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BRIEF REPORT

Avoidance-Related EEG Asymmetry Predicts Circulating Interleukin-6

Grant S. Shields
University of California, Davis

Wesley G. Moons
Moons Strategic Media, San Diego, California

Recent research has linked avoidance-oriented motivational states to elevated pro-inflammatory cytokine levels. According to one of many theories regarding the association between avoidance and cytokine levels, because the evolutionarily basic avoidance system may be activated when an organism is threatened or overwhelmed, an associated inflammatory response may be adaptive for dealing with potential injury in such threatening situations. To examine this hypothesis, we tested whether the neural correlate of avoidance motivation associates with baseline levels of the circulating pro-inflammatory cytokine interleukin-6 (IL-6). Controlling for covariates, greater resting neural activity in the right frontal cortex relative to the left frontal cortex—the neural correlate of avoidance motivation—was associated with baseline IL-6. These results thus support the hypothesis that the avoidance motivational system may be closely linked to systemic inflammatory activity.

Keywords: avoidance motivation, frontal asymmetry, interleukin-6 (IL-6), MIDUS, cytokines

Approach and avoidance may be two of the most fundamental ways in which organisms interact with their environment. Because of the fundamental necessity of approach and avoidance behaviors for survival, humans have ostensibly evolved two relatively independent motivational systems driving approach and avoidance behaviors (Elliot & Covington, 2001). Here, we propose that the neural correlate of avoidance motivation may be reflected in baseline levels of inflammatory activity.

Moons, Eisenberger, and Taylor (2010) proposed that avoidance-oriented emotions like fear may be associated with greater inflammatory activity because of their shared link to the motivational avoidance system. They proposed that the avoidance system was likely activated in situations in which an organism felt vulnerable, which throughout evolution was potentially indicative of impending injury (Marks & Nesse, 1994). Thus, Moons et al. (2010) argued that in such situations, individuals are likely to experience avoidance-oriented emotions like fear, and further, may benefit from psychogenic activation of the immune system because preemptive immune system activation facilitates subsequent healing, should injury occur (Dhabhar, 2002). Indeed, greater inflammatory activity has been linked to avoidance emotions including fear (Moons et al., 2010), shame (Dickerson, Kemeny, Aziz, Kim, & Fahey, 2004), and anxiety (Moons & Shields, 2015), but not the approach-oriented emotions of anger (Moons et al., 2010; Moons & Shields, 2015; though see Puterman et al., 2014) or guilt (Dickerson et al., 2004). In line with the proposition by Moons and colleagues (2010), we tested whether brain systems associated with avoidance also related to inflammatory activity.

Avoidance motivation is associated with greater right frontal cortex activity relative to the left (Rutherford & Lindell, 2011). Conversely, approach motivation is associated with relatively greater left frontal cortex activity. It is important to not that this relative frontal activity is associated with approach/avoidance motivation, independent of affective valence (Harmon-Jones, Gable, & Peterson, 2010), indicating that the neural correlate associated with avoidance motivational states is indicative of avoidance itself (Rutherford & Lindell, 2011). Consistent with the above model, resting frontal asymmetry has been linked to dispositional approach/avoidance tendencies (Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997). As might be expected from the stability of dispositional approach/avoidance, people appear to have a default level of resting frontal asymmetry (Tomarken, Davidson, Wheeler, & Kinney, 1992). Indeed, as summarized by a recent review (Rutherford & Lindell, 2011), numerous studies have linked asymmetrical frontal activity and approach/avoidance motivation.

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Grant S. Shields, Department of Psychology, University of California, Davis; Wesley G. Moons, Moons Strategic Media, San Diego, California.

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Correspondence concerning this article should be addressed to Grant S. Shields, Department of Psychology, University of California, One Shields Avenue, Davis, CA 95616. E-mail: gsshields@ucdavis.edu

Inflammatory activity can be assessed by plasma levels of the cytokine interleukin-6 (IL-6), which fluctuate reliably in response to psychological factors (Segerstrom & Miller, 2004) and serve as a reliable index of inflammation within an organism (Ohzato et al., 1992). Moreover, IL-6 is clinically relevant, as it plays a causal role in the development and exacerbation of inflammatory diseases, such as coronary heart disease (IL6R MR Consortium, 2012), which makes understanding IL-6 and its associates a top priority for public health (Slavich, 2015). Thus, if the avoidance system shares a connection to inflammatory processes, then relatively greater baseline right frontal activity—reflective of avoidance orientation—should associate with higher levels of baseline IL-6. We tested this hypothesis by performing a secondary data analysis of the project Midlife in the United States (MIDUS) II (Ryff & Davidson, 2010; Ryff, Seeman, & Weinstein, 2010), which explored factors that influence midlife health in America.

Method

Participants

Participants were contacted for the MIDUS study (Ryff & Davidson, 2010; Ryff et al., 2010) through a random-digit dial across the United States, i.e., a national random sample. Our sample included the 331 individuals who completed both the neuroscience and the biomarker MIDUS projects, 308 of whom were right-handed. Consistent with approach/avoidance literature (Sutton & Davidson, 1997), we excluded left-handed participants,[1] leaving 308 participants, nine of whom had missing electroencephalogram (EEG) data. As discussed here later, our analysis followed published recommendations and excluded another 141 participants, leaving our final sample at 158 participants.[2] Of these participants, 66% identified their racial origins as White, 30.2% as Black/African American, 1.3% as Native American or Alaska Native/Eskimo, 0.6% as Asian, and 2% as Other.

Materials

Interleukin-6. A fasting blood draw was taken during the MIDUS biomarker project (Ryff et al., 2010). Blood was centrifuged on site and stored in a −60-°C to −80-°C freezer. Samples were then shipped on a monthly basis to the MIDUS Biocore Lab on dry ice, where they were stored at −65 °C until assayed. The Quantikine High-Sensitivity Enzyme-Linked Immunosorbent Assay (ELISA) kit (R&D Systems, Minneapolis, MN) was used to measure IL-6. Detectable range was 0.156–10 pg/mL. Interassay coefficient of variation (CV) was 12.31%; intra-assay CV was 3.25%. Although there were missing IL-6 data in the overall biomarker project sample, there were no undetectable or missing values of IL-6 in the sample of participants used in this study.

EEG data. A 128-channel geodesic net (Electrical Geodesics, Inc., Eugene, OR) of saline-dampened, sponge-encased silver metal/silver chloride (Ag/AgCl) electrodes was used to record EEG activity. Signals were sampled at a rate of 500 Hz (band-pass filtered from 0-100 Hz) after amplification. Recordings were filtered using 60-Hz notch and 0.5-Hz high-pass filtering. Data were submitted to a principal components analysis/independent components analysis (PCA/ICA), forcing the identification of 20 components. Subsequently, artifacts were removed. Epochs, 2 s each, were then created; the average spectral power densities for each participant were computed from each of the 2-s epochs for each electrode. The spectra were then averaged across these epochs. Individual measures of upper (10 Hz to 13 Hz) and lower (8 Hz to 10 Hz) α bands were created by averaging the power within these bands separately. These average values were subsequently log-transformed to normalize the distribution. Laterality scores were calculated for each pair of electrodes in both α frequencies by subtracting the α power of the left hemisphere from the α power of the right hemisphere.

We used the laterality scores derived from the FP1/FP2 (frontpolar), F3/F4 (frontal), and F7/F8 electrodes in analysis, as they comprise the frontal electrode pairs in the MIDUS dataset (Ryff & Davidson, 2010; Ryff et al., 2010), and because each of these pairs has previously been linked to approach/avoidance (e.g., Sutton & Davidson, 1997; Prause, Staley, & Roberts, 2014). Because greater α power typically indicates inhibition of a neural area, greater α power is often conceptualized to indicate a reduction in the processes linked to that area (Ryff & Davidson, 2010). Consequently, higher laterality scores (i.e., relatively greater right-sided α power) indicate greater left-hemisphere activity (i.e., approach motivation) than right-hemisphere activity (i.e., avoidance motivation).

Procedure

Participants reported to one of three MIDUS (Ryff & Davidson, 2010; Ryff et al., 2010) general clinical research centers for an onsite, overnight study. On day two, a fasting blood draw was taken between 6:30 and 7:00 a.m., from which IL-6 was assayed. If participants awoke before the blood draw, they were instructed to engage in no physical activities. Participants who also completed the neuroscience project later went to the University of Wisconsin–Madison campus, where their resting EEG activity was recorded.

Data Reduction and Analysis

We log-transformed body-mass index (BMI) and IL-6 to normalize their distributions.[3] We created the overall frontal asymmetry score by standardizing and then averaging the laterality scores from the FP1/FP2, F3/F4, and F7/F8 electrodes across both α frequencies.[4] This score thus provides an index of total frontal asymmetry.

Our analytic strategy followed O'Connor et al.'s (2009) recommendations.[5] We described diet, fitness level, menopausal status, medication use, and smoking history. We controlled for age, sex, socioeconomic status (i.e., standardizing and then averaging income and education), smoking history (dummy-coded; 0 = *never*

[1] Analyses including left-handed participants controlling for handedness did not alter the results.

[2] Analyses including these 141 participants while controlling for exclusion-criteria covariates did not alter the results.

[3] These variables' skew statistics were greater than three times their standard error. Using the untransformed BMI values did not alter the results.

[4] We chose to combine the α frequencies a priori because they are not typically separated in approach/avoidance literature. Analyses using the individual α bands did not alter the results.

[5] Although O'Connor et al. (2009) did not discuss corticosteriods, we chose to exclude participants taking these medications given the influence corticosteriods have on inflammatory markers. Including and controlling for use of these medications did not alter the results.

Table 1
Regression Analysis of Interleukin-6 on Covariates and Frontal Asymmetry

	Outcome: Interleukin-6					
	Model 1			Model 2		
Predictor	*B*	*SE B*	β	*B*	*SE B*	β
Intercept	–5.354	.971		–5.242	.960	
Female gender	–.101	.110	–.068	–.086	.109	–.057
Age	.010	.006	.159†	.009	.006	.138
Body-mass index	1.605	.273	.443***	1.612	.270	.444***
Sleep problems	–.032	.023	–.100	–.035	.023	–.109
Alcohol-use frequency	.015	.050	.024	.006	.050	.010
Former smoker	.158	.115	.104	.186	.115	.123
Blood-pressure med use	.055	.127	.035	.023	.127	.015
Statin med use	–.070	.136	–.041	–.103	.135	–.060
Aspirin dose	.000	.001	.048	.000	.001	.049
Socioeconomic status	.009	.072	.010	–.004	.071	–.005
Black ethnicity	.316	.126	.196*	.320	.125	.199*
Native American ethnicity	.112	.471	.017	.158	.466	.024
Asian ethnicity	–.011	.657	–.001	.067	.650	.007
Other ethnicity	–.570	.392	–.105	–.543	.388	–.100
Frontal asymmetry				–.150	.070	–.156*
ΔR^2		.334***			.021*	
F for ΔR^2		5.12***			4.65*	

Note. $N = 158$.
$^{\dagger} p < .10$. $^{*} p < .05$. $^{***} p < .001$.

smoked),[6] ethnicity/race (dummy-coded; 0 = *White ethnicity/race*), BMI, alcohol use, sleep quality (scores on the Pittsburgh Sleep Quality Inventory (PSQI; Fichtenberg, Putnam, Mann, Zafonte, & Millard, 2001), aspirin dosage, statin use (dummy-coded; 0 = *nonuse*),[7] and antihypertensive use (dummy-coded; 0 = *nonuse*). Finally, we excluded excessive coffee/caffeine drinkers (>10 cups/day), current smokers, heavy alcohol drinkers (>14 drinks/week for women and >20 drinks/week for men), individuals with sleep disorders (above a clinical cutoff on the PSQI; Fichtenberg et al., 2001), and individuals taking antidepressants or corticosteriods.[8] The MIDUS (Ryff & Davidson, 2010; Ryff et al., 2010) 2-day procedure ensured against acute exercise, caffeine use, and acute sleep deprivation.

To assess whether any outliers significantly influenced the association between frontal asymmetry and IL-6, we assessed the standardized differences of β (DFBETAs), which quantify the effect of each observation on the slope, regressing one variable on another (Cohen, Cohen, West & Aiken, 2003). A significant DFBETA value is DFBETA $>\pm 2/\sqrt{N}$, or in this sample, DFBETA $>\pm 0.44$. Similarly, to assess outliers within the entire regression model, we examined externally standardized residuals, which quantify how different a given observation's residual is from the average residual in the model. Significant outlying observations are those with an externally standardized residual $>\pm 3$.

Results

Descriptive Statistics

Of the 299 right-handed participants with usable data, 55 participants were current smokers, 41 were on antidepressants, 16 were on corticosteroids, three drank more than 10 cups of coffee per day, two drank alcohol heavily, and 74 had a sleep disorder. We excluded all participants in the above conditions (141 total). In the final sample of 158 participants, 91 participants were women, 68 followed a special diet, 50 regularly engaged in moderate-to-vigorous exercise, 61 were former smokers, 100 took at least one prescription drug, 39 took statin medication, 57 took antihypertensives, 39 took aspirin, and 28 of the women had entered menopause. Participant age in this sample ranged from 37 to 83, $M = 57.26$, $SD = 11.56$.

Asymmetry and IL-6

In a bivariate analysis, frontal asymmetry correlated with IL-6, $r = -.191$, $p = .016$. As Table 1 illustrates, even after controlling for age, gender, sleep quality, BMI, smoking history, socioeconomic status, aspirin dosage, race/ethnicity, alcohol use, and the use of antihypertensive or statin medication, frontal asymmetry remained significantly associated with circulating IL-6, $\beta = -.156$, $t(142) = -2.156$, $p = .033$, $\Delta R^2 = .021$. Figure 1 illustrates this association. Examination of DFBETAs revealed no influential outliers on the slope regressing IL-6 on frontal asymmetry (all DFBETAs $<\pm 0.16$). Removal of all variable cases contributing to externally standardized residuals $>\pm 3$ in the overall model only strengthened the association: Frontal asymmetry remained significantly associated with IL-6 even after outliers were removed, $\beta = -.171$, $t(138) = -2.399$, $p = .018$, $\Delta R^2 = .025$. Finally, the relation between frontal asymmetry and IL-6 was not moderated by

[6] O'Connor et al. (2009) recommend potentially controlling for former smoking status. In our sample, former smoking status significantly predicted IL-6, $p = .034$, so we chose to statistically control for former smoking status.

[7] We were not able to control for the dosage of statins or antihypertensives, as participants took multiple different types of these medications.

[8] Including depressive symptomatology as a covariate, which was not discussed by O'Connor et al. (2009), did not alter the results.

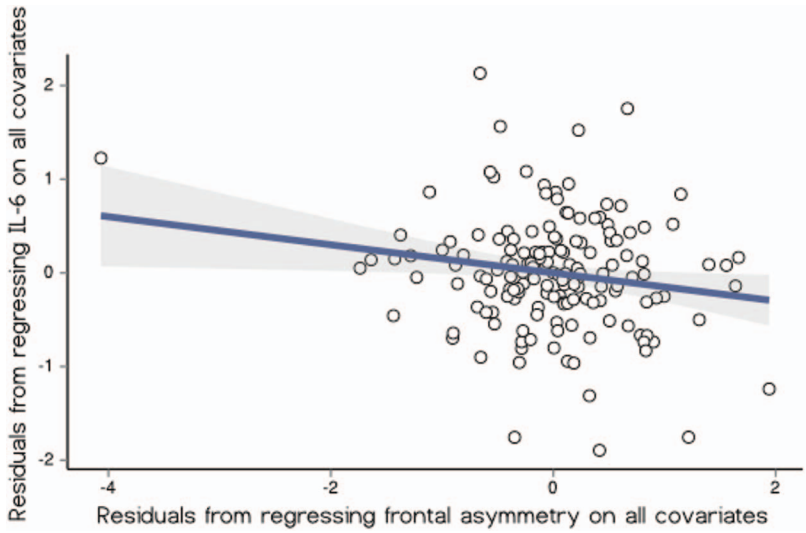

Figure 1. Regression of Interleukin-6 (IL-6) on frontal asymmetry IL-6, controlling for all covariates. Examination of DFBETAs revealed that the far left observation was not a significant influence on the slope regressing IL-6 on frontal asymmetry (DFBETA = −0.044). This graph illustrates that frontal asymmetry was significantly associated with IL-6, even after controlling for age, gender, sleep quality, body mass index, smoking history, socioeconomic status, aspirin dosage, race/ethnicity, alcohol use, and the use of antihypertensive or statin medication, β = −.156, p = .0328. See the online article for the color version of this figure.

any covariate (all *ps* > .120). Thus, we found a reliable pattern linking the neural correlate of avoidance orientation to inflammatory activity.

Discussion

This study adds to the growing body of literature relating inflammatory markers to neuropsychological variables (e.g., Master et al., 2009; Moons et al., 2010). In particular, we found that the neural correlate of avoidance significantly associated with baseline levels of the pro-inflammatory cytokine IL-6. More specifically, resting asymmetry in the brain's frontal cortex associated with baseline IL-6, such that greater right frontal activity was associated with higher IL-6. These findings are therefore consistent with Moons et al.'s (2010) suggestion that the human avoidance system is linked to inflammatory processes.

It should be noted that the effect size relating IL-6 to frontal asymmetry was small by traditional statistical convention. Although this may be seen as cause for concern, it is worth noting both that a 1-*SD* increase in right frontal asymmetry was associated with an IL-6 increase that predicts an 18% increased risk for developing coronary heart disease (Danesh et al., 2008), making the effect size obtained in this manuscript far from trivial.

Although the link between IL-6 and avoidance is potentially adaptive in the short term (Dhabhar, 2002), the health implications of this link are speculative. Higher baseline levels of IL-6 may continue to facilitate rapid recovery from injury (e.g., Dhabhar, 2002) or provide some other adaptive value within the context of dispositional avoidance. Conversely, higher baseline IL-6 may also be maladaptive, contributing to allostatic load. Future researchers should attempt to elucidate the health outcomes of dispositional avoidance to understand the consequences of these findings.

Our findings are similar to those of Master et al. (2009), who found an association between baseline oral-mucosal IL-6 and frontal EEG asymmetry. However, the results of Master et al. (2009) differ from the results of this study. Most important to note is that Master et al. (2009) did not intend to study the neural basis of avoidance in relation to cytokine levels; they were investigating a specific form of emotional coping, which led to their analyses using an electrode pair, FP1 and FP2, which is more strongly associated with mood than with avoidance orientation (Papousek & Schulter, 2002). In contrast, in the current study we examined total frontal asymmetry. The results of the current study thus allow for a discussion of the relationship of pro-inflammatory cytokines and the neural correlate of avoidance, which, to our knowledge, is the first time this association has been demonstrated.

There are at least two possible explanations for this study's findings. One explanation is that the upregulation of cytokines in situations involving avoidance is an adaptation to promote healing (Moons et al., 2010). Individuals who are typically avoidant may view themselves as less able to engage the world around them, which may translate into a pervasive sense of vulnerability to harm or infection. Under this view, then, the relationship between avoidance-related neural activity and pro-inflammatory cytokines is seen as a biological adaptation that promotes and maintains health.

A second explanation of these findings, which is not opposed to the first, notes the avoidance-oriented sickness behaviors brought about by increases in some cytokines (e.g., Dantzer, 2001). For example, withdrawal characteristics of sickness behaviors could increase the distance between an organism and a potential opponent or threat, which could benefit the organism. Cytokines could then facilitate further avoidance of a potentially harmful stressor.

This study has limitations. First, IL-6 is one of many pro-inflammatory immune system proteins; others, such as tumor necrosis factor α (TNF-α), may have different relationships with avoidance neural activity—future researchers should explore this relationship

with other pro-inflammatory cytokines. Second, the single time point for sample collection is a limitation; future researchers should longitudinally examine these variables. Finally, it should be emphasized that the directionality of these results is unknown. Future researchers should attempt to elucidate the causal pathways involved.

Conclusion

We have demonstrated that the neural correlate of avoidance was significantly associated with the cytokine IL-6, even after controlling for all relevant covariates. Although we posited two explanations for this association revolving around physiological and behavioral adaptations, further research is needed to elucidate the causal mechanisms underlying this association. However, the current evidence suggests that the basic motivational systems of avoidance and approach are potentially important factors in inflammatory processes and, consequently, health outcomes.

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