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REVIEW

Cognitive impairment in bipolar disorder: Neurodevelopment or neurodegeneration? An ECNP expert meeting report

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Abstract

This is a report arising from an ECNP expert meeting. Recent studies have focussed on cognitive problems in manic-depressive illness and a few have addressed premorbid neuropsychological functioning. The results are not fully consistent but seem to point to a neurodegenerative model, rather than a neurodevelopmental one, for some cognitive domains. There is agreement that cognitive dysfunction is highly correlated with psychosocial functioning. The neurobiological and clinical implications of recent findings will be discussed. Treatments to reduce subsyndromal symptoms and relapses may indirectly improve neurocognitive deficits and this should be better documented. Moreover, neurocognitive impairment in bipolar disorder should be considered a potential therapeutic target, so that research should focus on new drugs and psychological interventions, including neurocognitive rehabilitation, addressed to improve not only the cognition but also the functional outcome of this population.

1. Introduction

There is a broad consensus that patients with bipolar I and bipolar II disorders have cognitive impairments when, compared with age matched controls of similar educational background (Bearden et al., 2001; Quraishi and Frangou, 2002). Furthermore, these impairments appear to be somewhat independent of affective state, as they are present in euthymic or symptom free individuals (Martinez-Aran et al., 2004b; Robinson et al., 2006). The cognitive domains that

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appear to be most consistently impaired are: attention, memory and executive function (Quraishi and Frangou, 2002). On average, the magnitudes of the detected effects are between, on average, 0.2 to 1 standard deviation unit (Thompson et al., 2005; Robinson et al., 2006) and they are, broadly speaking, smaller than those seen for cohorts with schizophrenia of a similar age (Martinez-Aran et al., 2002). A recent meta-analysis found moderate to large effect sizes in most neurocognitive measures especially on verbal memory, attention/processing speed and executive functions (Torres et al., 2007). In a two-year follow-up study by Mur et al. (2008), euthymic bipolar patients showed a poorer neurocognitive performance between −1 and−2 SD compared to healthy controls on executive function and processing speed measures.

However, it would be wrong to say that there exists an obvious pattern of impairment that specifically characterizes bipolar disorder, although some studies have sought to define differences from schizophrenia or psychosis (Clark et al., 2005b; Glahn et al., 2006, 2007). However, the cause (s), consequences and potential prevention of cognitive impairments in bipolar disorder are of great contemporary interest. Of particular importance is the nature of these impairments and how they may inform us about the aetiology of bipolar disorder. The primary aim of this review is to determine if the current literature can address the following question. Specifically, are cognitive impairments found in bipolar patients more consistent with neurodevelopmental or neurodegenerative disorders?

2. Evidence of neurodevelopmental pathology?

Clearly the preferred approach to understanding neuropsychological differences from normal controls would be a prospective study starting in childhood. Since there exist several large cohorts of children followed up to adulthood, some of whom develop psychiatric disorders, limited small scale studies of this kind have been described. Thus, the Dunedin study found generally superior rather than impaired function in some domains for children who subsequently grew up to have bipolar disorder (Cannon et al., 1997). Indeed, they tended to have a higher verbal and performance IQ than the average, whereas children who subsequently developed schizophrenia performed lower than normal. Reichenberg et al. (2002) reported that healthy adolescents who later developed non-psychotic bipolar disorder had normal IQ compared to a population cohort, but confirmed that individuals who later developed schizophrenia showed a low premorbid intellectual functioning. Other findings were similar, with schizophrenia cases having poorer premorbid intellectual functioning in comparison with bipolar patients (Zammit et al., 2004). Differential patterns are still reported: so, a recent study conducted in Finland showed that both schizophrenic and bipolar patients had a poorer premorbid visuospatial reasoning than healthy controls, while bipolar patients were superior in mathematics (Tiihonen et al., 2005). Although the literature is inconsistent, bipolar disorder does not appear to be associated with premorbid intellectual decline as would be expected in a neurodevelopmental illness.

While bipolar disorder appears to be significantly influenced by genetic factors, genes alone are not sufficient for the manifestation of the illness. However, putative environmental risk factors that contribute to the development of this illness are not well understood. In comparison with schizophrenia, bipolar disorder seems to lack evidence for either social clustering in urban areas or perinatal injury as a potential additional factor, contributing to the risk of disorder (Scott et al., 2006). Therefore, the most obvious implication of the developmental studies is that young people who develop bipolar disorder have superior to average cognitive ability: this must subsequently be impaired in the wake of onset of bipolar I or II disorder. Measures made in childhood may, however, be inadequate or even irrelevant to more specific measures possible in adults.

If neurocognitive deficits are present in unaffected family members of bipolar disorder, it is possible that these deficits are genetic in origin, suggesting possible neurodevelopmental processes. Several differently designed studies have yielded inconsistent results for cognitive impairment in first-degree relatives of bipolar probands (Ferrier et al., 2004; McIntosh et al., 2005a; Clark et al., 2005a,b). However, there appears to be some evidence for minor cognitive impairments, particularly in executive function. Some caution is required in interpreting executive deficits, since the failure to perform as predicted or as normal on particular tests may be a style rather than an impairment. For example, (Clark et al., 2005b) showed increased errors on the CANTAB ID-ED switch task, implying an increased tendency among relatives to perseveration when called to make attentional switches. This was not specific to bipolar disorder and was also seen in controls with recurrent unipolar disorder. Perseveration may have advantages in some situations, and not in others. In these subjects, memory and sustained attention were normal (Clark et al., 2005a,b). A recent meta-analysis of cognitive functioning described mild (small effect sizes, Cohen's $d<0.5$), but statistically significant executive functioning and verbal memory impairments in healthy relatives of bipolar patients (Arts et al., 2007) (Table 1).

Whatever the details it remains quite possible that some neurocognitive abnormalities may represent endophenotypic abnormality and that an innovation in the investigation of cognitive function (Glahn et al., 2004), particularly in relation to reward and decision making may be particularly advantageous in this regard. Many of the test batteries hitherto employed have been large and unfocussed. This may only incidentally and approximately capture differences that really matter and also increases the dangers of multiple post hoc testing. Furthermore, finding that particular cognitive deficits are associated with a genetic liability for bipolar disorder does not necessarily imply neurodevelopmental pathology. Thus, neurodegenerative illnesses like dementia are significantly influenced by genetic factors.

3. Evidence of neurodegenerative pathology?

Whatever the abnormalities that may exist either before the onset of illness or in first-degree relatives, there is a general consensus that those abnormalities seen in patients with established bipolar disorder are more severe and affect a greater number of cognitive domains. Could this be an expression of neurodegeneration? In other words, is there a loss of function and an underlying functional neuropathology

subsequent to the onset of bipolar disorder? The major confound for the many cross sectional studies that have been completed is current mood. Absolute mood stability is unusual in bipolar patients and subclinical depressive symptoms are by no means uncommon. Hence, there is the potential for an effect of prevailing depression to reduce function in tests of cognition. Indeed, there is a correlation in some studies between subsyndromal depression ratings and cognition (Ferrier et al., 1999; Clark et al., 2002). However, both depression and cognitive impairment could be the common outcome of the same morbid process expressed in two different ways. In any case, the most important cross sectional observation is the apparently harmful effects of repeated episodes of illness.

4. Cross sectional clinical studies

A number of studies have described an association between intensity of illness history and current cognitive impairment in the memory and executive domains, independent of current symptoms (Cavanagh et al., 2002; Clark et al., 2002; Martinez-Aran et al., 2004a; Bearden et al., 2006). This has also been consistently reported in recent meta-analyses and systematic reviews (Robinson et al., 2006; Torres et al., 2007). Some authors analysed differences on neurocognitive performance between first- and multiple-episode bipolar patients (Nehra et al., 2006). While the study reported that overall, first-episode patients performed more poorly than multiple episode patients or controls, multiple episode patients demonstrated significantly worse performance on a subtest of executive functions, specifically perseverative errors on the WCST task, than either of the other two groups. Further, multiple episode patients also achieved lower overall scores on a memory task compared with the other groups, again compatible with progressive cognitive impairment with repeated clinical episodes. Deficits on executive functions may appear early in the course of bipolar disorder, prior to the effects of multiple episodes, and may be associated with clinical outcome (Gruber et al., 2008).

To our knowledge, there is only one study examining executive functioning in patients with a first manic episode relative to those with a more chronic course (Fleck et al., 2008). In that study, a detectable but weak cognitive decline was found during the early course of bipolar disorder, consistent with findings over a longer illness course (Denicoff et al., 1999; Martinez-Aran et al., 2004b). One problem is as the definition of a first-episode in bipolar disorder. It is very common to see a latency in the correct diagnosis of bipolar disorder, partly due to the fact that the first episode of illness is typically depressive (Daban et al., 2006). A first manic episode may seem like the start of the illness but it will often have been preceded by undocumented depressive episodes. Atypical presentations or high rates of mood incongruent psychotic symptoms may lead to misdiagnosis, most often with schizophrenia. For this reason, studies on neurocognition focused on first episodes in bipolar disorder are scant. A long-term evolution is sometimes needed to establish a bipolar diagnosis, so that follow-up studies are required. Finally, psychotic symptoms also have consequences for neurocognitive performance (Albus et al., 1996; Glahn et al., 2007; Martinez-Aran et al., 2008). The choice of a cohort weighted towards severe psychotic presentations is likely to see a worse pattern of cognitive impairment.

Table 1 The most common neurocognitive deficits in bipolar disorder

Verbal learning
Verbal recall
Sustained attention
Inhibitory control
Processing speed
Working memory
Abstraction/Cognitive flexibility and planning
Verbal fluency

5. Longitudinal clinical studies

There are few follow-up studies on neurocognition in bipolar disorder longer than one year. A 3 year follow-up study comparing schizophrenic and bipolar patients suggested that both patient groups were more impaired in several neuropsychological measures than the healthy controls (Balanza-Martinez et al., 2005). Cognitive deficits persisted in the long term not only in schizophrenic but also in bipolar patients, but controls were only assessed once and samples size was small. A four year follow-up of bipolar patients and controls suggested worsened cognitive function in those patients with greatest intensity of illness (Moorhead et al., 2007) and see below). To our knowledge, only one study has been conducted in euthymic bipolar patients (more than three months in remission), with a follow-up of 2 years; this suggested that impairments of executive function constitute a core deficit of the illness and seem to persist over time, in spite of euthymia (Mur et al., 2007, 2008). The small number of follow-up studies does not allow us to conclude anything about whether deficits are static or progressive or perhaps may improve with sustained euthymia.

6. Cross sectional neuroimaging studies

Structural imaging studies are complementary to, if usually less sensitive than neuropsychology. They have also usually adopted a cross sectional design, comparing patients with controls. In a meta-analysis, only right ventricular enlargement was consistently found in bipolar patients (McDonald et al., 2004). Although the literature contains several non-replications (McDonald et al., 2004), there is increasing evidence for medialtemporal (e.g. enlarged amygdala) and prefrontal (e.g. reduced anterior cingulate) abnormalities and increased rates of white matter hyperintensities in bipolar disorder (Brambilla et al., 2005). (Strakowski et al., 2005) proposed a neuroanatomical model of bipolar disorder that involves dysfunction within striatal–thalamic–prefrontal networks and associated limbic regions (amygdala, midline cerebellum). Thus, diminished prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (amygdala, anterior striatum and thalamus) was suggested to underpin the mood dysregulation found in bipolar disorder. Amygdala enlargement has been documented in bipolar patients, but not in patients with

schizophrenia, suggesting specificity of amygdala enlargement for affective disorder (Velakoulis et al., 2006). In addition, (Strakowski et al., 2005) note that some abnormalities (e.g. subgenual prefrontal cortex (anterior cingulated, striatum and amygdala) exist early in the course of illness and may predate illness onset, while other anatomic regions appear to degenerate with repeated affective episodes (e.g. cerebellar vermis, lateral ventricles and inferior prefrontal regions) and may represent the effects of illness progression. Effects in white matter may also be relevant (McIntosh et al., 2005b). Currently, like the neuropsychology, imaging findings are neither wholly consistent (especially when apparently specific) nor convincing for specific hypotheses of illness causation.

7. Longitudinal neuroimaging studies

The hypothesis that illness progression can produce cognitive impairment and relevant structural change can only be proved by prospective studies. In one of the first of its kind, a 4 year follow-up study of patients and age matched controls suggested a reduction in memory function and loss of gray matter volume in medial temporal cortex related to illness intensity (Moorhead et al., 2007). This is the strongest evidence that we have to date in favour of a direct correlation between the illness course, brain changes and cognition, but of course it does not prove the direction of effect. Such associations have often been taken, perhaps too readily, to represent a cellular effect on the brain of repeated intra-episode hypercortisolaemia (Daban et al., 2005), given its alleged propensity to cause cellular degeneration in animal models (Yusim et al., 2000; Nichols et al., 2005). Alternatively, of course, non-specific acceleration of ageing could be the cause of the greater illness intensity (Kapczinski et al., 2008).

8. The effects of medication

Finally, there must always be concerns that polypharmacy, especially when sedative medicines are used in high doses. Such medications may contribute to the cognitive impairments observed in cross sectional studies of bipolar disorder. To date, there has not been a cohort of patients with a really severe illness history who could be studied drug free. The forgoing evidence is against this being the exclusive explanation for why patients with bipolar disorder have impaired cognitive function, but from the patient perspective it may still be part of the problem and merits clarification in clinical studies. There may be a relationship between polypharmacy and cognition, as those patients taking more drugs or at higher doses may show more cognitive problems (Martinez-Aran et al., 2005). Yet, bipolar patients receiving monotherapy with lithium or valproate also showed impaired memory, suggesting that memory deficits might be intrinsic to bipolar disorder or the two medications may influence immediate verbal memory similarly (Senturk et al., 2007).

To sum up, there are many different potential confounds, such as the effect of subsyndromal symptoms, euthymia criteria that are frequently variable across the studies, selected populations, psychotic symptoms, predominant polarity (Colom et al., 2006; Rosa et al., 2008) (manic episodes may have a stronger impact than the depressive ones), comorbidities especially with substance misuse, all or any of which may worsen neuropsychological performance. Polypharmacy will be variably associated with or interact with these confounds to impair cognition. On the other hand, inadequate treatment or non-adherence may increase the risk for relapses or persistent subclinical symptoms which may, rather, worsen neurocognitive functioning.

9. Clinical implications

The consequences of cognitive impairment are of functional significance (Martinez-Aran et al., 2002, 2007; Jaeger and Vieta, 2007) There are clearly confounds of depression and previous illness intensity as already described. However, it seems reasonable to suppose, and it is certainly sometimes confirmed by patients themselves, that memory and concentration can be a limiting factor in their returning to demanding executive work. Indeed it would be very surprising if this were not so. Indeed, recent findings suggest that the relationship between neurocognitive deficits and functioning may be stronger than between subsyndromal symptoms and psychosocial functioning (Martinez-Aran et al., 2004b, 2007). Martinez-Aran et al. (Martinez-Aran et al., 2007) found that delayed verbal recall was the cognitive measure that best predicted psychosocial functioning as measured through the GAF, accounting for nearly 21% of the variance, after controlling for the effect of subclinical symptoms (which only accounted for 7%). In a recent study, (Tabares-Seisdedos et al., 2008), a Global Neurocognitive Index and, specifically, the executive/reasoning domain at baseline, was associated with occupational adjustment one year later, after controlling for the effect of subclinical symptoms, which seemed also negatively to influence psychosocial functioning. Similarly, Jaeger et al. (2007) also found that ideational fluency and attention were the best predictive factors of functioning after controlling for subclinical symptoms.

Understanding how cognitive impairments and subsequent rehabilitation can be improved and if possible personalised to facilitate individuals returning to preferred spheres of work is an area of little current activity or understanding. Impairments in some cognitive domains, such as verbal memory and executive function, seem to be related to poor performance (Martinez-Aran et al., 2007). For this reason, cognitive impairment constitutes a potential therapeutic target, so future directions for potential cognitive enhancement strategies in bipolar disorder may include medications that influence dopaminergic or glutamatergic neurotransmission. The role of established mood stabilizers as neuroprotective agents is being increasingly established. There is an accumulation of evidence supporting neuroprotection as a key therapeutic target in early intervention (Conus et al., 2006). On the other hand, there is growing evidence to suggest that increased availability of dopamine (DA) may have positive effects on neurocognition in bipolar disorder, e.g. pramipexole, a novel D2/D3 agonist, may be a useful adjunctive treatment in bipolar disorder (Goldberg et al., 2004). A number of reports have claimed that in large samples of patients with schizophrenia followed for lengthy periods and treated with atypical antipsychotics, there were clinically significant improvements in domains of cognitive function, which may have an impact on "real-world performance" (Kasper and Resinger, 2003). Such findings, were not replicated in the CATIE study (Keefe et al., 2007). Similar

studies are now needed in patients with BD, to understand if cognitive benefits, with improvements in social, occupational, and interpersonal function are also attainable using the atypical antipsychotics (Reinares et al., 2000; Harvey et al., 2007). Atypical antipsychotics appear set to play an essential role in current treatment of bipolar disorder (Brugue and Vieta, 2007).

Further work is required adequately to assess the safety and effectiveness of drugs in bipolar patients (Burdick et al., 2007; Vieta and Rosa, 2007). Psychosocial intervention and/or cognitive remediation should be considered as adjunctives to medications; randomized controlled trials would be helpful in order to establish their efficacy as well as the need to implement these techniques or strategies in clinical practice. Optimizing and individualizing pharmacological treatment by small changes in dose or type of medication is good practice. It is usually directed to reducing side effects, subsyndromal symptoms and to reduce relapse: a positive impact on cognitive problems should also be an objective.

10. Conclusions

The lack of strong evidence for cognitive impairment prior to illness onset in bipolar disorder appears to be inconsistent with classically defined neurodegenerative illness causation. However, there is evidence for minor impairment of executive processes in unaffected adult relatives. Neurodegeneration may or may not be the correct term for the deleterious effects of repeated episodes and neurotrophic medications on cognitive performance. Evidence for accelerated cognitive decline in bipolar disorder is still preliminary. The current perspective does not strongly support a neurodegenerative model for this illness, but cognitive function is an underestimated factor in its outcome and a potential target for improved treatment.

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Contributors

All the authors have been sufficiently involved in the study submitted.

Conflict of interest

All the authors declares no conflict of interest.

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