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REVIEW ARTICLE

Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives

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Background. Previous work suggests that impairments in executive function and verbal memory in particular may persist in euthymic bipolar patients and serve as an indicator of genetic risk (endophenotype).

Method. A systematic review of the literature was undertaken. Effects sizes were extracted from selected papers and pooled using meta-analytical techniques.

Results. In bipolar patients, large effect sizes ($d > 0.8$) were noted for executive functions (working memory, executive control, fluency) and verbal memory. Medium effect sizes ($0.5 < d < 0.8$) were reported for aspects of executive function (concept shifting, executive control), mental speed, visual memory, and sustained attention. Small effect sizes ($d < 0.5$) were found for visuoperception. In first-degree relatives, effect sizes were small ($d < 0.5$), but significantly different from healthy controls for executive function and verbal memory in particular.

Conclusions. Executive function and verbal memory are candidate bipolar endophenotypes given large deficits in these domains in bipolar patients and small, but intermediate, cognitive impairments in first-degree relatives.

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Key words: Bipolar patients, cognition, meta-analysis, relatives.

Introduction

Christensen *et al.* (2006) investigated cognitive function in healthy twins discordant for bipolar disorder and found evidence for an association between cognitive dysfunction and genetic liability. The authors concluded that cognitive dysfunction may be a candidate indicator of genetic risk or endophenotype (Gottesman & Gould, 2003) for bipolar disorder. Thus, there is evidence that cognitive dysfunction persists in euthymic bipolar patients (Savitz *et al*. 2005*a*; Robinson *et al*. 2006) and also non-twin genetically sensitive studies suggest that aspects of cognition can possibly be regarded as endophenotypes for bipolar disorder (Glahn *et al*. 2004; Savitz *et al*. 2005*b*; Hasler *et al*. 2006). Possible candidate neurocognitive endophenotypes in bipolar disorder are executive function (Glahn *et al*. 2004; Savitz *et al*. 2005*b*), attention (Burdick *et al*. 2006; Hasler *et al*. 2006) and verbal memory (Glahn *et al*. 2004; Hasler *et al*. 2006). A recent meta-analysis of cognitive deficits in euthymic bipolar patients (Robinson *et al*. 2006) provides further evidence for executive function and verbal learning as possible endophenotypes for bipolar disorder.

The aim of the present review was to estimate the meta-analytical effect size of cognitive functioning in euthymic bipolar patients and their first-degree relatives, thus updating a previous systematic review of patients (Robinson *et al*. 2006), and adding a new review for first-degree relatives. The hypothesis was that first-degree relatives show cognitive deficits in the same areas as bipolar patients, albeit to a lesser degree.

Methods

Study selection

Articles were identified through a literature search in PubMed/Medline, PsycINFO and EMBASE covering the period between January 1985 and September 2006, using the keywords 'bipolar disorder' or 'manic depress*' and 'family'/'familial' or 'first-degree relative' with 'cognit*' or 'neuropsych*'.

The following criteria were used for inclusion: (i) the study evaluated cognitive performance using standardized and reliable neuropsychological testing procedures; (ii) the study compared adult asymptomatic

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bipolar patients who were diagnosed using a recognized criterion-based diagnostic system and/or first-degree relatives with a healthy control group, matched for age, sex and education; (iii) the study reported uncorrected mean test scores and standard deviations for both the patient and/or family and control group; (iv) the study was published as an original article in a peer-reviewed English language journal; and (v) the study with bipolar patients clearly defined euthymia or provided scores on mood rating scales indicating that patients were euthymic (euthymia defined as a cut-off score of <8 on the Hamilton Depression Rating Scale and the Young Mania Rating Scale, and/or a score on mood rating scales below this cut-off point).

The references of retrieved articles were hand-searched for further relevant articles. A second study on the same patient group was only included if it reported different tests.

Data analysis

Meta-analyses were performed using STATA (version 9.2; StataCorp, College Station, TX, USA), using a random effects model. For each test parameter an effect size was calculated, which was Cohen's *d*, the difference between the means of both groups (bipolar patients and/or first-degree relatives *v.* controls) divided by the pooled standard deviation. Effect sizes were weighted for sample size, in order to correct for upwardly biased estimation of the effect in small samples. Effect sizes were expressed in such a way that positive effect sizes always indicated poorer performance by the patient or family group. The corresponding z value and significance level provide an indication of the two-sided statistical significance of the association at 5% α. A homogeneity statistic was calculated in order to test to what degree the studies can be taken to share a common population effect size. A significant χ^2 statistic indicated heterogeneity of the individual effect sizes.

Meta-regression is a technique for trying to work out whether particular characteristics of studies are related to the sizes of the treatment effect. Thus, in the case of significant heterogeneity, meta-regression, using STATA (version 9.2; StataCorp), was performed in order to examine whether any heterogeneity found could possibly be explained by study differences in age structure, sex ratio and mean educational level.

Results

Bipolar patients

Twenty-eight studies were included in the meta-analysis (Table 1). Four of these stratified their samples by a third variable (van Gorp *et al*. 1998; Ferrier *et al*. 1999; Nehra *et al*. 2006; Torrent *et al*. 2006). For reasons of homogeneity, in the case of stratification, only one study group was included, with bias to the less severe patients or those with a better-established diagnosis. Thus, Ferrier *et al*. (1999) stratified by outcome, contrasting a good outcome *versus* a poor outcome group; for the purpose of the current meta-analysis only the good outcome group was included. The study by Nehra *et al*. (2006) used first- and multiple-episode patients; only established bipolar patients with multiple episodes were included in the current analysis. Van Gorp *et al*. (1998) included patients with and without prior alcohol dependence; only the group without alcohol dependence was used in the analysis. Finally, Torrent *et al*. (2006) used bipolar I and bipolar II patients; only bipolar I patients were included.

Neuropsychological domains

The neuropsychological tests used in these studies were divided into 11 categories measuring approximately the same cognitive construct (adapted from Krabbendam *et al*. 2005). A neuropsychological test was included by the *a priori* criterion of having been used in at least four different studies. Immediate verbal memory was assessed using word list learning [California Verbal Learning Test (CVLT; Delis *et al*. 1987); Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964); Auditory Verbal Learning Test (AVLT; Brand & Jolles, 1985)]. For the purposes of the analysis, results of these comparable tests were included together. Delayed verbal memory was assessed using the delayed recall version of the CVLT, RAVLT and AVLT. Delayed visual memory was measured using the delayed recall version of the Rey Osterrieth Complex Figure (Rey, 1941). Working memory was assessed using the Digit Span (Wechsler, 1955). Verbal fluency was measured using either words from a certain category or beginning with a certain letter (verbal fluency test; FAS) (Benton, 1978). Concept formation and shifting was assessed with the Wisconsin Card Sorting Test (WCST; Heaton, 1981); number of perseverative errors and categories achieved were separately analysed. Executive control was measured using the Stroop Color-Word interference (Stroop, 1935) and Trailmaking Test part B (Reitan, 1958). Sustained attention was assessed using a variant of the Continuous Performance Test (CPT; Kurtz, 2001). The test parameter used was number and/or percentage correct response. Mental speed was measured using the Digit Symbol Substitution Test (DSST; Wechsler, 1955) and the Trailmaking Test part A (Reitan, 1958). Visuoperception was assessed using the copy version

of the Rey Osterrieth Complex Figure (Rey, 1941). Intelligence was measured using the full-scale National Adult Reading Test (Grober & Sliwinski, 1991) or the revised Wechsler Adult Intelligence Scale vocabulary score (Wechsler, 1981), both good estimates of premorbid intelligence.

Meta-analytical results: patients

All effect sizes were in the same direction (Table 2), suggesting worse performance in euthymic bipolar patients compared with healthy controls.

In all instances, with the exception of visuoconstruction (Rey copy) and intelligence, bipolar patients displayed significantly poorer performance compared with controls. The largest effect sizes were evident for working memory (Digit Span backward), executive control (Trail B), concept shifting (WCST perseverative errors), fluency (categories), delayed and immediate verbal recall (CVLT) and mental speed (DSST) (effect sizes >0.8). Medium effect sizes ($0.5<d<0.8$) were observed for executive control (Stroop), mental speed (Trail A), delayed visual memory (Rey figure), fluency (FAS), sustained attention (CPT) and concept shifting (WCST categories). A small effect size ($0.2<d<0.5$) was noted for visuoperception (Rey copy) and working memory (Digit Span forward).

For eight out of 17 analyses there was evidence for significant heterogeneity between the results of the different studies. The largest heterogeneity was found for working memory (Digit Span backward), concept shifting (WCST perseverative errors), executive control (Trail B) and fluency (FAS). Three studies were largely responsible for this heterogeneity, namely the studies of Balanza-Martinez *et al*. (2005), Goswami *et al*. (2006) and Nehra *et al*. (2006). All showed larger effect sizes. In a sensitivity analysis of working memory (Digit Span backward) excluding the study of Goswami *et al*. (2006), the observed heterogeneity largely disappeared (before exclusion: $\chi^2=30.50$, $p=0.000$; after exclusion: $\chi^2=5.70$, $p=0.223$). The effect size reflecting bipolar–control differences remained significant ($d=0.73$, $p=0.000$). The studies by Goswami *et al*. (2006) and Nehra *et al*. (2006) caused most of the heterogeneity in the analysis on executive control (Trail B). Leaving these studies out resulted in non-significant heterogeneity (before exclusion: $\chi^2=69.44$, $p=0.000$; after exclusion: $\chi^2=10.54$, $p=0.160$), with significant bipolar–control effect size after exclusion ($d=0.57$, $p=0.000$). In the case of concept shifting (WCST perseverative errors), heterogeneity was largely caused by the studies of Balanza-Martinez *et al*. (2005) and Nehra *et al*. (2006) (before exclusion: $\chi^2=24.17$, $p=0.004$; after exclusion: $\chi^2=7.05$, $p=0.424$) (bipolar–control effect size after exclusion: $d=0.64$, $p=0.000$). Finally, heterogeneity in the analysis on fluency (FAS) was mostly due to the same two studies (before exclusion: $\chi^2=38.02$, $p=0.000$; after exclusion: $\chi^2=10.11$, $p=0.342$; bipolar–control effect size after exclusion: $d=0.43$, $p=0.000$). The fact that the most significant heterogeneity was due to only three studies suggests that certain characteristics of these studies may be responsible for this finding. The study by Balanza-Martinez *et al*. (2005) was relatively small and used a bipolar population with rather low educational level and no specification of characteristics of disease (duration, number of episodes etc). One could speculate that they described a rather severely ill population. The same probably applies to the study by Nehra *et al*. (2006). Their population of patients had a relatively large number of psychotic episodes and all patients used both a mood stabilizer and an antipsychotic, possibly indicating a negative effect of medication on cognitive functioning. Goswami *et al*. (2006) used a rather young population with a relatively long duration of illness and early illness onset. This study also probably included a rather severely ill group of patients.

Meta-regression revealed a significant effect of sex ratio on the concept formation and shifting case–control difference (WCST) ($p=0.001$, $B=-2.63$, 95% CI -4.156 to -1.11). This finding indicates that studies with higher male/female ratios showed smaller effect sizes. Age had a significant effect on the case–control difference of concept formation (WCST) and working memory (Digit Span backward) ($p=0.000$, $B=-32.51$, 95% CI -43.6 to -21.4; $p=0.029$, $B=-11.18$, 95% CI -21.2 to -1.18). Thus, studies with higher mean age showed smaller effect sizes. Finally, educational level had a significant effect on the working memory case–control difference (Digit Span backward), fluency (FAS) and concept formation (WCST) ($p=0.03$, $B=-0.014$, 95% CI -0.027 to -0.001; $p=0.007$, $B=36.93$, 95% CI 8.38–52.24; $p=0.014$, $B=2.53$; 95% CI 0.52–4.55). This points in the direction of larger effect sizes in studies with higher educated participants.

In conclusion, part of heterogeneity may be due to differences between the various studies in these independent variables.

Meta-analytical results: first-degree relatives

A total of fourteen studies were included (Table 3). Two of these studies used more than one family group (Sobczak *et al*. 2003; McIntosh *et al*. 2005). In the study by McIntosh *et al*. (2005), a group of unaffected relatives from bipolar families and a group from 'mixed' families was used; only the group from bipolar families was included in the analyses. Sobczak *et al*. (2003)

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Table 1. *Studies with bipolar patients included in the meta-analysis*

Author (year)	Subjects (*n*)		Definition of euthymia[a]	Neuropsychological test parameters	*d*[b]
	Patients	Controls			
Altshuler *et al*. (2004)	40	22	HAMD <6 YMRS <7 Prospectively for 3 months	CVLT immediate recall CVLT delayed recall Rey figure delayed FAS WCST perseverative errors WCST category Stroop time Trail A Trail B IQ Rey figure copy	0.75 0.78 0.57 0.16 0.77 0.89 0.41 0.38 0.40 0.20 0.30
Balanza-Martinez *et al*. (2005)	15	26	HAMD <8 HAMD 3.4 (2.9) CARS <8 CARS 1.3 (1.8) 2 months' euthymia	FAS Fluency category WCST perseverative errors WCST category Stroop time Trail A Trail B DSST	1.28 1.79 1.67 1.48 1.62 0.68 0.89 1.05
Blumberg *et al*. (2003)	15	20	HAMD <8 HAMD 7.3 (7.1) CARS <8 CARS 4.1 (5.0)	Stroop time	0.74
Bozikas *et al*. (2005)	19	30	MADRS <9 MADRS 1.53 (2.61) YMRS <9 YMRS 3.16 (2.48)	CPT	0.10
Cavanagh *et al*. (2002)	20	20	HAMD <8 1.0 (2.9) MMS <3 MMS 0.5 (1.5)	CVLT delayed recall FAS Stroop correct	0.96 0.29 0.61
Clark *et al*. (2002)	30	30	HAMD <9 HAMD 2.07 (2.26) YMRS <9 YMRS 1.67 (2.22)	CVLT immediate recall CVLT delayed recall CPT	0.48 0.95 0.96
Clark *et al*. (2005*a*)	15	15	HAMD <9 HAMD 3.2 (2.5) YMRS <9 YMRS 1.9 (2.5)	CPT	1.00
Deckersbach *et al*. (2004*b*)	30	30	HAMD 3.4 (2.6) YMRS 1.0 (1.6)	CVLT immediate recall CVLT delayed recall	1.40 1.67
Deckersbach *et al*. (2004*a*)	25	25	HAMD 3.3 (2.5) YMRS 1.2 (1.5)	Rey figure delayed Rey figure copy	0.70 0.06
Dixon *et al*. (2004)	15	30	BDI 6.5 (4.3) YMRS 2.7 (2.2)	FAS Fluency category Stroop correct IQ	0.17 0.30 0.82 −0.32
Ferrier *et al*. (1999)	20	20	HAMD 2.7 (2.1) MSS 4.1 (1.9)	RAVLT immediate recall Rey figure delayed Digit Span backward	0.93 0.92 1.11

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Table 1 (*cont.*)

Author (year)	Subjects (*n*)		Definition of euthymia[a]	Neuropsychological test parameters	*d*[b]
	Patients	Controls			
Ferrier *et al.* (1999) (*cont.*)				FAS	0.40
				Trail A	0.81
				Trail B	0.92
				DSST	0.81
				Digit Span forward	0.28
				Rey figure copy	0.64
Fleck *et al.* (2003)	14	40	HAMD <10	CVLT immediate recall	1.01
			HAMD 3.7 (2.8)	CVLT delayed recall	0.77
			YMRS <10		
Frangou *et al.* (2005*a*)	10	43	HAMD <6	WCST perseverative errors	0.55
			HAMD 3.0 (1.2)	WCST category	0.04
			YMRS <6		
			YMRS 1.1 (0.5)		
			At least 1 month		
Frangou *et al.* (2005*b*)	44	44	HAMD <10	FAS	0.88
			HAMD 7	WCST perseverative errors	0.38
			MRS <10	WCST category	0.25
			MRS 0	Stroop correct	0.57
				IQ	0.31
Goswami *et al.* (2006)	37	37	Euthymia >1 month	RAVLT immediate recall	0.69
			HAMD 2.35 (1.48)	Digit Span backward	2.28
			MSRS 7.91 (4.88)	Trail A	0.54
				Trail B	1.99
				DSST	0.19
				Digit Span forward	0.50
Krabbendam *et al.* (2000)	21	22	HAMD 3.4 (3.0)	AVLT immediate recall	0.94
			YMRS 0.77 (1.5)	AVLT delayed recall	0.93
				Fluency category	0.54
				Stroop time	0.67
				DSST	1.12
Larson *et al.* (2005)	18	18	HAMD 3 (3)	IQ	0.12
			YMRS 2 (3)		
			Follow-up for 4 to 8 weeks		
Malhi *et al.* (2005)	12	12	HAMD <7	Stroop time	1.02
			HAMD 4.3 (1.1)		
			YMRS <7		
			YMRS 0.9 (0.5)		
Martinez-Aran *et al.* (2004)	44	30	HAMD <9	CVLT immediate recall	0.84
			HAMD 3.6 (2.6)	CVLT delayed recall	0.96
			YMRS <7	Digit Span backward	0.86
			YMRS 1.4 (1.8)	FAS	0.56
			6 months' remission	Fluency category	0.83
				WCST perseverative errors	0.62
				WCST category	0.38
				Stroop correct	0.59
				Trail A	0.90
				Trail B	0.57
				Digit Span forward	0.56
				IQ	0.75
McIntosh *et al.* (2005)	27	50	HAMD 5	FAS	0.71
			YMRS 2	DSST	1.34
				IQ	−0.07

[*continues overleaf*

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Table 1 (*cont.*)

Author (year)	Subjects (*n*)		Definition of euthymia[a]	Neuropsychological test parameters	*d*[b]
	Patients	Controls			
Nehra *et al*. (2006)	30	20	HAMD <8	FAS	2.27
			HAMD 2.67 (0.92)	Fluency category	1.28
			YMRS <8	WCST perseverative errors	1.85
			YMRS 1.47 (1.25)	WCST category	0.36
				Trail A	2.02
				Trail B	3.43
Strakowski *et al*. (2004)	10	10	HAMD <8	CPT	0.21
			HAMD 3.1 (2.5)		
			YMRS <6		
			YMRS 1.6 (1.8)		
Thompson *et al*. (2005)	63	63	HAMD <8	RAVLT immediate recall	0.59
			HAMD 2.1 (1.7)	Digit Span backward	0.37
			YMRS <8	FAS	0.36
			YMRS 1.4 (2.0)	Stroop correct	0.58
			Prospectively verified for 1 month	Trail A	0.47
				Trail B	0.23
				DSST	0.91
				Digit Span forward	0.05
Thompson *et al*. (2006)	20	20	HAMD <8	Digit Span backward	0.75
			HAMD 1.90 (2.38)	Digit Span forward	0.25
			YMRS <8		
			YMRS 1.40 (2.08)		
Torrent *et al*. (2006)	38	35	HAMD <9	CVLT immediate recall	0.58
			HAMD 4.29 (2.51)	CVLT delayed recall	0.80
			YMRS <7	Digit Span backward	0.86
			YMRS 0.79 (1.19)	FAS	0.41
				Fluency category	0.76
				WCST perseverative errors	0.56
				WCST category	0.23
				Stroop correct	0.58
				Trail A	0.80
				Trail B	0.57
				Digit Span forward	0.70
Van Gorp *et al*. (1998)	13	22	HAMD <7	CVLT immediate recall	0.70
			YMRS <6	CVLT delayed recall	0.52
				Rey figure delayed	0.25
				FAS	−0.11
				WCST perseverative errors	0.95
				WCST category	1.00
				Stroop time	0.08
				Trail A	0.32
				Trail B	0.24
				Rey figure copy	−0.09
Varga *et al*. (2006)	19	31	MADRS 2.26 (3.69)	AVLT immediate recall	1.52
			MRS 2.32 (4.10)	AVLT delayed recall	1.04
				WCST perseverative errors	0.55
				WCST category	0.15
				Stroop correct	0.80
				Trail A	0.53
				Trail B	1.24
				DSST	0.54
				IQ	0.57

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Table 1 (*cont.*)

Author (year)	Subjects (*n*)		Definition of euthymia[a]	Neuropsychological test parameters	*d*[b]
	Patients	Controls			
Zubieta *et al*. (2001)	15	15	HAMD <6	Fluency category	0.77
			HAMD 3.4 (2.1)	WCST perseverative errors	1.52
			YMRS <4	WCST category	0.84
			YMRS 0.4 (0.6)	Stroop correct	1.12
			At least 6 months' euthymia		

HAMD, Hamilton Depression Rating Scale; CVLT, California Verbal Learning Test; YMRS, Young Mania Rating Scale; FAS, verbal fluency test; WCST, Wisconsin Card Sorting Test; IQ, intelligence quotient; CARS, Clinician Administered Rating Scale for Mania; DSST, Digit Symbol Substitution Test; MADRS, Montgomery–Asberg Depressive Rating Scale; CPT, Continuous Performance Test; MMS, Modified Manic Scale; BDI, Beck Depression Inventory; RAVLT, Rey Auditory Verbal Learning Test; MSS, Manic State Scale; MRS, Manic Rating Scale; MSRS, Manic State Rating Scale; AVLT, Auditory Verbal Learning Test.

[a] Values in parentheses are standard deviations.

[b] Effect size; positive values indicate better performance in controls.

used a group of first-degree relatives of bipolar I patients and a group of relatives of bipolar II patients; only the group of family-members of bipolar I patients was used in the meta-analysis.

The neuropsychological tests used in the studies were divided in the same categories as described earlier and included only if used in at least four different studies. This resulted in fewer cognitive domains analysed than in the bipolar studies. These domains were immediate and delayed verbal memory, working memory, concept formation and shifting, verbal fluency, executive control, mental speed, and intelligence. The Visual Verbal Learning Test used in the study by Sobczak *et al*. (2003), measuring immediate and delayed verbal memory and resembling the CVLT and RAVLT (Lezak, 1995), was added to the analysis.

Meta-analysis of the neuropsychological domains indicated that all meta-analytical effect sizes were in the direction of worse performance in the first-degree relatives compared with the healthy controls (Table 4). Effect sizes, however, were much smaller than in the bipolar–control comparisons (<0.5), with the exception of delayed verbal memory ($d=0.56$), and only significantly different for executive control (Stroop and Trail B) and immediate verbal recall (CVLT).

There was evidence of significant heterogeneity for four out of 12 analyses, namely for the domains of delayed verbal memory (CVLT), intelligence and working memory (Digit Span forward and backward). Thce greatest degree of heterogeneity was found in the same cognitive domains as in the patient group, with the exception of verbal memory. Heterogeneity may be due to the small number of studies with small, heterogeneous groups of first-degree relatives with different family histories and genetic load. The study by Gourovitch *et al*. (1999), for example, using monozygotic twins, showed relatively large but differential effect sizes for working memory and verbal memory, contributing to heterogeneity.

Meta-regression revealed no significant effects of the independent variables examined.

Discussion

Patients

This meta-analysis of cognitive functioning in euthymic bipolar patients provides evidence of cognitive impairments in these patients, particularly in the realm of executive functioning and verbal memory. Large effect sizes were found for working memory, executive control, concept shifting, fluency, verbal recall and mental speed.

The finding of both executive and memory impairments has been described in the quantitative meta-analysis by Robinson *et al*. (2006), despite the fact that we used somewhat stricter inclusion criteria for euthymia and included more recent studies.

There was substantial heterogeneity between the results of the different studies, the largest heterogeneity being noted for working memory, concept shifting, executive control and fluency. Three studies (Balanza-Martinez 2005; Goswami *et al*. 2006; Nehra *et al*. 2006) largely caused this heterogeneity, possibly because of inclusion of relatively severely ill patients with a higher number of (psychotic) episodes. Thus, greater number of episodes, greater length of illness and higher number of hospitalizations have been associated with greater level of neuropsychological dysfunction in bipolar patients (Robinson & Ferrier,

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Table 2. *Results of meta-analyses of cognitive test performance differences between bipolar patients versus normal controls*

Test	K[a]	Subjects (n)		d[b]	95% CI	z[c]	p	χ^2[d]	p
		Bipolar	Control						
Digit backward	6	222	205	1.02	0.49–1.54	3.85	0.000	30.50	0.000
Trail B	10	319	306	0.99	0.51–1.48	4.01	0.000	69.44	0.000
WCST perseverative errors	10	268	288	0.88	0.58–1.19	5.66	0.000	24.17	0.004
Fluency categories	7	178	178	0.87	0.54–1.19	5.27	0.000	12.09	0.060
CVLT delayed recall	10	269	282	0.85	0.60–1.09	6.83	0.000	16.27	0.061
DSST	7	202	249	0.84	0.53–1.14	5.32	0.000	13.76	0.032
CVLT immediate recall	12	369	382	0.82	0.65–0.99	9.25	0.000	13.96	0.235
Stroop time	6	116	124	0.73	0.32–1.13	3.49	0.000	11.00	0.051
Trail A	10	319	306	0.71	0.46–0.97	5.58	0.000	19.67	0.020
Stroop correct	8	258	268	0.65	0.47–0.83	7.17	0.000	2.37	0.937
Rey figure recall	4	98	89	0.62	0.32–0.92	4.04	0.000	2.01	0.570
FAS	12	369	382	0.59	0.30–0.88	4.04	0.000	38.02	0.000
CPT correct	4	74	85	0.58	0.09–1.08	2.31	0.021	6.52	0.089
WCST categories	10	268	288	0.52	0.26–0.77	3.95	0.000	18.07	0.034
Digit forward	6	222	205	0.37	0.15–0.59	3.33	0.001	6.19	0.288
Rey copy	4	103	94	0.22	−0.06 to 0.51	1.52	0.129	2.89	0.409
IQ	8	237	247	0.16	−0.11 to 0.44	1.15	0.250	15.36	0.032

CI, Confidence interval; WCST, Wisconsin Card Sorting Test; CVLT, California Verbal Learning Test; DSST, Digit Symbol Substitution Test; FAS, verbal fluency test; CPT, Continuous Performance Test; IQ, intelligence quotient.

[a] Number of studies included in the analysis.

[b] Mean, weighted effect size Cohen's d.

[c] Test of significance of effect size (p).

[d] Test of within-category heterogeneity between studies (p).

2006). Heterogeneity may also be caused by the differential effects of age, sex, and education on the cognitive domains mentioned above, as revealed by meta-regression.

Heterogeneity may additionally be caused by residual mood symptoms, because of the variation in the criteria used to define euthymia. It was not possible to include measures of mood as a variable for the meta-regression, however, as the studies included did not use, or did not report, uniformly measured items of mood. Another confounder is medication, the use and reporting of which varied between studies. The effects of different types of medication on cognitive function in bipolar patients are not systematically studied, but the effects of lithium may be rather modest, given the small effect size ($d = 0.3$) in the study by Goswami *et al*. (2002). Furthermore, cognitive deficits are still evident in medication-free patients (Goswami 2002; Strakowski *et al*. 2004). Another source of heterogeneity may be the type of bipolar disorder under investigation. Although most studies used bipolar I patients, not all studies specified the type of patients included. Bipolar I patients may show greater, and/or different, deficits in cognitive function than bipolar II patients (Harkavy-Friedman *et al*. 2006; Torrent *et al*. 2006). Matching on education *versus* IQ may be a confounder too, given the study by Glahn *et al*. (2006), who describe less educational attainment despite comparable IQ levels in bipolar patients *versus* normal controls. Matching on educational attainment could thus give rise to underestimation of the difference in cognitive function between bipolar patients and normal controls. Finally, differences in somatic comorbidity (and comedication) between bipolar patients and normal controls could contribute to differences in cognitive performance (Newcomer, 2006).

First-degree relatives

The meta-analysis in first-degree relatives showed worse performance in all cognitive domains studied, compared with controls. Effect sizes, however, were small, but significant in domains that also differentiated patients from controls: executive functioning and verbal memory. This suggests that these cognitive functions may be trait markers for the genetic liability for bipolar disorder. Heterogeneity between the results of the different studies may be due to the small number of studies with relatively small, heterogeneous groups of first-degree relatives with different

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Table 3. *Studies with first-degree family members included in the meta-analysis*

Author (year)	Subjects (*n*)		Sample characteristics[a]	Neuropsychological test parameters	*d*[b]
	Family	Controls			
Christensen *et al*. (2006)	7	36	MZ twins discordant for bipolar disorder	Stroop	0.37
				Trail A	0.20
				Trail B	0.63
Christensen *et al*. (2006)	14	52	DZ twins discordant for bipolar disorder	Stroop	0.45
				Trail A	−0.10
				Trail B	0.25
Clark *et al*. (2005*b*)	27	47	10 parents; 12 siblings; five children	CVLT immediate recall	0.20
			HAMD 1.2 (1.9)	CVLT delayed recall	0.12
			YMRS 0.4 (1.1)		
Ferrier *et al*. (2004)	17	17	First-degree relatives	RAVLT immediate recall	0.18
			HAMD 0.82 (1.01)	Digit Span backward	0.99
			YMRS 0.47 (1.28)	FAS	−0.12
			Controls	Stroop	0.00
			HAMD 0.35 (0.86)	Trail A	−0.07
			YMRS 0.18 (0.53)	Trail B	0.37
				DSST	0.24
				Digit Span forward	0.39
Frangou *et al*. (2005*b*)	15	43	Unaffected offspring of bipolar probands	WCST perseverative errors	−0.42
				WCST category	−0.53
				WAIS-R IQ	−0.09
Gourovitch *et al*. (1999)	7	15	MZ twins	CVLT immediate recall	0.33
				CVLT delayed recall	0.80
				Digit Span backward	0.97
				FAS	0.28
				WCST perseverative errors	0.52
				Trail A	−0.10
				Trail B	0.01
				Digit Span forward	1.16
				WAIS-R IQ	0.40
Kéri *et al*. (2001)	20	20	Unaffected siblings	Digit Span backward	−0.18
			BP-I probands	FAS	0.12
				WCST perseverative errors	0.10
				WCST category	0.11
				Digit Span forward	−0.33
Kieseppa *et al*. (2005)	19	114	Twins discordant for BP-I	CVLT delayed recall	0.08
				Digit Span backward	−0.18
				DSST	−0.12
Kremen *et al*. (1998)	14	44	Relatives of psychotic bipolar probands	WCST perseverative errors	0.09
				WCST category	0.45
				Trail A	−0.28
				Trail B	−0.11
				DSST	−0.05
				WAIS-R IQ	−0.58

[*continues overleaf*

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Table 3 (*cont.*)

Author (year)	Subjects (*n*)		Sample characteristics[a]	Neuropsychological test parameters	*d*[b]
	Family	Controls			
McIntosh *et al*. (2005)	24	50	Unaffected relatives with >one first- or second-degree BP proband	FAS	0.58
			HAMD 1.5 (median)	DSST	0.50
			YMRS 0		
			Controls		
			HAMD 0		
			YMRS 0		
Pirkola *et al*. (2005)	16	100	Unaffected co-twins	Digit Span backward	−0.30
			Three MZ, 13 DZ	Digit Span forward	−0.78
Sobczak *et al*. (2003)	22	15	First-degree relatives BP-I	VVLT immediate recall	1.07
				VVLT delayed recall	1.49
Szoke *et al*. (2006)	51	50	First-degree relatives of BP-I patients	WCST perseverative errors	0.22
				Trail A	0.41
				Trail B	0.54
Toulopoulou *et al*. (2006)	50	69	17 parents, 23 siblings 10 children	WAIS-R IQ	0.42
Zalla *et al*. (2004)	33	20	11 parents, 22 siblings	WCST perseverative errors	0.57
			MADRS <16	WCST category	0.12
			MAS <7	Stroop	1.03
				Trail A	0.31
				Trail B	0.60
				WAIS-R IQ	0.79

MZ, Monozygotic; DZ, dizygotic; CVLT, California Verbal Learning Test; HAMD, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; RAVLT, Rey Auditory Verbal Learning Test; FAS, verbal fluency test; DSST, Digit Symbol Substitution Test; WCST, Wisconsin Card Sorting Test; WAIS-R IQ, Wechsler Adult Intelligence Scale Revised intelligence quotient; BP, bipolar; VVLT, Visual Verbal Learning Test; MADRS, Montgomery–Asberg Depressive Rating Scale; MAS, Beck–Rafaelsen Mania Scale.

[a] Values in parentheses are standard deviations.

[b] Effect size; positive values indicate better performance in controls.

family histories and genetic load. Contrary to the patient meta-analysis, meta-regression revealed no effects of sex, education and age on the meta-analytical effect size, suggesting more robust results and less sources for underlying heterogeneity.

The possible influence of family history as a source of heterogeneity is illustrated by the study by Schubert & McNeil (2005), who described greater cognitive impairment in offspring of mothers with schizophrenia-spectrum psychosis *versus* offspring of mothers with affective-spectrum psychosis. Furthermore, Sobczak *et al*. (2003) found more pronounced cognitive impairments in first-degree relatives of bipolar I patients compared with relatives of bipolar II patients. Another possible source of heterogeneity is the fact that only a small number of studies controlled for subclinical mood symptoms in first-degree relatives and controls. Finally, only a small number of studies directly compared cognitive function between bipolar patients, first-degree relatives and healthy controls (Ferrier *et al*. 2004; Frangou *et al*. 2005*b*; McIntosh *et al*. 2005).

Our meta-analysis on cognitive function in first-degree relatives of bipolar patients is, to the best of our knowledge, the first in the literature. Comparison with other meta-analytical reviews is therefore only possible with first-degree relatives of other patient groups, for example patients with schizophrenia. Such a comparison is topical, given the fact that bipolar and schizophrenia phenotypes probably share genetic risk factors (Craddock *et al*. 2006). Various meta-analyses of cognitive function in first-degree relatives of patients with a diagnosis of schizophrenia (Sitskoorn *et al*.

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Table 4. *Results of meta-analyses of cognitive test performance differences between first-degree relatives v. normal controls*

Test	K[a]	Subjects (*n*)		*d*[b]	95% CI	*z*[c]	*p*	χ^{2}[d]	*p*
		Family	Control						
CVLT delayed recall	4	75	191	0.56	−0.06 to 1.18	1.76	0.078	12.00	0.007
Stroop	4	71	125	0.49	0.045–0.93	2.16	0.031	5.35	0.148
CVLT immediate recall	4	73	94	0.42	0.006–0.83	1.99	0.047	4.62	0.202
Trail B	7	143	234	0.37	0.15–0.60	3.27	0.001	4.98	0.546
FAS	4	68	102	0.27	−0.04 to 0.59	1.70	0.090	3.01	0.391
IQ	5	119	191	0.19	−0.27 to 0.65	0.82	0.414	12.77	0.012
Digit span backward	5	79	266	0.18	−0.33 to 0.69	0.69	0.490	13.29	0.010
WCST perseverative errors	6	140	192	0.17	−0.09 to 0.43	1.26	0.207	6.26	0.282
DSST	4	74	225	0.14	−0.16 to 0.45	0.91	0.361	3.66	0.300
Trail A	7	143	234	0.13	−0.09 to 0.35	1.14	0.256	5.28	0.508
Digit span forward	4	60	152	0.04	−0.72 to 0.81	0.11	0.911	15.23	0.002
WCST categories	4	82	127	0.04	−0.36 to 0.43	0.18	0.861	5.35	0.148

CI, Confidence interval; CVLT, California Verbal Learning Test; FAS, verbal fluency test; IQ, intelligence quotient; WCST, Wisconsin Card Sorting Test; DSST, Digit Symbol Substitution Test.

[a] Number of studies included in the analysis.

[b] Mean, weighted effect size Cohen's *d*.

[c] Test of significance of effect size (*p*).

[d] Test of within-category heterogeneity between studies (*p*).

2004; Szoke *et al*. 2005; Snitz *et al*. 2006) describe the largest effect sizes ($d = 0.5$ to 0.6) for executive functioning and verbal memory, with somewhat different effect sizes for different executive tests used and greater effect sizes in multiplex families (Heydebrand, 2006). This qualitative pattern of effects sizes and tests are rather similar to those presented here for the relatives of patients with bipolar disorder. In the review by Snitz *et al*. (2006), the type of biological relative, parent, sibling or offspring did not impact on effect sizes of cognitive deficits in unaffected first-degree relatives of patients with a diagnosis of schizophrenia. Asymmetric psychiatric exclusion criteria and screening controls more stringently than relatives did influence the effect sizes in the review by Snitz *et al*. (2006). Therefore, this source could also contribute to the heterogeneity observed in the current meta-analysis.

Heydebrand (2006), reviewing meta-analyses on cognitive function in relatives of patients with a diagnosis of schizophrenia, concludes that the most consistent deficit shown by relatives is impaired performance on 'maintenance plus' frontal-lobe tasks, requiring increased effort and higher central executive processing. This cognitive phenotype therefore may be a likely candidate endophenotype for both schizophrenia and bipolar disorder. In this respect it may be important that memory performance is affected by executive dysfunction, as shown by shared variance of 50–60% (Duff *et al*. 2005). A quantitative review of cognitive functioning in patients with schizophrenia and bipolar disorder yielded largest (differences in) effect sizes on executive function and verbal memory, bipolar patients generally better performing than patients with schizophrenia (Krabbendam *et al*. 2005). Important in this respect is the fact that there were only quantitative, and not qualitative, differences between bipolar patients and patients with a diagnosis of schizophrenia, which fits in with current models of the relationship between both disorders. Murray *et al*. (2004) hypothesize that certain shared susceptibility genes may predispose individuals to psychosis in general. A candidate gene may be neuregulin 1, which influences susceptibility to bipolar disorder and schizophrenia, especially in bipolar patients with mood-incongruent psychotic features and patients with a diagnosis of schizophrenia with mania (Green *et al*. 2005). Polymorphisms of neuregulin, influencing, amongst others, synaptic signalling by glutamate receptors, play possibly a role in cognition (Schillo *et al*. 2005; Harrison & Law 2006; Scolnick *et al*. 2006). Other candidate genes in this respect are Disc 1 (Cannon *et al*. 2005; Porteous *et al*. 2006; Ross *et al*. 2006) and brain-derived neurotrophic factor (Bath & Lee, 2006), both related to susceptibility to schizophrenia as well as bipolar disorder on the one hand, and cognitive dysfunction (executive function and memory) on the other. Finally, catechol-*O*-methyl transferase (COMT) polymorphisms may play a role as well, in

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particular the COMT Val[158]Met polymorphism and other polymorphisms on the same gene, that have been associated with prefrontal cognitive functioning in schizophrenia and bipolar patients and their first-degree relatives (Goldberg *et al*. 2003; Rosa *et al*. 2004; Bertolino *et al*. 2006; Mata *et al*. 2006; Minzenberg *et al*. 2006). Interestingly, the COMT Val[158]Met polymorphism influences the improvement of cognitive functioning in patients with a diagnosis of schizophrenia treated with clozapine (Woodward *et al*. 2007), and differential effects are described of these polymorphisms on the results of different tests of executive function (Tunbridge *et al*. 2006). Furthermore, the COMT Met[158]Met genotype is associated with heightened reactivity and connectivity in corticolimbic circuits, leading to inflexible processing of affective stimuli contributing to emotional dysregulation (Drabant *et al*. 2006). Tunbridge *et al*. (2006), reviewing the literature on COMT polymorphisms, conclude that the Met allele is associated with improved executive function compared with the Val allele, but also with impaired emotional processing. Bilder *et al*. (2004) hypothesize that the COMT Met allele, associated with low enzyme activity, results in increased levels of tonic dopamine (DA) and reciprocal reductions in phasic DA in subcortical regions and increased D_1 transmission cortically, leading to increased stability but decreased flexibility of neural networks. This model fits in with results from, amongst others, functional magnetic resonance imaging studies pointing in the direction of dysregulation of prefrontal area influence on subcortical neural regions, explaining cognitive dysfunction and mood symptoms (Strakowski *et al*. 2005; Brooks *et al*. 2006; Yurgelun-Todd & Ross, 2006).

To summarize, executive function and verbal memory may be candidate endophenotypes for the genetic liability for bipolar disorder, as suggested by the current meta-analyses on bipolar patients and their first-degree relatives.

Guidelines for future research on cognitive deficits in schizophrenia and bipolar patients and their relatives (adapted from Heydebrand, 2006) are: (i) sufficient sample size to allow the examination of specific cognitive deficits as well as for genetic testing; (ii) use of cognitive measures that are sufficiently specific and sensitive, and have ecological validity; (iii) longitudinal studies; (iv) recruitment of heterogeneous control samples; (v) control for psychopathology; and (vi) investigation of heterogeneity of cognitive function in patients and relatives, in relation to neurobiological findings.

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None.

Declaration of Interest

None.

References

Altshuler LL, Ventura J, van Gorp WG, Green MF, Theberge DC, Mintz J (2004). Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. *Biological Psychiatry* **56**, 560–569.

Balanza-Martinez V, Tabares-Seisdebos R, Selva-Vera G, Martinez-Aran A, Torrent C, Salazar-Fraile J, Leal-Cerbos C, Vieta E, Gomez-Beneyto M (2005). Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: a 3-year follow-up study. *Psychotherapy and Psychosomatics* **74**, 113–119.

Bath KG, Lee FS (2006). Variant BDNF (Val66Met) impact on brain structure and function. *Cognitive, Affective and Behavioral Neuroscience* **6**, 79–85.

Benton AL, Hamsher K (1978). *Multilingual Aphasia Examination Manual*, revised. University of Iowa: Iowa.

Bertolino A, Caforio G, Petruzzella V, Latorre V, Rubino V, Dimalta S, Torraco A, Blasi G, Quartesan R, Mattay VS, Callicott JH, Weinberger DR, Scarabino T (2006). Prefrontal dysfunction in schizophrenia controlling for COMT Val158Met genotype and working memory performance. *Psychiatry Research* **147**, 221–226.

Bilder RM, Volavka J, Lachman HM, Grace AA (2004). The catechol-*O*-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology* **29**, 1943–1961.

Blumberg HP, Leung HC, Skudlarski P, Lacadie CM, Fredericks CA, Harris BC, Charney DS, Gore JC, Krystal JH, Peterson BS (2003). A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. *Archives of General Psychiatry* **60**, 601–609.

Bozikas VP, Andreou C, Giannakou M, Tonia T, Anezoulaki D, Karavatos A, Fokas K, Kosmidis MH (2005). Deficits in sustained attention in schizophrenia but not in bipolar disorder. *Schizophrenia Research* **78**, 225–233.

Brand N, Jolles J (1985). Learning and retrieval rate of words presented auditorily and visually. *Journal of General Psychology* **112**, 201–210.

Brooks 3rd JO, Wang PW, Strong C, Sachs N, Hoblyn JC, Fenn R, Ketter TA (2006). Preliminary evidence of differential relations between prefrontal cortex metabolism and sustained attention in depressed adults with bipolar disorder and healthy controls. *Bipolar Disorders* **8**, 248–254.

Burdick KE, Goldberg JF, Harrow M, Faull RN, Malhotra AK (2006). Neurocognition as a stable endophenotype in bipolar disorder and schizophrenia. *Journal of Nervous and Mental Disease* **194**, 255–260.

Cannon TD, Hennah W, van Erp TG, Thompson PM, Lonnqvist J, Huttunen M, Gasperoni T, Tuulio-Henriksson A, Pirkola T, Toga AW, Kaprio J, Mazziotta J, Peltonen L (2005). Association of DISC1/TRAX

haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. *Archives of General Psychiatry* **62**, 1205–1213.

Cavanagh JT, Van Beck M, Muir W, Blackwood DH (2002). Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. *British Journal of Psychiatry* **180**, 320–326.

Christensen MV, Kyvik KO, Kessing LV (2006). Cognitive function in unaffected twins discordant for affective disorder. *Psychological Medicine* **36**, 1119–1129.

Clark L, Iversen SD, Goodwin GM (2002). Sustained attention deficit in bipolar disorder. *British Journal of Psychiatry* **180**, 313–319.

Clark L, Kempton MJ, Scarna A, Grasby PM, Goodwin GM (2005*a*). Sustained attention-deficit confirmed in euthymic bipolar disorder but not in first-degree relatives of bipolar patients or euthymic unipolar depression. *Biological Psychiatry* **57**, 183–187.

Clark L, Sarna A, Goodwin GM (2005*b*). 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.

Craddock N, O'Donovan MC, Owen MJ (2006). Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophrenia Bulletin* **32**, 9–16.

Deckersbach T, McMurrich S, Ogutha J, Savage CR, Sachs G, Rauch SL (2004*a*). Characteristics of non-verbal memory impairment in bipolar disorder: the role of encoding strategies. *Psychological Medicine* **34**, 823–832.

Deckersbach T, Savage CR, Reilly-Harrington N, Clark L, Sachs G, Rauch SL (2004*b*). Episodic memory impairment in bipolar disorder and obsessive-compulsive disorder: the role of memory strategies. *Bipolar Disorders* **6**, 233–244.

Delis DC, Kramer JH, Kaplan E, Ober BA (1987). *California Verbal Learning Test: Adult version*. The Psychological Corporation: San Antonio, TX.

Dixon T, Kravariti E, Frith C, Murray RM, McGuire PK (2004). Effect of symptoms on executive function in bipolar illness. *Psychological Medicine* **34**, 811–821.

Drabant EM, Hariri AR, Meyer-Lindenberg A, Munoz KE, Mattay VS, Kolachana BS, Egan MF, Weinberger DR (2006). Catechol *O*-methyltransferase Val158Met genotype and neural mechanisms related to affective arousal and regulation. *Archives of General Psychiatry* **63**, 1396–1406.

Duff K, Schoenberg MR, Scott JG, Adams RL (2005). The relationship between executive functioning and verbal and visual learning and memory. *Archives of Clinical Neuropsychology* **20**, 111–122.

Ferrier IN, Chowdhury R, Thompson JM, Watson S, Young AH (2004). Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: a preliminary report. *Bipolar Disorders* **6**, 319–322.

Ferrier IN, Stanton BR, Kelly TP, Scott J (1999). Neuropsychological function in euthymic patients with bipolar disorder. *British Journal of Psychiatry* **175**, 246–251.

Fleck DE, Shear PK, Zimmerman ME, Getz GE, Corey KB, Jak A, Lebowitz BK, Strakowski SM (2003). Verbal memory in mania: effects of clinical state and task requirements. *Bipolar Disorders* **5**, 375–380.

Frangou S, Donaldson S, Hadjulis M, Landau S, Goldstein LH (2005*a*). The Maudsley Bipolar Disorder Project: executive dysfunction in bipolar disorder I and its clinical correlates. *Biological Psychiatry* **58**, 859–864.

Frangou S, Haldane M, Roddy D, Kumari V (2005*b*). Evidence for deficit in tasks of ventral, but not dorsal, prefrontal executive function as an endophenotypic marker for bipolar disorder. *Biological Psychiatry* **58**, 838–839.

Glahn DC, Bearden CE, Bowden CL, Soares JC (2006). Reduced educational attainment in bipolar disorder. *Journal of Affective Disorders* **92**, 309–312.

Glahn DC, Bearden CE, Niendam TA, Escamilla MA (2004). The feasibility of neuropsychological endophenotypes in the search for genes associated with bipolar affective disorder. *Bipolar Disorders* **6**, 171–182.

Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR (2003). Executive subprocesses in working memory: relationship to catechol-*O*-methyltransferase Val158Met genotype and schizophrenia. *Archives of General Psychiatry* **60**, 889–896.

Goswami U, Gulrajani C, Moore PB, Varma A, Young AH, Khastgir U, Sharma AN (2002). Neurocognitive decline in bipolar mood disorder: role of mood stabilizers. *Journal of Psychopharmacology* **16**, A45.

Goswami U, Sharma A, Khastigir U, Ferrier IN, Young AH, Gallagher P, Thompson JM, Moore PB (2006). Neuropsychological dysfunction, soft neurological signs and social disability in euthymic patients with bipolar disorder. *British Journal of Psychiatry* **188**, 366–373.

Gottesman II, Gould TD (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry* **160**, 636–645.

Gourovitch ML, Torrey EF, Gold JM, Randolph C, Weinberger DR, Goldberg TE (1999). Neuropsychological performance of monozygotic twins discordant for bipolar disorder. *Biological Psychiatry* **45**, 639–646.

Green EK, Raybould R, Macgregor S, Gordon-Smith K, Heron J, Hyde S, Grozeva D, Hamshere M, Williams N, Owen MJ, O'Donovan MC, Jones L, Jones I, Kirov G, Craddock N (2005). Operation of the schizophrenia susceptibility gene, neuregulin 1, across traditional diagnostic boundaries to increase risk for bipolar disorder. *Archives of General Psychiatry* **62**, 642–648.

Grober E, Sliwinski M (1991). Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology* **19**, 933–949.

Harkavy-Friedman JM, Keilp JG, Grunebaum MF, Sher L, Printz D, Burke AK, Mann JJ, Oquendo M (2006). Are BPI and BPII suicide attempters distinct neuropsychologically? *Journal of Affective Disorders* **94**, 255–259.

Harrison PJ, Law AJ (2006). Neuregulin 1 and schizophrenia: genetics, gene expression, and neurobiology. *Biological Psychiatry* **60**, 132–140.

Hasler G, Drevets WC, Gould TD, Gottesman II, Manji HK (2006). Toward constructing an endophenotype strategy for bipolar disorders. *Biological Psychiatry* **60**, 93–105.

Heaton RK (1981). *A Manual for the Wisconsin Card Sorting Test*. Psychological Assessment Resources: Odessa, FL.

Heydebrand G (2006). Cognitive deficits in the families of patients with schizophrenia. *Current Opinion in Psychiatry* **19**, 277–281.

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

Kieseppa T, Tuulio-Henriksson A, Haukka J, Van Erp T, Glahn D, Cannon TD, Partonen T, Kaprio J, Lonnqvist J (2005). Memory and verbal learning functions in twins with bipolar-I disorder, and the role of information-processing speed. *Psychological Medicine* **35**, 205–215.

Krabbendam L, Arts B, van Os J, Aleman A (2005). Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. *Schizophrenia Research* **80**, 137–149.

Krabbendam L, Honig A, Wiersma J, Vuurman EF, Hofman PA, Derix MM, Nolen WA, Jolles J (2000). Cognitive dysfunctions and white matter lesions in patients with bipolar disorder in remission. *Acta Psychiatrica Scandinavica* **101**, 274–280.

Kremen WS, Faraone SV, Seidman LJ, Pepple JR, Tsuang MT (1998). Neuropsychological risk indicators for schizophrenia: a preliminary study of female relatives of schizophrenic and bipolar probands. *Psychiatry Research* **79**, 227–240.

Kurtz MM, Ragland JD, Bilker W, Gur RC, Gur RE (2001). Comparison of the continuous performance test with and without working memory demands in healthy controls and patients with schizophrenia. *Schizophrenia Research* **48**, 307–316.

Larson ER, Shear PK, Krikorian R, Welge J, Strakowski SM (2005). Working memory and inhibitory control among manic and euthymic patients with bipolar disorder. *Journal of the International Neuropsychological Society* **11**, 163–172.

Lezak MD (1995). *Neuropsychological Assessment*. Oxford University Press: New York.

Malhi GS, Lagopoulos J, Sachdev PS, Ivanovski B, Shnier R (2005). An emotional Stroop functional MRI study of euthymic bipolar disorder. *Bipolar Disorders* **7** (Suppl. 5), 58–69.

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

Mata I, Arranz MJ, Staddon S, Lopez-Ilundain JM, Tabares-Seisdedos R, Murray RM (2006). The high-activity Val allele of the catechol-*O*-methyltransferase gene predicts greater cognitive deterioration in patients with psychosis. *Psychiatric Genetics* **16**, 213–216.

McIntosh AM, Harrison LK, Forrester K, Lawrie SM, Johnstone EC (2005). Neuropsychological impairments in people with schizophrenia or bipolar disorder and their unaffected relatives. *British Journal of Psychiatry* **186**, 378–385.

Minzenberg MJ, Xu K, Mitropoulou V, Harvey PD, Finch T, Flory JD, New AS, Goldman D, Siever LJ (2006). Catechol-*O*-methyltransferase Val158Met genotype variation is associated with prefrontal-dependent task performance in schizotypal personality disorder patients and comparison groups. *Psychiatric Genetics* **16**, 117–124.

Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C (2004). A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophrenia Research* **71**, 405–416.

Nehra R, Chakrabarti S, Pradhan BK, Khehra N (2006). Comparison of cognitive functions between first- and multi-episode bipolar affective disorders. *Journal of Affective Disorders* **93**, 185–192.

Newcomer JW (2006). Medical risk in patients with bipolar disorder and schizophrenia. *Journal of Clinical Psychiatry* **67** (Suppl. 9), 25–30.

Pirkola T, Tuulio-Henriksson A, Glahn D, Kieseppa T, Haukka J, Kaprio J, Lonnqvist J, Cannon TD (2005). Spatial working memory function in twins with schizophrenia and bipolar disorder. *Biological Psychiatry* **58**, 930–936.

Porteous DJ, Thomson P, Brandon NJ, Millar JK (2006). The genetics and biology of DISC1 – an emerging role in psychosis and cognition. *Biological Psychiatry* **60**, 123–131.

Reitan RM (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills* **8**, 271–276.

Rey A (1941). Psychological examination in cases of traumatic encephalopathy: problems [in French]. *Archives de Psychologie* **28**, 215–285.

Rey A (1964). *L'Examen Psychologique dans les Cas d'Encephalopathie Traumatique*. Presses Universitaires de France: Paris.

Robinson LJ, Ferrier IN (2006). Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. *Bipolar Disorders* **8**, 103–116.

Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, Moore PB (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of Affective Disorders* **93**, 105–115.

Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, Fananas L (2004). New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *American Journal of Psychiatry* **161**, 1110–1112.

Ross CA, Margolis RL, Reading SA, Pletnikov M, Coyle JT (2006). Neurobiology of schizophrenia. *Neuron* **52**, 139–153.

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

Savitz JB, Solms M, Ramesar RS (2005*b*). Neurocognitive function as an endophenotype for genetic studies of

bipolar affective disorder. *Neuromolecular Medicine* **7**, 275–286.

Schillo S, Pejovic V, Hunzinger C, Hansen T, Poznanovic S, Kriegsmann J, Schmidt WJ, Schrattenholz A (2005). Integrative proteomics: functional and molecular characterization of a particular glutamate-related neuregulin isoform. *Journal of Proteome Research* **4**, 900–908.

Schubert EW, McNeil TF (2005). Neuropsychological impairment and its neurological correlates in adult offspring with heightened risk for schizophrenia and affective psychosis. *American Journal of Psychiatry* **162**, 758–766.

Scolnick EM, Petryshen T, Sklar P (2006). Schizophrenia: do the genetics and neurobiology of neuregulin provide a pathogenesis model? *Harvard Review of Psychiatry* **14**, 64–77.

Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS (2004). Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophrenia Research* **71**, 285–295.

Snitz BE, Macdonald AW 3rd, Carter CS (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophrenia Bulletin* **32**, 179–194.

Sobczak S, Honig, A, Schmitt, JA, Riedel WJ (2003). Pronounced cognitive deficits following an intravenous L-tryptophan challenge in first-degree relatives of bipolar patients compared to healthy controls. *Neuropsychopharmacology* **28**, 711–719.

Strakowski SM, Adler CM, Holland SK, Mills N, DelBello MP (2004). A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharmacology* **29**, 1734–1740.

Strakowski SM, Delbello MP, Adler CM (2005). The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Molecular Psychiatry* **10**, 105–116.

Stroop JR (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* **18**, 643–662.

Szoke A, Schurhoff F, Golmard JL, Alter C, Roy I, Meary A, Etain B, Bellivier F, Leboyer M (2006). Familial resemblance for executive functions in families of schizophrenic and bipolar patients. *Psychiatry Research* **144**, 131–138.

Szoke A, Schurhoff F, Mathieu F, Meary A, Ionescu S, Leboyer M (2005). Tests of executive functions in first-degree relatives of schizophrenic patients: a meta-analysis. *Psychological Medicine* **35**, 771–782.

Thompson JM, Gallagher P, Hughes JH, Watson S, Gray JM, Ferrier IN, Young AH (2005). Neurocognitive impairment in euthymic patients with bipolar affective disorder. *British Journal of Psychiatry* **186**, 32–40.

Thompson JM, Hamilton CJ, Gray JM, Quinn JG, Mackin P, Young AH, Ferrier IN (2006). Executive and visuospatial sketchpad resources in euthymic bipolar disorder: implications for visuospatial working memory architecture. *Memory* **14**, 437–451.

Torrent C, Martinez-Aran A, Daban C, Sanchez-Moreno J, Comes M, Goikolea JM, Salamero M, Vieta E (2006). Cognitive impairment in bipolar II disorder. *British Journal of Psychiatry* **189**, 254–259.

Toulopoulou T, Quraishi S, McDonald C, Murray RM (2006). The Maudsley Family Study: premorbid and current general intellectual function levels in familial bipolar I disorder and schizophrenia. *Journal of Clinical and Experimental Neuropsychology* **28**, 243–259.

Tunbridge EM, Harrison PJ, Weinberger DR (2006). Catechol-*o*-methyltransferase, cognition, and psychosis: Val158Met and beyond. *Biological Psychiatry* **60**, 141–151.

van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W (1998). Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. A preliminary study. *Archives of General Psychiatry* **55**, 41–46.

Varga M, Magnusson A, Flekkoy K, Ronneberg U, Opjordsmoen S (2006). Insight, symptoms and neurocognition in bipolar I patients. *Journal of Affective Disorders* **91**, 1–9.

Wechsler D (1955). *Wechsler Adult Intelligence Scale* (Manual). Psychological Corporation: New York.

Wechsler D (1981). *Wechsler Adult Intelligence Scale – Revised*. Psychological Corporation: New York.

Woodward ND, Jayathilake K, Meltzer HY (2007). COMT Val108/158Met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia. *Schizophrenia Research* **90**, 86–96.

Yurgelun-Todd DA, Ross AJ (2006). Functional magnetic resonance imaging studies in bipolar disorder. *CNS Spectrums* **11**, 287–297.

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 JK, Huguelet P, O'Neil RL, Giordani BJ (2001). Cognitive function in euthymic bipolar I disorder. *Psychiatry Research* **102**, 9–20.