Neurocognition in Bipolar Disorder and Juvenile Bipolar Disorder

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ABSTRACT

Introduction: In the ongoing quest for improved diagnostic markers of bipolar illness, the focus of research has gradually shifted to examining the onset of mood difficulties early in life and investigating the potential corollaries of such early onset such as cognitive impairment, disruption of social and emotional functioning, and constriction of quality of life. This article considers the disruptions to cognitive functioning that accompany bipolar disorder and compares adult and child profiles to ascertain the likelihood of identifying a neurocognitive biomarker of the illness. **Methods:** A succinct review of the literature pertaining to cognition in both adult and childhood populations is synthesised following Medline and PsychINFO searches using key-terms including 'cognition', 'bipolar disorder', 'neurocognitive' 'child', 'adolescent' and a range of neuropsychological domain names. In addition, literature known to the authors was scrutinised and relevant references further pursued. **Results:** Findings from the literature are contextualised and key findings are summarised and provide a basis for future recommendations. **Conclusion:** A number of deficits have been consistently identified in both adolescent and adult populations that perhaps reflect disease traits. Future research needs to focus on these and employ multimodal tests in pristine patient groups, with a view to identifying reliable biomarkers.

Key words: bipolar disorder, neurocognition, juveniles

RÉSUMÉ

Introduction: Le désir constant d'améliorer les marqueurs diagnostiques du trouble bipolaire a conduit les chercheurs à orienter leurs travaux vers la manifestation des troubles de l'humeur dans les premières années de la vie et à étudier les corollaires potentiels comme les déficiences cognitives; la perturbation du fonctionnement social et émotionnel; la détérioration de la qualité de vie. Cet article analyse les perturbations de la cognition qui accompagnent le trouble bipolaire; il compare le profil des adultes à celui des enfants et des adolescents pour tenter d'identifier un marqueur neurocognitif de la maladie. **Méthodologie:** Les auteurs ont procédé à une analyse succincte et à une synthèse de la littérature sur la cognition chez les adultes et les enfants. Ils ont interrogé les bases de données *Medline* et *PsychINFO* à partir des mots-clés suivants: *cognition*, *trouble bipolaire, neurocognitif, enfant, adolescent,* et de mots du domaine de la neuropsychologie; ils ont aussi analysé les articles avec lesquels ils étaient familiers et relevé les références pertinentes. **Résultats:** Les auteurs contextualisent les conclusions tirées de la littérature, résument les principaux résultats et jettent les bases des recommandations futures. **Conclusion:** Les adolescents et les adultes présentent des déficits permanents qui reflètent peut-être des traits de la maladie. Les chercheurs devront se concentrer sur ces points et effectuer des tests multimodaux sur des patients jamais diagnostiqués afin d'obtenir des marqueurs biologiques fiables.

Mots-clés: trouble bipolaire, neurocognition, enfants, adolescents

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Introduction

Classic bipolar disorder (BD) is a recurrent, episodic, cyclical illness characterised by episodes of major depression, interspersed with periods of hypomania or mania and periods of relative mood stability called 'euthymia'. Its strong heritability suggests a significant genetic loading. However, the clinical heterogeneity of the disorder remains a constant challenge to diagnosis and research. It is likely that its aetiology, in common with many psychiatric disorders, is varied, combining biological, social and psychological factors. As with many disorders, there is a strong desire on the part of researchers and clinicians to identify a specific 'marker' or diagnostic sign, and in the case of BD, this has been accompanied by a shift in the focus of research towards examining younger populations.

In this article, the literature pertaining to this search for a marker in BD is reviewed, with particular emphasis on juvenile populations.

Genetic studies are increasingly employed in researching neuropsychiatric disorders to assist with determining causality. In BD, findings such as high concordance rates (40-97%) in identical twins, compared with the much lower rates (14%) in dizygotic twins, drive the search for better identification of transporter, as well as susceptibility, genes

(Kieseppa et al. 2004). Genes that have been investigated in BD as potential susceptibility candidates include COMT, DAT and HTR4, amongst others (Kieseppa et al. 2004; Edvardsen 2008). Specific gene loci have been associated with subgroups of patients, such as those who respond to lithium (MacQueen 2005; Consoli 2007), and those with psychotic or suicidal features (Cheng 2006). As yet, however, a single or dominant gene contribution to bipolar disorder has not been identified and studies continue to focus predominantly on the exclusion of specific genes as transporters.

The lack of consensus surrounding the diagnostic boundaries of BD and the lack of a single genetic marker, has resulted in the expansion of studies into a search for endophenotypic markers for bipolar disorder. The definition of an endophenotype has been broadened from that described by Gottesman & Gould (2003), to include a replicable state and trait feature of the disorder. To date, several cognitive impairments, identified in the profiles of adult populations with BD, have already been proposed as endophenotypes. These include sustained attention deficits, difficulties in executive functioning and verbal memory deficits (Clark et al. 2002; Martinez-Aran et al. 2002; Martinez-Aran et al. 2004; Martinez-Aran et al. 2004; Clark et al. 2005; Olley et al. 2005; Malhi et al. 2007). MacMann and Barnett (1997; 1999) have highlighted many of the errors that potentially occur with profile analysis. The strengths and weaknesses of a profile analysis approach are frequently highlighted in relation to breaking down Wechsler scales into their subtest scores (McDermott 1989; Watkins 2005), and the caveats raised by such discussion should be kept in mind when interpreting the neuropsychological profiles of adolescents. Significant examples which relate to the population under discussion include correlation with associated skills (such as language) and motivation to perform.

Recently, Burdick et al (2006) investigated neurocognitive profile, and the potential for this to be a stable BD endophenotype, in a follow-up of 16 patients with schizophrenia and 16 patients with bipolar disorder who were participating in a larger, long term study. In the investigation, patients first completed neuropsychological assessment after 14/15 years of follow-up and they repeated the assessment at 19/20 years follow-up. The test battery used for assessment included measures of executive functioning, attention and short and long term memory. Interestingly, patients with BD were found to demonstrate improved performance in both short and long term delayed free recall and in number of perseverative errors and verbal fluency. No improvement was observed in measures of attention and therefore the authors hypothesised that attention per se may represent a 'stable' marker in bipolar disorder. Attention deficits are certainly found across mood states of bipolar disorder (Brand and Jolles 1987; Trichard et al. 1995; Clark et al. 2002) and may contribute to reduced executive functioning in BD (Sapin et al. 1987; Sweeney et al. 2000; Martinez-Aran et al. 2004; Malhi et al. 2007) as many tests evaluating this domain rely on sustained attention to a stimulus.

Memory deficits have also been consistently found in BD (van Gorp et al. 1999; Krabbendam et al. 2000; Rubinsztein et al. 2000), with verbal memory, in particular, shown to be impaired across mood states (Martinez-Aran et al. 2004; Malhi et al. 2007) and, akin to attention, this clearly warrants further investigation. However, different aspects of memory need to be studied in finer detail, as it has already been proposed that executive function and working and declarative memory may be the most viable endophenotype in subtypes of bipolar disorder, based on a comparison of BD patients with and without psychotic symptoms (Glahn 2006).

Verbal fluency is also compromised in bipolar disorder (Ali 2001), although there are indications that this fluctuates according to mood state (Martinez-Aran et al. 2004). Overall, it appears that verbal fluency, executive functioning (in particular perseveration), memory and selective attention are the domains most impaired in adults with bipolar disorder (Cahill 2007). Findings that these deficits persist even during euthymia (Martinez-Aran et al. 2004; Olley et al. 2005; Malhi et al. 2007) seem to support the proposal that these could serve as trait markers of the illness at least after the initial episode.

A recent meta-analysis has posited that response inhibition and fronto- temporal/fronto limbic cognitive impairments are the most prominent endophenotypic markers of bipolar disorder (Bora 2009). Increasingly, studies are attempting to discern more subtle cognitive impairments in bipolar disorder. Reward processing, sensitivity to negative feedback, short term spatial storage and response consistency have all been found deficient in research studies to date but have not yet been widely replicated across mood states and populations (Yechiam 2008; Roiser 2009).

Efforts to discern an endophenotypic marker in studies of adult BD often run into difficulties when disease related characteristics are considered as putative causes of cognitive deficits (Savitz 2005). For example, it is reasonable to link the long term and wide-ranging use of medication, frequently associated with bipolar disorder, to the cognitive deficits that are observed when patients are undergoing treatment (Donaldson 2003). In addition, bipolar disorder is associated with a high level of comor-

bid substance abuse, particularly cannabis, which, in and of itself, is frequently associated with cognitive impairment (Cahill 2006). Further, disease characteristics that may account for cognitive impairment include symptomatic changes that affect functioning, such as reduced motivation and concentration in the case of depression, and increased disinhibition in mania.

Essentially, as a person with BD gets older, environmental factors and illness-related sequelae, such as scarring and medication effects, begin to exert a stronger influence in parallel with a reduction in the proportional influence of genes. Partly as a result, research aimed at identifying markers of the illness is increasingly examining younger populations, based on the logic that a marker of BD will be more readily identifiable in this age group. The emergence of a genetic loading influencing age of onset has encouraged investigations in this area (Faraone 2004) as has the increased association in preliminary linkage studies of early onset bipolar disorder (Mick 2009)

The Phenomenology of Bipolar Disorder in Children and Adolescents

Clinically, BD usually manifests in adolescence and early adulthood, and therefore an increasing proportion is being successfully identified in under 18-year olds. A recent Spanish study, of rates of diagnosis, estimated that the annual number of youth office-based visits resulting in a diagnosis of BD, increased from 25 visits (per 100,000 population), in the mid-1990s, to 1003 almost a decade later (Lázaro 2007). Such findings correspond with indications that 46-65% of individuals report onset of illness prior to the age of 19 (Lish 1994; Perlis et al. 2006). BD in children and adolescents is often referred to as juvenile bipolar disorder (JBD). However, the diagnosis has raised much controversy, because although children who are identified as having JBD often demonstrate characteristic features of BD such as mood dysregulation, sleep disturbance and anxiety (Faedda et al. 2004), often these arise concurrently with symptoms of other disorders, such as Obsessive Compulsive Disorder (OCD), Conduct Disorder (CD) and, most frequently, Attention Deficit Hyperactivity Disorder (ADHD). Many of the commonly occurring symptoms of JBD are not unique to this illness, with aggression, hyperactivity, irritability and emotional outbursts being among the most typical symptoms (Kowatch et al. 2005; Carlson 2006). Indeed, the comorbidity of ADHD and JBD has been estimated at 85% in prepubescent children, diminishing only to about 50% in adolescents (Kowatch et al. 2005).

Carlson and Meyer (2006) highlight that classic 'manic depression' is rare in young people and that therefore, not surprisingly, lithium has a poor response rate in this group, even in children who have a strong family history of BD. Additional evidence indicating that JBD may be a variant unto itself and particularly treatment refractory is provided by Masi et al (2004) and Kowatch et al (2000) who also found a poor response to conventional mood stabilisers, namely lithium and valproate.

A peak in prevalence of BD has been documented between ages 15 and 19 years, producing what has been termed a 'hazard period' for the emergence of the illness (Weissman 1996). It is possible that this occurs because of increasing vulnerability during this time conferred in part by rapid cognitive and emotional development and the necessary learning of emotional regulation. This creates a tumultuous social and emotional milieu, within which the acquisition of regulatory skills is precarious to begin with, and may be further impeded by mood disturbance. It has been observed that prepubertal cases of bipolar disorder are more often male but that the gender imbalance is redressed during adolescence, intimating that this may be a risk period for girls (Geller 1995; Biederman 2005), but it is likely that this is a function of referral pattern (Youngstrom and Duax 2005). There is increasing acknowledgement of the existence of 'narrow' and 'broad' phenotypes of bipolar disorder in child and adolescent populations, and these have been described by Liebenluft and colleagues in a number of key studies devoted to better characterising these 'sub-types' (Leibenluft et al. 2003; Dickstein 2006). Briefly, narrow phenotype may be considered as replicating the adult criteria for BD with euphoria or grandiosity required to qualify for mania/hypomania, while broader phenotypes include children with behavioural dysregulation, as well as mood disruption.

Many researchers have adopted these groupings. However, equally many have not. Regardless, a variety of cognitive deficits have been reported in adolescents with BD (McClure et al. 2003; Dickstein 2004; McClure et al. 2005) and many of the findings have emerged from studies that have examined samples of both children and adolescents. The results of some of the key studies are considered further in the following sections, with a view to identifying means of synthesising findings to fuel future research, improve diagnosis and achieve earlier identification of BD.

Method

Pertinent literature was identified and retrieved using Medline and PsycINFO searches on the basis of selected keywords, namely 'juvenile' ,'child' , 'adolescent', 'bipolar disorder', 'cognition', 'neurocognitive', 'executive', 'memory', 'learning', 'verbal', 'problem-solving' and 'atten-

tion'. All of the studies included either tested patients where they were euthymic or did not specify mood state. Relevant articles and information were collated with respect to neurocognition in BD. In addition, the reference lists from specialised articles and book chapters were examined for relevant studies and, where appropriate, included in the review. Literature presenting cognitive findings in regard to juvenile BD is reviewed in broad terms and is contextualised so as to provide a basis for discussion of the likelihood of putative cognitive deficits warranting further consideration as an endophenotype.

Results

The cognitive domains thought to be compromised in populations of children and adolescents with BD, based on studies of these populations, are summarised in Table 1.

The literature examining neurocognition in child populations with BD indicates impairment across several domains, including verbal fluency, executive functioning, attention and working memory (Doyle 2005; Pavuluri et al. 2006). Further, verbal learning and memory deficits have been found (McClure et al. 2005; Bearden 2006), along with reduced cognitive flexibility, impaired pattern recognition and a lower performance IQ (PIQ) on the Wechsler Intelligence Scales for Children (WISC-III, (Wechsler 1991)) which is usually considered a good measure of non-verbal intelligence (Dickstein 2004; McCarthy et al. 2004).

In a study of non-medicated participants with BD that compared patients with controls, the researchers found deficits in problem solving, short term memory for names and faces, visual attention, visual motor speed and language (Castillo et al. 2000). Importantly, another study identified general intellectual functioning to be compromised in a group of adolescents with BD (Shiratsuchi 2000). However, both patient groups in these two studies were significantly unwell, with high comorbidity in the former and psychosis in the latter. More recently, Henin et al investigated a group of unmedicated 6-17 year olds with JBD + ADHD, and compared them to a group with ADHD and another with neither ADHD nor JBD. Impairments were evident in both the ADHD and the JBD + ADHD groups. However, the magnitude of impairment was comparable across the two groups, to that found in participants with JBD alone, with a slower performance on a single measure (that of processing speed) differentiating them (Henin 2007).

Attention deficits are consistently reported in studies of JBD (Doyle 2005; Pavuluri et al. 2006) and this holds true even when attention is manipulated as in, for example, a study by Ernst et al (2004), in which adolescents with bipolar disorder were found to be more sensitive to negative feedback than a control group. Similarly, a mixed sample of children and adolescents appeared to have more difficulty than controls in an object alternation task that required the ability to inhibit a previously reinforced response (McClure et al. 2005).

Discussion

Juvenile bipolar disorder, while increasingly gaining attention and undergoing intense investigation, remains poorly understood due to its clinical heterogeneity, a lack of diagnostic consistency across investigations and the shifting developmental period during which it emerges. Nonetheless, the nascent literature provides preliminary evidence that suggests there may be similar cognitive deficits in juvenile and in adult populations with BD and that these, either individually or collectively, insinuate potential BD endophenotypes that warrant further exploration and consideration.

Wide-ranging deficits have been found in many studies of JBD (Dickstein 2004; Doyle 2005; Olvera 2005; Bearden 2007). However, others suggest a more specific pattern of deficits involving, in particular, verbal memory compromise (Glahn et al. 2005; McClure et al. 2005; Pavuluri et al. 2006). Pavuluri et al (2006) have argued that their findings of cognitive deficits in an investigation of unmedicated adolescents with bipolar disorder, compared with both medicated adolescents with bipolar disorder and healthy individuals, represent a 'trait' marker of bipolar illness. The presence of these deficits, seemingly irrespective of mood state and medication status, strengthens consideration of these as potential signals of bipolar illness. While the pattern of deficits is similar for both JBD and adult BD, to date there have been fewer studies of JBD samples and the studies that have been conducted have often focused on attention and memory.

Limitations of many of the studies of cognition in BD and JBD

Comorbidity

Many participants in the studies reviewed in this paper presented with comorbidities, most commonly ADHD. The study by Pavuluri et al (2006), highlighted that patients with comorbid ADHD have more severe deficits in the domains of attention and executive function, although there has been some evidence that continuous performance tasks do not reliably demonstrate this difference. Further, it has also been suggested that ADHD may account for much of the cognitive impairment observed in studies of JBD to date (Henin 2007).

Heterogeneity

A major difficulty in identifying an endophenotype is amply exemplified by the populations involved in BD

Table 1. Neuropsychological domains found to be impaired in cognitive studies of children and adolescents with BD

Studies	Tests Used	Attention	Memory	Executive Functioning	Visuospatial Abilities	Facial Recognition	Academic Difficulties
Castillo et al 2000	Woodcock-Johnson Psychoeducational Battery-Revised NEPSY	☐		☐	☐	☐	
Shiratsuchi et al 2000	WISC-III						☐
Robertson et al 2003	WISC-III WCST CCPT	☐					
McClure et al 2003	Standardised photos of happiness, sadness, anger and fear					☐	
Lagace et al 2003	WRAT-R2 PIAT						☐
McCarthy et al 2004	WISC-III				☐		
Dickstein et al 2004	CANTAB			☐	☐		
Doyle et al 2005	WISC-III subtests WRAT-III SCWT WCST RCFT CVLT-II & CVLT-C CPT	☐	☐				☐
McClure et al 2005	Subtests from: Comprehensive Assessment of Spoken Language, Diagnostic Analysis of Nonverbal Accuracy Scale, Test of Language Competence			☐		☐	
Glahn et al 2005	CVLT-C TONI		☐				
Pavuluri et al 2006	WASI TMT WMS-III CVLT-C Subtests from UPenn Computerised Battery	☐	☐	☐			
Bearden et al 2007	TONI D-KEFS WISC subtests		☐	☐			
Henin et al 2007	WISC subtess CVLT-C	☐					

Abbreviations used: WISC-III; Wechsler Intelligence Scales for Children (1). Version 3, WRAT Wide Range Achievement Test version 2 (2), PIAT Peabody Individual Achievement Test (3), WCST; Wisconsin Card Sort Test (4), CCPT; Conner's Continuous Performance Test (5), CANTAB; Cambridge Automated Neuropsychological Test Battery (6), SCWT; Stroop Colour Word Test (7), RCFT; Rey Complex Figure Test (8), CVLT; California Verbal Learning Test (9), TOMAL; Test of Memory and Learning (10), TONI; Test of Non-Verbal Intelligence (11), WASI Wechsler Abbreviated Scale of Intelligence (12), TMT, Trail Making Test (13), WMS, Wechsler Memory Scale(14).

Key:
☐ ☐ indicates domains investigated by the study.
☐ indicates a deficit was found

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studies. Clinical heterogeneity is the norm, in regard to age, comorbidity and diagnosis, making it difficult to conclude with any certainty that any putative deficits identified relate with specificity to BD. At different points in time, symptoms of a comorbid disorder may be more salient than the characteristic symptoms of BD, which would feasibly contribute to invalid comparisons. The potential for confusion in investigation of heterogenous samples is further demonstrated when considering the investigation by Rucklidge (2006). This study showed that while a narrower age band of adolescents with bipolar disorder performed more like controls on a number of measures investigating memory, attention and control, a comparison ADHD group were more impaired, and the most impaired group of all were participants with BD I or II + ADHD.

The extent to which children with a diagnosis of bipolar disorder mature into adults with the disorder remains uncertain. The typical presentation of children with bipolar disorder includes longer episodes and ultradian cycling (Geller et al. 2004; Geller 2005). but with increased uncertainty regarding the boundaries of episodes in adults (Akiskal 2007) it is difficult to say with conviction that the same disorder persists across both populations. A recent investigation of juvenile bipolar disorder (Geller 2008) limited diagnosis to those children displaying a cardinal symptom such as mania or grandiosity. Follow up after eight years, when half the sample had reached the age of 18, indicated levels of mania supporting continuity of illness between adult and childhood. As further studies emerge, which investigate cohorts of children with bipolar disorder, there seems utility in clearly delineating and perhaps limiting inclusion criteria in an effort to ease comparability of different age groups.

In addition, our own research in this area indicates that there is merit in considering narrower age bands within JBD populations. In a current investigation, we have limited our recruitment to 15-18 year olds, as this population has several characteristics that simplify investigations. Firstly, externalising behaviour problems such as ADHD have often resolved in this group and hence the diagnosis of BD is simplified. In addition, simply by virtue of age, these adolescents have had the most, and a similar, time for brain maturation to occur. Although the data remain in the early stages, the indications are that there will be a similar pattern of deficits in attention, memory and planning/ problem solving.

Finally, in terms of clinical heterogeneity, there is the possibility that studies are not consistent in whether they test euthymic or mood disordered participants, or whether the same criteria are employed to describe euthymia, which may also limit comparability across different samples.

Nature of tests used

Emergent literature also reflects the need for refined tests to be used with juvenile populations as many of the tests used currently either assess scholastic performance, which may vary due to a range of psychosocial factors, or assess several abilities at once, such as sustained attention and cognitive flexibility. Of more value, however, is assessment of a *specific* ability in relation to a hypothesis, for example assessing impulsivity or decision-making. Computerised tests, such as the CANTAB, are likely to generate useful comparisons for a variety of reasons, the test material is presented in a comfortable milieu for children and adolescents and in addition, is used in both child and adult populations thereby enabling direct comparisons.

Lack of knowledge about family members

There is also value in researching the neurocognitive performance of family members, both with and without bipolar disorder (Antila 2007), to ascertain the heritability of the deficits associated with the disorder and, alongside this, the continuation of genetic investigations will help

establish a link between gene and gene expression via endophenotypes. Comparison with other psychiatric illnesses is an essential component of these investigations, as many genes and deficits overlap across BD, schizophrenia and ADHD. For this reason, recruitment across numerous sites and centres would be beneficial, as it would boost the numbers of candidates entering studies. In addition, standardising testing would maximise the comparability of data, permitting more specific inferences and wider generalisability of findings.

Neurobiological factors

A further caveat, in drawing strong conclusions with regard to adolescent patterns of performance as evidence of endophenotype, relates to the ongoing development of neurological structures during this time. Rapid change in the maturing brains of adolescents makes it difficult to conclude with certainty that many of the differences observed, in both neuroimaging and neuropsychological investigations, are not artefacts due to an immature brain, with underdeveloped pre-frontal regions. Other brain structures are also undergoing change during this period. For example, amygdala and hippocampal volumes have been shown to increase during adolescence alongside a reduction in caudate volume (Blumberg et al. 2003). There are also whole-brain changes associated with arborisation and pruning of cells during maturation (Chechik 1999).

Summary and Conclusions

To date, deficits that emerge in samples of younger people with bipolar disorder seem to reflect involvement of a broad sweep of cognitive domains, including sustained attention, verbal memory, learning and planning, and visuospatial skills. Impairment in these areas is also found in adults with bipolar disorder, suggesting there is utility in further investigating their potential to represent early expression markers or endophentypes of bipolar disorder. Further, there is a lack of long term follow up studies in bipolar disorder giving consideration to the expression of cognitive compromise through the course of illness. Such compromise is likely to effect emotion regulation in an ongoing way, hence influencing prognosis (Green 2006).

Such methodological enhancements would provide useful longitudinal data but, in addition, investigations that are ongoing require a narrower focus to ensure that findings relate to specific expressions of a disorder, rather than heterogenous compromise associated with a variety of illnesses. Current research is beginning to reflect this, with recent studies investigating processes such as attentional bias to threat in adolescents with bipolar disorder, with or without comorbid anxiety disorders (Brotman 2007), and ongoing research into the social and emotional implications of cognitive compromise (Malhi et al. 2007). Adopting more stringent methodologies in investigation, while acknowledging the clinical heterogeneity that is an endemic facet of BD, seems the only way to progress the search for better characterisation of key trait deficits to which will ultimately improve our diagnosis, understanding and treatment of this profoundly debilitating illness.

Acknowledgements/Conflict of Interest

The authors have no financial relationships or conflicts to disclose.

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