



**Mental Capital and Wellbeing:  
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**Neurocognition and Neuroimaging in Major Depressive Disorder and Bipolar Depression:  
Implications for Treatment and Functional Outcome**

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## Summary

**Bipolar disorder (BP) and major depressive disorder (MDD) are among the 10 most debilitating illnesses worldwide. They are chronic, recurring illnesses that have a considerable negative impact on everyday functioning, including occupational function and quality of life. BP depression is frequently misdiagnosed and inappropriately treated as the depression associated with MDD in patients without a clear history of mania. Even for MDD, the majority of patients presenting in a depressed episode do not receive the most appropriate initial treatment. Therefore, there are two major challenges for improving the mental health of depressed patients: improving the ability to distinguish accurately BP depression from the depression of MDD; and identifying new strategies of optimising treatment choice for depression as early as possible in the course of illness. To achieve such goals, neurocognitive and neuroimaging variables are indirect and direct measures, respectively, of abnormal activity in brain systems that may be related to underlying pathophysiological processes in MDD and BP depression. In order to meet these major diagnostic and clinical challenges, these measures may facilitate the identification of endophenotypes - objective markers closely related to genetic vulnerability and underlying pathophysiology - relevant to the differential diagnosis and treatment choice for each disorder. In this review, we discuss recent, promising findings from studies employing neurocognitive and neuroimaging methodologies that indicate the feasibility of identifying these endophenotypes, in order to increase diagnostic accuracy, optimise treatment choice, and improve the functional outcome of patients suffering from depression.**

## 1. Introduction

Bipolar disorder (BP) and major depressive disorder (MDD) are among the ten most debilitating illnesses worldwide (Murray & Lopez, 1996; Kessler et al., 2003). with a prevalence of at least 1% and 15%, respectively. Bipolar disorder type I (BPI) where patients experience episodes of mania and depression, is associated with a poor clinical and functional outcome, a high suicide rate (Baldessarini et al., 2003). and a huge societal cost (Wyatt and Henter, 1995). One reason for this poor prognosis of BP is the frequent misdiagnosis or late diagnosis of the disorder (e.g. Bowden et al., 2001, 2005) leading to unnecessary delays in the initiation of appropriate treatment. Indeed, while depression is the more common presentation in BPI, and a cause of greater psychosocial disruption than the manic episodes (e.g. Calabrese et al., 2004), BP depression continues to be frequently misdiagnosed and inappropriately treated as unipolar depression in individuals without a clear previous history of manic episodes (e.g. Ghaemi et al., 2002; Hirschfeld et al., 2003; Lish et al., 1994; Manning, 2003). BP depression shows a relatively poor response to antidepressants alone or even in combination treatment (Fagiolini et al., 2002; Ghaemi et al., 2003; Sachs et al., 2007), which can additionally elicit manic upswings in patients with a bipolar diathesis.

MDD, or unipolar depression, similarly presents a huge societal cost (Robins and Reiger, 1990). While diagnosis of depression associated with MDD usually poses less of an immediate diagnostic problem than diagnosis of BP depression, recent evidence from the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial indicates that the majority of patients with MDD may require more than one antidepressant for the treatment of a depressed episode, especially those with more complex clinical presentations (Rush et al., 2006). For MDD depression, therefore, the provision of alternative and sequential treatment strategies is more urgently required.

## **2. Current treatment options in MDD and BP depression**

Current treatment of depression is dominated by a longstanding pharmacological notion known as the 'monoamine hypothesis'. This, in its modern version, emphasises decreases in serotonin and noradrenaline neurotransmission in depressed patients, which can be gradually remediated over a period of several weeks by drugs that block the reuptake of extracellular serotonin (Selective Serotonin Reuptake Inhibitors – SSRIs) or noradrenaline (Selective Noradrenaline Reuptake Inhibitors – SNRIs) from the synapse.

Many antidepressants belong to these two classes, and the majority of MDD patients are treated with more than one drug before achieving an adequate response (e.g. Rush et al., 2006). In addition, these drugs have poor efficacy in BP depression, where patients are treated primarily with mood stabilisers such as lithium (e.g. Sachs et al., 2000; Sachs et al., 2007). General and well-accepted limitations of pharmacotherapy are: i) the presence of undesirable side-effects like nausea, weight gain, dry mouth; ii) lack of response in a proportion of patients; and iii) the induction of manic upswing rebound effects in BP patients.

Other types of treatments can be effective as alternatives or adjuncts to standard pharmacotherapy. Psychotherapies like Cognitive Behavioural Therapy and interpersonal psychotherapy have proven efficacy in the treatment of MDD, and may offer superior prevention of relapse over long-term follow-up compared to pharmacotherapy (Shea et al., 1992). Data on the effectiveness of psychotherapy in BP depression are more limited at the current time, but it seems likely that newer psychotherapies, including circadian and social rhythm therapy (e.g. Frank et al., 2005) may be helpful in reducing disruptive life events (e.g. sleep deprivation, recreational drug use) and in training patients to detect mood changes and initiate clinical contact prior to full-blown episodes.

Some alternative biological interventions are also available, which are predominantly examined in so-called treatment-refractory cases with severe depression that has failed to respond to multiple antidepressant drugs or psychotherapy. Deep-brain stimulation, where microelectrodes are surgically implanted into disrupted neural circuitry like the subgenual cingulate gyrus and nucleus accumbens (see below) has shown promising effects over one to six months in small groups of patients (Mayberg et al., 2005; Schlaepfer et al., 2007). However, the complex issues associated with placebo control in such severely affected patients preclude definitive conclusions at the current time, and the nature of the intervention makes it likely that this procedure will only ever be employed in the most extreme cases. Repetitive Transcranial Magnetic Stimulation (rTMS) may offer a promising alternative to electroconvulsive shock therapy. In rTMS, cortical brain regions are stimulated by placing an electromagnetic coil with rapidly alternating current against the skull. Brief daily sessions (e.g. 20-minute) of rTMS to left dorsolateral prefrontal cortex has reported efficacy in moderately depressed MDD patients (Loo and Mitchell, 2005).

Together, these findings indicate two major challenges for psychiatrists working with depressed patients:

1. Finding new ways to improve the accuracy of diagnosing BP versus MDD depression as early as possible in depressed patients, especially those who present without a clear history of mania;
2. Creating 'rational treatment advances' (e.g. DePaulo, 2006) for all depressed patients by identifying new ways of optimising treatment choice as early as possible in the illness course.

Advances in these aims are expected to have a major impact on improving quality of life and activities of daily living, such as occupational function, in patients with depressive disorders.

## **3. Towards rational treatments: the search for endophenotypes**

An endophenotype is an objective marker that is more closely related to the genetic vulnerability and underlying pathophysiology of a disorder than the 'fuzzy' psychiatric symptomatology of the condition

(Gottesman and Gould, 2003). Endophenotypes should be selectively associated with the disorder of interest, but should also be observable in groups at high risk for developing the disorder, like first-degree relatives.

Identifying differential endophenotypic markers for BP depression would aid diagnosis earlier on in illness history and revolutionise treatment choice in patients presenting with a first episode of depression, as we would be able to distinguish those cases with an underlying bipolar diathesis, and prescribe mood stabilisers rather than antidepressants, for example.

MDD is also a highly heterogeneous disorder (Grote and Frank, 2003). By characterising its pathophysiology in terms of objective endophenotypes, we may be able to construct treatment response groupings (Hasler et al., 2004) in order to decide, for example, which patients are more likely to respond to pharmacotherapy and which to psychotherapy. As such, the identification of *treatment-relevant endophenotypes* in MDD and BP depression would guide choice of treatment early in the illness, thus preventing the many years of dysfunction that rob young patients of critical development.

The recent research agenda for developing the fifth edition of the Diagnostic and Statistical Manual for psychiatric diagnosis (DSM-V) emphasises a need to translate research findings from basic and clinical neuroscience into a new psychiatric classification system based on pathophysiological and aetiological processes (Kupfer et al., 2002; Hasler et al., 2004 and 2006; Phillips and Frank, 2006). These processes involve complex relationships between genetic variables, abnormalities in brain systems and psychological mechanisms that give rise to symptom expression (e.g. Kraemer et al., 2002).

Brain imaging techniques, such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) can be used to quantify the neural system abnormalities associated with BP and MDD depression. Neurocognitive testing with standardised, computerised assessment procedures can also provide indirect measures of abnormal activity in brain systems, based on extensive validity research from lesion studies in humans, as well as translational data from rodents and non-human primates (Chamberlain and Sahakian, 2006; Clark and Sahakian 2006). Although the link to underlying brain function is indirect, neurocognitive testing has the significant advantage of being easily and inexpensively administered in an outpatient or inpatient setting. The processes tapped by neurocognitive tests such as attention and executive function may also provide insights into the ways that the underlying pathophysiology interacts with psychological mechanisms of symptom formation. Neurocognitive and neuroimaging variables may, therefore, enable us to quantify the pathophysiological processes, and may be employed as a first stage toward identifying *endophenotypes* associated with depression in MDD and BP.

In this critical review, we firstly examine the evidence for disorder-specific abnormalities in neural systems linked with *core domains of pathology* in MDD and in BP depression, drawing on both neurocognitive and neuroimaging studies. These findings are a first stage in the search for endophenotypes to aid the diagnosis of MDD and BP depression. We subsequently review findings from studies using these techniques that have the potential to help identify treatment-relevant endophenotypes of each disorder and thereby guide the choice of treatment early in illness for all people suffering from depression.

#### **4. Core domains of pathology in emotional processing and executive control**

MDD and BP are increasingly recognised as multisystem disorders involving disturbances across several symptom domains (e.g. Grote and Frank, 2003; Phillips and Frank, 2006). Mood instability is a core domain of pathology in these disorders, which appears to arise from the disruption of brain mechanisms involved in normal emotional processing. This domain is associated with mood variability in depression (e.g. diurnal variation) as well as other aspects of affective lability including irritability or anxiety. In BP, the mood instability domain also gives rise to hypomanic, manic and mixed affective states.

A second core domain of pathology common to the depression of both disorders is impaired executive control. Executive control refers to a collection of higher-level psychological processes that enable the flexible organisation of complex behaviour, including planning, working memory, inhibitory control, strategy development, and cognitive flexibility (Stuss and Levine, 2002). Deficits in executive control in depression give rise to symptoms including the inability to concentrate and difficulty in decision-making. They may also impact upon other cognitive domains including memory (Deckersbach et al., 2004). Executive dysfunction is likely to impact upon patients' ability to successfully carry out activities of daily living, including work-related activities, and impacts more broadly upon quality of life. Executive deficits are also likely to further impair the ability to control or regulate mood (e.g. Phillips et al., 2003). Thus the depression of MDD and BP are characterised by abnormalities in mood stability, associated with normal emotion processing, and in executive control, associated with normal emotional regulation.

Existing data from functional neuroimaging studies in healthy individuals point toward distinguishable neural systems for emotional processing and executive control. Normal emotion processing, as measured by tasks assessing the recognition of emotional facial expressions, for example, has been mapped to a neural system centered on subcortical limbic regions including the amygdala, the ventral striatum, the subgenual cingulate gyrus, and the ventromedial prefrontal cortex (e.g. Knutson and Cooper, 2005; Price, 2003; Phillips et al., 2003).

Executive control, in contrast, has been mapped to a lateral prefrontal cortical system, comprising the dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC) (Robbins, 1998). These act in concert with striatal mechanisms involved in response selection, and the hippocampus, important for memory encoding and retrieval (Zola-Morgan et al., 1991).

## 5. Neurocognitive function

### 5.1 MDD Depression

- **Mood instability:** Emotional processing in MDD is classically biased towards stimuli that are congruent with the low mood state. For example, patients are faster to respond to negative stimuli than to positive stimuli (Murphy et al., 1999), are over-sensitive to negative feedback (e.g. Elliott et al., 1996), and are more likely to recall negative autobiographical memories (Brittlebank et al., 1993). Attentional tasks like the dot-probe paradigm reveal biased processing towards negative information, which appears to occur as a controlled bias at reasonably long presentation times (contrasting with the automatic capturing of attention seen in anxiety disorders) (Mogg et al., 1995).
- **Impaired executive control:** MDD patients also display impaired performance on measures of executive control and memory function that employ non-emotional stimuli. Executive deficits on tests of planning (e.g. Tower of London) and cognitive flexibility (e.g. Wisconsin Card Sort Test) have been widely reported (Elliott et al., 1996; Merriam et al., 1999), and have been shown in unmedicated patients (Taylor-Tavares et al., 2007). The degree of executive impairment may be heterogeneous and related to overall symptom severity (Porter et al., 2003) or to specific symptom dimensions like apathy (Feil et al., 2003), melancholia (Austin et al., 1999) or psychosis (Schatzberg et al., 2000). Suicidal behaviour has also been associated with some specific neurocognitive changes including impaired decision-making (Jollant et al., 2005) and impulsivity (Horesh et al., 1999).

Performance on executive tasks improves significantly on symptom remission in MDD, although residual deficits may remain to some degree, particularly in older patients (Abas et al., 1990).

Memory impairments on basic list-learning tasks like the California Verbal Learning Test have been robustly demonstrated in depression (Burt et al., 2000). Memory deficits increase with illness chronicity (e.g. comparing multiple episode and first episode patients) and correlate with the total length of time spent in a depressed state (Kessing, 1998). This deficit is likely to be related to the progressive deterioration of the hippocampus, linked to the neurotoxic effects of hypercortisolemia in depression (MacQueen et al., 2003).

## 5.2 BP Depression

- **Mood instability:** The volume of research investigating neurocognitive function is much smaller in BP depression compared with MDD. Abnormal attentional biases have been reported to negatively-valenced stimuli in depression of BP, but they may additionally be present to positively-valenced stimuli (Lyon et al., 1999) in support of subcortical limbic dysfunction in the disorder.
- **Impaired executive control:** Impaired sustained attention on continuous performance tests has been reliably demonstrated in remitted patients with BP (e.g., Clark and Goodwin, 2004; Clark et al., 2002, 2005; Liu et al., 2002; Wilder-Willis et al., 2001; Zubieta et al., 2001) and it is likely that this deficit is exacerbated during depressed states (van den Bosch et al., 1996).

Other aspects of executive control are certainly impaired in BP depression (Basso et al., 2002; Borkowska and Rybakowski, 2001; Rubinsztein et al., 2006) and the magnitude of impairment is significantly greater than in MDD patients matched for length of illness and medication status (Borkowska and Rybakowski, 2001; Wolfe et al., 1987). Many of these deficits persist outside the illness episodes into periods of 'euthymia' defined by stringent symptom cut-offs (Ferrier et al., 1999; Frangou et al., 2006; Martinez-Aran et al., 2004a; Rubinsztein et al., 2000; Smith et al., 2006; Watson et al., 2006). These findings support dysfunctional DLPFC and VLPFC in BP depression.

Memory is also disrupted in BP depression (Sweeney et al., 2000. potentially more than in MDD depression (Burt et al., 2000; Wolfe et al., 1987). This may be state-specific (Clark et al., 2002; Ferrier et al., 1999) although other studies have detected persisting memory impairments in remission (Rubinsztein et al., 2000; Smith et al., 2006). As with MDD, memory dysfunction in BP increases with illness duration and the number of episodes (Bearden et al., 2006; Cavanagh et al., 2002; Robinson and Ferrier, 2006) and is also associated with functional outcome (Martinez-Aran et al., 2004b).

## 6. Neuroimaging measures

### 6.1 MDD Depression

There is a relatively large body of functional neuroimaging research in depressed patients with MDD. When patients have been scanned during the resting state, metabolism and blood flow are reliably reduced in regions of the dorsal prefrontal cortex and anterior cingulate gyrus, and these reductions are correlated with the severity of the depressed mood across patients (e.g. Baxter et al., 1989; Kimbrell et al., 2002). The resting state is, however, a psychologically unconstrained condition in which depressed patients may be engaged in a wide variety of tasks, such as rumination.

- **Mood instability:** As functional imaging analysis techniques have become more sophisticated, research has measured neural activity during the performance of emotion processing tasks,

such as the presentation of negative emotional faces. In MDD depression, abnormally increased amygdala activity is seen repeatedly in response to negative emotional faces (Fu et al., 2004; Neumeister et al., 2006; Sheline et al., 2001; Surguladze et al., 2005) and to negative emotional words (Siegle et al., 2002; 2006). Decreased ventromedial prefrontal activity during sad mood induction has been reported in both depressed and remitted patients with MDD (Liotti et al., 2002). By contrast, findings indicate *decreased* activity in subcortical limbic regions to positive emotional (happy) stimuli in these individuals (e.g. Epstein et al., 2006; Surguladze et al., 2005).

- **Impaired executive control:** Decreased DLPFC activity relative to healthy individuals has been reported in depressed patients with MDD during working memory trials following negative stimuli (Siegle et al., 2002) and during working memory and attention per se (e.g. Elliott et al., 1997; Goethals et al., 2005; Okada et al., 2003). In a probabilistic reversal learning task that required subjects to ignore misleading negative feedback, MDD depressed patients showed reduced activation of VLPFC during reversal, and failed to suppress amygdala activity during receipt of negative feedback, consistent with deficient top-down control of limbic circuitry by the prefrontal cortex (Taylor-Tavares et al., 2008). Fewer studies have shown increased DLPFC activity during working memory in these patients (e.g. Harvey et al., 2005).

## 6.2 BP Depression

- **Mood instability:** Findings from functional neuroimaging studies comparing patients with BP and healthy individuals indicate abnormally increased subcortical limbic activity to emotional stimuli such as facial expressions (Blumberg et al., 2005; Lawrence et al., 2004; Yurgelun-Todd et al., 2000) and to negative scenes (Malhi et al., 2004).

Decreased blood flow has been reported in medial prefrontal cortex during sad mood induction relative to baseline in remitted and depressed patients with type I BP (Kruger et al., 2003) but this study did not include a comparison group of healthy individuals. One study reported relative increases in subcortical limbic activity to happy faces in depressed compared with manic patients with BP (type I) and healthy individuals (Chen et al., 2006) in contrast to data showing decreased activity in subcortical limbic regions to happy stimuli in MDD depression (e.g. Epstein et al., 2006; Surguladze et al., 2005).

This distinction between BP and MDD depression is supported by a study directly comparing the two groups (Lawrence et al., 2004) discussed in the next section. Increased subcortical limbic activity (predominantly in the amygdala) has also been demonstrated in depressed and remitted BP patients (approximately 50% type I) studied at rest (Bauer et al., 2005; Drevets et al., 2002).

- **Impaired executive control:** Findings indicate decreased DLPFC/VLPFC activity during an attention task in depressed and remitted patients with BP (type I) compared with healthy individuals (e.g. Blumberg et al., 2003; Ketter et al., 2001; Kronhaus et al., 2006).

In summary, the depressed state of BP is associated with increased activity in subcortical limbic regions associated with mood stability, and decreased activity in DLPFC/VLPFC and hippocampus associated with executive control and memory.

## **7. Comparison of neurocognitive and functional neuroimaging studies: towards diagnostic biomarkers?**

Findings from neurocognitive studies indicate disrupted emotional processing and impaired executive control in depressed MDD and depressed BP patients. While there appears to be abnormal processing of negatively-valenced emotional information in both groups of patients, there are suggestions that BP depressed patients may also demonstrate abnormal processing of positively-valenced information. Both groups of patients show impaired executive control and memory; this impairment may be more severe in depressed BP relative to depressed MDD patients.

While findings from functional neuroimaging studies regarding neural activity during rest are somewhat discrepant in depressed patients with MDD, studies employing emotional challenge paradigms suggest that these patients show increased amygdala and subcortical limbic activity to emotional stimuli relative to healthy individuals. Unlike remitted and depressed patients with BP, however, in depressed MDD patients this abnormal pattern of neural activity is predominantly to negative rather than positive emotional stimuli. Furthermore, these abnormalities appear to be depression-dependent in MDD rather than abnormalities common throughout depression and remission (e.g. Fu et al., 2004, Sheline et al., 2001).

One study directly comparing neural activity to emotional stimuli in BP and depressed MDD patients found increases in amygdala and subcortical limbic activity predominantly to mild happy, but also to fearful, facial expressions, *versus* neutral facial expressions in remitted, but subsyndromally depressed, BP (type I) patients relative to depressed MDD patients (Lawrence et al., 2004). To date, studies indicate, predominantly, a pattern of decreased DLPFC activity during cognitive challenge paradigms in both MDD and BP depressed patients. However, there is clearly a need for studies that focus on comparing neural activity in depressed MDD and depressed BP patients during emotional and cognitive challenge paradigms.

## **8. Identifying treatment-relevant endophenotypes**

The increasing number of neurocognitive and neuroimaging studies in both MDD and BP depression suggest that we are now in a position to embrace the technological advances in neurocognitive study design and neuroimaging techniques to allow us to identify treatment-relevant endophenotypes. This will be crucial if we are to optimise the treatment and improve the clinical and functional outcome of people suffering with these disorders (Phillips, 2007).

Recent research has begun to use functional imaging to investigate markers associated with treatment response. In MDD depression, several studies have reported that pre-treatment metabolism in a reasonably focal area of the medial prefrontal cortex is associated with subsequent response to antidepressant medication. However, the direction of effect has been inconsistent, with some studies reporting increased metabolism associated with good response (e.g. Mayberg et al., 1997; Saxena et al., 2003) and other studies reporting decreased metabolism associated with good response (Little et al., 2005).

Findings also indicate post-treatment increases in activity in prefrontal cortical activity, and decreases in activity in subcortical limbic regions in MDD responders (e.g. Fu et al., 2004; Kennedy et al., 2001; Mayberg et al., 2000; Sheline et al., 2001). A pre-treatment pattern of neural activity linked with emotion dysregulation – a more sustained amygdala and decreased ventromedial prefrontal cortical activity to negative emotive stimuli – was associated with the response to Cognitive Behavioural Therapy in MDD depression (Siegle et al., 2006). Increased amygdala activity at pre-treatment baseline was also associated with a greater response to antidepressant treatment (Canli et al., 2005). Functional abnormalities in neural systems underlying mood stability in unipolar depression may therefore predict response to, and ameliorate with, antidepressants and CBT.

Following symptom remission in MDD, there is generally an amelioration of this abnormal neural activity. The increased amygdala response to negative emotional faces significantly reduces in remission after antidepressant medication (Fu et al., 2004; Sheline et al., 2001) although limbic (insular) and prefrontal cortical (anterior cingulate gyrus) regions also show increased activity to negative versus neutral scenes as MDD symptoms remit (Davidson et al., 2003). These findings are broadly supported by a number of resting state studies (e.g. Anand et al., 2005; Baxter et al., 1989; Mayberg et al., 2000, 2005; Brody et al., 2001; Martin et al., 2001; Goldapple et al., 2004; Kennedy et al., 2001; Goodwin et al., 1993; Holthoff et al., 2004; Tutus et al., 1998; Vlassenko et al., 2004).

There is considerably less research examining treatment response in relation to neurocognitive function, although neurocognitive testing is arguably more amenable than brain imaging for use in primary or secondary care settings. Preliminary data in geriatric depression show that impaired executive control on measures of attentional conflict were associated with the response to antidepressant treatment over eight weeks (Kalayam and Alexopoulos, 1999; Murphy and Alexopoulos, 2006). A similar protocol whereby event-related potentials were measured during an emotional 'Go/No-go' task found differences in evoked, error-related negativity between eventual responders and non-responders (Alexopoulos et al., 2007). These studies are broadly consistent with the functional imaging evidence that medial prefrontal and anterior cingulate gyrus integrity is associated with treatment response.

In BP, there is emerging evidence from cross-sectional studies that neurocognitive abnormalities adversely affect functional outcomes (e.g. Martinez-Aran et al., 2004b). A recent study reported that two classic neurocognitive measures of executive control (the Stroop interference score and FAS verbal fluency) predicted time-to-clinical-recovery in a group of bipolar patients experiencing their first hospitalisation (Gruber et al., 2007). These patients received naturalistic treatment, and clinical state at hospitalisation (presumably a mixture of manic and depressed cases) was not reported. Two functional imaging studies have examined treatment-related changes in neural responses in BP depression. The first reported decreased subcortical limbic activity (in ventral striatum, amygdala, hippocampus and insula) during the resting state, after response to a novel treatment, levothyroxine, in depressed BP (type I) patients (Bauer et al., 2005). The second indicated an amelioration of abnormal DLPFC activity to emotional stimuli in depressed BP patients who responded to sleep deprivation and light therapy (Benedetti et al., 2007). Further research is clearly required to examine neurocognitive and neuroimaging predictors of response to standard pharmacological or psychological treatments in BP depression.

## **9. Conclusions and future research**

Together, the findings from neurocognitive and neuroimaging studies indicate that MDD and BP depression can be distinguished, at least in part, by indirect and direct measures of brain activity in neural systems that are important for mood stability and executive control.

These abnormalities may underlie, respectively, the mood instability and impaired cognitive control of emotion observed clinically in both disorders. Increased subcortical limbic activity to happy stimuli may, in particular, be an important pathophysiologic process distinguishing the depression associated with BP from that associated with MDD.

While in their infancy, studies employing these techniques to identify neural system abnormalities that may represent treatment-relevant endophenotypes are promising in MDD, and suggest that identification of neurocognitive and neuroimaging variables that may predict treatment response in BP depression is feasible.

It is clear that, in the future, studies employing these newly-developed neurocognitive paradigms with functional neuroimaging techniques may be able to draw us closer to meeting the critical challenges of

early and accurate diagnosis and early optimisation of treatment of both MDD and BP depression. This should also prevent relapse and facilitate return to work as well as restoring quality of life in patients with depressive disorders. The final challenge will be to identify endophenotypic markers in order to identify at risk individuals prior to clinical onset.

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