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

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A B S T R A C T
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...
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 CD8 T 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 McClue, 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 (Slovich 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
of the present study were to (1) examine whether resting frontal asymmetry is associated with greater low-grade inflammation at midlife; (2) test whether self-reported childhood maltreatment experiences are associated with frontal EEG asymmetry; (3) investigate if childhood maltreatment interacts with frontal asymmetry to explain inflammation, as predicted by the diathesis-stress model; and, finally, (4) examine 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).

3. Methods

3.1. Participants

Participants were drawn from the nationally representative MIDUS study, which began in 1995–1996 with 7108 non-institutionalized adults selected via random-digit phone dialing from the 48 contiguous states. An average of 9 years later, 75% of surviving respondents participated in a follow-up study, known as MIDUS 2 (see Fig. 1 for visual depiction of the study’s data collection waves). The present report used data from participants who completed the Neuroscience Project (N = 331) during MIDUS 2 and also extracted data for these participants from the following other MIDUS 2 assessments: the Survey Project, which included extensive phone interview and self-administered questionnaire data; the Biomarker Project, for which participants traveled to a General Clinical Research Center for a two-day, overnight visit and provided fasting blood samples, among other biological specimens; and the Milwaukee Study, which consisted of recruiting an African American subsample recruited from the Milwaukee, Wisconsin area that completed all the measures from MIDUS 1 and MIDUS 2 at the same time.

For the analyses reported here, we included 314 participants from MIDUS 2 with available data for the EEG recordings, the inflammation indices and questionnaire measures of interest, as well as data on the sociodemographic and biomedical covariates. Participants included in this analysis were on average 55.3 years old (range: 36–84; SD = 11.2); 55.7% female and exhibited some diversity in terms of racial/ethnic background: 63.4% Non-Hispanic White, 31.8% African American, and 4.8% other. The average total annual household income in this sample was $61,537 (SD = $50,963, range $0–$300,000). There were 35 sibling sets in the Neuroscience Project and 31 among participants included in this report (see Section 4.5 of Results for details on how they were treated in analyses). All procedures were carried out with the adequate understanding and informed written consent of all participants.

3.2. Procedure

3.2.1. EEG acquisition and processing

Participants visited the Laboratory for Brain Imaging and Behavior at the University of Wisconsin-Madison. To derive measures of frontal brain asymmetry, electrical brain activity was recorded using a 128-channel geodesic net (Electrical Geodesics, Inc. [EGI], Eugene, OR). Participants had the net placed on their head and were then escorted into a soundproof booth where they were seated in front of a computer screen. A computer located outside the booth recorded the data. Each participant was instructed to rest for six 1-min periods. During three of the 1-min periods they were asked to keep their eyes open; for the remaining three 1-min periods they were asked to keep their eyes closed. EEG baselines were collected at the beginning and at the end of the session. The data used in this analysis was restricted to the first set of six baselines collected at the beginning of the session. To increase the reliability of the EEG baseline data, we collapsed across conditions and across minutes. Processing steps were conducted according to accepted guidelines and are described below (see Pivik et al., 1993 for additional information).

3.2.1.1. EEG recording. Electrical brain activity was recorded using a 128-channel geodesic net of Ag/AgCl electrodes encased in saline-dampened sponges (EGI). Electrode impedances were reduced to less than 100 KΩ, and analog EEG signals were amplified and sampled at a rate of 500 Hz (bandpass filtered from 0.1–100 Hz) with 16-bit precision using an online vertex (Cz) reference.

3.2.1.2. Data cleaning. After 60 Hz notch filtering and 0.5 Hz high-pass filtering to remove slow frequency drift, bad channels were identified and removed. Bad sections of data were also removed. Using EEGLAB6, the EEG data was then submitted to a PCA/ICA forcing the identification of 20 components. PCA/ICA was conducted for each individual. The PCA/ICAs were used to identify common artifacts in EEG, such as eye blinks and eye movements, and cardiac signals. Based on testing performed in the laboratory with ICA and forcing the identification of a range of PCA components, we concluded that forcing 20 components resulted in the best decomposition of these artifacts, and with maximal time efficiency both in processing the data and in identifying components capturing artifacts. Components containing obvious eye blinks, eye movements and other artifacts were then removed from the data. Bad channels were then replaced using a spherical spline interpolation. Epochs of 2 s length were then created. The EEGLAB automated artifact identification routine was then run on these epoched data files, identifying epochs containing deviations of ±100 µV, which were then subsequently removed.

3.2.1.3. Frequency analysis. Using LORETA-KEY, the spectral power density was then computed for each sensor using epochs of 2 s duration (with 50% overlap) following linear detrending and application of a Hanning window. Due to variability of the actual peak of the alpha frequency across age, an alpha power band was determined on the basis of each individual’s alpha peak frequency (Klimesch, 1999). The peak frequency was identified using an automated routine which picked the peak in a frequency window ranging from 6 to 14 Hz across the scalp. Lower and upper alpha bands were then defined as follows: lower band of Alpha 1 was the individual alpha peak frequency (IAP) – 30% of IAP, upper band of Alpha 1 was up to IAP; lower band of Alpha 2 was actual IAP, whereas upper band of Alpha 2 was IAP + 30% of IAP.

3.2.1.4. Missing data. The rate of missing EEG data due to participant refusal or excluding data having 50% or more bad EEG channels was low (3.6% total, or N = 12).

3.2.2. Biomarker collection

For the biomarker collection, participants arrived to the clinic and were checked in for their two-day overnight stay. On the first day, they were assisted by medical staff in completing their medical history, a physical exam, and a bone densitometry scan. The following morning, nursing staff collected fasting blood samples from which the inflammatory biomarker concentrations were later derived.

3.3. Measures

3.3.1. Frontal brain asymmetry

Log alpha power was averaged across multiple sites on the scalp to create more reliable indices that approximate sites in the standard 10–20 EEG system. Log alpha power in the right frontal
area was subtracted from log alpha power in the left frontal area (left–right) to create an index of laterality. To create a single measure of relative frontal alpha activity, the laterality indices for the FP1/FP2, F3/F4, and F7/F8 regions were averaged, as were the Alpha 1 and Alpha 2 bands. Because greater alpha activity indicates less neural activation, larger laterality scores indicate greater right hemisphere activation.

3.3.2. Inflammation composite

Three serum markers of low-grade inflammation derived from fasting blood samples were used to create our composite: C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen.\(^1\) CRP was measured using a particle enhanced immunonephelometric assay (BNII nephelometer, Dade Behring Inc., Deerfield, IL). Serum IL-6 was assessed using the Quantikine® High-sensitivity ELISA kit #HS600B according to manufacturer guidelines (R & D Systems, Minneapolis, MN). Fibrinogen antigen was measured using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). The laboratory intra- and inter-assay coefficients of variance (CV) for all protein assays were in acceptable ranges (<10%).

An inflammation composite was created by standardizing and combining the IL-6, CRP and fibrinogen measures. According to a Principal Components Analysis, these three measures loaded on a single common factor (with loadings of 0.81, 0.83, and 0.84, respectively). Cronbach’s alpha for this composite measure was 0.77.

3.3.3. Childhood trauma questionnaire

The CTQ (Bernstein et al., 2003) was completed by participants at the biomarker collection. The CTQ is a 28-item self-report questionnaire that assesses physical abuse, emotional abuse, sexual abuse, emotional neglect, and physical neglect caused by a family member before the age of 18 and has high external validity, such that self-reports on the CTQ questionnaire are consistent with information derived from clinical interviews and Child Protective Services records (Bernstein et al., 2003). The total score for items inquiring about the five types of maltreatment was used in analyses. The CTQ had high internal reliability in this sample (Cronbach’s alpha = 0.90).

3.3.4. Depressive symptoms

The 20-item Center for Epidemiologic Studies Depression (CES-D) Inventory was used at the time of biomarker collection to assess depressive symptoms in the prior week. In prior studies the measure has shown high internal consistency and test-retest reliability, as well as adequate validity assessed via correlations with other self-report measures and clinical ratings (Radloff, 1977). In this sample the measure also had high internal consistency (Cronbach’s alpha = 0.86).

3.3.5. Anxious symptoms

The 20-item Spielberger State-Trait Anxiety Inventory (STAI, Spielberger et al., 1983) was used to extract a measure of typical levels of anxious symptoms (only the trait measure was used here). Participants completed 4-point Likert-type items to describe how often they were faced with thoughts such as “I worry too much over something that doesn’t really matter.” The trait anxiety measure had a high Cronbach’s alpha in this sample (0.88).

3.3.6. Lifestyle indices

At the biomarker assessment, information regarding sleep quality, physical exercise, cigarette smoking, alcohol consumption, and waist circumference (measured in centimeters in the laboratory and standardized within each gender) was collected. Sleep quality was assessed using the Pittsburgh Sleep Inventory (PSQ, Buysse et al., 1988), which measures the following seven dimensions using a total of 19 self-rated items: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. The Global Sleep score was constructed by summing the seven sleep components for each case with complete data. Reverse-coded sleep components were re-coded such that higher scores represented greater sleep difficulties across all the scales. Global sleep scores were not computed for cases with erroneous reporting (e.g., Habitual Sleep Efficiency greater than 100%). Because the distributions of smoking, alcohol use, and exercise variables were extremely skewed and could not be corrected with transformations, they were recoded into ordinal variables. For smoking, the new variable was coded as 0 = never smoker, 1 = former smoker, and 2 = current smoker. For alcohol, it was 0 = zero drinks per week, 1 = less than 10 drinks per week, and 2 = 10 or more drinks per week. For physical exercise, number of minutes of weekly strenuous activity were coded as 0 = none, 1 = less than 50 min per week, 2 = 500–1000 min per week, and 3 = more than 1000 min per week. These categories were

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\(^{1}\) There were three other indices of inflammation measured in MIDUS (E-Selectin, ICAM-1, and serum soluble IL-6 receptor), however they had zero to small correlations with the other inflammation measures in this Neuroscience subsample of MIDUS (e.g., serum soluble IL-6 receptor had correlations ranging from \(r = -0.004\) to \(-0.08\), \(p > 0.13\) with four of the five other inflammatory indices and only had a significant but small association with ICAM-1). Additionally, E-Selectin and ICAM-1 had low loadings (0.31 and 0.33) on a common inflammation factor extracted through Principal Components Analysis, thus they were excluded from the inflammation composite to increase the internal consistency of the measure (from Cronbach’s alpha = 0.63 to a more acceptable alpha = 0.77). However, results were robust with or without E-Selectin and ICAM-1 in the inflammation composite (analyses available upon request).
chosen based on a previous MIDUS report, which significantly linked the exercise variable coded in this fashion to inflammatory outcomes (Strohacker et al., 2013).

3.3.7. Covariates
Basic sociodemographic, medical history, and medication usage information was obtained during the biomarker collection and MIDUS 2 assessments. Participants' age, sex, and educational level were included in our models. Additionally, race/ethnicity was dummy-coded for analyses, with the most numerous group (non-Hispanic Whites) serving as the reference and binary codes being used to denote African American and Other race/ethnicity (sample sizes were too small to account for any other racial/ethnic group – e.g., there were only n = 5 participants of Hispanic origin in this sample). Medical diagnoses and medications with potential associations with inflammation were also selected for inclusion – namely, history of heart disease or diabetes; use of anti-hypertensive, cholesterol-lowering, corticosteroid, or non-steroidal anti-inflammatory medications.

3.4. Data analysis plan

3.4.1. Data preparation
Variables were examined for outliers and for their approximation of the normal distribution before analyses. Values that exceeded four standard deviations from the mean were Winsorized and replaced with the value at the 99.9th percentile (CRP: n = 5; IL-6: n = 7; frontal asymmetry scores: FP1/FP2 alpha 1 band, n = 3; FP1/FP2 alpha 2 band, n = 4; F7/F8 alpha 1 band, n = 3; F7/F8 alpha 2 band, n = 3; F3/F4 alpha 1 band, n = 2; F3/F4 alpha 2 band, n = 2). A logarithmic transformation was also applied to normalize the distributions of skewed variables (CRP, IL-6, CTQ total, and CES-D scores; all had a right skew prior to log transformation).

3.4.2. Missing data
The rate of missing data for the variables used in our analyses was low, ranging from 0% to 8.5% (e.g., 8.5% out of the 331 participants were missing data on sleep difficulties). Data were missing completely at random (MCAR) according to Little’s MCAR test: \( \chi^2 = 137.31, df = 119, p = 0.12 \). Multiple imputation was used to verify that results are robust when including all the participants in the models. We generated 40 imputed datasets based on recommendations by Graham (2009) and re-conducted the primary analyses on the pooled data from these imputations using IBM SPSS Statistics 23 software. Our primary results were replicated in the analyses using the multiply-imputed pooled dataset (see Supplemental Table 1 for these results).

3.4.3. Statistical analyses
We used multiple linear regression models and analyses of covariance (ANCOVAs) to examine our four hypotheses. All the analyses adjusted for the set of sociodemographic and biomedical covariates described above, but unadjusted associations among the primary study variables are also presented in Table 1.

1. For our first question regarding the association between frontal asymmetry and inflammation, we regressed the inflammation composite onto frontal asymmetry and the panel of covariates.
2. For the second question regarding maltreatment as a potential predictor of asymmetry, we regressed frontal asymmetry onto maltreatment and the covariates. To further characterize differences between maltreated and non-maltreated individuals, we created a binary variable where 1 indicated meeting or exceeding the CTQ cutoff score for experiencing any one of the five possible maltreatment subtypes (physical abuse, sexual abuse, emotional

| Table 1: Bivariate correlations and descriptive statistics for primary study variables |
|----------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                                | (log 10 CTQ)      | (log 10 CES-D)   | (log 10 CTQ total)| (log 10 CRP)     |                  |                  |
| 1. Depression                  | 0.13             | -0.03            | 0.27             | 0.41             | 0.17             | 0.13             |
| 2. Anxiety                     | 0.13             | -0.03            | 0.27             | 0.41             | 0.17             | 0.13             |
| 3. Maltreatment                | 0.13             | -0.03            | 0.27             | 0.41             | 0.17             | 0.13             |
| 4. Smoking                     | 0.13             | -0.03            | 0.27             | 0.41             | 0.17             | 0.13             |
| 5. Abdominal adiposity         | 0.13             | -0.03            | 0.27             | 0.41             | 0.17             | 0.13             |
| 6. Age                         | 0.13             | -0.03            | 0.27             | 0.41             | 0.17             | 0.13             |

* p < 0.05
3. To test whether the interaction of frontal asymmetry and childhood maltreatment exposure in predicting inflammation best fits a diathesis-stress model, we used the criteria recommended by Roisman and colleagues (Roisman et al., 2012). Specifically, this included the following steps: a) showing a statistically significant interaction between frontal asymmetry and maltreatment; b) testing the significance of simple slopes at high and low values of the moderator (we chose +1SD and −1SD of the moderator; note that we tested simple slopes for both maltreatment and for frontal asymmetry, which were in turn considered the moderator); c) computing regions of significance (RoS) using the Johnson–Neyman technique (Johnson and Neyman, 1936) implemented using the SPSS process macro (Hayes, 2013), which is a technique that provides the full range of values of the moderator for which the independent and dependent variable are significantly associated, rather than testing single values through simple slopes analysis; Roisman et al. recommend identifying RoS on both the predictor and the moderator by reversing the role of the predictor and the moderator after the initial moderation analysis. Thus, we report both the RoS on maltreatment, which shows the range of maltreatment experiences for which asymmetry and inflammation are associated, and the RoS on frontal asymmetry, which reveals the range of frontal EEG asymmetry for which maltreatment is significantly associated with inflammation; d) plotting the interaction and these RoS in graphs that display values ranging from −2SD to +2SD of the predictor; to obtain the figures, we used the web-based program recommended by Roisman, Fraley and colleagues (Roisman et al., 2012), available at http://www.yourpersonality.net/interaction/; e) to test how well the data fit a diathesis-stress model where maltreatment is the stressor and frontal asymmetry is the diathesis, we computed the proportion of the interaction (Pol) index, a measure of how much a crossover interaction is “for better” versus “for worse” – i.e., how much the data fit a diathesis-stress model (values for Pol closer to zero) versus a differential susceptibility model (values of Pol are closer to 0.50; see Roisman et al., 2012 for a detailed explanation of how this index is derived); f) we further computed a proportion affected (PA) index, which captures the proportion of the sample that is affected by the statistical interaction; and finally, g) we ruled out the possibility of the diathesis-stress effects being due to a nonlinear interaction by adding terms for the predictor-squared and predictor-squared multiplied by the moderator. This final step is intended to demonstrate that the significant linear interaction of the predictor and the moderator is not an artifact of a nonlinear effect of one of the predictors.

4. Finally, to examine whether frontal asymmetry’s associations with inflammation and maltreatment are independent of or overlapping with depression, anxiety, and lifestyle indices, we aimed to conduct linear regression analyses (inflammation regressed onto frontal asymmetry and maltreatment regressed onto frontal asymmetry) that also entered one of the following covariates in separate analyses: depressive symptoms, anxiety symptoms, cigarette smoking, alcohol consumption, physical exercise, abdominal adiposity, and sleep difficulties. These analyses were conducted on the pooled multiply-imputed dataset (N = 331) to account for varying amounts of missing data on each of these additional measures. To equalize degrees of freedom across these analyses, listwise deletion would have resulted in a 14.5% loss of sample size (N = 283) and in these instances multiple imputation is recommended as it guards against loss of statistical power and possible bias of estimates (Bennett, 2001).

4. Results

Bivariate correlations and descriptive statistics for the main study variables are shown in Table 1. A total of 106 participants (33.8% of the sample) reported at least one abuse subtype according to clinical cut-off criteria for the CTQ subscales, as follows: 11.8% of the full sample endorsed physical abuse, 13.7% emotional abuse, 15% sexual abuse, 17.2% emotional neglect, and 15.9% physical neglect. These percentages add up to more than 33.8% of the sample due to comorbidity of maltreatment subtypes. Of the 106 of participants who experienced maltreatment, 45 reported one maltreatment subtype (14.3% of full sample), 25 reported two subtypes (8% of sample), 18 reported three subtypes (5.7% of sample), and 8 reported four subtypes (2.5% of sample) and 10 participants endorsed all five subtypes (3.2% of sample). The average maltreatment severity score on the CTQ scale in this sample was M = 37.7 (SD = 13.9, range = 25–106).

4.1. Frontal brain asymmetry and systemic low-grade inflammation

The regression analyses indicated that frontal brain asymmetry was significantly associated with low-grade inflammation (β = 0.13, SE = 0.06, p = 0.02) such that more right activity covaried with higher inflammation composite scores. This association remained significant after adjusting for sociodemographic and medical history covariates (β = 0.11, SE = 0.05, p = 0.04, see Model 2 in Table 2).

4.2. Frontal brain asymmetry and self-reported childhood maltreatment

Frontal brain asymmetry was not significantly associated with CTQ maltreatment scores (r = −0.009, p = 0.87). This association remained non-significant (β = 0.005, SE = 0.06, p = 0.93) when regressing frontal asymmetry on child maltreatment and including our panel of covariates. These results were consistent with those of an ANCOVA showing no significant main effect of maltreatment status on frontal asymmetry, F (1,301) = 0.49, p = 0.49 such that mean asymmetry for maltreated participants (M = −0.05, SD = 1.04) did not differ from that of non-maltreated individuals (M = 0.03, SD = 0.98). This analysis adjusted for our full panel of covariates, including gender, which was not a significant predictor of asymmetry, F (1,301) = 0.002, p = 0.96. Given prior literature regarding gender effects, we repeated this analysis to include an interaction term between maltreatment and gender, however this interaction was also not significant, F(1,301) = 0.16, p = 0.69. Additionally, associations between maltreatment scores and frontal asymmetry were also non-significant within each of the genders (p’s > 0.34).

4.3. Testing the diathesis-stress model

Regression analysis revealed a significant interaction between frontal asymmetry and childhood maltreatment exposure in predicting inflammation (β = 0.12, SE = 0.05, p = 0.02), and this remained significant after adjustment for sociodemographic and biomedical covariates (β = 0.10, SE = 0.05, p = 0.03, see Model 4 in Table 2). We followed up on this analysis by first considering maltreatment to be the moderator, and frontal asymmetry the predictor. Simple slopes analysis revealed that frontal asymmetry was significantly associated with inflammation at high (+1SD) levels of CTQ maltreatment scores (slope: β = 0.21, p = 0.003), but not at
Table 2: Multiple linear regression results with the inflammation composite as the dependent variable. Analyses were conducted on N = 314.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
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<td>Constant</td>
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Fig. 2. Right-sided frontal asymmetry (i.e., having a higher asymmetry score) was associated with more inflammation in those reporting high levels of maltreatment (top 40.8% of CTQ scores). The gray shaded area represents the region where the two lines differ significantly from each other. All variables were standardized, thus values represent Z-scores. Statistics for simple slopes are displayed next to each line.

Low (−1SD) levels of maltreatment (slope: β = −0.00, p = 0.99). The Johnson-Neyman technique identified the region of significance for the association between frontal asymmetry and inflammation as including individuals scoring above 0.013 on the Z-scored CTQ scale (i.e., the inflection point was close to the mean of the scale), which was equivalent to being in the top 40.8% scores for the CTQ in this sample. Fig. 2 illustrates this interaction.

When considering frontal asymmetry to be the moderator and maltreatment the predictor, we found that maltreatment was significantly associated with inflammation only for those with high asymmetry scores (i.e., with right-sided dominance). Specifically, simple slopes analysis revealed that maltreatment was marginally related to inflammation at +1SD levels on asymmetry (β = 0.14, p = 0.06), but not related to inflammation at −1SD on asymmetry (β = −0.07, p = 0.35, see Fig. 3). The region of significance for the association between maltreatment and inflammation included values of 1.15 or higher on asymmetry (Z-scored), which was equivalent to the top 10.8% of asymmetry scores in this sample.

We then computed the indices recommended by Roisman and colleagues to test whether our results best resemble a diathesis-stress pattern. Frontal asymmetry was considered the diathesis, and maltreatment the stressor (see Fig. 3 for the graph corresponding to this analysis). The Pol index was 0.10, suggesting that 10% of the interaction occurred left of the crossover point ("for better"), whereas 90% was right of the crossover point ("for worse"). The fact that the Pol value was closer to 0 than 0.50 is evidence supportive of a diathesis-stress model interpretation (in contrast, Pol values closer to 0.50, where the crossover point would be close to the middle of a graph spanning from −2SD to +2SD, would support a differential susceptibility model). Further supporting our diathesis-stress interpretation, the PA index was 0.13, suggesting that only 13% of individuals were affected by the interaction “for better”, whereas 87% were affected “for worse”. This result supported the diathesis-stress interpretation of our results given recommendations that at least 16% of the sample needs to be affected “for better” before a differential susceptibility interpretation would be preferred to a diathesis-stress interpretation (Roisman et al., 2012).
There was also no evidence of nonlinear effects, as terms for the predictor-squared and predictor-squared multiplied by the moderator were not significant (\( p = 0.30 \) and \( p = 0.13 \) respectively). This suggested that our diathesis-stress results were not an artifact of nonlinear associations between the predictor and the outcome.

### 4.4. Exploring the role of depression, anxiety and lifestyle indices

Given that frontal asymmetry was not associated with our measure of childhood maltreatment, we focused next on examining the role of depression, anxiety and lifestyle indices in potentially explaining some of the association between frontal asymmetry and inflammation. Multiple regression analyses revealed that the interaction between frontal asymmetry and inflammation remained significant when entering depression, anxiety, cigarette smoking, alcohol use, or physical exercise as covariates one at a time (Table 3). Furthermore, these were not significant predictors of inflammation in this sample (Table 3). In contrast, abdominal adiposity and sleep difficulties were each a significant predictor of inflammation independently of all other variables in the model \( (b = 0.44, SE = 0.05, p < 0.001, \) and \( b = 0.05, SE = 0.02, p = 0.003, \) respectively). Furthermore, the interaction between frontal asymmetry and inflammation no longer significantly predicted inflammation when either of these two variables were added to the multiple regression models (Table 3), suggesting that they explain shared variance in the outcome measure.

### 4.5. Sensitivity analyses

To rule out the potentially confounding role of handedness, we re-conducted the primary analyses with right-handed participants only \( (N = 293) \). All of the primary results were robust in this subsample. Furthermore, the frontal asymmetry scores of right-handed participants \( (M = -0.03, SD = 0.11) \) did not differ significantly from those of left-handed participants \( (M = -0.015, SD = 0.10, N = 21) \), \( t(312) = 0.68, p = 0.50 \). Nevertheless, we present our primary results
in the subsample composed exclusively of right-handed participants in Supplemental Table 2.

In this study we included frontal asymmetry scores aggregated across FP1/FP2, F3/F4 and F7/F8 electrode sites to reduce the number of statistical tests conducted. This was also suggested by prior literature supporting associations of asymmetries in these regions with measures of affective processes (for a review, see Coan and Allen, 2004). Given our significant results involving the frontal asymmetry composite, we further probed which of these locations were primarily responsible for the association with inflammation. As shown in Supplemental Table 3, our findings were driven by lateral frontal sites F7/F8, which were the only ones significantly associated with inflammation after partialing out the effect of sociodemographic and biomedical covariates. Childhood maltreatment was not associated with asymmetry scores at any of the frontal sites.

As measures of potential self-report biases, the CTQ Minimization/Denial Scale and the Neuroticism scale from the Midlife Development Inventory-Personality Scales were tested as covariates in sensitivity analyses to assess the role of under-reporting or over-reporting childhood maltreatment experiences, respectively. Our primary results reported above were robust when statistically adjusting for these measures of self-report bias and also when excluding participants whose scores were in the top 5% for these measures.

Finally, there were 31 sibling sets in this sample. Because their data are likely to be correlated and violate the assumption of independent and identically distributed observations, we repeated all our analyses including only one sibling from each family (selected using a random number generator) and all significant results were unchanged, thus results are reported on the full sample.

5. Discussion

Right-sided frontal EEG asymmetry has been proposed as a diathesis for experiencing negative affect when confronted with environmental challenges, and has been linked to an increased risk of depression and anxiety disorders (Davidson, 1998a; Fingelkurts and Fingelkurts, 2015; Jesulola et al., 2015; Nusslock et al., 2015; Thibodeau et al., 2006). However, much less is known about frontal asymmetry’s link with physical health, or its experiential correlates. The present study targeted these questions.

Our primary finding was a positive association between right-sided frontal EEG asymmetry and low-grade inflammation. This association was qualified by an interaction with childhood maltreatment, such that the association was only present for individuals with moderate to high levels of self-reported childhood maltreatment indices. This finding suggests that, in the context of major stressors, a trait-like tendency towards greater relative right frontal activity may not only be a vulnerability factor for affective disorders (Lopez-Duran et al., 2012), but also for low-grade inflammation. If sustained, that inflammation could have repercussions for physical health problems that have inflammatory underpinnings, such as coronary heart disease, diabetes, and metabolic syndrome (Black, 2003; Libby, 2012). Our findings also provided support for the diathesis-stress model of frontal brain asymmetry (Davidson, 1993). As already noted, that model posits that relatively greater right frontal activity creates vulnerability for individuals confronted with emotionally challenging major environmental stressors. Consistent with this view, our findings demonstrate that, in individuals exposed to maltreatment, frontal EEG asymmetry is a marker of risk for inflammation, and potentially also its long-term health consequences. Future studies should use natural or laboratory-based experiments to explicitly test the mechanisms hypothesized here. Namely, it will be important to test whether individuals who have greater right-sided frontal EEG activity respond to a randomly occurring or standardized laboratory stressor with greater inflammatory activity compared to those who show greater left-sided EEG activity. It would then also be informative to know whether this pattern is related to long-term patterns of chronic low-grade inflammation and cardiovascular risk.

A corollary of the statistical interaction we discovered was that childhood maltreatment was only related to inflammation in this sample in those with high asymmetry scores (i.e., right-sided dominance, at least 1.15 standard deviations above the mean). This finding is reminiscent of some reports in which maltreatment is more strongly coupled with inflammation in those who are also depressed (Danese et al., 2011; Miller and Cole, 2012), thus it is possible that intense negative affect may moderate the association between maltreatment and inflammation. The moderating role of affective style may explain why some studies find main effects of childhood maltreatment on inflammation, whereas a minority of studies do not (Coelho et al., 2014).

Another aim of this study was to examine the association between self-reported child maltreatment experiences and frontal asymmetry. The developmental origins of frontal brain asymmetry are not fully understood, with prior research suggesting contributions for environmental factors, prenatal conditions (Field and Diego, 2008), and modest genetic heritability estimates (Anokhin et al., 2006; Gao et al., 2009; Smit et al., 2007). We found that self-reported childhood maltreatment experiences in middle age were not associated with frontal asymmetry, consistent with another study of 6–12-year-old children which did not find a main effect of objectively-documented maltreatment on frontal EEG asymmetry (Curtis and Cicchetti, 2007). Maltreatment and asymmetry were also not correlated within each gender, contrary to one previous study showing greater right-sided asymmetry in 38 maltreated adolescent females compared to 25 non-maltreated female peers (Miskovic et al., 2009). One possible interpretation of the fact that maltreatment is not reliably associated with frontal asymmetry across these studies but appears to moderate its association with negative outcomes is that exposure to stressors may not be the root cause of resting frontal brain asymmetry. Consistent with this interpretation, Lopez-Duran and colleagues found that life events were not associated with frontal asymmetry scores at rest in 6–13-year-olds (Lopez-Duran et al., 2012), but asymmetrical patterns of frontal brain activity while watching sad and happy films were correlated with stressful life events (Lopez-Duran et al., 2012). Emotion-elicit conditions or events might be required to reveal these associations. With respect to the developmental origins of this vulnerability, parental depression (especially in mothers) is robustly associated with a right-sided bias in resting frontal EEG activity in the offspring, an effect that has been documented as early as infancy in multiple studies (Field and Diego, 2008; Peltola et al., 2014). It is possible that parent-child interactions during infancy may be shaped by withdrawn/depressed parent behavior and may establish a stable tendency towards avoidance/withdrawal in infants, which in the context of later adverse events like maltreatment or other life events may lead to persistent negative affect or excessive stress reactions. The same pathway might explain increased risk of low-grade inflammation.

In our exploratory analysis of the role of depression, anxiety and health behaviors in potentially explaining the links between frontal asymmetry and inflammation, sleep difficulties and waist circumference emerged as potential candidates that might be worth pursuing as mediators in future analyses. First, these were both significant predictors of inflammation independently of all other predictors in the model. Second, the interaction of frontal asymmetry and maltreatment was no longer significant in predict-
ing inflammation when accounting for the role of either sleep or abdominal adiposity. We discuss each of these findings in turn.

With respect to the role of sleep difficulties, individuals exposed to trauma can experience disruptive nocturnal behaviors such as nightmares, sleep terrors, nocturnal panic attacks and dream enactment behaviors for decades after the trauma (Cecil et al., 2015). Controlled experimental studies in humans have also convincingly established that sleep disruption can alter mediators of inflammation by activating components of the active phase response (Mullington et al., 2010). These associations between maltreatment and sleep difficulties, as well as between sleep difficulties and inflammation were also observed in this study (Table 1). Additionally, we found that the interaction between frontal asymmetry and childhood maltreatment was no longer significant after partialing out the effect of sleep. This pattern is suggestive of a pathway mediated by sleep, though the cross-sectional design in the present report was not optimal for testing mediation or moderated mediation models. We speculate that, in the context of maltreatment exposure, right-prefrontal activity may index a pattern of ruminate cognitions about past trauma that may be disruptive to sleep and conducive to inflammation, but the mediating role of sleep disruption and rumination will need to be explicitly tested in future studies that longitudinally track these processes as they unfold. Studies that shift patterns of EEG activity through interventions such as cognitive-behavioral therapy (Moscovitch et al., 2011) could test whether sleep improvements and decreases in systemic low-grade inflammation occur in trauma-exposed patients undergoing these treatments.

The association between adolescent adiposity and inflammation is not surprising, given the role of adipose tissue in releasing pro-inflammatory cytokines like IL-6. These cytokines recruit macrophages to the abdomen, where they attempt to clear necrotic adipocytes, and in doing so further potentiate inflammation (Hotamisligil, 2006). The novel finding in this study was that adolescent adiposity may explain some of the association between frontal brain asymmetry and inflammation in maltreated individuals. Stress eating may be the behavior that explains this association, given prior evidence that it mediates links between waist circumference and health (Tsenkova et al., 2013). Stress-evoked eating can stimulate endogenous opioid release and thereby improve mood (Adam and Epel, 2007), thus it is possible that individuals with right-sided frontal EEG asymmetry are using stress eating as a coping mechanism. Future studies should test this scenario more thoroughly.

Associations of depressive and anxious symptoms with inflammation were non-significant after stringent adjustment for our panel of covariates, but given the extensive literature linking depression with inflammation (Slavich et al., 2010) and some emerging evidence on possible connections between anxiety and inflammation (Vogelzangs et al., 2013), this pathway deserves further scrutiny in future studies. Nevertheless, these null findings suggest that the presence of psychopathology is not required for frontal asymmetry to be linked to deleterious physical health outcomes like inflammation. The significant and independent explanatory roles of sleep difficulties and abdominal adiposity inform us that other behavioral pathways may be at play in the realm of physical health outcomes. Furthermore, the diathesis-stress model may also explain the lack of direct associations of frontal asymmetry with depression and anxiety reported in some prior studies (Thibodeau et al., 2006). Based on the average effect sizes for the association between asymmetry and depression ($r = 0.26$) and asymmetry and anxiety ($r = 0.17$) reported in a prior meta-analysis (Thibodeau et al., 2006), we conducted power analyses to examine the sample size required to detect such effects with $\alpha = 0.05$ and power of 0.90 in this study. To detect the effect for depression, we needed at least 120 participants, whereas the anxiety effect size required at least 290 participants. Thus, our non-significant bivariate associations are not due to low statistical power. Instead, the discrepant findings across this literature suggest the presence of moderators that need further exploration (Thibodeau et al., 2006). Our study and the diathesis-stress model suggest that assessing stressful life events (e.g., maltreatment), which have only rarely been measured in studies of frontal asymmetry, might be fruitful.

As for the other lifestyle indices (cigarette smoking, alcohol consumption, and physical exercise), their lack of an association with frontal asymmetry in this study may be due to complex, non-linear associations between approach/avoidance brain systems and these lifestyle indices. For example, the appetitive/approach system (left-prefrontal) may promote a physically active lifestyle, whereas the avoidance/withdrawal system (right-prefrontal) might lead to higher levels of exercise as individuals use exercise to cope with prolonged stress reactions. Similarly, cigarette smoking and alcohol use may be driven by a motivational pull towards rewards (left-prefrontal) or the need to self-medicate negative affect (right-prefrontal). There is a paucity of studies on links between frontal asymmetry and health behaviors such as these, thus future studies should examine these possibilities in greater detail.

Finally, it must be noted that our frontal asymmetry findings were primarily driven by lateral frontal electrode sites (F7/F8), consistent with other studies that only find significant associations with psychopathology at these lateral frontal sites but not mid-frontal ones (Jacobs and Snyder, 1996; Lopez-Duran et al., 2012), though some reports detect stronger effects at F3/F4 sites (Coan and Allen, 2003). More research is needed to understand the neuroanatomical basis for these findings, and whether they are due to methodological differences, characteristics of the individuals, or the nature of the outcome that frontal asymmetry is being correlated with.

In conclusion, the present study had a number of strengths, including a large sample for psychophysiological research, which was drawn from a nationally representative study. Additionally, the in-depth assessment of inflammation using multiple biomarkers strengthens the reliability of our composite inflammation measure. Nevertheless, the study also had a number of limitations. Primarily, the correlational and cross-sectional nature of these analyses precludes any conclusions regarding causality, timing of effects, or mediating pathways. The patterns emerging from our analyses will need to be corroborated by longitudinal research, and by experimental studies that try to alter patterns of frontal EEG asymmetry (e.g., cognitive-behavioral therapy, Moscovitch et al., 2011). Future studies should explore whether interventions that can shift patterns of frontal EEG activity might also mitigate the risk of systemic, low-grade inflammation. It will be especially important to conduct such intervention studies with individuals exposed to past trauma.

**Conflicts of interest**

None.

**Contributors**

RJD, MEL, and TES designed the study. RJD and CMvR collected, processed, and prepared the data for analysis. CEH and GEM analyzed the data and interpreted the results. EKG and DKM provided statistical guidance. CEH wrote the first draft of the manuscript. CEH, RJD, EKG, DKM, MEL, TES, CMvR and GEM contributed to and have approved the final manuscript.
Role of the funding source

The funding agencies had no role in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.10.026.

References


