



Is cognitive impairment following early life stress in severe mental disorders based on specific or general cognitive functioning?

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ABSTRACT

Schizophrenia spectrum and bipolar disorder are characterized by high levels of childhood trauma as well as of cognitive dysfunction. Our aim is to investigate the association between these two factors in the largest study in the literature so far.

A total of 406 patients with schizophrenia spectrum- or bipolar disorders were recruited from a catchment area based organization in Oslo, Norway. Information about early life stress was obtained using the Childhood Trauma Questionnaire (CTQ). Cognitive function was assessed through a comprehensive and standardized neuropsychological test battery.

Physical abuse, sexual abuse and physical neglect were significantly associated with reduced scores on working memory and executive function scales ($p = 0.04$ to $p < 0.001$), and verbal and performance tasks from the Wechsler Abbreviated Scale of Intelligence (WASI) ($p = 0.059$ to $p < 0.001$). When verbal and performance tasks from the WASI were added into a multivariate regression model, the association between CTQ and the specific cognitive domains decreased, and only WASI scores remained statistically significant.

Our results indicate that childhood trauma is associated with a reduction in cognitive function across cognitive domains in patients with schizophrenia spectrum- and bipolar disorders, in particular working memory and executive function as well as general cognition. Moreover, these dysfunctions seem to be driven by underlying deficits in general cognitive tasks as measured by the WASI.

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1. Introduction

Cognitive dysfunction is a core abnormality in schizophrenia spectrum disorder (Flashman and Green, 2004). The majority of patients with schizophrenia function at a level at least one standard deviation below healthy comparison groups, even at the time of their first-episode (Rund et al., 2004; Faerden et al., 2009; Aas et al., 2011a; Zanelli et al., 2010). This dysfunction seems to endure after successful treatment of psychotic symptoms (Rund et al., 2007; van Os and Kapur, 2010). In addition to global cognitive deficits, specific cognitive domains including episodic memory, working memory and executive function are particularly affected (Flashman and Green, 2004). Parallel but less severe cognitive dysfunctions are also observed in bipolar disorder (Simon et al., 2007; Zanelli et al., 2010; Simonsen et al., 2011). Indeed, investigating the mechanisms behind psychosis across

DSM-IV diagnosis of schizophrenia, affective psychosis, and bipolar disorder is supported by recent findings of overlaps in genetics (Purcell et al., 2009; Williams et al., 2011) and brain structure (Rimol et al., 2010).

Patients with schizophrenia spectrum- and bipolar disorders report higher incidences of early life stress (ELS) when compared to the general population (Read et al., 2005; Etain et al., 2008; Fisher et al., 2010; Fisher et al., 2011). ELS have been linked to cognitive dysfunction in both children and adults (Perez and Widom, 1994). In children, adverse experiences are associated with deficits in general cognition (Koenen et al., 2003) and in the domains of attention, abstract reasoning and executive function (Mezzacappa et al., 2001; Beers and De, 2002). Both in the adult general population (Navalta et al., 2006) and in several different patient groups (Bremner et al., 2004), ELS appear associated with cognitive impairments, independent of social group. This includes tasks of intellectual and academic functioning (Perez and Widom, 1994; Navalta et al., 2006), memory (Bremner et al., 1995; Raine et al., 2001; Bremner et al., 2004; Navalta et al., 2006) and working memory (Raine et al., 2001; Navalta et al., 2006). These empirical findings are supported by studies indicating stress exposure as the likely mechanism

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behind the association between ELS and cognitive impairments (Sapolsky et al., 1986; Perez and Widom, 1994; Heim et al., 2000; McAllister-Williams and Rugg, 2002; Wolf, 2003; Lupien et al., 2005). Furthermore, some studies present total childhood trauma scores, while others have focused on subgroups of abuse, mainly sexual or physical abuse (Read et al., 2005; Carballo et al., 2008; Etain et al., 2010). There is also some evidence that specific subtypes of trauma may be particularly linked to bipolar disorder, such as emotional abuse (Etain et al., 2008; Etain et al., 2010). There is a higher prevalence of emotional abuse in bipolar patients than in healthy controls, even when controlling for other types of abuse (Etain et al., 2008; Etain et al., 2010). Physical abuse has on the other hand been linked to schizophrenia (Etain et al., 2008; Etain et al., 2010), indicating the importance of investigating the effect of ELS subtypes separately.

There are clear indications of an association between ELS and reduced functioning in the areas of executive function and working memory, both in patients with first-episode- (Aas et al., 2011b) and in chronic psychosis (Lysaker et al., 2001; Schenkel et al., 2005; Shannon et al., 2011). There is also a strong association between general IQ and specific cognitive domains such as executive function and memory (Leeson et al., 2008). It is thus possible that the main effect of ELS on cognition is mediated through general IQ. There are also indications that the association between ELS and cognition is stronger in affective- than in non-affective psychosis (Aas et al., 2011b). Previous studies have however had insufficient statistical power to explore both of these issues. The current study ($N=406$) is the largest study investigating the link between ELS and cognition in patients with schizophrenia spectrum and bipolar disorder to date. We will here specifically address the following questions: 1) Is the association between ELS and cognition mainly driven by an association with general IQ or are specific cognitive areas affected independently of IQ; and 2) Is the association between ELS and cognitive impairments stronger in patients with bipolar disorders than in schizophrenia spectrum disorders?

2. Methods

2.1. Subjects

Participants were recruited consecutively between 2007 and 2011 from psychiatric units (outpatient and inpatient) in 4 major hospitals in Oslo as part of the larger Thematically Organized Psychosis (TOP) Study. A total of 406 gave informed consent to participate, 239 with DSM-IV schizophrenia spectrum disorders (145 schizophrenia or schizophreniform disorder, 29 schizoaffective disorder, 65 psychosis NOS or delusional disorder), 167 with DSM-IV bipolar disorders (107 bipolar I, 11 bipolar II with psychotic symptoms during depression, 30 bipolar NOS, and 19 major depressive disorder with psychotic features), (Table 1).

Table 1
Demographics and clinical characteristics of the patients ($N=406$).

	Mean	S.D.
Age	30.07	3.00
Years of education	13.00	10.49
GAF S ^a	45.60	12.53
GAF F	45.32	11.89
PANSS ^b positive symptoms	14.07	5.45
PANSS negative symptoms	13.75	6.21
	<i>N</i>	%
Males	214	52.7
Diagnosis		
Schizophrenia spectrum disorder	239	58.9
Bipolar disorder	167	41.1
Severe childhood trauma		
Physical abuse, yes %	63	15.6
Sexual abuse, yes %	85	21.6
Emotional abuse, yes %	135	34.2
Physical neglect, yes %	37	9.3
Emotional neglect, yes %	180	46.4

^a GAF, Global Assessment of Functioning, Symptom(GAF-S) and Function (GAF-F).

^b PANSS, Positive and Negative Syndrome Scale.

2.2. Clinical assessment

Clinical assessment was carried out by trained MDs (psychiatrists or psychiatrists in training) and clinical psychologists. Diagnosis was based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). Diagnostic reliability was found satisfactory (Ringen et al., 2008) with overall agreement for DSM-IV diagnostic categories of 82% and the overall $\kappa=0.77$ (95% CI: 0.60–0.94). Current positive and negative symptoms were rated using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987). Inter-rater reliability was acceptable with intra-class correlation coefficients (Shrout and Fleiss, 1979) for PANSS subscales ranging from 0.71 to 0.73. Having a history of psychosis in bipolar patients was based on information from the SCID interview (one or more SCID-verified psychotic episode). Duration of psychosis (years since first contact with mental health services due to a primary symptom, i.e. psychotic symptoms for the schizophrenia group, psychotic or affective symptoms for the schizoaffective and bipolar groups), number of affective and psychotic episodes, hospitalization and use of medication at time of testing were determined through clinical interviews and medical charts. At time of examination, $n=283$ used one or more antipsychotics, $n=135$ used antidepressants and $n=123$ used mood stabilizers. Mean $\pm$ S.D. for IQ was 101 ± 15.2 ; mean $\pm$ S.D. for duration of psychosis was 3.4 ± 5.6 years.

2.3. Neurocognitive assessment

Psychologists trained in standardized neuropsychological testing carried out the neurocognitive assessment. A 3-hour test battery was administered in a fixed order with two breaks with refreshments. Included in this study are measures previously found sensitive to dysfunction in schizophrenia and bipolar disorder, with emphasis on measures sensitive to stress (Perez and Widom, 1994; Lupien et al., 2007; Zanelli et al., 2010). The following five domains were assessed: 1) memory 2) working memory 3) executive function 4) perception and visuo-spatial abilities; and 5) verbal abilities. To examine performance by domain, raw scores within each domain were averaged together. Confirmatory correlational analyses were conducted to ensure that test scores within each domain shared similar variance and could therefore be considered part of the same cognitive construct. Here, a Pearson correlation coefficient of 0.50 or greater was considered large enough for the test to belong to the same domain (Brickman et al., 2004). All cognitive scores conducted in the analyses were based on raw scores.

2.3.1. Memory

The California Verbal Learning Test (CVLT) II, was used to measure verbal memory at immediate and delayed (30 min) time points, together with, learning and recognition (Delis et al., 2004).

2.3.2. Working memory

Letter-number sequencing, Digit span forwards, and Digit span backwards were used to measure working memory (Wechsler, 1997).

2.3.3. Executive function

Verbal fluency test (semantic ["boys' names", "animals" and alternation between "fruits and furniture"]) and letter fluency (phonemic [F, A, and S]) tasks were used to measure executive functioning. (Delis et al., 2004).

2.3.4. Perception and visuo-spatial abilities

Block design task (Wechsler, 2007) and matrix reasoning (Wechsler, 2007) were used to measure perception and visuo-spatial abilities, which is a measure of performance abilities from the WASI.

2.3.5. Verbal abilities

Similarities and vocabulary (Wechsler, 2007) were used to measure verbal abilities from the WASI.

2.3.6. General cognitive function

Full-scale IQ was derived from the WASI (Wechsler, 2007) from subtests in the neuropsychological battery.

2.4. Childhood Trauma Questionnaire (CTQ)

Early life stress was rated using the Norwegian version of the Childhood Trauma Questionnaire (CTQ) (Aas et al., 2012). This is a 28-items self-report questionnaire shown to have high reliability and validity (Bernstein et al., 2003), yielding scores on five subscales of trauma; physical abuse (PA), sexual abuse (SA), emotional abuse (EA), emotional neglect (EN), and physical neglect (PN) (Bernstein et al., 1994; Bernstein et al., 2003). Each subscale is measured on a 5-point Likert scale from 1 (never true) through 5 (very often true). Not all patients gave information about all types of abuse. A total of 99.3% ($N=403$) of the patients completed the physical abuse subscale; 97.0% ($N=394$) completed the sexual abuse subscale; 97.3% ($N=395$) completed the emotional abuse subscale; 95.6% ($N=388$) completed the emotional neglect subscale, and 97.8% ($N=397$) completed the physical neglect subscale. N for the different analyses will thus vary slightly. The resulting scores were skewed, as many had not been exposed to ELS at all, while those with ELS had been exposed to several types of varying severity. For estimates of frequencies of ELS we used a predefined cutoff suggested by Bernstein (Bernstein and Fink, 1998) of ≥ 10 for physical abuse, ≥ 8 for sexual abuse,

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