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Research paper

Neurocognitive performance, psychopathology and social functioning in individuals at high risk for schizophrenia or psychotic bipolar disorder

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ABSTRACT

Introduction: Although cognitive deficits are consistent endophenotypes of schizophrenia and bipolar disorder, findings in psychotic bipolar disorder (BDP) are inconsistent. In this study we compared adult unaffected first-degree relatives of schizophrenia and BDP patients on cognition, psychopathology, social functioning and quality of life.

Methods: Sixty-six unaffected first-degree relatives of schizophrenia patients (SUnR), 36 unaffected first-degree relatives of BDP patients (BDPUnR) and 102 controls participated in the study. Between-group differences were examined and Discriminant Function Analysis (DFA) predicted group membership.

Results: Visual memory, control inhibition, working memory, cognitive flexibility and abstract reasoning were linearly impaired in the relatives' groups. Poorer verbal fluency and processing speed were evident only in the SUnR group. The SUnR group had higher depressive and somatization symptoms while the BDPUnR group had higher anxiety and lower social functioning compared with the controls. Individuals with superior cognition were more likely to be classified as controls; those with higher social functioning, prolonged processing speed and lower anxiety were more likely to be classified as SUnR.

Limitations: The relatives' sample is quite heterogeneous; the effects of genetic or environmental risk-factors were not examined.

Conclusions: Cognitive functions mediated by a fronto-parietal network, show linear impairments in unaffected relatives of BDP and schizophrenia patients; processing speed and verbal fluency impairments were evident only in schizophrenia relatives. Self-perceived symptomatology and social functioning also differ between schizophrenia and BDP relatives. The continuum seen in patients in several indices was also seen in the cognitive impairments in unaffected relatives of schizophrenia and BDP patients.

1. Introduction

The term "psychosis continuum" refers to either the absence of clear-cut boundaries between psychotic disorders or to the presence of psychotic features ranging from sub-threshold psychotic experiences observed in healthy individuals to clinical symptoms observed in patients (Pearlson, 2015; van Os et al., 2009). Despite long-lived categorical models of psychotic disorders, the "continuum view" has gained wide support and is now included in the diagnostic procedures proposed (American Psychiatric Association, 2013). Thus, in *DSM-5* (Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition; American Psychiatric Association, 2013) Bipolar Disorder (BD) and related disorders are found between schizophrenia spectrum and other psychotic disorders and depressive disorders *"in recognition of their place as a bridge between the two diagnostic classes in terms of symptomatology, family history, and genetics"* (American Psychiatric Association, 2013, page 123). This dimensional view was formulated based on findings indicating shared aspects of BD and schizophrenia in psychopathology (Rosen et al., 2012), structural and functional brain changes (Frangou, 2014), genetics (Craddock et al., 2006) as well as treatment strategies (Tamminga et al., 2014). A high percentage [ranging from around 30% (Keck et al., 2003) to around 70% (Morgan et al., 2005)] of the patients diagnosed with BD also present with psychotic symptoms which predict patients' outcome (Pallaskorpi et al., 2015). Interestingly, (i) psychotic and non-psychotic BD differ in familial aggregation rates (Potash et al., 2001, 2003), brain alterations (Radaelli et al., 2014) and genetic risk factors (Lett et al., 2011) and (ii) psychotic BD (BDP) resembles schizophrenia in all the afore-men-

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tioned and other indices (for a review see Buoli et al., 2016) in favor of the dimensional rather than the categorical approach.

Cognitive deficits in several domains are central features of schizophrenia as they are present from the prodromal phase of the illness (Corigliano et al., 2014) through the first episode (Haatveit et al., 2015; Zhang et al., 2015) and remain stable over time (Bergh et al., 2016; Haatveit et al., 2015) without significant improvement with antipsychotic treatments (Keefe, 2014); they predict conversion into psychosis (Zhang et al., 2015) and they are associated with the functional outcome of the patients (Bowie and Harvey, 2006). Cognitive deficits in BD have also been reported at the early stages of the illness (Bora and Pantelis, 2015; Martino et al., 2015), they remain stable over time (Samamé et al., 2014; Santos et al., 2014), they are independent of mood episodes (Bora et al., 2016; Bourne et al., 2015), they do not improve with treatment (Dias et al., 2012) and they are associated with the functional outcome of the patients (Baune and Malhi, 2015). The severity of impairment may follow a continuum with BD and schizophrenia occupying the lowest and highest ends of the continuum, respectively, while BDP shows intermediate levels of impairment (Kuswanto et al., 2016).

Cognitive deficits in schizophrenia and BD are considered heritable as they are consistently found in unaffected relatives of schizophrenia and bipolar patients (Bortolato et al., 2015; Hill et al., 2008); they may even present early in childhood or adolescence for both groups of relatives (Bora et al., 2014; Diwadkar et al., 2011; Doyle et al., 2009; Owens and Johnstone, 2006; Hill et al., 2008; Keshavan et al., 2005; Niemi et al., 2003). However, the topic of cognitive deficits in relatives of psychotic bipolar patients is understudied and the findings are inconsistent. Relatives of BDP patients have been reported to present with (i) verbal and visual memory impairments compared with relatives of schizophrenia patients (Kremen et al., 1998) although another study found non-significant differences (Kim et al., 2015), (ii) poorer cognitive flexibility compared with relatives of BD patients (Bora et al., 2008) and (iii) poorer working memory and processing speed compared only with controls (Antila et al., 2009; Hill et al., 2015; Kim et al., 2015; Wang et al., 2015). However, BDP relatives did not differ from relatives of schizophrenia patients or controls in a composite score of tasks assessing verbal and working memory, processing speed and reasoning/problem solving (Hill et al., 2013). Finally, although BDP patients have been reported to present with inhibitory control deficits, their unaffected relatives were found to be free of any such impairment (Ethridge et al., 2014). Interestingly, neurocognitive network studies have also revealed that these cognitive functions are subserved by a fronto-parietal brain network (Dajani and Uddin, 2015; Gu et al., 2015; Medaglia et al., 2015; van Amelsvoort and Hernaus, 2016), which is disrupted in both schizophrenia and BDP (Baker et al., 2014; Chaddock et al., 2009; Dutt et al., 2015; McDonald et al., 2004; Watson et al., 2012).

Apart from the deficits in cognition, impoverished quality of life (QoL) and poor social functioning have also been well-documented in schizophrenia (e.g. Jaracz et al., 2007; Wartelsteiner et al., 2016) and BD (e.g. Cotrena et al., 2016; Simonsen et al., 2010). Although less in known about the associations of these two factors with BDP, there is evidence that (i) BDP patients have poorer psychosocial functioning compared with BD patients (Levy et al., 2013) and controls (Tamminga et al., 2013) and (ii) that schizophrenia patients report lower psychosocial functioning than BDP patients (Tamminga et al., 2013) or that there are non-significant differences between the two groups (Simonsen et al., 2010). To our knowledge only two studies have examined social functioning in relatives of schizophrenia and BDP patients. They either reported poorer social adjustment in the pooled relatives group compared with the controls (Walshe et al., 2012), or they found non-significant group differences Tamminga et al. (2013).

In order to further elucidate the topic on similarities and differences between schizophrenia and BDP, the aim of the present study was to compare matched groups of unaffected first-degree relatives of schizophrenia and BDP patients and control individuals on a range of cognitive functions, psychopathology, social functioning and quality of life. We further examined potential discriminating effects of the aforementioned measures between the two groups of relatives and the control group.

2. Materials and methods

2.1. Participants

Seventy-one unaffected first-degree relatives of schizophrenia patients (SUnR) and 42 unaffected first-degree relatives of bipolar disorder patients with history of psychosis (BDPUnR) were recruited via the local psychiatric services in Peloponnese and the Ionian islands in Greece. Exclusion criteria were personal history of head trauma, medical or neurological conditions, current use of prescribed or recreational drugs and personal history of DSM-IV Axis I disorders. All participants underwent psychiatric assessment using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Based on these criteria, 5 participants were excluded due to detected Axis I pathology (3 from the SUnR and 2 from the BDPUnR group), 3 subjects were excluded due to personal history of head trauma, medical or neurological conditions (1 from the SUnR and 2 from the BDPUnR group) and 3 subjects were excluded due to self-reported current use of recreational or prescribed drugs (1 from the SUnR and 2 from the BDPUnR group). Therefore, the final sample consisted of (a) 66 SUnR participants; of those, 42 were siblings (age range: 20–45 years; age mean ± SD: 37.07 ± 6.26; 17 males: 25 females), 7 were offspring (age range: 21–41 years; age mean ± SD: 31.14 ± 7.03; 3 males: 4 females) and 17 were parents (age range: 40–46 years; age mean ± SD: 42.35 ± 12.81; 2 males: 15 females) and (b) 36 BDPUnR participants; of those, 19 were siblings (age range: 21–46 years; age mean ± SD: 37.11 ± 7.60; 7 males: 12 females), 16 were offspring (age range: 20–46 years; age mean ± SD: 32.25 ± 6.49; 6 males: 10 females) and 1 was parent (age: 43 years; female). Parents were included in the study only if they had at least one sibling diagnosed with either schizophrenia or BD in order to be as certain as possible that we included the parents carrying and passing on the genetic risk to their offspring. There was no overlap in the relatives for schizophrenia and BDP and only one first-degree relative of each patient was included in the.

One-hundred and nineteen control participants, matched for gender, age and years of education with the relatives' group, were also recruited. Exclusion criteria were identical to those in the relatives' group with the additional exclusion criterion of family (up to second-degree) history of DSM-IV Axis I disorders. This group also underwent psychiatric assessment using the MINI. Based on the exclusion criteria, 2 participants were excluded due to detected Axis I pathology, 5 subjects were excluded due to personal history of head trauma, medical/neurological conditions, 6 subjects were excluded due to self-reported current use of recreational/prescribed drugs and another 4 subjects dropped-out. Thus, the control group consisted of 102 participants.

The study was approved by the Research Ethics Committee of the Department of Psychology in the University of Crete, the Research Ethics Committee of the University of Crete and the Bureau for the Protection of Personal Data of the Greek State. Following presentation of the study's aims and methods, all participants received a detailed information sheet and gave written informed consent before participation.

2.2. Neuropsychological assessment

Participants were assessed for visual memory with the Modified Taylor Complex Figure test (MTCF; Hubley, 1996), verbal/category fluency with the Controlled Oral Word Association test (COWAT; Kosmidis et al., 2004), control inhibition with the Stroop Colour-