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Is Inconsistency in the Association between Frontal Alpha Asymmetry and Depression a Function of Sex, Age, and Peripheral Inflammation?

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Abstract: Although alpha asymmetry has been found to correlate with depression, there is some inconsistency across the wider literature, suggesting the influence of other factors. Some of these may be the presence of peripheral inflammation, age, and sex of participants. To test the interaction of these factors in terms of the association between alpha asymmetry and depression in a community sample, in this study, data were collected on resting frontal alpha asymmetry (FAA) under eyes closed and eyes open conditions, serum C-reactive protein (CRP), age, and self-rated depression in a sample of 44 males and 56 females aged from 18 to 75 years (M = 32.5 yr, SD = 14.1 yr). Using regression models, the results indicated a complex set of associations. FAA values across the FP2-FP1 sites predicted depression in the eyes open condition, but not for any other pairing of sites. Increases in CRP concentration predicted increases in depression for women but not for men. CRP predicted FAA across two frontal sites (F8-F7) under the eyes open condition only. As CRP increased, FAA favoured the left hemisphere for that pair of frontal sites, a result found more strongly for males. Age did not influence these associations. By reflecting a complex, multi-factor interaction, these findings may tentatively provide some explanation for the inconsistency in the wider literature for the FAA–depression hypothesis.

Keywords: depression; asymmetry; inflammation; sex; age

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1. Introduction

1.1. Depression

About 5% of the adult global population suffers from depression, with a higher prevalence among adult females (6%) than adult males (4%) [1]. As well as its considerable personal and social costs in terms of relationship stress and employment losses, depression imposes a disease burden cost of over USD 325 billion/year in the USA alone [2]. Despite this, the current frontline treatments of medication and psychotherapy are each successful in less than 40% of cases, rising to about 65% when combined [3]. Because some of this limitation in treatment efficacy may be due to inaccurate diagnosis, a good deal of research has sought to identify potential biomarkers of depression as a means of early diagnosis. One major recent focus of this research into depression has been its links with two potential biomarkers: inflammation, and asymmetry in brain activity.

1.2. CRP

Brain inflammation is now recognised as vital when considering the function of the nervous system and, consequently, how the brain interacts with the rest of the body.

Inflammation has mostly been measured via peripheral indices, usually from venous blood [4]. One of these indices is C-Reactive Protein (CRP), an important acute-phase protein found in blood plasma that identifies damaged cells or foreign micro-organisms and binds to a variety of ligands to stimulate phagocytosis as a key function of the immune response [5–7]. CRP is significantly correlated with other plasma inflammatory markers as well as CRP from the cerebrospinal fluid [8], and so has substantial generalizability power for drawing conclusions regarding inflammation in the brain. While such inflammation is typically associated with a broad range of physical pathologies, increased inflammation of the brain as measured via CRP has also been associated with increased prevalence of mental disorders [8–10]. Meta-analytic data indicate low-grade increases in CRP in patients with Major Depressive Disorder (MDD) [9], with some suggestion of a causal role evident between CRP and depression in longitudinal data [10].

1.3. Alpha Asymmetry

Frontal alpha asymmetry (FAA) is a common index of brain activity [11–15] in the frontal lobes of the brain. Alpha band activity in this region is typically associated with the inhibition of cognition via top-down processing, and is important for suppressing unnecessary neural processes such as those where attentional control is important [14]. FAA is calculated by subtracting the alpha power in the left frontal region from the alpha power in the right frontal region, usually based on resting EEG data [16–18]. The FAA-MDD hypothesis posits that EEG data from depressed individuals (as compared to the nondepressed) should display higher alpha band power activity in the right frontal lobe than the left [13,16,17,19–26]. However, a major meta-analysis of the FAA-MDD hypothesis concluded that this association was not consistently proven, and that future studies should address the interaction between depression severity, sex, and age [27] as a pathway to more comprehensive understanding of the relationship between this index of brain activity and depression.

1.4. CRP and FAA

Despite both FAA and CRP being associated with depression, relatively little has been reported regarding any potential connection between these measures. Some previous research suggested that right hemisphere frontal asymmetry was associated with lower antibody responses to an influenza vaccination [28], and lower natural killer cell activity [29], but this field has received relatively little attention recently, and no studies were identified that examined alpha asymmetry across the brain and its association with immune function at the time of writing (October, 2023). One possible hypothesis for the relationship between FAA and CRP is by way of the links between FAA and depression, and between depression and impaired immune function (see Sections 1.2 and 1.3), which may also be influenced by sex and age.

1.5. The Influence of Sex and Age

As mentioned in Section 1.1, depression is more prevalent among adult females than adult males [1], and females have been shown to have higher concentrations of CRP than males [30]. Perhaps relatedly, higher CRP was associated with poorer response to antidepressant treatment among females but not males [31]. By contrast, entire-brain FAA was not found to differ according to sex of participants in a sample of healthy university students [32], but another study found that FAA was influenced by a combination of the sex and age of the participant [33]. Taken with the findings of the meta-analysis of the FAA-MDD hypothesis reported above [27], the relevance of further investigation of the influence of sex, age, and depression severity on the association between FAA and CRP is a justified research aim.

1.6. Study Goals

The precise relationships between CRP, sex, age, FAA, and depression have yet to be elucidated, and they may hold potential in the formulation of a more complex biomarker of depression if they are investigated together rather than separately, as has most often been the case in the past. To achieve that aim, statistical methods such as regression analysis are needed in order to define the roles and weightings of different factors in their relative associations with depression.

To extend some of the previous findings, five pairs of right-minus-left frontal brain site EEG data calculations were used as the indicators of FAA; CRP was derived from serum samples; and depression was measured both as a dichotomous and a continuous variable to extend the comprehensiveness of statistical outcomes mentioned above when simple "depressed" versus "non-depressed" categorization is used [34].

2. Materials and Methods

2.1. Participants, Sex

The selection protocol used for this study has previously been employed and published [26]; however, the data processing and subsequent analyses are not the same as those conducted in the previous study. A total sample of 100 adults (54 males, 46 females, based on their assigned sex at birth) aged 18 yr or more from the New England region of New South Wales, Australia, was recruited from a media-advertised study to "investigate how you feel". Participants were screened for no previous medical history of severe physical brain injury, previous brain surgery, or past or current history of epilepsy or seizure disorder, or claustrophobia (EEG data were collected in a small booth). Although some previous research into FAA and depression has emphasised the handedness of participants, e.g., [35–38], because of the assumed association between right-handedness and left hemispheric dominance, e.g., [18,39,40], there is no certainty that left hemispheric dominance is determined entirely by right-handedness, as evidenced by the finding that 61% to 70% of left-handed people also have left hemispheric dominance [41,42]. Relevant to depression per se, a recent meta-analysis of over 35,000 individuals in 87 studies failed to find any meaningful effect on depression due to handedness [43].

2.2. Depression

The Zung Self-Rating Depression Scale (SDS) [44] is a 20-item self-rating depression scale used for diagnosis and quantifying the severity of various symptoms of depression [26]. The SDS includes ten positively worded and ten negatively worded questions which have been developed from factor analytic studies of the depression syndrome as defined by the DSM series and which remain current for MDD [45]. Respondents are asked to indicate the frequency of each of the 20 SDS depressive symptoms during the last two weeks by answering in one of four possible ways, i.e., "None or a little of the time" (score = 1), "Some of the time" (2), "Good part of the time" (3), or "Most or all of the time" (4), so that the range of possible total scores is from 20 to 80 [44,46]. SDS scores of 40 or above indicate the presence of "clinically significant depression" [46], while individuals with scores of less than 40 are classified as non-depressed. SDS raw scores were used in this study. The SDS has split-half reliability of 0.81 [44], 0.79 [47] and 0.94 [48], with an internal consistency (Cronbach's alpha) of 0.88 for depressed patients and 0.93 for non-depressed patients [49].

2.3. CRP Assays

The procedure for processing CRP samples is the same as that used previously by this research group [50]. Blood samples were collected and centrifuged at 1000 g for 15 min. The sera were frozen at −80 °C until analysis of CRP. Serum concentrations of CRP were determined using a Siemens Dimension XPand Plus Autoanalyser (Siemens, Newark, NJ, USA), using the CRP extended range (RCRP) Flex reagent cartridge (Siemens Dimension, Newark, NJ, USA) according to the manufacturers' instructions. This assay is based on the

particle-enhanced turbidimetric immunoassay (PETIA) technique, where synthetic particles coated with anti-CRP antibodies aggregate in the presence of CRP, increasing turbidity in proportion to CRP concentration. CRP concentrations are reported in mg/L.

2.4. EEG Measurements

2.4.1. EEG Signals

EEG data were collected via a 40-channel Digital EEG Amplifier (NuAmps), using a *Quik Cap*, which was used to record a continuous EEG measurement of 3 min eyes opened and 3 min eyes closed resting conditions.

2.4.2. Skin Preparation and Electrode Application

Participants came to the research setting with their hair washed at least 6 h previously with a normal shampoo that did not contain any conditioner. Following skull measurement, sites for the EEG electrodes were cleaned with *Nuprep* gel, plus an alcohol swab. The *Quik Cap* containing the EEG electrodes was applied to the participant's head, making sure that the Cz electrode was located at a site halfway between the glabella and the inion, and all EEG electrodes were loaded with *Quik gel*. Participants then sat in the experimental booth and the EEG cap was connected to the *Neuroscan* amplifier and a desktop computer. EEG signals were acquired and recorded using the *Curry 7* software.

2.4.3. AA Sites

A total of 10 active homologous EEG channels were used in this study to produce the following 5 right-minus-left pairs as indices of FAA, under the eyes open (EO) and eyes closed (EC) conditions: FP2-FP1, F4-F3, F8-F7, FT8-FT7, and FC4-FC3, using the modified universal 10–20 system recommended by American Clinical Neurophysiology Society Guideline 2 [51].

2.4.4. EEG Data Collection

Measurements at all scalp electrodes were referenced to the average of the two earlobe electrodes (A1, A2). The horizontal electro-oculographic electrodes (X2, X4) and the vertical electro-oculographic electrodes (X1, X3) were used for monitoring horizontal and vertical eye movements, and for off-line eye-movement artefact reduction of the EEG data. Data were collected at a sampling rate of 1 KHz with a bandpass of DC to 250 Hz, while impedance values at all electrodes were below <5 KΩ at the start of recording.

2.4.5. EEG Signal Processing, Data Reduction, and Data Extraction

The procedure for EEG data processing is the same as that used previously by this research group [52]. Data were processed using a 2–30 Hz 2nd-order Butterworth bandpass filter. Data tapering was performed by using a Hann window with a 10% width to prevent data loss. EEG data were visually examined to identify artefacts (eye movements, muscle movements, spontaneous discharges, or electrode pops, etc.), which were then removed from the data record. Bad block and eye blink detection (using the magnitude of eye blink deflections as a set threshold criterion to detect artefacts) was undertaken by three automated methods (subtraction, covariance, and principal component analysis) to produce clean EEG data.

Back-to-back epochs of 2 s duration were then created from the cleaned EEG data, as is common in the literature [53–57]. Epochs with bad blocks were excluded from averaged data. Most participants had over 90% usable artefact-free epochs for both the eyes open and eyes closed conditions, with the lowest frequencies of such usable epochs being 87% and 49%, respectively. The EEG data were then digitally filtered for alpha-band frequencies (8–13 Hz). Spectral analysis was performed on the generated epochs (for both conditions for each participant) with fast Fourier transform (FFT) to calculate the power spectra. The power values obtained from FFT were averaged across the 2 s EEG epochs. From this process, the total power within the alpha (8–13 Hz) frequency range was obtained for each

condition for each participant. The values of the total power within the alpha (8–13 Hz) frequency range were then extracted and transferred to an SPSS file for statistical analysis.

2.4.6. Alpha Asymmetry

FAA was calculated from the alpha power values obtained at corresponding cerebral sites using the process described above (i.e., right-minus-left alpha power: Rα–Lα).

2.5. Procedure

Participants read an explanatory statement and a consent Form, and were given an opportunity to ask any questions before written consent was given to participate. All participants gave their written consent to participate in the study. Participants completed a background questionnaire (age, sex) and the SDS, and then had their scalps prepared and the electrode cap fitted. Participants were then seated in the experimental booth so that external stimuli were minimised, had headphones placed upon their ears, and were asked to relax. After 15 min of sitting still (adaptation), the audio-recorded experimental protocol (3 min eyes open, 3 min eyes closed) was presented via headphones to ensure consistency across participants. Following the end of the protocol, participants left the experimental booth, had the headphones and electrode cap removed, and were thanked for their participation. This study was conducted according to the Guidelines of the Declaration of Helsinki. Ethics approval for this study was provided by the Human Research Ethics Committee of the University of New England, Australia (Approval No. HE14-051).

2.6. Statistical Analyses

Although EEG data are sometimes subject to logarithmic normalisation processes to remove non-normality, there are sound arguments against any form of normalisation because it can hinder interpretation of data [58]. As a result, it has been recommended that untransformed data should be analysed with statistical procedures that are robust to non-normality, where possible. Because psychological data (such as depression and EEG spectral power) are pervasively non-normal [59], data were analysed in this study by either non-parametric procedures (Spearman's correlation) or by parametric procedures that are robust to non-normality, such as ANOVA-based procedures [60] where possible. Regression was also used, and data were transformed for that analysis. The recommended method of identifying a meaningful outcome via effect size was followed [61] using Cohen's [62] definition of medium strength (i.e., $r \geq 0.3$) but only if at least 10% of the variance was accounted for. This was carried out to reduce the likelihood of a type II error that might occur if p values alone were used, due to the restricted size of some cells [63].

2.7. Study Aims

This study aimed to investigate the interaction between sex, age, CRP, FAA, and depression, and to formulate a comprehensive model of that interaction. To extend some of the previous findings regarding FAA at specific frontal brain regions, 5 pairs of right-minus-left calculations were used as the indicators of FAA.

3. Results

3.1. Participant Sex, Age

From the entire sample recruited, a subsample of 40 males and 52 females provided complete data without outliers on all variables. There was no statistical difference between the ages of the males (M = 34.52 yr, SD = 14.27 yr) and females (M = 32.40 yr, SD =14.61 yr: F (1, 91) = 0.486, p = 0.488, η^2 = 0.005). There were no significant Spearman's correlations between age and SDS score (ρ = 0.017, p = 0.870), CRP concentrations (ρ = 0.059, p = 0.578), or any of the FAA data (all $p > 0.05$).

3.2. SDS Scores

The mean SDS score for the entire sample was 36.7 (SD = 11.26), ranging from 21 to 66, representing 75% of the possible range of SDS scores (i.e., 20 to 80). Internal consistency for the 20 SDS items (Cronbach's alpha) was 0.905. Although there was some (non-significant) evidence of skewness towards the lower end of the scale for the SDS total scores, this is to be expected in a community sample, and is accommodated by Spearman's correlation procedure. There was no significant difference between the SDS scores for the males (M = 35.35, SD = 9.88) and females (M = 37.25, SD = 12.17: F = 0.647, p = 0.423, η^2 = 0.007).

3.3. CRP Data

The females had significantly higher CRP concentrations (M = 5.80 mg/L, SD = 3.51 mg/L) than the males (M = 4.07 mg/L, SD = 2.20 mg/L: F = 7.23, p = 0.009, η^2 = 0.078). There was no significant difference in CRP concentrations according to whether or not participants fell into the clinically significant depression category on their SDS score as defined by Zung [46] (i.e., a SDS score of 40 or greater): F = 0.38, p = 0.540, η^2 = 0.004.

3.4. FAA

The assumption of normality was violated across all but one FAA pairing due to abnormally high kurtosis values across a broad range (2.56–5.39). While regression analyses may be robust against mild deviations from normality, with reasonably large samples [64], the limitations in male and female sample sizes here, and the fact that high kurtosis can also result in unacceptably low variance and residuals which are inappropriate for regression analysis [59], challenged the use of regression with non-transformed data in this study. Since there is no practical equivalent non-parametric test for regression, a square root transform was applied to FAA values for the regression analyses. In order to preserve the positive/negative status of each score (and to avoid the inherent difficulties in taking the square root of a negative number), the square root of the score's absolute value was taken, and the score was made negative if originally so. The resulting values for each FAA pairing met all requirements regarding normality, and they can be seen in Table 1.

Table 1. Descriptive statistics for square root-transformed FAA values.

Sites	**All**		**Males**		**Females**	
Eyes Open	**M**	**SD**	**M**	**SD**	**M**	**SD**
FP2-FP1	0.051	0.293	−0.034	0.293	0.124	0.275
F4-F3	−0.021	0.334	−0.007	0.356	−0.033	0.316
FC4-FC3	−0.020	0.362	−0.052	0.369	0.008	0.357
F8-F7	0.044	0.401	−0.050	0.401	0.125	0.402
FT8-FT7	0.077	0.493	−0.098	0.514	0.227	0.423
			Eyes Closed			
FP2-FP1	−0.041	0.375	−0.114	0.318	0.019	0.409
F4-F3	−0.010	0.532	−0.062	0.503	0.033	0.556
FC4-FC3	−0.034	0.626	−0.147	0.610	0.059	0.629
F8-F7	−0.032	0.612	−0.136	0.599	0.056	0.615
FT8-FT7	−0.004	0.687	−0.188	0.687	0.149	0.655

For the eyes open condition, two-tailed independent sample t-tests showed that males had significantly lower FAA values than women in the FP2-FP1 pairing: $t(93)$ = 2.71, p = 0.008, Cohen's d = 0.558; the F8-F7 pairing: $t(93)$ = 2.12, p = 0.037, Cohen's d = 0.435; and the FT8-FT7 pairing: $t(93)$ = 3.38, p = 0.001, Cohen's d = 0.695. For the eyes closed condition, males had significantly lower FAA values than women in the FT8-FT7 pairing: $t(93)$ = 2.44, p = 0.016, Cohen's d = 0.504 [64].

3.5. Regression Analysis

Linear regression analyses were conducted in order to quantify any relationships between age, all FAA electrode pairings (in both the eyes open and closed conditions), CRP, sex, and SDS scores [64]. These variables were first considered individually, followed by an expanded set of multiple regression analyses conducted to explore any potential interactions, and mediation and/or moderation effects.

3.5.1. C-Reactive Protein

CRP concentration was a significant predictor of overall SDS scores: F (1, 85) = 5.03, p = 0.027, R^2 = 0.056 (see Table 2). This relationship was not mediated by age: F (1, 85) = 0.417, p = 0.520, R^2 = 0.005. Using sex as a moderator for the CRP-SDS relationship violated the assumption of homoscedasticity according to Levene's test: F (1, 85) = 14.85, $p < 0.001$ [65]. Therefore, separate regression analyses were conducted for males and females. CRP concentration was not a significant predictor of SDS scores in males: F (1, 38) = 0.10, p = 0.755, R^2 = 0.003. However, it was statistically significant in females: F (1, 45) = 4.17, p = 0.047, R^2 = 0.085 (see Table 2).

Table 2. Regression coefficients for CRP concentration as a predictor of SDS scores in full sample (top) and females only (bottom).

Variable	B	95% CI	β	t	*p*
Constant	32.15	27.60–36.70		14.05	<0.001
CRP	0.87	0.10–1.65	0.236	2.24	0.027
		Females Only			
Constant	31.46	24.50–38.43		24.50	<0.001
CRP	1.05	0.02–2.08	0.291	2.04	0.047

3.5.2. Age

Age was not a significant predictor of overall SDS scores: F (1, 98) = 0.50, p = 0.482, R^2 = 0.005. Moreover, no evidence was found that sex moderated this relationship: F (1, 96) = 0.78, p = 0.505, R^2 = 0.024.

3.5.3. FAA

Due to multiple cases of multicollinearity occurring between various FAA electrode pairings (e.g., F8-F7 and FT8-FT7), separate regression analyses were performed for each electrode pairing in both eyes open and eyes closed conditions. The only FAA electrode pairing that significantly predicted SDS scores was FP2-FP1 in the eyes open condition: F (1, 93) = 4.68, p = 0.033, R^2 = 0.048 (see Table 3).

Table 3. Regression coefficients for FP2-FP1 FAA in the eyes open condition as a predictor of SDS scores.

Variable	B	95% CI	β	t	*p*
Constant	36.42	34.16–38.69		31.90	<0.001
FAA	19.336	1.59–37.09	0.219	2.17	0.033

Conditional process analyses [64] indicated that age did not mediate the relationship between any FAA electrode pairing, CRP or SDS (all $p > 0.05$, $R^2 < 0.01$). Both CRP and sex were significant predictors for the F8-F7 FAA pairing in the eyes open condition: F (2, 80) = 4.05, p = 0.021, R^2 = 0.092 (see Table 4 and Figure 1). However, the interaction between CRP and sex was not significant, and F8-F7 FAA values were not a significant predictor of SDS scores. No direct or indirect effects were found between SDS and any other FAA electrode pairing (all $p > 0.05$).

Table 4. Regression coefficients for F8-F7 FAA in the eyes open condition as a predictor of SDS scores.

Variable	B	95% CI	β	t	*p*
Constant	0.174	0.065–0.283		3.18	0.002
CRP	−0.023	−0.004–0.042	−0.268	−2.42	0.018
Sex	0.124	0.007–0.240	0.234	2.11	0.038

Sex variable was mean centered, using −0.5 for males and 0.5 for females.

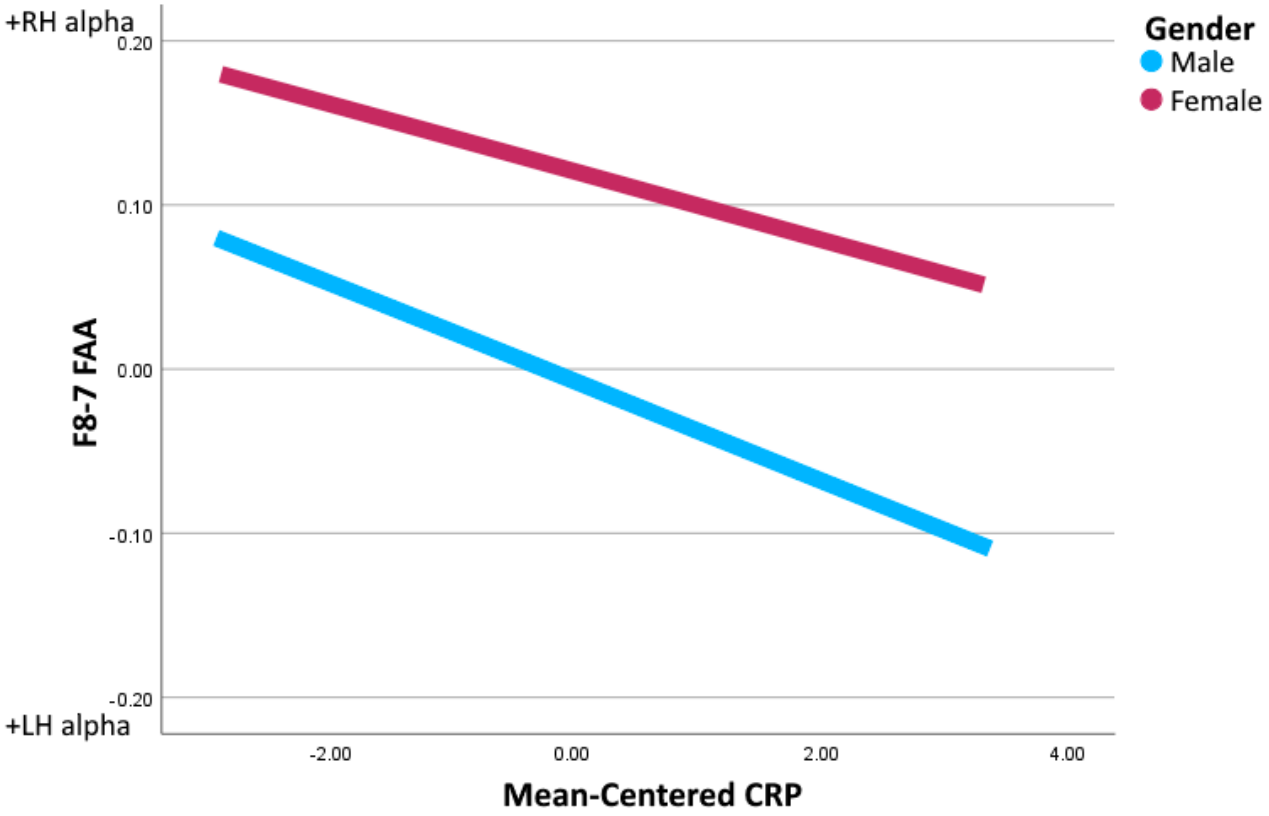

Figure 1. Sex-based differences in the relationship between CRP concentration and FAA at F8-F7 in the eyes open condition. Positive FAA values indicate stronger alpha band power in the right hemisphere, while negative FAA values indicate stronger alpha band power in the left hemisphere.

4. Discussion

4.1. Major Findings

This multi-factorial investigation of the possible roles of peripheral inflammation, frontal alpha asymmetry, age, and sex as predictors of depression suggested some interactions between these factors. Although age did not significantly contribute to the prediction of SDS scores, several sex-based differences were noted. First, males had lower FAA values (i.e., stronger alpha power in the left frontal region) than females in three pairings under the eyes open condition (FP2-FP1, F8-F7, and FT8-FT7), and one pairing under the eyes closed condition (FT8-FT7). As in some previous reports [30], CRP concentration was found to be higher in females than in males, and was also a consistent predictor of SDS scores in females but not in males, despite there being no significant difference in the SDS scores of males and females.

The FAA data derived from FP2-FP1 under the eyes open condition predicted SDS scores, suggestive of a direct association between the prefrontal cortex and depression, and supporting the large amount of previous data regarding alpha asymmetry and depression (as discussed in Section 1.3), particularly in that section of the brain commonly associated with decision making and rational thought. Although not undertaken here because of the focus on the interaction of age, sex, inflammation, asymmetry, and overall depression, this

finding suggests that the further investigation of depression "subtypes" that are based on cognitive symptoms of depression (e.g., difficulty making decisions, concentration difficulties) that are part of the heterogeneous definition of depression commonly used in clinical and research settings, i.e., MDD [43], might provide further understanding of the combined roles of age, sex, inflammation, and alpha asymmetry in specific subgroupings of the diagnostic criteria for MDD. The need to focus on the specific symptoms profiles of depressed persons when devising treatment protocols has been discussed in other studies [65,66], particularly in terms of the influence of inflammation [67].

The interaction between sex, CRP, and FAA that was found here adds some strength to the hypothesis under investigation. That is, while F8-F7 FAA (eyes open condition) did not predict SDS, there was a sex-based difference (see Figure 1), with men having increased alpha in the left hemisphere as CRP increased. This was also the case for women, but (as shown in Figure 1) the shift up the y-axis for women means that they tended towards greater right hemisphere alpha (across these electrodes at least).

4.2. Models of Depression

While no direct association between FAA and CRP was found, each measure was associated with depression in different populations. As mentioned above, separate predictors for depression (as measured by SDS) were found for each gender: in men, increases in SDS were predicted by an increase in left hemisphere frontal alpha band power. In women, increases in SDS were predicted by an increase in CRP concentration. Taken together, these findings may suggest the possibility of a "mind/body" separation in the predictors of depression, with the body (i.e., CRP) being a more reliable predictor of depression in women, and the mind (left hemisphere alpha activity) being a more reliable predictor of depression in men. This is consistent with previous findings showing that elevated CRP concentration is associated with increased risks of illness and all-cause mortality specifically in women [68], while increased left hemisphere frontal alpha has previously been associated with increased depression specifically in men [52].

Although this suggestion may re-enact a form of Cartesian dualism, open to dismissal if posited on purely philosophical grounds and without a substantial basis here, the defining of these different associations between depression and inflammation vs. brain activity may be considered from the perspective of two physiological systems that have separate (but sometimes interacting) associations with the psychological aspects of depression and any biological interactions that affect mental and emotional processing. While the association between alpha and depression is well established [20], as is the association between CRP and depression [9,10], these mechanisms have not been considered sex specific. The role of sex, which is defined biologically and which has attracted psychological profiles that appear to differ between males and females [69,70], has been challenged as a determinant of brain activity [71], although cogent arguments remain that support sex-based differences in some brain structures and concomitant behavioural and mental health dispositions. This would also apply to potential treatments: depression in women may be more effectively treated by considering therapeutics which address peripheral inflammation, while depression in men may be more susceptible to treatments directly influencing alpha band power in the brain such as transcranial magnetic stimulation. These issues remain relevant to the ongoing study of biomarkers of depression, especially when the heterogeneity of depression is considered [72].

4.3. Limitations

Although these exploratory findings are of value in unravelling the complex associations between brain activity, inflammation, and sex-based differences in behaviour and neurophysiology, this study has some limitations that call for caution until further research can be undertaken. There are geographical and cultural limitations to the sample of participants used here, and the voluntary nature of the males and females who provided data places a restriction on generalisation to other places and participants who may have

more severe depression. Self-reporting of depression is common, and (as described in Section 2.2) the SDS is a valid and reliable instrument for that purpose, but triangulation of self- with other- and clinician-reports might provide a more nuanced perspective. As is always the case with snap-shot studies, the data reported here represent a point in time and do not inform as to the variability in depression, CRP, or FAA that may occur over time or in response to stressor events. The sample size was satisfactory for the data analysis undertaken, but larger samples confer greater confidence in outcomes, and so replication of this study would be beneficial to understanding the associations examined here.

4.4. Conclusions

Notwithstanding these limitations that apply to much research, these findings provide some initial support for the concept of interaction effects between three of the major predictors of depression: sex, frontal alpha asymmetry, and peripheral inflammation. As such, they represent a basis for further research into these associations, particularly if less general forms of depression are used as target variables. The sex-specific predictors for depression (frontal left alpha for men, CRP concentration for women) have implications both in the detection and potential treatments for depression. Although not conclusive, the results of this study confirm the need to include the heterogeneity of depression in future studies, perhaps by examining depression "subtypes" rather than a total score derived from 20 different manifestations of depressive behaviour (i.e., the 20 SDS items).

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