeded patients with schizophrenia (but not controls) in the use of task-oriented coping strategies. The three groups did not differ in the use of the distraction type of avoidance-oriented coping.

To examine the relationships between distinct interpersonal distances and specific measures of psychopathology in the depressed and schizophrenia groups, we calculated Pearson's correlations among the CID, BDI and PANSS scores. In the depressed group, the depression severity positively and moderately correlated with distances from significant others and self-images (both *r* = 0.40, *P* < 0.01) and from neutral people (*r* = 0.41, all *P* < 0.001) and also significantly correlated with distance from family members (*r* = 0.26, *P* < 0.05). In the schizophrenia group, a significant positive correlation was found between distance from threat-related images, PANSS total score (*r* = 0.28, *P* < 0.05) and General Psychopathology scale score (*r* = 0.38, *P* < 0.001), and between the latter and distance from family members (*r* = 0.27, *P* < 0.05).

Table 3 shows the significant correlations between each interpersonal distance and the PANSS individual items for the schizophrenia group, as well as between each distance and the BDI items for the depression group. As can be seen, for the former group, most significant correlations were found between the distance from threat-related stimuli and selected psychotic and affective symptoms (excitement, *r* = 0.35, *P* < 0.01; suspicious-

ness/persecution, *r* = 0.26, *P* < 0.05; lack of judgment and insight, *r* = 0.34, *P* < 0.01; anxiety, *r* = 0.27, *P* < 0.05; tension, *r* = 0.33, *P* < 0.05; motor retardation, *r* = 0.34, *P* < 0.05). For the latter group, significant correlations were noted between the distance from self-images and most BDI items (8 items out of 13), as well as highly significant correlations were found between the distance from significant others and neutral persons and BDI items of self-dislike (*r* = 0.44 and 0.30, respectively, *P* < 0.01) and social withdrawal (*r* = 0.40 and 0.41, respectively, *P* < 0.01) and between the distance from neutral persons and self-image change (*r* = 0.32, *P* < 0.01).

To explore the relationship between the two affect-regulation strategies, Pearson intercorrelations between CID and CISS scale scores were calculated separately for each disorder. In depression, distance from self-images negatively correlated to task-oriented coping (*r* = -0.27, *P* < 0.05) while positively to emotion-oriented coping (*r* = 0.27, *P* < 0.05). Distancing from significant others was associated negatively with both task-oriented coping (*r* = -0.29, *P* < 0.05) and avoidance-oriented coping in the form of social diversion (*r* = -0.38, *P* < 0.001). In schizophrenia, distance from self-images was significantly and positively correlated only to social diversion coping strategy (*r* = 0.34, *P* < 0.05).

To test the hypothesis that the distinct affect-regulation strategies (interpersonal distancing and diverse coping styles) are differentially associated with the severity of affective psychopathology in both disorders, multiple regression analyses were performed on four models (Table 4). In model 1 (interpersonal distancing in schizophrenia) only two of the five distances under test (from family members and threat-related images) predicted the

**Table 4** Multiple regression models for predicting the severity of general psychopathology<sup>1</sup> in patients with schizophrenia and current depressive symptoms in patients with depression by regulation strategies

Predictor variables	Schizophrenia <sup>1</sup>				Depression <sup>2</sup>			
	$\beta$	$t$ value ( $\beta = 0$ )	$P$ value	Total% variance accounting for	$\beta$	$t$ value ( $\beta = 0$ )	$P$ value	Total% variance accounting for
Interpersonal distances <sup>3</sup> from								
Family members	0.22	7.3	0.007	7.1	0.28	6.8	0.011	9.5
Hostile images	0.29	12.7	< 0.001	11.8	0.01	1.8	--	--
Neutral people	0.04	0.15	0.148	--	0.23	9.1	0.012	6
Self-images	-0.06	0.35	0.179	--	0.32	7.5	< 0.001	13.4
Significant others	-0.05	1.3	0.091	--	--	6.2	0.017	8.7
Model properties	$R^2 = 0.48$ , adjusted $R^2 = 0.36$ , $F = 4.2$ , $P < .001$				$R^2 = 0.54$ , adjusted $R^2 = 0.37$ , $F = 5.7$ , $P < 0.001$			
Coping patterns <sup>4</sup>								
Task-oriented	-0.31	6.1	0.016	8.8	-0.17	2.8	0.009	4.2
Emotion-oriented	0.23	5.4	0.025	7.2	0.11	4.7	0.032	7.2
Social diversion	0.17	2.8	0.097	--	-0.09	5.1	0.027	7.6
Model properties	$R^2 = 0.45$ , adjusted $R^2 = 0.34$ , $F = 3.3$ , $P < 0.001$				$R^2 = 0.35$ , adjusted $R^2 = 0.23$ , $F = 3.1$ , $P = 0.002$			

<sup>1</sup>PANSS: Positive and negative syndrome scale (Kay *et al.*<sup>[47]</sup>); <sup>2</sup>BDI: Beck depression inventory (Beck *et al.*<sup>[48]</sup>); <sup>3</sup>CID: Comfortable interpersonal distance; <sup>4</sup>CISS: Coping inventory for stressful situations.

severity of PANSS general psychopathology, accounting for 18.9% of the total variance (7.1% and 11.8%, respectively;  $R^2 = 0.48$ ; Adjusted  $R^2 = 0.36$ ;  $F_{4,51} = 4.2$ ,  $P < 0.001$ ). In model 2 (interpersonal distancing in depression), all but distances from threat-related images predicted the severity of current depression, accounting for 37.6% of the total variance in BDI scores ( $R^2 = 0.54$ ; adjusted  $R^2 = 0.37$ ;  $F_{2,68} = 5.7$ ,  $P < 0.001$ ). The most robust predictor - distancing from self-images - accounted for 13.4% of the variance, followed by distance from family members (9.5%), significant others (6.7%), and neutral people (6%). In the third model (coping in schizophrenia), task- and emotion-oriented coping styles predicted PANSS general psychopathology scores, accounting for 8.8% and 7.2%, respectively, of the total variance ( $R^2 = 0.45$ ; adjusted  $R^2 = 0.34$ ;  $F_{4,51} = 3.3$ ,  $P < 0.001$ ). Finally, the fourth model showed that all coping styles contributed to the prediction of depressive symptoms, altogether accounting for 19% of total variance ( $R^2 = 0.35$ ; Adjusted  $R^2 = 0.36$ ;  $F_{2,70} = 4.2$ ,  $P < 0.001$ ).

## DISCUSSION

The results of this study confirmed the hypothesized associations between CIDs and (1) psychiatric diagnosis; (2) psychopathological syndromes; and (3) coping strategies used by the patients for emotional regulation.

### Distancing and diagnosis

Contrasting the study groups, we observed that each group had established a similar rank order of interpersonal distances, with maximum distance from emotionally neutral and hostile stimuli and minimum from family members and self-images, with the spacing pattern from significant others intermediating in between. This observation is consistent with the conception of "personal space as a dynamic process that is continually open to modification but that shows considerable stability due to the persistence of previously maintained distances"<sup>[39]</sup>.

However, as hypothesis 1 predicted, distances from generally positively-valenced stimuli (self-images, family members and significant others) were significantly larger for depressive individuals than for healthy subjects but they were similar to the analogous distances for patients with schizophrenia. However, contrary to our postulate, distances from strangers (emotionally neutral and hostile stimuli) were similar in the depressed and control participants, although substantially exceeded those in the schizophrenia group. The findings suggest that for depressed individuals the tendency to enlarge personal space is an attempt to down-regulate emotional distress resulting from interaction with generally close people; the distancing responses to strangers in depressed patients are in the normal range, whereas people with schizophrenia down-regulate their emotional distress by reducing distances from strangers. Thus, the same protective mechanism of emotion regulation (modulation of personal space) works differently in diverse mental disorders.

Regarding intra-personal distancing, we did find that compared with the controls, both clinical groups demonstrated a larger distance from themselves than from family members. This finding suggests that in psychopathology the intrusion-discomfort function of personal space<sup>[55]</sup> is impaired in such a way that approaching the patient's own self-images induces a greater feeling of discomfort (emotional distress) than if others would intrude into his/her personal space. This internal self-alienation may play an important role in defending the patient's ego from emotional distress associated with psychopathology.

### Distancing and symptomatology

There were surprising findings highlighting the role paranoid symptoms play in avoidant social behavior of the patients with schizophrenia. In contrast to previous studies which found an association between safe interpersonal distance and negative syndrome<sup>[44,45]</sup>, in this study interpersonal distancing from threat-related and hostile figures was associated with psychotic and affective fea-

tures of the disorder. The findings suggest that patients with increased paranoid symptoms (“suspiciousness/persecution” and “excitement” items) selectively maintain a greater distance from hostile images.

In order to take into account findings from literature<sup>[56-59]</sup> that comorbid depression occurs approximately in 50% of patients with schizophrenia at some point in the course of the disorder, we also analyzed the relation of affective symptoms to safe distancing. We found that affective symptoms (PANSS anxiety, tension, and motor retardation items) were associated with safer distancing from threat-related figures, confirming previous findings that mood-related disorders (anxiety and depression) are closely related to certain problems in emotion regulation<sup>[9,10,19]</sup>, especially to focusing on the inability to separate oneself from threatening situations<sup>[60]</sup>.

Another important finding was that patients with expressed thinking disorders (“conceptual disorganization”) maintained similarly smaller distances from both significant others and neutral people. In line with previous research which showed that a negative syndrome attenuates differences in distances from generally close and distant persons<sup>[44]</sup>, this finding suggests that conceptual disorganization (*e.g.*, loosening of associations) could also operate in the same way, attenuating normal differences in the maintenance of safe interpersonal distance from persons with different emotional valences.

In depression, our findings support the view that distancing is a passive defensive strategy to secure a “safety zone”, which protects one from external and internal threats<sup>[41]</sup>. In accordance with our predictions, we found positive correlations between intra-personal distancing and the severity of depressive symptomatology. Although interpersonal distancing (from significant others and neutral people) also demonstrated the role of specific symptoms in the avoidant social behavior of depressive patients, it accounted for a significantly smaller number of associated symptoms than intra-personal distancing. The associations were mostly with cognitive symptoms, indicating the characteristic negative self-appraisals of depressed individuals accounting for guilt feelings, self-dislike, indecisiveness, and self-image change. However, there were also associations with mood (sadness), behavioral (social withdrawal, self-harm, work difficulty) and physical (fatigability) symptoms of depression. In sharp contrast with patients with schizophrenia, there was only one symptom (self-dislike) associated with distancing from threat-related/hostile images.

The between-group differences in the objects of distancing associated with the specific symptomatology deserve further consideration. Distancing themselves from threat-related/hostile figures reduces anxiety and fear (and, in turn, enhances a sense of safety) among patients with paranoid schizophrenia as well as among depressed and normal individuals in stressful situations. However, patients with depression distance from themselves more than patients with schizophrenia and controls. These findings suggest that depressive individuals perceive and appraise

themselves as an additional source of threat for their safety and well being. Therefore, like interpersonal distancing, intra-personal distancing could play an important role in emotion regulation strategy, enhancing the patient’s sense of security and coping with distressing symptoms.

### **Distancing and coping**

In this regard, there was a counterintuitive finding. Despite the fact that depressed patients adopted task-oriented coping more frequently than patients with schizophrenia, they experienced a more intense emotional distress. In other words, this adaptive coping strategy, actively directed towards transformation of a more stressful situation into a less stressful one, did not reach its goal. In accordance with studies showing that depressive individuals lack social support<sup>[61,62]</sup>, we found that they employed social diversion (*i.e.*, the coping strategy oriented to social support seeking) significantly less often than their non-clinical counterparts.

Regarding inter- and intra-personal distancing and coping with stress as the distinct emotion regulation strategies having the common aim of reducing clinical symptoms and associated emotional distress, we examined the relationship between the two. Correlation analysis revealed several significant findings. In depression, the use of adaptive task-oriented coping was associated with reduced distance from themselves and others, whereas the use of maladaptive emotion-oriented coping strategies correlated with increased self-alienation. In schizophrenia, distancing from self-images was associated with the increased use of avoidance-oriented coping in the form of social diversion. In other words, the more the patients were alienated from themselves, the more they looked for social support and emotional help from others (by contrast, the use of social diversion by depressed patients was associated with reduction of distance from significant others). Another coping pattern, the task-oriented coping, was associated with greater distancing from neutral surroundings.

The robust regression models supported, in general, our findings obtained at the bivariate level of analysis. They showed that distancing from threat-related/hostile images was the strongest predictor of the severity of general psychopathology in patients with schizophrenia, whereas distancing from self-images strongly predicted the severity of depressive symptoms in depressed patients. The analogous models for the relations of coping patterns with psychopathology severity also were consistent with the previous results, demonstrating that task-oriented and emotion-oriented coping strategies predicted, respectively, reduction and increasing in general psychopathological symptoms in the schizophrenia group, as well as in the severity of depressive symptoms in the depression group.

### **Clinical Implications**

Consistent with other studies<sup>[10]</sup>, our findings emphasize the importance of a multi-sample approach in psychopathology research, consisting of simultaneous investigation of both

clinical and normative populations. Direct comparisons between different clinical and normative groups can be critical in delineating how and when normative processes become pathological. The relationship between emotion-regulation strategies and psychopathology may be stronger, once more extreme groups are compared. In this study, we were able to show that specific symptoms in patients with depression and schizophrenia were differentially associated with emotion dysregulation in the form of a larger intra-personal distancing (self-alienation), and a greater use of emotion-oriented coping relatively to social diversion. This is consistent with research demonstrating that emotion regulation plays a central role in the etiology and maintenance of clinical levels of psychopathology<sup>[6-9,63]</sup>.

Of particular interest are the findings of greater self-alienation in the depressive subgroup of patients, an issue that has implication for treatment interventions such as CBT, aiming at creating a more positive relationship with the patient's own self. For people with schizophrenia, training to improve task-oriented coping skills could reduce the use of passive-avoidant coping strategy of social diversion (associated with increased self-distancing) in favor of greater self-confidence and self-efficacy. For example, a recent study<sup>[64]</sup> showed that an intervention enhancing specific self-efficacy for coping with stress significantly reduced psychotic symptoms in patients with schizophrenia or schizoaffective disorder, as well as heightening their well-being and satisfaction with outcomes, and that these effects were observed not only at post-intervention, but also at three- and six-month follow-ups.

Undoubtedly, more extensive studies on the relationship between interpersonal distancing (in both therapeutic and diagnostic aspects) and coping mechanisms in normal and clinical groups will increase our understanding of the psychopathological processes involved in reaction to stress in both conditions of depression and schizophrenia.

### Limitations

The main limitation of this study is its cross-sectional design which precludes inferring cause-effect relationships between parameters studied. Since mentally ill people may use different strategies over the course of their disorder or even during single emotional events, the temporal course of emotion-regulation strategies should be investigated in the future. Although we have confirmed the relationships between some emotion-regulation strategies (distancing and coping) and psychopathological symptoms (depressive and schizophrenic) severity, most relationships still remain untested. Another limitation is the relatively small sample size for both patient groups that precluded examining a greater number of predictors. Finally, a self-report measure (BDI) for assessing the severity of depression in clinical samples should be supported by an observer-rated instrument. However, relevant literature shows that BDI is among the most used self-rating scales for measuring depression due to its high internal consistency, high content validity, validity in differentiating between depressed

and nondepressed subjects, sensitivity to change and international recognition<sup>[65]</sup>.

In a conclusion, our results suggest that depressive patients use emotion-regulation strategies, such as inter- and intra-personal distancing to a greater extent than do normal controls and even patients with schizophrenia. Depressive symptomatology is associated with a greater self-alienation but also with a larger distancing from significant others and neutral people, whereas positive and affective symptoms in schizophrenia are related to a greater distancing from hostile figures. Training in stress management might provide patients with skills for more effective emotion regulation.

## ACKNOWLEDGMENTS

We wish to thank Podolski G, Levov K and Ifrah A for their help at different stages of this study.

## COMMENTS

### Background

Despite the increased interest in affective phenomena in psychopathology and emotion-regulatory strategies incorporated into psychopathology models, little is known about the interplay between emotion-regulation strategies (intra- and inter-personal distancing and coping with distressing symptoms) and individual symptoms of mental disorders, such as stress-induced depression and schizophrenia.

### Research frontiers

The important areas of research are (1) the differences in the use of distancing and coping strategies between patients with depression and schizophrenia; (2) the association between emotional regulation strategies and individual symptomatology of the mental disorders; and (3) the interplay between distinct forms of emotional regulation in these mental disorders.

### Innovations and breakthroughs

This is the first study that compared the use of emotional regulation in the form of safe distancing and coping with distressing symptoms in patients with different mental disorders versus healthy controls. The results showed that distancing from threat-related/hostile images was the strongest predictor of the severity of general psychopathology in patients with schizophrenia, whereas distancing from self-images strongly predicted the severity of depressive symptoms in depressed patients. The authors found also that task-oriented and emotion-oriented coping strategies predicted, respectively, reduction and increase in general psychopathological symptoms in the schizophrenia group, as well as in the severity of depressive symptoms in the depression group.

### Applications

The finding of greater self-alienation in the depressive subgroup of patients has implication for treatment interventions such as cognitive behavioral therapy, aimed at creating a more positive relationship with the patient's own self. For people with schizophrenia, training to improve task-oriented coping skills could reduce the use of passive-avoidant coping strategy of social diversion (associated with increased self-distancing) in favor of greater self-confidence and self-efficacy.

### Terminology

Emotion regulation is defined as a mixture of conscious and unconscious processes by which individuals modulate their emotions to appropriately respond to environmental stress. Similarly, coping strategies are used to change the person-environment relationship either by using strategies regulating emotional distress (emotion-oriented coping) or by using strategies directed to reframe the problem precipitating the distress (problem-oriented coping). The boundaries of personal space, with underlying interpersonal distances outline an invisible circle surrounding oneself, known as comfort, buffer, safe or security zone, which if violated, cause a person to become vulnerable or defensively aggressive to protect him/herself. These boundaries develop during infancy through interpersonal interactions, when a child develops his/her self-concept and becomes unique and distinct from others. During adult life, keeping a distance from strangers, potentially dangerous or threatening figures, as well as proximity seeking to attach-



ment figures, become important defensive mechanisms, the normal functioning of which are considerably disturbed in psychopathological states.

# Peer review

The paper is well-written; the topic is of interest and potential clinical relevance. The study has been completely described, results are clear and discussion is adequate; and only minor revisions are needed to enhance the quality of the paper.

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#### Name of journal

*World Journal of Psychiatry*

#### ISSN

ISSN 2220-3206 (online)



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### Launch date

December 31, 2011

### Frequency

Quarterly

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- 3 Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.00000035706.28494.09]

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- 5 Vallancien G, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 7 Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 Banit DM, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

### Books

Personal author(s)

- 10 Sherlock S, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 Lam SK. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

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- 15 Morse SS. Factors in the emergence of infectious diseases.

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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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