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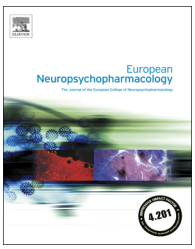

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Developmental trajectory of cognitive impairment in bipolar disorder: Comparison with schizophrenia

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Abstract
Both schizophrenia and bipolar disorder (BP) are associated with neurocognitive deficits. However, it has been suggested that schizophrenia, but not BP, is characterised by premorbid cognitive impairments and neurodevelopmental abnormalities. In this paper, studies investigating neurocognitive deficits in premorbid, high-risk and first-episode BP were reviewed and these findings were compared with outcome of studies in schizophrenia. Available evidence suggests that cognitive deficits are evident in first-episode BP and such deficits can be evident even years before the onset of the illness in some patients. Trajectory of cognitive deficits from childhood to adulthood can be very similar in schizophrenia and many patients with BP. Developmental lag in acquisition of cognitive skills is a risk factor for both disorders. However, unlike schizophrenia, not only impaired cognition but also supranormal premorbid cognitive/scholastic performance predict BP. Neurodevelopmental cognitive impairment is evident in some but not all patients with BP. A model suggesting that only BP patients who share common genetic risk factors with schizophrenia have premorbid neurodevelopmental cognitive deficits is proposed. In this model, combination of absence of neurodevelopmental abnormalities and BP-related temperamental characteristics explains the relationship between supranormal cognition and risk for BP.

1. Introduction

Cognitive dysfunction is a common and robust feature of schizophrenia (Gold and Harvey, 1993; Heinrichs and Zakzanis, 1998; Bora et al., 2010a). Bipolar disorder is also associated with cognitive deficits in a number of domains including executive functions, attention and memory that persists in remission (Bora et al., 2009a). The pattern of these cognitive deficits overlaps in schizophrenia and BP, but cognitive dysfunction is less severe in BP (Bora et al., 2009b; Krabbendam et al., 2005).

It is argued that cognitive deficits in BP and schizophrenia might have very different trajectories. In schizophrenia,

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there is a consensus that neurodevelopmental factors play an important role in cognitive deficits. A number of studies have provided evidence indicating that cognitive and intellectual deficits are evident early in neurodevelopment, including childhood, well before the onset of psychosis (Fuller et al., 2002; Kahn and Keefe, 2013; Reichenberg et al., 2010). It seems that cognitive development is abnormal in children and adolescents who develop adult schizophrenia. In addition to cognitive deficits, findings such as increased prevalence of neurological soft signs, childhood motor and language impairments, and prenatal and obstetric complications are among evidence supporting neurodevelopmental abnormality in schizophrenia (Murray and Lewis, 1987: Weinberger, 1986). Some authors also suggested that premorbid cognitive deficits in schizophrenia are not only related to problems in development of cognitive abilities but also to loss of acquired cognitive abilities before or around the onset of first-episode (Kahn and Keefe, 2013). In contrast to findings in schizophrenia, a number of studies have suggested normal, at times superior, cognitive abilities and school achievement in children and adolescents who develop adult BP (Kumar and Frangou, 2010). There is also good evidence suggesting a relationship between BP and creativity in adulthood (Kyaga et al., 2011). Therefore, it has been suggested that developmental cognitive abnormalities might be specific to schizophrenia (Kahn and Keefe, 2013; Murray et al., 2004). Patients with BP only develop cognitive deficits during the course of illness; whereas in schizophrenia cognition is impaired before the onset of the illness and at first-episode.

On the other hand, another evidence suggests that abnormalities in neurodevelopment can play a role not only in schizophrenia but also in BP. A number of potential common susceptibility genes for schizophrenia and BP have a role in neurodevelopment (Craddock and Owen, 2010). There is also evidence suggesting that neurological soft signs might be more common in BP than healthy controls (Zhao et al., 2013). Some studies also suggested a link between prenatal and perinatal abnormalities and BP. A recent study showed a four-fold increase in risk for BP in adult offspring of mothers who had gestational influenza (Parboosing et al., 2013). Some evidence suggests that cognitive impairment in BP can be associated with abnormalities in genes that have role in brain development (Tabarés-Seisdedos et al., 2008). Further studies have reported cognitive abnormalities in first-episode of BP and unaffected healthy relatives of BP patients (Bora et al., 2009a; Torres et al., 2010). It is also important to note that longitudinal studies in chronic patients with BP and few available studies in first-episode BP (Bombin et al., 2013; Torres et al., 2014) have not so far supported evidence for progressive cognitive decline in BP. These findings are rather similar to outcome of longitudinal studies in schizophrenia (Bora and Murray 2013; Szöke et al., 2008) which suggest that neurodevelopmental factors might play an important role in major psychoses. Therefore, it is important to revisit the question of specificity of neurodevelopmental cognitive deficits to schizophrenia and offer an explanation to reconcile the seemingly contradicting findings in BP.

The aim of the current paper is to review the studies investigating cognitive deficits in premorbid and early BP, compare these findings to schizophrenia and explore the relationship between premorbid cognitive functioning and BP risk. In the first part of the paper, neurocognitive studies in first-episode and high-risk samples were reviewed. In the second part of the paper, studies investigating premorbid cognitive deficits in BP and schizophrenia and course of these deficits were explored. In the final part, a proposal to explain the dual nature of relationship between cognitive/scholastic performance and risk for BP is introduced.

2. Cognitive impairment in early "phases" of schizophrenia and BP

2.1. Cognitive impairment in first-episode

It is well established that robust cognitive deficits are already evident in first-episode schizophrenia (FES) (Bora and Pantelis, 2013; Mesholam-Gately et al., 2009). However, in BP, it was suggested that cognitive deficits develop after the onset of the illness (Goodwin et al., 2008). It was argued that cognitive deficits should be absent or very modest in first-episode BP (FEBP) (Demjaha et al., 2012). It was also suggested that this might be a key difference between BP and schizophrenia. Recently, a number of neuropsychological studies have been conducted in FEBP and the bulk of these studies have not supported the preserved cognition argument in FEBP. In Table 1, findings of FEBP studies are summarised. These studies were selected through a literature search in the databases Pubmed, PsycINFO, ProQuest and Scopus to identify the relevant studies (January 1990–July 2014). Inclusion criterion investigated cognitive functions in FEBP in comparison to healthy controls. Any study that did not examine cognitive functions within 2 years after the onset of first-episode was excluded. In the case of overlapping samples only studies with largest sample sizes selected with the exception of studies investigated different cognitive domains or different symptomatic state in comparison to larger study. Most of these cross-sectional studies suggest that neurocognitive deficits are already evident in FEBP, including euthymic patients, which is also confirmed in a recent meta-analysis (Lee et al., 2014). Another meta-analysis (Bora and Pantelis, unpublished data) suggest that the deficits with medium to large effect sizes are evident in all cognitive domains investigated (verbal memory, processing speed, sustained attention, problem solving and reasoning, working memory, fluency and visual memory) (d=0.36–0.83). Magnitude and pattern of such deficits in FEBP are very similar to findings in chronic BP patients (Bora et al., 2009a). Findings of these meta-analyses also suggest that cognitive deficits in FEBP cannot be explained by mood symptoms.

2.2. Cognitive impairment in high risk schizophrenia and BP

While FE studies fail to support specificity of early cognitive deficits to schizophrenia, it might be argued that effects of recent illness and treatment might cause emergence of cognitive impairment in BP which might not be evident before the onset of the illness. Therefore, studies investigating cognitive deficits in at-risk subjects before the first-episode