Clinical implications of cognitive function in bipolar disorder

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Abstract: In recent years there has been increased interest in cognitive function in bipolar disorder (BD) as a means of understanding and exploring biological mechanisms relating to predisposition, disease expression and outcome. Despite significant methodological differences between studies we can begin to discern meaningful patterns from existing data. The evidence reviewed suggests that: (a) premorbid cognitive dysfunction is not a dominant feature of BD; in contrast to other severe psychiatric conditions, enhanced cognitive function may be a risk marker for BD; (b) in BD patients with established syndromal disease, trait-related cognitive impairment is reliably seen in the speed of information processing, verbal learning and memory and response inhibition; (c) cognitive function appears to remain stable post-disease onset in the majority of patients although the risk of dementia in old age is increased; (d) cognitive impairment is a key predictor of functional outcome in BD. These findings underscore the importance of cognition in BD as a marker of neural integrity across all phases of the illness and as a therapeutic target in disability reduction.

Keywords: bipolar disorder, cognition, disease expression, executive function, general intellectual function, longitudinal, memory, outcome, premorbid

Introduction

Bipolar disorder (BD) is characterized by episodic pathological mood alterations that can be manic, depressive or mixed [American Psychiatric Association, 1994]. In the last 10 years there has been increased emphasis on the role of cognition in BD attested by the exponential growth in the number of relevant publications. A significant turning point was the realization that cognitive impairment was a replicable feature of BD with measurable changes being present both during episodes and in remission [Quraishi and Frangou, 2002]. Subsequent evidence for cognitive alterations, albeit of small to modest degree, in unaffected first-degree relatives of BD patients [Glahn *et al.* 2010; Arts *et al.* 2008] reinforced the notion that cognition may inform about the biological mechanisms relating to genetic risk and disease expression. More recently, the focus has been on the role of cognition as a predictor of functional outcome in BD patients [Wingo *et al.* 2009a]. The present review is focused on the relationship between cognition and disease expression along three dimensions: during the premorbid phase, after disease onset

and as a determinant of psychosocial function throughout the course of the illness. The aim is to not be exhaustive in our review, but to highlight key studies that have contributed to our current understanding of the relationship between cognition and BD and identify areas of uncertainty that could inform future research.

Cognitive function as a premorbid risk factor for BD

A number of epidemiological studies, based on population-based cohorts, have examined premorbid cognitive function in BD. The advantage of this approach is that cognitive data are collected prospectively and are unbiased by recall and attributions based on outcome. On the other hand, cognitive evaluation in epidemiological studies is rarely detailed but based mostly on estimates of general intellectual function often using proxy measures such as academic performance. Further potential drawbacks with regards to affective disorders relate to case identification: first, ascertainment based on hospital contacts or admissions is likely to identify more severe and less representative cases; and, second, BD has

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rarely been examined separately but has been variably grouped within broadly defined clusters of patients with affective disturbances.

Birth cohort studies

One of the first studies in the field by van Os and colleagues was based on the British 1946 National Survey of Health and Development [van Os *et al.* 1997]. In this study, 5362 individuals born in the period 3–9 March 1946 were followed from childhood to adulthood. Educational test scores at the ages of 8, 11 and 15 years were used as a measure of cognitive function. Psychopathology was assessed at ages 13 and 15 using teachers' questionnaires and, at age 36 and 43, using the Present Status Examination and Present Symptoms Frequency. The study adopted a very broad definition of clinical outcomes that encompassed any childhood affective disturbance (CAD) and any affective disorder in adulthood. Lower test scores at ages 8, 11, and 15 were associated with both childhood and adult affective disturbance.

The National Child Development Study birth cohort included 98% of all births in England, Scotland and Wales during the week 3–9 March 1958 [Jones and Done, 1997; Done *et al.* 1994]. Individuals were followed up four times in 1965, 1969, 1974 and 1981 (ages 7, 11, 16 and 23) to monitor their development. In 1974 and 1986 all subjects who had hospital treatment for psychiatric conditions as adults were identified. Diagnoses of schizophrenia, affective psychosis (including mania, psychotic depression and depression with psychomotor retardation) and neuroses were derived from case notes. Differences in premorbid educational achievement were small to modest for those with affective psychosis and neurosis, and in the case of the latter they were attributed to social disadvantage.

Data from the Northern Finland 1966 birth cohort [Isohanni *et al.* 1998] included 11,017 individuals of whom 383 were diagnosed with schizophrenia, other psychoses or nonpsychotic disorders as recorded in the Finnish Hospital Discharge Register at 28-year follow up. School performance was used as a proxy for intellectual ability and was measured in two ways. First, at the age of 14 children were classified as 'not in normal class' if below their age-appropriate class or in a special school and 'in normal class' if in a class appropriate for their age. Second, at the age

of 16 years, results from school marks were extracted from national records. The proportion of those 'not in normal class' was higher for all psychiatric diagnoses and lower school marks at age 16 were noted in those with nonpsychotic (including affective) disorders.

Based on these earlier studies, it was assumed that some degree of cognitive dysfunction may indeed be a premorbid feature of affective disorders, including BD. However, findings from the Dunedin Multidisciplinary Health and Development Study have challenged this view. In this study, a cohort of 1037 children born in Dunedin, New Zealand, between April 1972 and March 1973, was followed up for 32 years [Koenen *et al.* 2009; Cannon *et al.* 2002]. Cognition was assessed between the ages of 3 and 11 years using the Reynell Developmental Language Scales, the Auditory Reception and Verbal Expression subtests of the Illinois Test of Psycholinguistic Abilities, the Peabody Picture Vocabulary Test, the Stanford–Binet Intelligence Scale and the Wechsler Intelligence Scale for Children—Revised. At the age of 26 years, the National Institute of Mental Health Diagnostic Interview Schedule was administered to 976 of the still living cohort members and three diagnostic groups were established, namely schizophreniform disorder, manic episodes and anxiety/depressive disorders. Individuals who later developed mania, anxiety or depressive disorder showed no significant differences in IQ or language measures compared with the healthy comparison group [Cannon *et al.* 2002]. However, after reassessment at age 32, higher childhood IQ was found to be significantly associated with mania [Koenen *et al.* 2009].

These results resonate with findings from a Swedish whole-population cohort study where educational scores of all individuals completing compulsory schooling between 1988 and 1997 were used as a proxy for intellectual function [MacCabe *et al.* 2010]. In this cohort, cases of BD with onset between the ages of 17 and 31 years were identified through the Swedish National Hospital Discharge Registry. Compared with individuals with average scholastic performance, those with the poorest grades were twice as likely to develop BD but the risk was even higher in those with an excellent academic record.

Conscript studies

Mason was the first to notice in a very early cohort study of US Army recruits that better general intellectual function was associated with higher risk for BD [Mason, 1956]. Several subsequent and methodologically more rigorous studies have either failed to find an association between general intellectual function and BD or have reported higher risk for the disorder in individuals with the highest cognitive test scores.

David and colleagues studied a cohort of approximately 50,000 18-year-old males conscripted into the Swedish Army in 1969–1970 [David *et al.* 1997]. Tests of verbal and visuospatial abilities, general and mechanical knowledge were aggregated into an overall standardized general intelligence score ranging from 1 to 9, corresponding to specific IQ bands. At 13-year follow up, 195 individuals with schizophrenia and 192 with nonschizophrenic psychosis were identified using the Swedish National Register of Psychiatric Care. A linear relationship between low IQ and psychiatric outcome was found for schizophrenia only. At the 27-year follow up, the Swedish National Hospital Discharge Registry was used to identify four diagnostic groups, namely schizophrenia (including schizoaffective disorder), other nonaffective psychoses (such as substance-induced psychosis and delusional disorder), BD and severe depression [Zammit *et al.* 2004]. Lower premorbid IQ was associated with increased risk for all disorders except BD.

A similar finding was reported by Reichenberg and colleagues who examined an unselected population of 16–17-year-old Israeli males assessed by the Israeli Draft Board Registry between 1985 and 1991 [Reichenberg *et al.* 2002]. Cognition was assessed using the Otis-R, a modified verbal intelligence test, Similarities-R, a revised version of the ‘similarities’ subtest of the Wechsler Adult Intelligence Scale, Arithmetic-R, and a modified version of Raven’s Progressive Matrices. These were combined to yield a total score reflecting general intellectual functioning. Cases were identified using data from the Israeli National Psychiatric Hospitalisation Case Registry covering the period from 1970 to 1995. Healthy comparison subjects were selected from individuals who attended the same school as the patients. Unlike patients with schizophrenia and schizoaffective disorder, no significant

premorbid intellectual functioning impairments were found in BD patients.

The absence of premorbid cognitive dysfunction in mood disorders was further supported by Mortensen and colleagues in a study of 3289 male army volunteers derived from the Copenhagen Perinatal Cohort of 9125 individuals born between October 1959 and December 1961 [Mortensen *et al.* 2005]. General intellectual ability in these individuals was assessed by the Danish military draft board with the Børge Priens Prøve (BPP) test. The Danish Psychiatric Central Register was used to identify patients admitted between 1994 and 1999 with a diagnosis of schizophrenia and schizotypal disorder, other psychotic disorders, mood disorders (including BD), neuroses, adjustment disorders, personality disorders, alcohol and other substance-abuse disorders. Low premorbid scores were associated with increased risk for all psychiatric conditions apart from mood and neurotic disorders.

Tiihonen and colleagues partly replicated this finding in a study of 195,019 military conscripts born between 1962 and 1967 who served in the Finnish Defence Forces between 1982 and 1987 [Tiihonen *et al.* 2005]. In this study, cognition was assessed using the Finnish Defence Forces Basic Ability Test which comprises verbal, arithmetic and visuospatial reasoning (analogous to Raven’s Progressive Matrices) subtests. The Finnish Hospital Discharge Register was then used to identify cases with schizophrenia, bipolar disorder, and other psychoses after a mean follow-up period of 7 years. Premorbid visuospatial reasoning was impaired in all three disorders. However, there was a 12-fold risk of BD in those with the highest performance scores in the arithmetic subtest.

In summary, a large body of evidence suggests that, on balance, premorbid impairment in measures of general intellectual ability is not a key feature of mood disorders. There is even a suggestion that when BD is considered independently a pattern of enhanced premorbid cognitive ability is observed. Although further investigations are needed to establish the validity of this observation, this link between higher cognitive function and disease risk appears unique to BD as nearly all other psychiatric conditions have been associated with variable degrees of premorbid cognitive impairment.

Cognitive function and the extended clinical phenotype of BD

It is now firmly established that BD is associated with persistent cognitive deficits. There has been an exponential proliferation in the number of studies reporting on cognitive function in BD. For the purpose of this review we focus on the pattern of results emerging from meta-analytic studies, when available, as they are currently the most informative source regarding the profile of cognitive dysfunction in BD and its relationship with clinical variables. Additional consideration is given to individual studies that provide key information pointing to new avenues of research.

Cross-sectional studies

Recent meta-analyses [Bora *et al.* 2009; Stefanopoulou *et al.* 2009; Arts *et al.* 2008; Torres *et al.* 2007; Robinson *et al.* 2006] have consistently identified trait deficits of moderate to large effect size in processing speed, verbal learning and memory, attention, and in measures of executive function particularly abstract formation and response inhibition. Significant moderator variables include residual, primarily depressive symptoms [Torres *et al.* 2007], number of episodes [Martínez-Arán *et al.* 2004a, 2004b] and duration of illness [Robinson and Ferrier, 2006]. Evidence from elderly BD patients is currently limited by the small number of available studies which have mostly employed dementia screening tools (reviewed by Young *et al.* [2006]). However, it appears that although the majority of elderly BD patients show little or no deficit compared with age-matched controls [Martino *et al.* 2008; Nunes *et al.* 2007] the rates of dementia in this group are higher than those in the general population [Kessing *et al.* 2008; Nunes *et al.* 2007].

The effect of medication on cognition remains an unresolved issue, although any such effect is unlikely to account fully for the cognitive changes observed in BD. A recent review [Wingo *et al.* 2009b] suggested a minor but measurable negative effect of lithium treatment on memory and creativity but at the same time there is evidence that long-term lithium treatment may in fact reduce the risk of dementia later in life [Kessing *et al.* 2008; Nunes *et al.* 2007]. The contribution of antipsychotics to cognition in BD is also controversial with evidence of negative [Donaldson *et al.* 2003] as well as beneficial effects [Macqueen and Young, 2003] on measures of executive function.

Longitudinal studies

To date there have been three longitudinal studies of cognitive function in BD. Engelsmann and colleagues focused on verbal memory function in 18 BD patients over a 6-year period and found no evidence of progressive changes [Engelsmann *et al.* 1998]. Balanza-Martinez and colleagues used a wider cognitive battery that included measures of general intellectual ability and tasks of executive function (verbal fluency, the Stroop Colour Word Test and the Wisconsin Card Sorting Test) in addition to verbal memory [Balanza-Martinez *et al.* 2005]. Their sample of 15 BD, type I, patients was followed up over 3 years. During this time, there was no evidence of deterioration with the possible exception of a small increase in perseverative errors in the Wisconsin Card Sorting Test, which is considered sensitive to prefrontal cortical dysfunction. A similar pattern of stability over time was reported by Mur and colleagues who examined executive function, attention, processing speed, verbal and visual memory in 33 lithium-treated BD patients over a 2-year period [Mur *et al.* 2008]. These findings resonate with the results of Sarnicola and colleagues [Sarnicola *et al.* 2009] who used a quasilongitudinal design to investigate the effect of illness duration in 71 BD patients assessed using the Wechsler Adult Intelligence Scale, Revised, the Wechsler Memory Scale, third edition, the Hayling Sentence Completion Task, a measure of response inhibition, and the Wisconsin Card Sorting Test. Despite a mean duration of illness of 19 years there was no differential age-related change in any measure of cognitive function in patients compared with matched healthy controls. Although this may be true for the majority of BD patients, as discussed already, a subgroup of elderly patients may be more susceptible to dementia.

In summary, cross-sectional studies support the view that cognitive impairment can be considered part of the extended phenotype of BD. These deficits are of small-to-medium effect and seem to be relatively specific to particular domains. Existing evidence suggest that the pattern of cognitive deficits after disease onset remains largely stable. However, data from first-episode BD patients are not available and therefore the possibility of cognitive deterioration during the early stages of syndromal expression cannot be excluded. In fact, cognitive deterioration associated with disease onset would reconcile the

postonset findings of impairment with the pre-morbid evidence of normal or even superior cognitive function. Studies from older patients suggests that BD is associated with higher rates of dementia [Kessing *et al.* 2008; Nunes *et al.* 2007] than the general population which underscores the need for a lifelong view on the interaction between disease mechanisms and cognition.

Cognitive function as a predictor of outcome in BD

BD is associated with substantial functional impairment as it affects patients' personal and occupational function even when during periods of clinical remission [Sanchez-Moreno *et al.* 2009]. For example, around 62% of BD patients who participated in a longitudinal study by the Stanley Foundation Bipolar Network (SFBN) reported moderate-to-severe functional impairment [Suppes *et al.* 2001]. In this study, approximately 50% of patients reported working below qualifications, part time, in a limited capacity (e.g. volunteer) or were unable to work; in addition, nearly 40% of patients had very limited annual income despite high (college degree or above) educational attainment. Striking levels of morbidity have also been noted in patients' personal relationships and ability to live independently; up to 23% of BD patients never marry and between 20% and 60% live with family members (as reviewed by Huxley and Baldessarini [2007]).

Clinical factors such as severity, chronicity and residual symptoms have an influence on functional impairment in BD but do not account fully for it [Gyulai *et al.* 2008; Martínez-Arán *et al.* 2007; Frangou, 2002]. STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) is the largest and most recent study to examine the contribution of key clinical variables to functional recovery [Gyulai *et al.* 2008]. Persistent depressive symptoms emerged as the most important predictor of poor outcome but 40% of the variance remained unaccounted for suggesting that explanatory models of the functional outcome in BD that are focused on clinical variables only do not capture the full range of possible predictors. These findings have shifted research interest towards cognitive dysfunction as the potential 'missing link' mediating psychosocial disability in BD (reviewed by Wingo *et al.* [2009a]).

In cross-sectional studies, memory deficits [Mur *et al.* 2009; Martínez-Arán *et al.* 2004a, 2004b, 2007] as well as executive function impairment [Goswami *et al.* 2006; Zubieta *et al.* 2001] have been consistently associated with lower psychosocial functioning. Recent longitudinal studies suggest that baseline cognitive impairment is a better predictor of future psychosocial functioning than clinical symptoms. Jaeger and colleagues [Jaeger *et al.* 2007] were amongst the first to examine the association between cognitive function at baseline and functional outcome 12 months later in a sample of 78 patients with BD, including BD type II and BD not otherwise specified. Attention and verbal fluency emerged as significant predictors even after controlling for residual symptoms. The same conclusions were reached by Martino and colleagues in a smaller sample of 35 patients with BD type I who were also followed up for a period of 12 months [Martino *et al.* 2009]. Using a different cognitive battery, global cognitive function and visuomotor speed were identified as predictors of outcome at 12 months in a sample of 43 patients with BD type I [Tabarés-Seisdedos *et al.* 2008]. The most recent study by Bonnín and colleagues focused on a sample of 32 subjects who met criteria for BD type I or II and had an extensive cognitive evaluation at baseline [Bonnín *et al.* 2010]. At 4-year follow up, they were interviewed with the Functioning Assessment Short Test (FAST) to assess functional outcome. Two measures of cognitive function, namely digit backwards and free delayed recall, contributed significantly to the variance in terms of functional outcome.

In summary, there is general agreement that both cognitive and clinical variables make an important independent contribution to the functional recovery of patients with BD. However, several problems and questions still need to be addressed.

First, to date, studies have used global ratings of outcome and have not examined how specific cognitive domains may relate to specific domains of functional (e.g. vocational or interpersonal) outcome. Second, real-world performance has not been explored and functional outcome has simply been based on self-report. Third, current evidence fails to provide an evidence-based framework for developing interventions. This is primarily because existing studies have not attempted to model the strength and independence (or otherwise) with which each cognitive

domain contributes to different aspects of patients' outcome and their relationship with measures of clinical severity. Fourth, the diversity of cognitive test batteries used in individual studies hinders the generalizability of the findings with regards to cognitive predictors of outcome in BD.

Clinical implications

At the present time, the literature on cognitive function in BD presents us with several challenges in the way we conceptualize the relationship of cognition to symptomatic disease expression.

Can premorbid cognitive function help predict BD?

The evidence presented here argues that BD, unlike most other major psychiatric conditions, is not associated with premorbid cognitive deficits [MacCabe *et al.* 2010; Koenen *et al.* 2009]. There is even a suggestion that the premorbid function of individuals who later develop BD is better than the normative average at least in some cognitive dimensions or skills. However, the predictive value of these observations appears low and therefore of no utility for primary prevention.

Is cognitive impairment of diagnostic value in BD?

The overwhelming weight of evidence suggests that the difference in any cognitive test measure or domain between BD patients and controls [Bora *et al.* 2009; Arts *et al.* 2008; Torres *et al.* 2007; Robinson *et al.* 2006] and between BD patients and those with other psychiatric disorders [Stefanopoulou *et al.* 2009] is of small-to-medium effect size. Therefore, most patients' performance across a number of cognitive tests would fall within one standard deviation (SD) of the normative mean [Stefanopoulou *et al.* 2009]. This suggests that using a cut-off of 1SD would classify the majority of BD patients as unaffected and a cut-off of 2SD would miss all BD patients. This would apply even to elderly BD patients whose cognitive profile in general appears comparable to that of younger patients [Martino *et al.* 2008]. Therefore, it is unlikely that cognitive measures be used to establish a 'point of discontinuity' that could serve as a diagnostic criterion for BD.

Are measures of cognition useful in understanding the pathophysiology of BD?

There are two key issues to be considered here. First, the evidence discussed points to a common onset of cognitive dysfunction and syndromal symptoms. In fact, the close link between level of affective psychopathology and cognitive impairment is one of the most replicated observations in BD [Martínez-Arán *et al.* 2004b; Goldberg *et al.* 1993]. This suggests the possibility that the neural circuitry involved in the modulatory control of emotions may overlap with brain regions implicated by the cognitive evidence. In this aspect, harmonizing data collection using a standardized cognitive battery [Yatham *et al.* 2010] would greatly enhance our ability to identify those cognitive processes that are most consistently abnormal in BD.

Second, the evidence presented hints at possible pathophysiological heterogeneity. The risk for BD appears increased both at the lower and higher end of the spectrum of academic performance during the premorbid phase of the disorder [MacCabe *et al.* 2010]. At the same time, data from older adults suggest that BD is a risk factor for dementia [Kessing and Nilsson, 2003]. It is therefore important to explore whether significant cognitive impairment either premorbidly or after disease onset may be a marker for a particular subgroup of patients.

Are measures of cognition useful in the treatment of BD?

The possibility that cognitive decline is associated with the onset of syndromal disease highlights the value of early recognition and intervention in BD. Furthermore, as existing research suggests that the degree of cognitive dysfunction in BD increases with each significant mood episode [Kessing and Andersen, 2004] early intervention in BD should be viewed as a key priority for service development.

The relationship of cognitive impairment to functional outcome in BD highlights its significance as a treatment target; it also directs attention to the potential neuroprotective effects of existing medication, such as lithium, and encourages the development of new pharmacological and psychological interventions.

Concluding remarks

The examination of cognition in BD provides important information about the integrity of

brain function before and after disease onset. It is however of questionable usefulness in primary prevention or as a diagnostic criterion. Given the link between cognitive impairment and functional outcome, therapeutic interventions that target cognitive impairment may be helpful in reducing the significant disability associated with BD.

Conflict of interest statement

The authors declare they have no conflicts of interest in writing this manuscript.

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