REGIONAL BRAIN ASYMMETRIES DURING VERBAL AND SPATIAL TASKS IN DEPRESSION WITH HIGH OR LOW TRAIT ANXIETY

by

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Abstract

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Depression is a common disorder with various clinical presentations and is frequently comorbid with anxiety disorders. The relationship of regional brain asymmetry to mood disorders has been informed by neuropsychological models in which emotion is lateralized along positive/negative and approach/withdrawal dimensions and by clinical reports of affective disturbances following localized brain damage. Studies of regional hemispheric asymmetries point to relatively less activity in left frontal and right posterior regions in depression. Anxiety has also been associated with less left frontal, but *increased* right posterior activity, which has been related to arousal and may, in anxious-depressed individuals, offset the posterior asymmetry normally seen in depression. These asymmetries have been indexed by EEG or inferred through the use of lateralized auditory and visual tasks (e.g., dichotic listening and chimeric face tasks). However, associations between regional EEG activity and neurocognitive function in depression or anxiety remain unclear. A number of neurocognitive deficits have been associated with depression, including poorer spatial than verbal skills, supporting right posterior deficits.

The present study used matched verbal (Word Finding) and spatial (Dot Localization) tasks to compare task-related alpha asymmetries in depressed patients grouped according to level of trait anxiety. EEG was recorded from depressed patients

with high anxiety (n=14) or low anxiety (n=14) and 21 age- and education-matched healthy adults during the two tasks, and alpha power was averaged within each task. Task performance was also recorded.

As predicted, the two patient groups exhibited opposite patterns of regional hemispheric alpha asymmetry. Greater right than left central-parietal activation was seen in the high-anxiety depressed group during the spatial task, whereas the verbal task elicited greater left than right frontal-central activation in the low-anxiety depressed group. Additionally, low-anxiety depressed patients and controls performed better on the verbal than the spatial task, whereas there was no asymmetry of performance within the high-anxiety depressed group. These results are consistent with Heller's two-dimensional model of depression and anxiety and highlight the sensitivity of task-related alpha in discriminating among subgroups of depressed patients differing in trait anxiety.

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Introduction

Major depressive disorder is among the most common of psychiatric illnesses, with a lifetime prevalence of 13 percent (Hasin, Goodwin, Stinson, & Grant, 2005). Depression encompasses a range of affective, physical, and cognitive symptoms, and its clinical heterogeneity may present an obstacle to research on its biological bases. To describe this heterogeneity, several subtypes have been identified, including those specifying melancholic or atypical features (Diagnostic and Statistical Manual, 4th Ed., American Psychiatric Association, 1994). Individuals having melancholic depression experience anhedonia or lack of reactivity to pleasurable stimuli, psychomotor retardation, decreased appetite, and decreased sleep. In contrast, those with atypical depression have preserved mood reactivity with *increased* appetite and sleep. That these subtypes are in some respects opposite in their symptoms suggests that there may be different underlying neural dysfunction and the necessity for differential treatment approaches.

To further complicate the clinical picture, depression is frequently comorbid with anxiety disorders. Approximately one third of individuals with depression also have an anxiety disorder (Hasin, et al., 2005; Schatzberg, Samson, Rothschild, Bond, & Regier, 1998). Individuals with this comorbidity are often more severely depressed (Kessler, Chiu, Demier, Merikangas, & Walters, 2005) and less likely to respond to antidepressant treatment (Fava et al., 1997). A 12-year longitudinal study revealed that patients with comorbid depression were half as likely to recover from panic disorder with agoraphobia or generalized anxiety disorder than those who were not depressed (Bruce et al., 2005). Thus, comorbid depression and anxiety represent a distinct challenge to treatment.

Comorbid depressive and anxiety disorders may exist in part due to overlap in diagnostic criteria. For example, difficulties related to social interactions may be features of both social phobia and atypical depression. Likewise, fatigue, sleep disturbance, and diminished concentration are common to major depression and generalized anxiety disorder. Yet anxiety and depression represent distinct disorders which may be reliably discriminated using clinical diagnostic scales (Gibb, Coles, & Heimberg, 2005). The tripartite model of anxiety and depression (Clark & Watson, 1991) proposes that anxiety and depression share a common feature of high *negative affectivity* (NA; comprised of negative mood states including anger, guilt, fear, and sadness). Depression is additionally characterized by an independent factor of low *positive affectivity* (PA; defined as "expressions of energy and pleasurable engagement" and including feelings of delight, interest, and enthusiasm). A lack of PA may be expressed as fatigue or sluggishness. A third factor, *physiological hyperarousal*, is specific to anxiety. Thus comorbid depression and anxiety would involve high NA, low PA, and physiological hyperarousal.

The existence of clinically distinct subtypes and the comorbidity with anxiety disorders suggest that there may be both shared and distinct areas of brain dysfunction among individuals with depression. Many studies of depression, however, have treated depression as a single disorder, which may contribute to conflicting conclusions. Linking particular brain abnormalities with symptom profiles should lead to an increased understanding of the pathways to clinical impairment and could highlight the importance of subtype and comorbidity in treatment planning and research design.

One approach has been to identify regions of the depressed brain that are more or less active relative to the nondepressed brain. Early evidence for lateralization of systems

involved in depressive disorders began with observations of changes in affective functioning in patients with lateralized brain damage. Left hemisphere damage was noted to be associated with "catastrophic" reactions (including anxiety, tearfulness, and depressed mood), whereas right hemisphere damage was observed to produce joking, denial, or minimization of illness, labeled "indifference" reactions (Gainotti, 1972; Starkstein Robinson, & Price, 1987). These changes are long-lasting and affect emotional experience as well as expression. In a self-report study of mood one to two years after surgery, left anterior temporal lobectomy patients reported increased depression and decreased socialization and right temporal lobectomy patients reported increased general happiness (Burton & Labar, 1999). Comparisons of patients with brain lesions at various sites revealed that individuals with left frontal damage were most likely to be depressed (Jorge et al., 1993; Robinson & Szetela, 1981; Starkstein et al., 1987). A longitudinal study revealed that left anterior lesions were associated with depression shortly following stroke, but that one year after a stroke, right posterior lesions were associated with depression (Shimoda & Robinson, 1999). Together, these findings suggest involvement of both left anterior and right posterior systems in depression.

Models of Regional Asymmetry

Lesion studies suggest that depression may be associated with abnormal anterior asymmetry consisting of a shift towards relatively greater right activity (due to reduced left hemisphere function). The approach/withdrawal model relates left anterior regions to approach motivation and right anterior regions to withdrawal motivation (Davidson, 1984; 1998). According to this model, innate differences in regional brain activity determine one's "affective style," and in some individuals act as a diathesis, predisposing

them to depression in the presence of emotionally significant life events ("stress"). Approach and withdrawal are also components of the Behavioral Activation/Inhibition Systems (BAS/BIS; Gray, 1990). The Behavioral Activation System is sensitive to reward and provides motivation to approach a stimulus. The Behavioral Inhibition System is sensitive to punishment, absence of expected reward, novelty, or fear activation. When activated, it increases arousal and inhibits behavior, while increasing vigilance to environmental stimuli. Depression may result from a deficit in the BAS (approach), while anxiety involves an overactive BIS (excess of withdrawal emotion and motivation).

Comparisons of EEG activity within the alpha frequency band in homologous right and left regions have been used to study regional brain asymmetry in depression. Alpha is the most prominent EEG frequency and is characteristic of resting wakefulness. In its most common pattern, it is maximal in amplitude over occipital regions, becoming smaller at more anterior sites. This pattern results from synchronous firing of posterior cortical neurons, with anterior propagation of activity (Niedermeyer, 2004). The source of synchronization remains unclear, with evidence for both thalamocortical (Buzsaki, 1991), and cortico-cortical circuits (Lopes da Silva, 1991). An independent, topographically distinct mu rhythm within the alpha frequency band is seen in some individuals. Prominent over the motor cortex, the mu rhythm desynchronizes during motor activity. A midtemporal "third rhythm" within the alpha frequency band has also been described but is rarely detectable on scalp recordings (Niedermeyer, 1997). Alpha power increases during childhood and adolescence, and periods of rapid brain growth have been shown to coincide with increases in both power and frequency (Epstein, 1980).

Alpha is largest when eyes are closed and decreases in response to visual stimulation. Alpha is taken to indicate relative deactivation of brain regions in which it occurs (Shagass, 1972) and regional alpha power at rest is inversely correlated with cerebral blood flow as measured by PET (Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998) and fMRI (Laufs et al., 2003). Individuals vary in peak alpha frequency (the frequency at which alpha power is greatest), and there is also some evidence for separate slow and fast sub bands within individuals that occur during different cognitive processes (Klimesch, 1999).

There is some evidence that depressed patients display a frontal asymmetry characterized by relatively less alpha power (therefore, greater activity) over right than left frontal regions (Henriques & Davidson, 1990; 1991; but see Harmon-Jones et al., 2002; Nitschke, Heller, Palmieri, & Miller, 1999; Reid, Duke, & Allen, 1998 for inconsistent findings). Conversely, there is evidence that individuals higher on measures of BAS display an opposite asymmetry, characterized by greater left than right frontal activity at rest (Coan & Allen, 2003; Harmon-Jones & Allen, 1997). Asymmetry findings for BIS have been mixed, with some linking higher levels of BIS to the asymmetry found in depression (Sutton & Davidson, 1997) but others finding a weak or absent relationship (Coan & Allen, 2003; Harmon-Jones & Allen, 1997). Evidence for an inverse relationship between BAS and bilateral frontal alpha (Harmon-Jones & Allen, 1997; Hewig, Hagemann, Seifert, Nauman, & Bartussek, 2006) has lead to suggestions that BAS might instead encompass both approach and withdrawal motivations (Hewig et al., 2006).

Regional alpha asymmetries have been documented in both currently and previously depressed individuals, which is consistent with a stable, trait characteristic (Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1990). There is some evidence for a genetic contribution. Overall alpha power has been shown to be highly heritable in a study of twins (Smit, Posthuma, Boomsma, & De Geus, 2005). Another study estimated that approximately 60% of the between-individual alpha asymmetry variance is due to stable individual differences, with 40% due to situational variables (Hagemann, Hewig, Seifert, Naumann, & Bartussek, 2005). Alpha asymmetries have also been detected in children of depressed mothers (Jones, Field, & Davalos, 2000). It has been proposed that an alpha asymmetry indicative of greater activity over right than left frontal regions acts as a diathesis which predisposes certain individuals to develop depression (Davidson, 1992).

The neural substrates of frontal alpha rhythms remain unclear, leading some researchers to questions their validity as measures of asymmetry (Tenke & Kayser, 2005). One criticism is that frontal alpha is more susceptible to contamination from artifacts such as eye movements, eye blinks, and muscle tension. The scalp EEG represents a spatial and temporal summation of volume-conducted brain electrical activity and "noise" from physiological (e.g., muscle activity, eye movements, EKG) and non-physiological (e.g., environmental and recording equipment) sources. Ocular and facial muscle activity has been found to exhibit asymmetries which may artifactually distort hemispheric alpha asymmetries (Friedman & Thayer, 1991; Goncharova, McFarland, Vaughan & Wolpaw, 2003; Hagemann & Naumann, 2001a). This is a particular concern for frontal alpha because of its relatively low signal-to-noise ratio,

which results from the fact that alpha is smallest frontally and these artifacts tend to be largest frontally.

A second concern is the influence of reference scheme on frontal alpha asymmetries. In asymmetry research, EEG is typically recorded as the difference in electrical potential between each electrode and a common reference. Because activity at either the target or reference site will affect the recording, different reference schemes may introduce unique noise profiles which may affect interpretation of the data (Hagemann, Naumann, & Thayer, 2001; Reid et al., 1998; Tenke and Kayser, 2005). Frequently used references include the tip of the nose and linked ears, the latter being susceptible to artifactual asymmetry when there is differential impedance between the ears (Lopes da Silva, 2004). The use of the highly active vertex reference is also fairly common but inadvisable, as it has the potential to distort or reverse asymmetries (Hagemann et al., 2001). An alternative to a single reference is the use of a common average reference (usually an average of all scalp electrodes), to which all individual electrodes are referred; however, this is most appropriate when a larger number of electrodes are used and may risk contamination of the reference by high amplitude in a few channels, particularly when fewer electrodes contribute to the average (Fisch, 1999). When selecting a particular reference montage, it is important to consider its influence on the signal of interest. Comparison of the same data under multiple reference schemes has been employed to validate results and select the most appropriate reference (Lopes da Silva, 2004). Frontal alpha is more broadly susceptible to reference related distortion due to its poorer signal-to-noise ratio.

In contrast, posterior alpha asymmetries are likely to be more stable as a result of their higher signal-to-noise ratio (Hagemann et al., 2001). Posterior alpha in depression has been shown to exhibit an asymmetry opposite to that of frontal alpha, indicative of greater left than right activity. This asymmetry has been found in both currently and previously depressed individuals (Bruder et al., 1997; Henriques & Davidson, 1990) and in offspring of two depressed parents (Bruder et al., 2005). Posterior asymmetries were also found to be to unchanged by antidepressant treatment (Bruder et al., 2007). In individuals with a history of depression, asymmetries were stable across a 1- to 3-year interval in both frontal and parietal regions and were unrelated to depression severity or changes in severity (Vuga et al., 2006). However, not all have found this pattern of posterior asymmetry (Schaffer, Davidson, & Saron, 1983).

In a variation on the approach/withdrawal model, Heller and colleagues have proposed a two-dimensional model in which frontal laterality is governed by a pleasant/unpleasant dimension, with pleasant emotion related to greater left and unpleasant emotion to greater right frontal activity. A second dimension of arousal is mediated by right parietotemporal regions (with less activity in this region reflecting reduced arousal), thus accounting for both anterior and posterior alpha asymmetries in depression (Heller, Etienne, & Miller, 1995). This model derives from associations between right lateralized brain damage and hypoarousal (Heilman, Schwartz & Watson, 1978) and psychomotor slowing (Benton, 1986). Importantly, the model provides a biological basis for the clinical links between anxiety and depression in terms of shared and separate clinical features. It proposes that in both anxiety and depression, there is an asymmetry consisting of right greater than left frontal activity, thought to be associated

with increased unpleasant affect in both disorders. In contrast, greater right parietotemporal activity is thought to reflect increased arousal, which is characteristic of some anxiety disorders, whereas less activity in this region reflects decreased arousal, seen in depression as symptoms of fatigue and hypersomnia (Heller & Nitschke 1998). When listening to sad or fearful stories, individuals high in trait anxiety symptoms had a rightward shift in parietal alpha asymmetry, indicative of greater right parietal activity (Heller, Nitschke, Etienne, & Miller, 1997). In a study of patients with PTSD, level of arousal appeared to predict posterior alpha asymmetry more than did severity of depression (Metzger et al., 2004). However, this asymmetry is not necessarily a feature of all anxiety disorders. Whereas an alpha asymmetry indicating greater right activity was found in individuals high in anxious arousal, individuals with anxious apprehension, characterized by worry and a tendency to ruminate, did not show an asymmetry (Nitschke et al., 1999). Finally, there is some evidence that individuals higher on BIS scales show the parietotemporal alpha asymmetry characteristic of anxious arousal (Hewig et al. 2006).

It is possible that conflicting research findings for posterior asymmetries in depression may be due to the presence of comorbid anxiety, in which posterior asymmetry may be opposite to that seen in depression alone. This possibility was illustrated by a study of comorbid depression and anxiety, in which depressed patients without anxiety disorders had posterior alpha asymmetry indicative of greater left than right activity, whereas those with anxiety and depressive disorders had an opposite pattern (Bruder et al., 1997). Similarly, in adolescents, the presence of anxiety comorbid

with a depressive disorder reduced the typical posterior alpha asymmetry (Kentgen et al., 2000).

As both the approach/withdrawal and two-dimensional models predict, anxiety and depression appear to have similar frontal asymmetry. Adults with panic disorder showed the rightward alpha asymmetry found in depression, both at rest and when viewing anxiety provoking stimuli (Wiedemann et al., 1999). This asymmetry may also be linked to symptom severity. The magnitude of the resting frontal EEG asymmetry was related to symptom severity in melancholic but not non-melancholic depression, with increasing depression and anxiety symptoms associated with greater asymmetry (Pizzagalli et al., 2002). These commonalities are likely to underlie shared symptoms of increased negative or withdrawal mood and/or reduced positive or approach mood in anxiety and depression.

A relationship between mood and alpha asymmetry may also exist in psychiatrically healthy individuals. An asymmetry indicating greater right than left activity has been found in normal sadness (Tucker, Stenslie, Roth, & Shearer, 1981). When healthy adults were trained to shift frontal alpha using biofeedback, resulting in greater left activity, they rated their mood as less negative. Conversely, those who shifted alpha in the opposite direction rated their mood as less positive (Allen, Harmon-Jones, & Cavender, 2001). These state-dependent asymmetries contrast with asymmetries seen in depression which are more stable and do not typically change with clinical improvement (Vuga et al., 2006). This suggests that the relationship between asymmetry and mood may differ in healthy and depressed individuals.

Depressed patients appear to show alterations in facial emotional expression that are consistent with an approach/withdrawal or valence model. In one study, they displayed sadness with greater intensity and pleasant emotions (happiness and pleasant surprise) with less intensity than controls (Jaeger, Borod, & Peselow, 1986). While this study did not directly measure anterior asymmetry, lesion studies suggest that facial emotional expression is associated with anterior brain regions (Weddell, Miller, & Trevarthen, 1990). Thus, differences in expression by emotional valence are consistent with both the Heller and Davidson models of anterior asymmetry in depression which posit that more negative/withdrawal emotion and less positive/approach emotion result from a frontal shift towards greater right activity. Another study found that facial emotional expression was more asymmetrical in depressed than healthy adults. Depressed individuals expressed sadness, interest/excitement, and neutral expressions with more intensity on the left side of the face and happiness more intensely on the right side of the face. In contrast, healthy adults were only (right-faced) lateralized for anger (Yecker et al., 1999). These results are not entirely consistent with depression models, as they suggest that interest/excitement, seemingly more of an approach-related or pleasant emotion, is mediated by the right hemisphere (at least in depressed individuals). Yet they do indicated that in depression there may be increased lateralization of emotion, with the right hemisphere more dominant in its expression than it is in non-depressed adults.

While emotional expression and experience are more frontally mediated, emotional perception appears to be mediated primarily by (right) posterior systems. There is evidence that healthy individuals perceive facial emotion (Ley & Bryden, 1979) and emotional language (Atchley, Illardi, & Enloe, 2003) more accurately in the left visual

field, and that this lateralization is reduced in depressed individuals (Jaeger, Borod, & Peselow, 1987). Individuals with right brain damage have shown impaired perception of emotion in facial, prosodic, and lexical domains (Adolphs, Tranel, & Damasio, 2001; Borod et al., 1998). It may be speculated that depressed individuals have a tendency towards reduced right posterior activity which predisposes them to have greater difficulty perceiving social cues, making these interactions inherently more difficult and leading to social withdrawal. Anxiety, on the other hand, having increased right posterior activity, might be accompanied by a hypersensitivity to social and environmental cues.

Behavioral Measures of Laterality

Resting EEG may provide information about baseline brain activity but does not necessarily allow inferences regarding brain-behavior relationships. The numerous tasks with which the brain is engaged may produce patterns of activity that may look very different from those of the brain at rest. It is also a somewhat ambiguous measure, as during these recording periods it is not known exactly what the brain is doing (e.g., some depressed individuals may tend to ruminate while "resting"), confounding between-group comparisons. Thus, resting EEG measures are limited in the extent to which they reveal differences between the depressed and normal brain, and it is important to also obtain evidence from tasks which clearly define the brain's role.

Dichotic listening. In assessing functional correlates of the posterior asymmetries, which would be expected to differ in anxiety and depression, a number of behavioral measures have employed lateralized presentation of stimuli to infer asymmetrical processing. As sensory afferents project primarily to the contralateral hemisphere, a tendency to favor one side indicates relatively greater involvement of the

contralateral region in task execution. In dichotic listening tasks, individuals are presented with different simultaneous auditory stimuli in the right and left ears. In healthy left hemisphere dominant adults, there is a left hemisphere (right ear) bias for processing verbal information (e.g. fused rhyming words) and a right hemisphere (left ear) bias for processing nonverbal information (e.g. complex tones). Studies have found that depressed patients exhibit an increased left hemisphere bias for verbal and a reduced right hemisphere bias for nonverbal material, both of which point to relative impairment in right posterior regions (Bruder, Wexler, Stewart, Price, & Quitkin, 1999). Like patterns of EEG asymmetry, dichotic listening asymmetry does not appear to change with treatment and symptom remission, suggesting that it is a state-independent marker of vulnerability to depression (Bruder et al., 1996).

Patterns of perceptual asymmetry measured using dichotic listening tasks vary among diagnostic subtypes, with melancholic, but not atypical, depression associated with reduced right hemisphere bias (Bruder et al., 1989). Perceptual asymmetry may also discriminate between depression with or without comorbid anxiety. As predicted by Heller's model, dichotic studies support opposite posterior asymmetries in depression with and without comorbid anxiety. In a dichotic fused words task, depressed adults without anxiety disorders had an increased left hemisphere lateralization for fused words (relative to healthy adults), whereas those with both depressive and anxiety disorders showed reduced left-lateralization (Pine et al., 2000). In another study, a combined index of verbal/nonverbal perceptual asymmetry indicated a left hemisphere advantage in depression without anxiety, a right hemisphere advantage in depression with anxiety, and no asymmetry in controls (Bruder et al., 1999). Social phobia in the presence of a

depressive disorder was found to reduce the left hemisphere advantage for words, especially in women (Bruder, Schneier, Stewart, McGrath, & Quitkin, 2004).

Perceptual asymmetry on dichotic listening tasks has also been related to antidepressant treatment response, with responders having a greater pre-treatment left hemisphere advantage than either nonresponders or healthy controls (Otto, Fava, Rosenbaum, & Murphy, 1991; Bruder, Stewart, McGrath, Deliyannides, & Quitkin, 2004). On the other hand, increased right hemisphere bias may index poor response to treatment. Since patients with comorbid anxiety are also relatively less likely to respond to treatment (Fava et al., 1997), this comorbidity may help to explain the variability in dichotic listening task asymmetries and adds support for the tasks' use in treatment planning.

Chimeric face perception. A free-vision task has yielded asymmetries in the same direction as those from dichotic listening studies. The Chimeric Face Task (CFT; Levy, Heller, Banich, & Burton, 1983) assesses the extent to which the perception of emotion in faces is lateralized. Chimeric faces show happy emotion on one half and a neutral expression on the other. In right-handed adults, there is a tendency to perceive faces with emotion on the left as happier, indicating right hemisphere lateralization. This asymmetry is consistent with right hemisphere specialization for emotion perception. Depressed patients show a reduced left-hemifield bias, suggesting that they are less right-lateralized for this function (Jaeger et al., 1987). However, atypical depression has been associated with increased right hemisphere lateralization (Bruder et al., 2002b). Chimeric face studies of normal individuals grouped according to levels of trait anxiety and depression have provided an important dissociation of the distinct relationships of anxiety and

depression to right posterior emotion processing, with higher trait depression associated with reduced right hemisphere bias and higher trait anxiety associated with increased right hemisphere bias (Heller et al., 1995; Keller et al., 2000). Factors from the tripartite model of depression and anxiety have also been related to hemispheric bias on the CFT (Voelz et al., 2001). Results from this study indicated that increased right hemisphere biases predicted increased anxiety (physiological hyperarousal), and decreased right hemisphere biases predicted decreased positive affectivity. A study of simple reaction times to lateralized visual stimuli produced a similar pattern of results; mild unipolar depression was associated with relative slowing to left visual field (right hemisphere) targets, whereas comorbid symptoms of both anxiety and depression were associated with slowing to right visual field (left hemisphere) targets (Liotti, Sava, Rizzolatti, & Caffarra, 1991).

Motor. A measure which has been used to infer asymmetry in anterior regions is the right-left difference in motor activity (e.g., grip strength or manual dexterity). Some depressed individuals have shown asymmetry on measures of psychomotor function suggestive of a shift towards greater right-sided activity. In a study of grip strength, depressed boys showed reduced right-hand dominance, and asymmetry was related to depression severity (Emerson, Harrison, Everhart, & Williamson, 2001). Similarly, a reduced right-hand advantage on grip strength was seen in high-anxiety adult men without depression (Everhart, Harrison, Shenal, Williamson, & Wuensch, 2002). In a study using transcranial magnetic stimulation (TMS) of motor cortex, depressed patients required greater TMS intensity to produce motor evoked potentials in left than in right motor cortex, with no asymmetry in controls (Maeda, Keenan, & Pascual-Leone, 2000).

This reduced activation in motor cortex may underlie asymmetries in motor function. From these direct and indirect measures of activity in motor cortex, there is evidence of functional changes that corroborates EEG evidence of either left frontal hypoactivation or right frontal hyperactivation in both anxiety and depression.

Information processing bias. According to cognitive models, depression is related to disturbances in processing emotional information. Specifically, both healthy and depressed individuals display biases in attention and memory in favor of information consistent with their mood (mood congruent bias). According to these models, healthy individuals counteract negative mood states by preferentially attending to, storing, and recalling positive information about the world, whereas depressed individuals lack this ability. Instead, they more readily attend to negative information, which can lead to sustained negative mood states (Beck, 1967; Bower, 1981). Mood congruent bias in depression has had electrophysiological support from experiments involving verbal memory (Deldin, Deveney, Kim, Casas, & Best, 2001) and face processing (Deldin, Keller, Gergen, & Miller, 2000). The latter study found a reduction in the N200 potential over right posterior regions during the viewing of positive (but not negative) faces, linking right posterior dysfunction to deficits in positive emotion perception. Further support for a relationship between abnormal emotion appraisal and right posterior ERP abnormalities may be found in a study employing negative facial stimuli (photographs of dermatological patients), in which depressed patients showed a reduction in late P3 ERP amplitude and failed to show the normal enhancement of the right-parietally maximal potential to negative (versus neutral) stimuli (Kayser, Bruder, Tenke, Stewart, & Quitkin, 2000). An investigation using a split-field paradigm supported a relationship between

mood congruent processing biases and right hemisphere lexical emotional perception. In that study, depressed patients were faster and more accurate in responding to negative words than positive words (and an opposite bias was seen in healthy controls) only when the material was presented to the right hemisphere (Atchley et al., 2003). These studies provide preliminary links between a bias in processing emotional information and right posterior deficits. They suggest that the decreased positive affect which may be seen in depression is related to reduced processing of positive emotional information by right posterior cortex. It remains unclear whether there is a relationship to deficits in other types of information processing in depression, e.g., a reduction in an early novelty P3 ERP with a vertex source, which may reflect problems with early processing of novel sounds (Tenke, Kayser, Stewart, & Bruder, *in press).* Further, the issue of comorbidity and information processing deficits has not yet been addressed.

Neurocognitive Deficits

Despite evidence of cognitive difficulties in depression and their association with particular clinical features, only the subjective report of "diminished concentration" is a diagnostic criterion. As cognitive functions recruit particular brain regions, the presence of certain deficits might act as markers to distinguish among subtypes of depression, providing links between clinical symptoms and neuropathology. They may also aid in predicting which patients will respond to treatment. One study linked psychomotor slowing (which may reflect dopaminergic dysfunction) to lack of response to drugs that increase serotonin (Taylor et al., 2006). Another found that the serotonin-modulated loudness dependence of the auditory evoked potential (the degree to which the N1/P2 amplitude increases with increasing tone intensity) predicted response to an SSRI

antidepressant (Mulert et al., 2007). Identification of cognitive abnormalities in depressed patients may aid in both diagnosis and treatment by suggesting medications that are more likely to be effective for a particular individual based on a symptom profile that includes cognitive features.

Identification of deficits through neuropsychological testing is a relatively simple method of assessing regional brain dysfunction in individuals with depressive symptoms. Mild to significant impairments have been identified in a number of functional domains, including memory, psychomotor, and executive functions. The most consistently found impairment is in episodic memory encoding and retrieval (Austin el al., 1992; Lawrie, MacHale, Cavanagh, O'Carroll, & Goodwin, 2000; Palmer et al., 1996; Zakzanis, Leach, & Kaplan 1998), consistent with PET evidence that depression is associated with decreased hippocampal metabolism (e.g., Saxena et al., 2001). Psychomotor slowing may also be present (Lawrie et al., 2000) and has been associated particularly with an endogenous profile of depression (Austin et al., 1992). Deficits have also been found in frontal executive functions including selective attention, working memory, fluency, and inhibition (Landro, Stiles, & Sletvold, 2001; Langenecker et al., 2005; Okada, Okamoto, Morinobu, Yamawaki, & Yokota, 2003; Zakzanis et al., 1998). However, in contrast to the stability seen in EEG and other measures of laterality, for which abnormalities are seen in both currently depressed and remitted depressed individuals (Henriques & Davidson, 1990), there is evidence that cognitive deficits are more state-dependent and improve with remission of depression (Austin et al., 1992; Cassens, Wolfe, & Zola, 1990). Although the majority of studies have not systematically examined symptom

subtypes, the variety of these deficits suggest that, as with other measures of regional abnormalities, cognition may be differentially affected as a function of subtype.

Some researchers have classified depressed patients based on degree and type of cognitive deficits. Cognitive deficits, in general, are more typical of geriatric depression than of the depression seen in younger adults (Cassens et al., 1990). Older depressed patients, in addition to showing memory deficits, are more likely to also have executive or attention deficits (Lockwood, Alexopoulos, Kakuma, & van Gorp, 2000). Depressed patients have shown greater cognitive declines with age in confrontation naming, complex visuomotor ability, and set shifting (King, Caine, & Cox, 1993). However, these findings may be confounded by comorbidity with other disease processes in the elderly. Depression may present as the first sign of a dementing disorder, before cognitive deficits become prominent. Comparisons of the brains of geriatric depressed patients revealed that those who had late-onset depression showed greater ventricular enlargement than those with early-onset depression, suggesting similarities to dementia (Alexopoulos, Young, & Shindledecker, 1992). In a recent longitudinal study that compared elderly depressed patients who eventually developed dementia with those who did not and with healthy controls, the depressed patients scored lower at baseline in a number of cognitive domains than controls; however, they did not decline over time as did the individuals who eventually developed dementia (Ganguli, Du , Dodge, Ratcliff, & Chang, 2006). There is evidence that depression may be related to subcortical pathology in older adults. Subcortical white matter abnormalities in depressed patients are more prevalent in those with no family history and are associated with decreased motor speed (Hickie et al., 1995). Thus, cognitive deficits in the depressed elderly are more likely to be permanent

and related to other disease processes than those of younger or middle-aged depressed adults.

Frontal executive functions. The frontal lobes are crucial to executive functions, including working memory, inhibition, set-shifting, fluency, abstraction, and problem solving. Impairments have been found on a number of measures including novelty processing (Tenke et al., *in press*), response initiation and inhibition (Langenecker et al., 2005; Zakzanis et al., 1998) and verbal fluency (Okada et al. 2003). In a sample of depressed outpatients, the executive functions of selective attention and working memory were found to be areas of particular weakness within an overall lower neuropsychological profile (Landro et al., 2001). These deficits appear to be more frequent in some subtypes of depression. On a test requiring learning, maintaining, and switching rules in a card-sorting procedure, depressed patients having primarily vegetative symptoms showed deficits, but those with primarily psychological symptoms, such as apathy, depressed mood, and guilt, did not (Palmer et al., 1996). Similarly, an endogenous patient subsample showed impairment on a measure of psychomotor speed, sequencing, and set-shifting (Trailmaking Test) and on a speeded visuospatial coding and set-shifting task (WAIS-III Digit Symbol Coding); however, a "neurotic" subsample did not differ from healthy controls (Austin et al., 1992). Another study failed to find executive deficits in a sample of depressed young women with high levels of state and trait anxiety (Crews, Harrison, & Rhodes, 1999). The authors speculated that the increased arousal associated with anxiety may have offset performance declines related to hypoarousal in depression.

Impairments on tests of frontal lobe functioning have also been associated with abnormal regional brain activity. On a planning and problem-solving task (Tower of

London), depressed individuals showed impaired performance and failed to exhibit task-related increases in blood flow in prefrontal and anterior cingulate regions on PET (Elliott et al., 1997). In an fMRI study, medicated depressed patients had performance deficits and reduced activation in left prefrontal cortex during a verbal fluency task (Okada et al., 2003). In another PET study, differences were found between cognitively impaired and non-impaired depressed patients, with the impaired patients having reduced left prefrontal activity, (Dolan et al., 1992). On a controlled processing go/no-go task, depressed patients with blunted affect and psychomotor-retardation had smaller and delayed frontal P3 (bilaterally), whereas those with anxious-agitated depression had faster latencies and larger amplitudes (Pierson et al., 1996). The association of both cognitive deficits and symptom subtypes with abnormal brain activity highlights the importance of determining whether cognitive deficits may reliably differentiate among clinical subtypes.

The identification of cognitive deficits may also have applications for treatment. Executive function tests have shown promise in identifying patients who are not likely to respond to antidepressant medication. Patients who failed to respond to antidepressant treatment had pre-treatment problems on a card-sorting task reflecting difficulty inhibiting a dominant response, diminished ability to learn, and problems maintaining and switching rules in response to feedback (Dunkin et al., 2000). Psychomotor slowing (Taylor et al., 2006) and poorer performance on tasks of letter fluency, working memory and executive functions (Gorlyn et al., 2008) have also been associated with poor treatment response. In elderly depressed patients, verbal perseveration (Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004), psychomotor retardation, and a low score on the

Initiation and Perseveration subscale of the Mattis Dementia Rating Scale (Kalayam & Alexopolous, 1999) also predicted poor response. It is not clear whether executive function deficits in younger and older depressed patients are of a similar etiology.

Bringing together evidence from cognitive and neuroimaging studies may help to uncover markers of treatment response. Goodwin (1997) described abnormalities in orbital and anterior cingulate, rather than dorsolateral, regions of the frontal cortex, affecting functions such as set-shifting and inhibition more than those such as organization and working memory, and provided evidence that these changes are likely to be transient and to resolve with treatment. Rostral anterior cingulate activity at rest has been correlated with eventual treatment response, with hypermetabolism or increased activity as measured by both PET (Mayberg et al., 1997) and EEG alpha suppression (Pizzagalli et al., 2001), predicting treatment response. Higher levels of pretreatment anterior cingulate activation, recorded by fMRI when patients viewed emotionally negative pictures, was correlated with a greater degree of improvement in depressive symptoms (Davidson, Irwin, Anderle, & Kalin, 2003). Evidence of decreased vertex novelty source in depressed patients in a novelty oddball task was also suggestive of abnormalities in anterior cingulate cortex (Tenke et al., *in press*), thus it is possible that this task may also aid in predicting which patients will respond to treatment. It may also be possible to identify neurocognitive tests that discriminate between responders and nonresponders on the basis of performance.

Right Posterior. Electrophysiological asymmetries pointing to right posterior hypoactivation, along with behavioral asymmetries on lateralized tasks, suggest that there may also be abnormalities in cognitive functions controlled by right posterior brain

regions in some depressed individuals. In others, in particular those with comorbid anxiety, there may be relative *hyperactivation* of these regions, which might be expected to result in better performance on cognitive tasks mediated by right posterior regions. A phonetic oddball study of patients with either depressive disorder or anxiety disorder or comorbidity of these disorders yielded group differences in the left greater than right N2-P3 event-related potential (ERP) asymmetry over temporopatietal regions, with the largest asymmetry in patients with depression alone and the smallest difference in patients with anxiety disorder alone (Bruder et al., 2002a). ERP's recorded during a dichotic oddball task in depressed patients revealed reductions in the left-lateralized P3 potential but no group differences in asymmetry, however, level of anxiety was not examined (Tenke et al., 2008). One way to test the hypothesis that depression and anxiety exhibit opposite functional asymmetries in posterior regions is to compare performance and EEG recorded during verbal and spatial tasks which selectively engage the left or the right posterior regions, respectively. There is evidence that, like resting EEG asymmetry, patterns of task-related EEG alpha asymmetry elicited by verbal versus spatial tasks are stable across recording sessions (Ehrlichman & Weiner, 1979), suggesting that they are a reliable index of traitlike individual differences.

A few studies have pointed to right posterior cognitive weaknesses in depression. One study found that depressed inpatients had broad impairments on simple pattern identification, as well as face discrimination tasks, indicating a broader visuospatial deficit (Asthana, Mandal, Khurana, & Haque-Nizamie, 1998). Nearly all depressed patients performed better on a verbal than on a nonverbal recall task, whereas controls were evenly split (Deptula, Manevitz, & Yozawitz, 1991). In the same study, there was a

significantly larger difference between Wechsler Performance IQ and Verbal IQ in depression than in controls, as a result of lower Performance IQ in depression. It has also been suggested that lower nonverbal IQ occurs only in patients with predominantly vegetative symptoms (Palmer et al., 1996). Patients with more melancholic depression had longer latencies of the P3 event-related potential during an audiospatial discrimination task, but not a temporal discrimination task, indicating slowing of right hemisphere mediated spatial function (Bruder et al., 1991). Not all studies, however, have found a verbal/non-verbal difference (Calev, 1996), and other studies have supported impairments in visual attention for effortful, but not more automatic, processes, which were present even after patients' symptoms improved (Hammar, Lund, & Hugdahl, 2003).

One problem is that many studies have compared verbal and spatial tasks that differ in terms of extraneous variables such as sensory and motor requirements or psychometric properties, making it difficult to draw conclusions regarding the causes of functional asymmetries. Another is their lack of specificity for posterior brain functions (e.g., the Wechsler nonverbal IQ includes tests of psychomotor speed as well as visuospatial ability). Finally, as cognitive deficits in depression are typically relatively small, they often require a more sensitive measure than neuropsychological instruments designed to assess primary brain damage. To address these issues, a set of verbal/nonverbal tasks was developed and matched psychometrically (Fujioka, 1986; Miller, 1986; Miller, Fujioka, Chapman, & Chapman, 1995a). The Word Finding task, a verbal analog of the Boston Naming Test (used to assess aphasia; Goodglass & Kaplan, 1983), presents subjects with a written definition of a word and requires them to identify

the word. The Dot Localization Task presents subjects with two rectangles, one containing a pair of dots and another with an array of numbers, and requires them to identify the numbers corresponding to the position of the dots. Among patients with unilateral brain damage, a study found that those with right-sided lesions were impaired on dot localization, whereas patients with left-sided lesions did not differ from controls (Hannay, Varney, & Benton, 1976).

EEG recorded during these tasks in healthy adults confirmed greater right hemisphere activation, as measured in the alpha band, during the spatial task and greater left hemisphere activation during the verbal task in central and parietal regions (Davidson, Chapman, Chapman, & Henriques, 1990). Further, task performance was correlated with increased involvement of the mediating hemisphere, particularly in the verbal task. This is in line with other associations between poor performance on neuropsychological tasks and reduced activation in regions mediating the particular function (Elliott et al., 1997; Okada et al., 2003; Papousek & Schulter, 2004). Identification of mediating regions through an analysis of theta band power revealed that the Word Finding task is mediated by left central and bilateral frontal regions, whereas the Dot Localization task is mediated by right central and bilateral posterior regions (Koles, Flor-Henry, & Lind, 2001). Links between frontal midline theta and the frontal novelty P3 potential (Demiralp, Ademoglu, Comerchero, & Polich, 2001; Isler, Grieve, Czernochowski, Stark, & Friedman, 2008) suggest that the reduction of the latter in depression (Tenke et al., *in press)* may also be associated with task-related changes in theta power.

As would be expected given a right posterior deficit, depressed patients are less accurate on the Dot Localization than on the Word Finding task (Miller, Fujioka, Chapman, & Chapman, 1995b). When compared with healthy adults, depressed patients performed worse on the spatial task but equally well on the verbal task (Henriques & Davidson, 1997). Further, depressed patients failed to demonstrate the task-specific posterior asymmetries found in controls, instead showing relative left-sided activation during both tasks. In frontal regions, there was an asymmetry in depressed (but not control) participants, with relatively greater left frontal activation during the verbal task and relatively greater right frontal activation during the spatial task. Additionally, in controls, performance on the verbal task was associated with greater left activation, while performance on the spatial task was associated with greater right activation. In contrast, better performance in depressed patients was associated with greater left activation in both tasks, linking performance to electrophysiological abnormality.

These tasks have not yet been used to compare subtypes of depression. It would be expected that patients with comorbid anxiety or atypical depression, lacking the right-posterior deficit found in depressed patients without anxiety, would not show the relative performance deficit on Dot Localization, instead having more similar performance on the two tasks, or better Dot Localization than Word Finding performance as a result of increased activation in right posterior regions. The association of task scores with EEG asymmetry should shed light on the issue of whether asymmetries result from over- or underactivation of a particular region. For example, a posterior asymmetry shifted toward greater right than left activation, in conjunction with a specific deficit on the Word Finding task relative to controls, would suggest that the left hemisphere is underactive in

depressed patients with high trait anxiety. The same asymmetry in conjunction with superior performance on the Dot Localization task relative to controls would suggest that the right hemisphere is overactive.

Gender Differences

Finally, it is important to consider gender differences in depression, laterality, and cognition. Women are nearly twice as likely to be depressed as men (Hasin et al., 2005; Kessler, et al., 1993). One possible risk factor is the greater tendency for women to ruminate in response to stress (Heller, 1993; Nolan-Hoeksema, Larson, & Grayson, 1999). Verbal rumination is a key feature of "anxious apprehension," the type of anxiety associated with increased left hemisphere activity (Heller et al., 1997). Heller has hypothesized that particular cognitive styles of women, such as a tendency towards verbal coping strategies and rumination, predispose them to depression by promoting certain patterns of brain activity, particularly in posterior regions (Heller, 1993). These gender differences in the development of depression may affect the clinical presentation as well. In women, fatigue may "dominate the clinical picture" (Hamilton, 1989). Another study found that in depression, anxiety symptoms were associated with motor retardation in women and with hostility in men (Katz et al., 1993). A tendency for depressed women to ruminate in the presence of anxiety (anxious apprehension), shifting the posterior asymmetry towards greater left activity (thereby decreasing activity in right posterior regions that may be overactive in individuals with anxious arousal) may be linked to these symptoms of slowing and lack of energy. Women with depression and high anxiety might, therefore, demonstrate a less pronounced right greater than left posterior asymmetry than do men.

Neuropsychological gender differences in non-depressed individuals may predispose them to particular clinical presentations. Women are more accurate in perceiving emotional stimuli (Grunwald et al., 1999; Hall, 1978) and more expressive of emotions than are men, yet studies have found that emotional experience, either self-report or physiological reactivity (skin conductance), does not differ by gender (Kring & Gordon, 1998), or have had equivocal findings (Borod & Madigan, 2000). However, there may be gender differences in laterality. Women showed greater lateralization for the perception of facial emotion than men in accordance with a valence hypothesis, discriminating negative emotional expressions more accurately when presented to the left side, and positive emotional expressions more accurately when presented to the right side (Burton & Levy, 1989; Rodway, Wright, & Hardie, 2003). ERP evidence has suggested greater right than left hemispheric activation in response to negative emotional pictures in men, but greater left than right hemispheric activation in response to the pictures in women (Gasbarri et al., 2007). Some studies have indicated that men perform better on some spatial tasks, such as mental rotation, while women are better at verbal fluency and verbal memory (Kimura, 1996). Men and women showed different dichotic listening predictors of treatment response, with dichotic word asymmetry in women and dichotic tone asymmetry in men associated with a positive response to treatment (Bruder, et al., 2004b). Brain imaging has shown women to have more bilateral cortex devoted to language (Shaywitz et al., 1995). In a matched task paradigm, women performed equally to men on a verbal task and worse than men on a nonverbal task (Calev, 1996).

Gender differences in emotion and cognition are likely to be related to hormonal fluctuation, as well as differences in brain development and structure. The right

hemisphere may be more involved in modulating the Hypothalamic-Pituitary-Adrenal axis, which is critically related to normal hormonal function and often abnormal in depression (Heller, 1993). It has also been found that women have increased spatial performance and decreased verbal performance during the phase of the menstrual cycle when estrogen is low (Chiarello, McMahon, & Schaefer, 1989).

In summary, abnormal patterns of regional brain activity in depression are well-established; however, there is also evidence for differences among clinical subtypes (e.g., atypical versus melancholic) and among patients with or without comorbid anxiety. Models of asymmetry in depression and anxiety have linked these disorders to similar anterior (right greater than left) but opposite posterior asymmetries; depression associated with reduced and anxiety associated with increased right posterior activity. Evidence has come from behavioral and electrophysiological sources. However, few studies have attempted to directly link abnormal physiology with performance on measures of cognitive function. This study attempted to do so in order to better understand the neural bases and functional correlates of depression and anxiety.

Hypotheses

The present study aimed to evaluate predictions based on Heller's dimensional model of posterior asymmetries in depression and anxiety using EEG recorded during matched verbal and spatial tasks (Fujioka, 1986; Miller, 1986; Miller et al., 1995a). The tasks have been shown to distinguish depressed patients from controls on the basis of both cognitive performance and EEG asymmetry. This study is the first to assess whether the tasks may also differentiate depressed patients grouped according to trait anxiety.

Specifically, according to Heller's model, a task-related regional deficit in right temporoparietal function was expected in depressed patients with low levels of anxiety relative to healthy controls. This deficit would result in an increase in the expected normal asymmetry of greater left than right activation during the verbal task and a reduction in the expected normal asymmetry of greater right than left activation during the spatial task, with an associated performance deficit on the spatial task.

In depressed patients with high levels of anxiety, the right temporoparietal region was expected to show increased activation during both tasks, with an opposite effect of decreasing the normal asymmetry in the verbal task and increasing the normal asymmetry in the spatial task, along with no deficit in spatial function. Group differences in resting alpha were expected to be in the same direction, reflected as asymmetry of greater left than right posterior activity in the depressed patients with low anxiety and greater right than left posterior activity in the depressed group with high anxiety, with no asymmetry in controls. Women were expected to perform worse than men on the spatial task, whereas verbal performance was not expected to differ by gender. The results should help to clarify the relationships of depression and anxiety to neurocognitive function.

Method

Participants

Thirty-two currently depressed patients who met DSM-IV criteria for major depressive disorder, dysthymia, bipolar II disorder, or depression not otherwise specified were recruited from inpatient and outpatient clinics at the New York State Psychiatric Institute. Diagnoses were made by research psychiatrists based on structured interview. Patients were contacted if they met inclusion criteria and had agreed to be contacted. Patients were tested during a period when they were off antidepressant medication or during the first week of treatment; however, the majority of patients were unmedicated at the time of testing (86% of patients in the final sample, with an equal proportion in the two patient groups). Tests were scheduled so as not to interfere with or delay their regular treatment. Twenty-six age-matched healthy comparison participants were recruited from postings around the medical center and from online advertisements. Healthy controls were free of past or present DSM-IV diagnosis, as assessed by the Structured Clinical Interview for DSM-IV – Nonpatient Version (SCID-IV/NP; First, Spitzer, Gibbon, & Williams, 1995) on a day prior to testing.

All participants were fluent in English and had learned English prior to age 7. Handedness was determined via the score on the Edinburgh Handedness Inventory (Oldfield, 1971), and left-handed participants (laterality quotient < 0) were excluded. Participants ranged from 19-58 years of age (cutoff of 60 years) and, by their own report, were free of organic brain impairment, head injury, and other significant medical illness (e.g., cancer or diabetes). As required by auditory tasks from a separate study, participants were screened for hearing loss greater than 30 dB HL in either ear or

asymmetry greater than 10 dB. All participants signed informed consent forms before participating in the research, and outpatient and healthy controls were paid $15 per hour for their time.

Self-ratings were obtained from the Beck Depression Inventory (BDI; Beck et al., 1961) and the State-Trait Anxiety Inventory (STAI-Y; Spielberger et al., 1983). The patients were classified as *high-anxiety depressed* or *low-anxiety depressed* via the median split procedure based on level of self-rated trait anxiety (STAI-Y). Patients with trait anxiety scores ≥ 82 (median score) were classified as high-anxiety depressed (range = 82 – 97) and those with scores < 82 were classified as low-anxiety depressed (range = 60 – 80). For descriptive purposes, these groups are referred to as high- and low-anxiety, although patients in the low-anxiety depressed group may still have some level of anxiety. Trait anxiety scores from healthy controls did not overlap with patient scores (range = 34 – 58).

Data from one control were excluded from the statistical analyses because a BDI score at the time of testing reflected mild depression, and one patient's data were dropped because a BDI score indicated a subclinical level of depression at the time of testing. Data from four other participants (two patients and two controls) were not used because the participants responded correctly to less than 50% of items from both tasks combined, suggesting possibly reduced comprehension of, or attention to, the tasks. (No cognitive pre-screen was used.) Finally, data from three participants (one patient, two controls) were not used because of a lack of sufficient artifact-free EEG sweeps on one or both tasks.

The final sample included 14 participants in the high-anxiety depressed group, 14 participants in the low-anxiety depressed group, and 21 participants in the control group. Of the 28 patients, 22 had a diagnosis of major depressive disorder, 7 had a diagnosis of dysthymia (3 of whom also met criteria for major depressive disorder), and 2 had a diagnosis of bipolar II disorder. Nine of the patients also met criteria for an anxiety disorder (1 social phobia, 4 simple phobia, 1 panic disorder, and 3 obsessive-compulsive disorder). These nine included 8 of 14 in the high-anxiety depressed group and 1 of 14 in the low-anxiety depressed group. Demographic information for the final sample is reported in Table 1. To test whether the groups differed on factors that have been shown to affect alpha power, such as age and gender (Duffy, McAnulty, & Albert, 1993), demographic differences were evaluated using one-way Analysis of Variance (ANOVA), and significant main effects were followed with Bonferroni adjusted paired comparisons. There were no significant group differences in age, F (2,46) = 1.20, p = .21; years of education, F (2,46) = 0.35, p = .71; handedness score, F (2,46) = 0.10, p = .28; or in the proportion of men to women (χ^2 (2, N = 49) = 2.33, p = .31).

Self-ratings of depression (BDI) and trait anxiety (STAI-Y) were compared among groups and are summarized in Table 1. As expected, trait anxiety differed significantly between groups F (2,46) = 170.13, p < .001. Pairwise testing indicated that all groups differed from each other (all p-values < .001), with highest anxiety in the high-anxiety depressed group and lowest anxiety in the control group. A significant group difference in depression was also found F (2,46) = 106.25, p < .001. Pairwise testing revealed that both patient groups were significantly more depressed than controls (p-values. < .001). Additionally, the high-anxiety depressed group was significantly more

depressed than the low-anxiety depressed group (p = .003). These results are unsurprising in light of evidence that self-report measures of depression and anxiety are highly correlated (Tanaka-Matsumi & Kameoka, 1986). Overall, depressed men and women did not differ on level of depression, t (26) = .54, p = .59 or anxiety, t (26) = -0.42, p = .68. Mean BDI scores for the depressed men and women are presented in Table 2.

Tasks

A pair of existing verbal (Word Finding) and spatial (Dot Localization) tasks that have been psychometrically matched on mean difficulty, standard deviation and internal consistency reliability (Fujioka, 1986; Miller, 1987; Miller et al., 1995a) were used to examine EEG asymmetries related to verbal and nonverbal task performance in depression. The Word Finding task is a naming task modeled after the Boston Naming Test (Goodglass & Kaplan, 1983). In the Boston Naming Test, individuals view line drawings of various objects and then give the name of the object. It is used to assess left-hemisphere function in naming. Healthy individuals are expected to score at or near ceiling. In the Word Finding task, individuals are presented with a written definition instead of a line drawing (e.g., "A person who works for a skilled worker to learn a trade" Answer: "apprentice"; see Figure 1). In addition to allowing items that are not easily represented pictorially, this modification also minimizes confounding demands on right-hemisphere visual perception. To ensure that words were within participants' vocabularies, they were selected from children's dictionaries (Miller et al., 1995a).

The Dot Localization task is a measure of visual localization, which studies of patients with lateralized brain damage have shown to be primarily mediated by the right hemisphere. The Dot Localization task presents individuals with two open rectangles, one

above and slightly to the left of the other (see Figure 2). The top rectangle contains two dots, and the bottom rectangle contains a matrix of numbers. Individuals are required to indicate the two numbers in the matrix that would be covered by dots if the rectangle containing dots were placed over the rectangle containing numbers. To include items of varying difficulty, number matrices ranged from 13 to 50 numbers.

The Word Finding and Dot Localization tasks were adapted from their original booklet form to be administered on a PC. Thirty-item forms of each task were created, and approximately equal difficulty of the forms was verified by calculating the mean and standard deviation percent correct and response latency for each item based on a separate, preliminary sample of nine healthy adults. The tasks were administered in a fixed order (Word Finding first, Dot Localization second) consistent with the normative procedure and prior studies (Fujioka, 1987; Miller et al., 1995). In both tasks, participants were instructed to fixate on a cross that was centered on a computer screen. After three seconds, the cross was replaced by a task stimulus. Participants were instructed to focus on the screen and to press a button with their right hand when they had decided on their response. This button press then cleared the screen, and the participant gave his response verbally. Responses were recorded by an examiner. Participants were instructed to respond as soon as they knew an answer, and there was no time limit. During the recording, participants were instructed to remain relaxed but awake and to avoid eye or body movements. The tasks each included 30 trials (plus five additional practice trials). Word Finding score was the number of definitions correctly identified. Dot Localization score was the number of trials on which *both* numbers were correctly identified. Both numbers were required to improve reliability and decrease the contribution of guessing to

accuracy (Miller et al., 1995a). Prior to the two tasks, baseline EEG was recorded during both eyes-open and eyes-closed rest periods, with four blocks (two per condition) of two minutes each for each participant, counterbalanced across participants within each group.

Data Analysis

The EEG analyses used 4 midline (Fz, Cz, Pz, Oz) and 13 lateral pairs of electrodes (FP1/2, F3/4, F7/8, FC5/6, FT9/10, C3/4, T7/8, CP5/6, TP9/10, P3/4, P7/8, P9/10, O1/2) selected from an extended recording montage. These channels were selected to maintain methodological consistency with previous studies from our laboratory in order to replicate and extend previous findings. Continuous DC EEG with 24-bit analog-digital conversion was recorded using an electrode cap from 64 scalp sites (extended 10-20 system) as well as bipolar recordings of vertical and horizontal eye movements (BioSemi) and sampled at 256 Hz. During acquisition, the active recording reference was composed of sites PO1 (common mode sense) and PO2 (driven right leg). Data were converted to the 16-bit continuous data format (CNT) used by NeuroScan and re-referenced to the nose using PolyRex software (Kayser, 2006). The nose reference scheme was selected based on its use in a previous study of depressed patients with or without an anxiety disorder (Bruder et al., 1997). In that study, the nose reference was found to reveal significant group differences in both anterior and posterior asymmetries, whereas a vertex reference revealed differences only in posterior regions.

One-second EEG epochs, overlapping by 50%, were extracted from the continuous recording. The overlap was used to restore data attenuated by tapering across the entire epoch with a cosine window in order to suppress spectral side lobes prior to spectral analysis (Bendat & Piersol, 1971). In the two task conditions, epochs were

obtained from the period beginning at the onset of each task stimulus and ending with the participant's button press, indicating that they were ready to respond. In the resting conditions, epochs were obtained from the entire continuous recording. A high pass filter of 0.3 Hz was applied. Volume-conducted blink artifacts were removed from the raw EEG using a spatial singular value decomposition filter generated from identified blinks and artifact-free EEG periods (NeuroScan, 2003). This PCA-based blink correction procedure's effectiveness in reducing blinks was verified by visual inspection for each participant. In cases of marked blink-related artifact throughout a participant's recording that could not be successfully reduced, that participant's data were dropped from further analysis. Because both tasks required visual scanning, horizontal eye artifacts were removed from task EEG epochs using a linear regression of lateral EEG differences to remove correlated activity (+/- beta weight/2) of each lateral channel (Kayser et al., 2006). EEG epochs were screened for electrolyte bridges (Tenke & Kayser, 2001). To maximize the number of artifact-free epochs, a reference-free approach was used to identify artifactual EEG epochs for any given trial (Kayser & Tenke, 2006), which is based on the electrical distance measure introduced by Tenke and Kayser (2001). Using this measure, channels with extreme values outside a median-based range (Junghofer, Elbert, Tucker, & Rockstroh, 2000) were flagged, and these artifactual surface potentials were replaced by spherical spline interpolation, (Perrin, Pernier, Bertrand, & Echallier, 1989, 1990) from artifact-free channels. The spherical spline interpolation method employs a mathematical function to estimate surface scalp potentials between electrodes using a spherical model. A trial was rejected if it contained artifacts in more than 8 channels. Artifact detection and electrode replacement were verified by visual inspection.

Artifact-free EEG epochs were subjected to a power spectrum analysis using a Fast Fourier Transform, converting the data from the time to the frequency domain. Each 1-second epoch contained 256 sample points, and the resulting frequency resolution was 1 Hz. At each electrode, power spectra were averaged across all available epochs for each task. The dependent measure was power density in the alpha frequency band averaged across 8-13 Hz (alpha), and the appropriateness of this frequency band for alpha activity in both groups was assessed visually. Natural logarithms of alpha power were computed to normalize the data. To evaluate whether there were separate effects within the low-alpha (8 – 10) or high-alpha (10-13) frequency bands, these bands were also evaluated. Secondary analyses of power in the delta (1-4 Hz), theta (4-8 Hz), and beta1 (13-19 Hz) frequency bands were also conducted to determine whether group differences in hemispheric asymmetry for alpha were also evident for these bands.

It was unknown whether participants would display similar task-related alpha power during trials on which they eventually gave correct versus incorrect responses. To verify that power spectra were not markedly affected by the inclusion of both correct and incorrect trials, separate averages were created for each participant on each task using only trials that elicited correct responses and compared visually with averages including both correct and incorrect trials. Since the averages appeared to be nearly identical for all of the participants (confirmed via correlational analyses between group averages from the two conditions; at all electrodes, *r*-values > .999), the averages including all sweeps were used in order to maximize reliability of the power spectra.

The three groups did not differ in the number of artifact-free sweeps contributing to the averages, $F\ (2,43) = 1.95$, $p = .82$, nor was there an interaction between group and

task, F (2, 43) = 0.77, p = .47. Mean number of sweeps for each group and task are presented in Table 3.

Statistical Analysis

All analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL). Due to some small cell sizes, it was not possible to assess Group x Gender interactions. Nonetheless, gender was included as a factor in the ANOVA models on an exploratory basis. F-ratios were evaluated using degrees of freedom computed with the Greenhouse-Geisser ε correction on tests involving more than 1 degree of freedom on within-subjects factors, with appropriate adjustments to p-values. Significant omnibus F-tests involving factors with more than two levels were followed-up with Bonferroni-adjusted pairwise comparisons.

Performance data. To test the hypothesis that the groups would differ with regard to accuracy on the verbal and spatial tasks, the data were analyzed using repeated-measures ANOVA, with between-subjects factors of group (high-anxiety depressed, low-anxiety depressed, and control) and gender (male and female) and a within-subjects factor of task (verbal and spatial). A significant interaction between group and task was expected, with follow-up pairwise comparisons indicating different patterns of performance in each group. Namely, low-anxiety depressed patients were expected to show poorer accuracy on the spatial (Dot Localization) than verbal (Word Finding) task. High-anxiety depressed patients were expected to perform equally on the two tasks (non-significant t-test) or to show an opposite behavioral asymmetry (i.e., verbal worse than nonverbal performance). No significant difference between performance on the two tasks was expected for the control group. In the normative samples of Fujioka and Miller,

gender differences were present on the spatial but not the verbal task; thus a significant Gender x Task interaction was possible.

Task-related EEG data. Log power measures were evaluated using repeated-measures ANOVA. The between-subjects factors were group (high-anxiety depressed, low-anxiety depressed, and control) and gender (male and female). The within-subjects factors were task (verbal and spatial), hemisphere (left and right), and region (frontal, central, and parietal). Frontal electrodes were F3, F4, F7, and F8. Central electrodes were C3, C4, T7, and T8. Parietal electrodes were P3, P4, P7, and P8 (Bruder et al., 2005; 2007). Within each region, power was averaged across medial and lateral sites after preliminary analyses indicated no significant effects of interest for this variable. This was done in order to assess regional effects and reduce the amount of data in statistical analyses (Bruder et al., 1997).

In the alpha band, a 4-way Group x Task x Hemisphere x Region effect was expected. Healthy adults were expected to display opposite alpha asymmetries in the two tasks, consisting of greater activation (less alpha power) over left than right temporal and parietal regions during the verbal task and greater activation over right than left central and parietal regions during the spatial task. Consistent with a right posterior deficit, low-anxiety depressed patients were expected to show an asymmetry in the verbal task but no asymmetry in the spatial task. High-anxiety depressed patients were expected to show an asymmetry in the spatial task but no asymmetry in the verbal task.

Power measurements in the delta, theta, and beta1 frequency bands during the two tasks were also evaluated using the same repeated-measures ANOVA factors of group, gender, task, hemisphere, and region to determine the specificity of task results to the

alpha band. Although task-related midline frontal theta is well established and likely to be associated with both tasks as a result of general cognitive demands, no specific group differences in theta power were anticipated. No group differences were expected for delta or beta1 bands.

Resting EEG data. Predictions for resting alpha power were evaluated using repeated-measures ANOVA. The between-subjects factors were group (high-anxiety depressed, low-anxiety depressed, and control) and gender (male and female). The within-subjects factors were condition (eyes open and eyes closed), hemisphere (left and right), and region (frontal, central and parietal). The classic alpha topography was expected to produce main effects of condition (greater power with eyes closed than eyes open) and region (greatest power in the posterior region and least power in the frontal region, with intermediate power in the central region). A Group x Hemisphere x Region interaction was expected. Follow-up pairwise testing was expected to reveal asymmetrical resting alpha in the same direction as task-related EEG, with relatively greater alpha (less activity) in right posterior regions in low-anxiety depressed patients and relatively less alpha (greater activity) in these right posterior regions in high-anxiety depressed patients.

Results

Performance

To test the hypothesis that the groups would differ with regard to accuracy on the verbal and spatial tasks, the data were analyzed using repeated-measures ANOVA, with between-subjects factors of group (high-anxiety depressed, low-anxiety depressed, and control) and gender (male and female) and a within-subjects factor of task (verbal and spatial). Mean accuracy for the three groups on the verbal and spatial tasks is presented in Table 4. Overall accuracy on the tasks did not differ significantly by group, F (2,43) = 0.43, p = .66. Contrary to expectation, there was no Group x Task interaction, F (2,43) = 1.31, p = .28. There was also no significant effect of gender on accuracy, F (1,43) = 1.58, p = .22, and no Gender x Task interaction, F (1,43) = 0.84, p = .36.

Although the omnibus ANOVA revealed no significant Group x Task interaction, post- hoc analyses were used to determine whether there were more subtle group differences in verbal versus spatial task performance. To control for between-subject variability in overall level of performance due to general cognitive factors such as attention, and also for motivation, which can be assumed to influence the tasks equally, asymmetry scores were calculated as the accuracy difference between spatial and verbal tasks (Deptula et al., 1991). A positive score, indicating better performance on the spatial than the verbal task was achieved in 36 percent of high-anxiety depressed participants, 18 percent of low-anxiety depressed participants and 24 percent of controls. Although these proportions are in the expected direction based on the hypothesis of increased right hemisphere activation in anxiety states, Fisher's exact test revealed that they did not differ significantly (p = .37). Despite the lack of between-group differences, evaluation of

whether scores on verbal and spatial tasks differed *within* each group was made using two-tailed paired t-tests (Miller et al., 1995b). Better performance on the verbal than the spatial task was seen in the low-anxiety depressed, t (13) = 2.64, p = .02, and control, t (20) = 2.29, p = .03, groups, but the high-anxiety depressed group had essentially equal performance on the two tasks, t (13) = 0.28, p = .79 (see Table 4).

Resting alpha

Predicted group differences in regional resting alpha asymmetries were evaluated using repeated-measures ANOVA. The between-subjects factors were group (high-anxiety depressed, low-anxiety depressed, and control) and gender (male and female). The within-subjects factors were condition (eyes open and eyes closed), hemisphere (left and right), and region (frontal, central, and parietal). A significant Group x Hemisphere x Region interaction was expected. Power spectra from the resting eyes open and eyes closed conditions, averaged across all participants (Figure 3), show the classic alpha topography, with a larger peak within the alpha band (8-13 Hz) for the eyes closed condition than the eyes open condition. A component at 1 Hz representing low-frequency artifact is similar for the two conditions. ANOVA of the resting EEG revealed main effects of condition, F (1, 43) = 85.39, p < .001) and region, F (2, 86) = 357.85, p < .001) indicating greater log alpha power during the eyes closed than the eyes open condition, and an anterior to posterior power gradient (parietal > central > frontal; p-values < .001), consistent with a normal resting alpha topography. There was no hemispheric asymmetry, F (1, 43) = 0.70, p = .41. Power spectra, averaged separately for the high-anxiety depressed, low-anxiety depressed, and control groups, are displayed in Figure 4. Alpha power did not differ significantly by group, F (2,43) = 0.33, p = .72, or gender, F (1,43)

< .001, $p > .999$. Although there was greater alpha power in the low-anxiety depressed group than in the high-anxiety depressed or control groups in the eyes-closed condition, this difference was not significant when tested in a separate ANOVA of alpha power in the eyes closed condition alone, $F(2, 43) = .992$, $p = .38$. There were no significant interactions of group or gender with condition, hemisphere, or region, including the expected Group x Hemisphere x Region interaction.

Task-Related Alpha

Figure 5 shows the EEG spectra averages for the three groups in the verbal and spatial task conditions. In both tasks, peaks are present within the 8-13 Hz alpha range and largest over central and parietal electrodes. In the verbal task, this peak is comparable in size and topography to the alpha peak evident in the eyes open resting condition (Figure 4), and larger than the peak within the alpha range observed in the spatial task.

Note that the groups appear to differ in peak alpha frequency for the task-related EEG (see Figure 5), but not resting EEG (see Figure 4). The most obvious difference is in the verbal task between the high-anxiety depressed group, who show a peak at approximately 8 Hz, and the low-anxiety depressed group, who show a peak at approximately 10 Hz. The peak frequency of the control group is less pronounced but appears intermediate between those of the two depressed groups. As different peak frequencies between groups could impact the measurement of alpha power, particularly if they fall outside the normal 8-13 Hz band, the significance of this difference was tested using one-way ANOVA. Alpha peak frequency was identified visually in all participants excepting two controls who lacked a clearly defined alpha peak. The verbal task was used, as it appeared to more reliably elicit a distinct alpha peak, although the differential

peak frequency is apparent in both tasks. Peak frequency for the individual participants ranged from 8 Hz to 13 Hz, and group differences were found to be nonsignificant, F (2, 44) = 0.81, p = .45. Additionally, examination of group differences in the adjacent theta band revealed no significant group differences or interactions in task-related theta power (see also *Other Frequency Bands* subheading, page 49), further supporting the use of an 8-13 Hz alpha band for all three groups. The spectral and topographic specificity of alpha activity was verified via statistical comparisons of the EEG spectral bands (particularly alpha and theta) for resting and task conditions, which are included in the Appendix.

An ANOVA was conducted including alpha power from all four conditions (two resting and two task), and it did not reveal any significant main effects or interactions involving group. But, because large differences in overall alpha between the eyes closed and the verbal and spatial task conditions may have obscured smaller differences associated with group and task, task-related alpha was also analyzed separately from resting alpha.

To test the hypothesis that the groups would differ in terms of task-related regional alpha asymmetries, log power measures were evaluated using repeated-measures ANOVA. The between-subjects factors were group (high-anxiety depressed, low-anxiety depressed, and control) and gender (male and female). The within-subjects factors were task (verbal and spatial), hemisphere (left and right), and region (frontal, central, and parietal). A significant 4-way Group x Task x Hemisphere x Region interaction was expected. Figure 6 shows the topography of log alpha power for the verbal and spatial tasks. Results from the overall ANOVA are presented in Table 5. The main effect of task was not significant, but significant main effects were found for hemisphere, F (1, 43) =

9.89, $p = .003$, and region, F (2, 86) = 269.8, $p < .001$, and indicated greater alpha power (less activation) over the right than left hemisphere, overall, and the expected anterior to posterior alpha power gradient (parietal > central > frontal). However, the main effect of hemisphere was modified by a Task x Hemisphere interaction, F (1, 43) = 38.3, $p < .001$, consisting of greater alpha power (less activation) over the right than left hemisphere in the verbal task ($p = .003$) but no significant task asymmetry in alpha in the spatial task. Additionally, the main effect of region was modified by a Task x Region interaction consisting of greater alpha in the spatial than the verbal task in the frontal ($p < .001$) and central ($p = .04$) regions but no significant difference in the parietal region. Further, a Task x Hemisphere x Region interaction indicated that the Task x Hemisphere interaction was dependent on region. Follow-up comparisons revealed significant Task x Hemisphere effects in the frontal F (1, 43) = 21.65, $p < .001$, central F (1, 43) = 36.12, $p < .001$, and parietal F (1, 43) = 27.27, $p < .001$ regions. However, in the left hemisphere, there was greater alpha (less activation) in the spatial than the verbal task in the frontal ($p < .001$) and central ($p < .001$) regions, but not in the parietal region, and in the right hemisphere there was greater alpha (less activation) in the spatial than the verbal task only in the frontal region ($p < .001$), with no significant differences in the central and parietal regions.

Examination of group differences revealed no main effect of group ($F = .40$, $p = .67$). There was a significant Group x Hemisphere interaction, F (2, 43) = 3.45, $p = .04$, that resulted from greater right than left alpha power (less right hemisphere activation) in the low-anxiety depressed ($p = .02$) and control ($p < .001$) groups across tasks, but a non-significant hemispheric asymmetry in the high-anxiety depressed group ($p = .78$). Group

x Task and Group x Region interactions were not significant. Second-order interactions involving group were also not significant, and there was no main effect of gender, nor significant interactions involving gender (see Table 5).

The predicted 4-way Group x Task x Hemisphere x Region interaction was significant F (4,86) = 2.80, p = .04. Log alpha power means are displayed in Table 6. This interaction was the result of the groups having different patterns of regional asymmetry for each task. Significant hemispheric asymmetries were in the expected direction for the spatial and verbal tasks, but each group showed an asymmetry predominantly in only one or the other of the tasks. Specifically, follow-up *t*-tests of hemispheric effects with group, task and region held constant indicated that the high-anxiety depressed group had a pattern of greater alpha (less activation) over left than right central (p = .003) and parietal (p = .03) regions in the spatial task, but had no significant asymmetries in the verbal task. In contrast, the low-anxiety depressed group showed a pattern of greater alpha (less activation) over the right than left hemisphere in frontal (p = .01) and central (p = .03) regions in the verbal task, while displaying no significant asymmetry in the spatial task. The control group had a pattern similar to that seen in the low-anxiety depressed group, with significantly greater alpha (less activation) over right than left hemisphere in all regions in the verbal task (frontal p = .002, central $p < .001$, parietal $p < .001$), and no significant asymmetry in the spatial task. Task-related asymmetries (right – left log alpha power) for the frontal, central, and parietal regions are displayed in Figures 7 - 9.

Post-hoc analyses. Evaluation of these task-related asymmetries within each region separately revealed only non-significant Group x Task x Hemisphere interactions.

Nonetheless, the effect was stronger in the central region, F (2,46) = 2.21, p = .12, than in the frontal, F (2, 46) = 0.17, p = .84, or parietal, F (2,46) = 0.25, p = .78, regions. Figures 7 - 9 also suggest that overall group differences in regional hemispheric asymmetries are most prominent in the central region (Figure 8), in which low-anxiety depressed patients and controls had a tendency to favor the left hemisphere (greater right alpha), whereas high-anxiety depressed patients had a tendency to favor the right hemisphere (greater left alpha). In order to better localize regional differences, a combined asymmetry score was computed for each region, by averaging alpha asymmetries (right – left log alpha power) across the two tasks. The results (means and standard deviations presented in Table 7) confirmed that group effects were strongest in the central region, where the groups showed significant differences in combined asymmetry, F (2,46) = 3.71, p = .03. The control group differed significantly from the high-anxiety depressed group (p = .04), with relatively stronger left activation across tasks, but the low-anxiety depressed group did not differ from either the high-anxiety depressed (p = .14) or control (p = 1.0) groups. There were no group differences in combined asymmetry in either the frontal, F (2,46) = 1.32, p = .28, or parietal regions F (2,46) = 0.95, p = .39.

As BDI and STAI-Y scores were significantly correlated in the combined sample of depressed patients (Pearson r = .57, p = .002), correlations between each score and the combined asymmetry score were examined to determine whether depression or trait anxiety had a stronger relationship to hemispheric asymmetry. While neither reached significance, the association of combined central asymmetry with trait anxiety approached significance (r = -.309, p = .06) in the expected direction, i.e., greater right-sided activation (less alpha) associated with higher trait anxiety, whereas the association

of combined central asymmetry with depression was not significant (r = -.10, p = .31). Nonsignificant correlations with BDI and STAI-Y scores were obtained for the combined frontal asymmetry and combined parietal asymmetry scores, and for the individual task asymmetry scores in each of the three regions. A multiple linear regression was used to test the effects of anxiety and depression on combined central asymmetry. When anxiety and depression were entered into the model, the result was not significant, F (2, 25) = 1.45, p = .25. Removing depression improved the predictive ability, yielding a result that approached significance, F (1, 26) = 2.73, p = .11. However, removing anxiety from the original model did not improve the predictive ability, F (2, 25) = .244, p = .63, suggesting that trait anxiety is a better predictor of asymmetry than either depression alone or the combination of depression and anxiety.

Because it is possible that results may be affected by activity in the alpha band as a result of eye movements, alpha power from VEOG and HEOG channels was submitted to a separate repeated-measures ANOVA. No group main effects or task interactions were significant: VEOG group F (2,43) = .46, p = .63, Group x Task F (2,43 = 0.31, p = .74; HEOG group F (2,43) = 0.90, p = .41, Group x Task F (2,43) = 0.16, p = .98. Thus, it can be surmised that the observed effects are not the result of differences in ocular activity within the alpha band.

Other Frequency Bands

The four-way interaction observed in the broad alpha band did not reach significance in either of the narrower alpha bands: alpha1 (8-10 Hz), F (4,86) = 2.51, p = .06 or alpha2 (10-13 Hz), F (4,86) = 1.96, p = .11.

The specificity of the task differences among groups for the alpha frequency was investigated via additional analyses of power in delta, theta and beta1 bands. ANOVA results are presented in Tables 8 - 10. Task x Hemisphere interactions were significant in the delta and beta1 bands. In the delta band, follow-up tests revealed simple effects that only approached significance, consisting of greater delta power over the right than left hemisphere in the verbal task ($p = .06$) and greater delta power over the left than right hemisphere in the spatial task ($p = .06$). In the beta1 band, simple effects were similar to those observed in the alpha band, with greater beta1 power over the right than left hemisphere in the verbal task ($p = .003$) but no significant hemispheric asymmetry in the spatial task.

There were no significant main effects of group in the delta, theta or beta1 bands. In the beta1 band, there was a significant Group x Hemisphere x Region interaction. Follow-up comparisons revealed a significant Group x Hemisphere effect in the parietal region alone, $F(2, 43) = 3.78$, $p = .03$, that was driven by an asymmetry in the high anxiety depressed group, which had significantly greater parietal beta1 power over the left than the right hemisphere ($p = .02$). There were no interactions involving group and task in any of the other frequency bands. (A Group x Task interaction in the delta band was marginally significant, $p = .053$.)

Gender main effects were evident in all bands. In the delta band (1-4 Hz) the main effect of gender (see Table 8), $F(1,43) = 5.25$, $p = .03$, indicated that women had greater delta power than men. Women also had greater power in the theta (see Table 9) and beta1 (see Table 10) bands.

Linked Mastoids Reference

While in prior studies the use of a nose reference scheme has revealed both anterior and posterior resting alpha asymmetries associated with anxiety and depression (Bruder et al., 1997), and is unlikely to distort asymmetries due to its midline location, its suitability for detecting task-related asymmetries has not been proven. To test the stability of the present results using a different reference, the EEG data were mathematically re-referenced to the averaged mastoids, and new averages were created. When submitted to the same repeated-measures ANOVA, the task-related alpha asymmetry was preserved, as indicated by a significant Task x Hemisphere interaction, F (1, 43) = 13.95, p = .001. This interaction resulted from an asymmetry of greater left than right activation (less alpha) that was significantly larger in the verbal ($p < .001$) than spatial ($p = .046$) task. Additionally, there was a main effect of task, F (1, 43) = 9.88, p = .003, that was not found for the nose-referenced data, reflecting greater alpha power (less activation) in the verbal than the spatial task. No significant group or gender main effects or interactions emerged. Most notably, the Group x Task x Hemisphere x Region interaction of interest was not significant, F (4, 86) = 1.43, p = .24. As with the nose-referenced data, there were no task-related group differences in power or asymmetry for the delta, theta, or beta1 bands. Gender differences continued to be significant in delta (F (1, 43) = 13.42, $p < .001$; theta, F (1, 43) = 6.43, p = .02; and beta1, F (1, 43) = 5.29, p = .03 bands.

Discussion

Electrophysiological Data

The results were in accordance with predictions made on the basis of the two-dimensional model of depression and anxiety (Heller et al., 1995; Heller & Nitschke, 1998). The task-related hemispheric asymmetries were in the expected direction and were modified by group. Group differences in task-related regional hemispheric alpha asymmetries were found using a nose reference, with different asymmetry patterns for depressed patients with high and low trait anxiety. Significant task-related hemispheric asymmetries were all in the expected direction, but the groups differed in terms of which task produced an asymmetry. In the high-anxiety depressed group, the Dot Localization (spatial) task was accompanied by greater alpha suppression (activation) over right than left central and parietal regions, but no hemispheric asymmetries were present during the Word Finding (verbal) task. In contrast, the low-anxiety depressed group had no significant regional asymmetries in the spatial task. Instead, they showed greater activation (less alpha) over left than right frontal and central regions during the verbal task. These results were not found for the linked-mastoids reference, suggesting that the nose reference scheme is more sensitive in detecting task-related asymmetries. This is likely the result of alpha activity at the mastoids that attenuated alpha recorded at several electrodes of interest, due to their greater spatial proximity.

It has been previously demonstrated that these tasks asymmetrically activate brain regions in non-depressed adults, with greater right-sided activation (less right than left alpha power) during the spatial task and greater left-sided activation (less left than right alpha power) during the verbal task in both the central and parietal regions, using both

averaged-ears and vertex reference montages (Davidson et al., 1990; Henriques & Davidson, 1997), with no task-related alpha asymmetry present in a depressed sample (Henriques & Davidson, 1997). Results for the healthy participants in the present study suggested a pattern consisting of the expected significant asymmetry only in the verbal task, with a nonsignificant opposite asymmetry in the spatial task. Upon closer inspection, this lack of asymmetry in the spatial task in healthy adults is not inconsistent with previous findings in which hemispheric differences appeared to be primarily the result of asymmetries in the verbal task (Henriques & Davidson, 1997). Similarly, in the dichotic listening literature, left hemisphere advantages for verbal tasks are typically more robust than right-hemisphere advantages for nonverbal tasks (Bruder et al., 1999; Bruder et al., 2004b). It is also a possibility that the right-handed button press and verbal responding increased the left-hemisphere demand of both tasks, reducing the right greater than left asymmetry in the spatial task.

The lack of significant task-related asymmetry in a prior depressed sample (Henriques & Davidson, 1997) is likely to be related to lack of distinction between depressed patients with high and low trait anxiety levels. From the current group differences, it may be inferred that depressed individuals with low trait anxiety have a tendency toward greater left-sided activity, which in effect maintained the expected task-related asymmetry in the verbal task but reduced it in the spatial task, whereas depressed individuals with high trait anxiety have an opposite tendency, which heightened the right hemisphere advantage on the spatial task and decreased the left hemisphere advantage on the verbal task (See Figure 6). These results are in line with previous evidence for greater left than right hemisphere activity in both currently and previously depressed individuals

(Bruder et al., 1997; Henriques & Davidson, 1990), as well as a reduction in depression of the normal perceptual asymmetry associated with right posterior superiority for face processing (Jaeger et al., 1987) and complex tones (Bruder et al., 1999). The opposite pattern observed in the high-anxiety depressed patients in the present study is consistent with evidence for an asymmetry consisting of greater right that left posterior brain activity measured by dichotic listening studies in patients with comorbid major depressive and anxiety disorders (Bruder et al., 1999; Bruder et al., 2004; Pine et al., 2000), opposite patterns of asymmetry in reaction time to lateralized stimuli in depressed versus anxious patients (Liotti et al., 1991), chimeric face perception studies in individuals grouped according to levels of trait anxiety and depression (Heller, et al., 1995; Keller et al., 2000; Voelz et al., 2001), and resting EEG in patients with comorbid major depressive disorder and anxiety disorders (Bruder et al., 1997; Kentgen et al., 2000). While few studies have examined electrophysiological asymmetries associated with cognitive functions, results from this study are also consistent with an ERP study that suggesting opposite effects of anxiety and depression in terms of functional asymmetry (Bruder et al., 2002a).

As in previous work (Henriques & Davidson, 1997; cf. Koles et al.2001), the lack of task-specific group differences in other spectral bands (i.e., delta, theta and beta1) helps further specify the effects of the tasks to the alpha band. In addition to supporting a distinction between depressed patients with high and low levels of anxiety, these results provide support for past findings of regional specificity of the tasks, localizing the verbal task to frontal and central regions (via strongest asymmetry effects in the low-anxiety

depressed group) and the spatial task to central and parietal regions (via strongest asymmetry effects in the high-anxiety depressed group) (Koles et al., 2001).

Performance Data

The prediction of differential task performance between the groups was only tentatively supported. As can be seen in Table 4, low-anxiety depressed patients and controls performed better on the verbal than spatial tasks, whereas high-anxiety depressed patients performed approximately equally on the two tasks; however, the interaction of group and task did not reach statistical significance. These results are in agreement with the group differences in alpha power asymmetries. Given our three-group design and smaller sample sizes, there may have been insufficient power to detect significant group differences. It is also possible that differences in results are related to variability in the specific task stimuli that were administered. To ensure an equal amount of artifact-free EEG data from each task, 30-item versions of the verbal and spatial tasks were developed, requiring selection from among the original 41 verbal items, and creation of new spatial items in addition to the original 20. Preliminary matching of the 30-item tasks on a smaller sample of healthy volunteers may have been insufficient to ensure equal validity across groups.

Gender Differences

Gender differences in task performance were not found, in contrast to expectation. However, the sample sizes in this study restricted its ability to detect these differences, preventing evaluation of interactions between group and gender. An unexpected EEG gender difference was found that was unrelated to group or task. Women had greater power than men in delta, theta and beta1 bands using both nose and linked-mastoids

references. While there is relatively sparse evidence regarding gender differences in power within specific frequency bands, these results are consistent with a previous study assessing gender differences in resting EEG across the lifespan (Duffy et al., 1993). That study found greater absolute power in theta and beta bands, along with reduced alpha power, in women relative to men. Women were also found to have greater beta activity than men across the lifespan (Matsuura et al., 1985). The cause of these gender differences is unclear, and it is possible that they are due to some factor unrelated to brain activity [e.g., head size, which, when controlled for, eliminated gender differences in visual evoked potential latency (Gregori, Pro, Bombelli, La Riccia, & Accornero, 2006)].

Resting EEG

Although resting, eyes closed alpha power was greater in the low-anxiety depressed group than the control and high-anxiety depressed group, consistent with prior studies (Pollock & Schneider, 1990; Shagass, Roemer, & Josiassen, 1988), this difference was not statistically significant. The present study also failed to uncover group differences in alpha asymmetries in resting EEG, in contrast to a previous study of depressed patients with and without comorbid anxiety disorders (Bruder et al., 1997). Of note, another recent study also failed to find a relationship between task-related and resting alpha topography in healthy adults (Michels, Moazami-Goudarzi, Jeanmonod, & Sarnthein, 2008). It is possible that the null finding in the present study relates to the inclusion of depressed patients with sub-clinical levels of anxiety (i.e., without a comorbid anxiety disorder). Patients may not have been sufficiently anxious to yield the predicted asymmetries at rest. This explanation is supported by other studies grouping individuals on the basis of self-report anxiety that have also failed to find significant

posterior asymmetries in resting alpha (Mathersul, Williams, Hopkinson, & Kemp, 2008; Nitschke et al., 1999). In contrast, engaging patients in tasks that recruit particular regions of the brain likely restricted both within- and between-subject variance in brain function, allowing asymmetries to be detected in even this sub-clinical sample. It logically follows that the most sensitive tasks would be those that recruit the brain regions of interest. In the present study, task-related hemispheric asymmetries were most evident in the central region, and results suggest that there may have been relatively greater anterior involvement in the verbal task, and greater posterior involvement in the spatial task. It is possible that verbal and spatial tasks with more similar regional specificity (ideally, involving the parietal regions) within the respective left and right hemispheres would have revealed stronger between-group differences in asymmetry.

The failure to find differences in resting EEG argues against a simple additive effect of baseline and task-related asymmetry as responsible for the observed opposite asymmetries in depressed patients with high and low levels of trait anxiety, and in favor of an interactive process whereby functional asymmetry is modified under certain cognitive processing demands. Results from the present study are consistent with a previous report of college students with high levels of anxiety showing a rightward hemispheric asymmetry only when listening to stories designed to elicit anxious arousal (Heller et al., 1997). It is possible that in participants with only sub-clinical levels of anxiety, right posterior regions are overactive in response to stimuli that may be only mildly anxiety provoking in healthy individuals (e.g., a moderately challenging visual-spatial task). Under non-stimulating conditions, however, the regional activity would still return to baseline and appear relatively normal. In contrast, patients whose level of

anxiety is clinically significant might have more sustained elevations in the activity of right posterior circuits which are slower to return to baseline following activation or do not normalize under non-stimulating conditions.

Directions for Future Research

Future studies would benefit from the use of more sensitive measures to discriminate between depression and anxiety. Scales used to measure depression and anxiety have been found to be correlated (Tanaka-Matsumi & Kameoka, 1986). It is likely that the overlap of symptoms measured by the BDI and STAI-Y scales, which was clearly reflected in higher levels of depression, as well as anxiety, in the high-anxiety than the low-anxiety depressed group, resulted in non-optimal classification of depressed patients as high- or low-anxiety. While results from the present study showed a correlation between depression and anxiety ratings, trait anxiety was found to be a better predictor of alpha asymmetry than was the combination of trait anxiety and depression. Nonetheless, it remains possible that greater depression severity also contributed to greater relative right-sided activation in the high-anxiety depressed group, but this appears unlikely in light of evidence that depression severity is unrelated to posterior asymmetry (Metzger et al., 2004; Vuga et al., 2006). Partialing out shared features of depression and anxiety (i.e., the tripartite model's factor of negative affectivity or general distress; Clark & Watson, 1991) would allow more effective evaluation of their separate effects on cognitive function. Examination of the effectiveness of these tasks in differentiating patients with anxiety disorders without depression from those having either depression alone or comorbidity of anxiety and depressive disorders would further clarify relationships between psychiatric symptoms and cognitive functions, and could

aid clinicians in diagnosis. Future research might also explore whether task-related hemispheric asymmetries are associated with treatment response in depressed patients.

Summary

This study tested predictions based on the two-dimensional model of depression and anxiety using verbal and spatial tasks that are equal in motor demands, response properties, and difficulty. These tasks have been shown to differentially activate the right and left hemispheres and to discriminate depressed patients from healthy controls. The presence of electrophysiological and perceptual findings indicative of opposite posterior asymmetries in subgroups of depressed individuals with low and high anxiety has been fairly well supported. The present investigation extends previous work by revealing these same patterns during the execution of verbal and spatial cognitive tasks. While in their current form, the tasks do not reliably discriminate between individual patients with high and low anxiety on the basis of performance, the ability of task-related alpha asymmetry to distinguish between groups in the absence of asymmetry at rest indicates the sensitivity of EEG spectral analysis in detecting subtle neurocognitive abnormalities.

Appendix

In order to confirm the spectral and topographic specificity of activity within the alpha band for all four conditions, measurements of resting and task alpha power were compared with each other and with power from other frequency bands. Alpha was distinguished from other frequency bands via differential condition and region effects. A main effect of condition, F (3, 129) = 42.50, $p < .001$), indicated that alpha was greater during the eyes closed than the eyes open and task conditions (p-values < .001), but that the other three conditions did not differ in terms of overall alpha power. In contrast, in the delta, theta and beta1 bands, power was greatest in the spatial task, with least power in the eyes open condition, and intermediate power in the verbal task and eyes closed conditions: delta, F (3, 41) = 27.43, $p < .001$; theta, F (3, 41) = 56.51, $p < .001$; and beta1, F (3,41) = 30.79, $p < .001$.

Because it was possible that greater activity in the neighboring theta band might have influenced measurements of alpha power, it was especially important to determine whether these two bands were distinguishable on the basis of condition and region effects. A significant Band x Condition x Region interaction, F (6, 38) = 46.61 $p < .001$, indicated a more frontally localized distribution for the theta band in general, with different regional effects in each condition. In the eyes closed resting condition, there was greater theta than alpha power in the frontal region, F (1, 43) = 4.70, $p = .04$, no significant power difference in the central region, F (1, 43) = 1.37, $p = .25$, and greater alpha than theta power in the parietal region, F (1, 43) = 21.25, $p < .001$. In the eyes open resting condition, there was greater theta than alpha power in the frontal region, F (1, 43) = 35.30, $p < .001$, and no significant differences in the central, F (1, 43) = 2.73, $p = .12$,

or parietal, F (1, 43) = 0.08, p = .79 regions. In the spatial task, there was greater theta than alpha power in all three regions: frontal, F (1, 43) = 103.1, p < .001; central, F (1, 43) = 37.93, p < .001; and parietal, F (1, 43) = 48.71, p < .001. In the verbal task, there was greater theta than alpha power in the frontal, F (1, 43) = 64.21, p < .001, and central, F (1, 43) = 7.38, p = .01, regions, but no significant difference in the parietal region, F (1, 43) = 2.18, p = .15. As expected, these results indicated that theta was more frontally localized and alpha more parietally localized. In addition to revealing greater total theta in the spatial than the verbal and resting tasks and greater theta in the verbal than eyes open resting task, they also show patterns of more widely distributed theta relative to alpha in task than resting conditions, likely related to increased attention. There was no significant main effect of group F (2, 43) = 0.85, p = .43, nor were there significant interactions involving group. These results support the presence of separate spectral components in the alpha and theta bands.

Table 1. Participant Characteristics

	High-anxiety depressed	**Low-anxiety depressed**	**Control**
Gender			
M/F	8/6	4/10	9/12
Age (yrs.)			
Mean	39.9	31.4	34.0
SD	11.7	12.8	11.8
Education (yrs.)			
Mean	15.1	15.9	15.8
SD	2.8	1.8	3.1
Handedness (Laterality Quotient)			
Mean	79.6	79.1	82.5
SD	18.7	29.0	26.3
BDI[a]			
Mean	31.1	22.9	1.8
SD	9.6	5.9	2.3
STAI-Y Trait Anxiety[b]			
Mean	86.7	71.7	44.1
SD	4.6	7.4	7.8

[a] Significant difference among groups in BDI score, F (2,46) = 106.25, $p < .001$; High-anxiety depressed > Low-anxiety depressed > Control.

[b] Significant difference among groups in STAI-Y Trait Anxiety, F (2,46) = 170.13, $p < .001$; High-anxiety depressed > Low-anxiety depressed > Control.

Table 2. Mean BDI and STAI-Y scores for male and female depressed patients

	BDI Mean (*SD*)	STAI-Y Mean (*SD*)
Male	26.2 (9.4)	80.4 (7.9)
Female	27.6 (8.7)	78.4 (11.1)

Table 3. Mean number of sweeps contributing to each task average for the three groups

	High-Anxiety Depressed Mean (*SD*)	Low-Anxiety Depressed Mean (*SD*)	Control Mean (*SD*)
Word Finding	372 (246)	318 (171)	301 (135)
Dot Localization	485 (241)	547 (321)	465 (241)

Table 4. Percent accuracy on verbal Word Finding and spatial Dot Localization tasks

	Word Finding Mean (*SD*)			Dot Localization Mean (*SD*)		
	Total	Male	Female	Total	Male	Female
High-anxiety depressed	75.0 (17.3)	77.1 (15.8)	72.2 (20.4)	72.9 (23.2)	72.9 (22.5)	72.8 (26.4)
Low-anxiety depressed	83.6 (9.1)	89.2 (5.7)	81.3 (9.5)	71.2 (16.2)	65.8 (22.2)	73.3 (14.0)
Control	81.1 (13.4)	87.8 (8.5)	76.1 (14.6)	72.9 (20.4)	80.7 (20.1)	66.9 (19.4)

Table 5. Results of ANOVA comparing log alpha power with factors of task, hemisphere, region, group and gender

	df	*F*	*p*
Task	1, 43	3.07	.09
Hemisphere	1, 43	9.89	< .01*
Region	2, 86	269.81	< .001*
Task x Hemisphere	1, 43	38.29	< .001*
Task x Region	2, 86	43.24	< .001*
Hemisphere x Region	2, 86	.67	.51
Task x Hemisphere x Region	2, 86	6.49	< .01*
Group	2, 43	.40	.67
Group x Task	2, 43	.76	.48
Group x Hemisphere	2, 43	3.45	.04*
Group x Region	4, 86	.94	.41
Group x Task x Hemisphere	2, 43	1.04	.36
Group x Task x Region	4, 86	.61	.59
Group x Hemisphere x Region	4, 86	.77	.54
Group x Task x Hemisphere x Region	4, 86	2.80	.04*
Gender	1, 43	1.14	.29
Gender x Task	1, 43	< .001	> .99
Gender x Hemisphere	1, 43	.65	.43
Gender x Region	2, 86	.47	.54
Gender x Task x Hemisphere	1, 43	.01	.93
Gender x Task x Region	2, 86	.28	.66
Gender x Hemisphere x Region	2, 86	.20	.81
Gender x Task x Hemisphere x Region	2, 86	.26	.74

* Significant at the .05 level

Table 6. Log alpha power for the three groups by task, hemisphere and region

	High-Anxiety Depressed Mean (*SD*)			Low-Anxiety Depressed Mean (*SD*)			Control Mean (*SD*)		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
Word Finding									
Left									
Frontal	-.207 (.354)	-.233 (.361)	-.171 (.374)	-.089 (.538)	-.270 (.141)	-.017 (.626)	-.266 (.476)	-.312 (.470)	-.232 (.498)
Central	.343 (.455)	.270 (.432)	.439 (.508)	.415 (.666)	.157 (.055)	.518 (.773)	.273 (.560)	.297 (.638)	.254 (.523)
Parietal	.734 (.516)	.629 (.485)	.873 (.569)	.872 (.888)	.541 (.185)	1.004 (1.029)	.683 (.607)	.736 (.719)	.642 (.539)
Right									
Frontal	-.178 (.418)	-.230 (.409)	-.108 (.458)	-.011 (.546)	-.092 (.178)	-.011 (.546)	-.168 (.493)	-.168 (.508)	-.167 (.504)
Central	.393 (.588)	.247 (.518)	.587 (.665)	.549 (.771)	.333 (.140)	.636 (.907)	.501 (.580)	.624 (.685)	.409 (.500)
Parietal	.816 (.655)	.629 (.572)	1.065 (.726)	.981 (.966)	.677 (.261)	1.103 (1.126)	.840 (.665)	.998 (.840)	.722 (.505)
Dot Localization									
Left									
Frontal	.107 (.375)	-.033 (.323)	.292 (.383)	.254 (.367)	.329 (.309)	.224 (.399)	-.075 (.475)	-.205 (.407)	.023 (.515)
Central	.545 (.426)	.390 (.375)	.752 (.429)	.628 (.418)	.573 (.258)	.650 (.478)	.461 (.491)	.429 (.622)	.484 (.395)
Parietal	.736 (.363)	.595 (.315)	.922 (.361)	.831 (.444)	.732 (.192)	.870 (.516)	.651 (.513)	.601 (.679)	.688 (.373)
Right									
Frontal	.054 (.395)	-.121 (253)	.287 (.448)	.222 (.425)	.390 (.308)	.155 (.460)	-.068 (.441)	-.173 (.422)	.010 (.456)
Central	.420 (.440)	.241 (.376)	.658 (.432)	.657 (.503)	.687 (.385)	.645 (.562)	.437 (.456)	.399 (.572)	.466 (.372)
Parietal	.658 (.431)	.471 (.345)	.907 (.430)	.813 (.463)	.824 (.230)	.808 (.541)	.633 (.493)	.594 (.671)	.663 (.334)

Table 7. Combined Asymmetry (right – left log alpha power) across tasks

	Frontal Mean (SD)	Central Mean (SD)	Parietal Mean (SD)
High-anxiety depressed	-.012 (.100)	-.038 (.141)	.002 (.153)
Low-anxiety depressed	.023 (.161)	.082 (.153)	.046 (.122)
Control	.052 (.085)	.101 (.165)	.070 (.149)

Table 8. Results of ANOVA comparing log delta power with factors of task, hemisphere, region, group and gender

	df	*F*	*p*
Task	1, 43	28.84	< .001*
Hemisphere	1, 43	< .001	.99
Region	2, 86	179.78	< .001*
Task x Hemisphere	1, 43	17.99	< .001*
Task x Region	2, 86	8.37	.003*
Hemisphere x Region	2, 86	2.33	.11
Task x Hemisphere x Region	2, 86	1.53	.23
Group	2, 43	.825	.45
Group x Task	2, 43	3.15	.05
Group x Hemisphere	2, 43	.20	.82
Group x Region	4, 86	2.45	.09
Group x Task x Hemisphere	2, 43	.27	.77
Group x Task x Region	4, 86	2.00	.14
Group x Hemisphere x Region	4, 86	1.44	.23
Group x Task x Hemisphere x Region	4, 86	.69	.56
Gender	1, 43	5.25	.03*
Gender x Task	1, 43	1.37	.25
Gender x Hemisphere	1, 43	< .001	> .99
Gender x Region	2, 86	.02	.92
Gender x Task x Hemisphere	1, 43	.17	.68
Gender x Task x Region	2, 86	3.19	.07
Gender x Hemisphere x Region	2, 86	.57	.55
Gender x Task x Hemisphere x Region	2, 86	.60	.46

* Significant at the .05 level

Table 9. Results of ANOVA comparing log theta power with factors of task, hemisphere, region, group and gender

	df	*F*	*p*
Task	1, 43	47.79	< .001*
Hemisphere	1, 43	1.17	.29
Region	2, 86	260.89	< .001*
Task x Hemisphere	1, 43	.06	.81
Task x Region	2, 86	1.03	.33
Hemisphere x Region	2, 86	4.75	.02*
Task x Hemisphere x Region	2, 86	.05	.90
Group	2, 43	.17	.85
Group x Task	2, 43	.90	.41
Group x Hemisphere	2, 43	1.11	.34
Group x Region	4, 86	2.55	.07
Group x Task x Hemisphere	2, 43	.69	.51
Group x Task x Region	4, 86	.31	.79
Group x Hemisphere x Region	4, 86	1.46	.23
Group x Task x Hemisphere x Region	4, 86	.95	.42
Gender	1, 43	5.40	.03*
Gender x Task	1, 43	1.03	.32
Gender x Hemisphere	1, 43	.84	.37
Gender x Region	2, 86	.01	.97
Gender x Task x Hemisphere	1, 43	2.91	.10
Gender x Task x Region	2, 86	2.14	.15
Gender x Hemisphere x Region	2, 86	.66	.50
Gender x Task x Hemisphere x Region	2, 86	.16	.76

* Significant at the .05 level

Table 10. Results of ANOVA comparing log beta1 power with factors of task, hemisphere, region, group and gender

	df	*F*	*p*
Task	1, 43	14.54	< .001*
Hemisphere	1, 43	1.91	.17
Region	2, 86	61.45	< .001*
Task x Hemisphere	1, 43	20.66	< .001*
Task x Region	2, 86	19.70	< .001*
Hemisphere x Region	2, 86	1.33	.27
Task x Hemisphere x Region	2, 86	1.57	.21
Group	2, 43	.70	.51
Group x Task	2, 43	1.55	.22
Group x Hemisphere	2, 43	1.03	.37
Group x Region	4, 86	.82	.47
Group x Task x Hemisphere	2, 43	.08	.92
Group x Task x Region	4, 86	.39	.74
Group x Hemisphere x Region	4, 86	3.35	.02*
Group x Task x Hemisphere x Region	4, 86	.52	.72
Gender	1, 43	4.28	.05*
Gender x Task	1, 43	1.88	.18
Gender x Hemisphere	1, 43	.93	.34
Gender x Region	2, 86	.94	.36
Gender x Task x Hemisphere	1, 43	.28	.60
Gender x Task x Region	2, 86	.50	.54
Gender x Hemisphere x Region	2, 86	.92	.39
Gender x Task x Hemisphere x Region	2, 86	2.38	.10

* Significant at the .05 level

Figure 1. Sample Word Finding task stimulus

A person who works for a skilled worker to learn a trade

Figure 2. Sample Dot Localization task stimulus

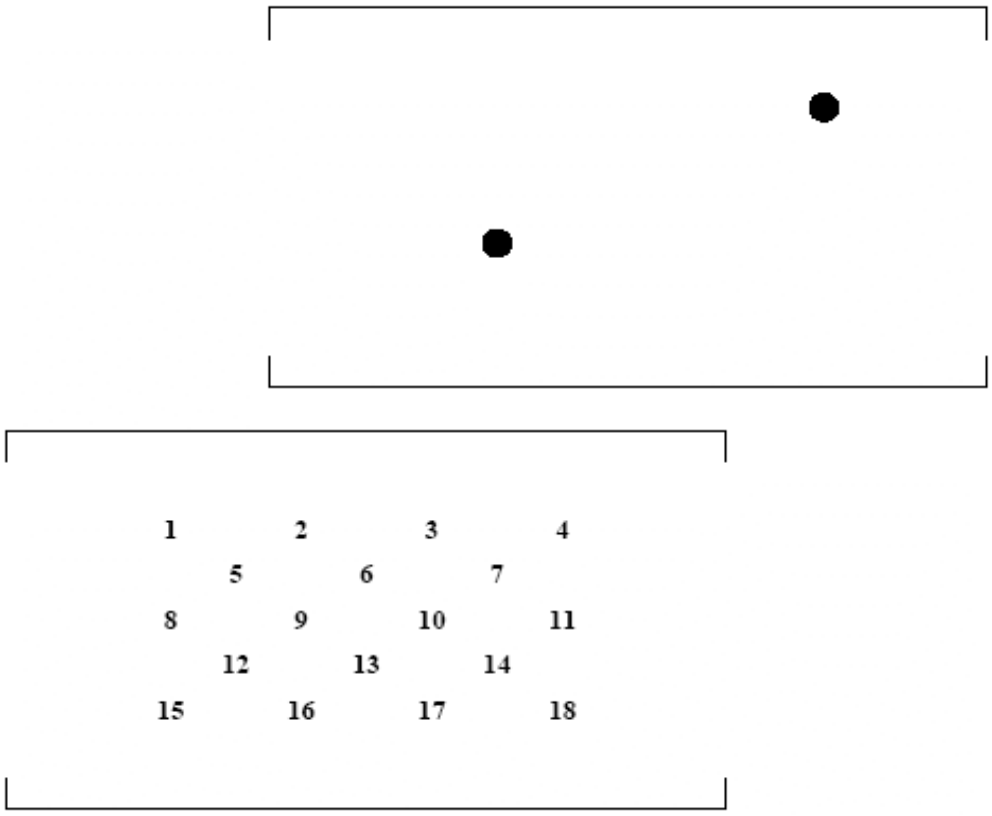


Figure 3. Resting EEG spectral power across all participants, recorded with eyes closed and eyes open

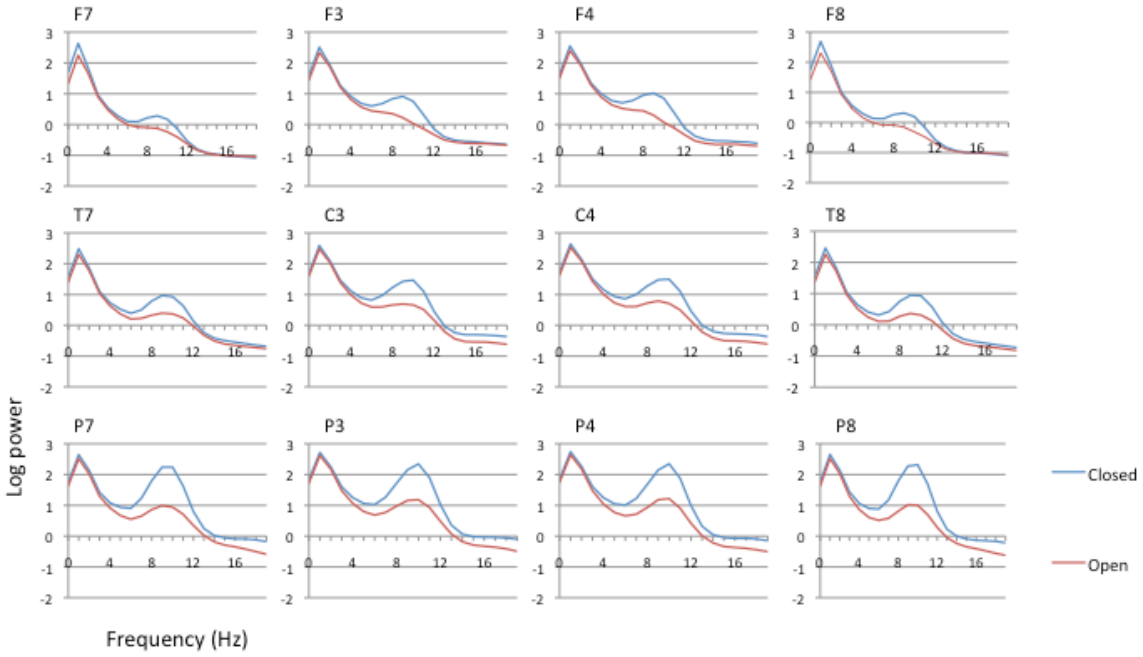


Figure 4. Resting EEG spectral power for the High-Anxiety Depressed (HA), Low-Anxiety Depressed (LA), and Control (Con) groups recorded with eyes closed (A) and eyes open (B)

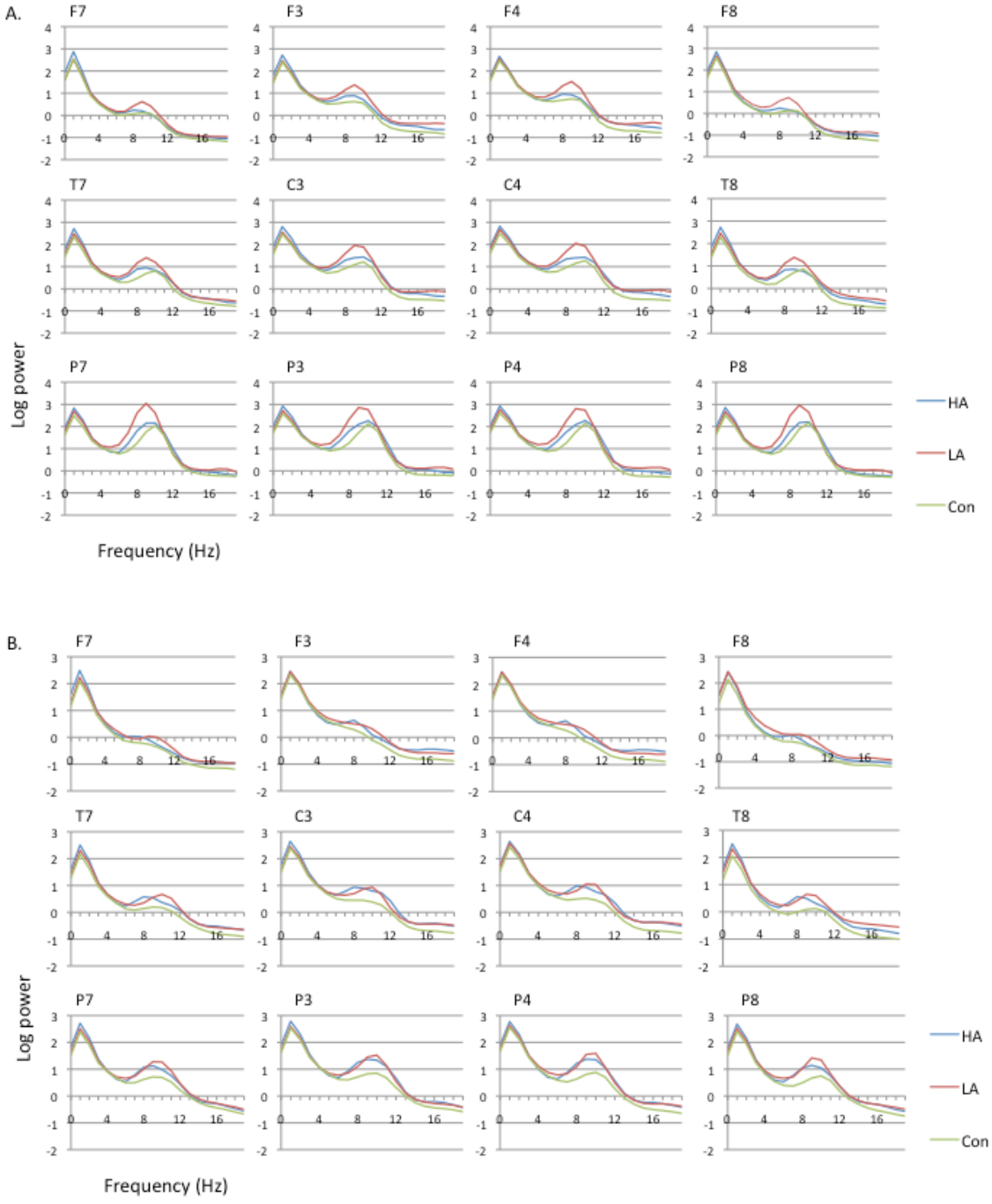


Figure 5. Spectral power for the High-Anxiety Depressed (HA), Low-Anxiety Depressed (LA), and Control (Con) groups recorded during Word Finding (A) and Dot Localization (B) tasks

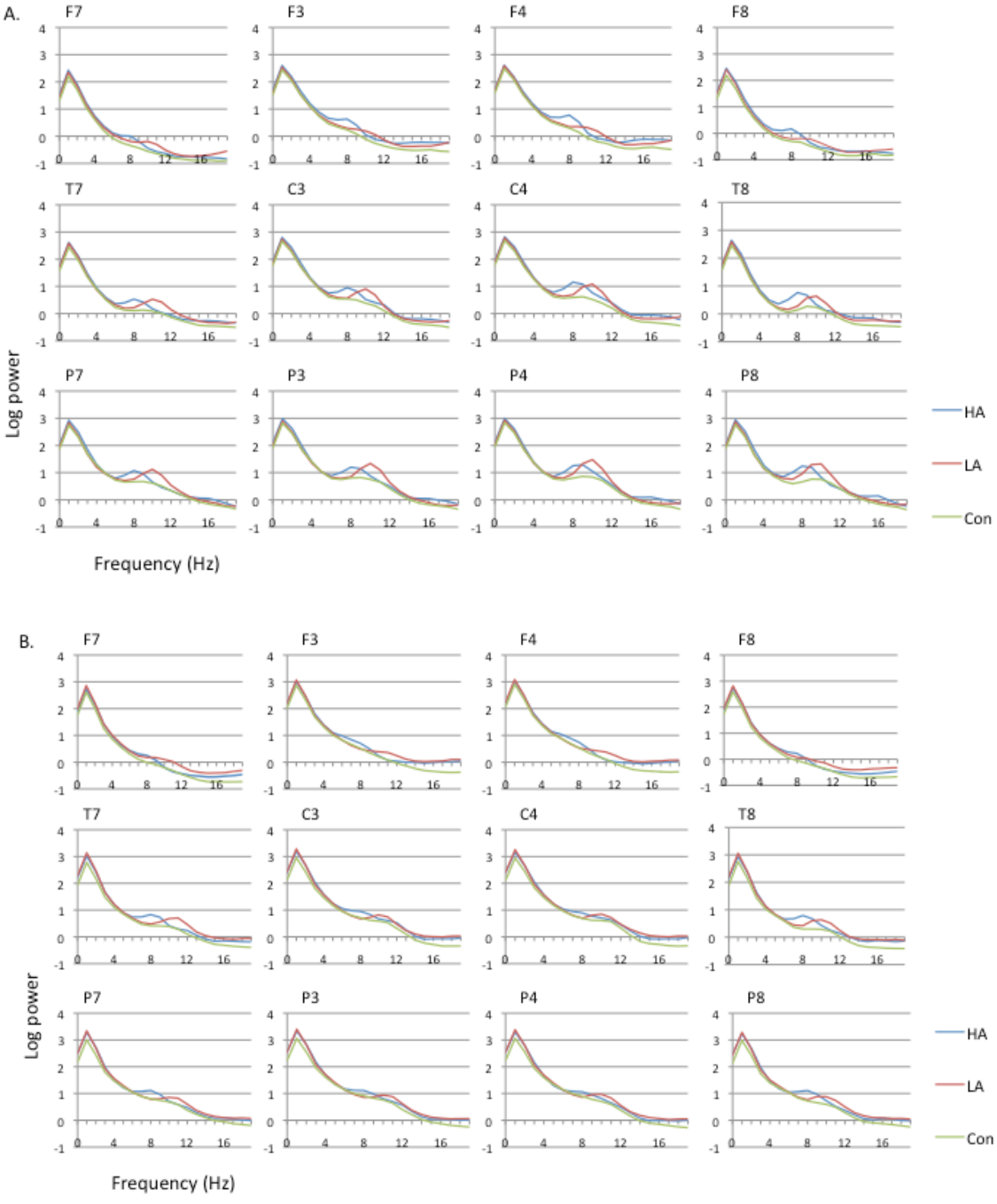


Figure 6. Alpha topography for the high-anxiety depressed, low-anxiety depressed, and control groups on the Dot Localization and Word Finding tasks. illustrating the significant Group x Task x Hemisphere x Region interaction

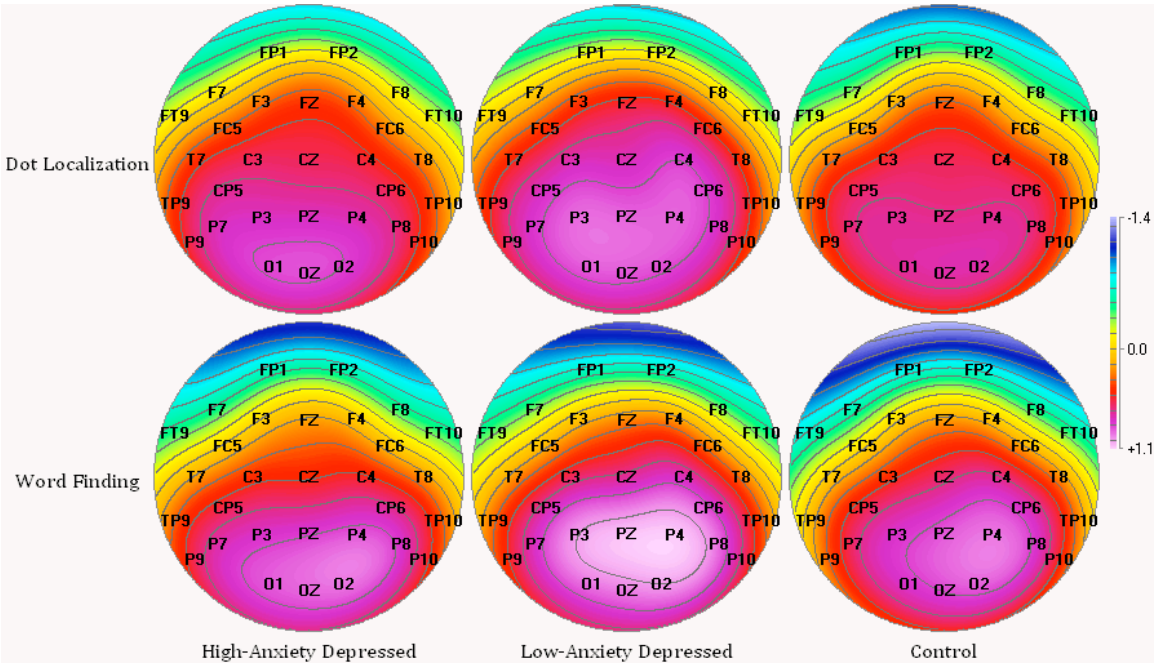


Figure 7. Task-related asymmetries in the frontal region

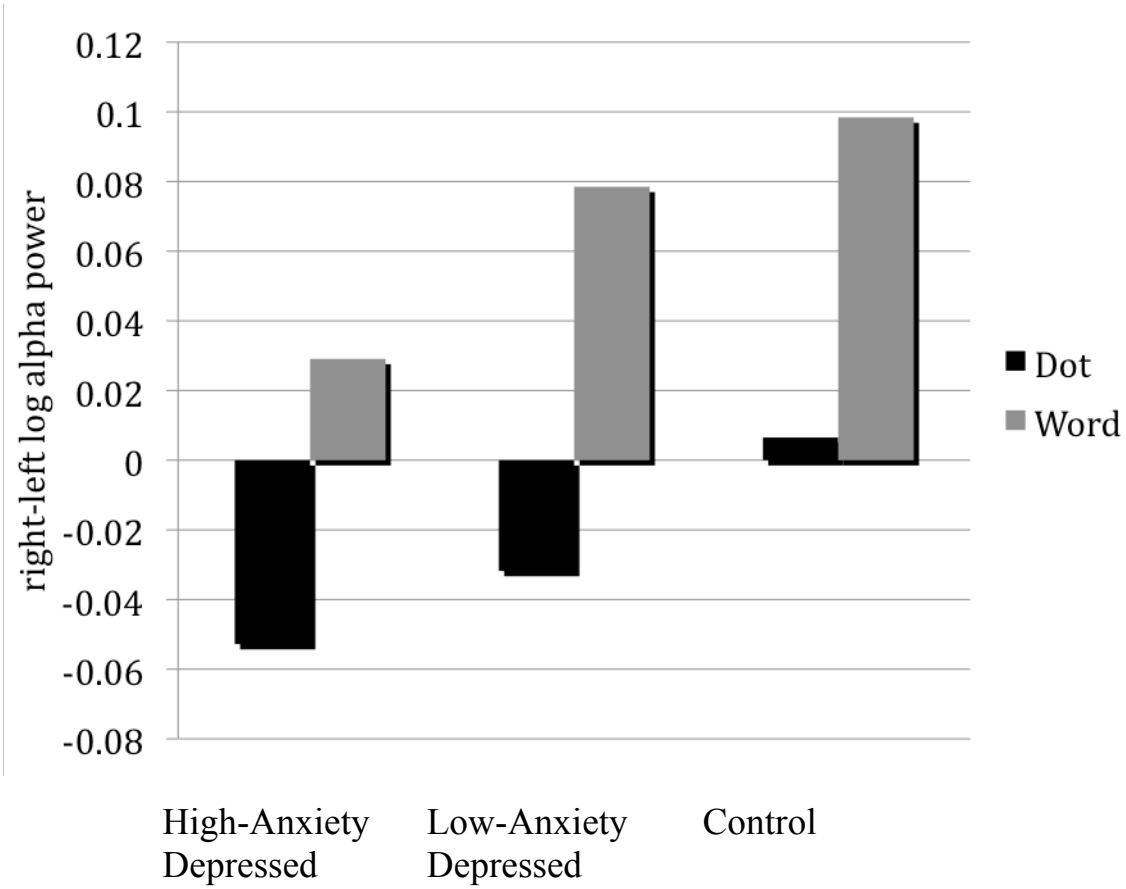


Figure 8. Task-related asymmetries in the central region

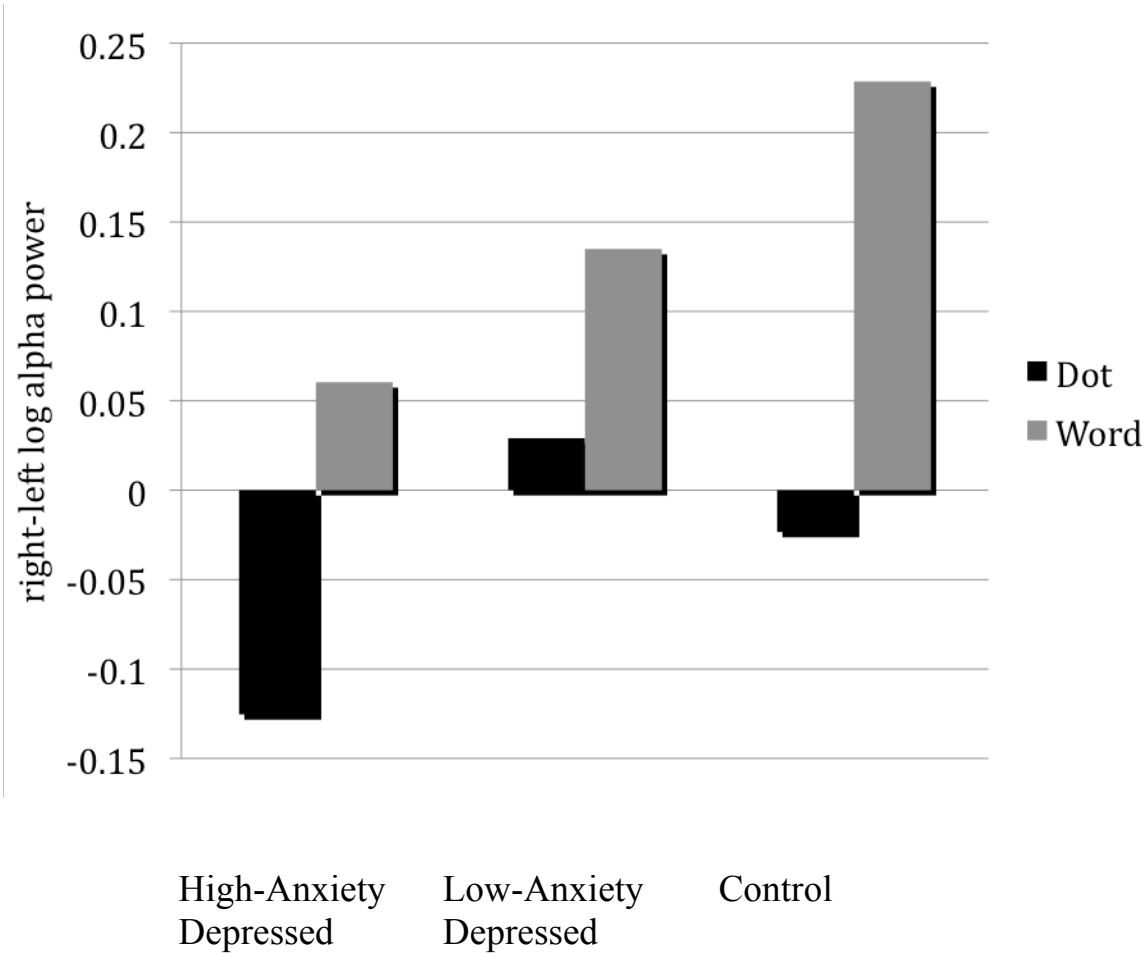
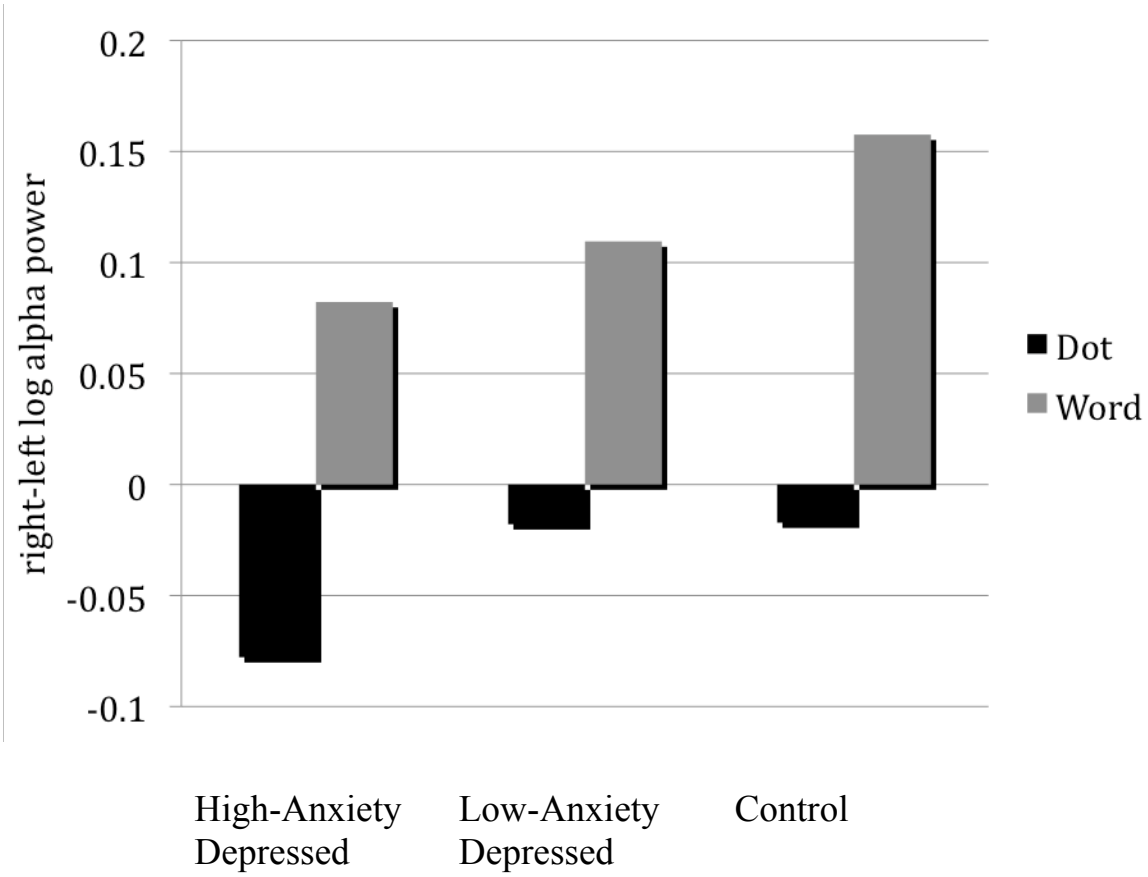


Figure 9. Task-related asymmetries in the parietal region



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