Psychological Medicine, 2003, **33**, 959–967.
DOI: 10.1017/S0033291703008432 Printed in the United Kingdom

EDITORIAL

Cognition in mania and depression[1]

The inclusion of cognitive symptoms in the DSM-IV criteria for major depressive and manic episodes highlight the importance of cognition in both of these psychiatric disorders (American Psychiatric Association, 1994). For example, criteria for diagnosis of these conditions include a diminished ability to concentrate and indecisiveness. In addition, numerous studies have demonstrated wide-ranging cognitive deficits in depression (for example Elliott *et al*. 1996; Purcell *et al*. 1997; Murphy *et al*. 2003) and mania (Goldberg *et al*. 1993; Murphy *et al*. 1999, 2001; Sweeney *et al*. 2000). These include deficits in early information processing (Tsourtos *et al*. 2002), recollection memory (MacQueen *et al*. 2002) and planning (Elliott *et al*. 1996) as well as affective biases (Murphy *et al*. 1999) and abnormal responses to negative feedback (Elliott *et al*. 1996, 1997; Murphy *et al*. 2003). Some residual deficits are also evident in a proportion of remitted subjects, even when controlling for mood (for example, Clark *et al*. 2002).

Residual deficits identified during remission for bipolar depressive disorders (BD) (Tham *et al*. 1997; van Gorp *et al*. 1998; Rubinsztein *et al*. 2000; MacQueen *et al*. 2001; Clark *et al*. 2002) indicate that some cognitive deficits may persist across mood episodes and occur independently of mood state. Consistent with evidence that such mood state independent deficits exist, several studies have suggested that during remission patients with BD may not achieve functional recovery (reviewed by Zarante *et al*. 2000). Furthermore Gourovitch *et al*. (1999) have identified impairments in monozygotic (MZ) twins discordant for BD (three affected twins were euthymic, two had depressive symptoms and two had manic symptoms) on measures of short delay cued recall and recognition from the California Verbal Learning Text (CVLT). If these findings can be confirmed in a larger sample this might suggest that impaired verbal recall memory may constitute an endophenotype for BD. Compatible with these data Kerí *et al*. (2001) have studied siblings of patients with BD and found impairments in verbal recall though not in a variety of other tests including verbal recognition, digit span, word span, letter fluency or the Wisconsin Card Sorting Test (WCST).

Within this editorial these wide-ranging cognitive deficits are examined with respect to motor and information processing speeds, memory and executive function. The Affective Go/No-go task, which identifies differences in performance and affective bias between depression and mania, will be discussed and recent findings of an abnormal response to negative feedback in depression will also be analysed.

The aims of this editorial are: to demonstrate the extent of these wide-ranging cognitive deficits by focusing on some of the recent studies which illustrate the broad range of impairment; to find tests with differential patterns of performance for mania and depression; to try to determine whether there may be an underlying psychological concept that might explain the pattern of deficits identified such as an abnormal response to negative feedback or narrowing of attentional focus; and to see whether the neural basis of some of the cognitive findings can be elucidated by recent neuroimaging studies.

MOTOR FUNCTION AND EARLY INFORMATION PROCESSING

Measures of cognitive task performance include motor speed and early information processing prior to conscious processing. It is important to separate these aspects of performance from other elements of cognitive processing that are more specifically assessed by a task. DSM-IV criteria for

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depression include psychomotor agitation or retardation suggesting that motor function is an important feature of depression. Studies commonly report psychomotor slowing (for example on the pattern recognition task in MDD and simultaneous and delayed matching to sample tasks in MDD and mania (Elliott *et al*. 1996; Murphy *et al*. 1999)) and some studies have found slowing of latency even in the remitted state (for example Rubinsztein *et al*. 2000). Impairments in latency to respond have also been found in unmedicated remitted subjects with seasonal affective disorder (O'Brien *et al*. 1993). This suggests that psychomotor slowing, though not evident for all tasks, may play an important role in cognitive dysfunction in depression.

Studies suggest that depressed subjects also have impairments of early information processing. Inspection time (IT), unlike reaction time (RT), is thought to be a measure of the speed of these early stages of information processing which is independent of motor speed, speed-accuracy trade-off or other cognitive strategies (Nettelbeck, 1987; Deary & Stough, 1996). It is defined as the minimum duration of stimulus presentation necessary for near perfect performance on a two-choice visual discrimination task. A backward mask is superimposed to control stimulus duration (Nettelbeck, 1987). In a study by Tsourtos *et al*. (2002) unmedicated depressed in-patients with MDD had significantly longer inspection times than medicated in-patients (who had been depressed for significantly longer than unmedicated subjects) and healthy controls. The medicated in-patients with MDD did not perform significantly differently from controls. All subject groups in this study had a mean age of <40 years, suggesting that IT is an important aspect of the neuropsychological profile of younger depressed patients (Tsourtos *et al*. 2002). These data also suggest that medication normalizes IT, although a longitudinal study would be necessary to assess the presence of such an effect.

Results using visual backward masking (VBM) suggest that BD subjects also have deficits in early information processing. During VBM a stimulus is presented for a very short fixed period of time before being replaced by a non-informative mask. BD patients appear to have impaired performance both during and after a manic episode (Fleming & Green, 1995). MacQueen *et al*. (2001) found that medicated euthymic BD subjects were impaired at both identifying what the stimulus was and where on the display screen it had been located. The number of past depressive episodes was found to predict RTs at each ISI (interstimulus interval) of the identification task and there was a similar trend for error rate. This relation was not a function of age, current symptomology or duration of euthymia, none of which correlated with performance. This would suggest that the VBM identification task is dependent on neural pathways sensitive to past burden of depressive illness.

The neural pathways thought to be involved during this task project through the lateral geniculate nucleus and the visual cortex, terminating in the inferotemporal and parahippocampal cortices. Some studies have found decreased temporal lobe volumes in BD (Hauser *et al*. 1989; Altschuler *et al*. 1991) but others have failed to replicate this result (Johnstone *et al*. 1989; Swayze *et al*. 1992 or Pearlson *et al*. 1997). Post-mortem morphometric brain studies found an association between parahippocampal cortex size and suicide (reviewed in Husseini *et al*. 2001) suggesting that these tasks may tap into neural areas with important implications for depressive symptomology.

From these studies it would seem that early information processing is impaired in both MDD, as assessed by performance on the IT task, and BD, as assessed by performance on the VBM task. These deficits appear to persist into the euthymic state of BD (MacQueen *et al*. 2001). Although these studies do not directly compare the performance of subjects with MDD and BD they both involve similar early forms of processing. These tasks target very initial stages of information processing so it is difficult to directly assess whether there may be an attentional bias during task performance, or any other impairment, that could affect the results of many different cognitive tests as well as tasks performed during ones normal daily routine.

MEMORY

Memory involves the storage and retrieval of information and it has long been suggested that depressed subjects have memory deficits and biases (see meta-analysis by Matt *et al*. 1992). Results

suggest these are quite broad ranging, encompassing cognitive tasks of both verbal and spatial domains, as well as more emotional memories. For example, Lloyd & Lishman (1975) found that depressed subjects have a bias for memories of negative events. Studies have also shown that when asked to generate an autobiographical memory in response to an emotional cue, such as 'happy', depressed subjects are more likely to generate overgeneral, categorical memories, of a type of event, for example, a party, rather than mentioning a specific party (Moore *et al*. 1988; Williams & Scott, 1988). Recently several studies have investigated different facets of memory in both MDD and BD patients.

Deficits in verbal memory have been identified in currently depressed subjects and, perhaps more strikingly, in unaffected siblings of BD subjects. Using a verbal process dissociation task (see Jacoby *et al*. 1996; Jacoby, 1998, for detailed description) MacQueen *et al*. (2002) have found deficits in recollection but not habit memory in subjects with MDD, either in a current episode or with a past history of depression, half of which were medicated. This deficit was independent of current mood state but dependent upon number of previous depressions suggesting that past illness burden plays an important role in this impairment. Kerí *et al*. (2001) studied unaffected siblings of patients with BD and identified deficits in delayed verbal recall at a long delay during which the subject was required to read aloud for 1 min prior to recall (siblings of subjects with schizophrenia were similarly impaired). A comprehensive study comparing verbal memory performance in patients with MDD and BD would be useful. Recent studies have also focused on spatial working memory and spatial and pattern recognition memory, tasks which can be used across differing age groups and cultures without the need to account for verbal ability.

In a study by Elliott *et al*. (1996) using the Cambridge Neuropsychological Automated Test Battery (CANTAB; www.camcog.comm) (Robbins *et al*. 1994) medicated subjects with MDD (on a combination of medications including one on lithium) had impaired spatial recognition memory. Further studies have suggested that medicated manic subjects also have impaired spatial pattern and recognition memory and spatial working memory (Murphy *et al*. 1999), possibly more so than subjects with MDD (Sweeney *et al*. 2000), and that deficits are present even during the euthymic state of BD (Rubinsztein *et al*. 2000). However, not all studies find such deficits in MDD subjects, for example Purcell *et al*. (1997). Differing results might be attributable to different mean ages of groups, combinations of medication and severity of illness.

Another task, the Delayed Matching to Sample Task (DMTS), requires subjects to remember a complex abstract pattern and after a delay of 0 to 12 seconds select which of four presented stimuli it matches. Patterns of impairment in DMTS in MDD and BD persisting in the remitted state are again similar to those for spatial working memory and spatial and pattern recognition memory suggesting that these tasks may be tapping into similar underlying processes and deficits. Elliott & Dolan (1999) used functional magnetic resonance imaging (fMRI) to investigate the underlying neural substrates of DMTS and delayed non-matching-to-sample (DNMTS) in healthy controls. In the DNMTS task the correct response requires selection of the novel stimulus. They found that matching was associated with increases in activation of the medial caudate and ventromedial orbital frontal cortex (OFC) while non-matching was associated with increased activation of relatively anterior areas of the lateral OFC bilaterally.

Elliott & Dolan argue that areas of the lateral OFC inhibit the impulse to select the more familiar stimulus. This fits in with other evidence suggesting that areas of the OFC are associated with an inhibitory role (Jones & Mishkin, 1972; Kowalska *et al*. 1991; Casey *et al*. 1997). The orbital cortex has been implicated as a specific area (within the frontal lobe) where a cerebrovascular lesion or tumour is likely to increase the risk of developing major depression (MacFall *et al*. 2001) and results from PET (positron emission tomography) studies have identified abnormal blood flow in areas of the OFC in depressed patients (Mayberg *et al*. 1994, 1997; Drevets *et al*. 1997). It appears that results from cognitive DMTS tasks concur with neuroimaging data implicating OFC abnormalities in depression.

Results from studies of early information processing and memory in depression and mania have highlighted broad-ranging cognitive deficits in both disorders, some of which persist in the remitted

state. This suggests that, while patients may appear to be symptom free, underlying deficits that may subsequently increase the probability of relapse remain. Analysis of performance measures on these tasks has not identified any clear differentiation between patients with MDD and BD though perhaps more complex tasks of executive functioning would highlight greater differences between the two groups. Importantly, evidence from neuropsychological and neuroimaging data appear to be converging to implicate abnormalities of the OFC in depression.

EXECUTIVE FUNCTION

Executive function includes the more obvious processes of planning and problem solving as well as, for example, the ability to attend to relevant stimuli while trying to filter out irrelevant distractions (see Robbins, 1996). Executive tasks require flexibility to adjust plans or strategies, to suspend performance so as to prioritize another task in the light of new information and to monitor performance in relation to goals. Any deficits in executive function in depression could have a major impact on performance of normal daily routines so their identification could be crucial for the development of therapies to assist in everyday function and to gain a better understanding of the nature of depression.

The Tower of London Task (ToL) (Owen *et al*. 1990) is a planning task during which subjects rearrange coloured balls in vertical columns so as to match a desired final outcome that is shown to them. Subjects are told to try to plan their moves and perform the task in the minimum number of moves possible. Elliott *et al*. (1996) found that medicated subjects with MDD solved fewer problems in the minimum number of moves possible as well as failing to successfully complete more trials (more maximum number of moves). MDD patients also exhibited slower planning times.

More recently another version of the ToL task has been developed to reduce the motor demands of the task, the One-Touch ToL task (NToL task) (Owen *et al*. 1995, 1996). During this task subjects are asked to select the minimum number of moves required to transform one arrangement of coloured balls to another without actually having to move them. Medicated subjects with mania were impaired on the NToL task (Murphy *et al*. 1999). Impairments in accuracy do not appear to extend into the medicated remitted BD state (Rubinsztein *et al*. 2000) suggesting that BD deficits in planning may be state-dependent. Performance on the NToL task leads to increased activation of areas of the dorsolateral prefrontal cortex (PFC) (Baker *et al*. 1996; Elliott *et al*. 1998) as well as the anterior cingulate (Dagher *et al*. 1999), areas shown to have abnormal blood flow in MDD and BD (for example Bench *et al*. 1992; Drevets *et al*. 1997).

Another component of executive function is decision making. Rogers *et al*. (1999*a*) have developed a computerized decision-making task and found deficits in both MDD and BD, with BD subjects exhibiting deficits on more aspects of the task. During the task subjects are required to decide which of two outcomes is most likely and to then bet a proportion of their current points total on this decision. Both manic and MDD medicated subjects had slower deliberation times and made more conservative bets at the most favourable odds ratios than healthy controls (Murphy *et al*. 2001). Manic patients, unlike patients with MDD, also made suboptimal decisions, being more likely than controls to select the less likely of the two outcomes. This impairment correlated with severity of illness ratings as measured by the Young Mania Rating Scale (Young *et al*. 1978).

The pattern of deficit observed in mania is very similar to that of patients with damage to orbitofrontal areas of the PFC (Rogers *et al*. 1999*b*); which was found to differ from that of patients with damage to dorsolateral or dorsomedial regions of the PFC. An fMRI study using an adapted version of this task showed that areas of right inferior and orbital PFC are activated during task performance (Rogers *et al*. 1999*a*). The lack of suboptimal decision-making in MDD does not necessarily imply that OFC function is spared since evidence discussed above suggests that abnormalities in metabolic activity and grey matter volume exist in the vicinity of this area in MDD (Mayberg *et al*. 1994, 1997; Rajkowska *et al*. 1999; Drevets, 2000; MacFall *et al*. 2001). Rubinsztein *et al*. (2001), using a modified version of the task for a PET study, found task related increased activation in manic patients, as compared with controls, in areas of the left

dorsal anterior cingulate. Significant activation in regions of interest was not observed in depressed patients.

Rubinzstein *et al.* (2001) found a positive correlation between severity of manic symptoms, as measured by the Young Mania Scale (Young *et al.* 1978), and task related activity in the dorsal anterior cingulate. This region was shown to have abnormally reduced resting activity in MDD (Bench *et al.* 1992; Bell *et al.* 1999). Drevets *et al.* (1997) have previously demonstrated increased resting metabolism in a more ventral subgenual cingulate region in manic patients. Furthermore, Drevets *et al.* showed that the subgenual prefrontal cortex (PFC), within the ventromedial PFC, is differentially activated during periods of mania and depression. The orbital/ventromedial PFC is linked by extensive anatomical connections to the amygdala and other limbic and peralimbic structures, and is activated during tasks that assess a person's ability to make decisions and reverse associations between stimulus and reward (Rogers *et al.* 1999*b*; Rahman *et al.* 2001). The tasks of executive function described so far have made use of emotionally neutral stimuli. The Affective Go/No-go task (Murphy *et al.* 1999) uses positively and negatively valenced stimuli and has highlighted differences in performance between patients with mania and depression.

During this task 'happy' and 'sad' words are presented rapidly on the centre of a screen one at a time. One category of words are targets and the other distractors. Subjects are instructed to respond to targets by pressing the space bar as quickly as possible while withholding responses to distractors. After every two blocks subjects are instructed to switch responding and, for example, happy target words become distractors and sad words become targets (this is called a shift block). A particularly striking result is that the different patient groups were found to have opposite affective biases. Compared to controls manic patients were slower to respond to sad but not to happy targets while depressed patients were slower to respond to happy but not sad targets. Manic patients also made response inhibition errors. These performance deficits do not seem to extend into the remitted BD state (Rubinsztein *et al.* 2000) and therefore may prove useful in detecting relapse.

Elliott *et al.* (2000) used an adapted version of this task for fMRI and found that happy and sad words, as compared to orthographic control words, increased activation in the dorsal anterior cingulate in normal controls. In an fMRI study of medicated depressed subjects Elliott *et al.* (2002) found that when comparing responses to emotional *versus* neutral stimuli depressed subjects exhibited attenuated neural responses in the ventral cingulate, adjacent to the subgenual cingulate, and areas of the posterior orbitofrontal cortex. However, areas of the rostral anterior cingulate extending to the anterior medial prefrontal cortex were more activated by sad targets. Furthermore depressed subjects, unlike controls, exhibited differential activation in association with the emotional valence of the distractor, more specifically sad distractors were associated with a response in the right lateral orbitofrontal cortex. It would be of interest to compare fMRI data for MDD and BD subjects. As mentioned above Drevets *et al.* (1997) showed that the subgenual cingulate region was differentially activated in mania and depression.

It seems that while more standard tests of motor function, memory and planning do not appear to provide a significant means of differentiating between mania and depression other tasks of decision making or response inhibition appear to find differences between the two disorders. Sahakian and colleagues have highlighted the dichotomy between 'cold' or emotion-independent processing and 'hot' or emotion-dependent processing in MDD and BD (Roiser *et al.* 2003). It seems that tasks such as the decision making and affective Go/No-go tasks, which are more obviously 'hot' cognitive tasks begin to identify more robust differences in performance between BD, MDD and healthy controls. These tasks use affective material or produce an emotional response, for example, in the form of conflict situations. Another way in which a task may tap into 'hot' cognitive processes may be through the feedback that it provides.

RESPONSE TO NEGATIVE FEEDBACK

Sahakian and colleagues have identified a specific form of motivational impairment in depression, an abnormal response to negative feedback (Beats *et al.* 1996; Elliott *et al.* 1996, 1997; Murphy *et al.*

2003). Although it is as yet unclear whether this extends to all MDD and BD patient groups (Shah *et al*. 1999) an abnormal response to negative feedback has been found in MDD, particularly in the elderly (for example Steffens *et al*. 2001), and it appears to differentiate patients with MDD from other patient populations (Elliott *et al*. 1997; Lawrence *et al*. 1999; Swainson *et al*. 2000). Using a range of tests from the CANTAB neuropsychological test battery, the results of which have been discussed above, Elliott and colleagues (1996) showed that perceived failure on a problem had a detrimental effect on subsequent performance in subjects with MDD. They have suggested that this may represent a significant link between cognitive and emotional processes affecting performance, more specifically between negative affect and cognitive impairments in depression. This is consistent with evidence suggesting that depressed individuals often magnify the significance of failure while underestimating the significance of success (Buchwald, 1977; Nelson & Craighead, 1977; Gotlib, 1983). Depressed patients may tend to self-focus in response to negative feedback reflecting a ruminative response style (Nolen-Hoeksema, 1987).

This 'abnormal response' to negative feedback in MDD subjects has been shown to be a more specific impairment in processing only particular forms of negative feedback (Murphy *et al*. 2003). For example, negative feedback designed to be informative, in the sense that it may be used to improve performance on subsequent trials, did not affect performance by MDD subjects. Murphy *et al*. used two tasks, one a spatial working memory task in which feedback, though negative, involved a mnemonic aid and the other, a probabilistic visual discrimination and reversal task, in which intermittently misleading affective visual and auditory feedback was provided. MDD subjects were unimpaired in their ability to use negative feedback with a high information content to improve performance on the spatial working memory task. In contrast, during the second task, they had difficulty in maintaining a response set when presented with misleading 'emotional' negative feedback. MDD subjects were twice as likely as controls to incorrectly switch their response after receiving misleading feedback following a correct response while remaining unimpaired in their ability to acquire and reverse the probabilistic visual discrimination.

Drevets (2001) has suggested that activation in areas of the OFC during depressive states in humans may reflect endogenous attempts to interrupt unreinforced aversive thought and emotion. During the probabilistic reversal learning task such aversive thought may be triggered by negative feedback. An alternative explanation for perseverative cognition in MDD suggests that abnormal reductions in grey matter, glia and neuronal size in orbital cortex and ventrolateral PFC (Rajkowska *et al*. 1999; Bowen *et al*. 1989) may indicate disturbed interaction between these regions and the amygdala, striatum, hypothalamus or periaqueductal grey (PAG) in turn leading to maladaptive emotional, cognitive and behavioural responses (Drevets, 2001).

An fMRI study of the probabilistic reversal learning task by Cools *et al*. (2002) may help to suggest an underlying neural mechanism for the abnormal response to negative feedback in depression. Cools *et al*. (2002) found highly significant increased activation of the right ventrolateral PFC and regions near the ventral striatum during the final reversal error (this was the point at which a subject stopped responding to the previously correct stimulus and changed to the other, now correct, stimulus). Due to problems of signal susceptibility they were unable to obtain data for regions of the OFC and ventromedial PFC. Based on evidence from studies using, for example, the Go/No-go task (Garavan *et al*. 1999; Konishi *et al*. 1999) they suggest that the activation in the right ventrolateral PFC may reflect behavioural inhibition due to reversal learning while activation in the ventral striatum may reflect the learning of new associations. As mentioned above, Drevets (2001) suggested that reduced grey matter in the ventrolateral PFC in depression might be indicative of disturbed interactions with the amydala and striatum leading to maladaptive emotion, cognition and behaviour.

CONCLUSION

Results indicate that patients with MDD or BD have broad ranging cognitive deficits that extend from the very early stages of information processing to memory, planning and even responses to

feedback. Deficits of these key cognitive processes may underlie profiles of performance on differing tasks and may impair performance of everyday functioning. As would be expected from the symptomology of the two disorders patients do appear to have differences in cognitive profile, for example, with manic patients exhibiting positive biases and suboptimal decision making in contrast to depressed patients with negative biases and unimpaired quality of decision making (Murphy *et al*. 1999, 2001). Some cognitive deficits appear to persist in the remitted state, for example problems of sustained attention in BD (Clark *et al*. 2002). Particularly in BD cognitive symptoms may be the most sensitive indicators of incomplete remission and may in addition pose a barrier to effective rehabilitation (Roiser *et al*. 2003). There are few studies directly comparing cognitive performance in MDD and BD. Recent interest in conducting such studies has increased since other factors, such as variations in age, past burden of depression or medication status, can make it difficult to compare results across studies. Despite these limitations, the literature appears to present results from neuroimaging and neuropsychological studies that are converging to identify differences in neural activity which may be crucial to understanding the underlying neural basis of depression.

The differential pattern of performance between patients with depression and mania appears to be particularly significant on complex cognitive tasks subserved by neural networks including the orbitofrontal/ventromedial prefrontal cortex. These can be described as 'hot' cognitive tasks that involve some form of conflict or emotional response. Of course many tasks encompass aspects of both 'hot' and 'cold' processing but it seems that tasks involving more obviously 'hot' cognitive processing have been crucial for detecting specific profiles of performance in depression. Notably, the affective Go/No-go task highlights opposite attentional biases in MDD and BD. The profile of performance during the probabilistic reversal learning task is also exciting because although an abnormal response to negative feedback was found, performance on the task was otherwise unimpaired thus indicating a very specific deficit. This task points towards an underlying process, an abnormal response to negative feedback, which may explain deficits across a broad range of tasks. A better understanding of the dysfunctional reward system in depression may also help to explain the key symptom of anhedonia. The current understanding of depression is at an important stage since data from neuroimaging and cognitive studies appears to be synergizing and hence this area of neuropsychiatry seems poised to elucidate the core symptomology of depression and its underlying neural basis within this decade. This development should prove key to understanding the relationship between cognition and emotion and to developing effective treatments for these debilitating disorders of depression.

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J. V. Taylor Tavares is funded by the National Institute of Mental Health Intramural Research Programme as part of the National Institutes of Health – University of Cambridge Health Science Scholars Programme. W. C. Drevets is funded by the National Institute of Mental Health Intramural Research Programme. B. J. Sahakian's research is funded by a Wellcome Trust Programme Grant (Number 019407).

We would also like to thank Professor T. W. Robbins and J. P. Roiser for discussion.

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