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Resting frontal brain asymmetry is linked to future depressive symptoms in women

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ABSTRACT

This longitudinal pilot study examined whether baseline resting frontal electroencephalographic (EEG) asymmetry correlates with depressive symptoms during the most impaired two-week period in the following year. Current-source-density (CSD) transformed resting frontal EEG asymmetry, severity of depression symptoms (Beck Depression Inventory – II), and stress (indexed by negative life events; NLE) were recorded in never-depressed young adults with no current DSM-IV diagnosis (38 women, 16 men) at baseline. One year later, depression symptoms and NLEs experienced during the interim were assessed. Individuals who reported greater interim NLEs also endorsed interim higher depression symptoms, a pattern that replicated when first accounting for baseline stress and depression. For women, higher depression reported at follow-up was linked to lower left than right frontal EEG activity at baseline, a pattern that replicated when first accounting for depressive symptoms at baseline. Despite the modest sample size of the present analysis, findings are consistent with prior reports of sex differences in patterns of brain laterality and support the idea that CSD-referenced EEG asymmetry may be a risk marker for future depression in previously healthy young women.

1. Introduction

Given that major depressive disorder (MDD) is linked to severe impairment and chronic symptom recurrence, creating substantial burden both economically and personally (Burcusa & Iacono, 2007; Greenberg et al., 2003; Judd, Akiskal et al., 2000; Judd, Paulus et al., 2000; Judd, Akiskal et al., 2000; Judd, Paulus et al., 2000; Michaud et al., 2006), scientific research focused on the pathways from risk to symptom expression is a priority. With respect to candidate biological markers of MDD, a growing literature demonstrates that a pattern of relatively lower left than right frontal electroencephalographic (EEG) activity at rest (indexed by relatively greater right-than-left frontal alpha-band activity) differentiates individuals with a lifetime history of depression (MDD+) from non-depressed individuals (MDD-) (e.g., Allen, Coan, & Nazarian, 2004; Allen, Urry, Hitt, & Coan, 2004; Bruder et al., 2005; Jaworska, Blier, Fusee, & Knott, 2012; Kemp et al., 2010; Stewart, Bismark, Towers, Coan, & Allen, 2010; Thibodeau, Jorgensen, & Kim, 2006). Moreover, this EEG asymmetry is modestly stable over time in both MDD + and MDD- (e.g., Allen, Coan et al., 2004; Allen, Urry et al., 2004; Hagemann, Naumann, Thayer, & Bartussek, 2002; Hagemann, Hewig, Seifert, Naumann, & Bartussek, 2005). Although these findings are consistent with the hypothesis that resting EEG asymmetry may index risk for future depression, definitive prospective studies remain to be conducted.

Frontal asymmetry findings as a function of depression status have proven somewhat inconsistent (e.g., Reid, Duke, & Allen, 1998; Segrave et al., 2011), although the inconsistencies are thought to be at least partly attributable to methodological differences in EEG recording, depression assessments, and presence of comorbid psychopathology, thereby complicating interpretation (see Davidson, 1998; Hagemann, 2004, and Stewart et al., 2010 for discussion). Moreover, although the neural differentiation of those with a history of MDD (MDD+) versus with no history (MDD-) groups is a promising start in the search for markers of depression risk, viable risk indicators should also be able to provide clinical utility in sharing variance with future depressive symptoms and/or MDD onset/relapse within those who are vulnerable. A further complication is that risk markers correlating with first-episode MDD might be different from risk indicators of recurrent or past MDD after one has already experienced a period of depressive symptoms (Burcusa & Iacono, 2007). For instance, prior work suggests that life stress is a stronger predictor of first episodes than recurrent episodes of MDD (e.g., Lewinsohn, Allen, Seeley, & Gotlib, 1999; Monroe &

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Harkness, 2005). The question arises, then, whether resting frontal asymmetry not only distinguishes depressed from non-depressed individuals, but also is prospectively associated with future depressive symptoms and/or episodes of MDD in MDD- individuals as well as identifying those who have already experienced MDD.

Few studies address the prospective utility of prefrontal brain asymmetry relating to future depression, and available longitudinal findings provide somewhat conflicting results. For instance, within a twin sample that was not assessed for MDD status, lower left than right frontal brain activity was associated with future risk of depression, but only in women (Smit, Posthuma, Boomsma, & De Geus, 2007). With respect to resting EEG activity forecasting recurrent depressive symptoms in MDD+, extant research indicates that frontal asymmetry is not related to MDD status or number of depressive symptoms within two (Allen, Coan et al., 2004; Allen, Urry et al., 2004) or six (McFarland, Shankman, Tenke, Bruder, & Klein, 2006) month follow-up periods in MDD + individuals. Unlike null findings for MDD+, however, results for MDD- are more promising and warrant further examination. Although one study suggests that frontal asymmetry is not correlated with depressive symptoms in MDD- college students one year later (Blackhart, Minnix, & Kline, 2006), no clinical interview was performed to determine presence or absence of DSM-IV (American Psychiatric Association, 1994) disorders at baseline, so it is possible that participants had symptoms that could have influenced null results. In contrast, lower left than right frontal activity at rest is linked to future depression symptoms one year later in two adolescent MDD- samples after controlling for baseline depressive symptoms (Mitchell & Pössel, 2012; Pössel, Lo, Fritz, & Seemann, 2008), and prospectively is related to self-reported freshman-year home-sickness (Steiner & Coan, 2011). Furthermore, lower left than right resting frontal activity is associated with first-episode MDD onset within three years in 40 MDD- adults thought to be at risk for developing mood disorders: 3 participants subsequently met criteria for a major depressive episode and 10 met criteria for a minor depressive episode during this period (Nusslock et al., 2011). Within this sample, lower relative left frontal activity also correlates with higher depressive symptoms at three year follow-up when accounting for depressive symptoms at baseline. Collectively, these prospective studies differ in number of EEG visits, length of EEG recording, type of EEG reference and follow-up assessment of depressive symptoms, any of which may have contributed to the production of differential results. The research to date thus indicates that frontal EEG asymmetry could be a risk indicator for first-onset escalation of depressive symptoms in MDD-, although additional studies are warranted to investigate this issue.

The present investigation attempted to replicate and extend prior work on the prospective value of frontal asymmetry at baseline, examining whether it relates to future depressive symptoms over the next year within a sizeable sample of MDD- adults, incorporating several methodological improvements including: (1) use of the current source density (CSD) transformation (Perrin, Pernier, Bertrand, & Echallier, 1990; Kayser & Tenke, 2006; Perrin, Pernier, Bertrand, & Echallier, 1989) to reduce contributions of non-frontal sources to frontal asymmetry scores; (2) aggregation across several sessions and minutes of EEG recording to derive reliable estimates of trait asymmetry; and, (3) inclusion of life stress as a potential moderator of the prospective utility of EEG asymmetry. The CSD transformation is advantageous as a reference-free algorithm that greatly diminishes volume conduction contributions to EEG alpha power and, in contrast to conventional scalp EEG reference measures, results in unambiguous indices of current sources underlying EEG topography (Tenke & Kayser, 2012). Furthermore, findings indicate that CSD-transformed resting frontal asymmetry differentiates MDD + and MDD- more robustly than average reference, Cz-reference, and linked-mastoid reference montages traditionally used in the EEG asymmetry literature (Stewart et al., 2010; Stewart, Coan, Towers, & Allen, 2014).

Given that relating frontal asymmetry to categorical outcomes such as future MDD + versus MDD- status would require large sample sizes, extended follow-up periods, and pre-identified high-risk samples, one alternative to MDD categorization is to examine continuous measures of depressive symptom severity as the primary outcome measure. In line with this rationale, research demonstrates that higher depressive symptoms measured dimensionally are correlated with first-onset MDD + (Horwath, Johnson, Klerman, & Weissman, 1992; Lewinsohn et al., 1999).

On the basis of three studies demonstrating the association of frontal EEG asymmetry with future depressive symptoms (Mitchell & Pössel, 2012; Nusslock et al., 2011; Pössel et al., 2008), it was hypothesized relatively less left than right frontal activity in young adults with no history of MDD and free of any current DSM disorders (MDD-) at baseline would be associated with higher depressive symptoms for the most impairing two-week period within the following year, even after controlling for depressive symptoms at baseline. Given that the relationship between depression and frontal EEG asymmetry appears to be stronger in women than men (e.g., Smit et al., 2007), biological sex was included as a relevant variable in analyses. In addition, exploratory analyses examined relationships between baseline frontal EEG asymmetry, depressive symptoms over the next year, and number of stressful life events experienced between baseline and one-year follow-up, given that prior work shows that stress is linked to first-onset MDD+ (Lewinsohn et al., 1999; Monroe & Harkness, 2005).

2. Materials and methods

2.1. Participants

The study protocol was approved by the local Human Research Protections Program. All participants provided verbal and written informed consent in accordance with the Declaration of Helsinki. The sample for this study comprises the 163 never-depressed participants from among the 306 participants reported in Stewart et al. (2010). Right-handed participants were recruited from a pool of over 10,000 individuals on the basis of their scores on the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Individuals either completed the BDI online after learning about the study from campus fliers or during pre-testing in a large introductory psychology class. Participants were recruited to span the full dimensional range of depressive severity for a larger grant study investigating state and trait EEG asymmetry. Selected individuals were then phone screened to query exclusion criteria, which included no history of: head injury with loss of consciousness greater than 10 min, concussion, epilepsy, electroshock therapy, use of current psychotropic medications, and active suicidal potential necessitating immediate treatment.

Individuals who passed the phone screen were then invited to the lab for a baseline session wherein they completed the BDI-II (Beck, Steer, & Brown, 1996) as well as the Structured Clinical Interview for DSM-IV (SCID, First, Spitzer, Gibbon, & Williams, 1997) administered by a trained graduate clinical rater. The 163 participants in this study met criteria for no current DSM-IV Axis I disorder and no lifetime diagnosis of major depression (MDD-). Participants passing the screening were invited to participate in four additional EEG visits. The lifetime history negative (MDD-) participants were compared to a group (N = 143) of lifetime history positive (MDD+) participants on patterns of frontal brain asymmetry in Stewart et al. (2010) and Stewart et al. (2014), but no MDD + participants were included in the present analysis.

The original grant-funded study for which the baseline visits were collected did not originally have a follow-up phase planned. Given recently published work demonstrating a link between baseline asymmetry and future depression symptoms in MDD- (e.g., Mitchell & Pössel, 2012; Nusslock et al., 2011; Pössel et al., 2008), we realized that longitudinal data for this project could enable possible replication and extension. After obtaining Institutional Review Board approval to re-