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The role of cognitive functioning in the relationship between childhood trauma and a mixed phenotype of affective-anxious-psychotic symptoms in psychotic disorders

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ABSTRACT

Cognitive impairments in patients with psychotic disorder have been associated with poor functioning and increased symptom severity. Furthermore, childhood trauma (CT) exposure has been associated with worse cognitive functioning as well as co-occurrence of affective-anxious-psychosis symptoms or a 'mixed phenotype of psychopathology' (MP), which in turn is associated with greater symptom severity, and poor functioning. This study aims to evaluate if cognition could be associated with CT/MP.

532 patients with non-affective psychotic patients were assessed on CT, symptom profile, cognition, functioning, and symptom severity at baseline and 3 and 6-year follow-up. Four subgroups were made according to trauma exposure (CT− or CT+) and presence of a mixed phenotype (MP− or MP+): CT−/MP (n = 272), CT−/MP+ (n = 157), CT+/MP− (n = 49), and CT+/MP+ (n = 54). Mixed-effects multilevel regression, linear regression, and Tobit analyses were performed.

Patients with both CT and MP showed lower verbal learning and memory than CT−/MP+ individuals ($p < 0.001$). No other significant differences were found among the 4 subgroups. No cognitive decline was found at follow-up, neither in the CT+/MP− nor in CT−/MP− group. Lower cognition was not associated with increased symptom severity or poor functioning at follow-up, neither in the CT+/MP− nor in CT−/MP− group.

Although cognitive impairments and CT may be related to clinical or functional features of psychotic disorder, and cognitive functioning could be affected by CT exposure, cognition does not discriminate subgroups of patients stratified by CT exposure and MP.

1. Introduction

Cognitive impairments are considered core features in psychotic disorder (PD), suggesting neurocognition as an endophenotypic marker of psychosis (Aas et al., 2013; Mehta et al., 2013; Rajji et al., 2014; Reichenberg, 2005). Cognitive dysfunctions occur across several domains such as executive functioning, episodic and working memory,

Abbreviations: CT, childhood trauma; MP, mixed phenotype of psychopathology; PD, psychotic disorder.

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attention, language, explicit learning, and motor processing (Antonova et al., 2004). Generally, PD patients show a cognitive ability between 1.5 and 2 standard deviations below that of a sample of matched healthy controls (Antonova et al., 2004). Similarly, it has been shown that relatives of PD patients exhibit cognitive impairments that are milder than, yet similar to, those seen in patients (Reichenberg, 2005). Moreover, neuropsychological impairments are associated with lower general functioning in first episode psychosis (FEP) as well as in chronic psychosis (Rajji et al., 2014). Follow-up studies of 2–10 years (Malla et al., 2002; Smith et al., 2002; Stirling et al., 2003; Tandberg et al., 2011) have linked attention, executive function, and memory with both work performance and social functioning. Furthermore, there is some evidence linking cognitive impairment with psychotic symptom severity (de Gracia Dominguez et al., 2009).

It has also been shown that psychotic patients who have experienced childhood trauma (CT), an environmental risk factor for psychosis (Morgan and Gayer-Anderson, 2016; Rössler et al., 2016; Varese et al., 2012), score lower on a range of cognitive domains than those without CT (Aas et al., 2013). Cross-sectional studies on psychotic spectrum disorder found lower processing speed, and working and episodic memory deficits in patients with CT compared to patients without CT, after adjusting for premorbid intelligent quotient (IQ) (Lysaker et al., 2001) and depressive symptoms (Shannon et al., 2011). Schenkel et al. (2005) found some evidence of an association between childhood abuse and impairment in visual-perceptual organization (Schenkel et al., 2005). Furthermore, in a sample of 406 patients with PD or bipolar disorder, CT was related with lower working memory and executive functioning, although these associations seemed to be driven by IQ reductions (Aas et al., 2012a). Analogous findings have found in case-control studies on FEP patients, where CT was associated with deficits in language, verbal intelligence, executive functioning, and working memory (Aas et al., 2011a, 2012b), although other studies did not replicate these results (Aas et al., 2011b; Sideli et al., 2014). Furthermore, a recent study of individuals with ultra-high risk (UHR) for psychosis highlighted worse attention, interference inhibition, working memory, and cognitive flexibility, in subjects exposed to childhood physical abuse (Üçok et al., 2015).

Recent studies have also shown that PD patients with a history of CT, compared with their non-exposed counterparts, display a phenotype composed of an admixture of affective, anxious, and psychotic symptoms, rather than of any of these symptom clusters in isolation (Van Nierop et al., 2015). A follow-up study showed that the co-occurrence of CT and this mixed phenotype of affective, anxious, and psychotic symptoms (CT/MP) is associated with clinically and functionally meaningful differences within PD patients (Van Nierop et al., 2016). Psychotic patients with CT/MP had worse quality of life, lower educational levels, greater symptom severity, and higher prevalence of drug disorder, than patients without CT, patients without a mixed phenotype, or without both (Van Nierop et al., 2016). This subgroup of psychotic patients with CT/MP, given their poor functional outcome, may be more resistant to treatment (Van Nierop et al., 2016). However, the relationship between CT, MP and diminished general functioning is still unclear.

The current study aims to evaluate if cognition could be related with CT/MP, as well as with lower general functioning. It could be hypothesized that cognition may discriminate psychotic patients subdivided by CT and MP, and that diminished cognitive functioning may be associated with increased symptom severity and poor daily functioning. In order to test these hypotheses, we will examine cognitive functioning (i.e. verbal learning, memory, attention, and working memory) in a sample of non-affective PD patients, stratified by CT history and a mixed psychopathology phenotype. We expect that: (a) psychotic patients with both CT and MP compared with those without CT or without MP, or without both, may show lower cognitive functioning, and (b) poor cognition may predict a diminished general functioning.

2. Methods

This research is part of the 6-year longitudinal observational study called the "Genetic Risk and Outcome of Psychosis Project (GROUP)" (Korver et al., 2012). The GROUP study has enrolled a sample of patients with a diagnosis of non-affective PD, their unaffected siblings, parents, and controls. For the purpose of this study we have only used the patient sample. Patients were recruited from 5 university hospitals in the Netherlands and Belgium (Groningen, Amsterdam, Maastricht, Utrecht, and Leuven) and their affiliated mental healthcare institutions. Patients were eligible for inclusion if they: (i) were aged 16–65; (ii) met the Diagnostic and statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for non-affective PD (APA, 2000); (iii) had first contact with mental health care <10 years ago; (iv) were proficient in Dutch. Patients were excluded if their estimated level of intelligence was <70.

In Amsterdam, Maastricht, Utrecht, and Leuven patients were assessed with Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992), and in Groningen with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1; Wing et al., 1990). As this study used symptom data from the CASH we have only included participants from the Amsterdam, Maastricht, Utrecht, and Leuven sites (n = 532). The GROUP study included three measurements: at baseline, at 3-year follow-up, and 6-year follow-up.

The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and by local review boards of each participating institute. The study was designed in strict accordance with the declaration of Helsinki of the World Medical Association as revised in 2008. All subjects gave written informed consent in accordance with the committee's guidelines.

2.1. Measures

2.1.1. Childhood trauma

CT was assessed with the Dutch version of the Childhood Trauma Questionnaire (CTQ-SF; Bernstein et al., 2003), a 25-item self-report questionnaire rated on a scale of 1 (never true) to 5 (very often true). The CTQ-SF measures physical abuse, physical neglect, sexual abuse, emotional abuse, and emotional neglect. A total CT score was obtained by calculating the average of all 25 items.

2.1.2. Symptoms

Present state depression, anxiety, and psychotic symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The PANSS is a 30-item interview consisting of three subscales on a range from 1 (absent) to 7 (very severe): the positive scale (e.g. delusion/hallucinations), negative scale (e.g. blunted affect, difficulty in abstract thinking) and a general psychopathology scale (e.g. depression, feeling of guilt). Depression and anxiety were assessed with one item each (depression: have you felt sad, down or depressed; anxiety: worried, nervous, restless or panicked).

Present state mania was assessed with the CASH (Andreasen et al., 1992). The CASH includes the 34-item Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the 21-item Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1989) both on a range from 0 (no) to 5 (severe). Mania was assessed with one item (have you felt overly or abnormally exited or active).

All symptoms were assessed at all three measurements.

2.1.3. Definition of subgroups

Following previous studies (Van Nierop et al., 2015, 2016) a total score of the CTQ-SF (Bernstein et al., 2003) was dichotomized to 0 (low CT; n = 429; "CT−") and 1 (high CT; n = 103; "CT+") using the 80th percentile of the total childhood trauma score. The psychosis, depressive, anxiety scores of the PANSS (Kay et al., 1987), were dichotomized to 0 (score 1) and 1 (score of 2 or above). Similarly, the mania

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