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The neural correlates of emotion-based cognitive control in adults with early childhood behavioral inhibition

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Abstract

The present study is the first to assess whether the neural correlates of cognitive control processes differ in adults with and without a behaviorally inhibited temperament during early childhood. Adults with and without childhood behavioral inhibition completed an emotional conflict task while undergoing functional magnetic resonance imaging scanning. While no group differences in behavior were observed, adults with childhood behavioral inhibition, relative to adults without childhood behavioral inhibition, exhibited greater dorsomedial prefrontal cortex activity during conflict detection and greater putamen activity during conflict adaptation. Lifetime psychopathology predicted behavioral, but not brain-related, differences in conflict adaptation. These data suggest that the brain regions underlying cognitive control processes are differentially influenced by childhood behavioral inhibition, and may be differently related to psychopathology.

Keywords

behavioral inhibition; conflict detection; conflict adaptation; emotion regulation; fMRI; development

1. Introduction

Effective emotion regulation requires the engagement of multiple cognitive processes that modulate the expression and/or experience of negative affect. Cognitive control is one such process that facilitates the ability to filter out, and inhibit, prepotent responses to irrelevant stimuli (Botvinick et al., 2001). The capacity to exert cognitive control increases with development, and coincides with the maturation of brain regions in the prefrontal cortex that have been implicated in cognitive control (reviewed by Casey et al., 2000). Emotion regulation is particularly critical in the presence of irrelevant stimuli that signal danger or fear, which are known to interfere with normative cognitive processes (reviewed by

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LeDoux, 2000; Vuilleumier, 2005). Hence, delineating the neural mechanisms of cognitive control utilized in the service of emotion regulation is important, particularly when considering development and psychiatric disorders related to anxiety, where symptoms are associated with affective processing.

Etkin and colleagues have recently described procedures that can be used to map brain regions engaged by emotional stimuli in the context of a cognitive control task (Egner et al., 2008; Etkin et al., 2006; Etkin et al., 2010; Etkin and Schatzberg, 2011). This emotional conflict task requires subjects to identify the expression of an emotional face while ignoring an emotion word superimposed upon the face (see Figure 1A). Some trials include congruent word-face emotions, whereas others include incongruent word-face emotions. The emotional conflict task can be used to assess two aspects of cognitive control: conflict detection and inhibitory control in the form of conflict adaptation. Enhanced *emotional conflict detection* results in response time interference, or slowing, for incongruent, relative to congruent trials (Figure 1B). This interference is inhibited when an emotionally incongruent trial follows an incongruent trial, but not when it follows a congruent trial — an effect called *emotional conflict adaptation* (Figure 1C). This adaptation to emotional conflict reflects the activation of regulatory mechanisms, triggered by conflict on the previous trial, which then improves performance on the current incongruent trial (Egner et al., 2008; Etkin et al., 2006; Etkin et al., 2010; Etkin and Schatzberg, 2011). Unlike healthy adults, patients with generalized anxiety disorder fail to adapt to emotional conflict (Etkin et al., 2010; Etkin and Schatzberg, 2011). This failure to adapt has been associated with dysregulation in a neural circuit comprised of medial prefrontal cortex (mPFC) and amygdala, which facilitates emotion regulation in healthy individuals (Etkin et al., 2010; Etkin and Schatzberg, 2011)

Most research on the neural correlates of emotion regulation has examined adults who are healthy, or affected by psychopathology. To date, no study has assessed the degree to which behavioral characteristics during childhood prospectively predict the neural correlates of emotion regulation in adults. Such work is of major theoretical importance, since clinical factors during childhood predict risk for anxiety in adulthood (Pine et al., 1998). This raises vital questions about the degree to which such clinical factors also predict neural mechanisms engaged by emotion regulation, over and above any potential association with adult clinical factors. In the present study, we examined one such childhood behavioral characteristic, childhood temperament. Specifically, we examined adults who, during childhood, were characterized based on their expression of behavioral inhibition (BI). BI is a temperament that can be identified in infancy, and presents in children as extreme fear of social novelty that persists across early development (reviewed by Fox et al., 2005). Social reticence, a primary characteristic of children with BI (Henderson et al., 2004), is associated with low self-esteem, and high rates of peer victimization (reviewed by Rubin et al., 2009). Moreover, emerging fMRI research suggests that BI during childhood predicts brain function in adolescents and adults. However, only six such studies exist, and all six examine the relationship between early childhood BI and emotional reactivity (Bar-Haim et al., 2009; Guyer et al., 2006; Helfinstein et al., 2011; Perez-Edgar et al., 2007; Schwartz et al., 2011; Schwartz et al., 2003).. The current study is the first to examine the relationship between childhood BI and the neural mechanisms engaged by emotion regulation. Given that leading theories (Derryberry and Rothbart, 1997; Rothbart et al., 1994) propose that two central constructs contribute to temperament, emotional reactivity, as modeled in the six prior imaging studies, and emotional regulation, which has yet to be tested, this research is a critical extension of prior work,

Although some data suggest that children with BI are at risk for developing anxiety disorders (Chronis-Tuscano et al., 2009; Fox et al., 2005), the strength of this prediction varies as a function of the sample, the methods used to assess BI, and the type of anxiety

disorder. Indeed, there is substantial discontinuity in the expression of the BI phenotype with maturation into adolescence and adulthood. Thus, there is a great interest in identifying factors associated with both continuity and discontinuity in the expression of BI across development (e.g., Calkins et al., 1996; Fox et al., 2001). The current study sought to address this issue. Here we report on the first study to compare brain regions engaged by cognitive control in adults with and without childhood BI.

There is evidence to suggest dysregulation in the neural mechanisms associated with cognitive control in individuals with a history of BI. For example, during a flanker task, adolescents with childhood BI exhibited heightened error-related negativity (ERN) response, relative to those without childhood BI (McDermott et al., 2009). The ERN has been attributed to activity in mPFC, and is thought to reflect heightened attention to, and detection of errors in performance (e.g., Yeung et al., 2004). Similarly, Henderson and colleagues (Henderson, 2010) found that eleven year-old children with temperamental shyness exhibited a heightened N2 response while completing a flanker task, compared to age and gender-matched children without shyness. The N2 has also been attributed to activity in mPFC, and is thought to reflect heightened attention to anticipated conflict, which signals the need to up-regulate inhibitory control mechanisms in order to resolve forthcoming conflicts (e.g., Botvinick et al., 1999). In an even younger cohort of children, those with BI who were better able to engage inhibitory control, as measured by response accuracy on Stroop-like tasks, were more anxious than children who were less able to inhibit their responses (White et al., 2011). These and other data (for a review see Degnan and Fox, 2007; Fox, 2010) suggest dysregulation in cognitive control manifests in both the behavior and physiology of individuals with BI, and may contribute to psychopathology.

Until now, studies of cognitive control in BI have only employed tasks with neutral stimuli, such as letters, colors, or shapes (Henderson, 2010; McDermott et al., 2009; White et al., 2011). Therefore, it remains unclear if emotion also influences cognitive control in BI. Further, no functional magnetic resonance imaging (fMRI) study has investigated the neural correlates of cognitive control in adults with and without childhood BI. A study examining the impact of affective processing on cognitive control may reveal important information about the neural circuitry associated with BI after maturation. Prior studies have shown that childhood BI predicts hyper-reactivity in mPFC during adolescence, as demonstrated by measures of electrophysiological responses during a flanker task (McDermott et al., 2009). Likewise, fMRI studies have shown that childhood BI predicts heightened amygdala and striatal response to emotional stimuli in adolescence (Bar-Haim et al., 2009; Guyer et al., 2006; Helfinstein et al., 2011; Perez-Edgar et al., 2007) and adulthood (Schwartz et al., 2003). Activity in brain regions that distinguish individuals with and without BI largely overlap with those implicated by Etkin and others in emotion regulation (Egner et al., 2008; Etkin et al., 2006; Etkin et al., 2010; Etkin and Schatzberg, 2011; Hare et al., 2005). Thus, the current study tests the hypothesis that adults with childhood BI, relative to adults without childhood BI, will exhibit enhanced mPFC, amygdala, and striatal response to emotional conflict detection and emotional conflict adaptation.

2. METHODS

2.1 Participants

Thirty-five young adults (19.68 ± 1.46 years) completed the study. One additional subject was excluded from analysis due to poor behavioral performance. Subjects were selected from a larger longitudinal study of temperament. For a detailed description of the selection process, see (Calkins et al., 1996; Fox et al., 2001). At four months of age, 433 subjects underwent assessment for motor and emotional reactivity to novel olfactory, visual, and auditory stimuli. A subset of 153 infants who exhibited either minimal or heightened

reactivity to novel stimuli, determined based on frequency of motor and affective responses, was enrolled in the longitudinal study. Inhibited behavior to novel visual and auditory stimuli was coded at 14 and 24 months. Social reticence behavior during standardized social interactions with unfamiliar peers was coded at 48 months and 7 years. At each time point, parents completed questionnaires assessing their child's temperamental shyness. Behavioral and questionnaire scores were standardized by z-score at each time point. These standardized scores were used to create a single composite score of behavioral inhibition. Subjects with scores in the upper half of the distribution were categorized as having a behaviorally inhibited temperament (BI), and those with scores in the lower half of the distribution were categorized as having a non-behaviorally inhibited temperament (non-BI). This composite score was designed to ensure that individuals categorized as BI had a relatively consistent level of shyness and social reticence across early childhood. By definition, individuals in the non-BI category have lower levels of behavioral inhibition than those in the BI group. However, they do not have a history of a discrete temperament type. They are a more heterogeneous group with regards to their reactivity to social stimuli across early childhood (Calkins et al., 1996; Fox et al., 2001). At approximately 19 years of age, 21 adults characterized as BI in childhood and 14 characterized non-BI in childhood participated in the current study. All subjects were free from current use of psychotropic medication.

The characteristics of this sample are described in Table 1. The two groups did not differ in age, IQ, or gender. Furthermore, the groups did not differ on measures of current social anxiety symptoms (LSAS: Fresco et al., 2001), depression (BDI; Beck et al., 1988), or presence of current or lifetime psychiatric disorder, or comorbidity across disorders, as assessed by the Structured Clinical Interview for DSM IV (SCID; First et al., 2002).

2.2 Emotional Conflict Task

Photographs of five males and five females with happy or fearful expressions (Ekman and Friesen, 1976), overlaid with the words "FEAR" or "HAPPY" were presented (Figure 1), and subjects were told to indicate the facial expression of the photograph by button press. Half of the trials were congruent, such that the expression in the photograph and overlaid word matched (i.e., a fearful face overlaid with the word 'FEAR'), while the other half were incongruent, such that the expression in the photograph and the overlaid word did not match (i.e., a fearful face overlaid with the word 'HAPPY'). On incongruent trials, the facial expression (task relevant stimulus), and overlaid word (task irrelevant stimulus), are semantically incompatible, and thus generate conflict. Subjects were encouraged to respond as quickly and accurately as possible.

During scanning, stimuli were presented with EPrime (Sharpsburg, PA) via projection onto a screen, in a pseudorandom order, and counterbalanced across trial type for gender, identity, and facial expression of the photograph, and overlaid word. The stimulus presentation sequence was the same as prior studies using this paradigm (Egner et al., 2008; Etkin et al., 2006; Etkin et al., 2010; Etkin and Schatzberg, 2011). Each combination of gender, identity, expression, and overlaid word was presented 2–7 times during scanning. There were no direct repetitions of identity (i.e., photographs of the same person), or expression-word combinations (i.e., fearful expression overlaid with the word FEAR). This helps to reduce potential confounds such as negative priming or repetition priming effects (Mayr et al., 2003). Two additional emotion categories would be required to fully eliminate the potential influence of order effects on behavioral response (Puccioni and Vallesi, in press). However, presenting a sufficient number of repetitions for an adequately powered fMRI analysis for four emotions would be prohibitive due to the length of scan required.

Stimuli were presented for 1000 msec, with a varying interstimulus interval of 3000–5000 msec (mean=4000 msec). Data were acquired during a single functional run, which included 148 trials. To decrease subject fatigue, each run was divided into 4 blocks of 37 trials, with 8 sec of rest separating each block. Participants completed 10 practice trials, and were required to achieve 90% accuracy prior to scanning. Following prior studies using the emotional conflict task (Egner et al., 2008; Etkin et al., 2006; Etkin et al., 2010; Etkin and Schatzberg, 2011), response time outlier trials, defined as > ±2.5 standard deviations from the mean for each type of trial within each block, were excluded from analyses.

2.3 fMRI Data Acquisition

Functional neuroimaging data were acquired with a GE 3T-scanner (Waukesha, WI). For each subject, 340 functional image volumes with 35 contiguous axial 3mm slices (in-plane resolution = 2.5×2.5mm) were acquired using a T2*-weighted echo-planar sequence (TR/TE = 2300/25ms, flip = 90°; FOV = 240 mm, matrix = 96×96). To facilitate anatomical localization and coregistration of functional data, a high-resolution structural scan was acquired (axial plane) with a T1-weighted magnetization-prepared spoiled gradient-recalled echo sequence (TE/TI = min full/725ms, flip = 6°; FOV = 220mm, matrix = 256×256, in-plane resolution, 0.86×0.86mm).

2.4 Data Analysis

fMRI data were preprocessed and analyzed using AFNI (version 2.56b; Cox, 1996). To correct for head motion, functional imaging was co-registered to a base volume for each subject. The subsequent data were inspected for motion with censor.py (AFNI), using a censoring criteria of translation > 0.3 mm or rotation > 0.3° between consecutive TRs. TRs exceeding these parameters were removed prior to first-level analyses. For subjects characterized as BI, an average of 6.59% (SD=9.14%) of TRs were censored, while 9.67% (SD=12.89%) were censored for those characterized as non-BI. Groups did not differ in number of censored TRs, and no subject was eliminated from analysis due to excessive motion. Data were then corrected for slice timing and co-registered to the high-resolution structural scan, smoothed (6mm FWHM), spatially normalized to standard Talairach space, and resampled, resulting in $2.5mm^3$ voxels.

For first-level fMRI analyses, separate regressors were created for each stimulus event. Events were classified based on two criteria. First, whether the affective facial expression (happy/fear) and overlaid affective word (HAPPY/FEAR) on the current trial was congruent (C) or incongruent (I). Second, whether the preceding trial was congruent (c) or incongruent (i). Thus, task-specific regressors were modeled for the two types of congruent events (cC and iC), and two types of incongruent events (cI and iI). Following methods employed by prior studies using the emotional conflict task (Egner et al., 2008; Etkin et al., 2006; Etkin et al., 2010; Etkin and Schatzberg, 2011), three additional low-frequency events were modeled but excluded from analysis. These comprised error trials, post-error trials, and the first trial of each block, which did not include a preceding event. Task-specific regressors were convolved with a gamma-variate basis function approximating the BOLD response (Cohen, 1997). Additional regressors modeled motion residuals and baseline drift. For each subject, this analysis produced a β-coefficient and associated t-statistic for each voxel and regressor. A repeated measures ANOVA indicated that groups characterized as BI and non-BI did not differ in the number of TRs censored for motion across the events of interest (cC, iC, cI, and iI).

Following prior studies that assess differences across two groups on the emotional conflict task (Etkin et al., 2010), contrasts identifying neural activity for conflict detection and conflict adaptation were computed for each individual. Neural activity associated with

conflict detection was computed by subtracting congruent trials (iC + cC) from incongruent trials (iI + cI). Neural activity associated with conflict adaptation was computed by subtracting the typically faster, high regulation, incongruent trials preceded by incongruent trials (iI) from the typically slower, low regulation, incongruent trials preceded by congruent trials (cI). Percent signal change maps were generated by dividing signal intensity at each voxel by the mean voxel intensity, and multiplying by 100.

Group level analyses tested whether neural activity associated with conflict detection and conflict adaptation differed based on childhood BI status. An independent samples t-test assessed whether childhood BI categorization (BI or non-BI) differentially influenced neural activity during conflict detection. A second independent samples t-test assessed whether childhood BI categorization (BI or non-BI) differentially influenced neural activity during conflict adaptation. Corresponding behavioral analyses were conducted in SPSS and assessed whether response time for conflict detection and conflict adaptation differed based on childhood BI status. In brain regions where childhood BI categorization (BI or non-BI) differentially influenced neural activity for conflict detection or conflict adaptation, correlation analyses were conducted for each group to test for the relationship between neural activity and response time.

While the current study focuses on the relationship between BI and cognitive control processes, prior work also relates performance on the emotional conflict task to the presence of a psychiatric diagnosis (Etkin et al., 2010; Etkin and Schatzberg, 2011). While this study did not have a sufficiently large sample to assess a potential 2-way interaction between level of childhood BI and lifetime psychiatric diagnosis, examination of data for psychopathology nonetheless provides a useful benchmark against which to compare the current results and previous findings. Therefore, a secondary analysis was conducted in which subjects were classified based on the presence (N=17) or absence (N=18) of any lifetime psychiatric diagnosis, regardless of childhood BI categorization (see Table 1). Subjects with psychopathology were compared with subjects free of lifetime psychiatric diagnosis using the same analytic strategy described above.

Four a priori regions of interest (ROIs) were considered: dorso-medial prefrontal cortex (dmPFC), ventro-medial PFC (vmPFC), amygdala, and striatum. These ROIs were chosen based on prior studies using the emotional conflict task, which implicated the dmPFC, vmPFC (including the rostral anterior cingulate cortex), and amygdala in processing conflict detection or conflict adaptation (Egner et al., 2008; Etkin et al., 2006; Etkin et al., 2010; Etkin and Schatzberg, 2011). Similar regions have also been implicated in differentiating individuals with high and low levels of BI (McDermott et al., 2009; Perez-Edgar et al., 2007; Schwartz et al., 2003). The striatum was also selected as an ROI based on prior studies, which have identified differences in striatal activity across multiple tasks, based on BI classification (Bar-Haim et al., 2009; Guyer et al., 2006; Helfinstein et al., 2011). For dmPFC, a 20mm sphere was centered at 4, 38, 34 (MNI); for vmPFC/rACC, a 12 mm sphere was centered at −9, 44, −5. ROIs were positioned based on average peak coordinates from activation clusters found in previous studies using the identical task (Egner et al., 2008; Etkin et al., 2006; Etkin et al., 2010; Etkin and Schatzberg, 2011), while sphere size differences reflect the size of these previously identified clusters. The amygdala and striatum (dorsal and ventral aspects of the putamen, caudate, and nucleus accumbens) were defined anatomically, using masks from the Talairach-Tournoux Atlas.

ROI analyses were thresholded by an overall significance level (false detection probability) based on 1,000 Monte Carlo simulations (AFNI, AlphaSim), using a mean estimated spatial correlation of 8.81 × 8.78 × 8.09 mm FWHM, in the respective *x*, *y*, and *z* dimensions. Monte Carlo simulations were performed for each ROI to determine the cluster-size needed

to achieve a voxel-specific threshold of $p < .005$, with an overall family-wise error rate of $\alpha < .05$. After correcting for the small volume of each ROI, simulations determined the minimum number of contiguous voxels, activated at the $p < .005$ level, needed to identify significant activity in dmPFC (ke = 27, 422 mm^3), vmPFC/rACC (ke = 11; 171 mm^3), amygdala (ke = 2; 31 mm^3), and striatum (ke = 13; 203 mm^3). Exploratory whole brain analyses were also conducted. Monte Carlo simulations determined that a cluster-size of 70 voxels (1,094 mm^3) was needed to achieve a threshold of $p < .005$, with an overall family-wise error rate of $\alpha < .05$. For clusters exhibiting two-way interactions, subject-level percent signal-change values were extracted and plotted to facilitate interpretation.

3. RESULTS

3.1. Emotional Conflict Detection: (I - C)

3.1.1. Behavior—Behaviorally, the task elicited significant levels of emotional conflict in each group (see Table 1), as reflected by the relatively large overall slowing for incongruent ($M = 888.28$ ms, $SD = 107.64$ ms) compared with congruent stimuli ($M = 844.90$ ms, $SD = 105.11$ ms; $t(34) = 5.76$, $p < .001$). There was no main effect of group or group-by-trial-type interaction.

3.1.2. Brain Function—At a neural level, conflict detection produced significantly greater activity in right dmPFC for incongruent compared with congruent trials (see Table 2A). Whole brain analyses identified additional clusters that were more active for incongruent compared with congruent trials in right anterior insula and left parietal cortex. While there was no main effect of group, a significant group-by-trial-type interaction emerged in right dmPFC. In sub-groups considered individually, this between-group difference was shown to reflect significantly greater relative activity for incongruent compared with congruent trials in adults with childhood BI ($t(20) = 2.72$, $p < .01$), and the opposite pattern in the non-BI group ($t(13) = -2.72$, $p < .02$; see Figure 2A). No additional clusters were identified for the group-by-trial-type interaction with whole brain analyses. There was no significant correlation between response time and dmPFC for conflict detection in either group.

3.2. Emotional Conflict Adaptation: (iI – cI)

3.2.1. Behavior—Behaviorally, there was no main effect of trial-type or group, or trial-type-by-group interaction (see Table 1).

3.2.2. Brain Function—At a neural level, no main effects for trial-type or group emerged. However, a group-by-trial-type interaction emerged in the putamen bilaterally (See Table 2B). This reflected significantly greater relative activity for iI trials compared with cI trials in adults with childhood BI ($t(20) = 2.34$, $p < .05$), and the opposite pattern in the non-BI group ($t(13) = -3.43$, $p < .005$; Figure 2B). Whole brain analyses identified additional activation clusters for a group-by-trial-type interaction in right precuneus and occipital cortex. There was no significant correlation between response time and putamen, precuneus, or occipital cortex for conflict adaptation in either group.

3.3 Secondary Analyses: Lifetime Psychiatric Diagnosis

3.3.1. Emotional Conflict Detection: (I - C)—Behavioral analyses contrasting subjects with and without lifetime psychiatric diagnoses revealed no main effect of group or group-by-trial-type interaction for response time. Whole brain analyses for the presence or absence of any lifetime diagnosis revealed a group-by-trial-type interaction in right dorsolateral PFC (24, 47, 18; ke = 92; $t = 4.45$; see Figure 3). This interaction reflected significantly greater relative activity for incongruent compared with congruent trials in adults without a lifetime

diagnosis ($t(17) = 3.14$, $p < .01$), and the opposite pattern in adults with a lifetime diagnosis ($t(16) = -3.18$, $p < .01$).

3.3.2. Emotional Conflict Adaptation: (iI – cI)—For emotional conflict adaptation, behavioral differences emerged across groups with and without a lifetime psychiatric diagnosis. There was a group-by-trial-type interaction ($F(1,33)=4.85$, $p < .05$), such that subjects without a lifetime history of psychiatric disorder responded more rapidly to iI trials ($M = 887.67$, $SD = 106.46$) than cI trials ($M = 914.15$, $SD = 122.59$; $t(17)=3.03$, $p < .01$), while those with a lifetime history of any psychiatric diagnosis did not exhibit conflict adaptation, and responded similarly for iI trials ($M = 890.64$, $SD = 129.51$) and cI trials ($M = 871.65$, $SD = 88.98$; $p > .30$). No between-group differences emerged in either whole-brain or ROI analyses for subjects classified based on the presence or absence of a psychiatric disorder.

4. DISCUSSION

Four main findings emerged from the current study. First, childhood BI differentially predicted neural response during emotional conflict detection in adulthood. Specifically, adults with a childhood history of BI exhibited greater dmPFC activity for incongruent compared with congruent trials, while the opposite pattern manifested in adults without a childhood history of BI. Second, childhood BI differentially predicted neural response during emotional conflict adaptation in adulthood. Adults with a childhood history of BI exhibited greater activity in bilateral putamen for incongruent trials that occurred following incongruent, compared with congruent, trials. Again, the opposite pattern manifested in adults without a childhood history of BI. Third, while childhood BI predicted differences in neural response associated with cognitive control, it did not predict behavioral differences in response time associated with emotional conflict detection or adaptation. Finally, lifetime psychopathology predicted differences in behavioral, but not neural, response during conflict adaptation. Individuals who were free from lifetime psychopathology exhibited emotional conflict adaptation (i.e., responding more rapidly to incongruent trials preceded by another incongruent trial, compared to incongruent trials preceded by a congruent trial). Subjects with a lifetime diagnosis did not exhibit such emotional conflict adaptation.

Given that anxiety disorders typically develop in adolescence and early adulthood, it is critical to delineate the neural mechanisms that potentiate risk for anxiety disorders during childhood. Most studies assess brain function and risk for anxiety disorders using concurrent measures collected in adolescence. The present study investigated adults characterized by the expression of early childhood behavioral inhibition, a temperament that increases risk for psychopathology (Chronis-Tuscano et al., 2009), and assessed neural activity in the same individuals more than 10 years later. Using this prospective design, it is possible to quantify the lasting effects of temperament-based childhood risk on brain function during adulthood. Given the challenge of enrolling and retaining participants in longitudinal research that spans from infancy to adulthood, only six fMRI studies published to date have assessed the neural correlates of childhood BI on brain function (Bar-Haim et al., 2009; Guyer et al., 2006; Helfinstein et al., 2011; Perez-Edgar et al., 2007; Schwartz et al., 2011; Schwartz et al., 2003). Although these prior findings suggest that early childhood temperament continues to influence the neural mechanisms engaged for processing emotionally evocative stimuli, the current study is the first to demonstrate the enduring effect of BI on the neural mechanisms engaged by cognitive control processes. Thus, the previous six studies document lasting effects of childhood BI on emotional reactivity, whereas the current study is the first to document the effect of childhood BI on emotion regulation. Together, these data provide support for theories that suggest emotional reactivity and regulation are factors implicated in temperament (Derryberry and Rothbart, 1997; Rothbart et al., 1994), which in

turn relate to neural function in adulthood. These data have important implications for understanding how early childhood behavioral inhibition shapes brain function into adulthood, but more generally, underscores the idea that early childhood experiences may predict lifelong differences in brain function.

4.1. Emotional Conflict Detection

Our current finding, that adults with high childhood BI exhibit enhanced activity in dmPFC during emotional conflict detection, compared to adults without childhood BI, is consistent with existing data. Specifically, both current and existing data suggest that childhood BI predicts long-term hypersensitivity to conflict. Conflict monitoring or detection is often associated with increased activity in dmPFC in fMRI studies and enhanced ERN and N2 response, attributed to increased dmPFC activity, in electrophysiology studies (see review Ridderinkhof et al., 2004). Prior work has shown that adolescents with childhood BI, relative to those without childhood BI, have an enhanced ERN response when committing errors during a non-emotion-based conflict detection task (McDermott et al., 2009), and that eleven year-old temperamentally shy children have an enhanced N2 response during a similar task (Henderson, 2010). The present findings extend this work by capitalizing on the precise spatial resolution of fMRI to localize group differences to a particular portion of mPFC, and by demonstrating that enhanced responses can also occur in the context of emotional conflict. Taken together, current and prior work suggests that hypersensitivity to conflict found in children with BI is a persistent theme across development. Finally, at the neurophysiological level, as captured by fMRI and ERN data, the conflict-detection bias associated with BI appears to represent an enduring trait; it manifests consistently across time, even in studies targeting different age groups using discrete experimental paradigms and data collection modalities.

4.2. Emotional Conflict Adaptation

In the current study, a childhood history of BI predicted enhanced striatal response in bilateral putamen to emotional conflict adaptation in adulthood, while the opposite pattern emerged among those without a childhood history of BI. This finding is also consistent with prior work on the long-lasting influence of early childhood BI on later-life brain function. Specifically, three prior studies found that presence or absence of childhood BI differentially predicts striatal responding to incentive cues in adolescence (Bar-Haim et al., 2009; Guyer et al., 2006; Helfinstein et al., 2011). The present data therefore provide further support implicating the lingering influences of childhood BI on striatal function. More broadly, the current findings are also consistent with the idea that, at the neurophysiological level, relative to those without childhood BI, those with childhood BI may more readily engage brain regions associated with inhibitory control. Evidence suggests that putamen activity may be linked with successful inhibitory control (Dibbets et al., 2010; Rubia et al., 2006). However, this evidence largely stems from tasks where actions are inhibited explicitly in response to non-emotional conflict (i.e., day/night and left/right Stroop tasks), whereas the current data suggest that putamen engagement also occurs in emotional contexts, where inhibition occurs at an implicit level.

4.3. Behavioral Responding

Despite differences in brain activity, childhood BI did not predict behavioral differences in emotional conflict detection or adaptation. Although these findings may be the result of a Type II error due to the study's small sample size, these results are consistent with prior work on BI. Similar to the current study, childhood BI predicted neurophysiological differences during conflict monitoring and detection in adolescents, but not corresponding differences in response time (McDermott et al., 2009). Indeed, each of the five published fMRI studies of childhood BI in adolescents or adults has reported that childhood BI levels

predict differences in neural activity, but not in behavior (Bar-Haim et al., 2009; Guyer et al., 2006; Helfinstein et al., 2011; Perez-Edgar et al., 2007; Schwartz et al., 2003). In contrast, studies in children demonstrate associations between BI and behavioral indicators of cognitive control. For example, White and colleagues found that pre-school children who show behavioral signs of enhanced inhibitory control have more pronounced, enduring symptoms of BI than those without enhanced responding (White et al., 2011). Thus, current and prior findings suggest that the manifestations of BI may evolve with development.

4.4. Psychopathology and Behavioral Inhibition

The present study was not designed to assess differences between healthy individuals and those with psychopathology. Thus, while it is instructive to describe these findings as they relate to the current literature, it is difficult to draw broader clinical inferences about their meaning. Behavioral differences in emotional conflict adaptation based on lifetime psychopathology were not accompanied by corresponding differences in the brain. Recently, Etkin and colleagues demonstrated that patients with distinct forms of current psychopathology exhibit distinct patterns of neural response during conflict adaptation (Etkin and Schatzberg, 2011). Thus, the lack of brain-based differences in those with and without lifetime psychopathology may relate to the heterogeneous nature of psychopathology in participants in this study, as well as the small number of participants with anxiety-specific disorders or current psychopathology. Despite the heterogeneity of the sample, and the small number of participants with current psychopathology, group differences in activity were observed during conflict detection in dorsolateral PFC. Healthy individuals exhibited greater activity for incongruent relative to congruent trials, while the opposite pattern emerged in adults with a lifetime history of psychopathology. This is consistent with prior ERN-based studies of conflict monitoring and detection (e.g., Gehring and Knight, 2000), and studies that have used the emotional conflict task, where dorsolateral PFC has been implicated in both conflict detection and adaptation in healthy individuals (Etkin et al., 2006), and as serving a compensatory function in facilitating conflict adaptation in adults with current major depressive disorder (Etkin and Schatzberg, 2011). Thus, while neural activity associated with conflict adaptation may be sensitive to psychopathological distinctions and therefore masked in the current study, the dysregulation in the neural correlates of conflict detection may be more robust.

Prospective research shows that high levels of early-childhood BI predicts a two-to-fourfold increase risk for adolescent anxiety disorders (Chronis-Tuscano et al., 2009), and neuroimaging research implicates mPFC and striatum in adolescent and adult anxiety disorders, as well as in high levels of BI. Yet, research on the neural correlates of cognitive control suggests BI and anxiety disorders exhibit both similarities and differences. In both BI and anxiety disorders, increased ERN is commonly observed during ‘flanker’ tasks (Hajcak et al., 2003; Ladouceur et al., 2006; Weinberg et al., 2010), suggesting a common hyper-sensitivity to conflict. However, other findings on conflict tasks in the two phenotypes appear to differ. For example, prior work using the emotional conflict task employed in the current study finds reduced activity in dmPFC during conflict processing in adults with generalized anxiety disorder, relative to healthy individuals (Etkin et al., 2010), while the current study documents the opposite pattern in those with childhood BI.

Discrepancies also manifest for measures of conflict adaptation. For example, adults with generalized anxiety disorder differ from healthy adults in that the patients fail to adapt to emotional conflict behaviorally. This deficit is likely due to a failure to up-regulate mPFC, and diminished functional connectivity with amygdala (Etkin et al., 2010; Etkin and Schatzberg, 2011). However, in the current study, childhood BI did not predict behavioral adaptation to conflict during adulthood, nor did PFC or amygdala activation differ based on childhood BI. Instead, when participants were compared based on lifetime presence or

absence of a psychiatric disorder, only those with a lifetime disorder failed to adapt behaviorally to emotional conflict. Thus behavioral conflict adaptation may be more closely linked with the lifetime history of psychopathology than with early childhood temperament.

4.5. Limitations and Conclusion

The current study has a number of limitations. The current findings suggest that childhood BI influences neural response to emotional conflict and conflict adaptation during adulthood. Likewise, lifetime psychiatric diagnosis influences behavioral response to conflict adaptation. However, only a small number of subjects with or without childhood BI in the current sample had a lifetime psychiatric diagnosis (Table 1), and none had ongoing generalized anxiety disorder. As a result, there was not sufficient power to test the interaction between childhood BI and lifetime diagnosis on behavior and brain outcomes. Further, secondary analyses that classified subjects based on lifetime psychopathology found behavioral differences in emotional conflict adaptation, but no differences in neural response. It is intriguing to consider that history of a psychiatric illness may produce distinct cognitive and neural deficits from those that manifest with expression of childhood BI. However, because of the small sample size of this study, results must be interpreted with caution. For instance, the absence of group differences in response time across BI groups may be the product of insufficient statistical power, rather than evidence for the normalization of dysregulated cognitive control behavior that is typically apparent in children with BI. Additionally, fMRI studies typically require ~ 20 subjects per group to achieve sufficient statistical power (Friston et al., 1999). Although we obtained significant results with a smaller sample of adults without childhood BI, which suggests that the size of these effects are large, replication of these findings in a larger sample is needed.

The study of the long-term effects of childhood behavioral inhibition has typically focused on factors associated with consistent social avoidance There is however growing interest in a different childhood temperament called exuberance, in which children show consistent high levels of approach and often risk taking behaviors (Degnan et al., 2011; Dennis, 2006; Stifter et al., 2008). Because the present study did not employ assessments of approach or risk taking, children without BI cannot be definitively characterized with this temperament. On the other hand, adults without childhood BI exhibited a pattern of hypoactivation in dmPFC, precuneus, and putamen during conflict processing similar to adolescents with externalizing disorders such as attention deficit hyperactivity disorder and conduct disorder (e.g., Konrad et al., 2006; Rubia et al., 2009). However, given the small heterogenous sample of adults without childhood BI who participated in the present study, one must interpret the results from this group with caution.

Finally, BI has been linked with increased risk for anxiety disorders, and some evidence suggests the two phenotypes share common dysregulation in brain function. These similarities were not evident in the current study. This discrepancy underscores the importance of large-scale studies that cross-classify subjects based on childhood BI and current anxiety during adulthood. Such studies are clearly needed to evaluate definitively whether childhood BI interacts with ongoing anxiety to influence behavior and brain-based outcomes associated with cognitive control.

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Highlights

- Cognitive control is enhanced in children with behavioral inhibition (BI).
- BI may influence brain mechanisms driving cognitive control in adulthood.
- BI predicted brain response to emotional conflict monitoring and adaptation.
- Lifetime psychopathology, not BI, predicted behavioral differences in adaptation.
- Childhood BI differentially influences cognitive control mechanisms into adulthood.

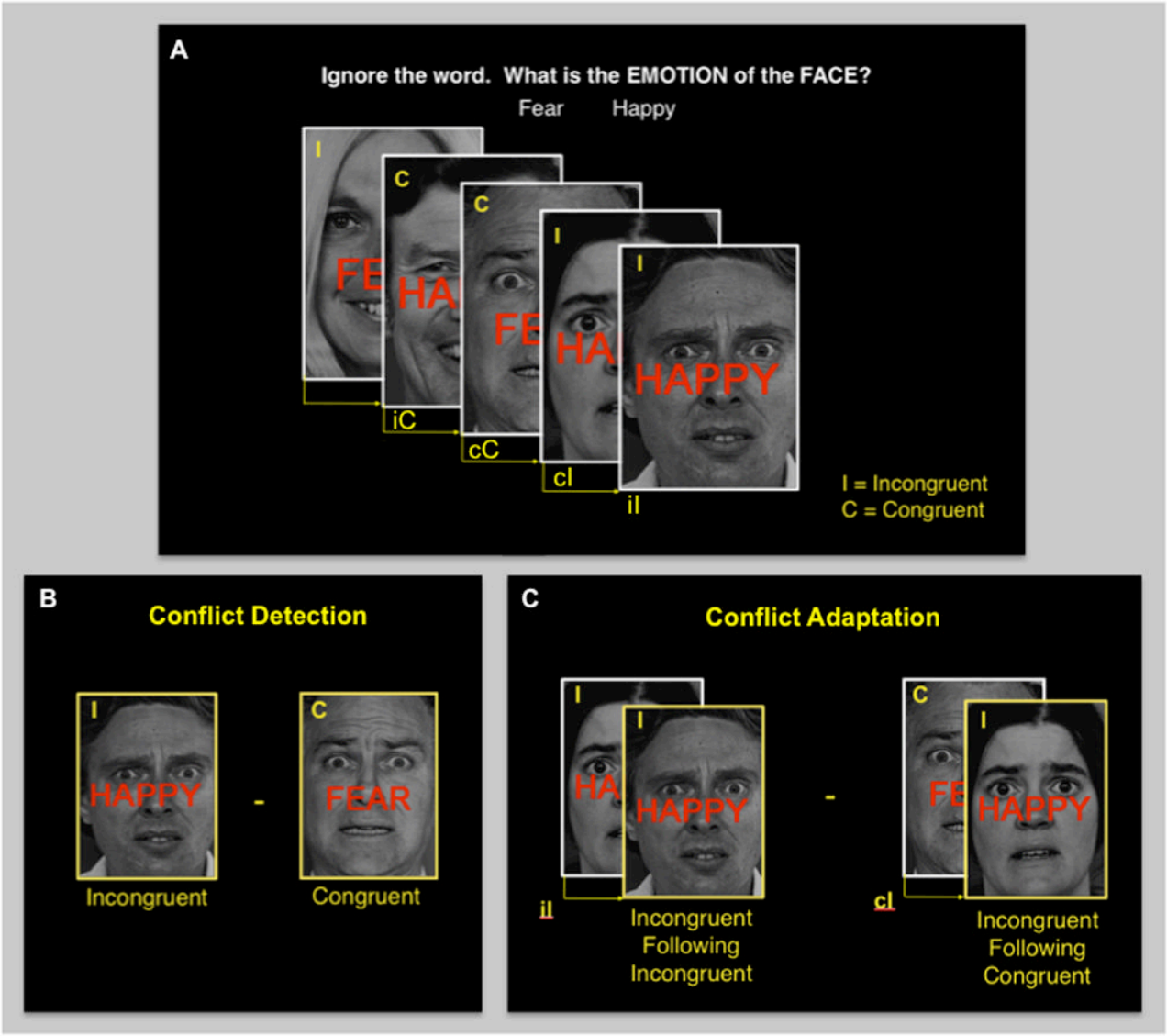

Figure 1.

Emotion conflict task. **A.** A sample of the experimental paradigm's stimulus presentation sequence. **B.** Emotional conflict detection is assessed by subtracting congruent trials (C) from incongruent trials (I). **C.** Emotional conflict adaptation is assessed by subtracting incongruent trials that follow congruent trials (cI), from incongruent trials that follow incongruent trials (iI).

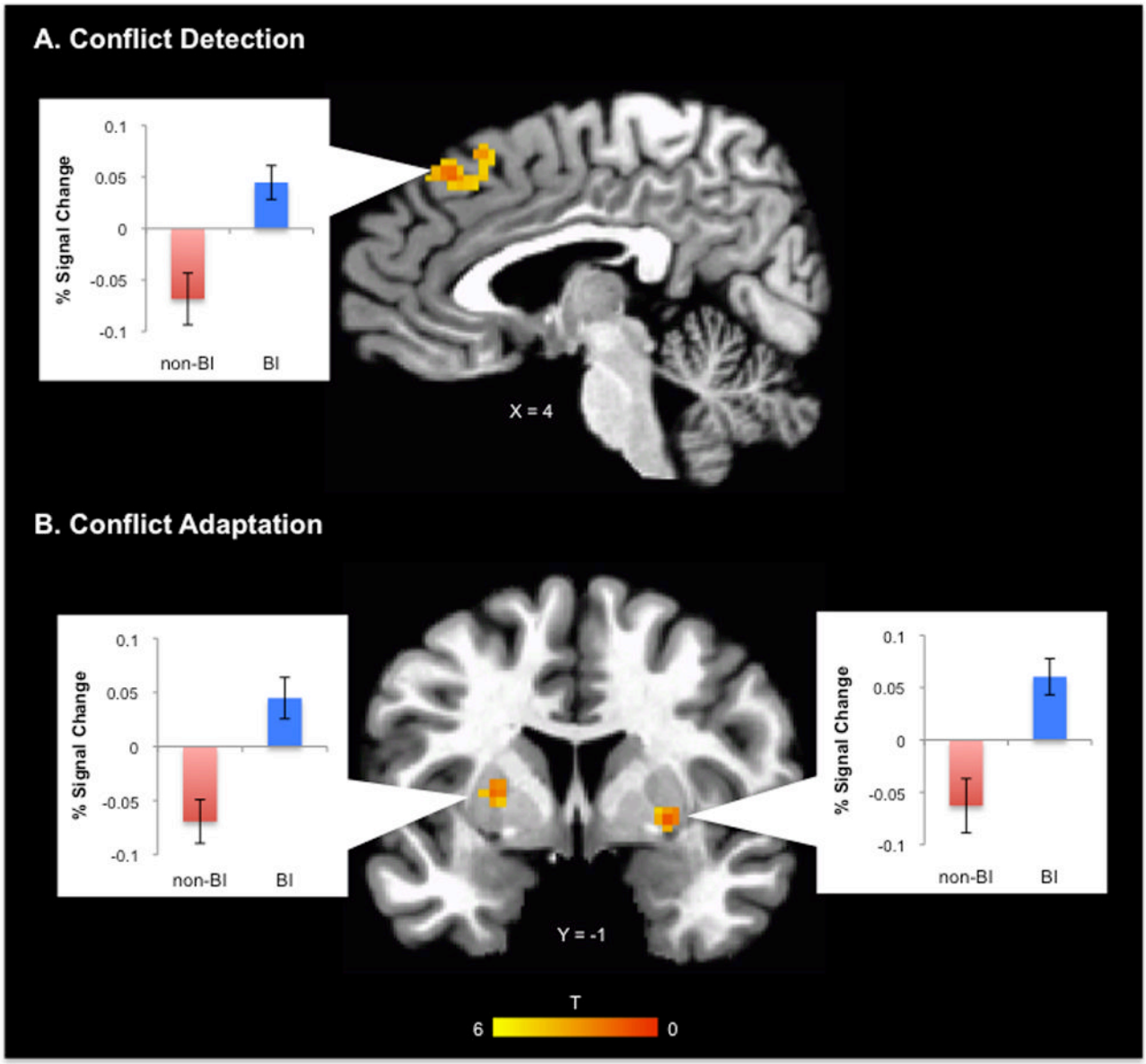

Figure 2.

Childhood behavioral inhibition-by-trial-type interaction in the brain. **A.** During emotional conflict detection (I – C), adults who were behaviorally inhibited (BI) as children had greater activity in the dorsomedial prefrontal cortex region of interest than those who were non-behaviorally inhibited (non-BI) as children. **B.** During emotional conflict adaptation (iI – cI), adults who were BI as children had greater activity in bilateral putamen within the striatal region of interest, than those who were non-BI as children. Bar graphs depict average percent signal-change values extracted from the activation cluster, plotted with standard error bars.

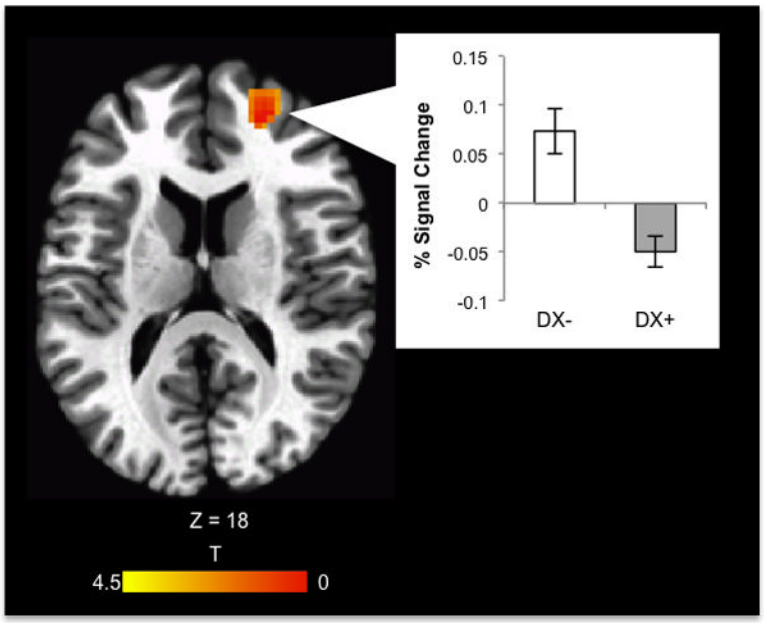

Figure 3.

Lifetime psychiatric diagnosis-by-trial-type interaction in the brain. During emotional conflict detection (I – C), adults without a lifetime psychiatric diagnosis (DX−) had greater activity in dorsolateral prefrontal cortex than those with a lifetime psychiatric diagnosis (DX +). Bar graphs depict average percent signal-change values extracted from the activation cluster, plotted with standard error bars.

Table 1

Subject characteristics (A) and behavioral response time for Emotional Conflict Task (B).

	Non-BI Adults		BI Adults	
	Mean	**SD**	**Mean**	**SD**
A. Demographics				
N (Female/Male)	7/7		11/10	
Age (years)	19.77	1.41	19.45	1.46
IQ	113.75	11.66	116.32	8.78
Psychological Characteristics				
BI Composite Score (14 mo - 7 yrs)	−0.67	0.27	0.69	0.63
Current Depression (BDI)	3.25	3.96	3.06	3.40
Current Social Anxiety (LSAS)	29	27.23	22.05	15.47
Liftetime SCID Diagnostic Frequency	6		11	
Anixety	4		6	
Depression	2		5	
Substance Use	1		3	
B. Response Time on Emotional Conflict Task (ms)				
Conflict Detection: Incongruent - Congruent	30.88	24.78	58.03	57.24
Incongruent	869.28	119.72	907.27	95.56
Congruent	838.40	112.50	849.24	97.72
Conflict Adaptation: iI – cI	−7.46	37.45	−2.35	78.32
iI	863.82	122.13	905.97	112.31
cI	871.28	124.71	908.32	95.98

BI = behaviorally inhibited; BDI = Beck Depression Inventory; LSAS = Liebowitz Social Anxiety; iI = Incongruent trials preceeded by incongruent trials; cI = Incongruent trials preceeded by congruent trials

Table 2

Activation clusters associated with emotional (A) conflict monitoring and (B) conflict adaptation. All coordinates in MNI space.

Region	Peak MNI Coordinates			Cluster Size	T
	x	y	z		
A. Conflict Monitoring					
Main Effect of Conflict Monitoring (Incongruent - Congruent)					
ROI Analyses					
Dorsomedial Prefontal Cortex	6	25	35	28	4.39
Corrected Whole Brain Analyses					
Anterior Insula	34	14	11	122	5.43
Inferior/Superior Parietal Lobule	−29	−55	45	72	3.85
Interaction between Conflict Monitoring and Behavioral Inhibition					
ROI Analyses					
Dorsomedial Prefontal Cortex	4	30	49	31	4.19
Corrected Whole Brain Analyses					
-	-	-	-	-	-
B. Conflict Adaptation					
No Main Effect of Conflict Adaptation (iI - cI)					
Interaction between Conflict Adaptation and Behavioral Inhibition					
ROI Analyses					
Putamen	−24	−1	6	18	4.18
	26	−1	−1	16	4.35
Corrected Whole Brain Analyses					
Precuneus	19	−70	50	184	4.51
Occipital Cortex	26	−79	6	91	4.23