NEUROPSYCHOLOGICAL ASSESSMENT OF MOOD DISORDER

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Summary

Cognitive dysfunction is central to our understanding of mood disorder in terms of everyday patient experiences, diagnostic criteria, and contemporary psychological models. Neuropsychological assessment can provide clinicians and researchers with convenient objective markers of disease that represent intermediaries between lower level neural dysfunction and the overt (top-level) expression of symptoms in patients. In this article, we provide an overview of practical and theoretical aspects of the neuropsychological assessment of mood disorder, focusing on the search for state and trait markers in the domains of memory, affective processing bias, response to negative feedback, decision-making, and sustained attention. Integrating the findings, we propose that neuropsychological assessment offers significant promise in improving detection of disease onset, monitoring recovery and relapse, assessing treatment efficacy, and developing more effective treatment algorithms for these highly debilitating and prevalent disorders.

Key Words: Depression – Mania – Bipolar – Fronto-striatal – Cognition

Declaration of interest: BJS Consults for Cambridge Cognition

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Introduction

Mood disorders are highly prevalent across cultures, and place an enormous burden on society. Depression was recently ranked by the World Health Organisation (WHO) as the leading cause of years lived with disability worldwide, and the fourth leading cause of disease burden (WHO 2001). By 2020, depression is expected to account for more burden of disease in developed countries than any other cause, even ischaemic heart disease. Major depressive disorder currently affects some 121 million people worldwide, and bipolar disorder some 27 million people (WHO 2000). These illnesses have substantial economic as well as social costs. To take but one example, the economic cost of depression was estimated at 83.1 billion dollars in the USA in 2000 (Greenberg et al. 2003).

Cognitive dysfunction is suggested by the everyday life experiences of people with mood disorders, and is integral to the diagnostic classification of these conditions according to the Diagnostic and Statistical Manual (DSM-IV 1994). Criteria for depression include diminished ability to concentrate, and indecisiveness. Likewise, criteria for mania include distractibility and poor decision-making, such as involvement in pleasurable activities that have a high potential for damaging consequences. Cognitive dysfunctions or distortions are also central to mainstream psychological models of depression. In Beck's Depressive Model, negative cognitive schemata develop during early life, and are activated later due to unpleasant or stressful life events. This leads to cognitive distortions such as all-or-nothing thinking, and modern cognitive therapy aims to help patients identity and modify these aberrant cognitive styles (Teasdale et al. 1984, Beck 1997).

Computerised neurocognitive tasks, such as those in the Cambridge Neuropsychological Test Automated Battery (CANTAB) (www.camcog.com), are well-suited for the assessment of cognition in individuals and in groups of patients. They can be readily administered between study sites in a consistent way, automate data collection, and reduce potential for human bias and error. These tests allow for the hypothesis-driven dissection of different domains of cognition, and for comparisons to be made between mood disorders, other psychiatric conditions, patients with focal neurosurgical lesions, and healthy volunteers. The diagnosis of mood disorders in patients, assessment of disease severity, monitoring of treatment response, and selection of treatment interventions, are all currently dependent

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on clinician assessment of top-level symptoms. Neuropsychological tests can act as sensitive and objective intermediate markers of disease that are closer to the underlying brain basis of psychiatric conditions than these top-level symptoms (Castellanos and Tannock 2002, Gottesman and Gould 2003). This search for intermediate disease markers (endophenotypes) is an exciting prospect at the forefront of current research that is likely to improve understanding of neurobiology and inform clinical practice.

In this article, we will first discuss some important background issues in neuropsychological assessment, before providing a précis of what is known of neurobiology and neurochemistry of mood disorders. We will then discuss neuropsychological assessment as applied to mood disorders, and bring the reader up-to-date with important findings in five key cognitive domains: memory, affective processing bias, response to negative feedback, decision-making, and sustained attention. We will finish by highlighting the growing role of neuropsychological testing in clinical and research environments, and discuss future research directions.

Background Considerations

The purpose of neuropsychological testing is to provide objective measures of brain dysfunction by indicating cognitive domains that are deficient or spared in individual patients or in groups of patients. There are several important considerations when undertaking any neuropsychological testing procedure. In order to select appropriate control data, it is vital to record age, level of education, and pre-morbid IQ of participants. In the UK for example, the National Adult Reading Test (Willshire et al. 1991) provides a useful estimate of pre-morbid verbal IQ. It is also important to ensure consistency of test administration, via the provision of standard instruction sets, and clear guidance for test administrators about interventions they are permitted to make during assessment (e.g. if questioned by the participant during a cognitive task). It should always be born in mind that it is possible for someone to fail a test for reasons other than 'primary' cognitive dysfunction. For example, a test of memory could be failed due to attentional dysfunction rather than memory deficits *per se*. This emphasises the need for the inclusion of well-validated background tests as part of any comprehensive testing battery. In studies using elderly patients and healthy volunteers, the Mini Mental State Examination (MMSE) should be used (Folstein et al. 1975).

Neuropsychological performance can be influenced by mood status at the time of testing, and it is critical to quantify these factors. Recommended clinical indices for depressive mood status include the Hamilton Rating Scale for Depression (HAM-D, Hamilton 1960), Montgomery-Asberg Depression Rating Scale (MADRS, Montgomery and Asberg 1979) and the self-complete Beck's Depression Inventory (BDI, Beck and Beamesderfer 1974). The BDI is also useful for quantifying mood status in healthy volunteers. Mania can be assessed in patients with Young's Mania Rating Scale (YMRS, Young et al. 1978). In studies seeking to use recovered depressed patients or euthymic bipolar patients, clinical rating scales should be used to help define cut-offs for what constitutes recovery. For example, a score of <10 on the MADRS represents an optimal cut-off for people who previously suffered from depression (Hawley et al. 2002).

Research to date has often overlooked the need to carefully screen for psychiatric co-morbidities in patients, and for psychiatric illnesses in putative healthy controls whose results will be used as normative data. For example, mood disorders are frequently co-morbid with anxiety disorders (Zimmerman et al. 2002), and yet anxiety disorders are in themselves associated with particular profiles of cognitive dysfunction (see e.g. Chamberlain et al. 2005). The need to screen controls is evident when one considers that psychiatric disorders in the background population are commonplace. In one large study in the United Kingdom, one in six adults were reported as having a psychiatric disorder in the week preceding the study interview (Singleton et al. 2003). The Structured Clinical Inteview for DSM-IV (SCID) represents a gold-standard screening tool for axis-I disorders (Spitzer et al. 1996), though the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al. 1998) is well-validated and more rapid to administer.

Neural Circuitry

The use of neuropsychological assessment in mood disorders presupposes that there are underlying brain dysfunctions in these conditions. Circuitry within the brain can be considered to form relatively segregated loops that connect thalamus, basal ganglia, and cortical structures (Alexander et al. 1986). Disruption to fronto-striatal circuitry is implicated in a variety of psychiatric conditions including mood disorders, Obsessive Compulsive Disorder (OCD), schizophrenia, Parkinson's disease, and others. In mood disorders, the focus to date has been on the 'affective' loop connecting orbitofrontal and anterior cingulate cortices to ventral striatum, ventral pallidum and thalamus (Chamberlain and Sahakian 2004). Evidence implicating this circuit in mood disorders comes from several sources, including structural neuroimaging, resting state functional neuroimaging, secondary mood disorders, and combined neuropsychological-neuroimaging studies.

Structural Magnetic Resonance Imaging (MRI) has facilitated the comparison of volumes of specific brain structures in patients with mood disorders and healthy volunteers. In bipolar disorder and depression, reduced grey matter volumes are frequently reported in the frontal lobes, especially anterior cingulate and dorsolateral prefrontal cortices (Drevets et al. 1997, Sheline 2003, Fossati et al. 2004, Lyoo et al. 2004). Additionally, reduced hippocampal volume is robustly reported in depression (Sheline 2003, Sheline et al. 2003, Campbell et al. 2004) but not bipolar disorder (Altshuler et al. 2000, Hauser et al. 2000), and it may be that lithium has neuroprotective effects in the hippocampus (Manji et al. 2000). Older patients with mood disorders show increased numbers of brain white matter signal hyperintensities, particularly around the ventricles, and in the deep white matter and sub-cortical structures (e.g. Aylward et al. 1994, Dahabra et al. 1998, Krishnan et al. 2004). These types of white matter hyperintensity

are associated with cardiovascular disease and hypertension, suggesting a possible ischaemic contribution to the development of depression in these more elderly patients (Levy et al. 2003).

Abnormalities in regional cerebral blood flow and brain metabolism in patients with mood disorders have been examined with Positron Emission Tomography (PET/SPECT) and functional Magnetic Resonance Imaging (fMRI) techniques. Hypoactivation of frontal lobe regions, especially dosolateral prefrontal and anterior cingulate cortices, have been reported in both depression and mania (Baxter et al. 1989, Bench et al. 1992, Ketter et al. 2001, Kruger et al. 2003, Mayberg 2003). In seminal work by Drevets and others using PET, familial bipolar depressive and unipolar depressive patients showed abnormally reduced activity in a specific area of prefrontal cortex ventral to the genu of the corpus callosum, associated with volume loss in the same region (Drevets et al. 1997). The degree of dysfunction in implicated neural regions in depressed patients has been shown to be predictive of response to pharmacological and psychotherapeutic interventions (Mayberg et al. 1997, Goldapple et al. 2004), and successful treatment of mood disorder appears to normalise dysfunction in these regions (Goodwin et al. 1993, Bench et al. 1995). Dysfunctional orbitofrontal cortex is implicated in mania, and bipolar patients withdrawn from lithium medication show increases in orbitofrontal cortex perfusion that correlate with increases in manic symptom scores (Goodwin et al. 1997).

The occurrence of secondary depression is also consistent with the involvement of fronto-striatal circuitry in mood disorders. Patients with brain injury to frontal lobes or basal ganglia regions from stroke, tumour resections, and head injury show higher than expected rates of depression (Pohjasvaara et al. 2001a, Pohjasvaara et al. 2001b). Further, neuropsychiatric conditions such as Parkinson's Disease, Huntington's Disease, and OCD show frequent co-morbidity with depression and share overlap in terms of implicated neural structures (e.g. see Chamberlain et al. 2005). Cases of secondary mania are considerably rarer, but frontal lesions can induce persistent mania (the disinhibition syndrome) (Starkstein et al. 1990, Starkstein and Robinson 1997).

In all, evidence supports involvement of fronto-striatal circuitry, especially the affective basal ganglia-thalamocortical loop, in the neurobiology of mood disorders. Volumetric and functional abnormalities are widely reported in frontal lobe regions, especially dorsolateral and anterior cingulate cortex. The challenge for modern day research is to dissociate distinct and overlapping neural contributions between mood disorders and other conditions and clarify the contribution of these dysfunctions to neuropsychological test performance and symptoms. One powerful way of tackling this challenge is to use neuropsychological paradigms that have been specially adapted for neuroimaging use.

Neurochemistry

Given the fronto-striatal dysfunction evident in mood disorders, it is necessary to question the status of underlying transmitter systems in these circuits. The classic monoamine hypothesis of depression holds that a reduction in serotoninergic, dopaminergic, and/or noradrenergic transmitter levels mediates depressive symptomatology, and that monoamine oxidase inhibitors improve symptoms by reversing this deficiency (see e.g. Coppen 1967). Selective Serotonin Reuptake Inhibitors (SSRIs) now represent the most common pharmacological treatment for depression and more recent research has tended to focus on serotoninergic involvement, especially the expression of 5-HT receptor subtypes (Cowen 1990).

In the tryptophan depletion technique, volunteers ingest an amino acid drink that lacks the precursor necessary for serotonin synthesis, thereby transiently reducing brain serotonin levels (Bell et al. 2001). Recovered patients who previously suffered from depression show a recurrence of depressive symptoms when serotonin transmitter levels are transiently reduced via this method (Young 1993). In studies using healthy volunteers and recovered depressive patients, tryptophan depletion has also been shown to modulate emotional processing and other aspects of cognitive functioning (Young et al. 1985, Murphy et al. 2002, Rogers et al. 2003). Though serotonin is clearly implicated in the neurochemistry of depression, the role of other transmitter systems should not be overlooked, as selective noradrenergic reuptake inhibitors (SNRIs) including atomoxetine (formerly tomoxetine) and reboxetine show efficacy in the treatment of depressive illness (Chouinard et al. 1984, Messer et al. 2005).

Neurochemical abnormalities in mania are less well characterised. While lithium is effective as a mood stabiliser in bipolar illness, it appears to have generalised effects on multiple cellular systems (Shastry 1997). Dopamine excess may be involved in the initiation of manic episodes, as amphetamines (which increase free levels of dopamine) induce manic-like symptoms in healthy volunteers (Jacobs and Silverstone 1986), and euthymic bipolar patients show greater increase in manic symptoms in response to amphetamine compared to controls (Anand et al. 2000). Further, the transient reduction of brain dopamine via tyrosine depletion (a procedure analogous to tryptophan depletion) has been found to improve manic symptoms in acute inpatients (McTavish et al. 2001).

The hypothalamo-pituitary-adrenal (HPA) axis regulates many biological factors including sleep/wake-cycles, weight and metabolic control, cardiovascular status, and responses to stressful situations. Abnormally raised plasma concentrations of cortisol have been reported in depression, mania, and bipolar depression (Carroll and Curtis 1976, Cassidy et al. 1998, Cervantes et al. 2001). Patients with Cushing's Disease, characterised by pathologically high secretion of cortisol into the bloodstream, show higher then expected incidence of mood disorders (Jeffcoate et al. 1979, Brown et al. 2004). In the dexamethasone suppression test, synthetic glucocorticoids are administered in order to record the feedback effects on the HPA-axis. Multiple studies report an abnormal axis response in patients with mood disorders (e.g. Rybakowski and Twardowska 1999, Varghese and Brown 2001). The HPA axis is increasingly implicated in developmental models of mood disorders (Goodyer et al. 2000), and

cortisol has been shown to regulate brain serotonin receptor expression in animals (Chalmers et al. 1993).

In summary, current pharmacological treatment algorithms and other evidence implicate serotoninergic and/or noradrenergic abnormalities in depression, and dopamine excess in the instantiation of manic episodes. Dysregulation of the HPA-axis is reported in many patients. Ongoing research is investigating the effects of SSRIs, SNRIs, and other medications on neuropsychological performance in healthy volunteers and in patients with mood disorders. This is likely to enhance understanding of neurochemistry, and suggest novel treatment directions.

Cognitive abnormalities, in search of state and trait markers

Studies to date have examined cognitive functioning across a broad range of domains in depression and mania (see e.g. Tavares et al. 2003 for review). Deficits have most frequently been reported on measures of attention, memory, psychomotor speed, and executive function. The diagnosis of major depression or mania according to DSM-IV allow for considerable variation in the criteria, and it should not be surprising that the precise pattern of cognitive dysfunction is somewhat variable between patients. Cognitive tasks continue to be developed and modified in light of clinical and research findings, and it is becoming increasingly feasible to identify trait and state markers of disease. Trait markers represent neurocognitive signatures (deficits or abnormalities) that persist even into full mood episode recovery (e.g. into the euthymic phase of bipolar illness). State markers represent neurocognitive signatures limited to mood episodes themselves – e.g. found only in depressed patients when they are clinically depressed. These two types of markers are likely to be of utility in the detection of disease onset, monitoring of treatment response, and assessment of treatment efficacy. Here we focus on five domains that are showing promise in the search for such markers: memory, affective processing bias, response to negative feedback, decision-making, and sustained attention.

Memory

Patients with depression often report memory problems, and these are also evident according to self-report inventories such as the Memory Complaints Inventory (MCI) (Rohling et al. 2002, Jorm et al. 2004). It is important to consider whether these subjective memory complaints can be more objectively quantified using neuropsychological tasks. The ability to encode, consolidate, and retrieve information all contribute to performance on neuropsychological tests of memory, and impairments have been widely reported in depressed and manic patients using a variety of tasks (Wolfe et al. 1987, Beats et al. 1996, Elliott et al. 1996). Further, these memory problems persist into the euthymic stages of bipolar illness and are associated with poor functional outcome (Rubinsztein et al. 2000, Martinez-Aran et al. 2004a, Martinez-Aran et al. 2004b). Temporal lobe regions (especially the hippocampus) represent important neural substrates of memory (Owen et al. 1996). The reduced hippocampal volumes observed in major depression are consistent with temporal lobe dysfunction contributing to memory impairments in this group. However, bipolar patients do not show evidence of hippocampus volume abnormalities, and it is necessary to question whether dysfunction in other neural regions might underpin the mnemonic deficits in these patients. Performance on some neurocognitive tasks can be greatly aided by the use of spontaneous strategies – i.e. breaking tasks down into meaningful sub-goals in order to optimise performance. The use of strategy is dependent on frontal lobe circuitry, and euthymic patients show impaired strategy on some memory tasks (Deckersbach et al. 2004), suggesting that trait memory impairments in bipolar disorder may be partly attributable to frontal lobe dysfunction.

Modern testing batteries such as the CANTAB include tests for different types of memory, including spatial working memory, spatial recognition memory and pattern recognition memory. Results from studies using these tests suggest that memory deficits emerge with advancing patient age and are not present in young depressed patients (Beats et al. 1996, Purcell et al. 1997). The contributory factors underlying this apparent worsening of mnemonic function with age are unclear, though the white matter signal hyperintensities (see previous discussion) may contribute in older patients. Irrespective of the causal issues, it is likely that memory problems impede not only the quality of life of patients with mood disorders, but also the ability of such patients to successfully undertake psychological and pharmacological treatments and make a full recovery – particularly given that the objective memory deficits persist into euthymia. Ongoing work is focussing on the cognitive enhancing effects of novel pharmacological agents. For example, the wake-promoting agent modafinil has been shown to enhance aspects of cognitive functioning including memory in healthy high-IQ volunteers, according to objective assessment with CANTAB tasks. Medications including modafinil may be of utility in the augmentation of the usual pharmacological treatment of mood disorders, in order to help patients overcome rehabilitation barriers and make a fuller recovery (Turner et al. 2003, Chamberlain and Sahakian 2004).

Affective processing bias

Depression and mania are characterised by diverse and debilitating symptoms, but fundamentally differ from each other in terms of affect. Whereas depression is characterised by the negative view of self, world, and future (Beck's negative triad, Beck et al. 1979), patients with mania show grandiosity, positive often unrealistic expectations, and socially inappropriate behaviour. We can think of these two states as being at opposite ends of a mood spectrum (Chamberlain and Sahakian 2004). Unlike the dysphoria or euphoria experienced by us all from time to time, the extreme polar states of depressed and manic mood are more persistent and are severely debilitating. Consistent with

the mood spectrum conceptualisation, depressed patients show a bias towards the recall of negative autobiographical material, and when they recall positive material it tends to lack detail (Williams and Scott 1988, Brittlebank et al. 1993). Depressed patients are also impaired at recognising happy facial expressions (Rubinow and Post 1992), whereas manic patients are impaired at recognising negative facial expressions (including sad faces) (Lembke and Ketter 2002). An important question that arises is whether these apparent affective processing biases are evident using objective computerised neurocognitive assessment methods.

On go/no-go tasks, subjects are typically shown a series of stimuli presented rapidly on a computer screen, and are asked to make simple motor responses to target stimuli but to ignore distractor stimuli. Several measures are recorded (for each stimulus class), including mean time taken to respond, number of commission errors (incorrectly making a motor response to a distractor stimulus), and number of omission errors (failing to make a motor response to a target stimulus). Seminal work has utilised 'hot' versions of the go/no-go paradigm, using words with positive or negative affective content, to explore affective processing biases in depression and mania. Intriguingly, there is evidence that healthy controls show some positive affective bias by default, they typically respond slightly more rapidly to happy compared to sad target words (e.g. Murphy et al. 2002, McLean et al. 2004, Chamberlain et al. in submission 2005). When responding to emotionally hot compared to neural words, healthy volunteers show an enhanced neural response in the subgenual cingulate cortex (Elliott et al. 2000), a region known to be involved in emotional processing and to be functionally abnormal in mood disorders. When levels of brain serotonin are reduced via tryptophan depletion in healthy volunteers, performance on the affective go/no-go task mimics that seen in depressed patients (Murphy et al. 2002), consistent with a central role for serotonin in emotional processing.

It has been possible to examine neural activity in depressed and manic patients when undertaking neuroimaging versions of the affective go/no-go task. Depressed patients respond more rapidly to sad versus happy words, consistent with bias towards negative environmental stimuli (Figure 1). They show an elevated neural response to sad target words in the rostral anterior cingulate extending to anterior medial prefrontal cortex (Elliott et al. 2002), and a differential neural response in the lateral orbitofrontal cortex to sad distractor words. These findings add to the corpus of work emphasising the importance of medial prefrontal and orbitofrontal cortices in emotional processing and behavioural inhibition. Manic patients show a latency bias towards happy words (Murphy et al. 1999) (Figure 1), enhanced response to emotional compared to neutral words in left ventrolateral prefrontal cortex, and enhanced response to happy distractor words in the ventral and medial prefrontal cortex (Elliott et al. 2004).

Response to negative feedback

In everyday life, patients with depression view even minor errors in a pessimistic light and ruminate about their failures, attributing events to internal, specific, stable factors. For example, after breaking a cup at home, a patient with depression might think I broke the cup because I am useless at everything rather than I broke the cup, but it doesn't matter and can be replaced. Negative automatic thoughts contribute to the perva-

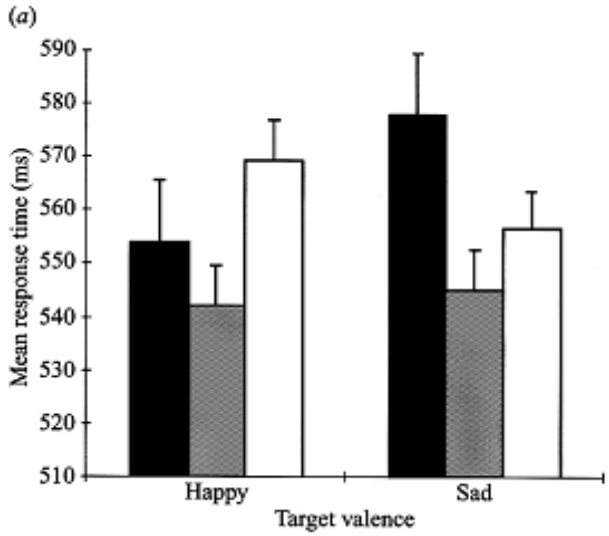

Figure 1. *Affective Go/no-go task. Mean reaction times to happy and sad target words. Manic patients respond more rapidly to happy versus sad words (black), depressed patients respond more rapidly to sad versus happy words (white), and controls show a slight bias towards happy words (grey). Reprinted with permission.*
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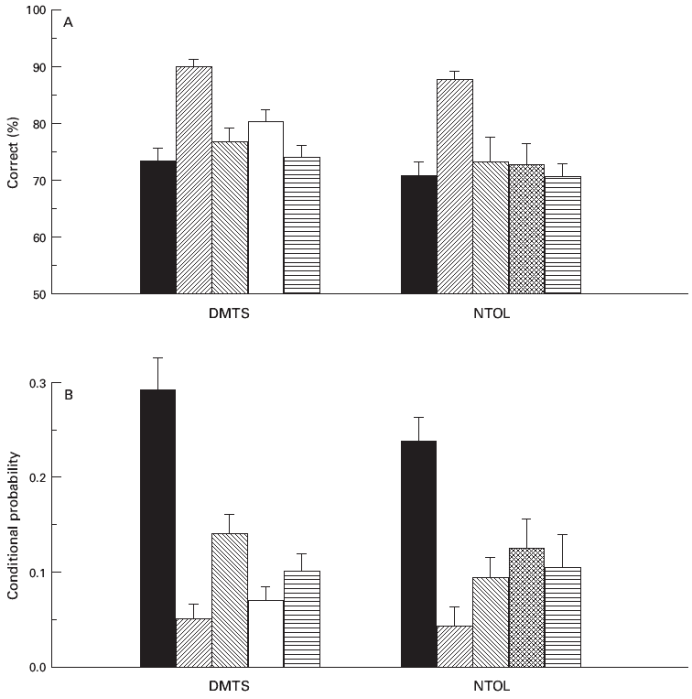

Figure 2. *DMTS and TOL task performance in (left to right) depression, healthy volunteers, Parkinson's disease, neurosurgical lesions, and schizophrenia (left to right). Clinical groups are similarly impaired on percentage of correct responses (top), but only depressed patients show an abnormal response to negative feedback (bottom).*
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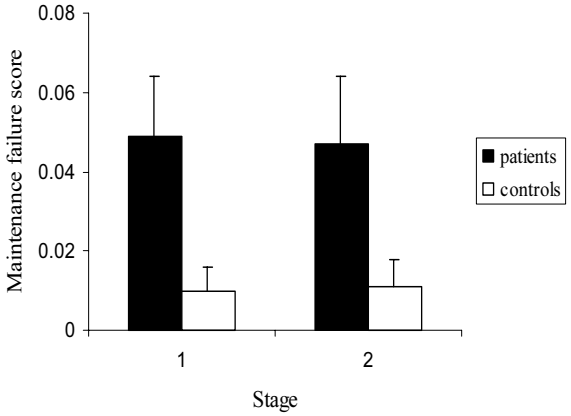

Figure 3. *Visual discrimination and reversal task. Depressed patients' performance is impaired by false negative feedback. Reprinted with permission.*
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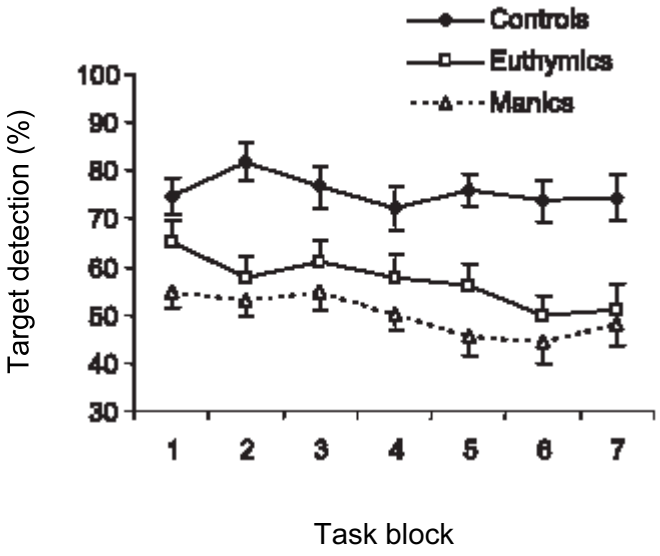

Figure 4. *RVIP task. Percentage of targets detected. Impaired sustained attention during manic episodes is also found during the euythymic phase of bipolar illness.*
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Cognitive Domain	Tasks	Key measures
Memory	Pattern Recognition Memory	% Correct, immediate and delayed recall
Affective processing	Affective Go / No-Go	Latency bias (happy versus sad mean reaction times)
		Commission errors
		Omission errors
Response to negative feedback	Tower of London	% Correct, latency, probability of incorrect response given previous response was incorrect
	Delayed Matching to Sample	% Correct, latency, probability of incorrect response given previous response was incorrect
	Probabilistic reversal learning	number of errors, maintenance score, probability of failing trial given negative feedback on previous trial
Decision making	Cambridge decision-making	% points gambled at each level, quality of decision-making
Sustained attention	Rapid Visual Information Processing (RVIP)	% targets detected, number of commission errors

Figure 5. *Details of CANTAB neuropsychological tasks of use in the assessment of mood disorders*

sive and persistent negative mood in a vicious cycle (Teasdale et al. 1984). It is important, therefore, to examine how patients with depression respond when they are informed they have make a mistake during cognitive assessment (when they are given 'negative feedback').

On the Delayed Matching to Sample (DMTS) test, subjects are shown a complex abstract pattern to memorise, and then attempt to correctly select this pattern from amongst others after a delay (www.camcog.com). On the new Tower of London (TOL) test of planning, developed from the Tower of Hanoi task, volunteers are asked to work out the number of moves it would take to move a set of snooker balls into a target arrangement shown by the computer. With both of these tasks, if an error is made then feedback is given and volunteers are asked to think through the problem again and try to figure out what the correct answer might be. Performance on these tasks is dependent on distributed neural networks, with NTOL perhaps dependent on more frontal circuitry than DMTS (Baker et al. 1996, Elliott et al. 1997a). Depressed patients are similarly impaired on both of these tasks compared to people with Parkinson's disease, neurosurgical lesions, and schizophrenia, in terms of percentage problems solved correctly at the first attempt (Elliott et al. 1997b). Importantly however, only depressed patients show an abnormal response to negative feedback; when informed that they have just failed a problem (n), they are far more likely to fail the next problem (n+1) (Figure 2). This abnormal response to negative feedback in depression has also been confirmed on a visual discrimination and rule-reversal task that gives false negative feedback (i.e. tells volunteers, on a subset of trials, that they were wrong when in fact they were correct) (Murphy et al. 2003) (Figure 3). The debilitating effect of negative feedback on task performance in depressive patients is likely to be related to the clinical anhedonia, or loss of interest in pleasurable activities, demonstrable in the symptomatology.

Decision-Making

Patients with mania often show excessive involvement in pleasurable activities with a high potential for negative consequences, such as spending sprees or erratic business decisions, and this is central to the diagnostic criteria (DSM-IV 1994). Impaired decision-making is also found in people with secondary mania (the disinhibition syndrome) (Starkstein and Robinson 1997). Computerised decision-making tasks have been shown to be dependent on the integrity of fronto-striatal circuitry (Bechara et al. 1994, Bechara et al. 1998, Manes et al. 2002, Clark et al. 2003), and it is logical to question whether the 'risk seeking' behaviour observable in manic symptoms are evident on these tasks.

On the Cambridge decision-making task, subjects attempt to win as many points as possible by choosing outcomes based on variably-weighted probabilities, and gambling a proportion of accumulated points. Medicated manic patients and depressed patients both show slower decision-making times and accumulate fewer points than healthy controls (Murphy et al. 2001). However, only manic patients make sub-optimal decisions, and the extent of this impairment correlates with severity of manic symptoms. Using a version of the Cambridge decision-making task modified for neuroimaging, it has been shown that manic patients have greater task-related activation than controls in the left anterior cingulate cortex, and that the extent of this hyperactivation correlates significantly with severity of manic symptoms (Rubinsztein et al. 2001).

Sustained Attention

Problems with attention are suggested by the diagnostic criteria for depression (diminished ability to concentrate) and mania (distractability). Deficits in the ability to sustain attention can be examined neuropsychologically with continuous performance tasks (CPTs). In these tasks, volunteers observe rapidly presented stimuli on a computer screen, and are asked to make motor responses to target sequences only. For example, in the Rapid Visual Information Processing task (RVIP) (www.camcog.com), single digits are presented in a continuous stream in a box at the centre of a computer screen, and subjects are asked to make motor response whenever a target three-digit sequence appears (e.g. '2' followed by '4' followed by '6'). These CPTs must be performed for several minutes, with targets occurring infrequently and unpredictably. CPT performance is dependent on a predominantly right fronto-parietal network (Coull et al. 1996).

Patients with depression and mania show impaired sustained attention on CPTs (Rund et al. 1992, Hart et al. 1998, Sax et al. 1999). Recovered previously depressed patients show intact performance on the RVIP task, whereas bipolar patients during the euthymic phase show persisting deficits (Clark et al. 2002, Clark and Goodwin 2004, Clark et al. 2005) (Figure 4). For this reason, Clark et al. have suggested that deficits on the RVIP sustained attention test may represent a trait marker for bipolar disorder. The finding of impaired sustained attention between mood episodes in bipolar disorder is likely to have implications for the functional recovery of such patients.

Conclusions

Mood disorders are prevalent, debilitating, and costly to society. Cognitive dysfunction is central to our understanding of these conditions in terms of everyday patient experiences, diagnostic criteria, and psychological models. Neuropsychological assessment techniques are ideally placed to provide researchers and clinicians with objective measures of brain dysfunction, by acting as intermediate markers between low-level manifestations of brain dysfunction (transmitter and receptor expression abnormalities; neuroimaging findings) and top-level symptom expression. In this article we have focused on memory, affective processing bias, response to negative feedback, decision-making, and sustained attention (see figure 5 for task overview). Neuropsychological assessment in these domains has provided us with evidence for state/trait markers of mood disorders.

Memory deficits are common to mania and depression and may represent a trait marker for bipolar disorder. State dependent affective processing biases, implicit from the symptoms of depression and mania, are evident on affective go/no-go tasks. Also consistent with a ruminative style in depression, depressed patients show an abnormal response to negative feedback on several neurocognitive tasks, including TOL, DMTS, and reversal learning. During manic episodes, patients often make irrational decisions in everyday life, and also show sub-optimal decisions on the Cambridge decision-making task, the extent of which has been shown to correlate with symptom severity. Diminished ability to concentrate in depression and distractibility in mania suggest problems with attention, and impairments in sustained attention are found in depression, mania, and in bipolar patients during the euthymic phase.

By 2020, mood disorders are likely to account for more disease burden in developed countries than ischaemic heart disease. The use of neuropsychological assessment methods is rapidly growing, and is likely to facilitate improvements in the detection of disease onset, monitoring of recovery and relapse, and assessment of treatment efficacy. Further, by using neuropsychological assessment to quantify the cognitive effects of pre-existing and novel pharmacological agents, we may be able to develop new treatments and improved treatment algorithms for mood disorders.

Acknowledgements

SRC is on the Cambridge MB/PhD programme, funded by a Medical Research Council (MRC) research studentship (UK).

This research work was funded by the Wellcome Trust (programme grant 019407) and the MRC (centre grant G0001354). The authors are grateful to all research participants, and to Dr Luke Clark (Department of Experimental Psychology, Cambridge University, UK) for discussion.

References

Alexander GE, MR DeLong, and PL Strick (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9, 357-81.

Altshuler LL, G Bartzokis, T Grieder, J Curran, T Jimenez, K Leight, J Wilkins, R Gerner and J Mintz (2000). An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. *Biol Psychiatry* 48, 2, 147-62.

Anand A, P Verhoeff, N Seneca, SS Zoghbi, JP Seibyl, DS Charney and RB Innis (2000). Brain SPECT imaging of amphetamine-induced dopamine release in euthymic bipolar disorder patients. *Am J Psychiatry* 157, 7, 1108-14.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV). American Psychiatric Association, Washington DC.

Aylward EH, JV Roberts-Twillie, PE Barta, AJ Kumar, GJ Harris, M Geer, CE Peyser and GD Pearlson (1994). Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. *Am J Psychiatry* 151, 5, 687-93.

Baker SC, CD Frith, RS Frackowiak and RJ Dolan (1996). Active representation of shape and spatial location in man. *Cereb Cortex* 6, 4, 612-9.

Baxter LR Jr, JM Schwartz, ME Phelps, JC Mazziotta, BH Guze, CE Selin, RH Gerner and RM Sumida (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 46, 3, 243-50.

Beats BC, BJ Sahakian and R Levy (1996). Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol Med* 26, 3, 591-603.

Bechara A, AR Damasio, H Damasio and SW Anderson (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50 1-3, 7-15.

Bechara A, H Damasio, D Tranel and SW Anderson (1998). Dissociation Of working memory from decision making within the human prefrontal cortex. *J Neurosci* 18, 1, 428-37.

Beck AT (1997). The past and future of cognitive therapy. *J Psychother Pract Res* 6, 4, 276-84.

Beck AT and A Beamesderfer (1974). Assessment of depression, the depression inventory. *Mod Probl Pharmacopsychiatry* 7, 151-69.

Beck AT, Rush AJ, Shaw BF, Emergy G (1979). *Cognitive Therapy of Depression.* The Guilford Press, New York.

Bell C, J Abrams and D Nutt (2001). Tryptophan depletion and its implications for psychiatry. *Br J Psychiatry* 178, 399-405.

Bench CJ, RS Frackowiak and RJ Dolan (1995). Changes in regional cerebral blood flow on recovery from depression. *Psychol Med* 25, 2, 247-61.

Bench CJ, KJ Friston, RG Brown, LC Scott, RS Frackowiak and RJ Dolan (1992). The anatomy of melancholia—focal abnormalities of cerebral blood flow in major depression. *Psychol Med* 22, 3, 607-15.

Brittlebank AD, J Scott, JM Williams and IN Ferrier (1993). Autobiographical memory in depression, state or trait marker? *Br J Psychiatry* 162, 118-21.

Brown ES, FP Varghese and BS McEwen (2004). Association of depression with medical illness, does cortisol play a role? *Biol Psychiatry* 55, 1, 1-9.

Campbell S, M Marriott, C Nahmias and GM MacQueen (2004). Lower hippocampal volume in patients suffering from depression, a meta-analysis. *Am J Psychiatry* 161, 4, 598-607.

Carroll BJ and GC Curtis (1976). Neuroendocrine identification of depressed patients. *Aust N Z J Psychiatry* 10, 1, 13-20.

Cassidy F, JC Ritchie and BJ Carroll (1998). Plasma dexamethasone concentration and cortisol response during manic episodes. *Biol Psychiatry* 43, 10, 747-54.

Castellanos FX and R Tannock (2002). Neuroscience of attention-deficit/hyperactivity disorder, the search for endophenotypes. *Nat Rev Neurosci* 3, 8, 617-28.

Cervantes P, S Gelber, FN Kin, VN Nair and G Schwartz (2001). Circadian secretion of cortisol in bipolar disorder. *J Psychiatry Neurosci* 26, 5, 411-6.

Chalmers DT, SP Kwak, A Mansour, H Akil and SJ Watson (1993). Corticosteroids regulate brain hippocampal 5-HT1A receptor mRNA expression. *J Neurosci* 13, 3, 914-23.

Chamberlain SR, AD Blackwell, N Fineberg, TW Robbins and BJ Sahakian (2005). The Neuropsychology of Obsessive Compulsive Disorder, the Importance of Failures in Cognitive and Behavioural Inhibition as Candidate Endophenotypic Markers. *Neuroscience and Biobehavioral Reviews* Neurosci Biobehav Rev. 2005 May; 29(3): 399-419.

Chamberlain SR and BJ Sahakian (2004). Cognition in mania and depression, psychological models and clinical implications. *Curr Psychiatry Rep* 6, 6, 451-8.

Chouinard G, L Annable and J Bradwejn (1984). An early phase II clinical trial of tomoxetine (LY139603) in the treatment of newly admitted depressed patients. *Psychopharmacology* (Berl) 83, 1, 126-8.

Clark L and GM Goodwin (2004). State- and trait-related deficits in sustained attention in bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* 254, 2, 61-8.

Clark L, SD Iversen and GM Goodwin (2002). Sustained

attention deficit in bipolar disorder. *Br J Psychiatry* 180, 313-9.

Clark L, MJ Kempton, A Scarna, PM Grasby and GM Goodwin (2005). Sustained attention-deficit confirmed in euthymic bipolar disorder but not in first-degree relatives of bipolar patients or euthymic unipolar depression. *Biol Psychiatry* 57, 2, 183-7.

Clark L, F Manes, N Antoun, BJ Sahakian and TW Robbins (2003). The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage. *Neuropsychologia* 41, 11, 1474-83.

Coppen A (1967). The biochemistry of affective disorders. *Br J Psychiatry* 113, 504, 1237-64.

Coull JT, CD Frith, RS Frackowiak and PM Grasby (1996). A fronto-parietal network for rapid visual information processing, a PET study of sustained attention and working memory. *Neuropsychologia* 34, 11, 1085-95.

Cowen PJ (1990). Antidepressants, current concepts of mode of action. *Int Clin Psychopharmacol* 5, suppl 3, 45-55.

Dahabra S, CH Ashton, M Bahrainian, PG Britton, IN Ferrier, VA McAllister, VR Marsh and PB Moore (1998). Structural and functional abnormalities in elderly patients clinically recovered from early- and late-onset depression. *Biol Psychiatry* 44, 1, 34-46.

Deckersbach T, CR Savage, N Reilly-Harrington, L Clark, G Sachs and SL Rauch (2004). Episodic memory impairment in bipolar disorder and obsessive-compulsive disorder, the role of memory strategies. *Bipolar Disord* 6, 3, 233-44.

Drevets WC, JL Price, JR Simpson Jr, RD Todd, T Reich, M Vannier and ME Raichle (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386, 6627, 824-7.

Elliott R, SC Baker, RD Rogers, DA O'Leary, ES Paykel, CD Frith, RJ Dolan and B J Sahakian (1997a). Prefrontal dysfunction in depressed patients performing a complex planning task, a study using positron emission tomography. *Psychol Med* 27, 4, 931-42.

Elliott R, A Ogilvie, JS Rubinsztein, G Calderon, RJ Dolan and BJ Sahakian (2004). Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. *Biol Psychiatry* 55, 12, 1163-70.

Elliott R, JS Rubinsztein, BJ Sahakian and RJ Dolan (2000). Selective attention to emotional stimuli in a verbal go/no-go task, an fMRI study. *Neuroreport* 11, 8, 1739-44.

Elliott R, JS Rubinsztein, BJ Sahakian and RJ Dolan (2002). The neural basis of mood-congruent processing biases in depression. *Arch Gen Psychiatry* 59, 7, 597-604.

Elliott R, BJ Sahakian, JJ Herrod, TW Robbins and ES Paykel (1997b). Abnormal response to negative feedback in unipolar depression, evidence for a diagnosis specific impairment. *J Neurol Neurosurg Psychiatry* 63, 1, 74-82.

Elliott R, BJ Sahakian, AP McKay, JJ Herrod, TW Robbins and ES Paykel (1996). Neuropsychological impairments in unipolar depression, the influence of perceived failure on subsequent performance. *Psychol Med* 26, 5, 975-89.

Folstein MF, SE Folstein and PR McHugh (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12, 3, 189-98.

Fossati P, A Radtchenko and P Boyer (2004). Neuroplasticity, from MRI to depressive symptoms. *Eur Neuropsychopharmacol* 14, suppl 5, S503-10.

Goldapple K, Z Segal, C Garson, M Lau, P Bieling, S Kennedy and H Mayberg (2004). Modulation of cortical-limbic pathways in major depression, treatment-specific effects of cognitive behavior therapy. *Arch Gen Psychiatry* 61, 1, 34-41.

Goodwin GM, MP Austin, N Dougall, M Ross, C Murray, RE O'Carroll, A Moffoot, N Prentice and KP Ebmeier (1993). State changes in brain activity shown by the uptake of 99mTc-exametazime with single photon emission tomography in major depression before and after treatment. *J Affect Disord* 29, 4, 243-53.

Goodwin GM, JT Cavanagh, MF Glabus, RF Kehoe, RE O'Carroll and KP Ebmeier (1997). Uptake of 99mTc-exametazime shown by single photon emission computed tomography before and after lithium withdrawal in bipolar patients, associations with mania. *Br J Psychiatry* 170, 426-30.

Goodyer IM, J Herbert, A Tamplin and PM Altham (2000). Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *Br J Psychiatry* 177, 499-504.

Gottesman II and TD Gould (2003). The endophenotype concept in psychiatry, etymology and strategic intentions. *Am J Psychiatry* 160, 4, 636-45.

Greenberg PE, RC Kessler, HG Birnbaum, SA Leong, SW Lowe, PA Berglund and PK Corey-Lisle (2003). The economic burden of depression in the United States, how did it change between 1990 and 2000? *J Clin Psychiatry* 64, 12, 1465-75.

Hamilton M (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23, 56-62.

Hart RP, JB Wade, VP Calabrese and CC Colenda (1998). Vigilance performance in Parkinson's disease and depression. *J Clin Exp Neuropsychol* 20, 1, 111-7.

Hauser P, J Matochik, LL Altshuler, KD Denicoff, A Conrad, X Li and RM Post (2000). MRI-based measurements of temporal lobe and ventricular structures in patients with bipolar I and bipolar II disorders. *J Affect Disord* 60, 1, 25-32.

Hawley CJ, TM Gale and T Sivakumaran (2002). Defining remission by cut off score on the MADRS, selecting the optimal value. *J Affect Disord* 72, 2, 177-84.

Jacobs D and T Silverstone (1986). Dextroamphetamine-induced arousal in human subjects as a model for mania. *Psychol Med* 16, 2, 323-9.

Jeffcoate WJ, JT Silverstone, CR Edwards and GM Besser (1979). Psychiatric manifestations of Cushing's syndrome, response to lowering of plasma cortisol. *Q J Med* 48, 191, 465-72.

Jorm AF, P Butterworth, KJ Anstey, H Christensen, S Easteal, J Maller, KA Mather, RI Turakulov, W Wen and P Sachdev (2004). Memory complaints in a community sample aged 60-64 years, associations with cognitive functioning, psychiatric symptoms, medical conditions, APOE genotype, hippocampus and amygdala volumes, and white-matter hyperintensities. *Psychol Med* 34, 8, 1495-506.

Ketter TA, TA Kimbrell, MS George, RT Dunn, AM Speer, BE Benson, MW Willis, A Danielson, MA Frye, P Herscovitch, et al (2001). Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biol Psychiatry* 49, 2, 97-109.

Krishnan KR, WD Taylor, DR McQuoid, JR MacFall, ME Payne, JM Provenzale and DC Steffens (2004). Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biol Psychiatry* 55, 4, 390-7.

Kruger S, D Seminowicz, K Goldapple, SH Kennedy and HS Mayberg (2003). State and trait influences on mood regulation in bipolar disorder, blood flow differences with an acute mood challenge. *Biol Psychiatry* 54, 11, 1274-83.

Lembke A and TA Ketter (2002). Impaired recognition of facial emotion in mania. *Am J Psychiatry* 159, 2, 302-4.

Levy RM, DC Steffens, DR McQuoid, JM Provenzale, JR MacFall and KR Krishnan (2003). MRI lesion severity and mortality in geriatric depression. *Am J Geriatr Psychiatry* 11, 6, 678-82.

Lyoo IK, MJ Kim, AL Stoll, CM Demopulos, AM Parow, SR Dager, SD Friedman, DL Dunner and PF Renshaw (2004). Frontal lobe gray matter density decreases in bipolar I disorder. *Biol Psychiatry* 55, 6, 648-51.

Manes F, B Sahakian, L Clark, R Rogers, N Antoun, M Aitken and T Robbins (2002). Decision-making processes following damage to the prefrontal cortex. *Brain* 125, Pt 3, 624-39.

Manji HK, GJ Moore and G Chen (2000). Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers, implications for the pathophysiology and treatment of manic-depressive illness. *Biol Psychiatry* 48, 8, 740-54.

Martinez-Aran A, E Vieta, F Colom, C Torrent, J Sanchez-Moreno, M Reinares, A Benabarre, JM Goikolea, E Brugue, C Daban, et al (2004a). Cognitive impairment in euthymic bipolar patients, implications for clinical and functional outcome. *Bipolar Disord* 6, 3, 224-32.

Martinez-Aran A, E Vieta, M Reinares, F Colom, C Torrent, J Sanchez-Moreno, A Benabarre, JM Goikolea, M Comes and M Salamero (2004b). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry* 161, 2, 262-70.

Mayberg HS (2003). Positron emission tomography imaging in depression, a neural systems perspective. *Neuroimaging Clin N Am* 13, 4, 805-15.

Mayberg HS, SK Brannan, RK Mahurin, PA Jerabek, JS Brickman, JL Tekell, JA Silva, S McGinnis, TG Glass, CC Martin, et al (1997). Cingulate function in depression, a potential predictor of treatment response. *Neuroreport* 8, 4, 1057-61.

McLean A, JS Rubinsztein, TW Robbins and BJ Sahakian (2004). The effects of tyrosine depletion in normal healthy volunteers, implications for unipolar depression. *Psychopharmacology* (Berl) 171, 3, 286-97.

McTavish SF, MH McPherson, CJ Harmer, L Clark, T Sharp, GM Goodwin and PJ Cowen (2001). Antidopaminergic effects of dietary tyrosine depletion in healthy subjects and patients with manic illness. *Br J Psychiatry* 179, 356-60.

Messer T, M Schmauss and J Lambert-Baumann (2005). Efficacy and tolerability of reboxetine in depressive patients treated in routine clinical practice. *CNS Drugs* 19, 1, 43-54.

Montgomery SA and M Asberg (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134, 382-9.

Murphy FC, A Michael, TW Robbins and BJ Sahakian (2003). Neuropsychological impairment in patients with major depressive disorder, the effects of feedback on task performance. Psychol Med 33, 3, 455-67.

Murphy FC, JS Rubinsztein, A Michael, RD Rogers, TW Robbins, ES Paykel and B J Sahakian (2001). Decision-making cognition in mania and depression. *Psychol Med* 31, 4, 679-93.

Murphy FC, BJ Sahakian, JS Rubinsztein, A Michael, RD Rogers, TW Robbins and ES. Paykel (1999). Emotional bias and inhibitory control processes in mania and depression. *Psychol Med* 29, 6, 1307-21.

Murphy FC, KA Smith, PJ Cowen, TW Robbins and BJ Sahakian (2002). The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. *Psychopharmacology* (Berl) 163, 1, 42-53.

Owen AM, RG Morris, BJ Sahakian, CE Polkey and TW Robbins (1996). Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Brain* 119, Pt 5, 1597-615.

Pohjasvaara T, R Vataja, A Leppavuori and T Erkinjuntti (2001a). Depression after cerebrovascular disorders. *Duodecim* 117, 4, 397-403; quiz 404, 441.

Pohjasvaara T, R Vataja, A Leppavuori, M Kaste and T Erkinjuntti (2001b). Suicidal ideas in stroke patients 3 and 15 months after stroke. *Cerebrovasc Dis* 12, 1, 21-6.

Purcell R, P Maruff, M Kyrios and C Pantelis (1997). Neuropsychological function in young patients with unipolar major depression. *Psychol Med* 27, 6, 1277-85.

Rogers RD, EM Tunbridge, Z Bhagwagar, WC Drevets, BJ Sahakian and CS Carter (2003). Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. *Neuropsychopharmacology* 28, 1, 153-62.

Rohling ML, P Green, LM Allen 3rd and GL Iverson (2002). Depressive symptoms and neurocognitive test scores in patients passing symptom validity tests. *Arch Clin Neuropsychol* 17, 3, 205-22.

Rubinow DR and RM Post (1992). Impaired recognition of affect in facial expression in depressed patients. *Biol Psychiatry* 31, 9, 947-53.

Rubinsztein JS, PC Fletcher, RD Rogers, LW Ho, FI Aigbirhio, ES Paykel, TW Robbins and BJ Sahakian (2001). Decision-making in mania, a PET study. *Brain* 124, Pt 12, 2550-63.

Rubinsztein JS, A Michael, ES Paykel and BJ Sahakian (2000). Cognitive impairment in remission in bipolar affective disorder. *Psychol Med* 30, 5, 1025-36.

Rund BR, AL Orbeck and NI Landro (1992). Vigilance deficits in schizophrenics and affectively disturbed patients. *Acta Psychiatr Scand* 86, 3, 207-12.

Rybakowski JK and K Twardowska (1999). The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. *J Psychiatr Res* 33, 5, 363-70.

Sax KW, SM Strakowski, ME Zimmerman, MP DelBello, PE Keck Jr. and JM Hawkins (1999). Frontosubcortical neuroanatomy and the continuous performance test in mania. *Am J Psychiatry* 156, 1, 139-41.

Shastry BS (1997). On the functions of lithium, the mood stabilizer. *Bioessays* 19, 3, 199-200.

Sheehan DV, Y Lecrubier, KH Sheehan, P Amorim, J Janavs, E Weiller, T Hergueta, R Baker and GC Dunbar (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.), the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59, suppl 20, 22-33;quiz 34-57.

Sheline YI (2003). Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry* 54, 3, 338-52.

Sheline YI, MH Gado and HC Kraemer (2003). Untreated depression and hippocampal volume loss. *Am J Psychiatry* 160, 8, 1516-8.

Singleton N, R Bumpstead, M O'Brien, A Lee and H Meltzer (2003). Psychiatric morbidity among adults living in private households, 2000. *Int Rev Psychiatry* 15, 1-2, 65-73.

Spitzer MB, G Miriam and JB Williams (1996). Structured Clinical Interview for DSM-IV Axis I disorders, clinician version (SCID). Washington, D.C. , American Psychiatric Press, Inc.

Starkstein SE, HS Mayberg, ML Berthier, P Fedoroff, TR Price, RF Dannals, HN Wagner, R Leiguarda and RG Robinson (1990). Mania after brain injury, neuroradiological and metabolic findings. *Ann Neurol* 27, 6, 652-9.

Starkstein SE and RG Robinson (1997). Mechanism of disinhibition after brain lesions. *J Nerv Ment Dis* 185, 2, 108-14.

Tavares JV, WC Drevets and BJ Sahakian (2003). Cognition in mania and depression. *Psychol Med* 33, 6, 959-67.

Teasdale JD, MJ Fennell, GA Hibbert and PL Amies (1984). Cognitive therapy for major depressive disorder in primary care. *Br J Psychiatry* 144, 400-6.

Turner DC, TW Robbins, L Clark, AR Aron, J Dowson and BJ Sahakian (2003). Cognitive enhancing effects of modafinil in healthy volunteers. *Psychopharmacology* (Berl) 165, 3, 260-9.

Varghese FP and ES Brown (2001). The Hypothalamic-Pituitary-Adrenal Axis in Major Depressive Disorder, A Brief Primer for Primary Care Physicians. *Prim Care Companion J Clin Psychiatry* 3, 4, 151-155.

WHO (2000). The Global Burden of Disease Report. www.who.int/ewvidence/bod, World Health Organization.

WHO (2001). Mental Health, New Understanding, New Hope. World Health Organization.

Williams JM and J Scott (1988). Autobiographical memory in depression. *Psychol Med* 18, 3, 689-95.

Willshire D, G Kinsella and M Prior (1991). Estimating WAIS-R IQ from the National Adult Reading Test, a cross-validation. *J Clin Exp Neuropsychol* 13, 2, 204-16.

Wolfe J, E Granholm, N Butters, E Saunders and D Janowsky (1987). Verbal memory deficits associated with major affective disorders, a comparison of unipolar and bipolar patients. *J Affect Disord* 13, 1, 83-92.

www.camcog.com Cambridge Neuropsychological Test Automated Battery (CANTAB), Cambridge Cognition.

Young RC, JT Biggs, VE Ziegler and DA Meyer (1978). A rating scale for mania, reliability, validity and sensitivity. *Br J Psychiatry* 133, 429-35.

Young SN (1993). The use of diet and dietary components in the study of factors controlling affect in humans, a review. *J Psychiatry Neurosci* 18, 5, 235-44.

Young SN, SE Smith, RO Pihl and FR Ervin (1985). Tryptophan depletion causes a rapid lowering of mood in normal males. *Psychopharmacology* (Berl) 87, 2, 173-7.

Zimmerman M, I Chelminski and W McDermut (2002). Major depressive disorder and axis I diagnostic comorbidity. *J Clin Psychiatry* 63, 3, 187-93.