



## Frontal brain asymmetry, childhood maltreatment, and low-grade inflammation at midlife



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### ABSTRACT

Frontal EEG asymmetry is thought to reflect variations in affective style, such that greater relative right frontal activity at rest predicts enhanced emotional responding to threatening or negative stimuli, and risk of depression and anxiety disorders. A diathesis-stress model has been proposed to explain how this neuro-affective style might predispose to psychopathology, with greater right frontal activity being a vulnerability factor especially under stressful conditions. Less is known about the extent to which greater relative right frontal activity at rest might be associated with or be a diathesis for deleterious physical health outcomes. The present study examined the association between resting frontal EEG asymmetry and systemic, low-grade inflammation and tested the diathesis-stress model by examining whether childhood maltreatment exposure interacts with resting frontal asymmetry in explaining inflammation. Resting EEG, serum inflammatory biomarkers (interleukin-6, C-reactive protein, and fibrinogen) and self-reported psychological measures were available for 314 middle-aged adults (age  $M = 55.3$  years,  $SD = 11.2$ , 55.7% female). Analyses supported the diathesis-stress model and revealed that resting frontal EEG asymmetry was significantly associated with inflammation, but only in individuals who had experienced moderate to severe levels of childhood maltreatment. These findings suggest that, in the context of severe adversity, a trait-like tendency towards greater relative right prefrontal activity may predispose to low-grade inflammation, a risk factor for conditions with inflammatory underpinnings such as coronary heart disease.

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## 1. Introduction

Contemporary models of how negative psychological experiences shape long-term human health are increasingly recognizing the role of bidirectional communication between the brain and the immune system (Danese and McEwen, 2012; Gianaros et al., 2013; Irwin and Cole, 2011; Kop and Cohen, 2007; Miller et al., 2011; Nusslock and Miller, 2016; Raison et al., 2006; Slavich et al., 2010). Neuro-immune transactions are thought to occur both directly and indirectly through multiple pathways that include psychological processes such as depression or health behaviors like sleep (Glaser

and Kiecolt-Glaser, 2005; Irwin and Cole, 2011). The present study sought to test associations between neural activity and inflammation, and to examine how this association may be differentially shaped by early-life adversity in the form of childhood maltreatment. We focused on functional brain asymmetry in the frontal region assessed by resting EEG as a marker of neural diathesis, given that frontal right-hemisphere dominance has been associated with a trait-like bias toward negative affect (Coan and Allen, 2004; Davidson, 2004; Fox, 1991) and enhanced risk for depression and anxiety disorders (Davidson, 1998a; Fingelkurts and Fingelkurts, 2015; Jesulola et al., 2015; Nusslock et al., 2015; Thibodeau et al., 2006). We aimed to (1) test whether resting frontal brain asymmetry is associated with systemic, low-grade inflammation; (2) explore whether those reporting childhood maltreatment show a pattern of greater relative right frontal EEG activity; (3) test a diathesis-stress model of frontal asymmetry whereby asymmetry

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interacts with maltreatment experiences to predict higher levels of inflammation; and finally (4) we conducted an exploratory analysis to probe whether frontal asymmetry's associations with inflammation and maltreatment are independent of or overlapping with depression, anxiety, and lifestyle indices (cigarette smoking, alcohol consumption, physical exercise, abdominal adiposity, and sleep difficulties). We describe the theoretical rationale for these goals next.

### 1.1. Associations of frontal brain asymmetry with mental and physical health outcomes

Frontal EEG asymmetry is thought to reflect the activity of brain systems involved in approach and withdrawal motivation. Relatively greater left-sided activity is associated with approach behavior and predominantly positive affect. By contrast, relatively greater right-sided activity is linked to avoidance behavior and negative emotions like fear or sadness (Davidson, 1998b). Most, but not all, research suggests an association between right-sided frontal asymmetry and risk for depressive and anxiety disorders (Davidson, 1998a; Fingelkurts and Fingelkurts, 2015; Jesulola et al., 2015; Nusslock et al., 2015; Thibodeau et al., 2006).

However, much less attention has been dedicated to examining the links between frontal asymmetry and physical health. A handful of studies have explored frontal asymmetry in relation to immune function, and predominantly found right-sided asymmetry to correlate with indicators of reduced immune activity – for example, lower antibody titers in response to the influenza vaccine (Rosenkranz et al., 2003), lower natural killer cell activity at baseline (Kang et al., 1991) and in response to challenge (Davidson et al., 1999), as well as lower CD8T lymphocyte counts in HIV-positive patients (Gruzelier et al., 1996). However, it is difficult to extrapolate from these findings to other compartments of the immune system or to broader health outcomes. Accordingly, the present study's goal is to examine the association between frontal asymmetry and proteins indexing low-grade inflammation (serum interleukin-6, C-reactive protein, and fibrinogen).

### 1.2. The developmental origins of frontal asymmetry

Despite almost four decades of research on the role of frontal asymmetry in affective processes and psychopathology, the developmental origins of frontal EEG asymmetry are not well understood. Twin studies reveal modest heritability estimates for this construct, ranging from 11% to 37% of variance being attributed to genetic factors (Anokhin et al., 2006; Gao et al., 2009; Smit et al., 2007). Additionally, there is some evidence linking prenatal conditions including maternal depression and substance abuse to newborns' frontal EEG activity (Field and Diego, 2008). A recent meta-analysis has also begun revealing some of the environmental risk factors associated with right-sided frontal asymmetry in children and adolescents (Peltola et al., 2014). The most robust association in terms of the number of studies supporting it and the consistency of the findings is that with parental depression, especially maternal depression (Peltola et al., 2014). The low genetic heritability estimates suggest that some of the pathways from parental psychopathology to offspring's EEG phenotype might be psychosocial. Isolated studies have supported this notion and linked frontal asymmetry to parental insensitivity (Hane and Fox, 2006) and parental deprivation (i.e., orphanage rearing) (McLaughlin et al., 2011), but not parental alcohol dependence (Ehlers et al., 2001). Only two studies have examined links to childhood maltreatment, including neglect and abuse, and their findings are mixed. Miskovic et al. (2009) found that adolescent females exposed to maltreatment had greater right-sided frontal EEG asymmetry compared to non-maltreated controls, whereas

Curtis and Cicchetti (2007) reported no main effect of maltreatment on frontal asymmetry and an interaction with gender such that there was no effect in females and the opposite effect from the typical prediction in males – i.e., greater left-sided asymmetry in maltreated males. More research is needed to clarify the experiential correlates of frontal asymmetry, thus the present study sought to examine its association with retrospectively-reported maltreatment experiences.

### 1.3. The diathesis-stress model of frontal asymmetry

The literature on associations between resting frontal EEG asymmetry and risk for mood and anxiety disorders also includes some mixed findings, such that not all individuals with right-sided asymmetry suffer from psychopathology (Davidson, 1998b). It has been theorized that the individual differences in underlying prefrontal brain activity bias towards approach or withdrawal tendencies, but are not in themselves sufficient for triggering psychopathology (Davidson, 1998b). A diathesis-stress model of frontal asymmetry has been advanced to propose that frontal asymmetry interacts with negative life events to precipitate psychopathology (Davidson, 1993). Most studies of frontal asymmetry and risk for psychopathology have not explicitly tested this hypothesis, but there is some empirical support for this idea. For instance, in 6–13-year-old children at-risk for depression, the number of negative life events experienced was associated with proportional increases in internalizing symptoms only in children with predominantly right-sided frontal activity (Lopez-Duran et al., 2012). It is currently unknown whether the diathesis-stress model would also apply to outcomes related to physical health. We sought to answer this question by examining whether the association between resting frontal asymmetry and low-grade inflammation varies as a function of exposure to childhood maltreatment. There is abundant evidence that maltreatment is a risk factor for affective disorders (Teicher and Samson, 2013), inflammatory activity (Coelho et al., 2014; Danese et al., 2007), and chronic health problems across the lifespan (Danese and McEwen, 2012; Miller et al., 2011; Repetti et al., 2002; Wegman and Stetler, 2009).

### 1.4. The role of depression, anxiety, and health behaviors

Inflammation is an adaptive response by innate immune cells to injuries and infections. However, if this response becomes sustained and disseminated, a low-grade chronic inflammation can develop, which has been linked to morbidity and mortality (Black, 2003; Libby, 2012). Frontal asymmetry may foster inflammation in a number of ways. It may predispose to depressive and anxious symptoms (Thibodeau et al., 2006), which have bidirectional connections with inflammation (Slavich et al., 2010; Vogelzangs et al., 2013). Additionally, frontal asymmetry is associated with positive and negative affective experiences (Coan and Allen, 2004; Davidson, 2004), which predict engagement in restorative or deteriorative health behaviors (e.g., sleep, physical exercise, cigarette smoking, alcohol consumption, weight gain) (Boehm and Kubzansky, 2012), all of which can influence inflammation (Kiecolt-Glaser and Glaser, 1988; Mullington et al., 2010; Raposa et al., 2014; Strohacker et al., 2013). For these reasons, it is plausible that the association between frontal asymmetry and inflammation may be accounted for by internalizing symptoms (depression, anxiety) or health behaviors. We aimed to test these possibilities in the current study.

## 2. The present study

This report is based on data from the Neuroscience Project of the Midlife in the United States (MIDUS) study. The primary goals

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