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Do common genotypes of FK506 binding protein 5 (*FKBP5*) moderate the effects of childhood maltreatment on cognition in schizophrenia and healthy controls?

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ABSTRACT

Common variants of the FK506 binding protein 5 (*FKBP5*) gene are implicated in psychotic and other disorders, via their role in regulating glucocorticoid receptor (GR) receptor sensitivity and effects on the broader function of the HPA system in response to stress. In this study, the effects of four *FKBP5* polymorphisms (rs1360780, rs9470080, rs4713902, rs9394309) on IQ and eight other cognitive domains were examined in the context of exposure to childhood maltreatment in 444 cases with schizophrenia and 292 healthy controls (from a total sample of 617 cases and 659 controls obtained from the Australian Schizophrenia Research Bank; ASRB). Participants subjected to any kind of maltreatment (including physical, emotional, or sexual abuse or physical or emotional neglect) in childhood were classified as 'exposed'; cognitive functioning was measured with Repeatable Battery for the Assessment of Neuropsychological Status, the Controlled Oral Word Association Test, and IQ was estimated with the Weschler Test of Adult Reading. Hierarchical regressions were used to test the main effects of genotype and childhood maltreatment, and their additive interactive effects, on cognitive function. For rs1360870, there were significant main effects of genotype and childhood maltreatment, and a significant interaction of genotype with childhood trauma affecting attention in both schizophrenia and healthy participants (C-homozygotes in both groups showed worse attention in the context of maltreatment); in SZ, this SNP also affected global neuropsychological function regardless of exposure to childhood trauma, with T-homozygotes showing worse cognition than other genotypes. The mechanisms of trauma-dependent effects of *FKBP5* following early life trauma deserve further exploration in healthy and psychotic samples, in the context of epigenetic effects and perhaps epistasis with other genes. Study of these processes may be particularly informative in subgroups exposed to various other forms of early life adversity (i.e., birth complications, immigration).

1. Introduction

Exposure to traumatic experiences in the early stages of life, including maltreatment (i.e., physical, sexual or emotional abuse, and various forms of neglect), parental loss or divorce, parental substance abuse, and poverty (Rosenberg et al., 2007) are known to influence the development of severe mental disorders, including schizophrenia (Kessler et al., 2010; Varese et al., 2012). These early

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life experiences may set about a cascade of biological effects that result in dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, a key system in stress response (van Winkel et al., 2008a; van Winkel et al., 2008b). Variation in genetic regions known to regulate the stress response system (e.g., the FK506 binding protein 5 [*FKBP5*] gene) have been implicated as risk factors for bipolar disorder (Willour et al., 2009), and psychotic symptoms in the general population (Collip et al., 2013). The *FKBP5* gene codes for the FKBP5 protein that is involved in the regulation of glucocorticoid function in response to stress; notably, elevated levels of FKBP5 confer reduced sensitivity of the glucorticoid receptor to circulating cortisol, leading to decreased negative feedback regulation of the HPA axis, and thus an abnormally prolonged stress response as the system takes longer to reduce cortisol secretion (Binder, 2009). The relevance of these genetic variations for stress-related psychopathology is thus well established.

For example, a number of studies demonstrate significant interactions between childhood adversity and single nucleotide polymorphisms (SNPs) of the *FKBP5* gene (most commonly rs1360870) affecting a range of psychopathologies, including post-traumatic stress disorder (Binder et al., 2008; Xie et al., 2010), depression (Appel et al., 2011; Zimmermann et al., 2011), suicide risk (Roy et al., 2010), aggression (Bevilacqua et al., 2012) and psychosis (Collip et al., 2013). This SNP has also been associated with biased attention toward threat and associated hippocampal function and structure (Fani et al., 2013), and neurophysiology of the cingulum (Fani et al., 2013). Taking one step further to study the interaction between several *FKBP5* SNPs and childhood maltreatment affecting threat-related amygdala reactivity, White et al. (2012) recently reported significant effects of two common variants (rs9470080 [in high Linkage Disequilibrium with rs1360780] and rs9394309) affecting amygdala function in healthy participants in the context of exposure to childhood emotional neglect (White et al., 2012).

Only two recent studies provide divergent evidence for the interaction of *FKBP5* genotypes and childhood trauma in psychotic samples: one study reports that subclinical psychotic symptoms in a general population sample (N = 401) are higher for certain FKBP5 genotypes (rs9296158, rs992105, rs1360780 [genotyped as rs3800373]) in the context of childhood trauma exposure (Collip et al., 2013); interestingly, only one of these SNPs (rs9296158) interacted with trauma to affect psychotic symptoms in a clinical group (N = 195), and two (rs4713916, rs1043805) were associated with psychotic-like symptoms in the unaffected relatives (N = 200) of psychosis patients. This study additionally examined genetic variation in association with cortisol levels, showing significant effects of two SNPs (rs9296158, rs4713916) in the context of childhood trauma, in which lower cortisol levels were found in A-homozygotes exposed to trauma in the general population sample. Notably, the analysis for rs1360780 (rs3800373) just failed to reach significance, but suggests that T-homozygotes in the general population (i.e., those reporting greater psychotic-like phenomena) also had lower cortisol levels (Collip et al., 2013). In another study by the same group, these four polymorphisms were examined in relation to their interactive effects with childhood trauma on cognitive performance and hippocampal volume in a relatively smaller sample of psychotic patients (N = 89) and their unaffected siblings (N = 95) (Hernaus et al., 2014); this study reported null results, and may have been underpowered considering that Collip et al.'s (2013) individual group sample sizes were significantly greater than those of Hernaus et al. (2014).

Childhood maltreatment has been shown to affect cognitive performance in later life in previous studies of ostensibly healthy adults (Koenen et al., 2003; Pears et al., 2008; Perez and Widom, 1994), people with schizophrenia (Green et al., 2014; Lysaker et al., 2001; Shannon et al., 2009) and people diagnosed with borderline personality disorder (Afifi et al., 2011; Minzenberg et al., 2008). This study thus sought to further investigate potential interplay between four previously implicated genetic variants of *FKBP5* (rs4713902, rs3800373, rs1360780, and rs9470080) and exposure to childhood maltreatment in relation to cognitive function (and symptom expression in patients) in a large sample of schizophrenia patients and healthy controls. It was hypothesized that these polymorphisms would moderate the influence of childhood maltreatment on cognitive performance in schizophrenia and healthy controls, and symptom expression in the schizophrenia cases.

2. Methods

All participants provided written informed consent according to study procedures approved by the Human Research Ethics Committee of the University of New South Wales (originally UNSW Protocol No. 07167; renewed in 2012 as HREC12384).

3. Participants

Research data obtained from the Australian Schizophrenia Research Bank (ASRB) included full sets of clinical and cognitive data for 617 clinical cases with an ICD-10 diagnosis of schizophrenia (n = 526) or schizoaffective disorder (n = 91), to be referred to collectively as 'SZ', and 659 healthy controls (HC). The ASRB represents a national bio-bank facility that is open for access by any team of scientists wanting to test hypotheses afforded by these data; formal access protocols ensure appropriate use of the data for relevant scientific purposes. The ASRB research data were collected over the years of 2006–2010 by scientific collaborators across five Australian states and territories (Loughland et al., 2011). Exclusion criteria comprised an inability to converse fluently in English, organic brain disorder, brain injury with greater than 24 h post-traumatic amnesia, mental retardation (IQ < 70), movement disorders, current substance dependence, and/or electroconvulsive therapy received in the last 6 months. In addition, the control participants had no personal history of DSM-IV Axis 1 disorder and no history of psychotic disorder in their first-degree biological relatives. The majority of clinical cases in the ASRB sample were medicated at the time of testing, with 398 participants taking anti-psychotic medication, 69 taking a mood stabiliser, and 145 taking anti-depressants. Overall 612 out of 617 (99.19%) were receiving some type of medication (See Table 1).

4. Materials

4.1. Clinical assessments

Clinical and diagnostic information was obtained using the Diagnostic Interview for Psychosis (DIP), conducted by trained research staff (Castle et al., 2006). The severity of positive symptoms was estimated by computing the total score of lifetime hallucination and delusion scores from the DIP (DIP items 49 to 53 and 58 to 64, respectively), and negative symptom severity was assessed with the Scale for the Assessment of Negative Symptoms (Andreasen, 1983).

4.2. Neuropsychological assessment

Premorbid IQ was assessed using the Wechsler Test of Adult Reading (Wechsler, 2001). Measures of neuropsychological function in seven cognitive domains was assessed using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS)