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Frontal EEG asymmetry as a promising marker of depression vulnerability: summary and methodological considerations

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Frontal EEG asymmetry is a promising neurophysiological marker of depression risk. It predicts emotional response and negative affect hours to years later. Yet, inconsistencies in the literature may be due to differing methodological approaches between research groups. Within the past two years, a number of studies have shown this line of research may be strengthened by augmenting resting assessments with emotionally evocative tasks, utilizing optimal recording montages, and taking an integrative neuroscience approach that links frontal asymmetry to other indices of neural function. This review will focus on recent work in frontal asymmetry and depression with a particular focus on promising future directions and methodological considerations that may increase consistency between research groups.

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Introduction

Investigating neurophysiological indices of depression may facilitate the identification of those at risk for the disorder, provide a metric to assess preventative measures, and lead to the development of biologically driven diagnosis and treatment. In particular, a large body of research suggests that frontal asymmetry may be a neurophysiological biomarker of depression risk.

Frontal asymmetry is a relative measure of the difference in electroencephalogram (EEG) alpha power between the right and left frontal regions and has high internal consistency reliability and good test–retest reliability over intervals from weeks to months [1,2]. As alpha activity has an inhibitory influence on cortical network activity, lower frontal asymmetry scores (right minus left alpha) reflect relatively less left than right cortical activity [1]. Less relative left frontal activity during rest has been associated with depressive symptoms [3] and current and past depression status [4,5,6••,7]. This pattern of frontal asymmetry has also been found in infants of depressed mothers [8,9,10•] and is related to mother's depression score [10•]. Less relative left frontal activity prospectively predicts first depressive episode in college students [11••]. This line of research suggests frontal asymmetry may indicate vulnerability to depression [12].

Although frontal asymmetry has emerged as a promising biomarker for depression risk, inconsistencies in this literature stem from differences in methodology between investigators. The present article will review recent work in frontal asymmetry and depression, focusing on promising future directions and methodological considerations that may increase consistency between research groups. In particular, frontal asymmetry has utility as a predictor of depression onset, but this line of research may be strengthened by: augmenting resting assessments with emotionally evocative tasks (i.e. replacing a trait model with a capability model); utilizing optimal recording montages that isolate local activity; and taking an integrative neuroscience approach that links frontal asymmetry to other indices of neural function.

The predictive power of frontal asymmetry

Recent findings indicate frontal asymmetry is a potential predictor of depressive symptoms and treatment response. Frontal asymmetry predicts emotional response and negative affect on a short-term scale. Less relative left frontal activity during rest predicted decreased neurophysiological change on subsequent emotional tasks [13•], and less relative left frontal activity during negative films predicted mood deterioration in the next week [14•]. Additionally, frontal asymmetry has predictive power over longer time frames: less relative left frontal activity predicted depressive symptoms in adolescent boys a year later [15•] and also predicted self-reported homesickness among college freshman [16].

A recent review focused on a number of EEG indices as biomarkers of depression treatment response. Although alpha asymmetry in regions other than the frontal sites predicted treatment response for participants taking tricyclic antidepressants and SSRIs, frontal asymmetry did not differentiate responders from non-responders [17–19]. A recent literature review of music therapy cited increased relative left frontal activity after music exposure as support for the effectiveness of music therapy [20•], although the longer-term impact of music therapy

must be examined. In a behavioral activation treatment study, absolute magnitude of frontal asymmetry (in either direction) predicted negative affect after treatment but not treatment response [21•]. The extent to which frontal asymmetry may mark treatment response more broadly — for psychotherapy, pharmacological, and deep-brain stimulation treatments — remains largely unexplored (as research has focused on alternate alpha measures) and is an important area for future research.

Research also suggests the possibility of treating depression by changing frontal asymmetry. Inpatients with treatment-resistant depression had reduced depressive symptoms after repetitive transcranial magnetic stimulation (rTMS) targeted to the left prefrontal cortex [22,23]. A less invasive neurofeedback procedure provides auditory feedback based on frontal asymmetry scores and can alter frontal asymmetry. Five-weeks of neurofeedback training increased relative left frontal asymmetry and decreased depressive symptoms in 24 participants with current depression [24]. A one-session manipulation of frontal asymmetry in individuals without history of psychopathology, however, did not change mood [25••]. Thus repeated neurofeedback may be a tenable intervention for depression, directly targeting the neural systems indexed by frontal asymmetry. Further research should examine the duration and course of neurofeedback necessary for efficacy on various populations. Additionally, tonic stimulation with weak direct currents (tDCS) changes cortical excitability and has been investigated as a potential non-invasive measure for depression [26]. Transcranial ultrasound (TUS) over the lateral prefrontal cortex improves mood acutely [27], although its longer-term impact on mood remains to be assessed. The impact of these new stimulation approaches, on frontal EEG asymmetry, however, has not been investigated and is an important direction for future research. Finally, transcranial alternating current stimulation (tACS) directly interferes with cortical rhythms but its potential to alter prefrontal asymmetry has never been investigated [28].

Resting assessments versus emotionally evocative tasks: support for the capability model

Given inconsistencies in the literature and the potential of frontal asymmetry to help identify those at risk for depression, finding the conditions under which frontal asymmetry can best serve as a marker of depression risk remains of great importance. The capability model proposes that frontal asymmetry may be best understood as the interaction between individual differences in emotion regulation and the emotional salience of a particular situation [29]. The major hypothesis of the capability model is that individual differences in frontal asymmetry will be more pronounced during emotionally evocative tasks than during rest. A growing body of research supports this hypothesis. A study of 306 currently, previously, and never depressed participants found that depression status was more strongly predicted by frontal asymmetry during a directed facial action task than frontal asymmetry during rest for Cz, linked mastoids, and average references [30].

Several recent studies found less relative left frontal activity associated with depressive affect during emotionally evocative tasks but not during rest. For example, frontal asymmetry did not differ between individuals with major depressive disorder and those with borderline personality disorder during rest, yet less relative left frontal activity was found in depressed but not borderline participants after a rejection task [31••]. Relatedly, women with premenstrual dysphoric disorder had less relative left frontal activity during both depression induction and relaxation tasks but not during rest [32•]. Furthermore, 27 mothers of infants 5–8 months old had EEG recorded during rest and during videos of their infants expressing emotions. Self-reported experiential sadness of the mothers related to less relative left frontal activity during videos of their infants expressing emotion but not rest [33•].

Similar findings derive from recent studies of children and older adults. Children aged 6–13 whose mothers have a history of depression had less relative left frontal activity in comparison with their peers during emotionally evocative films but not during rest [34•]. In a small sample of adults over 65, no relationship was found between frontal asymmetry during rest and depressive symptoms or depression status. The authors suggested that frontal asymmetry may not have the same relationship in older adults [35]. Although such an interpretation is possible, these results are consistent with the hypothesis that individual differences in frontal asymmetry are more pronounced during emotionally evocative tasks than at rest, thus supporting the capability model. Moreover, a linked mastoids reference montage may limit the ability to detect meaningful relationships between frontal asymmetry and depression (see section below). A comprehensive assessment of frontal asymmetry throughout the lifespan should include emotionally evocative tasks as well as resting state data.

Additionally, consideration must be given to the type of emotionally evocative tasks used. It might be reasonable to expect that tasks that call for emotion regulation that is partially dependent on lateral prefrontal activity would likely use systems that may be altered in those at risk for depression. For example, Meyer *et al.* found that frontal asymmetry was moderated by the extent to which the emotionally evocative videos allowed cognitive emotion regulation [36•]. Significant interactions between frontal asymmetry, electrodermal reaction, and internalizing and externalizing symptoms were found during sad and happy videos but not fearful or angry videos [37•].

The importance of recording montage

Further consideration should be given to recording montage in frontal asymmetry research. Electrical signals recorded at any given electrode are highly dependent on the reference site used. For over three decades, researchers have examined effects of several recording montages, including: average (the average of all sites); CZ (vertex); and, averaged ('linked') mastoids references [38,39]. These traditional references reflect not only frontal alpha but also substantial alpha power originating in other regions (e.g. the Occipital cortex). The reference-free current source density (CSD) transformation, however, uses an estimate of current sources and sinks on the scalp and attenuates the contribution of distal sources, thus highlighting the contribution of sources nearer the recording electrode. Some recent work suggests that CSD transformation may provide a more sensitive index of individual variations in frontal asymmetry and reduce non-frontal contributions to frontal asymmetry compared with these typical recording montages [40]. Stewart *et al.* found that only CSD transformed frontal asymmetry — but not average, nor linked mastoids, nor CZ referenced asymmetry — differed as a function of lifetime history of depression during the resting state for 306 participants [30,41••]. Another study found that the amount of time since a participant had woken up affected EEG recording more for average and linked mastoids references than for CSD [40]. Thus on both empirical and rational grounds, the CSD transformation should be the preferred approach for assessing the relationship of frontal asymmetry to depression, and for analyzing the asymmetrical activity of specifically frontal systems.

Using integrative neuroscience approaches to link frontal asymmetry to underlying neural systems

Despite considerable research indicating frontal asymmetry may be a marker of depression risk, few studies have linked frontal asymmetry to other neural systems. Functional magnetic resonance (fMRI) studies suggest the importance of lateral frontal systems in depression and depression risk [42,43]. Abnormalities in the cognitive control network (CCN) characterize depression [44]; the CCN serves basic cognitive control mechanisms (e.g. attentional control) and is located primarily in frontal and parietal regions. Individuals with depression have increased connectivity between the CCN and the dorsal nexus, an area in the bilateral dorsal medial prefrontal cortex region, [45] and higher dorsal to rostral anterior cingulate cortex connectivity [46]. Although frontal regions are often implicated in fMRI activation and connectivity studies, frontal asymmetry has seldom been tested explicitly in this work.

One recent study used simultaneous CSD-transformed EEG and fMRI during rest to examine correspondence between frontal asymmetry and connectivity. Less relative left frontal activity was associated with increased connectivity between the left inferior frontal gyrus and two anterior cingulate cortex resting networks [47]. This work suggests frontal asymmetry may relate to a hyper connected emotional verbalization network that may reflect ineffective attempts at emotion regulation such as rumination [48]. These results provide one of the few links between resting frontal EEG asymmetry and brain connectivity. These findings, however, reflect between-subjects correlations, and future work should examine whether fMRI connectivity is moderated within each participant by changes in asymmetry throughout the recording session. This research can provide clues about how frontal EEG asymmetry may influence network organization in ways that promote depression risk.

Additionally, linking frontal asymmetry to underlying neural network organization holds the promise for the development of neurally informed treatments by suggesting specific regional targets for intervention, such as rTMS, tDCS, TUS, and tACS.

Conclusion

Frontal asymmetry may serve as a prospective predictor of depression onset and, as such, has wide-ranging theoretical and translational applications. Frontal asymmetry can potentially identify those at risk for depression, although a large-scale prospective study is needed. Additionally, because frontal asymmetry may index the activity of neural systems that promote depression risk, research in this area can inform the development of neurally informed, individualized treatments, and allow for an assessment of how well treatments (including psychotherapy) alter activity within these neural systems. This important line of research may benefit from utilizing EEG not only during rest but also during emotionally evocative tasks (capability model), using the CSD-transformation to highlight specifically frontal activity, and employing multi-modal imaging to link an easily obtained and widely studied measure frontal asymmetry to other measures of brain activity involved in depression.

Conflict of interest statement

None declared.

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