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Theory of mind and executive functions in schizophrenia and bipolar disorder: A cross-diagnostic latent class analysis for identification of neuropsychological subtypes

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ABSTRACT

Objective: Executive dysfunction is a common feature of schizophrenia and bipolar disorder (BP). While deficits in social cognitive abilities, including theory of mind (ToM), have been suggested to be specific to schizophrenia, available evidence suggests that there is also a significant overlap in social cognitive performances of both disorders. However, there is significant heterogeneity of executive dysfunction and ToM deficits in BP and schizophrenia. Cross-diagnostic data-driven methods can reveal potential neurocognitive subtypes characterized by relatively selective deficits in social cognition.
Methods: Neurocognitive subgroups were investigated using latent class analysis, based on executive functions and ToM, in a mixed sample of 97 clinically stable patients with schizophrenia or BP and 27 healthy controls.
Results: Four neurocognitive subgroups, including a "neuropsychologically normal" cluster, a severe global impairment cluster and two clusters of mixed cognitive profiles were found. Severe impairment cluster was characterized by particularly severe ToM deficits and predominantly included patients with schizophrenia. Schizophrenia patients in this cluster had severe negative symptoms. In contrast, individuals with BP compared to schizophrenia patients were more likely to be included in the "neuropsychologically normal" cluster.
Conclusion: Identification of distinctive neurobiological subtypes of patients based on social and non-social cognitive profiles can improve classification of major psychoses. Neurocognitive subgroupings of patients might be also beneficial for intervention strategies including cognitive rehabilitation.

1. Introduction

Both schizophrenia and bipolar disorder (BP) is associated with neurocognitive deficits (Heinrichs and Zakzanis, 1998; Bora et al., 2009a; Mesholam-Gately et al., 2009; Bora and Pantelis, 2013; Bora and Pantelis, 2015). Cognitive impairment in schizophrenia is more severe than BP, but the pattern of neurocognitive deficits are similar in both conditions (Bora et al., 2009c; Bora et al., 2010). Another aspect of the neuropsychological profile of schizophrenia is deficits in social cognitive abilities including theory of mind (ToM) and emotion recognition (Bliksted et al., 2014; Bora et al., 2009b; Koelkebeck et al., 2010; Kohler et al., 2010; Lee et al., 2015; Savla et al., 2013). ToM is the ability to attribute mental states (feelings, beliefs and intentions) to others and understand and predict others' behaviour based on their mental states. While social cognitive deficits might be partly secondary to executive dysfunction, it is a mostly separable aspect of cognitive impairment in schizophrenia (Hoe et al., 2012; Sergi et al., 2007; van Hooren et al., 2008). Social cognitive impairment significantly contributes to persistent poor social functioning in schizophrenia (Bora et al., 2006; Green et al., 2013; Fett et al., 2011) and also partly mediates the relationship between neurocognition and functional impairment (Brekke et al., 2005; Schmidt et al., 2011). These findings might be relevant to understand the differences in social functioning between schizophrenia and BP, as it has been argued that deficits in ToM and other social cognitive abilities might be more specific to schizophrenia than BP (Lee et al., 2013). However, recent studies have found that ToM is also impaired in euthymic and symptomatic patients with BP (Bora et al., 2015a). Overlapping pattern of neurocognitive deficits between schizophrenia and BP is not surprising as both disorders share substantial genetic and familial vulnerability (Owen et al., 2007; Lichtenstein et al., 2009). However, there is also evidence for unique familial and genetic risk factors associated with each disorder (Owen et al., 2007; Lichtenstein et al., 2009; Hamshere et al., 2011). It might be expected that there might be neurocognitive subgroups of major psychoses that are associated with different genetic susceptibility factors and neuroanatomical abnormalities (Hallmayer et al., 2005; Wexler et al., 2009; Green et al., 2013).

There is indeed evidence for substantial variability in neuropsychological functioning in major psychoses (Palmer et al., 1997; Burdick et

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al. 2014; Lewandowski et al., 2014). To date, most cluster analytical studies have investigated within diagnosis rather than cross-diagnostic heterogeneity. Cluster analytical studies in schizophrenia have consistently found 3 to 5 clusters consistently including a subgroup with normal neuropsychological performance, and another subgroup with severe and widespread cognitive impairment (Heinrichs and Awad, 1993; Palmer et al., 1997; Goldstein et al., 1998; Seaton et al., 1999; Hill et al., 2002; Allen et al., 2003; Goldstein et al., 2005; Lewandowski et al., 2014). Several recent studies using data-driven methods (Burdick et al. 2014; Lewandowski et al., 2014) have also investigated cognitive subgroups in BP. These studies suggest that BP has also neurocognitive subgroups including neuropsychologically normal and several clusters with varying levels of cognitive deficits. We are aware of only a single cluster analytical study that has investigated heterogeneity of neurocognition in a cross-diagnostic sample of schizophrenia/schizoaffective disorder and BP (Lewandowski et al., 2014). The findings of Lewandowski et al. (2014) have supported a four-cluster solution including a 'neuropsychologically normal' cluster, a globally and substantially impaired cluster, and two clusters of mixed neurocognitive profiles. Schizophrenia and BP were distributed amongst all clusters, although patients with schizophrenia were more likely to be members of global impairment than 'neuropsychologically normal' cluster.

However, previous studies that used data-driven methods for investigating the heterogeneity of cognition in schizophrenia and BP have not included tasks measuring social-cognitive abilities including ToM. This is an important limitation as intact executive functions and other cognitive abilities have considered as a "necessary but not sufficient" prerequisite for social cognitive ability (Penn et al., 1997). Therefore, it is expected that there might be subgroups with isolated social cognitive deficits in schizophrenia. One relevant study (Fanning et al., 2012) has provided some support for this hypothesis in a sample of schizophrenia patients, as 68% of patients were impaired in both cognitive domains and 25% patients had isolated deficits in social cognition. However, as a limitation, cognitive subgroups in this study were based on arbitrary cut-off scores. Another important reason for investigating cognitive subgroups based on both neurocognition and social cognition is to further examine the hypothesis of specificity of social cognitive deficits in schizophrenia (Lee et al., 2013). In their study, Lee et al. (2013) found that BP patients showed less impairment on social relative to non-social cognitive performance, whereas schizophrenia patients showed more impairment on social relative to non-social cognitive performance. However, some other studies have not supported this finding (Donohoe et al., 2012; Thaler et al., 2013). There is a significant heterogeneity of social and neurocognitive performances in studies comparing schizophrenia and BP. Cross-diagnostic clustering methods can potentially reveal a cognitive subgroup with a relatively more severe social cognitive deficit in schizophrenia which differs from BP and other schizophrenia patients.

The current cross-diagnostic study investigates cognitive subgroups, based on executive functions and ToM, in a sample of euthymic patients with BP and schizophrenia. We hypothesized that: (1) there would be specific subgroups with severe global impairment and preserved cognition, and the latter one would be overrepresented in BP sample; (2) there would be a subgroup with a selective impairment in ToM and this cluster would be more specifically related to schizophrenia than BP. We also aimed to compare clinical and demographic characteristics of each group.

2. Methods

The study sample included 43 euthymic patients with bipolar disorder, 54 stable patients with schizophrenia and 27 healthy controls. We aimed to investigate cognitive subgroups of major psychoses in clinically stable samples as some cognitive deficits, particularly ToM impairment, are more severe during manic episodes (Bora et al., 2015a). The patients groups were recruited from psychotic disorders and affective disorders outpatient clinics of Ege University in İzmir in Turkey. All patients had DSM-IV diagnoses of bipolar type I or schizophrenia based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1997). Subjects who had other disorders that could have an effect on cognitive function (significant neurological and physical illness, substance abuse or dependence in the last year, electroconvulsive therapy in the preceding year) were excluded. Controls had no relatives with bipolar or psychotic disorders and no history of psychiatric treatment. Mood state of patients with BP was assessed by the Turkish versions of Young mania rating scale (YMRS) and Hamilton Depression Rating Scale (HDRS) (Akdemir et al., 2001; Karadag et al., 2002). Euthymia was defined as YMRS total score ≤ 7 and HDRS score ≤ 7. The patients with bipolar disorder were in remission for at least four months. All of the patients with schizophrenia were clinically stable and have had no history of acute psychotic exacerbation for at least 3 months. The Turkish version of the Positive and Negative Syndrome Scale (PANSS) was also administered to evaluate current symptoms in patients with schizophrenia (Kostakoğlu et al., 1999).

Demographical and clinical variables including mean scores are reported in Table 1. There was no significant between-group difference for gender and duration of education. Schizophrenia patients were significantly younger than BP patients and healthy controls. All but one BP patients were receiving lithium. Some of the patients with BP were also on valproic acid ($n = 10$) or atypical antipsychotic ($n = 6$). All patients with schizophrenia were treated with antipsychotic medications.

2.1. Neuropsychological variables

Executive functions: Stroop Color Word Test (SCWT) and Wisconsin card sorting test (WCST) were administered to assess executive functions (Lezak, 1995). In this study, interference score of SCWT was used as a measure of interference control. As a measure of abstract reasoning and cognitive flexibility, 'number of categories achieved' and 'perseverative errors' scores of WCST were calculated.

ToM: Reading the mind in the eyes test (RMET) and Hinting tasks were administered. The Hinting task is a test of the ability of subjects to infer the real intentions behind indirect speech utterances (Corcoran et al., 1995). RMET measures the ability to identify complex mental states, requiring decoding other's intentions and beliefs (Baron-Cohen et al., 2001). Both tasks are relatively well established social cognitive tasks. As a part of Social Cognition Psychometric Evaluation (SCOPE) study, a recent report investigated psychometric properties of both measures along with other social cognition measures (Pinkham et al., 2016). In this study, the Hinting task had one of the strongest psychometric properties across all evaluation criteria and the RMET was also rated as acceptable, but a concern included the potential dependence of performance on vocabulary.

2.2. Data analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 14 and R. Group differences for demographic variables were tested with ANOVA and chi-square tests ($\chi 2$) (significance level of $p < 0.05$). Neuropsychological variables were transformed to Z-scores (based on mean and SD of healthy subjects). Between-group differences for cognitive variables were tested with ANCOVA using age as a covariate. Cohen D values were calculated as a measure of effect sizes for between-group differences.

We used Latent class analysis (LCA) for investigating the clustering of data with Mclust package in R (Fraley et al., 2012). The main difference between LCA and other clustering algorithms is that LCA is a "model-based clustering" method that derives clusters using a probabilistic model that describes the distribution of original research data instead of finding clusters with chosen distance measures that are theoretical or arbitrary (Hagenaars and McCutcheon, 2002). LCA has also other advantages over traditional clustering methods (i.e. K-