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Neurocognitive performance as an endophenotype for bipolar disorder

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1. ABSTRACT

Identification of the underlying liability to develop bipolar disorders (BD) is hindered by the genetic complexity and phenotypic heterogeneity of the disease. The use of endophenotypes has been acknowledged as a promising approach that may detect the hidden manifestations of a genetic liability for an illness. One of the most commonly proposed endophenotypes in BD is neurocognitive performance. We identified and examined previously published review articles that had any data pertaining to endophenotypes in BD and combined this with an extensive review of studies of cognitive deficits in BD from 2000 onwards. Using criteria for a valid endophenotype, we identifed that the domains of executive functioning and verbal memory are the most promising candidate endophenotypes for BD. However, they do not meet the criteria for specificity as similar deficits present in

Table 1. Gottesman and Gould's (3) criteria for a valid endophenotype

The endophenotype is associated with illness in the population.
The endophenotype is primarily state-independent (manifests in an individual whether or not the illness is active).
The endophenotype (observed in affected family members) is found in non-affected family members at a higher rate than in the general population.
Within families, the endophenotype and illness co-segregate (ie. the endophenotype is more prevalent among the ill relatives of an affected proband compared with the well relatives of the proband).
The endophenotype is heritable.
The endophenotype should be a trait that can be measured reliably, and ideally is more strongly associated with the disease of interest than with other psychiatric conditions.

schizophrenia and/or severe or psychotic major depressions. Further research is needed as the findings regarding endophenotypes show between-study heterogeneity. In the future, examination of quantitative traits may offer a more promising approach to the study of endophenotypes rather than solely focusing on diagnostic categories.

2. INTRODUCTION

Bipolar disorder (BD) is a highly heritable condition, as demonstrated by family, twin, and adoption studies (1). However, progress in identifying the genetic basis and underlying aetiopathology of BD has been disappointing, probably due to genetic complexity and phenotypic heterogeneity (2). As such, several alternative strategies for identifying individuals at genetic high risk for developing BD have been employed, such as the identification of 'endophenotypes' (or intermediate phenotypes). With this in mind, this review has three goals. First, we identified and summarized the findings of review articles and meta-analyses of the neurocognitive profile of adults with BD that were published from January 2000-June 2013. Second, as this area of research is rapidly evolving, we supplemented and updated our 'review of reviews' with any evidence identified via a database search of new studies (PubMed, PsychLit, Medline). Thirdly and most importantly, we explored the validity of different neurocognitive domains as candidate endophenotypes for BD by examining the information gathered alongside the criteria described for an endophenotype that were proposed by Gottesman and Gould (3).

The review focuses only on studies that employed diagnostic criteria for adult subtypes of BD, not paediatric or juvenile BD. This was because the latter may differ in significant ways from adult prototype BD (4) and, the comorbidities reported in juvenile BD, such as attention deficit hyperactivity disorder (ADHD), may confound the comparison of neurocognitive profiles across childhood and adult studies. Also, the neurocognitive assessments employed for children are developmentally sensitive, with effects for age being most significant between 5-8 years; furthermore, the age of 11-12 years is suggested as the lower threshold for the maturation of neurocognitive performance (5). As such, we have excluded studies of paediatric BD from the main review.

3. CRITERIA FOR VALIDATING AN ENDOPHENOTYPE

Gottesman and Gould (3) proposed that it should be possible to detect some manifestation of a genetic liability for an illness within at-risk persons that (a) is not visible to common observation (but can be viewed with the appropriate tools), (b) is internal to the person (ie is similar to a trait), and (c) precedes observable signs or symptoms of illness (7). Also, family relatives of affected patients may carry the endophenotype, even if they do not develop the categorical phenotype (ie BD). Lenzenweger (7) and Hasler *et al.* (8) suggest that an endophenotype is not a risk factor, but a manifestation of the underlying disease liability; its utility is that theoretically it represents a simpler indicator of the genetic underpinnings of the disease than the clinical syndrome (i.e. symptom constellations). Gottesman and Goldman (3) proposed explicit criteria for defining a valid endophenotype, namely that it is: (1) associated with the illness, (2) state-independent, (3) observed in unaffected family members (4) heritable, and (5) co-segregates with the disease (see Table 1). Lastly, although more controversial, it was suggested that the endophenotype should be disorder or condition specific.

Merikangas *et al* (9) have recommended the widespread use of an endophenotype-based approach to help identify susceptibility genes for affective disorders. One candidate endophenotype is neurocognitive profile, it is generally regarded as a particularly promising candidate as cognitive performance shows high heritability (0.3 to 0.8; with large estimates for working memory and general intellectual ability) and it can be reliably measured (8). Given that there have already been many articles that give an overview of neurocognition and BD, the current paper will review these publications alongside the six criteria for an endophenotype listed in Table 1, and then highlight the confounding factors that may distort the reporting or assessment of cognitive performance in BD.

4. NEUROCOGNITIVE DEFICITS AND BIPOLAR DISORDER

Unlike schizophrenia (SZ), there is no consistent evidence that premorbid, predicted or current intellectual functioning (intelligence quotient; IQ) differs between BD cases and the general population. Systematic reviews and meta-analyses demonstrate evidence for deficits across nearly all other neurocognitive measures in euthymic BD cases as compared with healthy control (HC) populations (see ref. 10). According to Arts *et al* (11), the largest effect sizes (ES>0.8) are found for key aspects of working memory, executive control, set shifting, fluency, verbal memory and processing speed. Likewise, medium ES (0.5-0.8) are frequently observed for visual memory and sustained attention. Similar findings are reported in other reviews or meta-analyses that used different inclusion criteria (eg. ref.12). However, there is substantial heterogeneity in the studies included in the different reviews. This was often associated with the duration or severity of the illness and heterogeneity was especially

noticeable for working memory, set shifting, executive control and fluency (13-14). In addition, the proportion of BD I and/or BD II or other forms of BD in a sample may affect the ES estimates.

5. STATE INDEPENDENCE

Glahn and colleagues (15) and Daban *et al* (16) note that a valid endophenotype should be present across all phases of BD and should demonstrate other trait like qualities ie it should also be present in remission and in first episode and high risk populations (the latter are discussed in other sections of this review). Many publications have examined neurocognition in euthymia and some have compared cognitive performance in first episode BD versus multi-episode cases. This section will mainly focus on euthymia but will briefly review deficits in mania, hypomania and depressive phases of BD and comment on studies of first episode mania.

5.1. Euthymia

5.1.1. Intelligence

As noted previously there is no reliable evidence that any measure of IQ in euthymic BD differs from HC (11, 17-18).

5.1.2. Executive functioning

In the meta-analysis by Kurtz and Gerraty (19), euthymic patients exhibited impairments on measures of executive functioning for problem solving tasks (Wisconsin Card Sorting Test; WCST categories and perseverations), verbal interference (Stroop Color-Word Test; SCWT), and set-shifting tasks (Trail Making Test part B; TMT B). Heterogeneity was evident for all these assessments and moderator analyses revealed that age, years of education and gender were significant confounders. Patients in euthymia also showed impairments on measures of working memory (digits backward), but again there was between-study heterogeneity (moderated by years of education). Robinson *et al.* (12) also showed impairments for categorical verbal fluency and working memory, whilst Torres *et al.* (20) demonstrated that the executive functions that were most impaired were: cognitive flexibility/set shifting and response inhibition; less severe deficits were reported for verbal working memory and verbal fluency.

5.1.3. Memory

Kurtz and Gerraty (19) reported that euthymic BD patients showed impairments on measures of verbal learning (ES = 0.81), and delayed verbal and non-verbal memory (ES = 0.80 to 0.92), with lesser impairments for measures of visuospatial function (ES <0.55). Although these findings were confounded by years of education, the results suggest that in euthymic BD cases, marked deficits in verbal learning and memory are superimposed on more modest levels of generalized neuropsychological impairment. However, not all studies confirm this pattern and according to Bora *et al* (18), when publication bias is taken into account the ES for verbal learning are reduced to a medium level (0.66), and furthermore, memory performance can be significantly influenced by psychomotor speed and executive functioning (21). Delaloye *et al.* (22), also highlight that the encoding of verbal material may be mediated by working memory via internal auditory rehearsal processes that are sensitive to psychomotor speed and the ability to cluster information. Overall, these data suggest that there are significant inter-relationships between cognitive domains that can unilateral and/or bidirectional effects on performance in other domains.

5.1.4. Attention

In Torres *et al.* (20), it was found that patients had slower visuo-motor processing speed, as well as impaired accuracy and reaction times on sustained attention tasks compared to HC. Arts *et al* (11) found medium ES (0.58) for sustained attention (Continuous Performance Test; CPT), consistent with the findings of Robinson *et al.* (12) (ES for latency=0.60; ES for sensitivity=0.48). Kurtz and Gerraty (19), reported smaller ES for auditory attention (digit forward =0.41, 95% CI: 0.24 to 0.57), and moderate-large ES for sustained visual vigilance (CPT=0.69, 95% CI 0.54 to 0.83; moderated by years of education) and speeded visual scanning (TMT A=0.65, 95% CI 058 to 0.77). However, findings for sustained attention in BD vary across studies and reviews, reflecting that it is markedly influenced by a range of markers of disease severity and intensity (10, 23-25).

5.1.5. Processing speed

Euthymic BD I cases show medium-large ES (0.60 to 0.72) for impairments in psychomotor speed compared to HC, even after controlling for medication status (19, 26). This measure is considered by many researchers as a key construct for study due to the influence of this domain on a wide range of other cognitive operations (16,26).

5.2. Acute Illness Episodes

During mania, hypomania and depression, patients with BD demonstrate significant deficits across most cognitive domains, these impairments are usually similar to those seen in euthymia, but are often amplified during the active phase of the illness (27-31). Kurtz and Gerraty (19) tried to determine whether cognitive deficits are state-independent or phase-linked. The findings show that a subset of deficits are moderately worsen during different illness phases, with the largest ES for deficits being identified for verbal learning in acute episodes (of any polarity) compared to euthymia. Overall, groups of manic/mixed and of depressed patients demonstrated impaired executive functioning, verbal learning and memory, fluency and attention. Manic patients had greater deficits in attention (visual scanning-CPT) and depressed patients had greater impairments on phonemic fluency compared to euthymic patients. Ryan *et al* (32) noted that two components of executive functioning were different in groups defined by illness phase and compared to HC: inhibitory control was significantly impaired in (hypo)manic cases compared to all other groups whilst verbal fluency and processing speed was sensitive to active illness (any polarity) compared to HC even after controlling for clinical and treatment variables. Dixon *et al* (33) also reported that the wide range of deficits in executive

functioning observed were especially associated with mania and the performance deficit was related to the severity of positive thought disorder. Xu *et al.* (34) found deficits in processing speed in acute depression, whilst Malhi *et al.* (28) noted state-specific impairments for reaction times in hypomania and for motor speed in depression. However, it is unclear how much some of these impairments are worsened by or indeed reduced by medication effects. In summary, all studies suggest that the reported deficits extending beyond resolution of acute episodes but that the ES are especially exaggerated in manic episodes and mostly attenuated during periods of remission.

5.3. First Episode Mania

Another strategy to try to assess state-independence or trait-like elements of cognitive performance in BD is the assessment of cases of first episode mania. The rationale for this strategy is that any deficits present at this stage are more likely to have been present premorbidly rather than being simply a consequence of the illness process (the 'scar' hypothesis). However, it is important to note that about 70% individuals who experience a manic episode will have a prior history of depression. As such, first episode mania is not usually synonymous with first illness episode. Despite this, the studies can be more helpful in providing insights into neurocognitive functioning in affective disorders than those in long-established BD cases.

The available data suggest that about one in five individuals with first episode BD show impairments in executive functioning, learning and memory, psychomotor speed and attention (35). Torres *et al* (36) noted that in comparison to HC, first episode BD cases show a broad range of significant cognitive impairments. Specifically, deficits were evident in spatial working memory, attentional and mental set shifting, nonverbal reasoning, verbal learning and recall, and sustained attention ($p < .01$ for all analyses). At this early stage of the illness, few significant associations between clinical symptoms and neurocognitive deficits were found, and Torres *et al* (36) noted impairments could not be fully explained by comorbid substance abuse, medication status, or residual sub-syndromal mood symptoms. Overall, first-contact mania patients usually show more cognitive deficits than HC but with smaller ES than reported for cases with multiple previous BD episodes (35-38).

Neurocognitive profile has also been compared in first-episode affective and non-affective psychoses (eg ref. 39). Individuals with SZ display significant deficits in all cognitive domains, whilst individuals with psychotic affective disorders (unipolar or BD) show a similar range of impairments but with ES that are generally intermediate between the SZ and HC groups. Hill *et al* (2009) also report that six weeks post-treatment initiation, cognitive measures show significant improvements (about 6% increment from baseline scores) but the changes in patient groups mirror those seen in HC (ie the change most likely represents a practice effect). Another large scale epidemiological catchment area study confirms that early in the course, cognitive deficits are present in all psychotic disorders, but are less pervasive in psychotic BD/mania than in SZ (40). However, IQ is a highly significant covariate in that study and Barrett *et al.* (41) also reported that individuals with a first episode of SZ who have a preserved IQ performed similarly to a first episode BD group on all measures, whilst patients with SZ with a low IQ and more negative symptoms showed significantly greater cognitive deficits than BD cases. Taken together these findings indicate that different rates of impaired general intellectual functioning in BD/SZ or psychotic/non-psychotic groups influence the pattern and degree of cognitive deficits across diagnoses and conditions.

6. HEALTHY FIRST-DEGREE RELATIVES

First-degree relatives share 50% of their genes in common and, as genetic vulnerability for BD is high, it is anticipated that unaffected relatives of BD probands would show some similarities in their neurocognitive profile to that of the clinical cases (see Table 2 for the key findings of meta-analyses of cognitive deficits in unaffected relatives). Studying unaffected relatives also has the advantage of avoiding confounding of cognitive assessments associated with medication, comorbid disorders or residual symptoms.

6.1. Intelligence

Regardless of the tool selected to evaluate current IQ, the majority of studies show that unaffected first-degree relatives (UFDR) have similar scores to HC (eg 18,25, 42-44). Two studies reported current IQ differences between HC, UFDR and probands; although in one study the differences were marginal (45). Frantom *et al.*, (46), found non-significant differences in premorbid IQ, but significant differences in current IQ (cases performing worse than HC with UFDR intermediate between the groups). This study used a brief assessment of IQ; which is an approach that has been criticized as potentially unreliable (47).

6.2. Executive functioning

Frantom *et al* (46) demonstrated that, compared to HC, BD I cases and their UFDR showed impairments on a range of executive functions (as well as in verbal learning and memory and processing speed), with UFDR showing ES that were intermediate between probands and HC. Zalla *et al.* (48) found no significant differences between UFDR (n=33) and HC (n=20) on two standardized, widely employed tasks of executive functioning (WCST and TMT), but performance on the Stroop (a measure of mental flexibility), was significantly impaired in UFDR compared to HC. Szöke *et al.* (49) did not find differences between unaffected relatives and HC on the WCST, but there were statistically significant differences on the TMT part B, indicating some familial similarities in mental flexibility. Schulze *et al* (50) examined several components of executive functioning in groups of BD probands with a personal and family history of psychosis, their UFDR and unrelated HC (all groups n>40), and reported that response inhibition deficits were associated with psychotic BD and also with genetic liability for the disorder (ie the UFDR).

Table 2. Review of meta-analyses that reported cognitive performance in bipolar probands and their relatives compared to healthy controls

Meta-Analyses/ Domains	Robinson & Ferrier (12)	Torres *et al* (20)	Arts *et al* (11)	Bora *et al* (18)	Kurtz & Gerraty (19)	Mann-Wrobel *et al* (117)	ES ≥0.8 in ≥2 meta-analyses
Premorbid IQ	d = 0.19	d = 0.06	d = 0.16	d= 0.17	-	d = 0.12	
Verbal episodic memory (VEM)	d = 0.73	d = 0.72	d = 0.83	d = 0.73	d = 0.81	d = 0.64	VEM = 0.73*
Visual episodic memory (VisEM)	-	-	d = 0.62	d = 0.59	d = 0.80	d = 0.67	
Executive functioning							EXECUTIVE FUNCTIONING = 0.71*
	TMT B = 0.78	TMT B = 0.55	TMT B = 0.99	TMT B = 0.86	TMT B = 0.73	TMT B = 0.80	TMT B = 0.8*
	WCST P = 0.76		WCST P = 0.88	WCST P = 0.70	WCST P = 0.61	WCST P = 0.66	WSCT P = 0.7*
	WCST C = 0.62	WCST C= 0.69	WCST C = 0.52	WCST C = 0.66	WCST C = 0.54	WCST C = 0.56	
	Verbal fluency = 0.34		Verbal Fluency= 0.59	Verbal Fluency = 0.60	Verbal Fluency= 0.51		
	Category Fluency=1.09		Category Fluency=0.87			Category Fluency=0.58	Category Fluency=0.87*
	Stroop = 0.63	Stroop = 0.71	Stroop = 0.65	Stroop = 0.76	Stroop = 0.75	Stroop: Colour-Word= 0.71 Word = 0.74 Colour = 0.76 Interference=0.88	Stroop = 0.71*
Attention	TMT A = 0.52	TMT A =0.60	TMT A = 0.71	TMT A = 0.69	TMT A = 0.65	TMT A = 0.64	
	Sustained attention: Latency = 0.6 Sensitivity = 0.48	CPT = 0.74	CPT = 0.58	CPT omission = 0.83	CPT = 0.69		
		CPT reaction time=0.62		CPT commission=0.36			
Processing speed	DSST = 0.59	DSST = 0.79		DSST= 0.75	DSST = 0.66	DSST= 0.76	

Effect sizes are only reported if more than one meta-analysis provided data for the same test for that cognitive domain, d: Effect Size; Large effect size (d≥0.8); *Medium effect size (0.5 ≤d<0.8);* Small effect size (0.2 ≤d<0.5) *Median d is estimated for each cognitive domain using data reported in all meta-analyses, CPT: continuous performance test; DSST: digit symbol substitution test; TMT: trail making test, part A or part B; WCST: Wisconsin card sorting test, P=perseverations, C= categories.

A small scale study suggested that, when compared to a demographically matched HC group, unaffected siblings of BD probands (n=10) showed impairments on the WCST (51), whilst Kulkarni *et al.* (52) reported that unaffected siblings of BD I probands had significantly impaired performance on the Tower of London task, implying planning difficulties. In a small scale study cross-sectional study, Frangou *et al.*, (25) showed that unaffected offspring of BD I probands performed better than HC on the WCST (less perseverative errors and more categories achieved), but were significantly impaired on the Hayling Sentence Completion Task. The researchers suggested these findings were evidence of intact dorsal prefrontal cortex (DPFC)-related executive processes in relatives, but deficient ventral prefrontal cortex (VPFC)-related response inhibition. Taken together, these studies suggest that executive functioning such as planning; response inhibition and mental flexibility may be impaired in unaffected relatives of BD probands. However, using a visual backward masking (VBM) task to measure working memory, Keri *et al.*, (53) failed to show any significant difference between unaffected siblings of BD probands (n=20) and HC (n=20). Likewise, Ivleva *et al* (54) failed to find any significant differences between four groups defined by traditional diagnoses as schizophrenic or psychotic BD cases and their UFDR, indicating that sampling strategies and other study design factors may influence the findings.

6.3. Memory

Savitz *et al* (55) have shown that visual and verbal recall memory (measured using the Rey Auditory Verbal Learning Test; RAVLT) were significantly impaired in BD I cases compared to their UFDR even after controlling for clinical symptoms, alcohol misuse and childhood trauma. Frantom *et al* (46) also showed differences between probands, UFDR and HC on the California Verbal Learning Test (CVLT). Using the Wechsler Memory Scale (WMS), Quraishi *et al.* (56) found that UFDR or BDI probands were impaired in verbal (immediate and delayed) but not on visual memory; similar findings are reported by Kulkarni *et al*, (52).

6.4. Attention

Mechanisms of sustained attention, usually evaluated with the CPT (or variants) do not appear to be

impaired in mixed samples of unaffected relatives (24, 43, 57-59), although some of these studies include second as well as first degree relatives. The small scale study by Trivedi *et al.* (51) was an exception in finding some differences in UFDR compared to HC.

6.5. Processing speed

This is generally evaluated with the WAIS Digit Symbol Test (DST). Conflicting findings in UFDR are reported, with earlier meta-analyses indicating a preserved mechanism (eg ref.11), but later studies showing significant slowing in comparison to HC (46,16) with a medium ES (0.45; 26). Antila *et al.*, (60) again highlighted that a deficit in processing speed, as found in their BD I probands and UFDR, was an important co-variate for impairments across a range of cognitive domains.

7. CO-SEGRAGATION

Co-segregation means that within families, individuals with BD would be expected to show a greater level of cognitive impairment than family members without BD (as described in section 5, unaffected family members are expected to show worse performance than individuals from the general population). To examine this hypothesis, we review data from cross-sectional or prospective studies regarding the cognitive performance of siblings and offspring of BD probands. In contrast to the previous section (section 5), this section mainly focuses on family members who later develop mental disorders.

7.1. Intelligence

There is no evidence that general IQ shows co-segregation, but in a cross-sectional study of 28 offspring (mean age 10 years) of a BD parent and HC; about 40% of high risk children exhibited significant Verbal-Performance IQ discrepancies and had lower academic performance than the HC (61).

7.2. Executive functioning

One of the larger prospective studies of offspring of affectively ill parents (both unipolar and BD) included an evaluation of cognitive performance in 43 children of mothers with BD (62-63). When compared at the age of 15 years with HC offspring, the BD offspring exhibited deficits in selected domains of executive functions (eg WCST), irrespective of clinical state. When reassessed as young adults (mean age 22 years), nine offspring had developed BD (offspring of BD probands=6; offspring of unipolar probands=3). The BD offspring who went on to develop BD showed prior deficits on the WSCT.

MacQueen *et al.* (64) undertook a cross-sectional analysis of performance on a VBM task in triads comprising seven high-risk offspring of a BD parent who met criteria for a bipolar spectrum disorder, seven unaffected high-risk offspring and seven HC matched for age and gender. Affected offspring responded more slowly and made more errors than the other two groups. However, the same researchers failed to replicate this finding in a larger study of BD offspring compared with young adult patients with BD and HC; and it was found that psychotic symptoms rather than familiarity were =the most robust predictors of VBM performance (65).

7.3. Memory

Savitz *et al.* (55) compared BD I probands with their 'BD spectrum' relatives (including a broad range of affective diagnoses) and found that verbal recall deficits distinguished BD I cases from their BD spectrum affected relatives. Savitz *et al* (55) noted that childhood trauma, alcohol or drug abuse also showed an association with memory deficits. In an extended pedigree study (45 families with at least 2 siblings with BD) Glahn *et al.*, (26) reported that the cross-sectional performance on the CVLT had many characteristics of a candidate endophenotypes for BD.

7.4. Attention

In the at-risk population described previously, children of mothers with BD exhibited deficits in sustained attention as measured by the CPT and/or the Child Behaviour Checklist (CBCL) (62, 63). According to the authors, it is possible that these specific neuropsychological deficits represent a differential risk factor for later development of BD. However, these findings have not been replicated.

7.5. Processing speed

Population-based family studies (eg 58, 60, 66) suggest that delays in processing speed are present in BD cases and their relatives compared to HC, but also that the impairments are not unique to the offspring BD, SZ or schizoaffective disorder (54).

8. HERITABILITY

Heritability is a term that is usually used to describe the extent to which phenotypic variation is accounted for by genetic variation (26). Obviously, the data reviewed in previous sections (sections 5 & 6) overlap somewhat with any discussion of heritability, as the evaluation of high risk families is one of the most commonly used methods to distinguish if certain traits or markers have a genetic basis or not (67). Glahn *et al* (26) confirmed that several key cognitive domains show high heritability (IQ, executive functioning, verbal and visual learning and memory, sustained attention and processing speed) and that many of these were impaired in multiplex multi-generational families. Notably, measures of processing speed, working memory, and declarative (facial) memory were identified as the most promising candidate endophenotypes. In studying BD, Gourovitch *et al* (68) also noted that a paradigm involving the cognitive assessment of monozygotic (MZ) twins who are discordant for BD allows the examination of both disease-specific impairments (BD affected versus unaffected twins) and risk factors (unaffected BD twins versus HC twins). In this section we use this strategy and review some of the available twin studies of BD and neurocognition. However, there are relatively few studies and data are limited.

8.1. Intelligence

Studies of intelligence have not revealed any differences in IQ scores in discordant twin samples (57, 68). Interestingly, Vonk *et al* (69) noted that twin pairs affected by BD completed significantly fewer years of education than did unaffected control twin pairs, even when there were no differences in IQ scores. These findings appear to indicate that some factor associated with academic underperformance may be inherited, affecting individuals from the same family even if the illness is not manifested.

8.2. Executive functioning

In a small scale study, Gourovitch *et al.* (68) found no impairment in executive tasks (WCST) in unaffected twins. In a larger epidemiological study from Denmark (70,71), twins affected by BD and their healthy co-twins both performed worse than controls on the Stroop interference test, suggesting that impaired response inhibition may be associated with genetic risk of BD. However, Kravariti *et al.*, (72) reported that whilst BD I affected twins were impaired on the Stroop, their healthy co-twins were indistinguishable from HC twins; interference on the Stroop was more strongly associated with depressive symptoms not with BD-status. The researchers concluded that '*being a first-degree relative of an individual with BD I with increased familial loading, does not necessarily confer risk for enhanced susceptibility to interference*'.

8.3. Memory

Genetic factors explain over 50% variance in verbal memory functioning in twins. Kieseppa *et al* (57) demonstrated that the performance of unaffected co-twins of BD probands is comparable to HC or shows only mild impairment; the BD twins were impaired on nearly all memory and verbal learning tests. These findings were not affected by use of lithium or other mood stabilizers.

8.4. Attention

Christensen *et al.*, (70) showed that unaffected DZ co-twins of BD probands had lower scores on only TMT part A (a measure of sustained attention) than HC twins; findings in other studies are inconsistent.

8.5 Processing speed

The heritability of processing speed in BD (as measured by the DST), is estimated at 0.72, which is one of the highest values after vocabulary (58). Of the few twin studies available, Kieseppa *et al.*, (57) reported that BD1 affected twins showed delayed processing speed but their unaffected co-twins were unimpaired compared to HC twins.

9. SPECIFICITY

The final criterion suggested for a candidate endophenotype explores the specificity of any impairment. To examine this notion, this section compares neurocognitive impairments in BD with those identified in schizophrenia (SZ) and in unipolar disorders (UD).

9.1. Schizophrenia

A systematic review by Daban *et al.* (73) reported that BD and SZ exhibited a similar range of cognitive deficits, but the impairments in BD were usually less severe. A meta-analysis by Krabbendam *et al* (74) quantified the differences, suggesting the ES were 0.3–0.6 greater for impairments in SZ compared with BD. Between diagnostic group deficits are most pronounced for executive control, verbal fluency, working memory, verbal and visual memory, and processing speed (74-77). However, it is notable that the estimated differences are insufficient on their own to truly distinguish between the disorders. Furthermore, sampling strategies may influence study findings to an uncertain extent. For example, in a small scale study of individuals referred to an early intervention in psychosis service (78), there were no cognitive markers that uniquely identified individuals who later developed BD compared to those who later met diagnostic criteria for SZ.

A major issue in comparing BD and SZ is the current or past history of psychotic symptoms in the BD sub-group. Kurtz and Garrety (19) highlighted that only 12% studies included in their meta-analysis reported this information for BD, yet the studies where it was assessed reported levels of 50-75% on average. In all analyses of SZ and psychotic BD, the difference in cognitive performance is considerably less (10,77), and if the effects of current IQ are taken into account, the most obvious difference is in verbal learning (ES ~0.4), while the between-group differences for working memory, processing speed, executive control, and verbal fluency are minimal (77).

The longitudinal pattern of cognitive deficits in SZ and BD do show some differences as individuals who later develop SZ are more likely to have pre-illness onset cognitive deficits (79, 80) and the deficits in first episode schizophrenia are not radically different from those of multi-episode cases. However, individuals who later develop BD have premorbid impairments less frequently and the deficits present in multi-episode cases exceed those reported in first episode cases (81, 82). However, a review of previous studies suggests that in female only samples (and after controlling for current IQ), the UFDR of SZ often show higher levels of impairment in verbal and visual memory compared to UFDR BD, whose performance was similar to HC (83). However, there are few other similar studies available.

Overall, deficits in IQ are the most consistent cognitive measure that differentiates between SZ and BD populations. Murray *et al* (80) concluded that whilst BD and SZ show overlapping genetic vulnerabilities, this finding appears to indicate that additional neurodevelopmental factors specifically increase risk for SZ.

9.2. Unipolar Disorders

Many studies have demonstrated that cognitive deficits are often found in unipolar depression (UD) both during acute episodes and in remission (for a review see ref. 84). Iverson *et al* (85) reported that about 40% BD

compared to 30% of UD (and 8% HC) show significant impairments in two or more cognitive domains. As in BD, unipolar patients the degree of impairment in psychomotor speed, episodic memory and executive function is associated with illness severity (86). Studies suggest that when depressed, both BD and UD cases demonstrate impairments in episodic memory (eg 87, 88).

Findings for executive functioning are mixed. Borkowska and Rybakowski (89) noted that depressed BD adults had more severe deficits in executive functioning compared with depressed UD cases. Bearden *et al.* (2006) reported that BD and UD cases, matched for illness duration and severity of depressive symptomatology showed similar deficits in verbal recall and recognition. Maalouf *et al* (90) report that executive functioning is similar in BD and UD depression, but that impaired sustained attention is a marker of BD rather than UD, as it is impaired in BD cases in euthymia and depression. In contrast, Taylor Tavares *et al* (2007) found that a group of unmedicated BD II cases displayed intact executive functioning, memory and decision making compared with unmedicated UD, despite comparable levels of depressive symptoms and both groups being unmedicated at the time of testing. Hermens *et al.* (91) found that cases of UD or BD depression showed a very similar pattern of performance across all measures, with verbal memory impairment best differentiating cases (UD and BD) from HC. One study evaluated euthymic cases, recruiting young adults with a BD spectrum disorder (including depression with a family history of BD) or with UD; cases with a BD spectrum disorder showed more pronounced deficits in executive functioning and verbal memory when compared to cases with recurrent UD (92).

10. POTENTIAL CONFOUNDING FACTORS

Several factors, including sampling strategies, study inclusion criteria, diagnostic rigor or demography are likely to influence reported findings on neurocognitive performance. However, the detailed assessment of the impact of potential modifiers and confounders is undermined by the lack of detailed reporting of these data. As such this section briefly highlights issues that we anticipate will become increasingly important in future discussions of neurocognition and BD in the future.

10.1. Bipolar Sub-type

The majority of early studies of neurocognitive performance focused on BD I; this has changed somewhat in recent years, with a small number of studies of BD II or of BD spectrum disorders. However, some studies of BD fail to report the proportions of BD I, II and/or NOS cases and others that compare BD I and II report contrasting findings (93, 94). Overviews of the available studies that compare neurocognition in BD I and II and/or BD II and HC have been examined in two recent reviews. Sole *et al.* (2011) found more deficits in BD I than BD II, but findings were inconsistent (partly due to the problem of high levels of residual depressive symptoms in BD II in some studies). The main deficits in BD II included working memory, inhibitory control and verbal memory. Bora *et al* (95) found BD II cases were more impaired than HC, but less impaired that BD I cases on cognitive performance in verbal memory, with smaller differences on semantic fluency and visual memory tasks. In an earlier study, Torrent *et al.* (96) highlighted that executive function alongside subclinical depressive symptoms and early age at onset, were the best predictors of poor psychosocial functioning in BD II.

The presence or absence of psychotic symptoms in BD is also of significance in trying to establish the potential role of neurocognitive profile as an endophenotype. As noted in the comparison of BD and SZ there is evidence that symptom profile (ie current or past history of psychotic symptoms) may be a more important marker of cognitive deficits than diagnosis (eg 72, 97). However, the interpretation of these findings is complicated by the fact that SZ is associated with higher levels of impairment of general intellectual functioning, so studying psychotic and non-psychotic forms of BD is also of great interest; as Glahn *et al* (98) highlight psychotic BD without major intellectual impairment may provide avenues for the examination of the neural correlates of specific cognitive tasks. The recent meta-analysis by Bora *et al* (10) demonstrated that within BD populations, BD cases with a history of psychosis (BDP+) versus cases without any psychosis (BDP-) show greater severity of cognitive deficits; BDP+ cases especially show impairments in planning and reasoning, working memory, verbal memory and processing speed, but show minimal differences from BDP- cases on attention and visual memory tasks. However, it is clear that the presence of psychosis cannot fully explain all the cognitive deficits in BD (99); unanswered questions in BD populations include the possible differences in cognitive performance in individuals with mood incongruent or congruent psychotic symptoms (100).

A final issue regarding BD sub-types is whether age at onset is associated with neurocognitive impairments. There is insufficient data at present to fully answer this question. Cahill and colleagues (101) identify cognitive deficits in juvenile (or paediatric) BD, but interpretation of such studies are complicated by the issue of dynamic changes in neurocognitive performance that occur during the course of normal cognitive development as well as confounding due to high levels of comorbidity eg with ADHD (102). In studies of BD meeting adult diagnostic criteria, one of the only studies that stated it was examining early compared to late onset BD used age at onset definitions that conflict with current views of early, intermediate and late onset. Schouws *et al* (103) compared early onset (<40 years; n= 59) with late-onset BD (> 40 years, n=60) and elderly HC (n=78). Cases with a late-onset were more impaired in mental flexibility and psychomotor performance than patients with an early onset, even after covarying for age, education and cardio-vascular risk factors. However, many clinical studies and admixture analyses of BD samples (eg, ref. 104) identify three sub-groups with a mean age at onset of 17, 25, and 40 years old; as such the early onset sub-group described by Schouws *et al* (103) seems to includes all early and intermediate cases plus many of those with a later onset,

making the interpretation of the data difficult. The issue is an important one for researchers given that early onset BD shows strong genetic links and is more strongly associated with factors such as obstetric complications which may be associated with neurodevelopmental impairments (105)

10.2. Comorbidities

Studies of psychiatric comorbidities in the neurocognitive research of adult BD have mainly been limited to substance use disorders, especially showing impairments in those with BD and alcohol misuse disorders (eg, ref 106). Prior alcohol misuses have neuropsychological consequences (more impairment in visual memory, verbal recall and executive functioning), and that these effects persist over several months of substance abstinence (107). Levy *et al* (108) also demonstrate that deficits may extend to the long term (similar executive dysfunction for BD in full remission from alcohol dependence than for current dependence). Chronic abuse or dependence of other substances, such as cannabis, may also contribute to neurocognitive dysfunctions in BD (109). However, despite the common co-occurrence of these problems, past exposures to these substances is not usually taken into account (110).

There is very little data about the impact of co-occurring medical comorbidities; a recent review (17) found few references, although Tsai *et al* (111) have examined the negative impact of diabetes on neurocognition in BD.

10.3. Medication

The inter-relationship between cognitive deficits and medication in BD is complex: if individuals receive effective treatment and symptom levels are reduced, they often show some improvement in neurocognitive performance (112). As a corollary, non-adherence is associated with poorer cognitive performance (106), although it is not known whether the relationship is unidirectional (ie does non-adherence increase the likelihood of neurodegeneration or are individuals with neurocognitive deficits more likely to become non-adherent) or is it bi-directional. What is known is that a number of psychotropic medications, including most medications used to stabilize mood and mental state (lithium, anti-convulsants and atypical antipsychotics) can have cognitive adverse effects including sedation.

In a recent meta-analysis, Wingo *et al* (113) identified that lithium treatment was associated with small but significant impairment in immediate verbal learning and memory (ES = 0.2), whilst long-term lithium treatment also was associated with even greater impairment in psychomotor performance (ES=0.6). However, lithium is also neuroprotective, so it is still not clear those with poor cognitive performance who are taking lithium would have functioned better or worse if lithium-free. Individual studies of carbamazepine, valproate, lamotrogine and other medications eg topiramate show conflicting results depending on the phase of BD, whether the individual was previously medication-free and or whether medications were used as monotherapy or part of a combined approach (eg 17,13, 114). Most medications affect psychomotor speed, but as this may have implications for overall neurocognitive performance, it is unclear which medication effects are specific to certain cognitive task and which are indirect effects of slower processing speed.

One of the few studies to examine different medications simultaneously was reported by Gualtieri and Johnson (115). In a naturalistic cross-sectional study of 159 BD cases (aged 18-70 years) who were taking one of six different mood stabilizers (carbamazepine= 16; lamotrigine = 38; oxcarbazepine= 19; topiramate= 19; valproic acid= 37), the researchers found significant group differences were detected in tests of memory, psychomotor speed, processing speed, reaction time, cognitive flexibility, and attention. Rank-order analysis indicated that overall, lamotrigine was the least 'neurotoxic', carbamazepine had the most effects whilst lithium was ranked in an intermediate position.

11. CONCLUSIONS

There are three main implications from this review of recent studies of neurocognitive performance and BD. First, neurocognitive impairments are a feature of BD I and BD II and are more prevalent than any of the deficits observed in HC. Impairments are amplified during acute episodes but are also detectable in euthymia. The nature and range of neurocognitive impairments is similar to that seen in SZ, but the observed deficits are of lesser magnitude in BD, although those in BD may show greater progression across time than seen in SZ. These findings, and other evidence that deficits are correlated with functional outcomes in BD, led Anaya *et al* (116) to suggest that there is likely to be a role for cognitive remediation. This will probably become an important therapeutic option in the future, whether or not the neurocognitive abnormalities are an intrinsic part of BD or are a consequence of comorbidities or other factors (117).

Second, the overall level of neuropsychological impairment is lower when educational attainment and/or IQ are higher. However, some neurocognitive tests show greater heterogeneity across studies than would be expected by chance- highlighting the need for more complete descriptions of the study samples to allow moderator and mediator analyses (118). The use of different neurocognitive assessment protocols also undermines the benefits of the standardization of the procedures. Furthermore, the selective reporting of statistically significant findings also reduces confidence in the overall findings reported in review articles. Furthermore, failures to report the proportions of cases meeting diagnostic criteria for BD I (or other BD subtypes), or rates of psychotic symptoms, comorbid alcohol misuse, prescribed medications and/or rates of treatment non-adherence make it difficult to differentiate effects related to study characteristics versus those associated with the illness. Studies of first degree relatives may also be confounded by the inclusion of mixed groups of older and younger relatives (the former may be beyond the peak age at risk for onset, whilst the latter may be just entering the peak age

Table 3. Cognitive domains compared on endophenotype criteria

Domain	Heritability*(maximum % of h^2)	Associated with Disorder	State Independent	Co-segregate
Intelligence Quotient (IQ)	85%	NO	-	-
Executive Functioning/Working Memory	79%	YES	YES	YES
Verbal Learning & Memory	56%	YES	YES	YES
Visual Learning & Memory	55%	-	-	-
Sustained Attention	65%	YES	YES	-
Processing Speed	76%	YES	YES	-

*Estimates from literature (eg Refs 1-3,7,8,110), - Denotes not known or uncertain

range). All of these limitations become especially important when trying to distinguish potential genetic effects from the normal trajectories of neurocognitive change (eg associated with age) and in trying to identify intrinsic effects of illness from those related to population stratification effects (119). This is critical for identifying and using endophenotypes as these should be related to the causes rather than the effects of the disorder (87, 119).

Finally, although there are limitations in the data available to us to assess putative endophenotypes in BD, there are some consistencies in the findings reported across the whole range of data publications, review articles and meta-analyses that offer promising avenues for future research. For example, there is growing evidence that the cognitive domains of executive functioning and verbal memory are candidate endophenotypes for BD (see Table 3). Measures of both domains demonstrate that they are highly heritable, are impaired in BD probands and their first degree relatives and, according to findings in euthymia, are relatively independent of clinical state. Data on processing speed as an endophenotype show similarities to the findings for these domains. However, the evidence is undermined because the ES for processing speed are smaller and/or show heterogeneity, and medications frequently impact on performance on this test. The specificity of the impairments in executive functioning and verbal memory is still being debated. Most of the deficits are also present in SZ (and their family members), but at a more severe level than in BD. The use of dimensional approaches, such as exploring quantitative traits related to clinical syndromes (eg psychotic symptom levels across diagnostic groups) may be an important parallel approach to research to use alongside traditional approaches to categorical phenotypes (eg diagnostic categories), as this may help to establish if there are disorder-specific endophenotypes and the extent of shared or specific genetic liability for severe mental disorders (83, 87).

12. ACKNOWLEDGMENTS

All authors contributed equally to this article.

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