

Cognitive impairment in bipolar affective disorder: implications for the bipolar diathesis[†]

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Kraepelin separated manic–depressive illness (bipolar disorder) from dementia praecox (schizophrenia) on the basis that those suffering from the former tended to experience full remission, whereas the latter did not. However, although there may be qualitative differences in the remission state of these two conditions, there is accumulating evidence that recovery in bipolar disorder is not complete. Persistent psychosocial difficulties and cognitive deficits are common in patients with bipolar disorder even in euthymic or asymptomatic states (Scott, 1995; Ferrier *et al*, 1999). The nature of the latter is the focus of much research and debate and in this editorial we comment on two recent key papers in this area.

RECENT KEY PAPERS

The case–control studies by Cavanagh *et al* and Clark *et al* (this issue) lend support to the growing consensus of a persistent cognitive syndrome in patients with bipolar disorder. Both studies report that retrospectively verified euthymic patients with bipolar disorder show neurocognitive deficits on a task of verbal learning and memory. However, Clark *et al* (2002, this issue) demonstrated that these deficits disappear once residual affective symptoms are controlled statistically. Conversely, although Cavanagh *et al* (2002, this issue) report that patients' performance on tests of executive (frontal) function remains relatively intact (despite failing to control for residual affective symptoms), Clark *et al* report that their cohort of euthymic patients with bipolar disorder exhibit persistent deficits in spatial working memory, set-shifting and sustaining attention. Only this latter deficit remained when residual affective symptoms were controlled for.

Both studies found a negative correlation between the number of previous manic episodes and verbal learning. Clark *et al* found that performance in this domain also was related inversely to the time since the first episode and the number of depressive episodes. These clinical indices also showed similar significant relationships with sustained attention. It is noteworthy that Cavanagh *et al* computed correlations only for neuropsychological indices that illustrated between-group differences on univariate testing, whereas Clark *et al* conducted correlations on selected variables across all neuropsychological tasks and the clinical indices as an exploratory exercise. This differential analytical strategy is likely to account for the more numerous significant correlations reported in the Clark *et al* study.

In summary, although both papers suggest that the cognitive deficits worsen with severity/progression of illness, their basic findings are at variance. This variability can be accounted for by the lack of control for residual symptoms in the Cavanagh *et al* study, although it should be noted that the mean affective scores are very low in that sample.

STATE OF THE SCIENCE: GLOBAL OR SPECIFIC?

Published studies have implicated virtually every major cognitive domain in bipolar diathesis (Martínez-Arán *et al*, 2000), but the majority of these studies are confounded by their failure to control for residual affective symptoms. As illustrated by Clark *et al* (2002, this issue) and previously by Ferrier *et al* (1999), most deficits can be accounted for by residual depressive symptomatology. Thus, only those studies that have exerted adequate control over this confound are considered here.

To our knowledge there are five published studies that meet this criterion and such studies suggest that the cognitive profile of bipolar disorder is characterised by persistent deficits in *either* mnemonic or executive abilities, or a combination of these two functions.

Rubinsztein *et al* (2000) observed impaired visuospatial recognition memory in the face of relatively intact executive function in their bipolar cohort. Because declarative memory tasks are putative indices of the temporo-hippocampal memory system, they consider that bipolar disorder is characterised by a trait abnormality in temporal lobe functioning. However, although these authors found no difference between patients' and controls' residual depression scores as assessed by the Beck Depression Inventory (Beck *et al*, 1961) at test, they failed to assess residual manic symptomatology across both groups.

Conversely, Ferrier *et al* (1999) observed a specific deficit in the executive control of working memory in euthymic patients with bipolar disorder when residual depressive symptomatology was covaried for, and suggested that their findings may reflect frontal lobe damage or disruption of fronto-subcortical or mesolimbic circuitry. Such findings are in accord with those reported by Clark *et al* (2002, this issue). Similar findings were reported by Thompson *et al* (2001a,b) in prospectively verified euthymic patients with bipolar disorder who were matched with controls on both clinician- and self-rated mood ratings of depression and mania at test. Thompson *et al* also utilised different executive paradigms across their two studies, suggesting that the deficit was not task-specific.

Finally, in a separate investigation Thompson *et al* (2000) reported deficits in both verbal learning and executive function in prospectively verified euthymic patients with bipolar disorder whose mood was no different from that of controls on standard clinical ratings.

Clearly, the relative contribution of mnemonic and executive impairment to the bipolar diathesis remains uncertain and a matter for debate. However, it should be noted that the extent of overlap between the cognitive functions assessed by each test makes any interpretation of the pattern of results speculative. Furthermore, it is probable that complex higher cognitive functions involve a network of neural interconnections. Interpreting these contradictory results as independent behavioural

[†]See pp. 313–326, this issue.

indicators of dysfunction in either frontal or temporal regions is therefore problematic and embraces an oversimplistic dichotomy. A more parsimonious explanation for the hybrid nature of the cognitive profile reported in bipolar affective disorder resides in a consideration of the strong reciprocal neuroanatomical connections between the prefrontal cortex and the temporo-limbic circuit. The difference in the findings across studies to date is likely to reflect deafferentation in different regions of this extended circuit, probably related to the heterogeneity (e.g. severity, length of illness, presence or absence of psychotic features, etc.) of the clinical samples under study.

NEUROANATOMICAL ABNORMALITIES IN BIPOLAR DISORDER

In accord with this proposition, structural imaging studies have revealed a variety of morphological brain abnormalities in patients with bipolar disorder. Decreases in volume of the medial temporal lobes or cerebellum have been reported in some, but not all, structural magnetic resonance imaging studies in patients with bipolar disorder. More recent studies have observed significantly larger amygdala (but not hippocampal) volumes in prospectively verified euthymic patients with bipolar disorder, compared with patients with schizophrenia and normal subjects (Altschuler *et al*, 2000). The magnetic resonance imaging studies have indicated also that patients with bipolar disorder have somewhat larger lateral and third ventricles than controls. This latter finding has been interpreted as an indirect expression of a reduction in the volume of thalamus or hypothalamus, which are located at the sides of the ventricles (Videbech, 1997). Drevets *et al* (1997) reported that mood-state-dependent blood flow to the left subgenual area of the prefrontal cortex in familial bipolar patients is explained partly by a reduction of up to 39% grey matter in this region. This volumetric difference was reported also in the euthymic phase of the disorder, suggesting a trait abnormality. In addition, attention has focused recently on the unexpectedly high prevalence of cerebral white matter lesions in younger patients with bipolar disorder. Such lesions often are localised in the frontal lobes and the basal ganglia, possibly indicating a defective basal ganglia–frontal

circuit (Videbech, 1997), and have been shown recently to be associated with poor outcome (Moore *et al*, 2001).

The studies to date thus provide some evidence for structural pathology in specific circuits and cognitive impairment in a subset of patients with bipolar disorder. Whether these abnormalities are related remains to be elucidated further, although preliminary evidence suggests that they are (Coffman *et al*, 1990; Ali *et al*, 2000). Functional magnetic resonance imaging studies employing sensitive cognitive activation paradigms may provide a more direct technique to study the underlying pathophysiology of impaired cognition in euthymic probands with bipolar disorder.

CAUSAL MECHANISMS: STATIC OR PROGRESSIVE?

A retrospective study of probands with bipolar disorder by Sigurdsson *et al* (1999) reported that delayed language, social or motor development precedes the onset of bipolar disorder (in those with psychotic symptoms), which may imply that cognitive dysfunction is a vulnerability indicator for bipolar illness; further studies focusing on patients with non-psychotic illness are awaited. An alternative explanation for structural and cognitive change is that the continuing pathophysiology of bipolar illness may compromise brain tissue. This hypothesis would predict an association between illness characteristics (i.e. the number of episodes) and severity of cognitive decline; this has been borne out by current (Cavanagh *et al*, 2002 and Clark *et al*, 2002, this issue) and previous studies (Kessing, 1998; van Gorp *et al*, 1998), although relationships with other features of the illness are unclear or have not been tested.

To date there are no longitudinal studies to assess whether cognitive deficits in bipolar disorder show a progressive course or their association with age of illness onset. Such studies, alongside studies conducted in high-risk groups (i.e. first-degree relatives of probands with bipolar disorder), would help to establish the temporal evolution and aetiology of the bipolar 'encephalopathy'. Clark *et al* (2002, this issue) discuss interesting preliminary evidence that those at high risk of developing schizophrenia show deficits of sustained attention that, together with data from their current study, suggest that this is an

important, if non-specific, marker for major mental illness.

METHODOLOGICAL CONSIDERATIONS

Methodological problems limit the majority of studies conducted to date. Many studies, for example, include patients with both unipolar and bipolar illness. Studies that have directly compared these patient groups (e.g. Paradiso *et al*, 1997) illustrate that this is unwise. Although the specificity of the impairments observed in most studies militates against the cognitive deficits being accounted for by medication, the possibility that medication is contributing to the reported cognitive deficits must be considered. However, abnormalities in the domains of verbal learning and memory and executive function reported by our group and others have been confirmed in a cohort of patients who have been drug free for at least 6 months (Goswami *et al*, personal communication, 2001). It is therefore unlikely that these deficits are a medication-induced artefact.

Differences in classification schemes across studies make comparisons across studies difficult and many investigations lack an appropriate control group. One often overlooked factor is the importance of the exclusion of controls with a family history of affective illness in a first-degree relative.

However, by far the most limiting methodological factor to date is the affective state of the patients at the time of testing. Few studies utilise *a priori* operational definitions of euthymia on the basis of standardised clinical ratings in their patient inclusion criteria. Those studies that describe criteria for retrospectively confirmed remission (Rubinsztein *et al*, 2000) may fall prey to the biases in recall inherent in retrospective designs. Most fail to provide any measure of the degree of residual manic or depressive symptomatology, despite recent evidence that even small degrees of psychopathology can partially account for the cognitive impairment observed in euthymic patients (Ferrier *et al*, 1999; Clark *et al*, 2002, this issue). Future investigations of cognitive function in bipolar disorder should ensure that patients are prospectively verified as euthymic before test and have stringent euthymic inclusion criteria to minimise the impact of residual symptoms on cognitive performance. Control

via statistical means should be conducted only if patients' residual mood symptoms are still significantly higher than controls by this method alone.

CONCLUSION AND FUTURE DIRECTIONS

Despite the methodological shortcomings inherent in the majority of cognitive studies to date of euthymic patients with bipolar disorder, the weight of evidence suggests that the presence of cognitive dysfunction in bipolar affective disorder is a core and enduring deficit of the illness. The deficit is best characterised as an impairment in the attentional or executive control of action, and represents an important marker for future neurobiological and pharmacological research. In addition to the impact of cognitive dysfunction on an individual's quality of life, impaired processing of the kind reported in euthymic patients with bipolar disorder may have implications for treatment. For example, the demonstrated association between cognitive impairment and the number of affective episodes suggests that each affective episode is not biologically benign. Thus, early diagnosis and active treatment potentially could reduce the cognitive morbidity associated with bipolar disorder. Furthermore, as alluded to by Cavanagh *et al* (2002, this issue), impairments in verbal learning and memory may be detrimental to psychological treatments of bipolar disorder. Thus, psychotherapeutic approaches should take into account patients' difficulties in storing, retrieving and manipulating new information, which may limit their capacity to adopt new response patterns. In view of these implications, it is critical to ascertain whether bipolar affective disorder has a unique cognitive profile and whether distinct subgroups can be identified and to find out

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much more about the natural history of these difficulties.

DECLARATION OF INTEREST

None.

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