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Right Dorsolateral Prefrontal Cortical Activity and Behavioral Inhibition

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Abstract

Individuals show marked variation in their responses to threat. Such individual differences in “behavioral inhibition” (BI) play a profound role in mental and physical wellbeing. BI is thought to reflect variation in the sensitivity of a distributed neural system responsible for generating anxiety and organizing defensive responses in response to threat and punishment. Although progress has been made in identifying the key constituents of this behavioral inhibition system (BIS) in humans, the involvement of dorsolateral prefrontal cortex (dlPFC) remains unclear. Here, we acquired self-reported BIS-sensitivity and high-density EEG from a large sample ($n=51$). Using the enhanced spatial resolution afforded by source modeling techniques, we show that individuals with greater tonic activity in right posterior dlPFC rate themselves as more behaviorally inhibited. This observation provides novel support for recent conceptualizations of BI and clues to the mechanisms that might underlie variation in threat-induced negative affect.

Upon encountering a threat, mammals inhibit their on-going behavior and marshal a response appropriate to the imminence and danger posed by the threat (McNaughton & Corr, 2004). Typically this entails increased anxiety combined with various defensive behaviors, including freezing, risk assessment, and withdrawal/avoidance. While this response is prototypical, there is striking variation in individuals’ sensitivity to threat, or what has been termed their degree of *behavioral inhibition* (BI).

BI is thought to represent a fundamental dimension of temperament across phylogeny (Boissy, 1995), and is posited to underlie individual differences in trait anxiety, neuroticism, and related constructs in humans (Elliot & Thrash, 2002). Many theorists argue that individual differences in BI and its emotional and behavioral manifestations reflect variation in the neural system responsible for organizing responses to punishment, threat, and novelty (Elliot & Thrash, 2002). Among more inhibited individuals, a combination of genes and experience (Takahashi et al., 2007) sensitize this *behavioral inhibition system* (BIS; Gray &

McNaughton, 2000). Sensitization leads to exaggerated anxiety in the face of threat (Carver & White, 1994; Shackman et al., 2006) and likely accounts for inhibited individuals' heightened risk for psychopathology (Alloy et al., 2008).

Based on rodent work, the BIS has been conceptualized as a distributed neural circuit involving the periaqueductal gray (PAG), amygdala, anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (dlPFC; McNaughton & Corr, 2004). Direct support for the involvement of some of these regions comes from neuroimaging work showing that inhibited individuals exhibit greater activation in response to aversive images in the amygdala and PAG (Mathews, Yiend, & Lawrence, 2004). Studies using source-modeled electroencephalography (EEG) have also directly linked BI to task-evoked ACC activity (Amodio, Master, Yee, & Taylor, 2008).

By comparison, the contribution of dlPFC to BI remains ambiguous (McNaughton & Corr, 2004). Indirect evidence is provided by demonstrations that inhibited individuals show greater tonic EEG activity at sensors overlying right PFC (Sutton & Davidson, 1997). Convergent support comes from work linking greater EEG activity over right PFC to trait anxiety and negative-emotionality in adults (Coan & Allen, 2004) and measures of BI and distress in children and nonhuman primates (Buss, Davidson, Kalin, & Goldsmith, 2004). Moreover, individual differences in prefrontal EEG asymmetry possess a number of qualities required by BIS theory. They are predictive of threat-induced negative affect, psychometrically stable, and—particularly among women—heritable and associated with mood disorders (Buss et al., 2004; Coan & Allen, 2004; Smit, Posthuma, Boomsma, & De Geus, 2007).

Despite such evidence, the poor spatial resolution of prior EEG studies makes it difficult to infer which region of this large territory (~25% cerebral cortex) underlies individual differences in BI. Consequently, the degree to which BI is specifically related to dlPFC remains untested. This anatomical ambiguity also limits our ability to exploit regional heterogeneity in prefrontal function to understand the nature of its contribution to BI.

Here, we used high-density EEG (128-channels) and well-validated distributed source modeling techniques to test whether electrical activity generated in right dlPFC underlies individual differences in BI. Source modeling uses biophysical and neuroanatomical constraints to account for the spatial “blurring” imposed by the cerebrospinal fluid, skull and scalp (Pizzagalli, 2007). Particularly when combined with high-density recordings, this permits markedly greater resolution than conventional EEG analyses. In this study, tonic EEG and a well-validated measure of BI—the Behavioral Inhibition System (BIS) scale (Carver & White, 1994)—were acquired from a large sample ($n=51$). Tonic (i.e., “resting”) activity was used because it is especially conducive to measuring features of temperament, such as those ascribed to dlPFC by BIS theory (e.g., risk assessment, vigilance; McNaughton & Corr, 2004), that involve the sustained maintenance of anticipatory goals or sets (Buckner & Vincent, 2007).

Method

Participants

Seventy-three right-handed females were recruited from the University of Wisconsin—Madison as part of a larger investigation of the impact of temperament on cognitive performance. Given the challenges of collecting sufficiently large samples of artifact-free EEG for studying individual differences, the study was restricted to females in order to eliminate potential heterogeneity across the sexes (Smit et al., 2007) and maximize

statistical power. Participants were paid \$10/hour. Participants with insufficient artifact-free data (<360 epochs) were excluded from analyses, yielding $n=51$ ($M=19.5$ years, $SD=1.9$).

Behavioral Inhibition

Following Gray's theory (Gray & McNaughton, 2000), the seven-item *Behavioral Inhibition System* and thirteen-item *Behavioral Activation System* (BIS/BAS; Carver & White, 1994) scales were designed to index sensitivity to punishment and reward, rather than trait-like levels of affect. Nevertheless, the BIS scale is highly correlated with measures of related constructs (e.g., neuroticism; Elliot & Thrash, 2002). BIS items include I feel worried when I think I have done poorly at something and Even if something bad is about to happen to me, I rarely experience fear or nervousness [reverse-scored]). BAS items include When I go after something, I use a 'no holds barred' approach and When good things happen to me, it affects me strongly. Internal-consistency and test-retest reliability of the BIS/BAS is good, α s and r s > 0.66. BIS and BAS have been found to predict greater tonic EEG activity over right and left PFC, respectively (Sutton & Davidson, 1997).

Procedures

Procedures were similar to prior work (Sutton & Davidson, 1997). Participants came to the laboratory on two occasions separated by several weeks. In session-1, participants provided consent and completed the BIS/BAS. During session-2, sensors were applied shortly after arrival. After ensuring adequate data quality (30-45min), four or eight 60-s blocks of tonic EEG (half eyes-open/closed; order counterbalanced) were acquired. Otherwise, procedures were identical across participants. Most participants completed a state anxiety measure following EEG collection (see Results).

EEG

Similar to prior reports (McMenamin, Shackman, Maxwell, Greischar, & Davidson, *in press*), EEG was collected using a 128-channel montage (<http://www.egi.com>) referenced to Cz, filtered (0.1-200Hz), amplified, and digitized (500Hz). Data were filtered (60-Hz) and artifact-contaminated epochs were rejected. Artifact-free data were re-referenced to an average montage and power density ($\mu V^2/Hz$) was estimated for the alpha-1 band (8-10Hz). Asymmetries were computed as $\log_{10}(\text{right})$ minus $\log_{10}(\text{left})$. Because alpha-1 represents an *inverse* measure of cerebral activity (Coan & Allen, 2004), we interpreted reductions in power as greater cerebral activity, and negative asymmetry scores as relatively more right-than left-hemisphere activity.

Source Modeling

Following prior reports (McMenamin et al., *in press*), the Low Resolution Brain Electromagnetic Tomography (LORETA) algorithm (<http://www.unizh.ch/keyinst/NewLORETA>) was used to model cortical current density (A/m^2 ; 7-mm³ voxels). The validity of LORETA for modeling neural activation has been repeatedly established (McMenamin et al., *in press*). The forward-model was comprised of a 3-shell head model and electrodes normalized to the Montreal Neurological Institute's template (MNI305). Additional details are presented in the supporting on-line information.

Analytic Strategy

Analyses employed permutation-based significance testing, allowing correction for multiple comparisons. For each, 10,000 permutations were conducted. Details are presented in the supporting on-line information.

Scalp asymmetries—Regressions were used to test whether BIS predicted asymmetries on the scalp overlying PFC. BAS was included as a predictor to ensure specificity. Correlations are reported as semi-partial coefficients. Uncorrected p -values for each electrode-pair were derived from the distribution of coefficients across permutations of the predictor of interest (e.g., BIS). Analyses were restricted to previously identified regions of interest (Coan & Allen, 2004): the mid- (F3/4) and lateral-frontal electrodes (F7/8) and their nearest neighbors. Multiple comparison correction employed the distribution of minimum p -values across pairs and permutations.

Source modeling—Here, the aim was to test whether tonic activity in right dlPFC predicts individual differences in BIS. Consequently, regressions were restricted to areas 8, 9, 10, 44, 45 and 46 (<http://www.unizh.ch/keyinst/NewLORETA>). Permutation-based tests were used to calculate uncorrected p -values. Multiple comparison correction was performed using a cluster extent threshold.

Results

BIS and BAS

The mean and variance for BIS ($M=19.3$, $SD=2.9$) were comparable to prior EEG studies (Coan & Allen, 2004). They were somewhat smaller than previous reports for BAS ($M=40.5$, $SD=3.8$). BIS and BAS were uncorrelated, $r(49)=-0.09$, $p>0.50$.

Scalp Asymmetries

BIS predicts asymmetrically greater activity at right mid-frontal sites—As shown in Figure 1, more inhibited individuals showed asymmetrically greater right mid-frontal (F3/4) activity, $r(48)=-0.47$, corrected $p=0.007$. This effect was anatomically specific—no other sites demonstrated significant relations with BIS (corrected $ps>.09$). It was also psychologically specific—relations between BAS and asymmetry were *not* reliable at any site, corrected $ps>0.08$. Moreover, BIS ($r(49)=-0.47$) was a significantly stronger predictor than BAS ($r(49)=-0.09$) of mid-frontal asymmetry, $t(48)=-2.19$, $p=.03$.

Control analyses—It was possible that the effects ascribed to BIS represent a confound between BIS and state anxiety. To test this, we conducted an identical analysis using the 75% of participants who had completed the state version of the State-Trait Anxiety Inventory (STAI; Spielberger, 1983). Contrary to this hypothesis, relations between BIS and mid-frontal asymmetry remained significant after controlling for STAI, $r(34)=-0.46$, $p=0.003$.

It was also possible that the effects ascribed to BIS represent a confound between BIS and muscle tension artifacts (McMenamin et al., *in press*). Contrary to this hypothesis, BIS was unrelated to activity at extra-cerebral electrodes indexing ocular or muscle (e.g., temporalis/masseter) activity, $|r|s(49)<0.18$, uncorrected $ps>0.11$.

Source modeling

As displayed in Figure 2a, a 39-voxel cluster was identified in right dlPFC lying predominately in the right posterior middle frontal gyrus (MFG) and inferior frontal gyrus pars opercularis (IFGpo; areas 9/46v, 8Av, 44; corrected cluster $p=0.02$). As shown in Figure 2b, more inhibited individuals exhibited greater resting activity in this region, with the peak lying in right posterior dlPFC (right-pdlPFC; 53,24,29; area 9/46v), $r(48)=-0.37$, uncorrected peak $p=0.003$. This effect was psychologically specific—no voxels in lateral PFC demonstrated significant relations with BAS. Control analyses ruled out the possibility

that this effect was an artifact of brain-behavior relations originating in the neighboring ACC (see the supporting on-line information).

Discussion

Consistent with prior work (Sutton & Davidson, 1997), we found that individuals with relatively greater EEG activity on the scalp overlying right PFC rated themselves as more behaviorally inhibited. Control analyses indicated that these relations were anatomically and psychologically specific. Mirroring our scalp results, source modeling of the high-density EEG provided novel evidence that individual differences in BI are associated with greater tonic activity in right-pdIPFC. Taken with work showing that activation in this region predicts variation in threat-evoked anxiety (Dalton, Kalin, Grist, & Davidson, 2005), this observation provides compelling support for the hypothesis that dIPFC is a key constituent of the BIS (McNaughton & Corr, 2004). Current models of the BIS argue that it is hierarchically organized along the dorsal-ventral axis of the brain (McNaughton & Corr, 2004). The lateralization observed in the present study and prior research suggests the need to incorporate hemispheric asymmetries as a second key organizing principle of the BIS. While these findings provide a clear association between right-pdIPFC activity and BI, they do not address the issue of causation. Nevertheless, a causal role for right-pdIPFC is plausible, given evidence that biofeedback manipulations of EEG activity over right PFC can attenuate negative affect elicited by aversive stimuli (Allen, Harmon-Jones, & Cavender, 2001).

Various theories suggest that temperament's impact on health and disease is mediated by individual differences in emotional susceptibility (Elliot & Thrash, 2002). In the face of threat, behaviorally inhibited individuals are prone to generate greater stress and anxiety owing to alterations in the "set-point" (e.g., reduced threshold, amplified peak output) of threat-sensitive neural circuitry, the BIS. Taken with other work in the cognitive and affective neurosciences, our findings suggest three hypotheses for how individual differences in right-pdIPFC activity could amplify threat-induced anxiety.

First, greater susceptibility could arise from dysfunctional anxiety regulation. This hypothesis stems from work showing that individuals with greater tonic EEG activity over right PFC exhibit difficulties recovering from brief aversive challenges—indexed by the fear-potentiated startle reflex—suggesting that right-pdIPFC may play a role in spontaneous emotion regulation (Jackson et al., 2003). Convergent support comes from studies directly implicating this region in the instructed regulation of negative affect (Ochsner & Gross, 2008).

Second, increased anxiety susceptibility could stem from increased vigilance. Neuroimaging research implicates right dIPFC in vigilance and sustained attention (Robertson & Garavan, 2004). Although vigilance and other forms of risk assessment are a normative response across mammalian species to distal threats (Boissy, 1995; McNaughton & Corr, 2004), it is exaggerated among anxious individuals (MacLeod, Koster, & Fox, 2009; Poy, del Carmen Eixarch, & Avila, 2004). Likewise, electrophysiological markers of vigilance generated by PFC (e.g., mismatch negativity, P3a), are amplified by state (Cornwell et al., 2007) and trait anxiety (Hansenne et al., 2003). Heightened vigilance would tend to promote anxiety in situations where threat is ambiguous, remote, or task-irrelevant by increasing the likelihood that attention will be allocated to potential threats.

Third, increased susceptibility could reflect difficulties learning to resolve uncertainty. Right-pdIPFC is sensitive to uncertainty and ambiguity (Bach, Seymour, & Dolan, 2009; Huettel, Stowe, Gordon, Warner, & Platt, 2006; Vallesi, McIntosh, Shallice, & Stuss, *in*

press). Other research indicates that anxious individuals show difficulties learning to discriminate periods of threat from safety, making it harder for them to determine when to relax. They show overgeneralization of threat-evoked anxiety to safety cues and to contexts in which conditioning occurred (Baas, van Ooijen, Goudriaan, & Kenemans, 2008). In fact, elevated anxiety during periods of overt safety is more discriminative of many anxiety disorders than that observed during periods of overt threat (Baas et al., 2008). Exaggerated right-pdlPFC activity could represent a locally generated uncertainty signal or an attempt to resolve uncertainty signals generated by other regions of the BIS network (e.g., amygdala or ACC). Regardless, deficient uncertainty resolution can potentially account for both the enduring vigilance—representing an attempt to gather the information needed to resolve uncertainty—and the prolonged recovery from stressors characterizing threat-sensitive individuals.

Four limitations of this investigation represent key challenges for future research. First, our conclusions hinge upon a single self-report instrument acquired from an all-female sample. The degree to which these relations generalize to males or other measures of BI is unclear. Caution is warranted by evidence of sex differences in prefrontal asymmetries (Smit et al., 2007) and the well known limitations of ratings data (e.g., Sutton & Davidson, 1997). Ideally, future research will apply a multivariate approach, in which multiple measures of trait (e.g., neuroticism) and state affect (e.g., facial electromyography, momentary assessment) are collected from both sexes. This would facilitate a test of whether right-pdlPFC mediates or moderates individual differences in threat-evoked anxiety (Coan & Allen, 2004). Second, we did not replicate prior reports that more reward-sensitive individuals, indexed by the BAS, show relatively greater left-frontal EEG activity (e.g., Amodio et al., 2008). Nevertheless, null results have been reported elsewhere (e.g., Stewart, Levin-Silton, Sass, Heller, & Miller, 2008), which may simply indicate that the effect-size of such relations is modest. Alternatively, this may reflect the more truncated range of BAS scores in the present sample. Mass screening combined with stratified sampling would help to resolve this issue. Third, our conclusions rest upon a model, not a direct measurement, of the cerebral sources underlying the EEG. The use of an alternate algorithm or more complex head-model might alter these results somewhat. This concern is partially ameliorated by the knowledge that the algorithm used here, LORETA, has received more extensive validation than other algorithms (McMenamin et al., *in press*) and has been shown to exhibit sufficient resolution (~1-2cm; Pizzagalli, 2007) for testing our key hypothesis. Fourth, the present study did not address the degree to which individual differences in BI reflect altered functional connectivity between right-pdlPFC and other structures thought to underlie the BIS (e.g., amygdala, PAG, ACC). Future research designed to interrogate variation in connectivity is likely to yield substantial dividends for our understanding of BI.

Despite these challenges, our findings provide novel evidence linking right-pdlPFC to the BIS and a fresh source of insight into dlPFC's contribution to threat-evoked anxiety and defensive behaviors. Such mechanisms may help to explain why inhibited individuals are more likely to develop psychopathology. More generally, our results highlight the value of using neurophysiology to understand temperament.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Relations between individual differences in the Behavioral Inhibition System (BIS) scale and mid-frontal EEG asymmetry

Asymmetry was computed as right minus left mean power density, $\log_{10}(\mu V^2/Hz)$, for the alpha-1 (8-10Hz) band.

Figure 2. Relations between individual differences in BIS and tonic activity in right dorsolateral prefrontal cortex (dlPFC)

(A) Cluster lies at the intersection of the precentral and inferior frontal sulci, encompassing the right posterior middle frontal and inferior frontal gyri and including the Inferior Frontal Junction (IFJ), cluster corrected- $p=0.02$. Cross-hair shows the location in right posterior dlPFC of the peak correlation. “L” and “R” indicate the left- and right-hemispheres, respectively. (B) Scatter-plot depicting the peak partial correlation in right posterior dlPFC (area 9/46v), $r(48)=-0.37$, uncorrected- $p=.003$. Units reflect cortical current density, $\log_{10}(\text{A}/\text{m}^2)$.