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The effects of childhood trauma on neurocognitive functioning in Bipolar Disorder type I patients

Lisanne Stessen, Bsc

Academic year:	2012-2013
Studentnumber:	3521133
Internal supervisor:	Dr. L. Sternheim (University of Utrecht)
External supervisor:	A. Vreeker, Msc (PhD Student, UMC Utrecht)

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Abstract

Introduction: Cognitive impairment in Bipolar Disorder (BPD) patients, particularly in the domains of executive functioning and declarative memory, is well established in a number of studies. History of childhood trauma is also indicated to have negative effects on verbal memory and cognitive control. Childhood trauma is more prevalent in BPD patients than in the general population. So far, the interaction between BPD type 1 (BPDI) and childhood trauma hasn't been investigated in a large sample of euthymic participants. Therefore, the aim of the present study was to examine whether the presence of both BPDI and history of childhood trauma have negative effects on cognitive functioning.

Methods: A total of 353 participants were recruited, 280 were euthymic BPDI patients and 73 of them were controls. Diagnosis of BPDI was based on the SCID and the MINI. History of childhood trauma was assessed by the Childhood Trauma Questionnaire (CTQ). Cognitive function was assessed through a comprehensive and standardized neuropsychological test battery, a four-subtest short form of the WAIS-III. The cognitive domains that will be investigated are perceptual organization, working memory, processing speed and verbal comprehension.

Results: Patients showed lower scores in the cognitive domains of working memory and processing speed compared with healthy controls. Furthermore, history of childhood trauma was also associated with negative effects on the domains of working memory, perceptual organization and processing speed. The interaction of BPDI and history of childhood trauma showed that cognitive performance was significantly decreased for perceptual organization.

Conclusion: These data support the impact of BPDI and history of childhood trauma in decreased neurocognitive functioning, childhood trauma seems to be a moderating variable. The findings are a step in the process of identifying which cognitive domains are deteriorated due to BPDI, history of childhood trauma and a combination of both.

Introduction

Bipolar disorder

Bipolar disorder (BPD) is a pathological disturbance of mood, typically characterized by oscillating manic and depressive states. A distinction can be made between BPDI and II. To meet the qualifications for a diagnosis of BPDI, according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV), a patient has to have at least one major manic episode and will usually have had at least one major depressive episode. BPDII will be diagnosed when a patient has had at least one major depressive episode and at least one hypomanic episode, but never has experienced a full-on manic episode. In general BPD, especially BPDI, causes serious impairments, such as psychosocial problems and not being able to work, for those who suffer from it. Even when BPD patients are between episodes (manic or depressive) and are in a more stable or asymptomatic state (euthymic), they still experience neuropsychological deficits compared to healthy controls (Ferrier et al., 1999).

At least half of BPD patients experience psychotic symptoms, like hallucinations and bizarre delusions, in their lifetimes (Glahn et al., 2007; Goodwin & Jamison, 1990; Keck et al., 2003). The aetiology of BPD is yet unknown, but twin, adoption and epidemiological studies are suggestive of a strong genetic influence. First-degree relatives of bipolar probands have an elevated risk of developing both unipolar and bipolar depressive episodes. Twin and adoption studies reported widely in the literature that there might be a genetic basis with heritability scores between 60% and 85% (Savitz, Solms & Ramesar, 2005). Although BPD is classically theorized as a disorder of mood, evidence is emerging that patients with BPD show cognitive deficits both during the acute phase of the illness and during remission (Bearden et al., 2001). A meta-analysis by Robinson et al. (2006) shows that patients with BPD performed significantly more poorly than controls on all cognitive domains (executive, verbal learning, attention, psychomotor speed and immediate memory measures), except overall intelligence quotient (IQ). Most impairments were found in executive functioning and verbal learning, whereas attention, immediate memory and psychomotor speed were much less affected. More recent meta-analyses (Arts, Jabben, Krabbendam & van Os, 2008; Bora et al. 2009; Stefanopoulou et al. 2009; Torres, Boudreau & Yatham, 2007) have consistently identified deficits of moderate to large effect size in processing speed, verbal learning, memory, attention and executive function. Albus et al. (1996) suggest that cognitive deficits are evident at an early stage of the illness, and are also present in unaffected first degree relatives of BPD patients, who may possibly share genetic vulnerability of the disorder (Ferrier et al., 2004; Gourovitch et al., 1999; Kieseppä et al., 2005; Zalla et al., 2004). These results support the possibility that cognitive impairment is a trait marker of BPD. Even though the pathophysiological and genetic basis of BPD remains obscure, a degree of consensus that BPD is

characterized by state independent memory and executive deficits has been reached (Savitz et al., 2008). A recent meta-analysis of the literature drew similar conclusions, with aspects of executive function and verbal learning calculated to be most strongly associated with BPD (Robinson et al., 2006). These neurocognitive deficits have been assumed to form trait markers or endophenotypes of BPD. BPDI patients are more severely affected and therefore more likely to experience a greater number of affective episodes and a greater number of hospitalizations than their counterparts, like BPDII patients, with a more benign form of the illness. Few studies have been concerned with the proportion of BPD patients that actually have cognitive impairment in a clinically significant range. Thompson et al. (2005) demonstrated that between 3% and 42% of the euthymic patient with BPD have cognitive performances at the level of the 5% weakest in the general population. Although these impairments only occur in a subset of the BPD patient population, they can cause significant cognitive impairment. Ferrier and Thompson (2002) concluded that cognitive dysfunction is a core and enduring deficit in the illness in patients affected by BPD. Another study shows that cognitive limitations not only occur during dysphoric periods, but also persist during periods of recovery (Clark, Sarna & Goodwin, 2005) and during a euthymic state (Vieta et al., 2006).

Since cognitive impairments can cause emotional distress, affect the ability to work and study and lead to poor psychological functioning (Simonsen et al., 2008), it is clinically important to further investigate this. Besides, cognitive impairment most probably interferes with treatment by affecting medication compliance and the ability to benefit from psychotherapy and education (Martinez-Áran et al., 2002; Martinez-Áran et al., 2004; Zubieta, Huguelet, O'Neil & Giordani, 2001). It is thus important to further investigate the role of cognitive functioning in BPD patients.

Bipolar Disorder and childhood trauma

History of childhood trauma is claimed to be common in patients suffering from psychotic disorders, compared with the general population. As patients with BPD often experience psychotic symptoms, the illness shows many similarities with psychotic disorders like schizophrenia. History of childhood trauma is associated with an increased probability of having a psychiatric disorder in adulthood (Cicchetti, Toth & Maughan, 2000; Weiss, Longhurst & Mazure, 1999). Previous investigations have observed that histories of childhood maltreatment are common in a large percentage of adults with severe and persistent mental illness (Herman, 1992; Meyer, Struening & Ferber, 2003; Read, 1997; Read, Goodman, Morrison, Ross & Aderhold, 2004). A study by Garno et al. (2005) demonstrated that nearly half of all participants with BPD had experienced severe childhood trauma, which is much higher than the percentage of people in the general population. Read et al. (2004) reported that 60% of male and 69% of female psychiatric inpatients reported histories of physical or sexual abuse. These rates far exceed the rates of child maltreatment that has been estimated to be around 11% for sexual abuse and 24% for physical abuse in the general population of the United Kingdom (May-Chahal &

Cawson, 2005). A number of studies report associations between childhood abuse and increased hallucinations and delusions in adulthood (Beck & Van der Kolk, 1987; Goff, Brotman, Kindlon, Waites, & Amico, 2001; Lysaker, Meyer, Evans, & Marks, 2001; Read, Agar, Argyle & Aderhold, 2003). A finding by Read and Argyle (1999) shows that 77% of psychiatric inpatients with histories of physical and/or sexual abuse experienced hallucinations, delusions, or thought disorders. A number of large-scale investigations have more recently replicated earlier findings linking childhood trauma with adult psychosis. Bebbington et al. (2004) uses data from a large national survey in Great Britain and reported a significant relationship between the occurrence of early adverse experiences (especially for sexual abuse) and the development of psychotic disorders in adulthood. Likewise, Jansen et al. (2004) uses a large sample from the Netherlands Mental Health Survey and reported a significant relationship between the occurrence of childhood abuse and adult psychotic symptoms. Therefore, childhood trauma appears to be associated with an increased risk for development of psychosis in adulthood. Besides, Perez and Widom (1994) have demonstrated that trauma has an adverse effect on cognitive functioning, both observed in childhood and adulthood.

Cognitive functioning and childhood trauma

Numerous studies show an association between poorer scores on several cognitive tasks in adulthood and a history of childhood trauma. Including tasks measuring intellectual and academic functioning (Navalta, Polcari, Webster, Boghossian, & Teicher, 2006; Perez et al., 1994), memory (Bremner et al., 1995; Bremner, Vermetten, Afzal & Vythilingam, 2004; Navalta et al., 2006) and working memory (Navalta et al., 2006; Raine et al., 2001). It was demonstrated that childhood trauma may have effects on cognition that also persist into adulthood (Navalta et al., 2006). Early stressful life experiences are thought to act as vulnerability factors and offer an underlying neural substrate provocation of affective disorder by stressors occurring in adulthood (Post, 1992).

Deficits in short-term verbal memory have been seen in adults with childhood sexual abuse (Koenen et al., 2003). Koenen et al. (2003) found that children who were exposed to high levels of domestic violence had intelligence scores that were lower than unexposed children. In addition, domestic violence was associated with intellectual decline independent of latent genetic influences. It has been proposed by Aas et al. (2011) that developmental retardation due to under-nutrition, lack of stimuli and general physical and psychological neglect, which is more prevalent in these families, could lead to cognitive decline by childhood trauma in children and adults. The reverse causality is also possible; children with lower intelligence quotient (IQ) scores may be at greater risk for being maltreated compared to high functioning children (Aas et al., 2011). Or parents of abused children may have lower IQ scores, and this may be genetically transmitted to the abused children. Childhood trauma has been found to impact negatively on verbal recall memory and cognitive control, just as BPD impacts negatively on executive functioning and verbal learning.

Bipolar disorder, childhood trauma and impaired cognitive functioning

Whereas BPD related neurocognitive deficits have been hypothesized to possess a genetic or symptomatic aetiology, the role of environmental risk factors influencing the development of this pattern of neurocognitive impairment in BPD has not been sufficiently explored yet. As mentioned above, one variable that has been reported to influence cognitive performance, especially memory performance, is childhood trauma. Victims from childhood trauma and patients with psychosis have cognitive deficits in similar areas, they both show decline in general cognition, working memory and hippocampus-related memory tests (Aas et al., 2011). The prevalence of childhood trauma reported in patients with psychosis is high, therefore it seems reasonable to hypothesize that childhood trauma contributes to the cognitive deficits found in this patient group.

To date, there are only four studies investigating cognition and childhood trauma in people with psychotic symptoms. The first study by Lysaker et al. (2001) found that patients with schizophrenia and a history of childhood trauma had decreased performances in tasks measuring processing speed and working memory compared with patients without such a history. A second study by Schenkel, Spaulding, DiLillo & Silverstein (2005) showed significantly decreased scores on a task of learning and visual context processing by patients with schizophrenia and a history of childhood trauma compared with non-abused patients. Shannon et al. (2009) reported that schizophrenia patients exposed to childhood adversity compared to those without such a history had additionally poorer episodic narrative and working memory. However, a study by Aas et al. (2010) did not replicate these findings. They found that cognitive functioning was not related to a history of childhood trauma but to patient's cortisol awakening response, which is a biological measure of stress reactivity. As shown by three independent research groups, approximately half of the BPD patients had experienced severe childhood abuse (usually sexual but also emotional) (Garno et al., 2005; Huyn, Friedman & Dunner, 2000; Leverich et al., 2002). Given these results, and the relationships found between childhood trauma and cognitive impairments, it seems reasonable to assume that the cognitive deficits reported in BPD patients may be at least partially attributable to a previous history of sexual or emotional abuse (Savitz et al., 2008).

Although there is some evidence for a relation between childhood trauma and cognitive impairments in patients with experiences of hallucinations and delusions, most studies were conducted with schizophrenic patients. These previous studies were not able to test specific effects of a BPD diagnosis on the interaction between history of childhood trauma and cognition. Only two studies have investigated history of childhood trauma, cognitive functioning and specifically BPD patients. A study by Aas et al. (2011) investigated cognition and early trauma both in individuals with a psychotic disorder and BPD with a recognized diagnosis and long duration of illness. They found that after controlling for education, ethnicity and cannabis use, the scores of BPD patients were significantly

worse than for the controls on the majority of the individual cognitive tasks. This was especially true for verbal memory tasks. They investigated whether there is an association between childhood trauma and a range of cognitive domains and whether a similar relationship is found in a healthy control group from the same geographical catchment areas. They assumed that patients with a history of childhood trauma would show stronger deficits in cognitive function than patients without such past experiences. Furthermore, they expected diagnostic differences in the association between childhood trauma and cognition. Full-scale IQ was derived from the Wechsler Adult Intelligence Scale (WAIS-R). Significantly more experiences of childhood trauma were reported by patients with psychosis than controls. In patients, a history of childhood trauma was associated with a significant decrease in cognitive function for the verbal intelligence domain, the language domain, concentration and mental speed domain. A trend was also perceived for the executive function and working memory domain. The association between childhood trauma and cognitive function was only seen in BPD patients and in patients with psychotic depression. BPD patients with childhood trauma scored significantly poorer than BPD patients without childhood trauma. Patients with affective psychoses are possibly more vulnerable to the effects of stress on cognitive function. A possible explanation for this result could be that both BPD and psychotic depression have been associated with impaired cognitive function in the context of hyperactivity of the hypothalamic pituitary adrenal (HPA) axis (Belanoff, Kalehzan, Sund, Fleming Ficek & Schatzberg, 2001; Flores, Kenna, Keller, Solvason, & Schatzberg, 2006; Gallagher et al., 2005; Watson, Gallagher, Ritchie, Ferrier & Young, 2004; Young, Gallagher, Watson, Del-Estal, Owen, & Ferrier 2004).

A study by Savitz et al. (2008) reproduces the findings of a number of previous studies, by finding that visual recall and verbal recall and/or recognition memory deficits are characteristic of euthymic BPD cohorts. Furthermore, they found that the BPDI cohort was characterized by a pattern of impaired performance on both visual and verbal memory tasks compared with their unaffected and indeed affected relatives, when there was not significantly controlled for the effects of medication. They also found that self-reported childhood emotional and sexual abuse was associated with poorer performance on both visual and verbal recall memory as well as verbal and visual fluency and cognitively flexibility. Children that are abused may have BPD parents with an impulsive-hostile phenotype that is partially genetic in aetiology. Childhood trauma on its own did not account for the deficits in the BPD group compared to the rest of the cohort. It is thus likely that an alternative aetiology for this pattern of cognitive performance may be due to medication for instance. A possible explanation for these findings is that treatment with lithium, antipsychotics, and to a lesser extent, antidepressants was associated with impaired memory performance.

The current study

In sum, research on the role of childhood trauma on cognitive functioning in BPDI patients is lacking. There is a great need to collect and analyze data that can help shed light on the effect of BPDI

and childhood trauma on cognitive functioning. The aim of this study was to assess cognitive impairment in BPDI patients and BPDI patients with history of childhood trauma. Cognitive impairment will be measured by four subtasks of the WAIS-III. The cognitive domains that will be tested are perceptual organization (subtask Block Design), processing speed (subtask Symbol Substitution), working memory (subtask Arithmetic) and verbal comprehension (subtask Information). Three hypotheses will be studied. First of all, it will be examined whether *BPDI patients have significant lower scores on the four subtasks of the WAIS than healthy controls;* second, it is expected that *participants with a history of childhood trauma have significant lower scores on the subtasks of the WAIS than participants without childhood trauma;* and third the interaction will be investigated, by stating that *BPDI patients with a history of childhood trauma have significant lower scores on the subtasks of the WAIS than BPDI patients without history of childhood trauma.*

Methods

Subjects

The current study was conducted as part of a larger ongoing study, “Bipolar Genetics”, that investigates the genetics of BPDI conducted by the University Medical Center Utrecht (UMCU), Department Adult Psychiatry. The main study explores the genetic factors of BPDI patients, with the objective to examine 2500 patients, 2500 relatives and 400 controls within a period of 5 years. Participants were recruited through clinicians, healthcare institutions, at VMDB meetings (Association for manic-depressives and Stakeholders) and through pharmacies (patients who were prescribed with lithium). The patients were approached by telephone or letter by the Bipolar Genetics research team from UMC Utrecht to take part of the study.

Inclusion and exclusion criteria

There were a number of conditions that patients and controls had to meet to participate in the present study. Participants were included when they had at least three grandparents of Dutch descent and they were 18 years or older. Patients had to be diagnosed with BPDI in order to be able to take part to the current study. The criteria for a BPDI diagnosis were met when someone had experienced at least one full manic episode. Participants with a premorbid IQ under 80 were excluded. The presence of a somatic illness was also an exclusion criterion. Furthermore, the aim of the study was to include euthymic patients and controls. Therefore, participants with a current depression or manic/hypomanic state, assessed by the Altman Self-rating Mania Scale (ASMR-NL), the Self-completion list symptoms (IDS Self-Rating), the Structured Clinical Interview for DSM disorders (SCID) and the International Neuropsychiatric Interview (MINI and MINI +), were excluded. In addition, controls with a history of BPD or a psychotic disorder or first-degree family members with a history of these disorders, were excluded.

Comment [I1]: Enige criteria?

LS: Klopt, dit is het enige criterium dat gebruikt wordt om de diagnose BPDI te stellen.

Procedure

The assessment of the present study consisted of two parts: a web questionnaire and a psychiatric interview. The self-reported web questionnaire contained The Childhood Trauma Questionnaire (CTQ; English translation of the Jeugd Trauma Vragenlijst, JVT). Completing this list took place at the participant’s home. In addition, the participant was invited to visit UMC Utrecht where the research took place. During this visit, which took about 3 hours for patients, the psychiatric interview and several neuropsychological tasks were collected.

The questionnaires as part of the psychiatric interview for patients consisted of the following: the ASMR-NL and the IDS Self-Rating to determine current mood, the SCID was conducted to

determine whether there was in fact a BPDI diagnosis. The neuropsychological tasks were subtasks of the Wechsler Adult Intelligence Scale (WAIS III): Block design, Symbol Substitution, Arithmetic and Information. The Dutch reading test for adults (NLV, Nederlandse Leestest voor Volwassenen) was used to determine premorbid IQ score. The premorbid IQ scores of patients will be compared to the scores of controls, to make sure that both groups do not significantly vary from each other on premorbid IQ.

The psychiatric interview was less time consuming for the controls, an inclusion took approximately 1,5 hours. The interview consisted of the MINI and MINI+, the neuropsychological tasks consisted of the four subtasks of the WAIS.

The psychiatric interview and neuropsychological tasks were conducted in a quiet room where the test leader was seated next to the door and the patient/control sat at the opposite of the test leader. After a brief introduction and blood collection, the patient filled out the ASMR-NL and IDS to assess current mood. Prior to the study, all patients and controls gave written informed consent.

Participants

This study comprised 353 individuals, 73 of them are controls and 280 are BPDI patients. The age of the participants varied between 19 and 80 years, with an average age of 43 for the controls and 48 years for patients. For both groups, Higher Vocational Education (HBO) was the average educational level. As the focus of the current study was on cognitive function in patients and controls, an euthymic state was important to omit the risk of influencing the scores on the WAIS. Therefore, 23 participants with current hypomanic/manic or depressive symptoms or with these symptoms in the past month were excluded.

Table 1. Demographic characteristics of the participants: total (N) and percentage (%).

	Total N	Percent %
Participants		
Women	202	57.2 %
Men	151	42.8 %
Education		
No education	1	.3 %
LO	6	1.7 %
LTS	11	3.2 %
MAVO	32	9.2 %
MBO	54	15.5 %
HO	42	12 %
HBO	99	28.4 %
WO	92	26.4 %
Different	16	4.5 %
Total	353	100 %

Note: LO= Primary Education, LTS= Lower Vocational Technical School, MAVO= Lower General Secondary Education, MBO Intermediate Vocational Education, HO=Higher Education, HBO=Higher Vocational Education, WO= University Level.

Instruments

In the current study, the following instruments were used.

Bipolar disorder type 1

The Structured Clinical Interview for DSM Disorders (SCID) was used to establish the diagnosis of BPDI. The SCID is a semi-structured assessment tool to determine Axis I disorders. This interview was conducted during the three-hour examination by qualified researchers who had undergone SCID training. The internal reliability of the SCID is reasonable to very good with an average Kappa of 0.71 (Lobbestael, Leur, Goose, Arntz & 2011).

Childhood trauma

To determine whether a patient or control has experienced childhood trauma the JTV (Jeugd Trauma Vragenlijst) was used, this is a Dutch version of the Childhood Trauma Questionnaire (CTQ) (Bernstein, Fink, Handelsman, Foote, Lovejoy et al., 1994). The list consists of 28 items about childhood events. Each question is answered using a 5-point Likert scale (where 1 = never, 2 = rarely true, 3 = sometimes, 4 = often and where 5 = always true). It concerns 25 clinical items and 3 validity items. In the present study the 3 validity items were omitted. Research by Bernstein, Stein, Newcomb, Walker et al. (2003) shows that the list without these 3 items continues to be a reliable and valid tool to measure childhood trauma in a clinical population. The 25 items are divided into 5 categories; emotional abuse, physical abuse, sexual abuse, physical neglect, emotional neglect. There is a cut-off score for each subscale. For emotional abuse the cut-off score was 12, for physical abuse 9, for sexual abuse 7, for physical neglect 9 and emotional neglect 14. The internal consistency of the questionnaire is good with a Cronbach's alpha of .91. For the individual subscales Physical neglect has the lowest internal consistency and sexual abuse the highest. Physical abuse (α = .69), physical neglect (α = .58), emotional abuse (α = .83), emotional neglect (α = .85) and sexual abuse (α = 94) (Scher, Stein, Asmundson, McCreary & Forde, 2001). In this study childhood trauma is dichotomized into ‘Trauma’, (at least one of the five categories is scored above the cut-off score), or ‘No Trauma’.

Intelligence

Four subtasks of the Wechsler Adult Intelligence Scale (WAIS-III): Blocks design, Symbol Substitution, Arithmetic and Information, were used to study the independent cognitive domains. The subtask Blocks Design measures the perceptual organization, Symbol Substitution measures the processing speed, working memory was measured by using Arithmetic and Information measures verbal comprehension. These four subtasks of the WAIS-III seem to be the best combination to us as a short form. It has been used for many clinical and research purposes for patients with schizophrenia and controls (Blyer, Gold, Iannone & Buchanan, 2000).

The Dutch Reading test for Adults (Nederlandse Leestest voor Volwassenen, NLV) was used as an estimation of premorbid IQ. To determine IQ scores on the NLV there are standards that divide the subjects into two different age groups: subjects who were born before and after 1914. The test consists of a series of words which have an irregular pronunciation. The subject is asked to speak the fifty words, ranging from easy to difficult, out aloud. These can be scored on a scale of good, questionable or wrong. A good answer gets two points, a doubtful answer one and a fault answer zero points. The number of correctly pronounced words is a reliable representation of the verbal intelligence level (Schmand, Lindeboom & van Harskamp, 1992). This test was chosen because of the short time required for the test to make. The result is fast and reliable. The reliability of the NLV is rated by the Cotan as reliable, the validity is considered inadequate.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS). Distributions for each variable were checked for normality. To check the first hypothesis and to ascertain differences between patients with BPDI and healthy controls on the WAIS, an one-way multivariate analysis of variance was conducted (MANCOVA) on the scores of the various measures. With the WAIS scores as dependent variables and the illness, BPDI, as dichotomous independent variable. The second hypothesis was tested by MANCOVA, with the WAIS scores as dependent variables and the JTV scores as dichotomous independent variables (trauma or no trauma). The third hypothesis was tested by a MANCOVA to ascertain the relationship between BPDI, childhood trauma and the interaction of the two.

Results

The current study included 353 participants, 73 of them were controls and 280 were BPDI patients. Of 18 participants data were missing. Furthermore, 23 participants were excluded because they weren't euthymic at time of testing. There were no significant differences on level of education, age and premorbid IQ between the controls and patients, as shown in table 2. Cook's distance test was performed to see if there were any outliers. The test showed that there were no outliers. All three hypotheses were tested using MANCOVA, all assumptions were met.

Table 2. Means (M) and standard deviations (SD) for controls and BPDI patients on Premorbid IQ scores and Educational level.

	Controls (N=73)		Patients (N=280)	
	M	SD	M	SD
Premorbid IQ	86	9.13	86	9.89
Educational Level	5	1.60	5	1.70

Note: Educational level 5= Higher Education.

Cognitive function in both controls and patients

To test the first hypothesis, whether patients had lower cognitive performance on the four subtasks of the WAIS than controls, a multivariate analysis of covariance (MANCOVA) was used. After controlling for age and gender, patients performed significantly worse on working memory (subtask mathematics, partial $\eta 2 = .012$) and processing speed (subtask symbol substitution, partial $\eta 2 = .029$). Results are shown in table 3.

Table 3. Means (M), standard deviations (SD), range and statistics for controls and BPDI patients on the four cognitive domains (WAIS).

	Controls (N=73)			Patients (N=280)			Statistics		
	M	SD	Range	M	SD	Range	F,	df,	*p* value
WAIS									
Mathematics	12.23	2.98	5-18	10.95	2.96	4-18	4.07	1	.04*
Information	11.92	2.63	6-18	12.31	2.70	1-18	2.31	1	.13
Block Design	14.49	4.38	1-19	13.83	3.83	4-19	.02	1	.88
Symbol Substitution	15.40	3.60	4-19	13.71	3.17	3-19	10.04	1	.00*

WAIS; Wechsler Adult Intelligence Scale.
All analyses covaried for age and gender.
* $p<.05$

Cognitive function and childhood trauma in both controls and patients

To test the second hypothesis a MANCOVA was used. As table 4 shows, participants with a history of childhood trauma had lower scores on mathematics, block design and symbol substitution than participants without childhood trauma. Subtask mathematics (partial $\eta 2$ = .031) subtask block design (partial $\eta 2$ = .060) and subtask symbol substitution (partial $\eta 2$ =.020).

Table 4. Means (M), standard deviations (SD), range and statistics for childhood trauma on the four cognitive domains (WAIS).

	Trauma (N=149)			No Trauma (N=204)			Statistics		
	M	SD	Range	M	SD	Range	F,	df,	*p* value
WAIS									
Mathematics	10.64	3.01	4-18	11.63	2.94	4-18	11.04	1	.00*
Information	12.01	2.53	4-18	12.39	2.80	1-18	2.80	1	.10
Block Design	12.91	3.96	4-19	14.75	3.77	1-19	22.18	1	.000*
Symbol Substitution	13.27	3.28	3-19	14.64	3.26	4-19	6.95	1	.010*

WAIS; Wechsler Adult Intelligence Scale.
All analyses covaried for age and gender.
* $p<.05$

Cognitive function and childhood trauma in controls and patients

The effects of childhood trauma and BPDI on cognitive functioning were investigated in the third hypothesis. MANCOVA showed that the interaction between BPDI and childhood trauma had a significant effect on the subtask block design (partial $\eta 2$ = .014). As table 5 shows, patients with childhood trauma showed significantly lower scores on the subtasks block design compared to patients without childhood trauma. In patients, a history of childhood trauma was associated with a significant decrease in cognitive function for block design. A trend towards significance was also observed for working memory.

Table 5. Means (M), standard deviations (SD), range and statistics for controls and BPDI patients with and without childhood trauma on the four cognitive domains (WAIS).

	Controls				Patients				Statistics		
	No trauma (N=52)		Trauma (N=21)		No Trauma (N=152)		Trauma (N=128)				
	M	SD	M	SD	M	SD	M	SD	F	df,	*p* value
WAIS											
Mathematics	12.87,	2.77	10.67,	2.96	11.21,	2.88	10.64,	3.03	3.82	1	.05
Information	12.19,	2.47	11.24,	2.97	12.46,	2.91	12.13,	2.44	.67	1	.41
Block Design	15.58,	4.00	11.81,	4.19	14.46,	3.66	13.09,	3.90	4.80	1	.03*
Symbol Substitution	15.75,	3.53	14.52,	3.72	14.26,	3.08	13.06,	3.17	.00	1	.97

WAIS; Wechsler Adult Intelligence Scale.
All analyses covaried for age and gender.
* $p<.05$

Discussion

The aim of the present study was to examine whether having BPDI and history of childhood trauma has negative effects on cognitive functioning. This study has demonstrated that having BPDI indeed has negative effects on cognitive functioning. Patients showed lower scores in the cognitive domains of working memory and processing speed compared with healthy controls. Furthermore, history of childhood trauma was also associated with negative effects on the domains of working memory, perceptual organization and processing speed. The relation between having both BPDI and history of childhood trauma showed that the cognitive performance was significantly decreased for perceptual organization. Also, a trend towards significance was observed for decreased cognitive performance on working memory tasks. History of childhood trauma thus seems to significantly contribute to the relation between BPDI and cognitive functioning. These results were obtained after co-varying for age and gender. The deficits are not due to differences in premorbid IQ or educational level as generally BPDI patients and healthy controls have been well-matched on these variables.

Only two studies before this study have investigated the interaction between history of childhood trauma, cognitive functioning and BPD patients (Aas et al., 2011; Savitz et al., 2008). However, no attempt was made to make a distinction between BPDI and BPDII. These two previous studies did not systematically examine the interaction between history of childhood trauma and specifically BPDI patients. Therefore, the current study is the first study that investigated the role of the interaction between childhood trauma and BPDI on cognitive functioning. In comparison to previous studies, the current study clearly found decreased cognitive performance in the BPDI patients compared to healthy controls. BPDI patients have more difficulty with test components that rely on processing visual information as quickly as possible and the ability to remember, process and reproduce auditory information is weak compared to healthy controls. The same two decreased cognitive performances in BPDI patients were also found in participants with a history of childhood trauma, with an extra decreased cognitive performance for test items related to attention to detail, analyzing patterns and combining details to wholes. Looking at the interaction between history of childhood trauma and BPDI, results show that the cognitive performance was significantly decreased for perceptual organization. Meaning that patients with BPDI and a history of childhood trauma have more difficulty with test items related to attention to detail, analyzing patterns and combining details to wholes. These results are in line with results from a study by Savitz et al. (2008), who found decreased cognitive functioning in visual recall memory tests as well as verbal recall and recognition memory, and Aas et al. (2011), who found worse cognitive performances for attention, concentration, mental speed and language. Although the results from this study show that the means of BPDI patients and controls were significantly different on the measures of cognitive functioning, the effects sizes were small but nevertheless significant because of the large sample size. Meaning that the observed effects may not be overvaluated.

There are a number of factors that could have contributed to the found cognitive impairments. A possible explanation for the cognitive deficits in executive functioning and memory in BPDI patients is that these could be related to duration of the illness, severity of the illness and number of affective episodes (Cavanag, Van Beck, Muir & Blackwood, 2002; Clark, Iverson & Goodwin, 2002; Denicoff, Ali, Mirsky, et al., 1999; El-Badri, Ashton, Moore, Marsh & Ferrier, 2001; Lebowitz, Shear, Steed & Strakowski, 2001; Zubieta et al., 2001). Illness episodes were most likely correlated with performance in memory and executive tasks. A study by Kessing (1998) examined illness episodes and reported that patients with two or more episodes performed significantly worse on a neuropsychological task compared to patients with one single episode. Multiple affective episodes are also associated with significantly larger lateral ventricles than single episode BPD patients. This might indicate a progressive loss of tissue during the course of the disorder. These results appear to suggest presence of a structural neurodegenerative process. In patients with first time treatment for a manic episode, levels of cognitive impairment appear to be less extensive than levels found in more chronic or multiple episode BPD patients. This indicates that neurocognitive decline continues over the course of the disorder (Bora, Yucel & Pantelis, 2009; Thompson et al., 2005; Robinson et al., 2006). Another explanation is also possible, more severely affected patients are likely to experience a greater number of affective episodes and hospitalizations than their counterparts with a more benign form of the illness. These patients are likely to be treated with higher doses and greater combinations of medication (Paradiso, Lamberty, Garvey & Robinson, 1997). Unfortunatly this data was not available for this study.

Another possible reason for decreased cognitive functioning in patients with BPDI might be use of medication. In this study 268 of the 280 BPDI patients were using medication, in some cases even more than one class of drugs. The (negative) effect of medication is very difficult to control for. Problems that arise are a wide variation in dosage, patients are often treated with more than one drug and response to a particular medication may be reflective of aetiology and therefore cognition-medication related correlations may not be causal in nature (Savitz et al., 2008). In this study and in many other studies no attempt was made to control for treatment side effects. Wingo, Wingo, Harvey and Baldessarini (2009) suggested a minor negative effect of lithium treatment on memory and creativity. Another study investigated medication treatment side effects on cognitive functioning in BPD patients and stated that a significant predictor of lower full-scale IQ and poorer general memory performance was treatment with anti-psychotic medication at the time of testing (Donaldson et al., 2003). The BPD group still showed impaired verbal recall memory and a trend toward impaired visual recall memory compared with their bipolar spectrum and unaffected relatives. These results illustrate that after controlling for pharmacological effects recognition memory deficits are absent, suggesting that this recall memory impairment may partially result from a genetically driven dysfunction of frontal-striatal networks. Donaldson et al. (2003) raise the possibility that cognitive dysfunction is iatrogenic, meaning that it is caused by medical intervention. Lithium has been reported to have

contrary effects on memory and psychomotor functioning. The results for medication treatment side effects are controversial as Macqueen and Young (2003) have found that anti-psychotic medications have beneficial effects on measures of executive functioning. A longitudinal study by Engelsmann, Katz, Ghadirian & Schachter (1998) failed to detect evidence of cognitive decline in a sample of BPD treated with lithium over a 6-year period. Short-term and long-term lithium treatment groups comparison also failed to yield significant memory score differences. More recent work suggests that lithium rather than impacting negatively on cognition actually exert a neuroprotective effect on neuronal tissue. Medication is a topic worth of further investigation.

Returning to the issue of heritability, Gourovitch et al. (1999), Keri, Kelemen, Benedek & Janka (2001) and Toulopoulou et al. (2005) demonstrated that impairments in verbal memory were found in BPD patients and in their unaffected relatives. The cognitive performance on verbal memory was significantly more decreased compared to healthy controls. Future research is required to further investigate the possibility that verbal memory is associated with genetic risk for BPDI.

Besides the influence of BPDI, the current study has confirmed that childhood trauma has negative effects on cognitive functioning. What explanations can be given for the association between history of childhood trauma and cognitive deficits? It has been suggested that childhood trauma could lead to cognitive decline due to developmental retardation (Aas et al., 2011). In these families lack of stimulation, under-nutrition and general en physical neglect is more common. Future research could include a measure of family socio-economic status as a covariate in their analyses, in order to prevent that the difference results from this factor. Another explanation lies in the so called 'reversed causality'. Parents of children with a history of childhood trauma may have lower IQs, which are generally transmitted to the traumatized children. Or children with lower IQs may be at greater risk of being abused than high functioning children. In our study no difference was found between the premorbid IQ scores of BPDI patients and controls, therefore it is unlikely that our results are attributed to this factor. Furthermore, no causal relations can be readily inferred from this study. Traumatic experiences may directly contribute to the course of the illness, but the reverse is also possible, early behaviors associated with an adverse course of illness could provoke early abuse (Brown, Cohen, Johnson & Salzinger, 1998; Friedrich & Boriskin, 1976).

Cognitive deficits can also be explained by the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, which influences cognitive performance. It has been found by Heim et al. (2000) that trauma is associated with sensitization and increased levels of cortisol. It would be interesting to include cortisol levels in future studies, to investigate the role of cortisol levels in trauma patients and cognitive functioning. Of note, it is possible that the relationship between childhood trauma, cognitive functioning and psychotic disorders, like BPD, is different in males compared with females. Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum (2001) have shown that the cortisol increase in response to a standardized psychological stressor is negatively correlated with memory performance, but this applies only for men. Another more recent result that only accounts for men is stated by

Pesonen et al. (2010) who demonstrated that male adults who had been separated from parents in childhood have increased cortisol responses. A study by Aas et al. (2011) found decreased cognitive scores in BPD patients with a history of childhood trauma, but the decreased cognitive scores were also found in males only. Male subjects in general are possibly more vulnerable to the effects of stress on cognitive function (Belanoff, Kalehzan, Sund, Fleming Ficek & Schatzberg, 2001; Flores, Kenna, Keller, Solvason, & Schatzberg, 2006; Gallagher et al., 2005; Watson, Gallagher, Ritchie, Ferrier & Young, 2004; Young, Gallagher, Watson, Del-Estal, Owen, & Ferrier 2004). The current data can't clarify, but there is strong evidence from other studies supporting the hypothesis that the cognitive abnormalities found in subjects with first-episode psychosis and a history of childhood trauma may be due to diagnostic (BPD) and gender specific (male) aspects of HPA axis reactivity to stress.

Strengths and limitations

There are some methodological limitations relevant to the interpretation of the current findings. First, history of childhood trauma was obtained by a self-report questionnaire. The questionnaire used (CTQ) is a validated instrument, but abuse is not retrieved by using a clinician-administered structured interview. Since data is obtained retrospectively, the occurrence of recall bias is possible. Participants might underreport or exaggerated their recollection.

Secondly, the present study used the short version of the WAIS-III. The advantage of this short version is that it takes less time for testing and administration. On the other hand, Flashman and Green (2004) demonstrated that subjects with psychosis show more variations on subtests compared to healthy controls, using subtests of the battery may decrease the accuracy of the results. But it is also known that a short version of the WAIS is beneficial because subjects with psychosis have a limited attention span (Allen et al., 1997).

Another limitation of this study is that because of the inclusion criteria that the participants had to be from Dutch descent and even three out of four grandparents had to be from Dutch descent, our results may not be representative of other clinical bipolar populations. This can also be seen as strength of the study. By incorporating only participants from Dutch descent, a homogeneous group was created, which is an asset for genetic research and which provides the opportunity to decrease the possible influence of cultural differences.

A strength of this study is the large sample size, the largest sample size of BPDI patients available at this moment, which results in good power for estimating effect sizes. Another strength is that this study made use of a healthy control group to compare them to patients. Validated and reliable instruments were used to asses Axis I and II disorders, history of childhood trauma and cognitive functioning. Also, patients were assessed at a time of relative stability in mood, an euthymic state. A couple of previous studies have found similar cognitive impairments in schizophrenia and bipolar illness, but these results were often found when bipolar patients were inpatients and most likely manic (Albus et al., 1996; Goldberg et al., 1993; Gruzelier et al., 1988; McGrath et al., 1997; Zihl et al.,

1998). Or studies failed to report information about the symptom status of the patients at time of testing. Last, the primary diagnoses and other Axis I and II disorders were assessed by a structured clinical interview and by a researcher who was blind for the results of the self-report questionnaires.

Conclusion

The findings of the current study show that BPDI has a negative effect in the cognitive domains of working memory and processing speed, childhood trauma has a negative effect in the domains of working memory, perceptual organization and processing speed and the interaction of BPDI and history of childhood trauma showed that cognitive performance was significantly decreased for perceptual organization compared to healthy controls.

These results are therefore a step in the process of identifying which cognitive domains are deteriorated due to BPDI, history of childhood trauma and having both. In the context of unraveling the cognitive domains that are responsible for the variability in cognitive functioning seen in BPDI patients and healthy controls, this study provides support and evidence to the previously found affected cognitive domains.

Literature

Aas, M., Dazzan, P., Mondelli, V., Toulopoulou, T., Reichenberg, A., Di, F.M., Fisher, H.L., Handley, R., Hepgul, N., Marques, T., Miorelli, A., Taylor, H., Russo, M., Wiffen, B., Papadopoulos, A., Aitchison, K.J., Morgan, C., Murray, R.M. & Pariante, C.M. (2010). Abnormal cortisol awakening response predicts worse cognitive function in patients with first-episode psychosis. *Psychological Medicine, 9,* 1–14.

Aas, M., Dazzan, P., Mondelli, V., Toulopoulou, T., Reichenberg, A., Di, F.M., Fisher, H. L., Handley, R., Hepgul, N., Marques, T., Miorelli, A., Taylor, H., Russo, M., Wiffen, B., Papadopoulos, A., Aitchison, K.J., Morgan, C., Murray, R.M. & Pariante, C.M. (2011). Abnormal cortisol awakening response predicts worse cognitive function in patients with first episode psychosis. *Psychological Medicine, 41*, 463–476.

Aas, M., Dazzan, P., Fisher, H.L., Morgan, C., Morgan, K., Reichenberg, A., Zanelli, J., Fearon, P., Jones, P.B., Murray, R.M. & Pariante, C.M. (2011). Childhood trauma and cognitive function in first-episode affective and non-affective psychosis. *Schizophrenia Research, 129*, 12-19.

Albus, M., Hubmann, W., Wahlheim, C., Sobizack, N., Franz, U. & Mohr, F. (1996). Contrasts in neuropsychological test profile between patients with first-episode schizophrenia and first episode affective disorders. *Acta Psychiatrica Scandandinavia, 94,* 87–93.

Allen, D.N., Huegel, S.G., Gurklis Jr., J.A., Kelley, M.E., Barry, E.J. & van Kammen, D.P. (1997). Utility of WAIS-R short forms in schizophrenia. *Schizophrenia Research, 26*, 163–172.

Arts B., Jabben N., Krabbendam L. & van Os J. (2008). Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychological Medicine, 38*, 771 785.

Bearden, C.E., Hoffman, K. M. & Cannon T.D. (2001). The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. *Bipolar Disorder, 3*, 106–150.

Bebbington, P.E., Bhugra, D., Brugha, T., Singleton, N., Farrell, M., Jenkins, R., Lewis, G. & Meltzer, H. (2004). Psychosis, victimisation and childhood disadvantage. *The Britisch Journal of Psychiatry, 185,* 220–226.

Beck, J.C. & Van der Kolk, B.A. (1987). Reports of childhood incest and current behavior of chronically hospitalized psychotic women. *American Journal of Psychiatry, 144*, 1474–1476.

Belanoff, J.K., Kalehzan, M., Sund, B., Fleming Ficek, S.K. & Schatzberg, A.F. (2001). Cortisol activity and cognitive changes in psychotic major depression. *American Journal of Psychiatry, 158*, 1612–1616.

Bernstein, D., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E. & Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *American Journal of Psychiatry, 151*, 1132–1136.

Blyler, C.R., Gold, J.M., Iannone, V.N., & Buchanan, R.W. (2000). Short form of the WAIS-III for use with patients with schizophrenia. *Schizophrenia Research*, *46*, 209-215.

Bora, E., Yucel, M. & Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: a meta analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of Affective Disorders*, *113*, 1–20.

Bremner, J.D., Randall, P., Scott, T.M., Capelli, S., Delaney, R., McCarthy, G. & Charney, D.S. (1995). Deficits in shortterm memory in adult survivors of childhood abuse. *Psychiatry Research, 59*, 97–107.

Bremner, J.D., Vermetten, E., Afzal, N. & Vythilingam, M. (2004). Deficits in verbal declarative memory function in women with childhood sexual abuse-related posttraumatic stress disorder. *The journal of Nervous and Mental Disease*, *192*, 643–649.

Brown, J., Cohen, P., Johnson, J. G., & Salzinger, S. (1998). A longitudinal analysis of risk factors for child maltreatment: Findings of a 17-year prospective study of officially recorded and self reported child abuse and neglect. *Child Abuse and Neglect*, *22*, 1065–1078.

Cavanagh, J.T.O., Van Beck M., Muir, W. & Blackwood, D.H.R. (2002). Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. *The British Journal of Psychiatry*, *180*, 320-326.

Cicchetti, D., Toth, S.L. & Maughan, A. (2000). An ecological–transactional model of child maltreatment. In: Sameroff, A.J., Lewis, M., Miller, S.M. (Eds.), Handbook of Developmental Psychopathology, 2nd ed. Kluwer Academic/Plenum Publishers, New York, pp. 689– 722.

Clark, L., Iverson, S.D. & Goodwin, G.M. (2002). Sustained attention deficit in bipolar disorder. *The British Journal of Psychiatry*, *180*, 313–319.

Clark, L., Sarna, A. & Goodwin, G. M. (2005). Impairment of executive function but not memory in first- degree relatives of patients with bipolar I disorder and in euthymic patients with unipolar depression. *American journal of psychiatry*, *162*, 1980-1982.

Denicoff, K.D., Ali, S.O., Mirsky, A.F., et al. (1999). Relationship between prior course of illness and neuropsychological functioning in patients with bipolar disorder. *Journal of Affective Disorders*, *56*, 67–73.

Donaldson, S., Goldstein, L.H., Landau, S., Raymont, V. & Frangou, S. (2003). The Maudsley bipolar disorder project: the effect of medication, family history, and duration of illness on IQ and memory in bipolar I disorder. *Journal of Clinical Psychiatry*, *64*, 86–93.

El-Badri, S.M., Ashton, C.H., Moore, P.B., Marsh, V.R. & Ferrier, I.N. (2001). Electrophysiological and cognitive function in young euthymic patients with bipolar affective disorder. *Bipolar Disorders*, *3*, 79–87.

Engelsmann, F., Katz J., Ghadirian, A.M. & Schachter, D. (1998). Lithium and memory: a long-term follow-up study. *Journal of Clinical Psychopharmacology*, *8*, 207–212.

Ferrier, I.N., Chowdhury, R., Thompson, J.M., Watson, S. & Young, A.H. (2004). Neurocognitive function in unaffected first degree relatives of patients with bipolar disorder: a preliminary report. *Bipolar Disorders, 6*, 319–323.

Ferrier, I. N., Stanton, B. R., Kelly, T. P., et al. (1999). Neuropsychological function in euthymic patients with bipolar patients. *British Journal of Psychiatry, 175*, 246 -251.

Ferrier, I.N., Thompson, Jill M. (2002). Cognitive impairment in bipolar affective disorder: implications for the bipolar diathesis. *The British Journal of Psychiatry, 180*, 293-295.

Friedrich, W. N., & Boriskin, B. A. (1976). The role of the child in abuse. *American Journal of Ortho psychiatry, 46*, 580-590.

Flores, B.H., Kenna, H., Keller, J., Solvason, H.B. & Schatzberg, A.F. (2006). Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology, 31*, 628–636.

Gallagher, P., Watson, S., Smith, M.S., Ferrier, I.N. & Young, A.H. (2005). Effects of adjunctive mifepristone (RU-486) administration on neurocognitive function and symptoms in schizophrenia. *Biological Psychiatry, 57*, 155–161

Garno, J.L., Goldberg, J.F., Ramirez, P.M. & Ritzler, B.A. (2005). Impact of childhood abuse on the clinical course of bipolar disorder. *The British Journal of Psychiatry, 186*, 121–125.

Glahn, D.C., Bearden, C. E., Barguil, M., Barrett, J., Reichenberg, A., Bowden, C. L., Soares, J. C. & Velligan, D. I. (2007). The Neurocognitive Signature of Psychotic Bipolar Disorder. *Biological Psychiatry, 62*, 910-916

Goff, D.C., Brotman, A.W., Kindlon, D., Waites, M. & Amico, E. (1991). Self-reports of childhood abuse in chronically psychotic patients. *Psychiatry Research, 37*, 73–80.

Goodwin, F. & Jamison, K. (1990): *Manic-Depressive Illness*. New York: Oxford University Press.

Gourovitch, M.L., Torrey, E.F., Gold, J.M., Randolph, C., Weinberger, D.R. & Goldberg, T.E. (1999). Neuropsychological performance of monozygotic twins discordant for bipolar disorder. *Biological Psychiatry, 45*, 639–646.

Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., Miller, A.H. & Nemeroff, C.B. (2000). Pituitary adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA, 284*, 592-597.

Herman, J.L. (1992). Trauma and Recovery: The Aftermath of Violence from Domestic Abuse to Political Terror. Basic Books, New York.

Hyun. M., Friedman, S.D. & Dunner, D.L. (2000). Relationship of childhood physical and sexual abuse to adult bipolar disorder. *Bipolar Disorder, 2*, 131–135.

IBM SPSS Statistics 19.0 for Windows, Rel. august 2010. Chicago: SPSS Inc.

Janssen, I., Krabbendam, L., Bak, M., Hanssen, M., Vollebergh, W., de Graaf, R. & van Os, J. (2004). Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatrica Scandandinavia, 109*, 38–45.

Keck, P.E. Jr, McElroy, S.L., Havens, J.R., Altshuler, L.L., Nolen, W.A., Frye. M,A., et al. (2003). Psychosis in bipolar disorder: phenomenology and impact on morbidity and course of illness. *Comprehensive Psychiatry, 44*, 263–269.

Keri, S., Kelemen, O., Benedek, G. & Janka, Z. (2001). Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. *Psychological Medicine, 31*, 915–922.

Kessing, L.V. (1998). Cognitive impairment in the euthymic phase of affective disorder. *Psychological Medicine, 28*, 1027-1038.

Kieseppä, T., Tuulio-Henriksson, A., Haukka, J., Van Erp, T., Glahn, D., Cannon, T.D., Partonen, T., Kaprio, J. & Lönnqvist, J. (2005). Memory and verbal learning functions in twins with bipolar I disorder, and the role of information processing speed. *Psychological Medicine, 35*, 205.

Koenen, K.C., Moffitt T.E., Caspi A., et al. (2003). Domestic violence is associated with environmental suppression of IQ in young children. *Development and psychopathology, 15*, 297–311.

Lebowitz, B.K., Shear P.K., Steed & M.A. Strakowski S.M. (2001). Verbal fluency in mania: relationship to number of manicepisodes. *Neuropsychiatry Neuropsychology Behavioral Neurology, 14*, 177–182.

Leverich, G.S., McElroy, S.L., Suppes, T., et al. (2002). Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biological Psychiatry, 51*, 288–297.

Lichtenstein, P., Yip, B.H., Björk, C., Pawitan, Y., Cannon, T.D., Sullivan, P.F. & Hultman, C.M. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *The Lancet, 373*, 234 – 239.

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-Rater Reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). *Clinical psychology and psychotherapy, 18*, 75-79.

Lysaker, P.H., Meyer, P., Evans, J.D. & Marks, K.A. (2001). Neurocognitive and symptom correlates of self-reported childhood sexual abuse in schizophrenia spectrum disorders. *Annals of Clinical Psychiatry, 13*, 89– 92.

Macqueen G.M. & Young L.T. (2003) Cognitive effects of atypical antipsychotics: focus on bipolar spectrum disorders. *Bipolar Disorders, 5*, 53–61.

Martinez-Aran, A., Vieta, E., Colom, F., Torrent, C., Sanchez-Moreno, J., Reinares, M., Benabarre, A., Goikolea, J.M., Brugue, E., Daban, C. & Salamero, M. (2002). Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. *Psychotherapy and Psychosomatics, 159*, 2027–2035.

Martinez-Aran, A., Vieta, E., Colom, F., Torrent, C., Sanchez-Moreno, J., Reinares, M., Benabarre, A., Goikolea, J.M., Brugue, E., Daban, C. & Salamero, M. (2004). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *American Journal of Psychiatry, 161*, 262-270.

Martinez-Aran, A., Vieta, E., Colom, F., Torrent, C., Sanchez-Moreno, J., Reinares, M., Benabarre, A., Goikolea, J.M., Brugue, E., Daban, C. & Salamero, M. (2004). Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disorders, 6*, 224–232.

May-Chahal, C. & Cawson, P. (2005). Measuring child maltreatment in the United Kingdom: a study of the prevalence of child abuse and neglect. *Child, Abuse and Neglect, 29*, 969–984.

Muenzenmaier, K., Meyer, I., Struening, E. & Ferber, J. (1993). Childhood abuse and neglect among women outpatients withchronic mental illness. *Hospital and Community Psychiatry, 44*, 666 670.

Navalta, C.P., Polcari, A., Webster, D.M., Boghossian, A. & Teicher, M.H. (2006). Effects of childhood sexual abuse on neuropsychological and cognitive function in college women. *The journal of neuropsychiatry & clinical neurosciences, 18*, 45–53.

Perez, C.M. & Widom, C.S. (1994). Childhood victimization and long-term intellectual and academic outcomes. *Child Abuse & Neglect, 18*, 617–633.

Pesonen, A.K., Raikkonen, K., Feldt, K., Heinonen, K., Osmond, C., Phillips, D.I., Barker, D.J., Eriksson, J.G. & Kajantie, E. (2010). Childhood separation experience predicts HPA axis hormonal responses in late adulthood: a natural experiment of World War II. *Psychoneuroendocrinology, 35*, 758–767.

Post, R.M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of psychiatry, 149*, 999–1010.

Raine, A., Park, S., Lencz, T., Bihrle, S., LaCasse, L., Widom, C., Dayeh, L. & Singh, M. (2001). Reduced right hemisphere activation in severely abused violent offenders during a working memory task: an fMRI study. *Aggressive Behavior, 27*, 111–129.

Read, J. (1997). Child abuse and psychosis: a literature review and implications for professional practice. *Professional Psychology Research and Practice, 28*, 448– 456.

Read, J. & Argyle, N. (1999). Hallucinations, delusions, and thought disorder among adult psychiatric inpatients with a history of child abuse. *Psychiatry Services, 50*, 1467–1472.

Read, J., Goodman, L., Morrison, A.P., Ross, C.A. & Aderhold, A. (2004). Childhood trauma, loss and stress. In: Read, J., Mosher, L.R., Bentall, R.P. (Eds.), Models of Madness. Brunner Routledge, New York, pp. 223– 252.

Read, J., Agar, K., Argyle, N. & Aderhold, V. (2003). Sexual and physical abuse during childhood and adulthood as predictors of hallucinations, delusions and thought disorder. *Psychology and Psychotherapy, 76*, 1– 22.

Robinson, L.J. & Ferrier, I.N. (2006). Evolution of cognitive impairment in bipolar disorder: a systematic review of crosssectional evidence. *Bipolar Disorders, 8*, 103–116.

Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., et al. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of Affective Disorders, 93,* 105–115.

Savitz, J.B., van der Merwe, L., Stein, D.J., Solms, M. & Ramesar, R.S. (2008). Neuropsychological task performance in bipolar spectrum illness: genetics, alcohol abuse, medication and childhood trauma. *Bipolar Disorder*, 10, 479-494.

Savitz, J., Solms, M. & Ramesar, R. (2005). Neuropsychological dysfunction in bipolar affective disorder: a critical opinion. *Bipolar Disorders, 7*, 216-235.

Scher, C.D., Stein, MB., Asmundson, G.J.G., McCreary, D.R., & Forde, D.R. (2001). The Childhood Trauma Questionnaire in a community sample: Psychometric properties and normative data. *Journal of Traumatic Stress, 14,* 843-857.

Schenkel, L.S., Spaulding, W.D., DiLillo, D. & Silverstein, S.M. (2005). Histories of childhood maltreatment in schizophrenia: relationships with premorbid functioning, symptomatology, and cognitive deficits. *Schizophrenia Research, 76,* 273–286.

Schmand, B., Lindeboom, J., Harskamp, F. van. (1992) Nederlandse leestest voor volwassenen: handleiding (NLV). Lisse. Swetz & Zeitlinger.

Simonsen, C., Sundet, K., Vaskinn, A., Birkenaes, A.B., Engh, J.A., Hansen, C.F., Jonsdottir, H., Ringen, P.A., Opjordsmoen, S., Friis, S., & Andreassen, O.A. (2008). Neurocognitive profiles in bipolar I and bipolar II disorder: differences in pattern and magnitude of dysfunction. *Bipolar Disorders, 10*, 245–255.

Stefanopoulou E., Manoharan A., Landau S., Geddes J.R., Goodwin G. & Frangou S. (2009). Cognitive functioning in patients with affective disorders and schizophrenia: a meta analysis. *International Review of Psychiatry, 21*, 336–356.

Thaker, G.K., 2008. Neurophysiological endophenotypes across bipolar and schizophrenia psychosis. *Schizophrenia Bulletin, 34,* 760–773.

Thompson, J.M., Gallagher, P., Hughes, J.H., et al (2005). Neurocognitive impairment in euthymic patients with bipolar affective disorder. *The British Journal of Psychiatry, 186* , 32–40.

Torres I.J., Boudreau V.G. & Yatham L.N. (2007). Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatrica Scandandinavica Supplementum, 434,* 17–26.

Toulopoulou, T., Mapua-Filbey, F., Quraishi, S., et al. (2005). Cognitive performance in presumed obligate carriers for psychosis. *The British Journal of Psychiatry, 187*, 284–285.

Vieta, E., Torrent, C., Martínez-Arán, A., Daban, C., Sánchez-Moreno, J., Comes, M., Goikolea, J. & Salamero, M. (2006). Cognitive impairment in bipolar II disorder. *British journal of psychiatry, 189*, 254- 259.

Watson, S., Gallagher, P., Ritchie, J.C., Ferrier, I.N. & Young, A.H. (2004). Hypothalamic–pituitary adrenal axis function in patients with bipolar disorder. *British Journal of Psychiatry, 184*, 496–502.

Wechsler, D. (2000). WAIS-III Nederlandstalige Bewerking, Afname en scoringshandleiding. Swets Test Publishers, Lisse, Netherlands.

Weiss, E.L., Longhurst, J.G. & Mazure, C.M. (1999). Childhood sexual abuse as a risk factor for depression in women: psychosocial and neurobiological correlates. *American Journal of Psychiatry, 156*, 816–828.

Wingo, A.P., Wingo, T.S., Harvey, P.D. & Baldessarini, R.J. (2009). Effects of lithium on cognitive performance: a meta-analysis. *Journal of Clinical Psychiatry, 70*, 1588 -1597

Wolf, O.T., Schommer, N.C., Hellhammer, D.H., McEwen, B.S. & Kirschbaum, C. (2001). The relationship between stress induced cortisol levels and memory differs between men and women. *Psychoneuroendocrinology, 26*, 711–720.

Wolfe, J., Kimmerling, R., Brown, P.J., Chrestman, K.R. & Levin, K. (1996). The Life Stressor Checklist-Revised. Instrumentation in Stress Trauma and Adaptation.

Young, A.H., Gallagher, P., Watson, S., Del-Estal, D., Owen, B.M. & Ferrier, I.N. (2004). Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology, 29*, 1538–1545

Zalla, T., Joyce, C., Szoke, A., Schurhoff, F., Pillon, B., Komano, O., Perez-Diaz, F., Bellivier, F., Alter, C., Dubois, B., Rouillon, F., Houde, O. & Leboyer, M. (2004). Executive dysfunctions as potential markers of familial vulnerability to bipolar disorder and schizophrenia. *Psychiatry Research, 121*, 207–217.

Zubieta, J.K., Huguelet, P., O'Neil, R.L. & Giordani, B.J. (2001). Cognitive function in euthymic bipolar I disorder. *Psychiatry Research, 102*, 9–20.