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EDITORIAL

Recent findings in bipolar affective disorder*

Taking a position

Goodwin (2000) famously argued that bipolar disorder was the Cinderella of psychiatry. It certainly should not be: there is no doubt of the anguish caused by the condition, in particular the excess of natural mortality and the great excess of death by suicide (Ösby *et al*. 2001). In this issue, Mitchell *et al*. (2004) report that 26% of their cases of bipolar disorder had attempted suicide at some point. This reflects the sheer persistence of personal suffering: Judd and colleagues (2002, 2003) demonstrated in a long and detailed follow-up that patients with bipolar disorder were symptomatic at least half the time. The Australian National Survey of Psychotic Disorders found levels of disability in affective psychosis equal to those of schizophrenia (Jablensky *et al*. 2000), and bipolar cases are more likely to score highly on measures of disability than unipolar cases (Mitchell *et al*. 2004). People with bipolar disorder are more likely to be single, widowed or divorced than both the general populace and those with unipolar depression (Mitchell *et al*. 2004).

Das Gupta & Guest (2002) recently estimated the annual direct and indirect costs of bipolar disorder to the UK economy at £2 billion, of which only 10% were direct treatment costs. And yet, despite this burden, to sufferers, carers and the community alike, there is a real dearth of research activity in bipolar disorder in comparison to schizophrenia. This has been confirmed in the bibliographical study by Clement and colleagues (2003).

However, the good news is that the imbalance may be diminishing (Watson & Young, 2003). Recent initiatives have included the setting up of the Stanley Foundation Bipolar Network (Post *et al*. 2001). There has been a burgeoning of research studies and a growing interest in underlying processes, particularly in the new millennium, which is reflected in the contents of this issue of *Psychological Medicine*.

So what are the key explicanda in bipolar disorder? In schizophrenia research, after a period of dejection, genetic studies have now implicated several chromosomal regions and candidate genes. It is being acknowledged that genes do not themselves encode for mental disorders, and that explanation is required linking individual genes with neuroanatomical findings, with neurocognitive deficits, and with deficiencies in social cognition (Weinberger, 2002) in a cascade of processes including crucial gene-environment interactions that must precede symptoms (Garety *et al*. 2001). Symptoms have now become the target of explanatory research in their own right. The research agenda may appear Himalayan, but at least we can discern its outlines. It also feeds into the design of treatments.

Could it be that we are approaching a similar situation in bipolar disorder? I think we are. Although bipolar research may be 10 years behind that in schizophrenia, it is already following similar paths. Consequently, there are huge opportunities for collaborative and multidisciplinary investigation.

The definition and characteristics of bipolar disorder

Defining psychiatric disorders always faces similar difficulties to drawing the most coherent boundaries of a European state. It will always remain imperfect in the eyes of some people, both for

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what it contains and for what it leaves out, but is useful nonetheless for practical purposes. There are particular difficulties in bipolar disorder. It links episodes of depressed and elevated mood. Each has to be distinguished, largely arbitrarily, from normal mood variations – depressive symptoms certainly seem to follow an exponential distribution in the general population, with no obvious cut points (Melzer *et al*. 2002). There will be various combinations: mild depression with severe mania, mild mania with severe depression, and so on. This encourages divisions between 'splitters' and 'lumpers', with bipolar II disorder a child of the former (Dunner *et al*. 1970). The existence of mixed affective states has implications for what appear initially to be polar opposites.

The rather complex subclassifications of bipolar disorder have been listed by Ferrier *et al*. (2001), with the implication that they may obscure a range of subtle variations central to an understanding of the disorder. Judd and colleagues (2002, 2003) carried out a follow-up study over 13 years. Patients were symptomatic on around half of the individual weeks. Depressive symptomatology was more salient in the bipolar II group, and manic or hypomanic symptoms were much commoner in the bipolar I group. This could be taken as validating the separation of the two groups. It could also be taken as evidence that mood elevation and depression may combine in varying degrees, supporting continuities with normal mood variations (Akiskal, 2003). McGuffin and colleagues (2003) found little evidence in a twin study of a genetic basis for a multiple threshold disorder.

A further aspect of the central Kraepelinian distinction between dementia praecox and manic depressive illness is recovery between episodes. This was conceived around euthymia, an absence of affective symptoms. Even at this level, Kraepelin may have over-stated the case (Bebbington, 1982; Grof *et al*. 1995; Tohen *et al*. 2003). However, absence of apparent affective abnormality may not be sufficient to define recovery, and mood symptoms may turn out to be a crude way of assessing abnormality. Even in symptomatic remission, bipolar patients show poorer social adjustment and lowered self-esteem (Blairy *et al*. 2004), and abnormalities in psychological performance. If the Kraepelinian distinction between schizophrenia and bipolar disorder based upon course falls, differences may also be overstated in other ways. There are many sorts of overlap between affective illness and the schizophrenia spectrum.

Periodicity requires explanation. If people have a propensity to mood disorder, why is it not manifest at all times? There does appear to be a tendency for the intervals to shorten in a manner that exceeds explanation in terms of Slater's fallacy (Slater, 1938; Bebbington, 1982; Oepen *et al*. 2004). However, in individuals there may be considerable variation in successive inter-episode intervals. Slater (1938) argued that each individual patient with bipolar disorder had a rhythmicity of relapse that was biologically based. A more plausible answer is that periodicity relates to the ways the person has of interacting with their environment and its demands.

The greater propensity to relapse later in the course of the disorder may be due to damage done by preceding episodes, a sort of 'scar' hypothesis. Post (1992) interpreted this by analogy with kindling, the progressive reduction in the stimulus required to engender an epileptic fit. Some of the recent literature provides other evidence of 'scarring', for example the relationship between the number of episodes and impaired verbal learning and memory (Cavanagh *et al*. 2002; Martínez-Arán *et al*. 2004), and also inter-episode dysfunctional attitudes and difficulties with autobiographical memory found by Scott *et al*. (2002).

Bipolar disorder overlaps (is co-morbid) with a range of conditions other than schizophrenia. The best known is alcohol and drug abuse, but several others are important. Mitchell *et al*. (2004) found that bipolar disorders were very prone to co-morbid psychiatric conditions, particularly anxiety disorders and personality disorders, although not to co-morbid medical conditions. Sometimes the associated chaotic lifestyle may be interpreted as personality disorder. One study of bipolar patients suggested 40% also met criteria for borderline personality disorder, but these features appeared to ameliorate with lamotrigine (Preston *et al*. 2004). People with depressive mania in contrast to those with pure mania, also have increased susceptibility to social phobia and panic disorder (Dilsavers & Chen, 2003). Anxiety disorders are more associated with bipolar disorder if the predominant cast is depressive. Both a family history and individual experience of panic disorder were associated with rapid mood switching in bipolar disorder (MacKinnon *et al*. 2003).

The symptoms of mania and explanations of bipolar disorder

Many of the symptoms by which we recognize mania are closely related to neurocognitive deficits. While Taylor-Tavares *et al*. (2003) suggest the inclusion of cognitive symptoms in the modern classifications of affective conditions acknowledges their importance, they were central to the conceptualization of the conditions long before the classifications were formalized. They have now also become central to the research effort.

This is appropriate. It should encourage the detailed investigation of other key phenomena including emotional dysregulation, increased activity, increased and distorted emotional salience, and reduction of constraint.

Elevated mood, characterized variously as exhilaration, excitement or even exaltation, is central to mania. One key question is whether we can explain it in terms of micro-interaction with the environment and with other attributes of the person. Another is whether the emotional dysregulation is primary, driving the other features of the disorder. Thought contents in mania are closely consistent with the elevation of mood: increased self-esteem, feelings of well-being, and of great personal power and attributes. These may have some justification from the associated increase in motor and mental speed and efficiency, at least in the early stages. The content of thought may proceed to grandiose delusion formation, but this does not occur in everyone. Auditory and visual hallucinations, if they occur, certainly tend to be congruent with elevated mood.

Some grasp of the mechanisms for mood dysregulation should be apparent from prodromes. Little is known about the *initial* prodrome preceding bipolar disorder, but it may be relatively nonspecific, being hard to distinguish from psychotic prodromes (Thompson *et al*. 2003). At least 80% of people with mood disorders can recognize prodromal symptoms preceding episodes. The prodrome for episodes of mania is surprisingly prolonged, at around 3 weeks (Jackson *et al*. 2003). More than three quarters of people with mania identify sleep disturbance in the prodrome. This raises the possibility that the self-restriction of sleep is central to the emergence of the other symptoms, particularly over-activity. Sleep hygiene is reasonably a focus in psychological approaches to management (Lam *et al*. 2003).

Mania often first manifests itself through increased mental quickness – flight of ideas. Physical activity increases, and sleep decreases. Sufferers may write voluminously. Appetites are often increased. This increase in activity associated with mania might in itself be a primary driver.

Further detailed investigations of the time-course of evolution of episodes might be rewarding. Mansell & Lam (2003) described in detail the ascent into mania in a single patient, who believed he could ameliorate his depression by adopting demanding goals and rewarding activity. Small improvements in mood and energy triggered exaggerated positive thoughts about himself, leading to a range of ascent behaviours. These in turn had an effect on people around him that was additionally reinforcing.

Mania is also characterized by *reductions of constraints*, shown in intrusions and disinhibition. Intrusions may arise because of a failure to suppress associations in thought, hence clang associations. Distractibility is the result of intrusions from the external environment. Disinhibition represents a reduction of constraint from social compliance.

Finally, people with mania also have a *heightened sense of meaning*, with heightened perception, increased religious faith and so on, discussed further below.

Epidemiological problems

The concept of polarity has created particular difficulties for epidemiological study. It is difficult to establish the frequency of a disorder that can only be recognized at an unspecified point in its course, when polarity switches. In new cases of affective disorder, initial episodes may be manic, mixed or depressive, and any one of these presentations may herald a bipolar course. Thus, most cases of bipolar disorder cannot be diagnosed at the time of the first episode. The rate of conversion to a bipolar picture is, therefore, important.

Bebbington & Ramana (1995) concluded from their review that 5% of patients initially hospitalized for a depressive episode will have a bipolar course. Goldberg *et al*. (2001) have recently

reported much higher figures from a 15-year follow-up of patients initially hospitalized for unipolar depression. They found a conversion rate to bipolar disorder of 19% for mania, with a further 27% converting to hypomania. A pattern with more depressed than manic episodes is commoner in women, in line with their greater frequency of depressive conditions in general (Bebbington & Ramana, 1995). Thus, if we wish to establish the incidence of bipolar disorder, we must do so retrospectively. As with every psychiatric disorder, the prevalence depends on how widely the net is cast.

Bebbington & Ramana (1995) concluded that the incidence of bipolar disorder was around 8–10 per 100 000 when based on first admission rates. This would suggest a rare condition, with a morbid risk of the order of 0·5%. Community surveys, as might be expected, give higher values, with a lifetime prevalence of around 1% (lifetime prevalence in this condition would be perhaps half the morbid risk). However, the value for *period* prevalence of manic episodes in the ECA studies was quite high, approximately 0·5%; which casts some doubt on the quoted lifetime prevalence.

In this issue, Mitchell *et al.* (2004) provide data for the 12-month prevalence of DSM-IV bipolar disorder from an Australian national survey of nearly 11 000 people. Prevalence was determined by occurrence of a hypomanic/manic episode in the year before interview (13 cases), or an episode of major depression during that period with an earlier episode of hypomania/mania (40 further subjects). The overall prevalence of bipolar disorder was 0·5%, consistent with our earlier review (Bebbington & Ramana, 1995), and with subsequent studies (Kessler *et al.* 1994, 1997; Szádóczky *et al.* 1998; ten Have *et al.* 2002). The gender ratio was equal, and significantly different from the female preponderance in unipolar disorder.

There has been much debate about the association of bipolar disorder with social class (Bebbington & Ramana, 1995). One view is that the lower social status of bipolar subjects is the result of the disorder, but that genetic susceptibility to bipolar disorder carries an advantage in unaffected family members. Tsuchiya *et al.* (2004) (this issue), used the extensive registration of Danish citizens to assess links between socio-economic status and bipolar disorder. Subjects themselves were characterized by high levels of unemployment, receipt of benefits, poorer education, lower income and single marital status, but their parents were on average from relatively high education and income groups.

Recent epidemiological studies have indicated possible aetiological and process factors. Early parental loss seems more common in bipolar disorder (Tsuchiya *et al.* 2003), particularly if maternal (Mortensen *et al.* 2003). Zammit *et al.* (2004), in a male Swedish conscript cohort of 50 000 found pre-morbid IQ score normal in future bipolar patients, while schizophrenia was associated with lower IQ score, implying a neurodevelopmental distinction between the conditions.

The role of genetic factors

The genetics of bipolar disorder are likely to be complex, with different combinations of predisposing genes being translated into clinical pictures that may vary both quantitatively and qualitatively (Kelsoe, 2003; DePaulo, 2004). Different genes are likely to have different effects on function and symptoms, to interact with each other, and to interact with environmental factors.

The twin study by McGuffin and colleagues (2003) confirms that bipolar disorder has extremely high heritability. The inclusion of twins with unipolar depression suggested that over 70% of the genetic variance for bipolar disorder was *not* shared with depression, but was specific.

There is not only an increased frequency of bipolar disorder in family members, but also of schizoaffective disorder and schizophrenia (Mortensen *et al.* 2003). O'Mahony *et al.* (2002) showed the level of psychotic symptoms in bipolar disorder ran in families: this is almost certainly a reflection of the overlap of chromosomal regions associated with schizophrenia and bipolar disorder. Schürhoff *et al.* (2003) have demonstrated an equal proneness to delusions in the first-degree relatives of patients with schizophrenia and with psychotic bipolar depression.

Perhaps 16 chromosomal regions have been identified as relevant for bipolar disorder, although only five meet the criteria for significant linkage, of which the strongest evidence is for a region on chromosome 13q33. Moreover, four regions (including 13q33) are also associated with schizophrenia (Berrettini, 2003). Potash *et al.* (2003*a*, *b*) found evidence linking *psychotic* symptoms in

bipolar patients with 13q31 and 22q12 but not 10p12-14 or 18p11.2, all regions where bipolar and schizophrenia susceptibility overlap. The region 18q21-23 appears associated particularly with milder bipolar disorder, suggesting perhaps that bipolar II forms a valid subtype (McMahon *et al.* 2001). Faraone *et al.* (2004) have tentatively identified three new chromosomal regions associated with age of onset in bipolar disorder. This is still work in progress, and we are some distance from connecting specific mutations with, for instance, specific neurocognitive deficits.

Structure and function

Anatomical and neurochemical studies have been supplemented by neurocognitive and social-cognitive investigations. It is hard to argue that abnormalities occurring during a period of mood disturbance represent permanent states, unless the abnormality can also be detected during a euthymic period, but even here it may be the product of earlier episodes of disorder (our scar hypothesis again). The evidence is further strengthened if the deficits are also seen in their unaffected relatives. An even better study, if feasible, might involve the follow-up of non-affected relatives to examine the initial attributes associated with the later emergence of disorder.

There is some consistency in the areas of the brain implicated in bipolar disorder. Functional abnormalities of the amygdala and anterior cingulate cortex are associated with depression (Drevets, 2001; Davidson *et al.* 2002), and in some studies of mania (Drevets *et al.* 1997; Blumberg *et al.* 2000). Blumberg *et al.* (1999, 2000) have also found abnormalities in the orbital prefrontal cortex and amygdala. Abnormalities in the right subgenual prefrontal cortex were apparent on MRI (Sharma *et al.* 2003). There are also functional abnormalities in the prefrontal cortex and the basal ganglia that may be related to cognitive abnormalities (Bearden *et al.* 2001). These regions are implicated in a number of cognitive functions (error monitoring, inhibitory control, response generation, mental speed, affect regulation) that can be related to the clinical attributes of mania. Matsuo and colleagues (2002) used near-infrared spectroscopy to study hypofrontality in euthymic patients with mood disorders and demonstrated a reduction in the normal increase of oxygenated blood during a verbal fluency task, consistent with a reduced physiological response in cerebral blood vessels.

Blumberg *et al.* (2003*a*) found that some of the fMRI abnormalities in bipolar disorder in the medial prefrontal cortex were persistent. They have also studied adolescents to identify abnormalities operative at an early stage. Using fMRI they found evidence of abnormal functioning in the left putamen and thalamus, but no dysfunction in the prefrontal region (Blumberg *et al.* 2003*b*). Bipolar disorder was also associated from early in the illness with reduced volume in the hippocampus and amygdala (Blumberg *et al.* 2003*c*).

There is other evidence implicating the hypothalamus. Deicken *et al.* (2003) found progressive neuronal pathology in the hippocampus in familial bipolar I disorder. Bipolar disorder may also be specifically associated with hippocampal deficits in the mRNA expression for the enzyme that synthesizes GABA from glutamic acid (Heckers *et al.* 2002). In subjects with bipolar disorder, but not in those with schizophrenia, there is evidence of decreased hippocampal mRNA coding for mitochondrial proteins (Konradi *et al.* 2004).

There is considerable evidence of neuropsychological dysfunction in people suffering from bipolar episodes (Bearden *et al.* 2001), including slower deliberation and reduced ability to plan, both during depression and mania (Murphy *et al.* 2001). Psychological abnormalities in episodes extend towards social cognition too: Murphy & Sahakian (2001) reviewed contrasting biases towards positive and negative material in manic and depressed states.

Again, such abnormalities need investigation between episodes. There have been several well-conducted studies of neurocognitive abnormalities in euthymic bipolar subjects in recent years. There is some dispute about the degree of euthymia, and Ferrier & Thompson (2002) recommend control in analysis for residual affective symptoms in euthymic individuals. Cavanagh *et al.* (2002) did not do this, whereas both Ferrier *et al.* (1999) and Clark *et al.* (2002) did. Ferrier *et al.* (1999) showed impairment in euthymic bipolar patients in attention, working memory, learning and executive function. Clark *et al.* (2002) demonstrated impairment on tasks of attentional shifting,

verbal memory and sustained attention compared with normal controls. Martínez-Arán *et al.* (2004) also found deficits in verbal memory and frontal executive function in bipolar patients whether manic, depressed or euthymic. Cavanagh *et al.* (2002) found deficits in verbal learning and memory in euthymic bipolar patients, but *not* in other measures of executive function. Dixon *et al.* (2004), in this issue, compared 15 manic, 15 depressed and 15 remitted bipolar patients with 30 healthy controls. Using tests of executive function, they found abnormalities particularly during mania, and related particularly to thought disorder. Also, depressed and remitted groups, like the manic groups, showed difficulties in initiating responses, in inhibitory control, and in thinking strategically.

Episodic memory, remembering information relating to a specific episode, will be impaired if people cannot store and consolidate new memories, but equally if they cannot access strategies for organizing information. Since people with bipolar disorder show structural abnormalities in the prefrontal cortex, involved in organizing the encoding of memory, it is reasonable to predict that they will have difficulty with memory, particularly organizational difficulty and that it will be apparent during euthymia. Deckersbach *et al.* (2004), in this issue, compared euthymic bipolar patients with normals on a memory task relating to a complex figure. They were able to demonstrate that the euthymic bipolar group had impairments of recall that could be attributed to the lack of organizational strategy. The use of the figure confirmed that these difficulties were not restricted to verbally mediated memory. Nevertheless, it is difficult to be sure that these deficits are specific: they may be due to increased impulsivity, or decreased motivation and effort (it is quite effortful to organize memory).

Riedel (2004) describes the use of acute tryptophan depletion as a way of studying serotonin function, using cognitive changes as a proxy for particular disease states. Sobczak and colleagues (2002) investigated its effects on planning, memory and attention tasks. Unaffected relatives of people with bipolar disorder showed impaired performance in planning and memory tasks independently of tryptophan depletion, but depletion further impaired information processing on the planning task. This certainly indicates neurocognitive abnormalities in bipolar patients' relatives, but the evidence that this is due to serotonin metabolism abnormalities is equivocal. Post-mortem studies of the dorsal raphe nuclei, responsible for serotonergic projections, have shown a significant reduction in the number of neurones in bipolar patients (Baumann *et al.* 2002). Lower baseline cholesterol and increased total omega-6 fatty acids have been suggested as trait markers, as they are apparent both in healthy first-degree relatives and in bipolar patients. Changes in fatty acids may be related to abnormalities in serotonergic function (Sobczak *et al.* 2004). Noaghiul & Hibbeln (2003) have linked lifetime prevalence of bipolar disorder with increased community consumption of seafood.

Impairments of verbal memory and learning seems to be related to the duration of illness, and the number of episodes, particularly of mania (Cavanagh *et al.* 2002; Martínez-Arán *et al.* 2004). This raises the possibility that they are 'scars' rather than pre-existing traits. They may, nevertheless, increase the propensity to relapse in bipolar disorder.

Pinkham *et al.* (2003) have described the considerable research into abnormalities of 'social cognition' in schizophrenia, and similar studies, albeit fewer, have appeared in mania. The distinction between social cognition and neurocognition is unsatisfactory, mainly referring to a difference in the approach of the researcher. Areas of interest have included dysfunctional attitudes, autobiographical memory, goal striving, theory of mind, and emotion perception. It is not clear how these relate to the deficits described above.

Scott *et al.* (2002) compared euthymic bipolar patients with controls, and found increased dysfunctional attitudes (especially perfectionism and need for approval), over-general recall in autobiographical memory and less ability to generate solutions to social problem-solving tests. Scott & Pope (2003), in a large study of cognitive style, found subjects with elevated mood were intermediate in dysfunctional beliefs between euthymic individuals and those with depression. The hypomanic subjects scored more on negative as well as positive self-esteem. Negative self-esteem was the strongest predictor of relapse at 1 year. Euthymic bipolar patients have higher scores on

goal striving than euthymic unipolar patients (Lam *et al*. 2004). Bipolar patients exhibit impaired theory of mind when depressed or manic, but not in remission (Kerr *et al*. 2003). This may merely be the consequence of increased self-focus in episodes.

Emotion perception is essential to social survival. Phillips (2003) identifies three related subprocesses, the identification of emotionally salient environmental stimuli, the resulting generation of emotional experiences and responsive behaviour, and the regulation of these emotional experiences and behaviour. Within the limbic system, the amygdala and anterior insula appear particularly important for identifying emotional stimuli, including facial expression and non-facial displays, but also in emotional memory. These regions also mediate emotional experiences and responses, along with the anterior cingulate gyrus, and the ventromedial and ventrolateral prefrontal cortex. Less is known of the neural basis for emotional regulation, although dorsal prefrontal regions may be involved. It would be expected in a disorder characterized by dysregulation of mood homeostasis and by disturbances of meaning that abnormalities of emotional processing might be important.

The paper by Tai *et al*. (2004) is particularly relevant. They compared manic, depressed and euthymic bipolar patients with controls, using an emotionally salient and non-salient interview, and ascending 10-minute recordings of speech during the interviews for abnormalities of thought, language and communication. The speech of manic patients showed increased responsitivity to stimuli with heightened emotional salience compared with the other groups. However, the euthymic groups still showed increased responsiveness to the emotionally salient condition compared with the normal controls. The depressed group showed no capacity to respond to emotional salience at all, paralleling the tendency in depressed people to lose a sense of meaning.

The incorrect identification of social cues like facial emotion may help to maintain abnormal affective states. Depressed subjects over-recognize faces displaying negative emotions. The recognition of facial emotion is dependent on limbic and paralimbic brain structures that may function abnormally in mood disorders. Lennox *et al*. (2004), in this issue, have examined the responses to facial affect of bipolar patients in a manic state in an fMRI study. The authors not only showed that the manic patients under-recognized sad facial affect, but also that this was accompanied by an abnormal profile of brain activation in paralimbic regions. They were not more prone to recognize happy affect.

Conclusion

There is now a major research drive in bipolar disorder. There have been considerable advances in the genetics, the neuroanatomy and the neurocognitive aspects of the disorder. The resulting patchwork of findings remains to be integrated. This is a research agenda for the next few years, aiming to elucidate the detailed mechanisms that underlie this complex disorder. Given the genetic overlap with schizophrenia, what parts of the bipolar syndrome are clearly distinct? What is the relationship of the subdivisions within bipolar disorder, based on severity of clinical symptoms, to other correlates – the genome, neurocognitive deficits, 'social cognition'? Is it possible to distinguish clearly between the neurocognitive deficits in schizophrenia and in bipolar disorder? If so, can we relate this to genetic distinctions? Since many psychological abnormalities in bipolar disorder do not persist when sufferers are euthymic, which do represent genuine continuing vulnerabilities? How exactly is it that people move into and out of euthymia? How do interactions with the social microenvironment work? Recent advances have been made in the psychological management of bipolar disorder (Scott *et al*. 2001; Colom *et al*. 2003; Lam *et al*. 2003; Miklowitz *et al*. 2003). Further refinement of such treatments might with benefit incorporate insights from the neurocognitive and social cognitive findings described here.

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DECLARATION OF INTEREST

None.

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