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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

not current MDD, showed relatively less right parietal activity than women without a MDD. Also, women with a current MDD had higher relative right parietal activity than those with past MDD, which was moderated by caffeine intake. They suggest that women with a current MDD had higher levels of anxious arousal associated with caffeine and this was reflected in their higher right parietal activity than in women with past MDD. This is in accord with the hypothesized role of anxious arousal in heightened right hemisphere activity (Heller et al., 1995), but Stewart et al. (2011) did not have an independent measure of anxious arousal to evaluate this possibility.

Conflicting findings for both frontal and parietal alpha asymmetry could have stemmed from differences in subject characteristics (e.g., gender, age, recruitment strategy), clinical characteristics (e.g., diagnostic subtype, age of onset, or comorbidity with anxiety) and methodological differences (e.g., reference electrode, reliability or stability of measures), which have been previously discussed (Allen et al., 2004; Reid et al., 1998; Stewart et al., 2010). The clinical heterogeneity of depression is well known and yet, with the exception of comorbidity with anxiety, few studies have examined its impact on alpha asymmetry. Shankman et al. (2007) examined the effects of age of onset and chronicity of depression on EEG during reward (approach motivation) or no incentive task conditions. Individuals with an early onset of depression (before age of 17) failed to show the expected increase in left frontal activity during the approach condition, which was seen in late onset depression and healthy controls, but chronicity was not related to frontal alpha asymmetry.

Another critical factor that likely contributed to inconsistent findings is that most studies measured alpha asymmetry for "resting" EEG, where there was no control over ongoing cognitive or emotional processing during the recording. Findings of less left than right frontal activity in depression have been more consistent during emotionally-challenging tasks (Harmon-Jones et al., 2010; Stewart et al., 2011). Coan et al. (2006) found evidence to support a capability model, which proposes that frontal EEG asymmetry during an emotional challenge is a more powerful indicator of motivational differences than "resting" measures. Stewart et al. (2014) compared frontal alpha asymmetry in individuals having a lifetime MDD and non-depressed controls during both resting and a facial emotion task. Using standard reference-dependent (average, Cz, linked mastoids) EEG measures, individuals with current and past MDD displayed relatively less left frontal activity than non-depressed controls across approach (angry, happy) and withdrawal (afraid, sad) emotional conditions, but *not* in a resting condition. Children at high risk for depression were similarly found to show relatively less left frontal activity than low risk children during emotion-eliciting films, but not during a resting condition (Lopez-Duran et al., 2012). More recently, Mennella et al. (2015) found less left than right left frontal activity for individuals having non-clinical dysphoria during both pleasant and unpleasant imagery conditions. Moreover, the dysphoric individuals showed less right than left parietal activity during unpleasant but not pleasant or neutral imagery conditions. Allen and Reznik (2015) reviewed additional evidence that EEG alpha asymmetry findings in depression are more consistent for emotional challenge than resting conditions.

Conventional measures of frontal and parietal scalp potentials can also differ depending on specific electrode site and the reference electrode. In addition to EEG scalp potentials, Stewart et al. (2014) also employed "reference free" current-source density (CSD) measures that reduce volume conduction from distal locations and provide indices of current generators underlying EEG on scalp (Kayser and Tenke, 2006; Tenke and Kayser, 2015). The CSD measures yielded the most consistent differences in frontal alpha asymmetry between the depressed and non-depressed groups across emotional and resting conditions. CSD measures represent an important methodological development that refines quantification of EEG, improving topographical and spectral resolution (Tenke and Kayser, 2005; Tenke et al., 2015; Kayser and Tenke, 2015). The use of CSD measures deals not only with the EEG "reference problem", but can lead to greater consistency of EEG findings across studies using "resting" and emotional challenge conditions (Stewart et al., 2014).

Biological heterogeneity of depression was likely a major contributor to inconsistent alpha asymmetry findings. An approach for reducing this heterogeneity is to subtype patients on the basis of their clinical response to a specific treatment for depression. Patients who respond to an antidepressant with a specific mechanism of action, e.g., a selective serotonin reuptake inhibitor (SSRI), may have a common biologic abnormality not present in non-responders. This could also be important for developing biomarkers for personalizing treatment for individual patients. Studies have found considerable evidence that electrophysiological measures, including resting alpha and theta power, are related to clinical response to antidepressants (see Alhaj et al., 2011; Bruder et al., 2013; Pizzagalli, 2011 for reviews). Fewer studies have examined the potential value of alpha asymmetry in this context. Our initial study (Bruder et al., 2001) found a difference in pretreatment alpha asymmetry in an eyes open condition between responders to 12 weeks of SSRI treatment and non-responders. Non-responders showed an overall alpha asymmetry (across frontal, central and parietal sites) indicative of relatively greater activation of the right hemisphere, whereas responders did not. The difference in alpha asymmetry between SSRI responders and non-responders was dependent on gender, being present among women but not men. In a follow-up study using the same SSRI (Bruder et al., 2008), responders and non-responders showed the same difference in alpha asymmetry as our prior study, but it was not dependent on gender. Responders showed less activity over right than left posterior sites, whereas non-responders showed the opposite asymmetry. This difference in alpha asymmetry was present both before and after 12 weeks of treatment, which suggests that it may be a state- independent trait. In a later study (Tenke et al., 2011), the predictive value of alpha was examined for patients receiving a SSRI or dual treatment with an SSRI plus a noradrenaline/dopamine reuptake inhibitor (NDRI) or a serotonin/noradrenaline reuptake inhibitor (SNRI). EEG was recorded from a dense array of electrodes (67 channels) and reference-free CSD measures were quantified using principal components analysis (PCA) to derive empirically-based frequency bands. Although treatment responders showed greater alpha than non-responders, they did not differ in alpha asymmetry. One weakness of these studies was the relatively small samples. A multi-center international study (iSPOT-D; Arns et al., 2016) examined the value of alpha for predicting response in a large sample of 667 patients who were randomized to 8 weeks of treatment with one of two different SSRIs or a SNRI antidepressant. Differences in alpha asymmetry between responders and non-responders depended on drug class and gender, with females who responded favorably to a SSRI showing less activity over the right frontal region and non-responders showing the opposite asymmetry. This agrees with the original gender-specific findings of Bruder et al. (2001) and suggests that alpha asymmetry indicative of relatively less right than left hemisphere activity is predictive of positive response to an SSRI among women.

Quraan et al. (2014) investigated the potential value of alpha asymmetry as a marker of effectiveness of deep brain stimulation (DBS) surgery for treating patients with treatment resistant depression. They recorded resting EEG following implanting of electrodes for DBS in subgenual cingulate cortex when electrodes were turned on or off, and found significant differences between DBS responders (n = 6) and non-responders (n = 6) in frontal theta and parietal alpha asymmetry. Moreover, there were differences between these groups in long range functional connectivity between left frontocentral and right parietal regions. A limitation of this study was not only the small sample size, but also EEG was recorded only after surgery and the findings were the same on or off DBS. It is therefore not clear whether differences in EEG asymmetry or connectivity represent biomarkers that predict response or resulted from the surgery or DBS.

Repetitive transcranial magnetic stimulation (rTMS) and neurofeedback training based on frontal EEG has shown success in treating depression. The impact of these treatments on alpha asymmetry has, however, received little attention (Allen and Rezink, 2015). A recent novel study examined the effects of real-time fMRI neurofeedback training on simultaneous recordings of frontal alpha asymmetry and fMRI (Zotev et al., 2016). Patients having a MDD (n = 13) learned to upregulate activity in the left amygdala during happy emotion induction. The training was associated with a change in frontal alpha asymmetry, i.e., an increase in relative left frontal activity, consistent with the approach-withdrawal model (Davidson, 1998; Coan and Allen, 2003). Moreover, frontal alpha asymmetry changes were positively correlated with laterality of amygdala activity during neurofeedback. EEG changes indicative of greater approach motivation were associated with greater laterality of the target amygdala region, i.e., larger left amygdala activity. They concluded that frontal alpha asymmetry is a measure of emotion/motivation that may reflect activity in the amygdala, and the link between frontal alpha asymmetry and amygdala activity is of key importance for understanding its role in emotional regulation.

In summary, studies have found alpha asymmetry indicative of relatively less left frontal and right parietal activity in depressive disorders, as well as children at high risk for mood disorders, but there have been inconsistent findings suggesting the importance of moderating variables (such as gender, comorbidity with anxiety disorders, age of onset, and methodological differences). Clinical and biological heterogeneity of depression are also likely to be critical. Differences in alpha asymmetry between responders and non-responders to treatments for depression suggest a strategy for reducing this heterogeneity and may contribute to development of biomarkers for personalizing treatment for individual patients. Simultaneous recording of EEG and fMRI is an important new approach for relating frontal alpha asymmetry to specific neural sites (e.g., the amygdala) involved in emotional processing and regulation (Allen and Resnick, 2015; Zotev et al., 2016).

3. Dichotic listening asymmetry (Behavioral and ERP studies)

Early behavioral studies using neuropsychological tests of cognitive function in depressed patients reported greater deficits in functions related to the right (non-dominant) than left (dominant) hemisphere (Flor-Henry, 1976; Abrams et al., 1981). The greater right hemisphere deficits in depressed patients were more evident among women than men and clinical improvement during treatment was associated with improved cognitive function (Fromm-Auch, 1983). More recent studies have found deficits in cognitive function in MDD (Cotrena et al., 2016), which may improve following antidepressant treatment (Trivedi and Greer, 2014), but they did not report on implications of their findings for lateralized hemispheric function. A weakness in the use of neuropsychological tests to examine laterality effects in MDD is that they do not provide an asymmetry index, but rely on comparison across cognitive tests that may differ not only in hemispheric dominance but also in difficulty level, dependence on speed of processing, and other task demands. We review below findings for dichotic and visual hemifield tasks that provide behavioral measures of perceptual asymmetry (PA) and, in some cases, direct ERP measures of hemispheric asymmetry.

Abnormal PA has been found in depressed patients tested on dichotic listening and visual half-field tests (for reviews see Bruder, 2003; Gadea et al., 2011). In dichotic listening tests, different stimuli are simultaneously presented to the right and left ear and accuracy for perceiving items in each ear provides a measures of PA. Healthy adults show a right ear advantage for verbal stimuli, consistent with left hemisphere dominance for verbal processing, and a left ear advantage for nonverbal or emotional stimuli, consistent with right hemisphere advantage for tonal or prosodic processing (Bryden, 1982). We refer below to left or right hemisphere advantage to simplify exposition. Early studies reported that patients having affective disorders (either unipolar depression or bipolar disorders) showed reduced or no right hemisphere advantage for nonverbal dichotic listening (Bruder et al., 1981; Johnson and Crockett, 1982; Overby et al., 1989; Yozawitz et al., 1979), consistent with other evidence of right hemisphere dysfunction in depression (Flor-Henry, 1976). A study using both dichotic listening and visual hemifield tasks found differences in PA between diagnostic subtypes of depression (Bruder et al., 1989). Patients having a MDD with melancholia showed abnormal PA in both dichotic complex tone test and consonant-vowel syllable tests, whereas patients having a non-melancholic atypical depression did not differ from healthy controls. Additional evidence of right hemisphere dysfunction in at least a subgroup of depressed patients was found in a study measuring PA and event-related potentials (ERPs) in depressed patients and healthy controls during a dichotic complex tone test (Bruder et al., 1995). Depressed patients failed to demonstrate the right hemisphere advantage for complex tones and behavior-related hemispheric asymmetry of the P3 potential, which were found in healthy controls. A subsequent study (Bruder et al., 1998) recorded brain ERPs to binaural complex tones in depressed patients and healthy controls. Healthy adults and patients having low scores on a physical anhedonia scale showed greater P3 amplitude over the right than left hemisphere, whereas patients with high anhedonia scores did not show this asymmetry. These findings support the hypothesis that right hemisphere dysfunction for dichotic listening in MDD is most evident in patients having a melancholic depression or pervasive anhedonia. Reduced right hemisphere advantage for complex tones in depressed patients was also found to be dependent on gender, being more evident among men than women (Bruder et al., 2012b).

Findings for verbal dichotic listening tests in depressed patients have been less consistent, with some studies finding abnormally large left hemisphere advantage in adolescents and adults having a MDD (Bruder et al., 1989; Pine et al., 2000) and other studies finding normal PA for depressed patients in dichotic syllable tests (Hugdahl et al., 2003; Moscovitch et al., 1981; Wale and Carr, 1990). As seen for EEG alpha asymmetry, these differences in dichotic listening findings for depression could arise from comorbidity with anxiety disorders or from differences in other patient characteristics (e.g., diagnostic subtype or gender). In fact, we found that patients having a MDD with a comorbid anxiety disorder had smaller left hemisphere advantage for dichotic words (Bruder et al., 1999) and an alpha asymmetry indicating relatively less left than right hemisphere activity (Bruder et al., 1997a) when compared to patients having a MDD without an anxiety disorder. Moreover, patients having social phobia with or without a depressive disorder had smaller left hemisphere advantage for dichotic words or syllables than subjects without social phobia (Bruder et al., 2004a). It has also been reported that anxious arousal induced by threat of an electric shock reduces the left hemisphere advantage for dichotic syllables (Asbjörnsen et al., 1992). These findings support the hypothesis that anxious arousal, as seen in anxiety disorders, is associated with relatively greater right parietotemporal activity (Heller et al., 1995), which could act to *reduce* left hemisphere advantage for verbal dichotic listening tests in patients with an anxiety disorder.

Further evidence that depressive and anxiety disorders have opposing effects on lateralized hemispheric processing was seen in a multigenerational study of risk for depressive disorders (Weissman et al., 2005). In a later phase of the study (Bruder et al., 2016), biological offspring and grandchildren of probands with a MDD and the progeny of non-depressed probands were tested on a standard dichotic syllable test, and also a dichotic emotional recognition test, in which words presented to the right and left ear differ in emotional intonation (i.e., said in an angry, sad, happy or neutral voice). In healthy adults, the syllable test yielded the expected left hemisphere advantage (Hugdahl et al., 2003), and the emotional recognition test yielded a right hemisphere advantage (Bryden and MacRae, 1989; Voyer et al., 2009), consistent with evidence that affective prosody is strongly

lateralized to right hemisphere regions (Fröhholz et al., 2016). There was no difference in performance or PA between high and low risk subjects, but individuals with a lifetime diagnosis of MDD had a smaller right hemisphere advantage for emotional recognition than those without a MDD, particularly for items with sad intonation. In contrast, individuals with a lifetime diagnosis of an anxiety disorder did not differ from those without an anxiety disorder in the emotion test, but they showed less left hemisphere advantage in the syllable test. This indicated that lifetime diagnosis of MDD and anxiety disorders have a *differential* effect on right and left brain processing of emotional and verbal information, respectively.

Individual difference among depressed patients in dichotic listening have also been related to therapeutic response to antidepressants and cognitive-behavioral therapy. Bruder et al. (1990) found that depressed patients who responded favorably to a tricyclic antidepressant failed to show the right hemisphere advantage for complex tones seen for non-responders and healthy controls. This supported the prediction that tricyclic responders would show evidence of right hemisphere dysfunction similar to that seen for patients having a melancholic depression (Bruder et al., 1989), a subtype that typically responds to this antidepressant. The findings of this study were partially confirmed in a follow-up study (Stewart et al., 1999). While patients who responded to a tricyclic antidepressant did not differ from non-responders in the complex tone test, they showed evidence of right hemisphere dysfunction in a consonant-vowel syllable test. In a study conducted at two clinical centers (Bruder et al., 1996), patients having a MDD were tested on dichotic word and complex tone tests both before and after treatment with a SSRI antidepressant (fluoxetine). Patients who responded to treatment showed greater left hemisphere advantage for words and less right hemisphere advantage for complex tones when compared to non-responders, which was present both before and after 8–12 weeks of treatment. A subsequent study (Bruder et al., 2004b) again showed a relative favoring of left over right hemisphere processing in SSRI responders compared to non-responders, but this difference was dependent on gender and test. Greater left hemisphere advantage for words in responders was present among women but not men, whereas reduced right hemisphere advantage for complex tones was present among men but not women. This is consistent with gender effects seen for differences in resting EEG alpha asymmetry between SSRI responders and non-responders (Arns et al., 2016; Bruder et al., 2001). Bruder et al. (2001) found a significant correlation between PA for dichotic words and alpha asymmetry among women ($r = 0.51$, $p < 0.01$) but not men ($r = -0.15$, ns). Smaller left hemisphere advantage for dichotic words, particularly among women who were SSRI non-responders, was associated with greater overall cortical activity over the right hemisphere. A difference in dichotic listening for words between responders and non-responders was also found for an antidepressant with a different mechanism action, i.e., the noradrenaline/dopamine reuptake inhibitor (NDRI) bupropion (Bruder et al., 2007a). Patients who responded to bupropion had significantly larger left hemisphere advantage for dichotic words when compared to non-responders. A recent unpublished study did not, however, find a difference in dichotic listening between responders and non-responders treated with bupropion or treatment with a serotonin reuptake inhibitor (SSRI alone or dual therapy including a serotonergic agent). Patients were tested on dichotic word and complex tone tests before receiving bupropion alone (n = 25), SSRI alone (n = 18), dual therapy with a SSRI and bupropion (n = 18) or a SNRI (n = 10) antidepressant (see Bruder et al., 2014 for details). We found no significant difference in PA between responders (n = 14) and non-responders (n = 11) treated with a bupropion alone or between responders (n = 36) and non-responders (n = 10) treated with a serotonergic agent (SSRI alone or dual therapy). The reason for the negative findings in this one study are unclear, but may have stemmed from lack of a placebo control condition to distinguish spontaneous improvement from true drug response, small samples, or a yet unidentified mediating variable related to the clinical or biological heterogeneity of depression.

Three studies did replicate differences in left hemisphere advantage for verbal dichotic listening between responders and non-responders to cognitive behavioral therapy (CBT) for depression. In an initial study (Bruder et al., 1997b), depressed patients who responded to 16 weekly sessions of CBT showed greater left hemisphere advantage for dichotic consonant-vowel syllables when compared to non-responders and healthy adults, but they did not differ in their right hemisphere advantage for complex tones. The larger left hemisphere in CBT responders was due to their *better* right ear accuracy, which suggests superior left hemisphere processing of phonetic stimuli. There was no difference between placebo responders and non-responders in left hemisphere for dichotic syllables, which suggests that the difference between CBT responders and non-responders is not merely due to a non-specific placebo effect. The difference in left hemisphere advantage between CBT responders and non-responders was confirmed in a recent study using a dichotic word test (Kishon et al., 2015). Moreover, this finding was replicated at a different research center in a study that included clinically representative samples and community therapists (Bruder et al., 2017). CBT responders had greater left hemisphere advantage for dichotic words compared to non-responders, but they did not differ significantly in right hemisphere advantage for complex tones. Cognitive therapies are highly verbal treatments involving self-monitoring and reappraisal of negative thoughts and cognitive distortions, which may be mediated by cognitive processes that depend on verbal abilities and activation of left hemisphere regions (Otto et al., 1987; Price et al., 2013; Silvers et al., 2015). The dichotic listening findings supported the hypothesis that individuals with strong left hemisphere language dominance may be better able to recruit left cortical regions critical for the success of CBT.

In summary, evidence of right hemisphere dysfunction has been found in patients having depressive disorders, in particular for dichotic tests using non-verbal or emotional stimuli for which the right hemisphere is dominant. Abnormalities of PA in depressed patients were, however, dependent on clinical features, including diagnostic subtype and comorbidity with anxiety disorders. While depressive disorders were related to reduced right hemisphere advantage for non-verbal dichotic listening, anxiety disorders were associated with reduced left hemisphere advantage for verbal dichotic listening. This suggested that depressive and anxiety disorders are associated with opposing abnormalities of lateralized cognitive processing. Differences in dichotic listening among depressed patients were related to response to antidepressants or CBT, which indicates the potential of these measures as markers for predicting whether or not a patient will benefit from these treatments. There have, however, been some inconsistent findings for predicting response to antidepressants, and gender appears to be an important factor. Three studies found response to CBT for depression was related to increased left hemisphere advantage for verbal dichotic listening, but it is unlikely that dichotic listening tests in themselves would be of value for *differential* prediction of response to the variety of antidepressants and CBT available for treating depressive disorders.

4. Visual hemifield asymmetry (Behavioral and ERP findings)

Differences in PA were found between patients having a bipolar (primarily Bipolar II) and unipolar depressive disorders who were tested in a dot enumeration task, which requires subjects to report the number of dots projected to either the right or left of fixation (Bruder et al., 1989). Patients having a unipolar depressive disorder and controls showed the expected right hemisphere advantage seen previously for the dot enumeration test (McClone and Davidson, 1973), whereas bipolar depressed patients did not. Bruder et al. (1992) replicated this finding in separate samples of patients having a bipolar or unipolar depression. In contrast, there was no significant difference among these groups in left hemisphere advantage for perceiving consonant-vowel-consonant syllables presented to either the right or

left visual field. This provides further evidence that reduced right hemisphere advantage for non-verbal tasks depends on diagnostic subtype of depression. However, patients who responded to a tricyclic antidepressant showed reduced left hemisphere advantage for syllables compared to non-responders and healthy controls, but no difference in right hemisphere advantage for non-verbal stimuli, which was not found for dichotic listening (Bruder et al., 1990).

Studies have found evidence that depressive and anxiety disorders are associated with opposing patterns of hemispheric asymmetry to lateralized visual stimuli, which parallel findings for EEG alpha asymmetry and dichotic listening. In one of the first studies, Liotti et al. (1991) measured simple reaction times (RTs) to stimuli presented to the left or right of fixation. Patients having a unipolar depressive disorder showed slower RTs to left visual field (right hemisphere) stimuli, whereas patients having a generalized anxiety disorder showed the opposite asymmetry. Studies using a free-vision Chimeric Faces Test (CFT) have reported additional evidence for differences in hemispheric asymmetry between depression and anxiety. This test uses split faces with one half of the face smiling and the other half with a neutral expression and subject's indicate whether the face with the smile on the left or right side looks happier. Studies in healthy adults have found a bias for choosing the face with the smile on the left side (Levy et al., 1983), which is consistent with right parietotemporal advantage for processing facial and/or emotional content of stimuli. Jaeger et al. (1987) found that patients having a unipolar MDD showed reduced right hemisphere bias when compared to healthy controls, and this finding was replicated by David and Cutting (1990). In a study of college students classified as either high or low in depression and high or low in anxiety (Heller et al., 1995), depression was associated with decreased right hemisphere bias and anxiety was associated with increased right hemisphere bias. Similar opposing effects of depression and anxiety on right hemisphere bias for CFT in students were reported by Keller et al. (2000). Heller et al. (1995) hypothesized that depression is associated with right parietotemporal hypoactivation, whereas anxious arousal, such as seen in panic disorders, is associated with right parietotemporal hyperactivation. They also argued that opposing effects of depression and anxious arousal on PA may act to cancel each other out in depressed individuals with comorbid anxiety disorders.

An additional study in a non-clinical sample of 160 participants used a CFT with facial expressions of six basic emotions (Bourne and Vladeanu, 2013). A left visual field advantage was found for all six emotions, supporting right hemisphere bias for processing emotional chimeric faces. Most notably, a negative relationship between depression scores and PA was found for women but not men. Women with higher depression scores were less strongly lateralized to the right hemisphere, with this relationship being strongest for anger, disgust and fear. This accords with other evidence of sex differences in emotional lateralization (Bourne, 2005; Stevens and Hamann, 2012).

There is also evidence that hemispheric bias in the CFT depends on the diagnostic subtype of depressed patients. In agreement with findings for dichotic listening (Bruder et al., 1989), patients having an atypical depression differed from those having a typical or melancholic depression in hemispheric asymmetry for chimeric faces. Atypical depression is characterized by symptom features that are in some respects opposite those for melancholia, including reactivity of mood without anhedonia and reversed vegetative symptoms, e.g., hypersomnia and overeating. In two studies (Bruder et al., 2002), patients having an atypical depression differed from those having a typical depression in having abnormally *large* right hemisphere bias, whereas patients with melancholia had essentially no right hemisphere bias. A subsequent study (Kucharska-Pietura and David, 2003), compared CFT performance in patients having unipolar and bipolar disorders, as well as right or left brain damaged individuals. Unipolar MDD and right brain damaged patients showed reduced right hemisphere bias compared to healthy controls, whereas patients having a bipolar disorder (bipolar I or II, currently hypomanic) and left brain damaged patients did not differ from controls. These findings indicate that patients having a unipolar depressive disorder, in particular those with typical or melancholic features, showed abnormally reduced right hemisphere bias for emotional chimeric faces, which was not seen in patients having an atypical depression or bipolar disorder in a hypomanic state.

Pereira and Khan (2016) investigated the lateralization of emotional processing and regulation in depressed patients (n = 30) and healthy controls (n = 30) during a reaction time task involving attentional disengagement from positive and negative emotional stimuli presented to the left or right visual field. Controls showed a strong left visual field advantage, but depressed did not, which is in accord with evidence cited above that depressed patients failed to show a right hemisphere advantage for processing emotional stimuli. Although there is debate on the hemisphere primarily involved in downregulating or inhibiting emotional reactions, Pereira and Khan interpreted their findings as support for right hemisphere dominance for disengaging attention to emotional stimuli. As additional evidence, they cited a study by Beauregard et al. (2006), in which fMRI of depressed patients and controls were measured while they attempted to down-regulate emotional reactions to sad films. Depressed individuals rated the task as more difficult than controls, and showed greater activation of right dorsal anterior cingulate cortex (ACC), right anterior temporal pole, right amygdala, and right insula when compared to controls, which suggested less efficient functioning of a neural circuit for emotional regulation. On the other hand, Leyman et al. (2011) found high frequency rTMS over the left dorsolateral prefrontal cortex decreased depressive symptoms and was associated with improved inhibition of negative emotions. A recent ERP study measured amplitude of the N2 potential of adolescents with MDD and healthy controls in a go/no-go task with positive and negative faces (Trinkl et al., 2015). Depressed individuals showed greater N2 over right than left frontocentral sites, whereas controls showed the opposite asymmetry. This N2 asymmetry in depressed adolescents agrees with the frontal alpha asymmetry findings in adults having depressive or anxiety disorders, i.e., relatively greater right prefrontal activity. These findings support the hypothesis that deficits in emotional regulation in depression are related to alteration in lateralization of emotional processing, but the hemisphere involved in downregulating emotions varied across studies.

Three studies recorded ERP or magnetoencephalographic (MEG) responses of the brain to emotional stimuli, reporting direct evidence of reduced right parietotemporal activity in depressed patients (Deldin et al., 2000; Kayser et al., 2000; Moratti et al., 2008). Deldin et al. (2000) recorded ERPs to positive, negative and neutral face and word stimuli during a recognition memory task in patients having a unipolar MDD and healthy controls. Depressed patients showed reduced amplitude of the N2 potential over the right parietal region and this was most evident during the processing of pleasant faces. Kayser et al. (2000) measured ERPs of depressed patients (n = 30) and healthy controls (n = 16) during passive viewing of negative pictures of patients with dermatological diseases and neutral control pictures of these patients after surgical treatment. The pictures were briefly exposed to the right or left visual field so as to directly stimulate the contralateral hemisphere. As in prior studies (Cacioppo et al., 1993; Kayser et al., 1997), healthy controls showed greater amplitude of late positive P3 potential to negative stimuli compared to neutral stimuli, and this enhancement was more evident over right parietal regions. Unlike controls, depressed patients failed to show increased late P3 to negative than to neutral stimuli over either hemisphere. Moratti et al. (2008) measured steady-state MEG oscillatory activity to emotional and neutral pictures in female low-anxious patients with MDD (n = 15) and female controls (n = 15). MEG responses in right parietotemporal cortex were related to emotional arousal, but this was markedly reduced in depressed patients. These data are consistent with the hypothesis of right parietotemporal hypoactivation in depression, which is related to difficulty activating attention-related brain regions during processing of emotionally arousing stimuli. Moratti et al. (2015) also reported

initial evidence that this reduction was most evident in depressed patients with at least one parent with a MDD.

The influence of family history and MDD status on ERPs to emotion stimuli was also found in our multigenerational study of risk for depressive disorders (Kayser et al., 2016; Kayser et al., 2017). ERPs were recorded from individuals at high risk (N = 74) or low risk (n = 53) for MDD during the same visual half-field paradigm with negative and neutral emotional stimuli used in our prior study in depressed patients (Kayser et al., 2000). Three distinct ERPs reflecting consecutive stages in processing emotional stimuli were affected by risk status. Early enhanced activation of right occipitotemporal cortex to negative emotional stimuli, peaking at around 200 ms after stimulus onset (N2), was less evident in high risk than low risk individuals and this right-lateralized reduction was even stronger in those with a lifetime history of MDD. During a subsequent processing stage, peaking around 400 ms (P3 source), there was bilateral emotion-related activation of posterior cingulate cortex, which was also weaker in high risk individuals and those with lifetime MDD. Distributed inverse solutions (sLORETA) at a later processing stage (around 600 ms) implicated bilateral reduction of emotion-related activation in inferior temporal cortex and anterior insula in these individuals. These findings suggested that familial risk for MDD and history of MDD were associated with abnormal brain activation along the ventral visual pathway reflecting processing of motivationally salient emotional stimuli (Kayser et al., 2017). They are consistent with other evidence that blunted ERPs involving right parietotemporal cortex to emotionally arousing stimuli may be an endophenotype of depression risk (Moratti et al., 2015).

In summary, studies have found abnormal visual field asymmetries in patients having depressive disorders, in particular for processing nonverbal or emotional stimuli for which the right hemisphere is dominant. Evidence of reduced right hemisphere advantage or bias was related to diagnostic subtype of depression, and anxiety disorders were associated with the *opposite* asymmetry. ERP or MEG measures to visually-presented emotional stimuli showed greater activity over the right parietal region in healthy controls, but this was reduced in patients having a depressive disorder. Thus, the visual hemifield findings for depressed patients were generally in good agreement with those seen for dichotic listening, suggesting reduced right parietotemporal processing of non-verbal and emotional information in MDD. Electrophysiological studies have the distinct advantage of providing real-time measures of brain activity with fine temporal resolution, and multi-channel EEG recordings and source localization (e.g., CSD and sLORETA measures) have led to improvements in topographical resolution (Kayser et al., 2016; Pizzagalli, 2011). This has been useful in tracing the sequence of neural activation to negative emotional stimuli from right lateralized activation of visual cortex to activation of parietotemporal sites, which was reduced in individuals who are high risk for MDD or have a lifetime history of MDD.

5. PET, MRI and NIRS neuroimaging findings

Neuroimaging studies using PET and MRI measures have found evidence of abnormalities involving multiple brain regions in depressed patients, including prefrontal cortex (PFC), superior temporal cortex, anterior cingulate cortex (ACC), amygdala, insula, basal ganglia and cerebellum (Fitzgerald et al., 2008; Pizzagalli, 2011; Rive et al., 2013; Sacher et al., 2012), but the extent to which these are lateralized to the right or left hemisphere has received less attention. Most imaging studies were not specifically designed to examine hemispheric asymmetry, but rather used statistical analyses across the whole brain, which did not directly measure asymmetries between homologous regions of the right and left hemisphere, and used stimuli that were not lateralized to right or left hemifield. Although no attempt will be made to review the extensive neuroimaging literature in depression, we will highlight reports suggesting possible asymmetries of brain activity at rest and during cognitive or emotional processing.

Structural MRI studies have found smaller hippocampal volumes in patients with MDD compared to healthy controls, and two meta-analyses reported the effect size to be larger for right than left hemisphere hippocampal volumes (Cole et al., 2011; Videbech and Ravnkilde, 2004). Depressed youths have also been found to have smaller volume of the right hippocampus but only a trend for the left hippocampus (Jaworska et al., 2016). There is evidence that right hippocampal reduction may be linked to recurrent depressive episodes (Videbech and Ravnkilde, 2004). Mathias et al. (2016) found a correlation between genes and right hippocampal volume in patients having a recurrent MDD, and they suggested that right hippocampal volume is a possible endophenotype for recurrent MDD. Other studies have, however, found a bilateral or unilateral left reduction of hippocampal volume in MDD, which might reflect the clinical heterogeneity of depressive disorders or factors such as illness duration, recurrences of episodes, or comorbidity (Stratmann et al., 2014). Taking comorbidity of MDD and anxiety disorders into account may be particularly important in studies of brain volume (van Tol et al., 2010). They found reduced volume of right lateral inferior frontal cortex was specific to MDD, and reduced left middle superior temporal volume was specific to anxiety disorders, whereas reduced volume of rostral-dorsal ACC was a generic feature of both depressive and anxiety disorders. Similarly, Jaworska et al. (2016) found depressed patients with comorbid anxiety had smaller subgenual ACC, but not smaller hippocampal volumes when compared to those without anxiety disorders. Structural MRI findings have also been linked to clinical response to antidepressants. Thus, smaller hippocampal volumes were associated with poorer clinical response in several studies (Stratmann et al., 2014), and studies have reported that volume of left dorsolateral PFC was predictive of clinical response to antidepressants (Costafreda et al., 2009; Li et al., 2010; Liu et al., 2012). There is also considerable evidence for reduction of volume of the anterior insula in MDD, but the laterality varies across studies (Bora et al., 2012). Stratmann et al. (2014) found reduction of anterior right insula was more severe in patients having recurrent MDD than in 1st episode patients.

Several PET studies in a resting state have reported hypometabolism of left dorsolateral PFC in depressed patients (Baxter et al., 1985; Bench et al., 1993), which is consistent with EEG findings of relatively less left frontal activity (greater alpha) in depression (Thibodeau et al., 2006). There have, however, been conflicting findings with some studies finding bilateral or no reduction of dorsolateral PFC activity in depressed patients (Baxter et al., 1989; Sacher et al., 2012), and one study found reduction of metabolism in the right temporal lobe (Post et al., 1987). The possibility that differences between diagnostic subtypes of depression contributed to conflicting resting state findings is supported by a study measuring single photon emission computed tomography (Fountoulakis et al., 2004). Patients having an atypical depression showed a relative increase in right frontal lobe perfusion, whereas those having a melancholic depression showed a decrease in this region. Moreover, McGrath et al. (2013) found differences in regional glucose metabolism between depressed patients who responded to treatments for depression and non-responders. Pretreatment metabolic activity in the right anterior insula was greater in responders than non-responders to treatment with the SSRI escitalopram, whereas the opposite was true for responders vs. non-responders to treatment with CBT. These findings suggest that differences of resting metabolism among depressed patients in right hemisphere regions may be related to diagnostic subtype and treatment response.

A meta-analysis of resting-state fMRI studies reported evidence of decreased activity in ACC, dorsolateral PFC, insula, and superior temporal gyrus, with predominantly left-sided reductions, but bilateral hypoactivity in dorsolateral PFC (Fitzgerald et al., 2008). More recent fMRI studies of resting activity have, however, focused on functional connectivity within networks rather than single sites in the brain. Zhang et al. (2015) used pathway and network-based techniques to study resting functional connectivity in MDD and other disorders. In

depression, they found considerable evidence of reduced connectivity of right inferior orbitofrontal cortex with bilateral putamen, insula, and pallidum. They suggest that this may result in altered responses to negative emotional stimuli in depression. Moreover, they cite findings of overall reduction of functional connectivity between bilateral pairs of regions across the two hemispheres. Also, abnormal connectivity between regions may be produced by counterparts of pairs in the opposite hemisphere. These findings could be important for targeting treatments, including brain stimulation and neurofeedback. Dichter et al. (2015) reviewed resting-state fMRI studies with a focus on the relation of functional connectivity and treatment response in MDD. A consistent finding is that response to antidepressants is associated with increased connectivity between frontal and limbic brain regions, which may result in improved inhibitory control over neural circuits processing emotional information.

Other studies have measured glucose metabolism or regional cerebral blood flow in depressed patients during cognitive tasks. Two studies measuring fMRI during tasks tapping frontal executive functions reported evidence of reduced left PFC activity in depressed patients. Okada et al. (2003) measured performance and fMRI during a verbal fluency task, which is known to activate left prefrontal cortex. Depressed patients performed more poorly than controls and showed reduced left PFC activity. Also, Siegle et al. (2007) found reduced left dorsolateral PFC activity in patients having a unipolar MDD compared to healthy controls during a digit sorting task requiring executive cognitive control. Two prior studies, however, did not find left prefrontal hypoactivation in depressed patients during the Wisconsin Card Sorting Test (Berman et al., 1993) or a Stroop interference task (George et al., 1997). Also, Klumpp and Deldin (2010) reviewed behavioral and neuroimaging findings for verbal fluency. The majority of studies used phonemic fluency tasks, e.g., where subjects produce words beginning with a particular letter in one minute periods. Findings showed inconsistent performance deficits in depressed patients and the majority of phonemic fluency studies showed bilateral frontal lobe hypoactivation in depressed individuals. Differences in verbal fluency findings across studies may depend on the type of task. Klumpp and Deldin (2010) suggested that tasks requiring more rapid switching from one phenome to another, e.g., 30 s in the Okada et al. (2003) study compared to the typical 1 min period, may be more sensitive to left frontal deficits. Conflicting findings could also be related to diagnostic subtype and symptom severity. For instance, patients having a melancholic depression performed more poorly than those having an atypical depression in an animal naming fluency task (Lin et al., 2014). Similarly, in a study measuring multichannel near-infrared spectroscopy (NIRS) in a phonemic fluency task (Tsujii et al., 2014), patients having MDD with melancholic features had poorer performance than controls, but those with non-melancholic features did not. Moreover, regional hemodynamic increases during verbal fluency in frontal and temporal regions were smaller in patients than controls and those with melancholic features had smaller increases than those with non-melancholic features in the right temporal lobe region. Noda et al. (2012) also found reduced NIRS hemodynamic increases during verbal fluency in depressed patients than controls, and greater severity of depressive symptoms (HAM-D scale) was associated with less changes. Importantly, significant negative correlations were found between right frontotemporal changes and three individual HAM-D items (insomnia, psychomotor retardation, work and activity), which is consistent with other evidence suggesting that right temporal region dysfunction may be particularly evident in melancholic depression (Tsujii et al., 2014). Greater suicidal ideation was also found to be related with smaller hemodynamic increases during verbal fluency in right dorsolateral PFC and right frontopolar cortex (Pu et al., 2015).

Neuroimaging studies of depression have found lateralized alterations in PFC and other regions during emotional processing. In one of the first fMRI studies (Davidson et al., 2003), depressed patients showed less relative activation of left ACC and left insular compared to healthy controls in response to negative versus neutral pictures. Moreover, relatively greater activation in left ACC to negative versus neutral stimuli before treatment was associated with less severe depressive symptoms following treatment with the antidepressant venlafaxine. Grimm et al. (2008) found hypoactivity in the left dorsolateral PFC in patients with MDD during both unattended and attended emotional judgment of pictures, whereas hyperactivity of right dorsolateral PFC associated with *attention* to the emotional stimuli. They concluded that reduced left dorsolateral PFC activity in MDD is associated with emotional judgment rather than emotional perception or attention. Two meta-analyses agreed in finding less left dorsolateral PFC activity to negative emotions in patients having a MDD compared to controls (Diener et al., 2012; Groenewold et al., 2013). A different meta-analysis of neural responses to negative stimuli, however, found evidence of *bilateral* reduction of activity in dorsolateral PFC and increase of activity in the amygdala, insula, and dorsal ACC in MDD (Hamilton et al., 2012).

The role of the left PFC in downregulation of amygdala responses to negative emotional stimuli was observed when healthy individuals reappraise stimuli as less negative (Ochsner et al., 2002). Siegle et al. (2002) found a deficit in left dorsolateral PFC in MDD, which was related to the lack of reduction of amygdala activity over time. Using an affective reappraisal task, Johnstone et al. (2007) found left-lateralized activation of PFC in non-depressed individuals when downregulating negative affective stimuli, whereas depressed individuals showed bilateral PFC activation. Depressed individuals also failed to show an inverse relationship between activation of left ventrolateral PFC and the amygdala. Thus, hyperactivation of the right PFC and absence of left-lateralized PFC activity are involved in the emotional dysregulation in MDD. In a task involving positive emotion regulation, Light et al. (2011) found depressed individuals with lowest activity in right ventrolateral PFC when suppressing positive emotion showed greater reduction of anhedonia following antidepressant treatment. Rive et al. (2013) reviewed neuroimaging studies of emotional regulation in MDD in the context of a model proposed by Phillips et al. (2008). They cited evidence suggesting that MDD is associated with reduced activity in lateral PFC during voluntary emotional regulation. However, they referred to the lack of consistency of findings with nearly all studies using whole-brain analyses at relatively low significance thresholds, and they also argued that comorbidity with anxiety may be an important factor because corrections for comorbidity abolished the finding of decreased PFC and increased amygdala activity in MDD.

Studies have found that insula activity is associated with abnormal emotional and pain processing in patients having a MDD. In a meta-analysis of fMRI studies using affective processing tasks, youths (ages 4–24) having a MDD showed hypoactivity centered at the right posterior insula for positive emotion tasks, but hyperactivity of left dorsolateral PFC for negative emotion tasks (Miller et al., 2015). Meta-analyses of studies in adults with a MDD found reduced activity in the right insula during negative emotional processing (Diener et al., 2012) or in the right and left insula for positive emotions vs. neutral baseline (Groenewold et al., 2013). A separate report found patients having a MDD or anxiety disorder showed hypoactivity in the right hippocampus during positive vs. neutral word encoding, whereas only patients having a MDD showed hyperactivity in the left insula during negative vs. neutral word encoding (van Tol et al., 2012). Mutschler et al. (2012) found that pain, emotion and sensorimotor activity overlap within the right dorsal mid-anterior insula, suggesting that this site brings together information for emotional-cognitive evaluation of noxious stimuli. Disgust recognition has been found to be related to anterior insula activation (Woolley et al., 2015), and patients having a MDD showed marked impairment of facial disgust recognition, which was positively correlated with volume in the right and left anterior insula (Sprengelmeyer et al., 2011).

Reduced responsiveness to pleasant or rewarding stimuli has been found in depressed patients, which may be related to the symptom of

anhedonia (Pizzagalli et al., 2005). The striatum, consisting of the caudate, putamen and nucleus accumbens (NAcc), is thought to play a major role in hedonic processing. Pizzagalli et al. (2009) found reduced responsiveness to rewards in bilateral caudate, left putamen and left NAcc, and a meta-analysis by Diener et al. (2012) reported hypoactivation of the right caudate during processing of pleasant stimuli in depressed patients. Reduced activity of the right caudate during positive emotion perception was also found in a study of treatment resistant patients having a MDD (Murrough et al., 2015). Importantly, treatment with the NMDA receptor antagonist Ketamine selectively increased activity of the right caudate. Connolly et al. (2015) measured fMRI in women having a MDD (n = 51) and healthy controls (n = 61) to emotional stimuli varying in valence. Across groups and valence types, the right caudate showed greater activation than the left, but there was greater activation of the left than right putamen and NAcc. Depressed patients showed overall reduced activity in all sub-regions of the striatum compared to controls, but this did not depend on valence or hemisphere.

In summary, structural MRI studies have reported evidence of smaller hippocampal and anterior insula volume in MDD. Although right-lateralized in some studies, this appears to depend on factors such as illness duration, recurrences of episodes, or comorbidity with anxiety. Resting-state PET studies have found reduced left PFC metabolism in MDD, and a recent resting-state fMRI study found reduced functional connectivity between regions within the right hemisphere, and also between hemispheres. Reduced left PFC activation during cognitive or emotional processing has been found in MDD, which may result in reduced downregulation of amygdala response to negative emotion stimuli. Studies have found reduced activation of the insula to emotional stimuli in MDD, predominantly on the right side, and reduced activation of the striatum to pleasant or rewarding stimuli, with laterality depending on sub-regions within the striatum. Although Zotev et al. (2016) found that laterality of amygdala activity in MDD was positivity related to EEG measures of frontal asymmetry, the relation of asymmetric activity in the insula and striatum to asymmetries in frontal and parietotemporal cortical regions has received little attention. Studies measuring NIRS in depressed patients during phonemic fluency tasks have found deficits in right temporal lobe activation, which were greatest in patients having a melancholic depression and in those with greater severity of melancholic or suicidal symptoms. Inconsistent findings may be related to use of whole-brain analyses in neuroimaging studies, and differences in diagnostic subtype, comorbidity with anxiety, or severity of depressive symptoms in patients in different studies.

6. Conclusions

Studies using dichotic listening, visual hemifield, electrophysiological, and neuroimaging (PET, fMRI, NIRS) measures have found abnormalities of right-left asymmetries of brain function in depressive disorders. The bulk of evidence across studies using these diverse measures is consistent with reductions of left frontal and right parietotemporal function in depressive disorders. Relatively less left than right frontal activity in depression is in accordance with valence or approach/withdrawal models (Coan and Allen, 2003; Davidson, 1998). To account for the relative reduction of right parietotemporal activity in depression, Heller et al. (1995) expanded this model to include not only frontal asymmetry related to emotional valence, but also right parietal activity related to the arousal component of emotion. The findings reviewed here are generally in line with these models and support the need include the role of right parietotemporal dysfunction in depressive disorders. EEG evidence of decreased left frontal or right parietal activity has also been related to familial risk for development of depressive disorders. Moreover, individual differences in right-left asymmetries have been reported to predict clinical response to treatments for depression. There have, however, been conflicting findings, which appear to be related to differences in clinical features of patients (most notably, comorbidity with anxiety, diagnostic subtype, severity of depressive symptoms), gender, and methodological issues (including sample size, differences in resting or cognitive/emotional tasks, or specifics of EEG or fMRI procedures).

Recent electrophysiological (EEG, ERP) and fMRI studies have led to real progress in understanding the involvement of left frontal and right posterior regions in modulating emotional processing and regulation in patients having MDD. We reviewed new evidence for a network of left PFC and limbic (amygdala) regions of key importance for cognitive regulation of negative emotions, and a network of right occipital-parietal-temporal regions involved in emotional perception and directing attention to salient stimuli. These findings have important clinical implications for targeting of treatments, in particular brain stimulation and neurofeedback training, to reduce depression and improve cognitive and emotional processing in depressive disorders.

Evidence of relatively less left than right frontal activity in MDD has come from studies measuring EEG, metabolism or rCBF at rest or during cognitive or emotional processing. This is not, however, specific to depression but is also seen in anxiety disorders (such as panic disorder and social phobia). It may therefore be related not only to reduction of positive affect or approach-related behaviors associated with left frontal cortex, but also increased anxious arousal or withdrawal-related behaviors associated with the right hemisphere. Findings of less left than right frontal activity in depressed patients have been more consistent during emotionally challenging tasks than in resting state. Neuroimaging evidence for the role of dorsolateral PFC in emotional regulation supports the hypothesis that reduced left frontal activity in MDD may be responsible for decreased downregulation of negative affect. Indeed, increasing left frontal activity using repetitive transcranial magnetic stimulation (rTMS) is used in treating depression (Triggs et al., 2010; Nadeau et al., 2014; Vanderhasselt et al., 2015). Moreover, using frontal alpha asymmetry (Allen and Reznik, 2015) or fMRI (Zotev et al., 2016) neurofeedback training designed to increase left frontal or amygdala activity has had success in reducing depression. Also, CBT for depression, which involves self-monitoring or regulation of negative thoughts or emotions, may be mediated, in part, by verbal skills for which the left frontal and temporal cortex is dominant (Otto et al., 1997; Price et al., 2013; Silvers et al., 2015). This is supported by pupil measures associated with left dorsolateral PFC reactivity being predictive of response to CBT (Siegle et al., 2011) and greater left hemisphere advantage for verbal dichotic listening in patients who respond to CBT for depression (Bruder et al., 2017; Kishon et al., 2015).

Although there are conflicting findings and the mechanism underlying relatively less left than right frontal activity in MDD is not well understood, recent findings suggest a theoretical model in which left dorsolateral PFC hypoactivity is associated with reduced downregulation of negative emotions. There is considerable evidence that frontal regions normally act to regulate emotional processing in the amygdala. Reduced left dorsolateral PFC activity in MDD may hinder the downregulation of negative emotions and upregulation of positive emotions. This hypothesis received additional support in a recent study that involved simultaneous measurement of EEG and fMRI during neurofeedback (Zotev et al., 2016). Relatively higher left amygdala activity during happy emotion induction was associated with EEG evidence of greater left than right frontal activity indicative of stronger approach motivation. Their findings suggest that the link between left frontal and left amygdala activity is critical for emotional regulation. Also, fMRI studies indicate that increased functional connectivity between frontal and limbic structures is associated with favorable response to antidepressants (Dichter et al., 2015). Studies have also found reduction of activity in the striatum to emotional stimuli in MDD, but laterality varied depending on emotional valence and sub-regions of the striatum. Although further study is needed concerning the relation of asymmetries of the striatum and frontal activity, it is tempting to speculate that reduced left frontal activity in MDD is associated with decreased

response of striatum to rewards and positive stimuli.

Less right hemisphere advantage for the perception of non-verbal and emotional stimuli in patients having unipolar or bipolar depressive disorders was found in studies using dichotic listening and visual hemifield paradigms. In addition, electrophysiological studies measuring resting EEG or ERPs to non-verbal and emotional stimuli have provided evidence of reduced right parietotemporal activity in depressed patients. The *opposite* asymmetry indicative of relatively greater right than left parietotemporal activity was found for anxiety disorders, which could counteract the asymmetry associated with depression in patients having comorbidity of these disorders. Evidence of reduced right hemisphere advantage for processing non-verbal stimuli in dichotic listening and visual tasks was most evident in patients having a melancholic depression and absent in patients having an atypical depression. Although less evidence has come from neuroimaging studies, some studies have found reduced metabolism or perfusion of right frontotemporal regions in depressed patients, which was related to diagnostic subtype, severity of depressive symptoms or response to treatments for depression. In particular, studies measuring NIRS found that deficits in right temporal lobe activity in depressed patients during verbal fluency tasks were most evident in melancholic depression and were related to severity of melancholic symptoms and suicidal ideation.

Individuals having a MDD show marked deficits in emotion recognition for faces (Dalili et al., 2015) and for emotional intonation (prosody) in the auditory domain (Bruder et al., 2015). Affective prosody processing has been found to be strongly lateralized to right hemisphere regions in auditory cortex and amygdala (Fröhholz et al., 2016). In addition to behavioral evidence of right parietotemporal deficits in MDD for emotional processing, studies have found reduced ERPs to emotional stimuli over right posterior sites in individuals with family history of MDD or with a lifetime history of MDD (Kayser et al., 2000; Kayser et al., 2017; Moratti et al., 2008; Moratti et al., 2015). These ERP studies have the distinct advantage of not only providing direct measures of hemispheric asymmetry but also for the fine temporal resolution of these measures. The recent findings of Kayser et al. (2017) suggest a theoretical model for reduced right hemisphere processing of emotional stimuli in MDD, involving consecutive stages of motivated attention. An early right-lateralized deficit begins around 200 ms after onset of negative stimuli with reduced emotional responsivity in occipitotemporal cortex (N2), and subsequently involves posterior cingulate cortex (around 400 ms; P3) and later positive potential (around 600 ms) in inferior temporal and insula sites. Studies measuring fMRI have found evidence suggesting that the right anterior insula is involved in emotional-cognitive evaluation of noxious stimuli (Mutschler et al., 2012), and hypoactivation of the right insula has been reported in patients having a MDD during the processing of negative or positive stimuli (Diener et al., 2012; Groenwold et al., 2013; Miller et al., 2015). These right hemisphere regions may be critical for allocating attentional resources to motivationally salient stimuli, which is of importance for emotional perception and social interactions.

EEG and neuroimaging studies measuring functional connectivity have provided additional evidence of networks for emotional processing, which are dysfunctional in MDD. Most notably, an fMRI study found reduced functional connectivity in MDD between right inferior orbitofrontal cortex and bilateral putamen and insula, which are part of a network thought to regulate responses to negative emotional stimuli (Zhang et al., 2015). Moreover, they found reduced connectivity in MDD between homologous regions across the right and left hemisphere, pointing to the need for more studies of interhemispheric connectivity. The importance of frontocingulate regions in depressive disorders, in particular the rostral ACC, has received considerable support (Pizzagalli, 2011). In a study measuring both resting EEG and PET (Pizzagalli et al., 2003), current density of theta rhythm in the rostral ACC was associated with glucose metabolism in this region. Importantly, theta current density in healthy adults was positively correlated between rostral ACC and regions within the prefrontal and orbitofrontal cortices, particularly in the right hemisphere. The rostral ACC is known to be involved in emotional processing and is a hub of the default mode network (DMN), which includes the rostral ACC, posterior cingulate, lateral parietal and temporal regions, and the hippocampus. Pizzagalli (2011) reviewed EEG and neuroimaging findings of a relationship between greater rostral ACC activity and response to treatments for depression, and also findings suggesting that frontocingulate dysfunction may contribute to affective and cognitive abnormalities in MDD. The frontocingulate region may be part of a larger right-lateralized network, involving frontocengulate, posterior cingulate, temporal (insula), and parietooccipital regions involved in top-down inhibiting of negative information and emotional regulation.

Dichotic listening, EEG, and PET findings support the potential value of these measures for predicting clinical response to antidepressants. Patients who respond to a SSRI antidepressant had greater left hemisphere advantage for verbal dichotic listening than non-responders, which was most evident in depressed women (Bruder et al., 1996, 2004b). Enhanced left hemisphere advantage for verbal dichotic listening was not, however, specific for predicting response to a SSRI antidepressant. Three studies agreed in finding greater left hemisphere advantage in CBT responders than non-responders for verbal tests, which suggests that this may be prognostic of favorable response to CBT or antidepressant treatments (Bruder et al., 2017; Kishon et al., 2015). One PET study found glucose metabolism in the right insula to *differentially* predict response to CBT as opposed to an SSRI antidepressant (McGrath et al., 2013). EEG alpha asymmetry was found in some but not all studies to be associated with response to antidepressants. Although these studies included small samples, a multi-site iSPOT-D study with larger samples confirmed an earlier finding of a difference in EEG alpha asymmetry between responders and non-responders to a SSRI antidepressant, with less right than left frontal activity in responders than non-responders (Arns et al., 2015; Bruder et al., 2001). This was specific to depressed women in both studies, which underscores the importance of gender in this context. Gender has been found to play a role not only in alpha asymmetry findings for depressed patients and individuals at risk for depression, but also for dichotic listening predictors of response to antidepressants. Larger samples in multi-site studies will be particularly important for confirming these findings. One weakness in prior studies examining predictors of treatment response has been the failure to include a placebo control condition to differentiate between predictors of true drug response vs. placebo response. An ongoing multi-site EMBARC project (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) does include a placebo treatment condition and will provide an additional opportunity to assess the value of EEG alpha asymmetry, in combination with other electrophysiological, MRI, and neurocognitive measures, as mediators or predictors of clinical response to antidepressants (Trivedi et al., 2016).

Although gender differences can be difficult to replicate and are often not examined, particularly in studies with relatively small samples, there has been consistency in gender differences in laterality findings for depression. Differences in dichotic listening or EEG alpha asymmetry between responders and non-responders to a SSRI antidepressant, as well as between individuals with vs. without family history of MDD, were more evident among females than males. Also, greater severity of depressive symptoms was associated with reduced right hemisphere bias for chimeric faces among females, but not males. Gender differences in cognitive function and hemispheric organization could play an important role. Heller (1993) reviewed evidence that females tend to perform better on verbal tests and favor verbal strategies, whereas males tend to perform better on spatial tasks and favor nonverbal strategies. She suggested that the tendency to activate the left as opposed to right hemisphere among females may be associated with a neuropsychological vulnerability toward depression. She also referred to studies finding gender differences in neurotransmitter response involving serotonin, which suggests that serotonin

plays an important role in gender differences in psychiatric disorders and in laterality findings for depression, particularly those predicting response to SSRI antidepressants. Also, a meta-analysis of neuroimaging studies indicated that the majority of gender differences in brain activation to emotional stimuli favoring women were found for negative emotions (Stevens and Hamann, 2012). The greater activation of the left amygdala to negative emotion stimuli agrees with evidence that women respond more strongly to negative emotion stimuli, which may be linked to increased risk of MDD among women (Weissman et al., 1984).

Another subject characteristic that might modulate laterality findings in depression is handedness. The prevalence of left handedness is small (10–15%) and most studies reviewed in this report were limited to right handers, which makes it impossible to examine the role of handedness. We did not find a difference between depressed patients and healthy controls (Bruder et al., 2004a) or between treatment responders and non-responders (Bruder et al., 2004b; Bruder et al., 1997b; Kishon et al., 2015) in the strength of handedness on the Edinburgh Inventory. Although it is therefore unlikely that handedness impacted on laterality findings, further study in large samples including both right and left handers is needed to address this issue, and determine whether or not the laterality findings generalize to left handers.

Further studies are needed concerning the value of behavioral and neurophysiological measures of right-left asymmetry as biomarkers for differentiating subtypes of depression and personalizing treatment for depression, and also to uncover the neural mechanisms underlying these measures. A weakness of asymmetry measures is that it is often not clear whether abnormalities are due to hypoactivation (dysfunction) in one hemisphere, hyperactivation in the other hemisphere, or a deficit in interhemispheric connectivity. There is a need for converging evidence from behavioral, electrophysiological and fMRI measures obtained in the same patients and controls during the same tasks, which has rarely been the case in existing studies. Also, greater attention should be given in fMRI studies to directly examine differences in activation across homologous sites in right and left brain, and also to measure asymmetries during emotional processing tasks, ideally when stimuli are presented to either the left or right hemifield, rather than merely at midline. Most critically, translational studies of animal models of depression should examine asymmetries of brain regions known to be important for depression and mechanisms of antidepressants action. This was nicely illustrated by two recent studies in rats. Gordon and Goelman (2016) measured neural connectivity of the raphe nucleus in a chronic mild stress (CMS) model of depression. Exposure to 5 weeks of CMS resulted in behaviors thought to reflect anhedonia or depression. Connectivity was reduced in CMS rats suggesting overall reduction of excitability in the raphe, and these reductions were predominantly found in the right hemisphere, providing evidence of its importance in depression. Given the key role of the raphe nucleus in the serotonin neurotransmitter system, it could also provide a model for relating right-left asymmetry to response to SSRI antidepressants. To address the lack of translational studies on the approach-withdrawal model of emotion and brain lateralization, Farhang et al. (2014) studied hemispheric asymmetry in gene expression in rats using CMS and sucrose consumption to identify anhedonic and stress-resilient rats. RNA was extracted from right and left frontotemporal cortex. *BDNF* and *NTRK-3* were expressed at lower levels in right brains of anhedonic compared to stress-resilient rats, with upregulation in the right compared to left brain for BDNF only in stress-resilient rats. Given the importance of frontotemporal cortex to the model of approach-withdrawal motivation, these findings underscore the value of further translational studies to determine the underlying mechanism of emotional processing asymmetry and its disturbance in MDD. Additional electrophysiological and fMRI studies of functional connectivity between cortical and subcortical regions within each hemisphere and also between right and left hemisphere regions are also needed (e.g., see Fischer et al., 2016; Zhang et al., 2015), so as to identify neural circuitry underlying dysfunctions of right and left brain function in depressive disorders.

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References

Abrams, R., Redfield, J., Taylor, A., 1981. Cognitive dysfunction in schizophrenia, affective disorder and organic brain disease. Brit. J. Psychiatry 139, 190–194.
Alhaj, H., Wisniewski, G., McAllister-Williams, R.H., 2011. The use of the EEG in measuring therapeutic drug action: focus on depression and antidepressants. J. Psychopharmacol. 25, 1175–1191.
Allen, J.J.B., Reznik, S.J., 2015. Frontal EEG asymmetry as a promising marker of depression vulnerability: summary and methodological considerations. Curr. Opin. Psychol. 4, 93–97.
Allen, J.J.B., Urry, H.L., Hitt, S.K., Coan, J.A., 2004. The stability of resting frontal electroencephalographic asymmetry in depression. Psychophysiology 41, 269–280.
Arns, M., Bruder, G., Hegerl, U., Spooner, C., Palmer, D.M., Etkin, A., Fallahpour, K., Gatt, J.M., Hirshberg, L., Gordon, E., 2016. EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. Clin. Neurophysiol. 127, 509–519.
Asbjörnsen, A., Hugdahl, K., Bryden, M.P., 1992. Manipulations of subjects' level of arousal in dichotic listening. Brain Cogn. 19, 183–194.
Baxter, L., Phelps, M., Massiotta, J., 1985. Cerebral metabolic rates for glucose in mood disorders. Arch. Gen. Psychiatry 42, 44–447.
Baxter, L.R., Schwartz, J.M., Phelps, M.E., Mazziota, J.C., Guze, B.H., Selin, C.E., Gerner, R.H., Sumida, R.M., 1989. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch. Gen. Psychiatry 46, 243–250.
Beauregard, M., Paquette, V., Le, J., 2006. Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. Neuroreport 17, 843–846.
Bench, C.J., Friston, K.F., Brown, R.G., Frackowiak, R.S., Dolan, R.J., 1993. Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. Psychol. Med. 23, 579–590.
Berman, K.F., Doran, A.R., Pickar, D., Weinberger, D.R., 1993. Is the mechanism of prefrontal hypofunction in depression the same as in schizophrenia? Br. J. Psychiatry 162, 183–192.
Blackhart, G.C., Minnix, J.A., Kline, J.P., 2006. Can EEG asymmetry patterns predict future development of anxiety and depression? A preliminary study. Biol. Psychol. 72, 46–50.
Bora, E., Fornito, A., Pantclis, C., Yücel, M., 2012. Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. J. Affect. Disord. 138, 9–18.
Bourne, V.J., 2005. Lateralized processing of positive facial emotion: sex differences in strength of hemispheric dominance. Neuropsychologia 43, 953–956.
Bourne, V.J., Vladeanu, M., 2013. Examining the relationship between lateralization for processing emotional faces depression, and sex. Laterality 18, 748–766.
Bruder, G.E., 2003. Frontal and parietotemporal asymmetries in depressive disorders: behavioral, electrophysiologic and neuroimaging findings. In: Hugdahl, K., Davidson, R.J. (Eds.), The Asymmetrical Brain. MIT Press, Cambridge, MA, pp. 719–742.
Bruder, G.E., Alvarenga, J., Abraham, K., Skipper, J., Warner, V., Voyer, D., Peterson, B.S., Weissman, M.M., 2016. Brain laterality, depression and anxiety disorders: new findings for emotional and verbal dichotic listening in individuals at risk for depression. Laterality 21, 525–548. http://dx.doi.org/10.1080/1357650X.2015.1105247.
Bruder, G.E., Alvarenga, J.E., Alschuler, D., Abraham, K., Keilp, J.G., Hellerstein, D.J., Stewart, J.W., McGrath, P.J., 2014. Neurocognitive predictors of antidepressant clinical response. J. Affect. Disord. 166, 108–114.
Bruder, G.E., Bansal, R., Tenke, C.E., Liu, J., Hao, X., Warner, V., Peterson, B.S., Weissman, M.M., 2012a. Relationship of resting EEG with anatomical MRI measures in individuals at high and low risk for depression. Hum. Brain Mapp. 33, 1325–1333.
Bruder, G.E., Fong, R., Tenke, C.E., Leite, P., Towey, J.P., Stewart McGrath, P.J., Quitkin, F.M., 1997a. Regional brain asymmetries in major depression with or without an anxiety disorder: a quantitative electroencephalographic study. Biol. Psychiatry 41, 939–948.
Bruder, G.E., Haggerty, A., Siegle, G.J., 2017. A quick behavioral dichotic word test is prognostic for clinical response to cognitive therapy for depression. A replication study. Psychiatry Res. 248, 13–19.
Bruder, G.E., Otto, M.W., McGrath, P.J., Stewart, J.W., Fava, M., Rosenbaum, J.F., Quitkin, F.M., 1996. Dichotic listening before and after fluoxetine treatment for major depression: relations of laterality to therapeutic response. Neuropsychopharmacology 15, 171–179.
Bruder, G.E., Quitkin, F.M., Stewart, J.W., Martin, C., Voglmaier, M.M., Harrison, W.M., 1989. Cerebral laterality and depression: differences in perceptual asymmetry among diagnostic subtypes. J. Abnorm. Psychol. 98, 177–186.
Bruder, G.E., Schneier, F.R., Stewart, J.W., McGrath, P.J., Quitkin, F., 2004a. Left hemisphere dysfunction during verbal dichotic listening tests in patients who have social phobia with or without comorbid depressive disorder. Am. J. Psychiatry 161, 72–78.

Bruder, G.E., Sedoruk, J.P., Stewart, J.W., McGrath, P.J., Quitkin, F.M., Tenke, C.E., 2008. Electroencephalographic alpha measures predict therapeutic response to a selective serotonin reuptake inhibitor antidepressant: pre- and post-treatment findings. Biol. Psychiatry 63, 1171–1177.
Bruder, G.E., Stewart, J.W., Hellerstein, D., Alvarenga, J.E., Alschuler, D., McGrath, P.J., 2012b. Abnormal functional brain asymmetry in depression: evidence of biologic commonality between major depression and dysthymia. Psychiatry Res. 196, 250–254.
Bruder, G.E., Stewart, J.W., McGrath, P.J., Deliyannides, D., Quitkin, F.M., 2004b. Dichotic listening tests of functional brain asymmetry predict response to fluoxetine in depressed women and men. Neuropsychopharmacology 29, 1752–1761.
Bruder, G.E., Stewart, J.W., McGrath, P.J., Ma, G.J., Wexler, B.E., Quitkin, F.M., 2002. Atypical depression: enhanced right hemispheric dominance for perceiving emotional chimeric faces. J. Abnorm. Psychol. 111, 446–454.
Bruder, G.E., Stewart, J.W., Mercier, M.A., Agosti, V., Leite, P., Donovan, S., Quitkin, F.M., 1997b. Outcome of cognitive-behavioral therapy for depression: relation of hemispheric dominance for verbal processing. J. Abnorm. Psychol. 106, 138–144.
Bruder, G.E., Stewart, J.W., Schaller, J.D., McGrath, P.J., 2007a. Predicting therapeutic response to secondary treatment with bupropion: dichotic listening tests of functional brain asymmetry. Psychiatry Res. 15, 137–143.
Bruder, G.E., Stewart, J.W., Tenke, C.E., McGrath, P.J., Leite, P., Bhattacharya, N., Quitkin, F.M., 2001. Electroencephalographic and perceptual asymmetry differences between responders and nonresponders to an SSRI antidepressant. Biol. Psychiatry 49, 416–425.
Bruder, G.E., Stewart, J.W., Towey, J.P., Friedman, D., Tenke, C.E., Voglmaier, M.M., Leite, P., Cohen, P., Quitkin, F.M., 1992. Abnormal cerebral laterality in bipolar depression: convergence of behavioral and brain event-related potential findings. Biol. Psychiatry 32, 33–47.
Bruder, G.E., Stewart, J.W., Voglmaier, M.M., Harrison, W.M., McGrath, P., Tricamo, E., Quitkin, F.M., 1990. Cerebral laterality and depression: relations of perceptual asymmetry to outcome of treatment with tricyclic antidepressants. Neuropsychopharmacology 3, 1–10.
Bruder, G., Sutton, S., Berger-Gross, P., Quitkin, F., Davies, S., 1981. Lateralized auditory processing in depression: dichotic click detection. Psychiatry Res. 4, 253–266.
Bruder, G.E., Tenke, C.E., Kayser, J., 2013. Electrophysiological predictors of clinical response to antidepressants. In: Mann, J.J., McGrath, J.P., Roose, S.P. (Eds.), The Clinical Handbook for the Management of Mood Disorders. Cambridge University Press, New York, pp. 380–393.
Bruder, G.E., Tenke, C.E., Stewart, J.W., Towey, J.P., Leite, P., Voglmaier, M., Quitkin, F.M., 1995. Brain event-related potentials to complex tones in depressed patients: relations to perceptual asymmetry and clinical features. Psychophysiology 32, 373–381.
Bruder, G., Tenke, C.E., Towey, J.P., Leite, P., Fong, R., Stewart, J.E., McGrath, P.J., Quitkin, F.M., 1998. Brain ERPs of depressed patients to complex tones in an oddball task: relation of reduced P3 asymmetry to physical anhedonia. Psychophysiology 35, 54–63.
Bruder, G.E., Tenke, C.E., Warner, V., Nomura, Y., Grillon, C., Hille, J., Leite, P., Weissman, M.M., 2005. Electroencephalographic measures of regional hemispheric activity in offspring at risk for depressive disorders. Biol. Psychiatry 57, 328–335.
Bruder, G.E., Tenke, C.E., Warner, V., Weissman, M.M., 2007b. Grandchildren at high and low risk for depression differ in EEG measures of regional brain asymmetry. Biol. Psychiatry 62, 1317–1323.
Bruder, G.E., Wexler, B.E., Stewart, J.W., Price, L.H., Quitkin, F.M., 1999. Perceptual asymmetry differences between major depression with or without a comorbid anxiety disorder: a dichotic listening study. J. Abnorm. Psychol. 108, 233–239.
Bryden, M.P., 1982. Laterality: Functional Asymmetry in the Intact Brain. Academic Press, New York.
Bryden, M.P., MacRae, L., 1989. Dichotic laterality effects obtained with emotional words. Neuropsychiatry Neuropsychol. Behav. Neurol. 1, 171–176.
Cacioppo, J.T., Crites, S.L., Berntson, G.G., Coles, M.G., 1993. If attitudes affect how stimuli are processed, should they not affect the event-related brain potential? Psych. Sci. 4, 108–112.
Coan, J.A., Allen, J.J.B., McKnight, P.E., 2006. A capability model of individual differences in frontal EEG asymmetry. Biol. Psychol. 72, 198–207.
Coan, J.A., Allen, J.J.B., 2003. Frontal EEG asymmetry and the behavioral activation and inhibition systems. Psychophysiology 40, 106–114.
Cole, J., Costafreda, S.G., McGuffin, P., Fu, C.H., 2011. Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. J. Affect. Disord. 134, 483–487.
Connolly, M.E., Gollan, J.K., Cobia, D., Wang, X., 2015. Reduced striatal activation in females with major depression during the processing of affective stimuli. J. Psychiatr. Res. 68, 384–391.
Cook, I.A., O'Hara, R., Uijtdehaage, S.H.J., Mandelkern, M., Leuchter, A.F., 1998. Assessing the accuracy of topographic EEG mapping for determining local brain function. Electroencephalogr. Clin. Neurophysiol. 107, 408–414.
Costafreda, S.G., Chu, C., Ashburner, A., Fu, C.H., 2009. Prognostic and diagnostic potential of the structural neuroanatomy of depression. PloS One 4, e6353. http://dx.doi.org/10.1371/journal.pone.0006353.
Cotrena, C., Branco, L.D., Shansis, F.M., Fonseca, R.P., 2016. Executive function impairments in depression and bipolar disorder: association with functional impairment and quality of life. J. Affect. Disord. 190, 744–753.
Dalili, M.N., Penton-Voak, I.S., Harmer, C.J., Munafò, M.R., 2015. Meta-analysis of emotion recognition deficits in major depressive disorder. Psychol. Med. 45, 1135–1144.
David, A.S., Cutting, J.C., 1990. Affect, affective disorder and schizophrenia: A neuropsychological investigation of right hemisphere function. Br. J. Psychiatry 156, 491–495.
Davidson, R.J., 1998. Affective style and affective disorders: perspectives from affective neuroscience. Cogn. Emot. 12, 307–330.
Davidson, R.J., Chapman, J.P., Chapman, L.J., 1987. Task-dependent EEG asymmetry discriminates between depressed and non-depressed subjects. Psychophysiology 24, 585.
Davidson, R.J., Irwin, W., Anderle, M.J., Kalin, N.H., 2003. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am. J. Psychiatry 160, 64–75.
Davidson, R.J., Marshall, J.R., Tomarken, A.J., Henriques, J.B., 2000. While a phobic waits: regional brain electrical and autonomic activity in social phobics during anticipation of public speaking. Biol. Psychiatry 47, 85–95.
Dawson, G., Frey, K., Panagiotides, H., Osterling, J., Hessl, D., 1997. Infants of depressed mothers exhibit atypical frontal brain activity: a replication and extension of previous findings. J. Child Psychol. Psychiatry 38, 179–186.
Dawson, G., Klinger, L.G., Panagiotides, H., Hill, D., Spieker, S., 1992. Frontal lobe activity and affective behavior of infants of mothers with depressive symptoms. Child Dev. 63, 725–737.
Debener, S., Beauducel, A., Nessler, D., Burkhand, B., Heilemann, H., Kayser, J., 2000. Is resting anterior EEG alpha asymmetry a trait marker for depression? Findings for healthy adults and clinically depressed patients. Neuropsychobiology 41, 31–37.
Deldin, P.J., Keller, J., Gergen, J.A., Miller, G.A., 2000. Right-posterior face processing anomaly in depression. J. Abnorm. Psychol. 109, 116–121.
Dichter, G.S., Gibbs, D., Smoski, M.J., 2015. A systematic review of relations between resting-state functional- MRI and treatment response in major depressive disorder. J. Affect. Disord. 172, 8–17.
Diego, M.A., Field, T., Jones, N.A., Hernandez-Reif, M., 2006. Withdrawn and intrusive maternal interaction style and infant frontal EEG asymmetry shifts in infants of depressed and non- depressed mothers. Infant Behav. Dev. 29, 220–229.
Diener, C., Kuehner, C., Brusniak, W., Ubl, B., Wessa, M., Flor, H., 2012. A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. Neuroimage 61, 677–685.
Ehlers, C.L., Wall, T.L., Garcia-Andrade, C., Phillips, E., 2001. EEG asymmetry: Relationship to mood and risk for alcoholism in Mission Indian youth. Biol. Psychiatry 50, 129–136.
Farhang, S., Barar, J., Fakhari, A., Mesgariabbasi, M., Khani, S., Omidi, Y., Farnam, A., 2014. Asymmetrical expression of BDNF and NTRK3 genes in frontoparietal cortex of stress-resilient rats in an animal model of depression. Synapse 68, 387–393.
Feige, B., Scheffler, K., Esposito, F., Di Salle, F., Henning, J., Seifritz, E., 2005. Cortical and subcortical correlates of electroencephalographic alpha rhythm modulation. J. Neurophysiol. 93, 2864–2872.
Field, T., Diego, M., 2008. Maternal depression effects on infant frontal EEG asymmetry. Int. J. Neurosci. 118, 1081–1108.
Field, T., Pickens, J., Fox, N.A., Gonzalez, J., Nawrocki, T., 1998. Facial expression and EEG responses to happy and sad faces/voices by 3-month-old infants of depressed mothers. Br. J. Dev. Psychol. 16, 485–494.
Fischer, A.S., Corey, J.K., Etkin, A., 2016. The clinical applicability of functional connectivity in depression: Pathways toward more targeted intervention. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 1, 262–270.
Fitzgerald, P.B., Laird, A.R., Maller, J., Daskalakis, Z.J., 2008. A meta-analytic study of changes in brain activation in depression. Hum. Brain Mapp. 29, 683–695.
Flor-Henry, P., 1976. Lateralized temporal-limbic dysfunction and psychopathology. Ann. N. Y. Acad. Sci. 280, 777–795.
Fountoulakis, K.N., Iacovides, A., Gerasimou, G., Fotiou, F., Ioannidou, C., Bascialla, F., Grammaticos, P., Kaprinis, G., 2004. The relationship of regional cerebral blood flow with subtypes of major depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 28, 537–546.
Fromm-Auch, D., 1983. Neuropsychological assessment of depressed patients before and after drug therapy: clinical profile interpretation. In: Flor-Henry, P., Gruzelier, J. (Eds.), Laterality and Psychopathology. Elsevier Science Publishers, Amsterdam, pp. 83–102.
Frühholz, S., Trost, W., Kotz, S.A., 2016. The sound of emotions—towards a unifying neural network perspective of affective sound processing. Neurosci. Biobehav. Rev. 68, 1–15.
Gadea, M., Espert, R., Salvador, A., Martí-Bonmatí, L., 2011. The sad, the angry, and the asymmetrical brain: dichotic listening studies of negative affect and depression. Brain Cogn. 76, 294–299.
George, M.S., Ketter, T.A., Parekh, P.I., Rosinsky, N., Ring, H.A., Pazzaglia, P.J., Marangell, L.B., Callahan, A.M., Post, R.M., 1997. Blunted left cingulate activation in mood disorder subjects during a response interference task (the Stroop). J. Neuropsychiatry Clin. Neurosci. 9, 55–63.
Gold, C., Fachner, J., Erkkila, J., 2013. Validity and reliability of electroencephalographic frontal alpha asymmetry and frontal midline theta as biomarkers for depression. Scand. J. Psychol. 54, 118–126.
Gordon, N., Goelman, G., 2016. Understanding alterations in serotonin connectivity in a rat model of depression within the monoamine-deficiency and the hippocampal-neurogenesis frameworks. Behav. Brain Res. 296, 141–148.
Gotlib, I.H., Ranganath, C., Rosenfeld, P., 1998. Frontal EEG alpha asymmetry, depression, and cognitive functioning. Cogn. Emot. 12, 449–478.
Grimm, S., Beck, J., Schuepbach, D., Hell, D., Boesiger, P., Bermpohl, F., Niehaus, L., Boeker, H., Northoff, G., 2008. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol. Psychiatry 63, 369–376.
Groenewold, N.A., Opmeer, E.M., de Jonge, P., Aleman, A., Costafreda, S.G., 2013. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. Neurosci. Biohav. Rev. 37, 152–163.

Hamilton, J.P., Etkin, A., Furman, D.J., Lemus, M.G., Johnson, R.F., Gotlib, I.H., 2012. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. Am. J. Psychiatry 169, 693–703.
Harmon-Jones, E., Gable, P.A., Peterson, C.K., 2010. The role of asymmetric frontal cortical activity in emotion-related phenomena: a review and update. Biol. Psychol. 84, 451–462.
Heller, W., 1993. Gender differences in depression: perspectives from neuropsychology. J. Affect. Disord. 29, 129–143.
Heller, W., Etienne, M.A., Miller, G.A., 1995. Patterns of perceptual asymmetry in depression and anxiety: Implications for neuro-psychological models of emotion and psychopathology. J. Abnorm. Psychol. 104, 327–333.
Heller, W., Nitschke, J.B., 1998. The puzzle of regional brain activity in depression and anxiety: The importance of subtypes and comorbidity. Cogn. Emot. 12, 421–447.
Henriques, J.B., Davidson, R.J., 1990. Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects. J. Abnorm. Psychol. 99, 22–31.
Henriques, J.B., Davidson, R.J., 1991. Left frontal hypoactivation in depression. J. Abnorm. Psychol. 100, 535–545.
Hugdahl, K., Davidson, R.J., 2003. The Asymmetrical Brain. MIT Press, Cambridge, MA.
Hugdahl, K., Rund, B.R., Lund, A., Asbjørnsen, A., Egeland, J., Landrø, N.I., Roness, A., Sundet, K., 2003. Attentional and executive dysfunctions in schizophrenia and depression: Evidence from dichotic listening performance. Biol. Psychiatry 53, 609–616.
Ischebeck, M., Endrass, T., Simon, D., Kathmann, N., 2014. Altered frontal EEG asymmetry in obsessive- compulsive disorder. Psychophysiology 51, 596–601.
Jaeger, J., Borod, J.C., Peselow, E., 1987. Depressed patients have atypical biases in the perception of emotional chimeric faces. J. Abnorm. Pyschol. 96, 321–324.
Jaworska, N., Yücel, K., Courtright, A., MacMaster, F.P., Sembo, M., MacQueen, G., 2016. Subgenual anterior cingulate cortex and hippocampal volumes in depressed youths: the role of comorbidity and age. J. Affect. Disord. 190, 726–732.
Jesulola, E., Sharpley, C.F., Bitsika, V., Agnew, L.L., 2015. Frontal alpha asymmetry as a pathway to behavioural withdrawal depression: Research findings and issues. Behav. Brain Res. 292, 56–67.
Johnson, O., Crockett, D., 1982. Changes in perceptual asymmetries with clinical improvement of depression and schizophrenia. J. Abnorm. Psychol. 91, 45–54.
Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., Davidson, R.J., 2007. Failure to regulate: Counterproductive recruitment of top-down prefrontal-subcortial circuitry in major depression. J. Neurosci. 27, 8877–8884.
Jones, N.A., Field, T., Fox, N.A., Lundy, B., Davalos, M., 1997. EEG activation in 1-month-old infants of depressed mothers. Dev. Psychopathol. 9, 491–505.
Kayser, J., Bruder, G.E., Tenke, C.E., Stewart, J.W., Quitkin, F.M., 2000. Event related potentials (ERPs) to hemifield presentations of emotional stimuli: Differences between depressed patients and healthy adults in P3 amplitude and asymmetry. Int. J. Psychophysiol. 36, 211–236.
Kayser, J., Tenke, C.E., 2006. Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II Adequacy of low-density estimates. Clin. Neurophysiol. 117, 369–380.
Kayser, J., Tenke, C.E., 2015. On the benefits of using surface Laplacian (current source density) methodology in electrophysiology. Int. J. Psychophysiol. 97, 171–173.
Kayser, J., Tenke, C.E., Abraham, K.S., Alschuler, D.M., Alvarenga, J.E., Skipper, J., Warner, V., Bruder, G.E., Weissman, M.M., 2016. Neuronal generator patterns at scalp elicited by lateralized aversive pictures reveal consecutive stages of motivated attention. Neuroimage 142, 337–350.
Kayser, J., Tenke, C.E., Abraham, K.S., Alschuler, D.M., Alvarenga, J.E., Skipper, J., Warner, V., Bruder, G.E., Weissman, M.M., 2017. Motivated attention and family risk for depression: neuronal generator patterns at scalp elicited by lateralized aversive pictures reveal blunted emotional responsivity. Neuroimage Clin. 14, 692–707.
Kayser, J., Tenke, C., Nordby, H., Hammerborg, D., Hugdahl, K., Erdmann, G., 1997. Event-related potential (ERP) asymmetries to emotional stimuli in a visual half-field paradigm. Psychophysiology 34, 414–426.
Keller, J., Nitschke, J.B., Bhargava, T., Deldin, P.J., Gergen, J.A., Miller, G.A., Heller, W., 2000. Neuropsychological differentiation of depression and anxiety. J. Abnorm. Psychol. 109, 3–10.
Kemp, A.H., Griffiths, K., Felmingham, K.L., 2010. Disorder specificity despite comorbidity: resting EEG alpha asymmetry in major depressive disorder and post-traumatic stress disorder. Biol. Psychol. 85, 350–354.
Kentgen, L.M., Tenke, C., Pine, D.S., Fong, R., Klein, R.G., Bruder, G.E., 2000. Electroencephalographic asymmetries in adolescents with major depression: influence of comorbidity with anxiety disorders. J. Abnorm. Psychol. 109, 797–802.
Kishon, R., Abraham, K., Alschuler, D.M., Keilp, J.G., Stewart, J.W., McGrath, P.J., Bruder, G.E., 2015. Lateralization for speech predicts therapeutic response to cognitive behavioral therapy for depression. Psychiatry Res. 228, 606–611.
Klumpp, H., Deldin, P., 2010. Review of brain functioning in depression for semantic processing and verbal fluency. Int. J. Psychophysiol. 75, 77–85.
Kucharska-Pietura, K., David, A.S., 2003. The perception of emotional chimeric faces in patients with depression, mania and unilateral brain damage. Pyschol. Med. 33, 739–745.
Levy, J., Heller, W., Banich, M., Burton, L.A., 1983. Are variations among right handed individuals in perceptual asymmetries caused by characteristic arousal differences between hemispheres? J. Exp. Psychol. Hum. Percept. Perform. 9, 329–359.
Leyman, L., De Raedt, R., Vanderhasselt, M.A., Baeken, C., 2011. Effects of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex on the attentional processing of emotional information in major depression: a pilot study. Psychiatry Res. 185, 102–107.
Li, C.T., Lin, C.P., Chou, K.H., Chen, I.Y., Hsieh, J.C., Wu, C.L., Lin, W.C., Su, T.P., 2010. Structural and cognitive deficits in remitting and non-remitting recurrent depression: a voxel-based morphometric study. Neuroimage 50, 347–356.
Light, S.N., Heller, A.S., Johnstone, T., Kolden, G.G., Peterson, M.J., Kalin, N.H., Davidson, R.J., 2011. Reduced right ventrolateral prefrontal cortex activity while inhibiting positive affect is associated with improvement in hedonic capacity after 8 weeks of antidepressant treatment in major depressive disorder. Biol. Psychiatry 70, 962–968.
Lin, K., Xu, G., Lu, W., Ouyang, H., Dang, Y., Lorenzo-Seva, U., Guo, Y., Bessonov, D., Akiskal, H.S., So, K., Lee, T.M.C., 2014. Neuropsychological performance in melancholic, atypical and undifferentiated major depression during depressed and remitted states: a prospective longitudinal study. J. Affect. Disord. 168, 184–191.
Liotti, M., Sava, D., Rizzolatti, G., Caffarra, P., 1991. Differential hemispheric asymmetries in depression and anxiety: a reaction-time study. Biol. Psychiatry 29, 887–899.
Liu, F., Guo, W., Yu, D., Gao, Q., Gao, K., Xue, Z., Du, H., Zhang, J., Tan, C., Liu, Z., Zhao, J., Chen, H., 2012. Classification of different therapeutic responses of major depressive disorder with multivariate pattern analysis method based on structural MR scans. PLoS One 7, e40968. http://dx.doi.org/10.1371/journal.pone.0040968.
Lopez-Duran, N., Nusslock, R., George, C., Kovacs, M., 2012. Frontal EEG asymmetry moderates the effects of stressful life events on internalizing symptoms in children at familial risk for depression. Psychophysiology 49, 510–521.
Mathersul, D., Williams, L.M., Hopkinson, P.J., Kemp, A.H., 2008. Investigating models of affect: Relationships among EEG alpha asymmetry, depression and anxiety. Emotion 8, 560–572.
Mathias, S.R., Knowles, E.E., Kent Jr., J.W., Mckay, D.R., Curran, J.E., de Almeida, M.A., Dyer, T.D., Göring, H.H., Olvera, R.L., Duggirala, R., Fox, P.T., Almasy, L., Blangero, J., Glahn, D.C., 2016. Recurrent major depression and right hippocampal volume: a bivariate linkage association study. Hum. Brain Mapping 37, 191–202.
McClone, J., Davidson, W., 1973. The relation between cerebral speech laterality and spatial ability with special reference to sex and hand preference. Neurophsychologia 11, 105–113.
McGrath, C.L., Kelley, M.E., Holtzheimer, P.E., Dunlop, B.W., Craighead, W.E., Franco, A.R., Craddock, R.C., Mayberg, H.S., 2013. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry 70, 821–829.
Mennella, R., Benvenuti, S.M., Buodo, G., Palomba, D., 2015. Emotional modulation of alpha asymmetry in dysphoria: results from an emotional imagery task. Int. J. Psychophysiol. 97, 113–119.
Miller, A., Fox, N.A., Cohn, J.F., Forbes, E.E., Sherrill, J.T., Kovacs, M., 2002. Regional patterns of brain activity in adults with a history of childhood-onset depression: gender differences and clinical variability. Am. J. Psychiatry 159, 934–940.
Miller, C.H., Hamilton, J.P., Sacchet, M.D., Gotlib, I.H., 2015. Meta-analysis of functional neuroimaging of major depressive disorder in youth. JAMA Psychiatry 72, 1045–1053.
Moratti, S., Rubio, G., Campo, P., Keil, A., Ortiz, T., 2008. Hypofunction of right temporoparietal cortex during emotional arousal in depression. Arch. Gen. Psychiatry 65, 532–541.
Moratti, S., Strange, B., Rubio, G., 2015. Emotional arousal modulation of right temporoparietal cortex in depression depends on parental depression status in woman: first evidence. J. Affect. Disord. 178, 79–87.
Moscovitch, D.A., Santesso, D.L., Miskovic, V., McCabe, R.E., Antony, M.M., Schmidt, L.A., 2011. Frontal EEG asymmetry and symptom response to cognitive behavioral therapy in patients with social anxiety disorder. Biol. Psychol. 87, 379–385.
Moscovitch, M., Strauss, E., Olds, J., 1981. Handedness and dichotic listening performance in patients with unipolar endogenous depression who received ECT. Am. J. Psychiatry 138, 988–990.
Murrough, J.W., Collins, K.A., Fields, J., DeWilde, K.E., Phillips, M.L., Mathew, S.J., Wong, E., Tang, C.Y., Charney, D.S., Iosifescu, D.V., 2015. Regulation of neural responses to emotion perception by ketamine in individuals with treatment-resistant depressive disorder. Transl. Psychiatry 5, e509. http://dx.doi.org/10.1038/tp.2015.10.
Mutschler, I., Ball, T., Wankerl, J., Strigo, I.A., 2012. Pain and emotion in the insular cortex: evidence for functional reorganization in major depression. Neurosci. Lett. 520, 204–209.
Nadeau, S.E., Bowers, D., Jones, T.L., Wu, S.S., Triggs, W.J., Heilman, K.M., 2014. Cognitive effects of treatment of depression with repetitive transcranial magnetic stimulation. Cogn. Behav. Neurol. 27, 77–87.
Nitschke, J.B., Heller, W., Palmieri, P.A., Miller, G.A., 1999. Contrasting patterns of brain activity in anxious apprehension and anxious arousal. Psychophysiology 36, 628–637.
Noda, T., Yoshida, S., Matsuda, T., Okamoto, N., Sakamoto, K., Koseki, S., Numachi, Y., Matsushima, S., Kunugi, H., Higuchi, T., 2012. Frontal and right temporal activations correlate negatively with depression severity during verbal fluency task: a multi-channel near-infrared spectroscopy study. J. Psychiatric Res. 46, 905–912.
Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D., 2002. Rethinking feelings: An FMRI study of the cognitive regulation of emotion. J. Cogn. Neurosci. 14, 1215–1229.
Okada, G., Okamoto, Y., Morinobu, S., Yamawaki, S., Yokota, N., 2003. Attenuated left prefrontal activation during a verbal fluency task in patients with depression. Neuropsychobiology 47, 21–26.
Otto, M.W., Yeo, R.A., Dougher, M.J., 1987. Right hemisphere involvement in depression: Toward a neuropsychological theory of negative affective experiences. Biol. Psychiatry 22, 1201–1215.
Overby III, L.A., Harris, A.E., Leck, M.R., 1989. Perceptual asymmetry in schizophrenia and affective disorder: Implications from a right hemisphere task. Neuropsychologia 27, 861–870.
Peltola, M.J., Bakermans-Kranenburg, M.J., Alink, L.R., Huffmeijer, R., Biro, S., van Ijzendoorn, M.H., 2014. Resting frontal EEG asymmetry in children: Meta-analyses of

the effects of psychosocial risk factors and associations with internalizing and externalizing behavior. Dev. Psychobiol. 56, 1377–1389.
Pereira, D.M., Khan, A., 2016. Hemispheric specialization of impaired disengagement of attention in depression: a tachistoscopic method. Laterality 21, 161–176.
Phillips, M.L., Ladouceur, C.D., Drevets, W.C., 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of biopolar disorder. Mol. Psychiatry 13, 833–857.
Pine, D., Kentgen, L.M., Bruder, G.E., Leite, P., Bearman, K., Ma, Y., Klein, R.G., 2000. Cerebral laterality in adolescent major depression. Psychiatry Res. 93, 135–144.
Pizzagalli, D.A., 2011. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology 36, 183–206.
Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., Dougherty, D.D., Iosifescu, D.V., Rauch, S.L., Fava, M., 2009. Reduced caudate and nucleus accumbens response to rewards in unmedicated participants with major depressive disorder. Am. J. Psychiatry 166, 702–710.
Pizzagalli, D.A., Jahn, A.L., O'Shea, J.P., 2005. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biol. Psychiatry 57, 319–327.
Pizzagalli, D.A., Oakes, T.R., Davidson, R.J., 2003. Coupling of theta activity and glucose metabolism in the human rostral anterior cingulate cortex: an EEG/PET study of normal and depressed subjects. Psychophysiology 40, 939–949.
Post, R.M., DeLisi, L.E., Holcomb, H.H., Uhde, T.W., Cohen, R., Buchsbaum, M.S., 1987. Glucose utilization in the temporal cortex of affectively ill patients: Positron emission tomography. Biol. Psychiatry 22, 545–553.
Price, R.B., Paul, B., Schneider, W., Siegle, G.J., 2013. Neural correlates of three neurocognitive intervention strategies: a preliminary step towards personalized treatment for psychological disorders. Cogn. Therapy Res. 37, 657–672.
Pu, S., Nakagome, K., Yamada, T., Yokoyama, K., Matsumura, H., Yamada, S., Sugie, T., Miura, A., Mitani, H., Iwata, M., Nagata, I., Kaneko, K., 2015. Suicidal ideation is associated with reduced prefrontal activation during a verbal fluency task in patients with major depressive disorder. J. Affect. Disord. 181, 9–17.
Quraan, M.A., Protzner, A.B., Daskalakis, Z.J., Giacobbe, P., Tang, C.W., Kennedy, S.H., Lozano, A.M., McAndrews, M.P., 2014. EEG power asymmetry and functional connectivity as a marker of treatment effectiveness in DBS surgery for depression. Neuropsychopharmacology 39, 1270–1281.
Reid, S.A., Duke, L.M., Allen, J.J.B., 1998. Resting frontal electroencephalographic asymmetry in depression: Inconsistencies suggest the need to identify mediating factors. Psychophysiology 35, 389–404.
Rive, M.M., van Rooijen, G., Veltman, D.J., Phillips, M.L., Schene, A.H., Ruhé, H.G., 2013. Neural correlates of dysfunctional and emotion regulation in major depressive disorder: A systematic review of neuroimaging studies. Neurosci. Biobehav. Rev. 37, 2529–2553.
Sacher, J., Neumann, J., Fönfstöck, T., Soliman, A., Villringer, A., Schroeter, M.L., 2012. Mapping the depressed brain: A meta-analysis of structural and functional alterations in major depressive disorder. J. Affect. Disord. 140, 142–148.
Schaffer, C.E., Davidson, R.J., Saron, C., 1983. Frontal and partietal electroencephalogram asymmetry in depressed and nondepressed subjects. Biol. Psychiatry 18, 753–762.
Shankman, S.A., Klein, D.N., Tenke, C.E., Bruder, G.E., 2007. Reward sensitivity in depression: a biobehavioral study. J. Abnorm. Psychol. 116, 95–104.
Shankman, S.A., Tenke, C.E., Bruder, G.E., Durbin, C.E., Hayden, E.P., Klein, D.N., 2005. Low positive emotionality in young children: association with EEG asymmetry. Dev. Psychopathol. 17, 85–98.
Siegle, G.J., Steinhauer, S.R., Friedman, E.S., Thompson, W.S., Thase, M.E., 2011. Remission prognosis for cognitive therapy for recurrent depression using the pupil: utility and neural correlates. Biol. Psychiatry 69, 726–733.
Siegle, G.J., Steinhauer, S.R., Thase, M.E., Stenger, A., Carter, C.S., 2002. Can't shake that feeling: event- related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. Biol. Psychiatry 51, 693–707.
Siegle, G.J., Thompson, W., Carter, C.S., Steinhauer, S.R., Thase, M.E., 2007. Increased amygdala and decreased dorsolateral prefrontal BOLD response in unipolar depression: related and independent features. Biol. Psychiatry 61, 198–209.
Silvers, J.A., Weber, J., Wager, T.D., Ochsner, K.N., 2015. Bad and worse: neural systems underlying reappraisal of high- and low-intensity negative emotions. Soc. Cogn. Affect. Neurosci. 10, 172–179.
Smit, D.J.A., Posthuma, D., Boomsma, D.I., De Geus, E.J.C., 2007. The relation between frontal EEG asymmetry and the risk for anxiety and depression. Biol. Psychol. 74, 26–33.
Sprengelmeyer, R., Steele, J.D., Mwangi, B., Kumar, P., Christmas, D., Milders, M., Matthews, K., 2011. The insular cortex and the neuroanatomy of major depression. J. Affect. Disord. 133, 120–127.
Springer, S.P., Deutsch, G., 1998. Left Brain, Right Brain, 3rd ed. Freeman & Company, New York.
Stevens, J.S., Hamann, S., 2012. Sex differences in brain activation to emotional stimuli: a meta-analysis of neuroimaging studies. Neuropsychologia 50, 1578–1593.
Stewart, J.L., Bismark, A.W., Towers, D.N., Coan, J.A., Allen, J.J.B., 2010. Resting frontal EEG asymmetry an endophenotype for depression risk: sex-specific patterns of frontal brain asymmetry. J. Abnorm. Psychol. 119, 502–512.
Stewart, J.L., Coan, J.A., Towers, D.N., Allen, J.J.B., 2014. Resting and task-elicited prefrontal EEG alpha asymmetry in depression: support for the capability model. Psychophysiology 51, 446–455.
Stewart, J.L., Towers, D.N., Coan, J.A., Allen, J.J.B., 2011. The oft-neglected role of parietal EEG asymmetry and risk for major depressive disorder. Psychophysiology 48, 82–95.
Stewart, J.W., Quitkin, F.M., McGrath, P.J., Bruder, G.E., 1999. Do tricyclic responders and tricyclic responders have different brain laterality? J. Abnorm. Psychol. 108, 707–710.
Stratmann, M., Konrad, C., Kugel, H., Krug, A., Schöning, S., Ohrmann, P., Uhlmann, C., Postert, C., Suslow, T., Heindel, W., Arolt, V., Kircher, T., 2014. Insular and hippocampal gray matter volume reductions in patients with major depressive disorder. PLoS One 9, e102692. http://dx.doi.org/10.1371/journal.pone.0102692.
Tenke, C.E., Kayser, J., 2005. Reference-free quantification of EEG spectra: combining current source density (CSD) and frequency principal components analysis (fPCA). Clin. Neurophysiol. 116, 2826–2846.
Tenke, C.E., Kayser, J., Abraham, K., Alvarenga, J.E., Bruder, G.E., 2015. Posterior EEG alpha at rest and during task performance: comparison of current source density and field potential measures. Int. J. Psychophysiol. 97, 299–309.
Tenke, C.E., Kayser, J., Manna, C.G., Fekri, S., Kroppmann, C.J., Schaller, J.D., Alschuler, D.M., Stewart, J.W., McGrath, P.J., Bruder, G.E., 2011. Current source density measures of electroencephalographic alpha predict antidepressant treatment response. Biol. Psychiatry 70, 388–394.
Thibodeau, R., Jorgensen, R.S., Kim, S., 2006. Depression, anxiety, and resting frontal EEG asymmetry: a meta-analytic review. J. Abnorm. Psychol. 115, 715–729.
Tomarken, A.J., Dichter, G.S., Garber, J., Simien, C., 2004. Resting frontal brain activity: linkages to maternal depression and socio-economic status among adolescents. Biol. Psychol. 67, 77–102.
Triggs, W.J., Ricciuti, N., Ward, H.E., Cheng, J., Bowers, D., Goodman, W.K., Kluger, B.M., Nadeau, S.E., 2010. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. Psychiatry Res. 178, 467–474.
Trinkl, M., Greimel, E., Bartling, J., Grönewald, B., Schulte-Körne, G., Grossheinrich, N., 2015. Right- lateralization of N2-amplitudes in depressive adolescents: an emotional go/no-go study. J. Child Psychol. Psychiatry 56, 76–86.
Trivedi, M.H., Greer, T.L., 2014. Cognitive dysfunction in unipolar depression: implications for treatment. J. Affect. Disord. 152–154, 19–27.
Trivedi, M.H., McGrath, P.J., Fava, M., Parsey, R.V., Kurian, B.T., Phillips, M.L., Oquendo, M.A., Bruder, G., Pizzagalli, D., Toups, M., Cooper, C., Adams, P., Weyandt, S., Morris, D.W., Grannemann, B.D., Ogden, R.T., Buckner, R., McInnis, M., Kraemer, H.C., Petkova, E., Carmody, T.J., Weissman, M.M., 2016. Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): rationale and design. J. Psychiatr. Res. 78, 11–23.
Tsujii, N., Mikawa, W., Akashi, H., Tsujimoto, E., Adachi, T., Kirime, E., Takaya, M., Yanagi, M., Shirakawa, O., 2014. Right temporal activation differs between melancholia and nonmelancholic depression: a multichannel near-infrared spectroscopy study. J. Psychiatr. Res. 55, 1–7.
Vanderhasselt, M.A., De Raedt, R., Namur, V., Lotufo, P.A., Bensenor, I.M., Bogio, P.S., Brunoni, A.R., 2015. Transcranial electric stimulation and neurocognitive training in clinically depressed patients: a pilot study of the effects on rumination. Prog. Neuropsychopharmacol. Biol. Psychiatry 57, 93–99.
van Tol, M.J., Demenescu, L.R., van der Wee, N.J., Kortekaas, R., Nielen, M.M., Den Boer, J.A., Renken, R.J., van Buchem, M.A., Zitman, F.G., Aleman, A., Veltman, D.J., 2012. Functional magnetic resonance imaging correlates of emotional word encoding and recognition in depression and anxiety disorders. Biol. Psychiatry 71, 593–602.
Videbech, P., Ravnkilde, B., 2004. Hippocampal volume and depression: a meta-analysis of MRI studies. Am. J. Psychiatry 161, 1957–1966.
Voyer, D., Bowes, A., Soraggi, M., 2009. Response procedure and laterality effects in emotion recognition: implications for models of dichotic listening. Neuropsychologia 47, 23–29.
Wale, J., Carr, V., 1990. Differences in dichotic listening asymmetries in depression according to symptomatology. J. Affect. Disord. 18, 1–9.
Warner, V., Mufson, L., Weissman, M.M., 1995. Offspring at high and low risk for depression and anxiety: mechanisms of psychiatric disorder. J. Am. Acad. Child Adolesc. Psychiatry 34, 786–797.
Weissman, M.M., Leaf, P.J., Holzer III, C.E., Myers, J.K., Tischler, G.L., 1984. The epidemiology of depression: an update on sex differences in rates. J. Affect. Disord. 7, 179–188.
Weissman, M.M., Warner, V., Wickramaratne, P., Moreau, D., Olfson, M., 1997. Offspring of depressed parents. 10 years later. Arch. Gen. Psychiatry 54, 932–940.
Weissman, M.M., Wickramaratne, P., Nomura, P., Warner, V., Verdeli, H., Pilowsky, D.J., Grillon, C., Bruder, G.E., 2005. Families at high and low risk for depression: a 3-generation study. Arch. Gen. Psychiatry 62, 29–36.
Wiedemann, G., Pauli, W., Dengler, W., Lutzenberger, W., Birbaumer, N., Buchkremer, G., 1999. Frontal brain asymmetry as a biological substrate of emotions in patients with panic disorders. Arch. Gen. Psychiatry 56, 78–84.
Woolley, J.D., Strobl, E.V., Strum, V.E., Shany-Ur, T., Poorzand, P., Grossman, S., Nguyen, L., Eckart, J.A., Levenson, R.W., Seeley, W.W., Miller, B.L., Rankin, K.P., 2015. Impaired recognition and regulation of disgust is associated with distinct but partially overlapping patterns of decreased gray matter volume in the ventroanterior insula. Biol. Psychiatry 78, 505–514.
Yozawitz, A., Bruder, G., Sutton, S., Sharpe, L., Gurland, B., Fleiss, J., Costa, L., 1979. Dichotic perception: Evidence for right hemisphere dysfunction in affective psychosis. Br. J. Psychiatry 135, 224–237.
Zhang, J., Kendrick, K.M., Lu, Guangming, Feng, J., 2015. The fault lies on the other side: altered brain functional connectivity in psychiatric disorders is mainly caused by counterpart regions in the opposite hemisphere. Cereb. Cortex 25, 3475–3486.
Zotev, V., Yuan, H., Misaki, M., Phillips, R., Young, K.D., Feldner, M.T., Bodurka, J., 2016. Correlation between amygdala BOLD activity and frontal EEG asymmetry during real-time fMRI neurofeedback training in patients with depression. Neuroimage Clin. 11, 224–238.