

# Demand-Specific Alteration of Medial Prefrontal Cortex Response During an Inhibition Task in Recovered Anorexic Women

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## ABSTRACT

**Objective:** It is well known that individuals with anorexia nervosa (AN) are inhibited and over-controlled. This study investigated a prefrontal-cingulate network that is involved in inhibitory control.

**Method:** To avoid the confounds of malnutrition, 12 recovered (RAN) subjects were compared to 12 matched control women (CW) using a validated inhibition task (i.e., a stop signal task) during functional magnetic resonance imaging.

**Results:** Consistent with the *a priori* hypothesis, RAN subjects showed altered task-related activation in the medial prefrontal cortex (mPFC), a critical node of the inhibitory control network. Specifi-

cally, whereas RAN and CW showed similar mPFC activity during trials when inhibitory demand was low (i.e., easy trials), RAN relative to CW showed significantly less mPFC activation as inhibition trials became more difficult (i.e., hard trials), suggesting a demand-specific modulation of inhibitory control circuitry in RAN.

**Discussion:** These findings support a neural basis for altered impulse control symptoms in AN © 2010 by Wiley Periodicals, Inc.

**Keywords:** fMRI; anorexia; inhibition; stop task; prefrontal cortex

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## Introduction

Anorexia nervosa (AN) is a disorder of unknown etiology that most commonly begins during adolescence in women,<sup>1</sup> and is characterized by severe emaciation. AN individuals have a seemingly relentless drive to restrain food intake, an extreme fear of weight gain, and a distorted view of their body shape. Moreover, AN individuals tend to be over-controlled and rigid, and exhibit personality characteristics such as low impulsivity and high harm avoidance. These features are consistent with the formulation of AN as a neurobiologically based disorder that is characterized by accentuated inhibition and control<sup>2</sup> and may be due to fundamental

alterations in the neurobiological control mechanisms that govern behavior, emotion and physiology.<sup>3,4</sup>

Cognitive control is a set of higher order functions by which individuals regulate their movements, actions, thoughts, and emotions, according to current goals and environmental conditions.<sup>5</sup> One critical component of cognitive control is the ability to inhibit counterproductive thoughts, emotions, and behaviors, which is necessary for adaptive responding. An impaired ability to down-modulate inhibitory function or change inhibitory set may underlie symptoms in AN. Consistent with this formulation is research indicating that, while anorexics are quick to acquire a new set in the absence of a pre-existing cue, they also show marked impairments on set shifting tasks that require inhibitory control to direct attention away from a previously relevant stimulus dimension toward one that was previously irrelevant.<sup>6,7</sup> Collectively, this research emphasizes that alterations in inhibitory function are one important part of a broad-ranging profile of clinical deficits present in AN individuals.

Neuroimaging studies in healthy volunteers have defined a neural network that includes the prefrontal cortex and ACC, in which cognitive control is instantiated.<sup>8–10</sup> Within this network, the dorsal ACC and inferior, middle, and superior frontal gyri subserve cognitive control by regulat-

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ing selective attention and planning, via modulation of activity in posterior cortical and subcortical brain structures. Dysregulated activity of this network in symptomatic AN individuals has been observed at rest in prior neuroimaging studies.<sup>11,12</sup> In one such study using single photon emission computed tomography (SPECT), hypoperfusion in the mPFC and ACC was reported in AN patients.<sup>12</sup> Another study reported that blood flow dysregulation in this circuit differentiated between AN subtypes, with restricting type AN showing decreased blood flow compared to bulimic-type AN and healthy controls.<sup>11</sup> These findings may reflect either disengagement of inhibitory neurocircuitry or alternatively more efficient cognitive control processing in AN at rest. Uher et al.<sup>13</sup> found increased ventral mPFC (BA 11) response in ill AN, also finding increased ventral mPFC but decreased dorsolateral PFC (DLPFC) response in ill BN, when these subjects viewed images of savory and sweet foods. These group differences persisted when both eating disorder groups were combined. This paradigm challenges cognitive response with symptom-provoking stimuli and points to the prefrontal cortex as a potential locus for eating disorder pathology.

Supporting the hypothesis that AN symptoms may be perpetuated or caused by impaired cognitive control, brain perfusion in the superior frontal gyrus was found to correlate with the interference scores during a Stroop task in currently ill AN patients.<sup>14</sup> The Stroop interference score reflects increased cognitive control when the color of the word's ink and the color related by the word are incongruent. A recent fMRI study examining behavioral and cognitive set shifting similarly reported that, during shift trials of a target detection task, frontal-parietal networks were significantly more activated, and the dorsal ACC and ventral striatum were significantly less activated, in ill AN relative to control subjects.<sup>15</sup> Shift trials correspond to increased cognitive control as a dominant response and must be suppressed in favor of a non-primed response.

Together, these studies establish that although disruptions to frontal-striatal circuitry in AN can be imaged during cognitive control tasks, interference and set shifting represent different "flavors" of cognitive control, which are distinct from inhibition. Despite converging evidence describing the neural basis of altered inhibitory function in eating disorders, there have been no published studies examining the neural correlates of performance of an inhibitory stop task in recovered restricting-type AN subjects (RAN) relative to age and gender

matched control women (CW). The purpose of this study was to use a validated stop signal task that implemented individualized trials during fMRI to characterize the neural correlates of inhibitory processing in AN. We hypothesized that RAN compared to healthy CW would show altered activation in a prefrontal-cingulate network that is involved in inhibitory control. Support for this hypothesis could identify a target for therapeutic interventions and contribute to the development of a comprehensive model on which future treatment studies may be based.

## Method

### *Subject Recruitment and Screening*

Twenty-four right-handed female volunteers provided written informed consent and completed this cross-sectional study, which was approved by the University of California San Diego Human Research Protection Program. To be considered "recovered," subjects had to (1) maintain a weight above 85% average body weight,<sup>16</sup> (2) have regular menstrual cycles, and (3) have not binged, purged, or engaged in significant restrictive eating patterns for at least 1 year before the study. Additionally, subjects must not have used psychoactive medication such as antidepressants or met criteria for alcohol or drug abuse or dependence, major depressive disorder (MDD) or severe anxiety disorder within 3 months of the study. Trained doctoral level clinicians administered the Structured Clinical Interview for DSM-IV<sup>17</sup> and a psychiatric interview to determine eligibility and diagnosis. None of the CW met criteria for a current or lifetime diagnosis of an eating disorder or other Axis I disorder. Exclusion criteria for both groups included: (1) lifetime history of ADHD, psychotic or bipolar disorder, (2) current antidepressant or other psychiatric medication use, alcohol or substance abuse within 90 days of study participation, (3) active medical problems or suicidal ideation.

### *Subject Characteristics*

RAN ( $n = 12$ ; mean age = 29.4, age range = 22–44; mean body mass index [BMI] = 22.1, BMI range = 19.0–25.4) and CW ( $n = 12$ ; mean age = 29.0, age range = 22–39; mean BMI = 21.2, BMI range = 17.7–24.0) subjects were recruited via flyers and electronic bulletin boards. The groups did not differ in socio-demographic characteristics such as age [ $t(24) = 0.03, p = \text{NS}$ ] and ethnicity [ $\chi^2 = (1, N = 24) = 1.20, p = \text{NS}$ ], or in BMI [ $t(22) = 1.42, p = \text{N.S.}$ ]. RAN subjects met criteria for DSM-IV diagnosis of AN, but never for BN, with average disease onset of  $13 \pm 3$  (Range: 10–19) years and average disease duration of  $8.4 \pm 8.5$  (Range: 1.5–29.0) years. RAN did not meet AN

diagnostic criteria for at least 12 months (average  $100 \pm 62$  months since last eating disorder episode, Range: 13–186 months) before the study. Three RAN subjects met criteria for current obsessive compulsive disorder (OCD). Of those three subjects, one presented with current and one with prior history of trichotillomania. Several RAN subjects also met criteria for lifetime (but not current) anxiety and mood disorders such as social phobia (three individuals), post-traumatic stress disorder (three individuals), MDD (six individuals), and generalized anxiety disorder (one individual). One RAN individual met criteria for past alcohol dependence.

### **Stop Signal Task**

Subjects performed a stop signal task<sup>18–20</sup> during fMRI. All subjects were scanned during the first 10 days (early follicular phase) of the menstrual cycle to control for hormonal effects of task performance and brain response. Immediately before scanning, subjects practiced the task to determine their mean reaction time (RT). Subjects were asked to respond as quickly as possible by pressing left and right buttons when they saw “X” and “O” stimuli, respectively, (i.e., the “go” signal), but not to press either button when they heard a tone (i.e. the “stop” signal) in conjunction with the “go” signal. One of the advantages of this task is that trials were individualized for each participant. Specifically, individualized hard (i.e., tone delivered at RT or 100 ms less than RT) and easy (i.e., tone delivered at 400 ms less than RT or 500 ms less than RT) trials were constructed for each individual.

During scanning, subjects viewed “X” and “O” stimuli that appeared on a black background back-projected to the subjects positioned inside the MRI scanner, at a visual angle of  $\sim 6^\circ$ . Every trial began with the presentation of “X” and “O” visual stimuli (i.e., the “go” stimuli). During 25% of the trials, these visual stimuli were followed by an auditory tone (i.e., the “stop” signal). Subjects were instructed to use their right hand to press the left mouse button when an “X” appeared on the screen, press the right button when an “O” appeared, but not press either button when either the “X” or “O” were accompanied by a tone. After each scan, subjects were asked to confirm that they clearly heard the tones. Each trial lasted at most 1300 ms, or until the subject responded. Trials were separated by 200 ms interstimulus intervals (blank screen). Subjects performed 72 total stop trials, which were pseudo-randomized throughout the task and counterbalanced. Six blocks were performed, each containing 48 total trials (12 stop and 36 nonstop trials in each block). Task instructions were presented for 12 s between blocks. All subjects received the same amount of hard and easy trials, which were unique to each individual based on their prescan RT.

To compare the groups on vigilance during the task, mean RT during the nonstop trials was compared

between the groups. Since the task was constructed based on each subject’s RT, the performance on the task was measured by percent correct (i.e., the ability of each individual to successfully inhibit easy and hard trials). To test for main effects of task and group, and for a group by task interaction, error rate for each individual was entered into a 2-way ANOVA, i.e. with task condition (hard/easy) and group (RAN/CW) as factors.

### **Scan Parameters**

During imaging, a fast event-related fMRI design was used. During the task, an fMRI run sensitive to blood oxygenation level-dependent (BOLD) contrast<sup>21</sup> was collected for each subject using a Signa EXCITE (GE Healthcare, Milwaukee) 3.0 T scanner (T2\* weighted echo planar imaging, TR = 2,000 ms, TE = 32 ms, FOV =  $230 \times 230$  mm,  $64 \times 64$  matrix, 30 2.6 mm axial slices with a 1.4 mm gap, 256 scans, 512 seconds). fMRI acquisitions were time-locked to the onset of the task. During the same experimental session, a T1-weighted image (MPRAGE, TR = 8.0 ms, TE = 4.0 ms, flip angle =  $12^\circ$ , FOV =  $250 \times 250$ ,  $\sim 1$  mm<sup>3</sup> voxels) was obtained for cross-registration of functional images. Image processing and analysis was performed with the Analysis of Functional NeuroImages (AFNI) software package.<sup>22</sup>

### **Image Processing**

To minimize motion artifact, echo-planar images were realigned to the 128th acquired scan. Additionally, data were time-corrected for slice acquisition order, and spikes in the hemodynamic time course were removed and replaced with an interpolated value from adjacent time points using 3dDespike. A multiple regression analysis was performed to test the proposed hypotheses regarding alterations in the neural substrates of inhibitory processing in RAN. Specifically, preprocessed time series data for each individual were analyzed using a multiple regression model consisting of three task-related regressors: (1) noninhibit trials, i.e. trials where no auditory stop signal was administered, (2) hard stop trials, i.e. difficult to inhibit trials (RT and RT-100), and (3) easy stop trials, i.e. easy to inhibit trials (RT-400 and RT-500). Five additional regressors were included in each model as nuisance regressors: three movement regressors to account for residual motion (in the roll, pitch, and yaw directions), and regressors for baseline and linear trends to account for signal drifts. A Gaussian filter with a full width-half maximum of 6 mm was applied to the voxel-wise percent signal change data to account for individual variation in the anatomical landmarks. Data from each subject were normalized to Talairach coordinates.<sup>23</sup>

### **Group Analysis**

Primary contrasts between regression coefficients from the AFNI program 3dDeconvolve were entered into

a two-sample t-test to examine activation differences between the groups for hard inhibit – easy inhibit trials. A threshold adjustment method based on Monte-Carlo simulations was used to guard against identifying false positive areas of activation.<sup>24</sup> Based on the whole brain analysis, an *a priori* voxel-wise probability of  $p < .05$  in a cluster of 1408  $\mu\text{L}$  with 22 connected voxels resulted in an *a posteriori* cluster-wise probability of  $p < .05$ . RAN functional data during stop trials were correlated with trait characteristics, including perfectionism (Multidimensional Perfectionism Scale),<sup>25</sup> harm avoidance (Temperament and Character Inventory),<sup>26</sup> state and trait anxiety (State-Trait Anxiety Inventory-Version Y),<sup>27</sup> depression (Beck Depression Inventory),<sup>28</sup> and impulsivity (BIS-11).<sup>29</sup> Due to equipment failure, behavioral responses during the task were not recorded in 1 CW and 5 RAN subjects; thus, the error-related behavioral analysis represents data from 11 CW and 7 RAN.

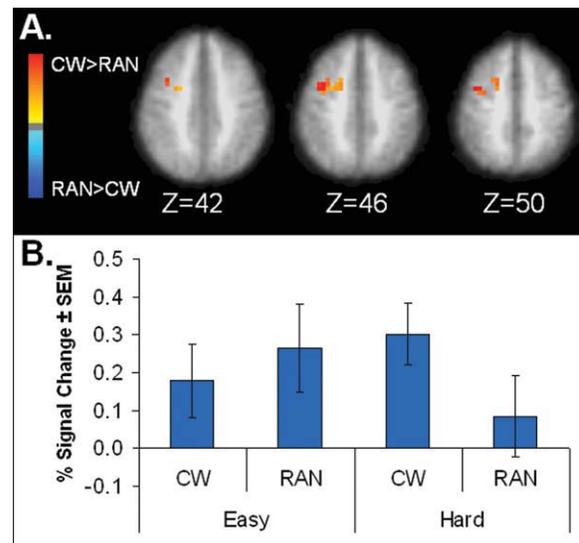
## Results

### Behavioral

CW and RAN groups did not differ in their mean RT ( $F(1,17) = 1.68, p = 0.21$ ) during the nonstop trials, suggesting that the groups did not differ in vigilance during the task. By design, a significant effect of task (easy/hard) on error rate was observed, that is, significantly more errors were made during hard trials than easy trials in both groups ( $F(1,17) = 51.02, p < .001$ ). The RAN and CW were not significantly different in mean % correct during hard (CW:  $21\% \pm 31\%$ ; RAN:  $21\% \pm 21\%$ ) or easy (CW:  $81\% \pm 22\%$ ; RAN:  $78\% \pm 20\%$ ) trials. No significant group ( $F(1,17) = 0.02, \text{NS}$ ) or group by task ( $F(1,17) = 0.02, \text{NS}$ ) effects on error rate were observed, indicating that the RAN and CW were not significantly different in their accuracy during hard or easy trials.

### Functional Neuroimaging

A whole brain analysis revealed one significant cluster of activation in Brodmann's Area 6 of the mPFC, related to a group (CW/RAN) by condition (hard/easy) interaction ( $F(1,23) = 11.12, p = 0.003$ ) (Fig. 1). Whereas the RAN and CW showed similar mPFC activity during trials when inhibitory demand was low (i.e. easy trials), RAN subjects showed significantly less mPFC activity during hard trials, suggesting a demand-specific modulation of inhibitory control circuitry in RAN. No statistically significant correlations were observed in RAN between mPFC activation during stop trials and trait characteristics, including perfectionism, harm



**FIGURE 1** Differential medial prefrontal cortex (mPFC) activation during Hard-minus-Easy stop trials in recovered anorexics (RAN) compared to control women (CW). (A) Significant group (CW/RAN) by condition (Easy/Hard) interaction was observed in the mPFC (Talairach coordinates: XYZ = 30, 1, 45; Volume = 1664  $\mu\text{L}$ , 26 contiguous voxels). (B) CW showed greater, whereas RAN showed lesser, mPFC percent blood oxygen level dependent (BOLD) signal change during hard trials compared to easy ( $F(1,23) = 11.12, p = 0.003$ ). [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

avoidance, anxiety, depression, impulsivity, as well as state anxiety and depression measured immediately before scan. Likewise, mPFC activation during stop trials was not significantly correlated with age of onset, months since last eating disorder episode, or disease duration. Finally, inhibition-related mPFC activation did not significantly correlate with task performance as measured by error rate.

## Discussion

During a stop inhibition task, women recovered from AN showed decreased mPFC activation as inhibitory load increased, whereas healthy controls with no history of eating disorder showed increased mPFC activation with increased difficulty. This finding is consistent with our *a priori* hypothesis that RAN would show altered inhibition-related activation in a prefrontal-cingulate network, and specifically implicates the mPFC in inhibitory control processes related to AN symptoms. One interpretation of these observations is that AN individuals require less inhibitory resources (i.e., less mPFC activation) to maintain behavioral performance as inhibitory load is increased. Inefficient performance of cognitive tasks can lead to increased activa-

tion in clinical populations,<sup>30</sup> and more experience, corresponding to greater task efficiency, can reduce activation.<sup>31</sup> Such an interpretation is in line with clinical observations of AN individuals, who often have obsessional personalities and are over-controlled in their behaviors. However, there is no direct validation of this mechanism in AN, so this hypothesis is speculative. The degree to which clinical symptoms of AN map onto the neuroimaging findings observed in the current study should be explored in future studies.

Alterations in cognitive control are manifested in the inflexible patterns of thinking that are observed in ED individuals.<sup>32</sup> Numerous behavioral studies have reported that impairments of set shifting are a trait characteristic of ill and recovered AN.<sup>6</sup> Employing a battery of neuropsychological tests that specifically probe different facets of set shifting behaviors, Tchanturia et al. described a perceptual shift deficit in AN.<sup>7</sup> Indeed, the possibility that impaired set shifting is an endophenotype of AN was proposed after finding similar deficits in unaffected sisters of women with anorexia, but not in unrelated healthy controls.<sup>33</sup> These findings are consistent with clinical evidence that AN is associated with increased cognitive control and overregulation.<sup>34</sup> Our findings build on this literature by identifying a neural correlate of altered inhibitory function in AN.

Behavioral studies specifically probing impulsivity and inhibition in eating disorder subjects suggest that, while closely linked, set shifting and inhibition are distinct phenomena. Set shifting measures cognitive rigidity in that it requires simultaneous acquisition of a new set while inhibiting adherence to the previously relevant set.<sup>6,7</sup> "Stop" or "Go-NoGo" tasks, in contrast, are a more direct measure of cognitive inhibition in that subjects are responding and inhibiting response within one set. Using a stop task similar to the one employed in the present study, in a behavioral experiment, Claes et al. found that mean RT and trial error rate were statistically similar between restricting type AN, purging type AN, and BN eating disorder groups, and healthy controls.<sup>35</sup> By modulating the stimulus presentation time according to error, this study design resulted in uniform difficulty adjusted for individual performance; therefore, it is not surprising that error rates across groups were similar. Conversely, the stop task administered in the current study was designed to vary inhibitory difficulty across trials according to individual mean RTs calculated before the scanning session, resulting in a more precise modulation of inhibitory load. In agreement with data from Claes

et al., we observed that percent error did not differ between the groups in either the easy or hard conditions, suggesting that our imaging findings were not confounded by behavioral differences between the groups.

Given high prevalence of perfectionistic personality traits reported in AN individuals, lower error rates during hard trials might be expected in AN versus control groups. Indeed, Butler and Montgomery commented on a similar discrepancy between behavioral and self-reported impulsivity data.<sup>36</sup> Employing a continuous performance task, ill AN relative to control subjects demonstrated significantly faster RTs and more errors (i.e. inappropriately responding in the absence of a cue), indicating increased impulsivity. However, these behavioral data are contrary to the lower levels of self-reported impulsivity that have been reported by AN individuals.<sup>36</sup> These seemingly discrepant findings suggest a complex underlying mechanism, and potentially, that discreet subgroups of AN individuals may show different clinical, behavioral and neural manifestations across a broad range of set shifting, impulsivity and inhibitory paradigms. Alternatively, a diminished capacity for self-reflection evidenced in AN may underlie the discrepancy between behavior and self-reported characteristics.<sup>36</sup> Further research is needed to investigate these possibilities and to develop a comprehensive neurobiological model of AN.

Since eating disorders are highly comorbid with mood and anxiety disorders, it is critical that such a model account for comorbidities. Specifically, MDD and OCD are characterized by alterations in inhibitory control and are both consistently reported in the literature to have high comorbid diagnosis in AN.<sup>37</sup> Anxiety disorders such as post-traumatic stress disorder, panic disorder, and social phobia, also share considerable comorbidity with AN. Neuroimaging studies suggest that these related psychiatric populations have altered engagement of frontal-striatal and frontal-cingulate networks.<sup>38</sup> For example, a recent study revealed that MDD subjects relative to healthy controls showed altered inhibition-related subgenual ACC activation, which correlated with symptom severity.<sup>39</sup> Likewise, subjects with obsessive-compulsive disorder (OCD) showed decreased mPFC, and IFG activation compared to healthy subjects during inhibitory trials.<sup>40</sup> Thus, a stop task elicited abnormal frontal-striatal-cingulate response, which mediates cognitive control, in both MDD and OCD groups. It is indeed possible that the presence of these comorbidities in the RAN patient cohort, and

their absence in the healthy comparison group, may account for the mPFC findings presented in this study. However, no significant comorbidity effects were observed on mPFC activation when OCD, depression, and anxiety were designated as covariates (data not shown). Furthermore, comparison of mPFC activation in RAN using these comorbidities as dependent variables showed no significant interaction effect (data not shown). In future work, it will be important to quantify the degree to which specific brain-based alteration during inhibitory control are related uniquely to psychopathology in AN, and not to comorbid mood and anxiety disorders.

Recent functional neuroimaging studies have contributed to an emerging model of eating disorders as brain-based disorders affecting integrated neurocircuits that are involved in fundamental processes such as cognitive control. Both AN and BN showed decreased frontal-striatal activation when they were challenged by a set shifting task<sup>15,41</sup> and dysregulated striatal response to positive and negative feedback in a monetary choice task.<sup>42</sup> Reward-related neural responses in anorexia and bulimia nervosa after recovery using functional magnetic resonance imaging. Another study indirectly challenged cognitive control in AN and BN by presenting symptom-provoking images of food, finding increased mPFC and ACC activity in both eating disorder groups.<sup>13,43</sup> The disparity of these findings with data presented in this study is likely attributable to paradigm differences, whereby inhibitory processing in AN elicited by symptom-provoking stimuli is more “difficult” than inhibition in a task unrelated to food. These studies together suggest a potential common prefrontal neuropathology in disorders with divergent behavioral symptoms.

Disturbances in ill AN patients may be a consequence of malnutrition or premorbid traits that contribute to a vulnerability to develop AN. Determining whether abnormalities are a consequence or a potential antecedent of pathologic feeding behavior is a major question in the study of eating disorders. It is impractical to study AN prospectively because of the young age of onset and difficulty in premorbid identification of people who will develop the disorder. Another strategy is to study women who are recovered from AN. Any persistent psychobiological abnormalities might be trait related and potentially contribute to the pathogenesis of this disorder. In fact, temperament and personality traits such as negative emotionality, harm avoidance and perfectionism, and over-control are premorbid child-

hood traits and persist after recovery,<sup>44,45</sup> as does delayed set shifting.<sup>7</sup> Importantly, fMRI studies have also demonstrated altered activation of networks mediating cognitive control in recovered AN subjects. Uher et al. found increased mPFC response to food images in participants who have recovered from AN compared to currently ill AN patients and to healthy controls.<sup>43</sup> Wagner et al.<sup>46</sup> found that RAN had increased DLPFC response to a monetary choice task compared to healthy controls. Frank et al.<sup>47</sup> found that RAN had altered serotonin functional activity in anterior cingulate/subgenual regions.

One possible explanation for the present data is that AN have a developmental mismatch due to a lag in frontal lobe development. In depressed adolescent subjects who performed the stop task, Yang et al.<sup>48</sup> found increased subgenual cingulate activity during stop trials compared to healthy controls but decreased activation in the bilateral medial frontal gyrus (BA 10). In contrast to our findings in RAN subjects, which showed a significant condition interaction, these group differences in depressed adolescents were consistent across easy and hard stop trials. In an adolescent OCD population, Wooley et al.<sup>49</sup> likewise reported decreased activation compared to controls in the DLPFC (BA9,10) and dorsal ACC (BA 32) during error-related stop trials. However, because the study design fixed error rate at 50% by modulating trial difficulty, a direct comparison of easy versus hard trials with the present data is not possible.

One strength of the current study was the unique sample, which consisted of unmedicated, young, and healthy individuals, eliminating potentially confounding effects of medication and medical comorbidities. However, it will also be important in future studies to examine the degree to which the current findings generalize to other populations of ED individuals, such as bulimics and ill anorexics. Additionally, due to equipment failure in several experimental sessions, there was inadequate power to examine error-related activity, and we cannot exclude the possibility that the observed findings were in part due to error processing. It will be important in future studies to examine the neural correlates of both inhibitory and error processing in AN. Despite these limitations, our findings represent preliminary evidence of a neural basis of aberrant impulse control in RAN.

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