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Thesis

Cognitive functioning deficits in borderline personality disorder

A meta-analysis

Anouk Ziech
Studentnumber > 0327085

Supervisors:
Ineke Brands
Ineke van der Ham

Abstract

Background: Borderline Personality disorder (BPD) is characterized by unstable affect, behaviour, mood, interpersonal relationships and self-image. Several cognition deficits have been found in BPD patients, but the cognitive functioning profile is far from complete. Recently, more studies have looked at the neuropsychology of BPD and these results can now be used to create a clearer profile for BPD. *Objective*: A meta-analysis to compare and discuss the results of neuropsychological studies of BPD and integrate them with neuroimaging/biological findings. *Methods:* A total of 16 studies compromising 809 participants on cognitive functioning in BPD patients were selected. *Results*: BPD patients showed significant deficits across all cognitive domains compared to controls. Effect sizes (Cohen´s *d*) ranged from –0,36 for verbal delayed memory to -1,34 for planning and problem solving. *Conclusion*: BPD patients demonstrated impaired performance on all cognitive domains. The results were consistent with neuroimaging findings. Study limitations were heterogeneity and possible publication bias for several significant domains. Clinical implications are limited.

1. Introduction

Borderline personality disorder (BPD) is a diagnosis on axis II of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, American Psychiatric Association 2000). BPD patients are characterized by unstable affect, behaviour, mood, interpersonal relationships and self-image. Their behaviour is unpredictable and often self-destructive. Women have twice as many a chance of being diagnosed with BPD compared to men and the prevalence is 1 to 2% (Saddock & Saddock 2003). Affective dysregulation seems to lie at the core of the characteristics and symptoms of BPD (Schmall & Bremner 2006). The suggestion has been made that BPD results from acquired or developmental brain dysfunction and is associated with early traumatic experience (Skodol et al 2002; Tebartz van Elst et al 2003).

The underlying neurobiology and cognitive dysfunction of BPD has been the subject of several studies (Schmall & Bremner 2006; Lis et al 2007; Ruocco 2005) and this profile is far from complete. Magnetic resonance imaging (MRI) studies found a smaller frontal lobe, amygdala, hippocampus, orbitofrontal and anterior cingulated cortex, a reduction in parts of the parietal cortex and corpus collosum and increased putamen in BPD patients (Driessen et al 2000; Tebartz van Elst et al 2003; Schmall et al 2003; Brambilla 2004; Zetsche et al 2007; Rusch et al 2007; Irle et al 2007; Lyoo et al 1998). Functional magnetic resonance imaging (fMRI) studies confirm differences in these brain regions as activation of these areas are shown to be dissimilar between BPD patients and healthy subjects (Beblo et al 2006; Schnell et al 2007; Herpertz et al 2001; Schmall & Bremner 2006; Minzenberg et al 2007). Damage to the prefrontal cortex, amygdala and hippocampus, brain regions implicated in BPD, could lead to disturbances in executive functions, attention, working memory, long- and short-term memory and the perception and processing of emotion (Godefroy & Rousseaux 1996; Manes et al 2002; Simons and Spiers 2003; Graham et al 2007; Honk & Schutter 2006; Davidson & Irwin 1999). Some studies suggest that fronto-limbic abnormalities differentiate BPD from other disorders (Tebartz van Elst et al 2003; Silbersweig et al 2007; Minzenberg 2007). Behaviour that is characteristic for BPD is also seen after injury to the frontal cortex. In view of this, Kunert and others (2003) have linked BPD to frontal dysfunction, which could result in deficits in executive functioning, attention and working memory.

Several studies did report that the performance was worse for BPD patients than controls on attention, working memory and executive functions tasks (Bazanis et al 2002; Dinn et al 2004; Lenzenweger 2004; Domes 2006). Haaland & Landrø (2007) measured decision making with the IOWA gambling task and found the BPD participants showed less advantageous choices than the controls. BPD patients also exhibited greater difficulty in their ability to resolve conflict among stimulus dimensions in the attentional network task (ANT, Posner & Petersen 1990), but displayed no deficit in overall reaction time, errors, or the alerting and orienting network (Posner et al 2002). Impaired memory and visuo-spatial functions are also reported in patients with BPD (Hurlemann et al 2007; Stevens et al 2004). Korfine and Hooley (2000) found that BPD subjects had a memory bias for words that were congruent with borderline. The results of Beblo and others (2006) showed primarily visual memory, visuo-spatial abilities and executive functioning deficits for BPD patients. Harris and others (2002) established that

BPD participants exhibited deficits on immediate and delayed recall of the Rey-Osterrieth Complex Figure and produced distorted drawings of the Rey Figure (Osterrieth, 1944). But other studies did not find that BPD patients performed worse on cognitive functioning tasks compared to healthy comparison subjects (Sprock et al 2000; Kunert et al 2003). Bazanis and others (2002) found no evidence of impaired visual recognition memory in patients with BPD, whereas Dinn and others (2004) reported unimpaired alternation learning, response inhibition, divergent thinking, verbal fluency and verbal working memory functions in BPD patients. In addition, Driessen and others (2000) found no significant differences on various cognition tasks between BPD participants and healthy subjects. According to Ruocco´s meta-analysis (2005) BPD patients performed less on all cognitive domains than healthy controls. He included ten studies compromising 488 participants in his meta-analysis and selected six domains of cognitive functioning: attention, cognitive flexibility, learning and memory, planning, speeded processing, and visuo-spatial abilities. On all domains BPD subjects performed worse than the healthy controls; planning was impaired the most in BPD participants and cognitive flexibility the least.

A possible explanation for these conflicting results is the high co-morbidity rate among BPD patients. It is almost impossible to exclude participants with co-morbid psychiatric disorders. Furthermore, the generalizability of a study will be reduced when excluding these participants, because most people with BPD have an additional mental disorder, often major depression or post traumatic stress disorder (PTSD). When excluding persons with co-morbid diagnoses the found brain abnormalities or cognitive deficits are ensured to be associated with BPD, but the results may not apply to the larger BPD population that do have other psychiatric disorders (Lis et al 2007 Brambilla 2004).The variety of diagnostic systems utilized across studies to define BPD, if patients were medicated or not and the different tests used across studies to assess particular domains of function contribute to the fact that BPD studies are per definition heterogeneous (Ruocco 2005).

Recently, more studies have looked at the neuropsychology of BPD and these results can now be integrated in the cognitive functioning profile of BPD. Furthermore, specific cognitive (sub)domains like language, selective attention or (psycho)motor activity should be included in the cognitive profile of BPD.

To further explore the neuropsychological profile of BPD, it is needed to examine the results as a whole and to integrate the findings with biological findings to create a clearer profile of BPD. This meta-analysis wants to compare and discuss the results of neuropsychological studies of BPD. First, the cognitive domains that are mainly impaired in BPD are reported. Second, these results will be reviewed and integrated with neuroimaging/biological findings.

2. Methods

2.1 Selection of Studies

Scopus, Psycinfo and Pubmed search engines were used to identify studies on cognitive performance and studies using MRI. The following were the key words or truncated versions: borderline, personality disorder, cognition, function, attention, learning, memory, executive

functioning, information processing, intelligence, spatial, brain, neural circuits, MRI and imaging. References of published studies were examined to identify additional studies.

Studies were examined to establish if they fulfilled the following inclusion criteria: 1) included only adults aged > 18 who were diagnosed with BPD using the DSM-III, DSM-IV, DSM-IV-TR, 2) had a defined control group, 3) used MRI or assessed cognitive performance by using standard neuropsychological testing methods, 4) test scores (means and SD) were presented value for the experimental and control groups. For both the control group and the experimental group, characteristics and inclusion and exclusion criteria were recorded.

A total of 16 studies compromising 809 participants (BPD:410, control:399) on cognitive functioning in BPD patients were selected that met the inclusion criteria. Table 1 displays the descriptive data for the included studies.

2.2 Method of Analysis

Effect sizes (Cohen's *d)*, which are the standardized differences between the experimental en control group, were calculated for every test result.

In the meta-analysis, a combined *d* value was included, expressing the magnitude of associations across studies and was weighted for sample size. If the performance of the BPD group was worse than the controls the direction of the effect size was negative. Stouffer's Z, also weighted for sample size, offered an estimate of the significance of the difference in cognitive performance between the two groups.

Heterogeneity was determined by calculating the statistic *Q.* To examine if the observed significant effect cannot be explained by publication bias, the fail-safe *N* was calculated to estimate the number of studies needed to falsify the significant result. Also, the actual number of existing non-significant studies was estimated to establish if the fail-safe *N* exceeded the estimate of existing unpublished studies reporting non-significant results.

Neuropsychological test that were used in the included studies were classified according to the following cognitive domains: attention, learning and memory, (psycho) motor activity and speed processing, visuo-spatial abilities, cognitive flexibility, language and intelligence. These general domains were subdivided, if possible, in more specific cognitive domains to perform more specific analysis (Lezak 2004). All cognitive domains were first pooled in an overall *d* value (overall cognition) to compute an index of differences in cognitive function.

The domain attention was subdivided in attentional capacity, which assesses the short-term storage capacity and selective attention, which measures the ability to selectively attend to visually presented information. Learning and memory consisted of working memory, verbal learning and immediate memory, visual learning and immediate memory, visual delayed memory and verbal delayed memory. Cognitive flexibility was subdivided into the ability to shift concepts, planning and problem solving strategies and disinhibition, which measures problems in braking or modulating ongoing behaviour. One specific cognitive domain could be identified within visuo-spatial abilities: drawing. Motor activity and speed of processing was subdivided in speed of information processing and motor speed for motor activity. Tests measuring the same cognitive domain were taken together in the analysis. Overall cognition

Table1 Decriptive data for participants across cognition studies in the meta-analysis

Study	First Author	*n* BPD	*n* controls	Age (Years) BPD	Age (Years) controls	subjects matched for	Gender BPD % female	measures	Type of BPD diagnosis	exlusion criteria	co-morbidity current/history/lifetime	medication BPD
1	Swirsky-Sacchetti (1993)	10	10	30,3	29	A, ED, H	100	SCID-II; DIB	DSM-III-R	HI, MD, HT, AU ID, AD, EC	history of LD, DD, SE, LH HI, FS, MD	current (8)
2	Jones (1999)	23	23	31,1±7,7	31,2±8,6	A, ED, G	78	SCID-II	DSM-IV	SP, BD, LD, SAD	unknown	
3	Korfine (2000)	45	20	29,5±6,7	28,5±6,3	A, G, ED, ET	84,6	IPDE	DSM-IV	SP, SCD	unknown	unknown
4	Driessen (2000)	21	21	29,9±6,0	29,3±6,7	G, R, H, A, ED	100	SCID-II	DSM-IV	P, ESD, MAD, LC, ND, HI, MR current ID, AN, SP, SCD, MDP during last 6 months DA/AD	PTSD(12), other unknown	free at least 1 week
5	Posner (2002)	39	30	30	22	unknown	97	IPDE	DSM-IV	unknown	unknown	unknown
6	Harris (2002)	25	25	30,2±6,4	31,3±5,5	G, H, ED	64	unknown	DSM-IV	unknown	unknown	unknown
7	Bazanis (2002)	42	42	30,6±1,5	33,3±1,4	A, G, IQ, H	59	SCID-II	DSM-III-R	SP, DED, MDP, ME, OMD, ND, history of PDS, current MDE previous 2 months AD/DA	APD (23), other unknown	unknown
8	Kunert (2003)	23	23	29,9±8,7	38,3±12,9	A, G, SES	87	IPDE	DSM-IV	MD, SP, SAD	history of MD(4), EAD(5), SAD(8), AS(15)	current (10)
9	Stevens (2004)	22	25	31,9±9,1	30,5±10,4	A, ED, G	100	DIB	DSM-IV	CD, PSS, LH	unknown	not current except AND
10	Dinn (2004)	9	9	30,1±8,7	27,2±8,7	unknown	100	unknown	DSM-IV	unknown	current SCD(5), PTSD(5), MUS(1)	all current

A=Age, AD=Alcohol use/abuse/dependence, ADD=adjustment disorder, AG=agoraphobia, AN=anorexia, AND=Antidepressants, AND=anxiety disorder, APD=antisocial personality disorder, AS=attempted suicide, BD= Bipolar disorder, CD=other current psychiatric or neurological diagnosis, DA=drug use/abuse/dependence, DD=Developmental delay, DD=dysthymic disorder, DED=delusional disorder, DIB=Diagnotic Interview for Borderlines (Gunderson et al 1998),DIB-R=Diagnostic Interview for Borderlines-Revised (Gunderson & Zanarini 1983; Zanarini et al 1989), EAD=eating disorder, EC= ECT, ED=Education, EP=epilepsy, ESD=endocrine system disorders, ET=Ethnicity, FS= First-degree family members with schizophrenia, G=Gender, GAD=generalized anxiety disorder, H=Handedness, HI=Head Injury with loss of consciousness, HI=positive serology for HIV, HT=Head Trauma, ID=infectious diseases, IPDE=International Personality Disorder Examination (Loranger 1996,1999), LC=liver cirrhosis, LD=Learning disabilities, LH= Left-handedness, MAD=malignent disorders, MD=Major Depression, MDE=major depressive episode, MDP=major depression with psychotic symptoms, ME=manic episode, MED=memory disorder, MR=mental retardation, MUS=Munchhausen syndroom, ND= neurological diseases, OAD=other axis 1 disorders, OCD=obsessive compulsice disorder, OMD=organic mental disorder, OPD=other personality disorder, P=pregnant, PD=panic disorder, PH=phobia, PSD=primary substance dependence, PSD=psychotic disorder, PSS=present suicidal state, PTSD=post traumatic stress disorder, R=race, SAD=substance abuse disorder, SAM=substance abuse within the six months before testing, SBA=structural brain abnormalities, SCD=Schizoaffective disorder, SCID-II=Structured Clinical Interview for DSM-III-R / DSM-IV personality disorders (Spitzer et al 1990; First et al 1997), SE=Seizures, SES=social economic status, SOM=somatization disorder, SOP=social phobia, SP=Schizophrenia.

Table1 (continued) Decriptive data for participants across cognition studies in the meta-analysis

Study	First Author	*n* BPD	*n* Controls	Age (Years) BPD	Age (Years) controls	subjects matched for	Gender BPD % female	measures	Type of BPD diagnosis	exlusion criteria	co-morbidity current/history/lifetime	medication BPD
11	Lenzenweger (2004)	24	68	31,9±9,15	29,2±6,67	G, A, ED	100	IDPE	DSM-IV	BD, DED, SP, PSD, MR, current SAD	EAD(1), lifetime DA/AD (2), current DD(41,7%), PD(12,5%),SOP(12,5%), PTSD(4,2%), GAD(16,7%), EAD(33,3%), OCD(8,3%) MD(4,2%), history and axis 2 unknown	unknown
12	Beblo (2006)	22	22	32±7,9	32±7,9	A, G, ED	100	SCID-II	DSM-IV	SP,SCD, MDP, AN, SBA SAD 6 months before testing	MD(6), DD(3), SAD(2), PD(5), PH(4), GAD(2), PTSD(11), EAD(4), SOM(2), OCD(2), axis 2 unknown	testday free
13	Domes (2006)	28	30	24,9±5,85	32±5,88	G, IQ,	100	IPDE	DSM-IV	lifetime SP, MD, BD, PD, AG, SOP, GAD, PTSD, ADHD, current DA, AD, history HT, ND, IQ below 85, OAD	unknown	free for at least 4 weeks before testing
14	Lampe (2007)	41	20	25,5±6,6	32±6,9	A, ED, IQ	90	IPDE	DSM-IV	current SP, BD, MD AD, MED, DA	lifetime ADHD (20), OPD (9), SAD (8) AND(1), PTSD(1), DD(3), ADD(1), EAD(4), axis 2 unknown	free for at least 4 weeks before testing
15	Hurlemann (2007)	16	16	25,2±4,3	25,6±4,6	A, ED	100	DIB-R	DSM-IV	current AD, DA, lifetime OPD, OAD, history of ND, SOM	unknown	free 4 weeks before testing (10) drug naive(6)
16	Haaland (2007)	20	15	24,4±9,7	22,7±5,3	unknown	75	SCID-II	DSM-IV	severe SAD, history of HT, EP	MD(12), PTSD(10), AND(10), OPD(7), SAD(7)	current (19)

A=Age, AD=Alcohol use/abuse/dependence, ADD=adjustment disorder, AG=agoraphobia, AN=anorexia, AND=Antidepressants, AND=anxiety disorder, APD=antisocial personality disorder, AS=attempted suicide, BD= Bipolar disorder, CD=other current psychiatric or neurological diagnosis, DA=drug use/abuse/dependence, DD=Developmental delay, DD=dysthymic disorder, DED=delusional disorder, DIB=Diagnotic Interview for Borderlines (Gunderson et al 1998),DIB-R=Diagnostic Interview for Borderlines-Revised (Gunderson & Zanarini 1983; Zanarini et al 1989), EAD=eating disorder, EC= ECT, ED=Education, EP=epilepsy, ESD=endocrine system disorders, ET=Ethnicity, FS= First-degree family members with schizophrenia, G=Gender, GAD=generalized anxiety disorder, H=Handedness, HI=Head Injury with loss of consciousness, HI=positive serology for HIV, HT=Head Trauma, ID=infectious diseases, IPDE=International Personality Disorder Examination (Loranger 1996,1999), LC=liver cirrhosis, LD=Learning disabilities, LH= Left-handedness, MAD=malignent disorders, MD=Major Depression, MDE=major depressive episode, MDP=major depression with psychotic symptoms, ME=manic episode, MED=memory disorder, MR=mental retardation, MUS=Munchhausen syndroom, ND= neurological diseases, OAD=other axis 1 disorders, OCD=obsessive compulsice disorder, OMD=organic mental disorder, OPD=other personality disorder, P=pregnant, PD=panic disorder, PH=phobia, PSD=primary substance dependence, PSD=psychotic disorder, PSS=present suicidal state, PTSD=post traumatic stress disorder, R=race, SAD=substance abuse disorder, SAM=substance abuse within the six months before testing, SBA=structural brain abnormalities, SCD=Schizoaffective disorder, SCID-II=Structured Clinical Interview for DSM-III-R / DSM-IV personality disorders (Spitzer et al 1990; First et al 1997), SE=Seizures, SES=social economic status, SOM=somatization disorder, SOP=social phobia, SP=Schizophrenia.

a general index of differences in cognitive function, was measured by calculating an overall *d* value, in which all cognitive domains were included.

All analyses were performed using the statistical program META (Schwarzer 1988).

3. Results

For two studies (Posner et al 2002; Haaland & Landrø 2007) it was not clear with which criteria they matched their subjects. Twelve studies matched for age, for both the patients and controls the ages within and across all studies were similar. Ten studies matched for education and/or gender. Other co-occurring psychiatric disorders and medication intake of the BPD patients is also displayed in table 1. In general this information was not fully disclosed.

According to Cohen (1988) an effect size (*d*) of 0.2 is considered small, 0.5 medium and 0.8 or higher large. Table 2 and table 3 show the results of the general cognitive domains and subdivided cognitive domains respectively.

3.1 Overall cognition

Overall cognition was significantly worse for the BPD patients (d=-0.88, p<0.01), but not homogeneous (Q=111.37, p<0.01).

3.2 Language

Compared to healthy subjects BPD patients showed significant impaired language (d=-0.62, p<0.01). The sample of effect sizes is homogenous (Q=1.62, p=0.44).

3.3 Attention

The effect size for attention was significant (d=-0.47, p<0.01) but not homogeneous (Q=28.18, p<0.01). BPD patients did have reduced attentional capacity (d=-0.62, p<0.01) and selective attention (d=-0.37, p<0.01) compared to controls. Both were homogeneous (selective attention: Q=2.30, p=0.51; attentional capacity: Q=1.74, p=0.42).

	CI low	CI high	Effect Size	Sign
Overall cognition (410)a	-1,3247	-0,4320	-0,87834	*p* <0,01
Language (41)b	-1,0745	-0,1587	-0,61664	*p* <0,01
Attention (196)c	-0,8825	-0,0488	-0,46561	*p* <0,01
Learning and memory (276)d	-0,8540	0,2372	-0,54556	*p* <0,01
Cognitive flexibility (203) e	-1,7469	-0,3991	-1,07299	*p* <0,01
Psychomotor activity and information processing (183) f	-0,8825	-0,4010	-0,64177	*p* <0,01
Visuo-spatial abilities (118) g	-1,0964	-0,2444	-0,67043	*p* <0,01

Table 2 – Standardized effect sizes (Cohen's d) and 95% CIs for the cognitive domains in BPD patients compared with healthy control subjects. Number of patients included in each domain is listed between brackets. Non-significant P values are not shown. Refs (see table 1): a = (1-16), b=(1,10,12), c=(1,5,8,10-14), d=(1-4,6,8-10,12-15), e=(1,4,7,8,10-12,14,16), f=(1,4,8-10,12-15), g=(1,4,6,10-12,15).

3.4 Learning and Memory

The sample of effect sizes for learning and memory was significant (*d*=-0.55, *p*<0.01), but not homogeneous (Q=29.60, *p*<0.01). Large significant effect sizes were found for verbal learning and immediate memory (*d*=-0.77, *p*<0.05) and visual delayed memory (*d*=-0.85, *p*<0.05), the BPD patients performed worse on these specific cognitive domains than the healthy subjects. Both these domains were heterogeneous (verbal learning and immediate memory: Q=13.92, *p*<0.01; visual delayed memory: Q=20.05, *p*<0.01). BPD patients showed also impaired working memory (*d*=-0.39, *p*<0.01; Q=2.83, *p*=0.59), visual learning and immediate memory (*d*=-0.46, *p*<0.05; Q=2.22, *p*=0.33) and verbal delayed memory (*d*=-0.36, *p*<0.05; Q=1.80, *p*=0.61), all homogeneous.

3.5 Cognitive flexibilty

This domain was significant, but not homogeneous (*d*=-1.07, *p*<0.01; Q=72.44, *p*<0.01). The subdivided domains planning and problem solving (*d*=-1.35, *p*<0.01; Q=61.67, *p*<0.01), disinhibition (*d*=-0.41, *p*<0.05; Q=4.11, *p*=0.13) and concept shifting (*d*=-0.61, *p*<0.01; Q=2.24, *p*=0.52) were significant, BPD patients needed more time to shift concepts, plan and solve problems and performed worse tasks measuring disinhibition than healthy controls. The domain planning and problem solving was still heterogeneous.

	CI low	CI high	*d*	Sign
Attention				
Attentional capacity (41)a	-1,0651	-0,1653	-0,61518	*p*<0,01
Selective attention (102)b	-0,6646	-0,0684	-0,36648	*p*<0,01
Learning and memory				
Working memory (117)c	-0,6653	-0,1141	-0,38971	*p* <0,01
Visual learning and immediate memory(44)d	-0,9739	0,0527	-0,46061	*p* <0,05
Verbal learning and immediate memory(69)e	-1,5070	-0,0404	-0,77371	*p* <0,05
Visual delayed memory (94)f	-1,5739	-0,1328	-0,85337	*p* <0,05
Verbal delayed memory (53)g	-0,7509	0,0232	-0,36385	*p* <0,05
Cognitive Flexibilty				
Planning and problem solving(160)h	-2,1583	-0,5333	-1,34578	*p* <0,01
Concept shifting (65)i	-0,9437	-0,2686	-0,60616	*p* <0,01
Disinhibition (73)j	-0,9116	0,0796	-0,41602	*p* <0,05
Psychomotor activity and information processing				
Motor speed (57)k	-1,2841	-0,0722	-0,67814	*p* <0,05
Speed of information processing(124)l	-0,9203	-0,4073	-0,66385	*p* <0,01
Visuo-spatial abilities				
Drawing (94)m	-1,2057	-0,2181	-0,71189	*p* <0,01

Table 3 – Standardized effect sizes (Cohen's d) and 95% CIs for the cognitive domains in BPD patients compared with healthy control s ubjects. Number of patients included in each domain is listed between brackets. Non-significant P values are not shown. Refs (see table1) : a=(1,10,12), b=(1,8,13,14), c=(8 - 10,12,14), d=(1,4,12), e=(1,4,10,12,15), f=(1,4,10,12,15,16), g=(1,4,10,12), h=(1,4,7,8,10,12,16), i=(1,10-12), j=(8,10,14), k=(1,10,12,15), l=(1,8,9,13,14), m=(1,4,6,10,12,15).

3.6 Motor activity and information processing

The sample of effect sizes was significant and homogeneous (*d*=-0.64, *p*<0.01; Q=5.84, *p*=0.66). Patients and controls did differ on speed of information processing (*d*=-0.66, *p*<0.01; Q=0.94, *p*=0.97). Motor speed performance was worse for BPD patients (*d*=-0.68, *p*<0.05; Q=5.34, *p*=0.15), the patients needed more time when motor activity was required.

3.7 Visuo-spatial abilities

Visuo-spatial abilities were impaired in BPD patients compared to controls (*d*=-0.67, *p*<0.01). This domain was heterogeneous (Q=18.50, *p*<0.01). Patients performed worse on drawing tasks than healthy subjects (*d*=-0.71, *p*<0.01). This specific domain was still heterogeneous (Q=15.25, *p*<0.01).

3.8 Fail-safe N

For cognitive domains language, attentional capacity, disinhibition, visual and verbal immediate memory, verbal delayed memory and motor speed the fail-safe *N* did not exceed the estimate of existing unpublished studies reporting non-significant results. It is possible these significant results could be explained by publication bias. The fail-safe *N* for the other cognitive domains all exceeded the estimated existing unpublished studies.

4. Discussion

This meta-analysis compared the results of 16 studies on cognitive dysfunction in BPD patients. The key findings were:

1) BPD patients performed significantly worse on all cognitive domains.
2) Large effect sizes were found for cognitive domains overall cognition, cognitive flexibility, verbal immediate learning en memory, visual delayed memory and planning and problem solving.
3) Language, attention, learning and memory, psychomotor activity and information processing, visuo-spatial abilities, attentional capacity, visual immediate learning and memory, concept shifting, disinhibition, speed of information processing, motor speed and drawing resulted in medium effect sizes.
4) Small effect sizes were demonstrated for selective attention, working memory and verbal delayed memory.

The significant effect sizes suggest that BPD patients show deficits across all cognitive domains. Impairments were the greatest in cognitive flexibility, visual delayed memory and planning and problem solving. Attention, learning and memory, psychomotor activity and information processing, visuo-spatial abilities, concept shifting, speed of information processing and drawing were impaired to a lesser degree. Deficits in selective attention and working memory were the smallest.

According to Zakzanis (2001) only effect sizes above 3.0 indicate that tests are reliable sensitive to the presence of a disorder. An effect size of 3.0 indicates an overlap of 7%, which means that 93% of the

participants obtained scores on a neuropsychological test that are unlike those obtained by the healthy controls. The largest effect size in this study, -1.34, still demonstrates an overlap of 34.7% in test measures between BPD and healthy controls, implicating that 65.3% of the BPD patients acquired the same scores on planning and problem solving tasks as the healthy subjects. As a result of this criterion of clinical utility, neuropsychological testing does not seem to specify discrete cognitive functioning test markers to classify BPD with. Furthermore, recent research suggests differences in cognitive functioning results when other disorders co-occur along with BPD. In a study of Lampe and others (2007) differences in performance on inhibitory tasks were found for co-morbid BPD and ADHD group and a BPD group, suggesting that it is important to separate BPD from other mental disorders. In view of this it is not possible to contribute the found deficits across all cognitive domains solely to BPD and not to other psychiatric disorders. But the findings do have clinical implications. Deficits in attention, memory and cognitive flexibility could have a negative effect on the ability to communicate effectively (Ruocco 2005). Additionally, cognitive deficits might influence the success of the treatment of BPD.

The findings of this study are largely consistent with the results of Ruocco (2005) and strengthen the theory that BPD diagnosed patients are impaired on all cognitive functions. As mentioned before he only looked at the larger cognitive domains and did not subdivide these in specific functions, except for verbal and non-verbal memory, therefore results could only be compared on the domains attention, memory and learning, visuo-spatial abilities, information processing and cognitive flexibility.

Ruocco's (2005) medium effect sizes for domains attention, learning and memory and speeded processing were consistent with our results. Differences in results between the two studies were found for the domain cognitive flexibility. His study reported a small effect size for his cognitive flexibility, whereas this study found a large effect size. A possible explanation could be that Ruocco (2005) separated planning tasks from cognitive flexibility tasks and this study included planning tasks in the cognitive domain cognitive flexibility. Furthermore, Ruocco's (2005) planning domain had a large effect size comparable to the large effect this study established for the specific domain problem and problem solving.

Ruocco (2005) established a medium effect size for verbal memory and a very large effect size for non-verbal memory, the nature of these deficits was not examined any further and it is not clear how the proportion of tasks measuring immediate or delayed memory was for these domains therefore it is difficult to compare to the results found here. This study separated immediate memory and learning from delayed memory and participants were the most impaired on tasks that measured visual, and thus non-verbal, delayed memory and less on visual immediate memory and learning.

The significant results reported in this study are consistent with neuroimaging findings on BPD patients. Deficits in cognitive flexibility, psychomotor activity and information processing, attention processes and working memory can point to frontal abnormalities, which have been reported in BPD patients. Differences between BPD participants and healthy controls have been found in relation to frontal cortex volume or activation of prefrontal, orbitofrontal and dorsolateral areas (Lyoo et al 1998; Beblo et al 2006; Schmall et al 2006; Silbersweig et al 2007). In a fMRI study of Schmall and Bremner (2006) BPD subjects had increased activity of the dorsolateral prefrontal cortex and decreased activity

of the posterior parietal cortex, perigenual anterior cingulated gyrus and the amygdala in response to heat stimuli compared to healthy controls. It is established that BPD patients have higher thresholds for pain. The anterior cingulated gyrus and dorsolateral prefrontal cortex are thought to be involved in pain processing and pain control respectively. Lyoo and others (1998) found a smaller frontal lobe in BPD participants compared to controls. A left orbitofrontal cortex and the right anterior cingulated cortex reduction was found in patients with BPD. (Tebartz van Elst et al 2003). Brambilla and others (2004) reported increased bilateral putamen volumes in patients.

Impaired memory functions and visuo-spatial abilities suggest damage to the hippocampus and temporal lobe, which have been shown in BPD patients (Driessen et al 2000; Schmall et al 2003; Brambilla 2004; Zetsche et al 2007). MRI studies found smaller volumes of the amygdala and the hippocampus in BPD subjects (Driessen et al 2000; Tebartz van Elst et al 2003; Schmall et al 2003; Brambilla 2004; Zetsche et al 2007). Distinctions between BPD participants and healthy subjects were found in fMRI studies in the activation of the amygdala, parietal, occipital, parahippocampal, orbitofrontal, medial prefrontal, insular and cingulate areas during processing of autobiographical retrieval cues and recalling unresolved en resolved life events (Beblo et al 2006; Schnell et al 2007; Herpertz et al 2001).

Two MRI studies focused solely on the corpus callossum volume in BPD patients. Corpus callossum abnormalities could lead to slowed motor, perception, language, concept formation, reasoning and problem solving performances (Lezak et al 2004). Rusch and others (2007) did find that BPD women had a thinner isthmus of the corpus callosum compared with healthy women, but Zanetti and others (2007) reported no significant differences in corpus callosum regions. Irle and others (2007) found a smaller right-sided precuneus, part of the parietal cortex, in patients with BPD.

Not all studies found significant differences in brain pathology. New et al 2007 did not find a difference in amygdala volume between BPD participants and healthy controls. Tebartz van Elst (2003), Brambilla (2004), Zetsche (2006) and others did not establish significant volume differences for the amygdala, temporal lobes and the dorsolateral prefrontal cortex. Furthermore, incoherent results are reported when studying the neurobiology of BPD, for instance both hypometabolism and hypermetabolism of the anterior cingulate have been found in patients with BPD (Juengling et al 2003; Lange et al 2005). Complexity of neuroimaging studies, medication and co-morbidity and other factors could explain these differences (Lis et al 2007).

Zetsche and others (2006) found that patients with BPD and also major depression had significantly larger amygdala volumes than patients with BPD alone. The left postcentral gyrus of the parietal cortex was significantly increased in BPD patients with co-morbid dissociative amnesia or dissociative identity disorder compared to BPD patients without these disorders (Irle et al 2007).

Other factors also seem to effect the underlying neurobiology of BPD. Hippocampal volume of the left hemisphere was shown to inversely correlate with lifetime history of aggressive behaviour (Zetsche et al 2007). Rusch and others (2007) found that a history of sexual abuse was associated with a thinner posterior body of the corpus callosum. Tebartz van Elst and others (2003) suggest that fronto-limbic abnormalities differentiate BPD from other disorders. They examined the frontal and limbic regions at the same time and propose that a pattern of abnormalities in these regions are specific for BPD.

Further studies should look at these regions together and not apart. This is supported by the findings of this study that shows deficits in cognitive functions that are associated with fronto-limbic regions. Further research should focus on separating BPD brain pathology and cognitive performance from other disorders.

A few limitations of this study should be mentioned. It is possible that the significant deficits in language, verbal and visual immediate memory and learning, verbal delayed memory, attentional capacity, disinhibition and motor speed could be a result of publication bias, because the included studies did not exceed the estimated existing unpublished studies. More studies on BPD and these cognitive domains are necessary to be able to exclude this bias.

Despite the effort to make all domains as homogeneous as possible, specific cognitive domains verbal learning and immediate memory, visual delayed memory, planning and problem solving and drawing were still heterogeneous. This could be a consequence of the diverse tests used across studies to assess particular domains of function and the different diagnostic systems utilized across studies to define BPD. Other co-occuring psychiatric disorders and medication intake limit the external validity of the findings of this study. The fact that 88% of the BPD patients were female could mean that it is not generalizable to male BPD patients.

In conclusion BPD patients showed impaired performance on all cognitive domains, with the largest deficit for planning and problem solving and the smallest deficit for verbal delayed memory. The results were consistent with neuroimaging findings that associate frontal, temporal and hippocampal areas with BPD. More studies are necessary to see if the cognitive domains that are heterogeneous in this study could be made more homogeneous and if the significant results on impaired language, attentional capacity, visual and verbal immediate memory and learning, verbal delayed memory, disinhibition and motor speed are not an effect of publication bias. Also, more research should be done to differentiate BPD cognitive deficits and brain pathology from other psychiatric disorders.

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