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Review article

Right brain, left brain in depressive disorders: Clinical and theoretical implications of behavioral, electrophysiological and neuroimaging findings

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ABSTRACT

The right and left side of the brain are asymmetric in anatomy and function. We review electrophysiological (EEG and event-related potential), behavioral (dichotic and visual perceptual asymmetry), and neuroimaging (PET, MRI, NIRS) evidence of right-left asymmetry in depressive disorders. Recent electrophysiological and fMRI studies of emotional processing have provided new evidence of altered laterality in depressive disorders. EEG alpha asymmetry and neuroimaging findings at rest and during cognitive or emotional tasks are consistent with reduced left prefrontal activity in depressed patients, which may impair downregulation of amygdala response to negative emotional information. Dichotic listening and visual hemifield findings for non-verbal or emotional processing have revealed abnormal perceptual asymmetry in depressive disorders, and electrophysiological findings have shown reduced right-lateralized responsivity to emotional stimuli in occipitotemporal or parietotemporal cortex. We discuss models of neural networks underlying these alterations. Of clinical relevance, individual differences among depressed patients on measures of right-left brain function are related to diagnostic subtype of depression, comorbidity with anxiety disorders, and clinical response to antidepressants or cognitive behavioral therapy.

1. Introduction

Studies in healthy adults and neurological patients have provided considerable evidence for asymmetries of right and left brain function (Springer and Deutsch, 1998; Hugdahl and Davidson, 2003). For over 30 years, studies have reported abnormalities of right-left asymmetry in depressive disorders. We review the findings of these studies and, in particular, examine how they are relevant to diagnosis and treatment of these disorders. Numerous studies have reported evidence of abnormal frontal and parietotemporal asymmetries in depressive disorders. The bulk of findings for frontal asymmetry have come from electroencephalographic (EEG) studies measuring alpha, which has received considerable attention in prior reviews and meta-analyses (Jesulola et al., 2015; Peltola et al., 2014; Thibodeau et al., 2006), and also in studies measuring glucose metabolism with positron emission tomography (PET) and regional cerebral blood flow (rCBF) with functional magnetic resonance imaging (fMRI). Although parietotemporal asymmetries have received less attention (Stewart et al., 2011), behavioral and event-related potential (ERP) studies using dichotic listening or visual hemifield tasks that tap functions mediated by this region have found considerable evidence of abnormal lateralized cognitive and emotional processing in patients having depressive disorders (see Bruder, 2003 for an earlier review). More recent studies have provided additional evidence of altered laterality in depression, particularly for processing emotional information. The present report gives particular attention to reviewing converging evidence from behavioral, EEG, ERP, and neuroimaging studies, which support hypotheses of reduced left frontal and right parietotemporal function in depression, and provide a new understanding of neural networks that may underlie this altered laterality. The relevance of right-left asymmetries for risk of developing a depressive disorder, diagnostic subtypes of depression, and clinical responsiveness to pharmacological and cognitive-behavioral treatments will also be a focus.

2. EEG alpha asymmetry

The EEG alpha rhythm (8–12 Hz) is maximal when one is in a relaxed, wakeful state with eyes closed, but is reduced when one becomes alert or opens the eyes. Alpha power has been found to be inversely related to cortical activity as measured by rCBF (Cook et al.,

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1998) or blood oxygen level in posterior regions where alpha is greatest (Feige et al., 2005). This inverse relation can lead to some confusion as to whether one is referring to hemispheric asymmetry of alpha power or cortical activity. To avoid this, the convention will be to refer to the asymmetry of *cortical activity* that is reflected by alpha asymmetry. Studies have found an abnormal frontal alpha asymmetry in currently depressed individuals or those with prior history of depression, with depressed individuals showing relatively less activity over left than right frontal sites (Allen et al., 2004; Gotlib et al., 1998; Henriques and Davidson, 1991; Kemp et al., 2010; Mennella et al., 2015; Stewart et al., 2010). There have, however, been conflicting findings for depressed patients, which led to a search for possible mediators that could account for these inconsistencies (Reid et al., 1998). In a meta-analysis of alpha asymmetry findings for depression, Thibodeau et al. (2006) found a moderate effect size (Cohen's d = .54) for the frontal alpha asymmetry difference between depressed and control groups.

The finding of relatively less activity over left than right frontal sites is not specific to depressive disorders, but also occurs in patients having panic disorder (Wiedemann et al., 1999), social phobia (Davidson et al., 2000; Moscovitch et al., 2011) or obsessive-compulsive disorder (Ischebeck et al., 2014). We found that depressed patients having a co-morbid anxiety disorder (primarily social phobia or panic disorder) showed a frontal alpha asymmetry indicative of relatively less left than right frontal activity, whereas patients with a depressive disorder alone did not show this asymmetry (Bruder et al., 1997a). Across studies, Thibodeau et al. (2006) found relatively small correlations of frontal alpha asymmetry with both depression (r = 0.26) and anxiety (r = 0.17) symptoms, and more recently, Gold et al. (2013) found a significant correlation of frontal asymmetry and anxiety symptom ratings (r = 0.33) but not depression symptom severity (0.17). Also, Blackhart et al. (2006) reported that an alpha asymmetry indicative of relatively greater right frontal activity predicted greater trait anxiety one year later, but was not associated with depression. These findings are consistent with findings in a non-clinical sample indicating that individuals high in anxious arousal showed relatively greater right frontal activity, which was not seen in individuals with high depression scores (Mathersul et al., 2008).

Offspring of depressed parents are at increased risk for depressive and anxiety disorders (Warner et al., 1995; Weissman et al., 1997). Several studies have found an alpha asymmetry reflecting less left than right frontal activity in infants and adolescents at high risk, particularly those with maternal depression (Dawson et al., 1997; Field and Diego, 2008; Lopez-Duran et al., 2012; Tomarken et al., 2004), but other studies did not find risk for depression to be associated with frontal alpha asymmetry (Bruder et al., 2007b; Dawson et al., 1992; Ehlers et al., 2001; Field et al., 1998). In a meta-analysis of 38 studies, Peltola et al. (2014) reported that psychosocial risk (parental depression or child maltreatment) was associated with greater right than left frontal activity, with a significant effect size (d = 0.36). The effect was moderated by gender being larger in samples with a higher percentage of girls. Also, the association of parental depression and greater right frontal activity was moderated by age, with longer exposure to parental depression weakening the effect. Other studies also found that alpha asymmetry indicating relatively greater right frontal activity was evident only among *females* with a history of childhood-onset depression (Miller et al., 2002) or at risk for depression or anxiety (Smit et al., 2007).

Individual differences in frontal alpha asymmetry have been interpreted in terms of an approach-withdrawal model (Coan and Allen, 2003; Davidson, 1998), in which left frontal activity is related to approach motivation (positive affect) and right frontal activity is related to withdrawal motivation (negative affect). The frontal alpha asymmetry in depressive and anxiety disorders could therefore reflect decreased left hemisphere approach-related motivation, increased right hemisphere withdrawal-related motivation or some combination of both. Conflicting alpha asymmetry findings for depressed patients or individuals at risk for MDD could stem from multiple factors, including comorbidity of depression and anxiety (Reid et al., 1998). In this regard, it is important to distinguish between two types of anxiety, anxious apprehension (e.g., worry) and anxious arousal (e.g., in panic disorder). Heller and Nitschke (1998) found individuals high in anxious apprehension displayed an alpha asymmetry favoring the left hemisphere. Moreover, participants with symptoms of depression and anxious apprehension failed to show less left than right frontal activity, whereas those with anxious arousal showed more right than left hemisphere activity (Nitschke et al., 1999). This suggests that anxious apprehension could act to suppress the finding of less left than right frontal activity in depressed individuals, whereas anxious arousal could enhance this finding.

Some studies have found the opposite alpha asymmetry at parietal sites in depressed or previously depressed individuals, i.e., *less* activity over right than left hemisphere, when compared to never depressed controls (Davidson et al., 1987; Henriques and Davidson, 1990; Reid et al., 1998). We also found offspring or grandchildren of depressed probands had an alpha asymmetry indicative of relatively less right parietal activity (Bruder et al., 2005, 2007b). In this study, alpha power was inversely correlated with MRI measures of cortical thickness, particularly over right parietal cortex (Bruder et al., 2012a). EEG evidence of reduced cortical activity at the right parietal site (P4), but not the left parietal site (P3), was associated with cortical thinning. There was a significant difference in the correlation of MRI cortical thickness and alpha power over right and left parietal sites, but no significant hemispheric difference in correlations at frontal sites. Children with low positive emotionality, which was hypothesized to be a risk factor for depression, also showed an alpha asymmetry with less right than left activity (Shankman et al., 2005). Given evidence that right posterior cortex is critical for processing emotional stimuli (Deldin et al., 2000; Kayser et al., 2000; Moratti et al., 2008), children who have relatively low right parietal activity, possibly related to reduced cortical thickness, may be less able to perceive or process emotional information placing them at increased risk for depression. However, other EEG studies failed to find reduced right parietal activity in depressed individuals (Debener et al., 2000; Henrique and Davidson, 1991; Nitschke et al., 1999; Schaffer et al., 1983) or children of depressed mothers (Dawson et al., 1997; Diego et al., 2006; Field and Diego, 2008; Jones et al., 1997; Tomarken et al., 2004), which may be due to the opposing effects of anxious arousal. Heller et al. (1995) hypothesized that anxious arousal, e.g., as seen in panic disorder, is associated with right parietotemporal hyperactivation, whereas depression is associated with right parietotemporal hypoactivation. Anxious arousal in depressed patients having a comorbid anxiety disorder could thereby result in increased right parietal activity or cancel out the relatively less right parietal activity in depression. EEG evidence supporting this hypothesis was found for both adolescents and adults having a major depressive disorder (MDD) with vs. without a comorbid anxiety disorder (Bruder et al., 1997a; Kentgen et al., 2000). Patients having a major depressive disorder and comorbid anxiety disorders showed an alpha asymmetry indicative of greater activity over right than left parietal site, whereas patients having a "pure" depressive disorder showed less activity over right parietal site. A study of alpha asymmetry in a non-clinical sample (Mathersul et al., 2008) also found greater right parietotemporal activity in comorbid depression/anxiety group compared to healthy controls, but the depression group also tended to have higher right parietotemporal activity. Blackhart et al. (2006) found higher depression scores, but not trait anxiety scores, to be associated with relatively less right parietotemporal activity, but other studies have not found a significant association of current depressive symptoms and parietal alpha asymmetry (Stewart et al., 2011). Importantly, Stewart et al. examined parietal alpha asymmetry in women and men having a MDD without comorbid anxiety disorders. Patterns of parietal asymmetry depended on gender and whether individuals had a current or past MDD. Women with a past MDD, but