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Familial resemblance for executive functions in families of schizophrenic and bipolar patients

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Abstract

Executive dysfunctions are considered to be putative markers of familial/genetic vulnerability to both schizophrenia and bipolar disorder. However, familial resemblance must be demonstrated before executive functions are used as a potential endophenotype. The aim of this study was to investigate familial resemblance for executive functions in families of schizophrenic and bipolar subjects. We assessed executive functions by means of two tests – the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT) – in 351 subjects from five populations: schizophrenic patients, bipolar patients, a group of relatives for each patient group and controls. For both tests, cognitive assessment results were consistent with previous studies: schizophrenic patients showed the greatest impairment, followed by bipolar patients and then the two groups of relatives. In families of bipolar patients we observed familial resemblance for the WCST and part A and part B of the TMT. However, by contrast with the classical point of view, considering executive measures to be markers of genetic vulnerability to schizophrenia, we did not demonstrate familial resemblance for either of the two executive tests in families of schizophrenic patients. Thus, executive measures, as assessed by the WCST or the TMT, should not be used as endophenotypes in genetic studies of schizophrenia unless confounders are identified and their effects eliminated.

Keywords: Executive dysfunction; Genetics; Endophenotype; Cognition

1. Introduction

Despite the existence of strong evidence for a genetic component in schizophrenia and bipolar disorder, no single gene has convincingly been shown to increase the risk for those disorders. One reason for this is the complexity of psychiatric disorders at the clinical and etiological level. Several authors (Gottesman and Shields, 1973; Leboyer et al., 1998; Freedman et al., 1999; Leboyer, 2003) have advocated the use of the endophenotype approach to circumvent this problem. Endophenotypes are measurable traits, associated with the liability to the disorder and having a simple

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genetic determinism. As such, they provide a means of reducing clinical and genetic heterogeneity in psychiatric research. Gottesman and Gould (2003) recently summarized criteria for a good (i.e. an useful) endophenotype as follows: a) associated with illness, b) more frequent in non-affected relatives than in general population, c) heritable and d) associated with a candidate gene or gene region. Several authors have suggested that measures of executive functions (EF) could be used as endophenotypes in schizophrenia and bipolar research. EF are cognitive processes that allow the subject to adapt to unusual situations in which automated responses are not sufficient. Among various tests that are used to assess EF, the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT) are of particular interest as they are well standardized, are widely used and could represent, at least in families of schizophrenic probands, markers of two distinct risk factors (Yurgelun-Todd and Kinney, 1993). With these two tests, executive dysfunctions were repeatedly found in schizophrenic patients (Koren et al., 1998; Bustini et al., 1999; Laurent et al., 2000), and impairment has also been detected in most studies of bipolar patients (Coffman et al., 1990; Morice, 1990; Ferrier et al., 1999), although some exceptions are known (Rubinsztein et al., 2000). Several studies of relatives of schizophrenic or bipolar patients have investigated whether executive dysfunction could be used as a marker of familial vulnerability. Recently, two meta-analyses (Sitskoorn et al., 2004; Szöke et al., 2005) showed that relatives of schizophrenic patients have impaired performance on tests of executive functions. The impairments observed were less severe than those observed in patients. Fewer studies have compared the relatives of bipolar patients with controls (Kremen et al., 1998; Keri et al., 2001), and no firm conclusions can be drawn from the results obtained in these studies. In a previous study, we (Zalla et al., 2004) found no significant difference in WCST or TMT scores between relatives of bipolar patients and controls. However, this may reflect the limited statistical power of the study, due to small sample sizes.

The heritability of executive impairments was assessed by calculating relative risk in siblings of schizophrenic patients (Egan et al., 2001a). In this population, the authors found an increased risk of impaired performance on Trails B and the WCST (4.0 and 2.0, respectively). However, relative risk is not a direct measure of heritability. Instead, as pointed out by Egan et al. (2001a), it assesses its upper limit.

Based on these results and on the hypothesis linking EF and catechol-*O*-methyl transferase (COMT) activity (see Weinberger et al., 2001 for further discussion), several studies have looked for an association between executive dysfunctions and COMT gene polymorphisms in schizophrenic patients and their relatives. The Val158Met functional polymorphism of the COMT gene was found to affect WCST performance if schizophrenic patients and controls were pooled together (Egan et al., 2001b; Joober et al., 2002), but not if schizophrenic patients were assessed separately (Rosa et al., 2002; Bilder et al., 2002; Ho et al., 2005). This effect was also found in the siblings of schizophrenic patients in one study (Rosa et al., 2002) but not in another (Egan et al., 2001b). It was also found in healthy volunteers (Malhotra et al., 2002). In bipolar subjects, a positive association was found between WCST performance and a polymorphism (Val66Met) of another candidate gene, the brain-derived neurotrophic factor (BDNF) gene (Rybakowski et al., 2003). Inconsistencies in the results of association studies using WCST score as the endophenotype may be accounted for by as yet unidentified confounders, which could limit the value of EF as an endophenotype.

The aim of our study was to investigate the causes of discrepancies between the promising results of studies showing impairments in patients and their relatives and the disappointing results of association studies. To do this, we assessed familial resemblance for performances on two widely used tests of EF – the WCST and the TMT – in families of schizophrenic and bipolar patients. Familial resemblance, which, unlike relative risk, is sensitive to incorrect individual evaluation and classification (i.e. to confounders not accounted for), is an indicator of actual heritability and, as such, is a more stringent indicator of the usefulness of a putative endophenotype for genetic research.

Discrepancies between studies investigating executive dysfunctions may be partly explained by differences in inclusion criteria for bipolar patients (euthymic or not), for relatives (including or excluding affected relatives) and for controls (including or excluding controls with a positive family history). To limit the probability of identifying spurious differences due to the inclusion of acutely ill patients and of false-negative results due to "fuzzy" borders between groups, we used strict inclusion criteria. We included only patients in remission and excluded subjects presenting a personal history of psychotic or bipolar disorders from the non-patient groups, and subjects with affected first-degree relatives from the control group.