European Neuropsychopharmacology (2016) 26, 1338–1347

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Executive dysfunction and cognitive subgroups in a large sample of euthymic patients with bipolar disorder

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Received 6 January 2016; received in revised form 9 March 2016; accepted 14 April 2016

KEYWORDS
Bipolar disorder;
Neurocognition;
Cognitive heterogeneity;
Latent class analysis

Abstract
Bipolar disorder (BP), at the group level, is associated with significant but modest cognitive deficits, including executive dysfunction. Among executive functions, response inhibition deficits have been suggested to be particularly relevant to BP. However, BP is associated with significant heterogeneity in neurocognitive performance and level of functioning. Very few studies have investigated neurocognitive subgroups in BP with data-driven methods rather than arbitrarily defined criteria. Other than having relatively small sample sizes, previous studies have not taken into consideration the neurocognitive variability in healthy subjects. Five-hundred-fifty-six euthymic patients with BP and 416 healthy controls were assessed using a battery of cognitive tests and clinical measures. Neurocognitive subgroups were investigated using latent class analysis, based on executive functions. Four neurocognitive subgroups, including a good performance cluster, two moderately low-performance groups, which differ in

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http://dx.doi.org/10.1016/j.euroneuro.2016.04.002

response inhibition and reasoning abilities, and a severe impairment cluster were found. In comparison to healthy controls, BP patients were overrepresented in severe impairment cluster (27% vs 5.3%) and underrepresented in good performance cluster. BP patients with lower educational attainment and older age were significantly more likely to be members of cognitively impaired subgroups. Antipsychotic use was less common in good performance cluster. These results suggest that there is a considerable overlap of cognitive functions between BP and healthy controls. Neurocognitive differences between BP and healthy controls are driven by a subgroup of patients who have severe and global, rather than selective, cognitive deficits.

1. Introduction

Bipolar disorder (BP) is associated with neurocognitive deficits (Torres et al., 2007; Bora et al., 2009a, 2016; Bourne et al., 2013; Aydemir et al., 2014; Levent et al., 2014; Bora and Pantelis, 2015; Hıdıroğlu et al., 2015) and these deficits are already evident at the first-episode (Lee et al., 2014; Bora and Pantelis, 2015). However, cognitive impairment in BP is relatively less severe than schizophrenia (Krabbendam et al., 2005; Bora et al., 2009b). Neurocognitive functioning in BP is also more heterogeneous than schizophrenia. While, there is some heterogeneity in cognitive functioning in schizophrenia, only a minority of patients perform at the level of population average or above (Palmer et al., 1997; Kremen et al., 2000; Reichenberg et al., 2009; Bora et al., 2010; Lewandowski et al., 2014). As a result, patients with schizophrenia are much less likely to be employed and have long-term relationships (Mueser and Bellack, 1998). In contrast, bipolar disorder (BP) has been associated not only with poor functioning in many patients but also preserved functioning and success in academic, creative and professional life in others (MacCabe et al., 2010; Kyaga et al., 2011; Bora, 2015a). As a group, meta-analytical studies in euthymic BP suggested that most of the deficits have medium to large effect sizes (Cohen d=0.5–0.8) and are most pronounced in executive functions, processing speed, sustained attention and verbal memory (Torres et al., 2007; Bora et al., 2009a). These findings suggest that relatively large number of patients with BP perform at the level of population average or above. Variability of neurocognitive and social functioning in BP might likely reflect the heterogeneity of aetiology in BP including potential subtypes associated with different genetic susceptibility factors (Bora, 2015a). Current subtyping of BP in existing diagnostic criteria (BP-I vs II) is based solely on clinical symptoms (presence or absence of full manic episode) and naturally does not well reflect the variability of neurocognition in BP. Better characterisation of cognitive heterogeneity in BP can potentially facilitate genetic and biological studies to define more valid subtypes of BP and can also help clinicians and researchers to develop more effective intervention strategies (i.e. cognitive rehabilitation and cognitive enhancers) targeting cognitive deficits (Fuentes-Durá et al., 2012; Vreeker et al., 2015).

Very few studies have investigated neurocognitive subgroups in BP. Several studies have categorised BP patients into cognitively impaired and unimpaired groups based on arbitrary cut-off scores (Thompson et al., 2005; Martino et al., 2008). These studies have relatively small number of BP patients included (n=50–110) and used variable cut-off scores such as scoring 1–2 SD below controls or scoring at or below the 5th percentile (Thompson et al., 2005; Martino et al., 2008, 2013; Sánchez-Morla et al., 2009; Iverson et al., 2011; Volkert et al., 2015). Findings of these studies suggest that around 40% of patients with BP have no neurocognitive deficits at all (Martino et al., 2008; Volkert et al., 2015) and other patients have variable levels of cognitive deficits. Studies using strict cut-off scores (such as 2 SD below) found that 25–30% patients with BP have severe cognitive deficits (Gualtieri and Morgan, 2008; Iverson et al., 2011). At the other hand, two other studies have attempted to identify cognitive subgroups of BP with a data-driven approach (rather than arbitrary cut-off scores) using cluster analysis (i.e. K-means and hierarchical). Burdick et al. (2014) have investigated 136 BP patients and found 3 clusters according to neurocognitive performance. These clusters included a neuropsychologically intact (30%), selectively impaired (30%) and globally impaired (40%) groups. In another cluster analysis study, Lewandowski et al. (2014) found that 40% of 73 BP were neuropsychologically normal, 15% had a global cognitive impairment. In this study, other patients were members of two different selective cognitive impairment clusters (total number of clusters 4). Both of these studies have included BP patients who were not strictly euthymic and latter study included acutely symptomatic patients. Also, these cluster analytical studies have not investigated variability in cognitive functioning in healthy controls and cannot tell whether any of the subgroups are more specifically related to BP than controls.

Potential cognitive subgroups in BP might be the product of differences in developmental and post-illness onset trajectories of global or selective cognitive factors in distinct neurobiological subtypes (Bora, 2015a). There might be a subgroup of BP patients with very severe and global cognitive deficits (Bora, 2015a). Other subgroups of patients with BP might have more selective deficits. As premorbid IQ differences between BP and healthy controls are marginal (Torres et al., 2007; Bora et al., 2009a), global cognitive impairment in most patients with BP should reflect deficits in fluid intelligence (but not crystallised intelligence), which is robustly correlated with executive functions and complex aspect of other cognitive functions including processing speed, attention and working memory,