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The Bewildered Brain: Asymmetric Brain Activity as a Source of Cognitive Impairment in Depression

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Abstract

Individuals with depression commonly complain about cognitive deficits such as memory loss and poor decision making ability (Lahr, Beblo, & Hartje, 2007). However, despite considerable research, no single profile of cognitive deficits in depression has emerged (Ravnkilde et al., 2002). This may be a result of heterogeneity within the diagnostic category of depression. While typically diagnosed as a single disorder, the symptoms of depression may stem from different neurobiological causes leading to different profiles of cognitive deficits. Shenal, Harrison, and Demaree (2003) theorised that subtypes of depression could arise from dysfunctional brain activity in each of the quadrants of the brain (right frontal, left frontal, right posterior, and left posterior). For example, reduced left frontal activity in depression may be associated with impairments in tasks reliant on left frontal regions. Little research has directly investigated the possible link between variability in cognitive deficits and different patterns of dysfunctional brain activity in depression. The current paper reviews evidence for this link by describing depressed individuals' performance on lateralised cognitive tasks, and discusses possibilities for future research.

Keywords: Alpha Power, Brain Asymmetry, Cognitive Impairment, Cognitive Deficits, Depression, Depression Subtypes, Lateralisation, Neuropsychology

Introduction

Depression is a common disorder that affects approximately 25% of New Zealanders during their lifetime (Browne, Wells, Scott, & McGee, 2006). Although depression is usually characterised by negative affect, there is considerable evidence to suggest that individuals with depression may also suffer from cognitive impairment (Hammar & Ardal, 2009; Ravnkilde et al., 2002; Rose, Simonotto, & Ebmeier, 2006). Both the affective and cognitive symptoms of depression seem to be highly heterogeneous suggesting that depression is not a unitary construct and may consist of subtypes (Abramson et al., 1997; Merikangas, Wicki, & Angst, 1994). Different subtypes of depression may be associated with different neurobiological bases which may also result in different patterns of cognitive impairment (Shenal, Harrison, & Demaree 2003). Unfortunately, research into this possibility is sparse. An improved understanding regarding the heterogeneity of depression will help to improve diagnosis and treatment of individuals with depression.

Subtypes of Depression

The heterogeneity observed in the symptoms of depression suggests that depression may not be a unitary construct and may consist of subtypes (Abramson et al., 1997; Merikangas et al., 1994). This observation has led to the development of a multitude of classification systems.

One of the earliest methods used to classify depression described two symptom-based subtypes of depression: exogenous or neurotic and endogenous depression (Kiloh & Garside, 1963). Endogenous depression was said to stem from an internal source and could be diagnosed by somatic symptoms such as psychomotor retardation, weight disturbance and a lowered pulse rate (Pollitt, 1965). In contrast, exogenous depression was characterised by emotional reactivity with hysteria, irritability and could often be linked to a psychological stressor (Pollitt, 1965). These terms were later replaced with the terms 'melancholic depression' to describe endogenous depression and 'non-melancholic depression' to describe exogenous depression (Parker, 2000). Melancholic depression is currently listed as a specifier of depression type in the DSM-IV-TR (American Psychiatric Association, 2000) and is now characterised by loss of pleasure (anhedonia) as well as the somatic symptoms described by the endogenous subtype (Parker, 2000). The term non-melancholic depression has been replaced by atypical depression in the DSM-IV-TR, which is distinguished from typical/melancholic depression by mood-reactivity (Singh & Rais, 2007). Each subtype appears to respond to different treatment

providing evidence for distinct syndromes (e.g., Kiloh & Garside, 1963). Despite such evidence, 'binary' classification systems have been criticised as representing differences in severity as opposed to being qualitatively different (Cole et al., 2008; Parker, 2000).

Although symptom based approaches to classifying depression seem appealing due to their relative ease of use, symptoms may appear superficially similar but may result from different neurobiological causes. Classifying depression using neurobiological markers could lead to less diagnostic heterogeneity and may be more useful in developing treatment plans (Gruenberg, Goldstein, & Pincus, 2005). For example, Shenal et al. (2003) theorised that depression could be separated into four subtypes based on abnormal brain activity. Shenal et al. (2003) proposed dividing the brain into four quadrants: left frontal, right frontal, left posterior and right posterior. Dysfunction in each of these regions was theorised to lead to a different subtype of depression. Left frontal regions have been associated with the experience and processing of positive/approach emotions while right frontal regions have been associated with the experience of negative/withdrawal emotions. Therefore, individuals suffering from a relative reduction of activity in the left frontal region they may experience diminished positive emotion and approach motivation accompanied by increased negative/withdrawal motivated emotions leading to depression. In contrast, relatively reduced right frontal activity could lead to depression due to a lack of avoidance of negatives situations leading to depression characterised by learned helplessness. Furthermore, right posterior regions have been linked to arousal and responsiveness. Therefore, an individual with reduced right posterior brain activity may be diagnosed with depression due to reduced arousal and responsiveness. The gap in this model is that little research examined the role of left posterior regions in depression (Shenal et al., 2003). These examples show how different presentations of depression could result from different patterns of brain activity and may reflect different subtypes of depression. As discussed later in this article, there is limited evidence to support this hypothesis (e.g., Bruder et al., 1995; Bruder et al., 2002). Further research into different underlying patterns of brain activity in depression may help to explain the substantial variability observed in the symptoms of depression. One domain in which this could be particularly useful is in understanding cognitive deficits in depression.

Cognitive Deficits in Depression

Individuals suffering from depression commonly report difficulties such as poor decision making abilities, reduced memory capacity and impaired concentration (Gualtieri, Johnson, & Benedict, 2006; Lahr, Beblo, & Hartje, 2007). However, depressed individuals tend to negatively evaluate their own performance making self-reports of their performance deficits unreliable (Lahr et al., 2007). As a result, research using objective measures has been conducted to determine the true nature and extent of cognitive deficits in depression (e.g. McClintock, Husain, Greer, & Cullum, 2010; Porter, Bourke, & Gallagher, 2007). Deficits have been observed in a wide variety of cognitive domains including short-term memory (e.g., Porter, Gallagher, Thompson, & Young, 2003), decision making (e.g., Taylor-Tavares et al., 2007), attention (e.g., Ravnkilde et al., 2002), and working memory (e.g., Rose et al., 2006). However, the findings have been inconsistent and no single profile of cognitive impairment in depression has been compiled (Hammar & Ardal, 2009). Some research has found evidence of global impairments with deficits in a wide variety of cognitive domains (e.g., Harvey et al., 2004; Ravnkilde et al., 2002) while other research only revealed impairment in a narrow set of cognitive functions (e.g., Sweeney, Kmiec, & Kupfer, 2000). Furthermore, several studies found no evidence of impairment (e.g., Fossati, Amar, Raoux, Ergis, & Allilaire, 1999; Wang et al., 2006).

Inconsistent findings are typically attributed to methodological and sampling differences (Hammar & Ardal, 2009; Porter et al., 2007; Rose et al., 2006). Alternatively, such inconsistencies may not be an artefact of study design but may instead reflect heterogeneity within the construct of depression. Although most diagnoses of depression appear superficially similar, there are subtle differences in symptoms and illness course that suggest clinical depression may consist of subtypes (Merikangas et al., 1994). Unfortunately, subtypes have been given little consideration when investigating cognitive deficits in depression. Different subtypes of depression are likely to have different underlying causes and are likely to show different patterns of cognitive impairment. In order to study the link between cognitive deficits and subtypes of depression, the source of cognitive deficits in depression needs to be considered.

Cognitive impairment in depression has typically been attributed to downstream effects of the acute affective symptoms of depression such as reduced motivation or a bias towards processing information in a negatively-valenced manner (Schmand et al., 1994). However, cognitive impairment how been found to remain following remission and may represent a trait marker for vulnerability to depression instead of a state marker that results from being depressed (Hammar & Ardal, 2009;

Rogers et al., 2004; Sweeney et al., 2000). Further evidence that cognitive impairment is distinct from acute affective symptoms is in research showing severity of cognitive impairment to be unrelated to symptom severity (e.g., Harvey et al., 2004). These observations suggest that cognitive deficits in depression may have an enduring cause that persists beyond the affective component of depression. One possible cause for cognitive deficits in depression, that may also represent one of the underlying causes of depression, is abnormal underlying brain activity. If different subtypes of depression have different patterns of underlying brain activity, then inconsistent findings regarding cognitive deficits in depression could result from a failure to account for subtypes (Shenal et al., 2003).

Brain Activity in Depression

One of the least invasive and easily employed ways to measure brain activity in depression is using electroencephalograms (EEG). Brain asymmetry is calculated by comparing brain activity across the left and right hemispheres, known as the difference metric (Gotlib, Ranganath, & Rosenfeld, 1998). This methodology can only elucidate relative functioning of the hemispheres and cannot categorically show which hemisphere is dysfunctional or if the asymmetry itself is problematic (Davidson, 1988). EEG research commonly finds a bilateral reduction in frontal brain activity with a pattern of relatively greater right than left frontal activity in depressed individuals (Heller & Nitschke, 1998; Thibodeau, Jorgensen, & Kim, 2006). A meta-analysis of EEG studies conducted by Thibodeau et al. (2006) found this to be a moderate effect (d=.54).

The cognitive/behavioural correlates of this pattern of brain activity can be understood by reviewing models of emotional processing. Evidence suggests that the right hemisphere is specialised for processing negatively-valenced emotion such as sadness (Demaree, Everhart, Youngstrom, & Harrison, 2005). For example, sad faces appear to be processed faster when presented to the left-visual field (right hemisphere) (Natale, Gur, & Gur, 1983; Reuter-Lorenz, Givis, & Moscovitch, 1983). In contrast, the left hemisphere is specialised for the experience and processing of positive emotions, such as happiness (Demaree et al., 2005). This has been termed the valence model of emotion. A similar model of emotion suggests that the right hemisphere is specialised for withdrawal-motivated emotions such as fear while the left hemisphere is responsible for approach-motivated emotions (Davidson, 1992; Demaree et al., 2005). This is commonly called the approach-withdrawal model of emotion (Davidson, 1992; Demaree et al., 2005). While the two models appear similar, they classify several emotions differently. For example, anger is a negatively-valenced emotion but is associated with approach motivation. EEG asymmetry has been found to predict the extent of negative reaction to a negatively-valenced film (Tomarken, Davidson, & Henriques, 1990). Using these models, one would expect that an individual with greater right than left frontal activity, as in depression, may experience more negative/withdrawal emotions and may also be predisposed to processing stimuli and events in a negative manner (Gotlib et al., 1998). Therefore, an individual born with greater right than left frontal activity may be vulnerable to developing depression (Gotlib et al., 1998).

Alternatively, it is possible that individuals with depression may display a relative increase in right frontal activity as a result of suffering from predominantly negative affect during depression. However, similar to cognitive deficits in depression, asymmetric frontal activity also appears to remain following remission from the affective component of depression indicating that asymmetric brain activity is unrelated to mood state (Gotlib et al., 1998; Henriques & Davidson, 1997). Furthermore, this pattern of asymmetry activity has been observed in those deemed to be at a high risk for developing depression such as infants of depressed mothers (Davidson, 1995; Tomarken, Dichter, Garber, & Simien, 2004). These observations suggest that asymmetrical brain activity may represent a trait marker for depression vulnerability rather than a state marker resulting from depressed mood. .

Despite the promising use of asymmetry as a marker for vulnerability to depression, inconsistent findings have prevented this model from being widely accepted. For example, some research has found individuals with depressed mood performed poorly on tasks thought to rely on the right hemisphere compared with controls (e.g., Heller, Etienne, & Miller, 1995; Tucker 1981). This finding was interpreted as evidence for reduced right hemisphere dysfunction in depression which seems to contradict EEG findings suggesting a relative left frontal reduction in activity during depression. This conclusion gave little consideration to differences in anterior/posterior brain function and as a result does not provide strong evidence against a relative left frontal reduction in activity in depression. The tasks used in such research may have relied on posterior brain function. Therefore, impaired performance may imply right *posterior* dysfunction but does not conflict with a possible left *frontal* impairment. The other main problem for the hypothesis of brain activity as a marker for depression is that a subset of research has also found non-

significant results, or the opposite pattern of asymmetry (e.g., Kemp et al., 2005; Reid, Duke, & Allen, 1998). Although inconsistent findings are generally explained by methodological differences between studies and small sample sizes (Reid et al., 1998; Thibodeau et al., 2006), they may reflect heterogeneity in the classification of depression (Heller & Nitschke, 1998; Kemp et al., 2005; Shenal et al., 2003).

There is evidence in favour of this possibility in the form of different patterns of brain activity in different subtypes of depression. For example, perceptual asymmetries, indicative of asymmetries in frontal lobe activity, have been found to differ for individuals with melancholic compared with non-melancholic depression (Bruder et al., 1995). Bruder et al. (2002) found that individuals with atypical depression showed an exaggerated right hemisphere advantage for the perception of emotional faces in a chimeric face viewing task. In contrast, individuals with typical depression showed an absence of the normal right hemisphere advantage suggesting right hemisphere dysfunction. Additionally, there is evidence that individuals suffering from depression with low levels of reassurance-seeking behaviour may display the typical pattern of relatively increased right frontal activity, while depressed individuals with high reassurance-seeking scores had the opposite pattern (Minnix et al., 2004). These findings suggest that depression is not a unitary construct and that brain activity in depression may differ according to subtype and symptom characteristics.

The most common finding regarding brain activity in depression is relatively reduced left frontal activity in depression that may indicate that the most prevalent subtype of depression (Thibodeau et al., 2006). Alternatively, it is possible that depression resulting from right hemisphere dysfunction may be under-represented in clinical research (House, Dennis, Warlow, Hawton, & Molyneux., 1990). Right hemisphere dysfunction has been linked to reduced ability to express and understand emotion (Heliman, Bowers, & Valenstein, 1993). Therefore, individuals suffering from depression with right hemispheric dysfunction may be less aware of and less able to communicate their problems resulting in a lower likelihood of diagnosis and participation in research (House et al., 1990).

While the bulk of EEG research has focussed on frontal brain activity in depression, due to the frontal lobes links to emotion, a smaller number of studies have investigated parietal brain activity. Right parietal regions have been associated with arousal (Heller & Nitschke, 1998). As depression is commonly associated with reduced arousal, one would expect a relative reduction in right parietal activity in depressed patients. This pattern has been observed in a number of studies but has been less consistently detected than the pattern of frontal asymmetry (e.g., Bruder et al., 1997; Kentgen et al., 2000; Stewart, Towers, Coan, & Allen, 2011). Inconsistencies are usually explained by the presence of co-morbid anxiety (Bruder et al., 1997; Kentgen et al., 2000). In contrast to depression, anxiety is associated with increased arousal and increased right parietal activity (Heller et al., 1995). In patients suffering from both depression and anxiety, alterations in parietal brain activity may cancel each other out (Heller & Nitschke, 1998). Unlike frontal EEG asymmetry, there is evidence that parietal asymmetry may be related to the severity of depression symptoms and may represent a marker of the depressed state as opposed to a trait marker for vulnerability to developing depression (Stewart et al., 2011). Reduced brain activity in right parietal regions in depression, leading to reduced arousal, may help to explain the overall decrement in performance observed in depression but is unlikely to explain specific cognitive deficits that remain following remission due to its relationship to mood state.

As discussed previously, different patterns of brain activity may underlie different types of depression. In general, increased brain activity is associated with an increased ability to perform tasks associated with that region (Levin, Heller, Mohanty, Herrington, & Miller, 2007). Therefore, variation in patterns of brain asymmetry could help to explain variation in the pattern of cognitive deficits in depression.

The Missing Link

Evidence suggests that abnormal brain activity and impaired cognition in depression are linked. Two main types of studies have been conducted to investigate this possibility. In the first method researchers have investigated depressed individuals' performance on cognitive tasks thought to draw on certain brain regions. Impaired performance in such tasks was interpreted as evidence for dysfunction in those brain regions. For example, Miller, Fujioka, Chapman, and Chapman (1995) asked individuals to complete a dot localisation task thought to rely on right hemispheric regions and a word-finding task thought to rely on the left hemisphere. Depressed individuals were found to perform worse on the dot localisation tasks than the word-finding task indicating right hemispheric dysfunction. Furthermore, the loss of normal left hemi-spatial bias during chimeric face tasks in depression has been interpreted as evidence of right hemisphere dysfunction (e.g., Bruder et al., 2002; Heller et al., 1995). However,

this method is heavily reliant on assumptions about how different brain regions are involved in performing the tasks in question. Conclusions from such research may give an inaccurate picture of the link between brain activity and cognition deficits in depression.

A second commonly used method involves measuring individuals' brain activity while they perform a cognitive task. For example, Okada, Okamoto, Morinobu, Yamawaki, and Yokota (2003) found that depressed individuals displayed reduced task-related activity in the left dorso-lateral prefrontal cortex during verbal fluency tasks compared with control participants. Such research should be interpreted with caution as depressed individuals may employ alternative strategies during task performance (Fitzgerald et al., 2008). For instance, Fitzgerald et al. (2008) found evidence that patients with depression show intact performance but may achieve this by recruiting more cognitive resources as evidenced by increased brain activity relative to controls in abnormal brain regions. Therefore, abnormal brain activity during the performance of cognitive tasks may not represent the dysfunctional brain region and may instead represent an intact region overcompensating for a dysfunctional region. Given that compensatory brain activity may mask the link between cognitive deficits in depression and brain activity, it is not surprising that a review study conducted by Rogers et al. (2004) cited numerous inconsistent and conflicting results. Such inconsistencies may also result from a failure to account for heterogeneity within the diagnostic category of depression.

Different presentations of depression could result from different patterns of underlying brain activity (Shenal et al., 2003). As a result of dysfunction in one or more regions of the brain, depressed patients are likely to experience impairment of cognitive functions reliant on the affected brain regions. This hypothesis may help to explain the inconsistencies of cognitive deficits in patients diagnosed with depression.

Despite this promising potential explanation for the heterogeneity in the literature regarding cognitive impairment in depression, few experimental studies have directly investigated this possibility and there are problems with the few that have. One of the most direct attempts to investigate this possibility was conducted by Thompson (2010). Tasks thought to be reliant on left and right frontal regions were selected to assess hemispheric dysfunction relative to cognitive impairment. However, these tasks were not matched and the order of the tasks was not counterbalanced. As a result, group differences may have been confounded by task differences. Furthermore, the EEG component of the research was not completed due to time constraints. In other evidence, when depression is divided into subtypes there seems to be clear differences in the pattern of cognitive deficits between different subtypes. For example, Bruder et al. (1989) assessed performance of melancholic and non-melancholic depressed patients on a dichotic listening task. The melancholic patients showed evidence of right hemispheric dysfunction while the non-melancholic patients did performed no differently from non-depressed controls. Furthermore, Austin et al. (1999) also found that melancholic and non-melancholic patients showed distinct patterns of memory impairment suggestive of different patterns of underlying brain activity. However, care should be taken in interpreting these studies as no measurement of brain activity was attempted and the conclusions are largely based on assumptions about how the brain functions when engaged in different cognitive tasks.

Research in this field is plagued by inadequate task design. Several studies did not counterbalance task order (e.g., Miller et al., 1995; Thompson, 2010). As a result, interpretation of task performance is confounded by possible order effects such as reduced concentration. Furthermore, some studies have combined the use of the relative difference metric of brain activity with the performance on single tasks. However, if depressed patients suffer from reduced arousal they are likely to perform more poorly than controls on all tasks. As a result, impaired performance on a single task, relative to controls, cannot be interpreted as evidence of asymmetry. Researchers need to look at relative performance on matched tasks thought to rely more heavily on one hemisphere than the other instead of performance on single tasks. A further problem is using brain activity during task performance to infer dysfunctional brain regions. Compensatory mechanisms may mask patterns of underlying brain dysfunction and make it difficult to assess how abnormal brain activity and cognitive impairment in depression are linked (Fitzgerald et al., 2008). Finally, research involving tasks reliant on parietal regions is problematic. Parietal brain activity is confounded by anxiety and there is evidence that parietal brain activity in depression may represent the depressed state and not an underlying trait (Stewart et al., 2011). Differences in performance on cognitive tasks reliant on parietal regions may reflect severity of depression or be mood related and may not provide evidence of an underlying relationship between cognitive deficits and brain activity in depression.

Proposed Research

To address these problems and to investigate the potential link between variability in cognitive deficits and brain activity in depression more thoroughly, a single aspect of cognitive performance with dissociable components should be investigated. One possible cognitive domain for this research is working memory. Working memory can be divided into spatial and verbal components. Verbal working memory appears to be dependent on left frontal regions while spatial working memory seems to be dependent on right frontal functioning (D'Esposito et al., 1998; Smith, Jonides, & Koeppe, 1996). Therefore, verbal and spatial working memory may be differentially impaired in depression. Such a dissociation will allow detection of how brain asymmetry and cognitive performance in depression are linked. Depressed individuals and control participants will provide a resting EEG and assessment of spatial and verbal working memory function. It will then be possible to assess the link between variability in cognitive performance in depression and variability in brain activity in depression. For example, if an individual diagnosed with depression shows the pattern of relatively reduced left frontal activity then this model would be supported by a disproportionate impairment in verbal working memory compared with relatively spared spatial working memory. On the other hand, another participant diagnosed with clinical depression may show the opposite pattern of frontal asymmetry and display a greater impairment in spatial working memory than verbal working memory.

It is hypothesised that the majority of depressed participants will show relatively reduced left frontal activity as this pattern of frontal activity may be more likely to be diagnosed with depression than patients with depression resulting from reduced right-sided activity (House et al., 1990). It is also hypothesised that individuals suffering from depression with low anxiety may show reduced right parietal activity. Reduced right parietal activity is likely to lead to reduced arousal (Heller & Nitschke, 1998). As a result, it is likely that all individuals suffering from depression and low anxiety will display impaired performance on both working memory tasks. However, due to frontal asymmetry such individuals will show a disproportionate impairment in one of the tasks.

Conclusion

Depression is a highly heterogeneous disorder in which cognitive symptoms vary greatly for reasons that are poorly understood. Cognitive deficits may vary as a function of subtypes of depression. Different subtypes of depression may be associated with different patterns of underlying brain activity. Reduced regional brain activity could lead to differences in performance on cognitive tasks thought to draw on the impaired regions. Unfortunately, few experimental studies have been conducted to investigate this possibility. A research design is proposed in which brain activity in depressed participants will be measured and compared to their performance in spatial and verbal working memory tasks. The proposed task design should help to elucidate the relationship between variability in brain activity in depression and variability in cognitive deficits thereby overcoming some of the problems seen in earlier studies.

Conducting this research will help to find support for the theory that variation in brain activity in depression, resulting from different subtypes, accounts for the inconsistencies observed in the research regarding cognitive deficits in depression. A deeper understanding of these factors may aid in diagnosing and treating depression.

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