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Archival Report

Neural Correlates of Failed Inhibitory Control as an Early Marker of Disordered Eating in Adolescents

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ABSTRACT

BACKGROUND: Binge eating and other forms of disordered eating behavior (DEB) are associated with failed inhibitory control. This study investigated the neural correlates of failed inhibitory control as a potential biomarker for DEB.

METHODS: The study used prospective longitudinal data from the European IMAGEN study adolescent cohort. Participants completed baseline assessments (questionnaires and a brain scan [functional magnetic resonance imaging]) at 14 years of age and a follow-up assessment (questionnaires) at 16 years of age. Self-reported binge eating and/or purging were used to indicate presence of DEB. Neural correlates of failed inhibition were assessed using the stop signal task. Participants were categorized as healthy control subjects (reported no DEB at both time points), maintainers (reported DEB at both time points), recoverers (reported DEB at baseline only), and developers (reported DEB at follow-up only). Forty-three individuals per group with complete scanning data were matched on gender, age, puberty, and intelligence (N = 172).

RESULTS: At baseline, despite similar task performance, incorrectly responding to stop signals (failed inhibitory control) was associated with greater recruitment of the medial prefrontal cortex and anterior cingulate cortex in the developers compared with healthy control subjects and recoverers.

CONCLUSIONS: Greater recruitment of the medial prefrontal and anterior cingulate regions during failed inhibition accords with abnormal evaluation of errors contributing to DEB development. As this precedes symptom onset and is evident despite normal task performance, neural responses during failed inhibition may be a useful biomarker of vulnerability for DEB. This study highlights the potential value of prospective neuroimaging studies for identifying markers of illness before the emergence of behavior changes.

Keywords: Binge eating, Biomarkers, Eating disorders, Inhibitory control, Neuroimaging, Stop signal task

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Eating disorders (EDs) are characterized by disturbed eating behaviors and extreme concerns about weight and shape. Onset usually occurs during adolescence (1), and early symptomatic behavior is predictive of later development of clinical disorders (2). It would be advantageous to be able to identify vulnerable individuals; however, few prospective community-based studies have been conducted to investigate potential behavioral, biological, or neural biomarkers of vulnerability.

Adolescence is associated with more impulsive, risky, and sensation-seeking behavior compared with childhood and adulthood, attributed at least partly to heterochronous regional brain development (3)—for example, maturity of subcortical regions associated with arousal versus immaturity of prefrontal and parietal regions integral to evaluative control over behavior (4). Such developmental events may lead to more impulsive behavior and confer risk of impulsive disordered eating behaviors (DEBs). Indeed, neuroimaging studies of inhibitory control in adolescents with EDs have reported altered recruitment of frontostriatal networks implicated in reward processing and self-regulation, though the direction of effect is not consistent (5,6). Thus, differences in neural functioning related to inhibitory control may contribute to the development of impulsive DEBs (7). It is unclear whether differences in neural activity associated with inhibitory control precede EDs, develop with the illness, or are a consequence of DEB.

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Prospective longitudinal neuroimaging are necessary to address these questions.

Altered behavioral control has been implicated in ED pathology (8). Many symptoms revolve around the experience of control: e.g., loss of control during binge eating episodes and attempting to regain control over weight or food intake through food restriction/purging, while simultaneously being unable to stop engaging in restrictive or purging behaviors (9). These are transdiagnostic symptoms that are characteristic across ED diagnoses, with bulimia nervosa (BN) characterized by binge eating and purging, binge-eating disorder (BED) by binge eating in the absence of compensatory purging, and the binge-purge subtype of anorexia nervosa (AN) involving binge eating and/or purging. Moreover, EDs (particularly BN and BED) are often comorbid with impulse control disorders (1,10,11) such as substance misuse disorders (12), and behavioral dyscontrol outside of eating contexts is common, suggesting that self-regulatory difficulties occur across EDs (6). Additionally, a perceived loss of control (over behaviors, thoughts, and/or environment) has been retrospectively identified by patients as contributing to the development of their ED (13–16) and thus may constitute a risk factor for future ED development.

This study used a large multinational prospective neuroimaging dataset (17) to explore whether neural activity associated with motor inhibitory control can distinguish between individuals reporting DEBs at the time of a brain scan (14 years of age), those who develop these behaviors later (at 16 years of age), and individuals who do not develop these behaviors. Such studies are difficult given the early onset of these disorders and the typical delay in presentation to the clinic. This pioneering project is the first to identify possible neural biomarkers of vulnerability to an ED.

METHODS AND MATERIALS

Participants

Participants were selected from a large European cohort study [the IMAGEN study (17)]. At time 1 (T1), 14-year-olds (n = 2225) were recruited from secondary schools at eight sites (United Kingdom, Ireland, Germany, and France). A total of 1607 completed a follow-up assessment at ~16 years old (time 2 [T2]). Participants were excluded from the IMAGEN study if they had any magnetic resonance imaging (MRI) contraindications, neurological/neurodevelopmental disorders, nutritional/metabolic diseases, certain historical/current medical conditions (e.g., congenital heart defects), or IQ <70, or were receiving treatment for schizophrenia/bipolar disorder [see Schumann *et al.* (17)]. Participants in the present study were further excluded if they did not complete the diet, weight, and shape element of the Development and Well-Being Assessment interview at both time points, did not provide complete demographic data, or had inadequate/incomplete structural and functional stop signal task (SST) MRI data.

Eligible participants were categorized into four groups according to self-reported binge eating and purging (DEB): individuals reporting DEB at both time points (maintainers; n = 83 [71 girls]), individuals reporting DEB at T1 only (recoverers; n = 59 [49 girls]), individuals reporting DEB at T2 only (developers; n = 159 [122 girls]), and individuals reporting no DEB (healthy control subjects [HCs], n = 1265 [567 girls]). Owing to differences in group sizes, participants in each category were matched at an individual level to control for potential confounders in neuroimaging analyses of adolescents: age, gender, pubertal stage, and IQ (matching procedure outlined in the Supplement). Thus, a total sample of 172 participants comprising 43 individuals (40 girls) from each group was analyzed (Supplemental Figure S1). A description of the endorsed DEBs is provided in Supplemental Tables S1 and S2.

Questionnaires

DEB, anxiety, and depression were assessed using the Development and Well-Being Assessment, which assesses the presence and frequency of symptoms of several psychiatric disorders (18). The Dieting, Weight and Shape section of the youth version was used to assess DEB: a positive response for either binge eating (eating an objectively large amount of food with associated loss of control; questions 15 and 16) and/or purging (actively getting rid of ingested food by self-induced vomiting or pill use; questions 1c, 18f, and 18g) was used to indicate the presence of DEB. Owing to insufficient frequency data, only the self-reported presence/absence of DEB was assessed in this study. Probability band scores for anxiety and depression, calculated using information provided by the adolescent, his or her parent, and his or her teacher, were used to assess anxiety and depression. Pubertal stage was determined using self-reports on the Pubertal Development Scale (19). The short form of the Wechsler Intelligence Scale for Children–Fourth Edition (20) was administered to estimate cognitive ability. Lifetime cigarette, alcohol, or hash use (i.e., substances known to affect appetite) was assessed at baseline and follow-up using the European School Survey Project on Alcohol and Drugs questionnaire (21).

Body Mass Index

Height and weight were measured at both time points to calculate body mass index (BMI) (kg/m^2). Standardized BMI Z scores were calculated to provide age- and sex-adjusted relative weight-for-height assessments (22).

Stop Signal Task

Neural responses to successful and failed inhibitory control were assessed using a functional MRI SST. This reactive response inhibition task assesses action cancellation (23) and involves two concurrent tasks: a choice reaction time (RT) task ("go" trials: 80%, 400 trials) in which participants must indicate the direction (left/right) of a presented arrow (i.e., target; 1000-ms stimulus duration) using a button-press response; and a stop task in which participants must inhibit their motor response ("stop" trials: 20%, 87 trials) when an unpredictable stop signal (upward arrow, shown for 100–300 ms) is presented at a variable delay after target onset. Stop trials were infrequent to encourage rapid responding. The delay between the target and stop signal (stop signal delay [SSD]) was dynamically adjusted in a stepwise manner (in 50-ms increments/decrements, range = 0–900 ms, initial delay = 150 ms) to ensure that participants' stop accuracy converged at approximately 50% correct inhibition. The intertrial interval was 1800 ms. Behavioral dependent variables from this task included the mean SSD, stop accuracy, mean RT on correct go

trials, and the stop signal RT (SSRT). SSRT reflects the latency of the stop process (24), calculated by subtracting the mean SSD from the mean RT (25).

Procedure

Neuroimaging and questionnaire data were obtained from adolescents at T1; follow-up questionnaires were completed online at T2. The Development and Well-Being Assessment, Pubertal Development Scale, and European School Survey Project on Alcohol and Drugs questionnaire were completed on a computer. A researcher administered the Wechsler Intelligence Scale for Children–Fourth Edition at both time points.

Ethical Approval

Procedures were approved by local ethics committees at each site. Written informed consent from the parents and written assent from the children were obtained prior to participation.

Data Analysis

Between-group differences in demographic data and SST measures were explored using one-way analyses of variance. Significant group differences were further assessed using Bonferroni-corrected post hoc *t* tests. Square root transformations were effective in normalizing the positively skewed mean RT, SSD, and post-error slowing data, and reflected square root transformations were effective in normalizing the negatively skewed SSRT data. The go trial accuracy data distribution was strongly negatively skewed. Non-normally distributed demographic and task-based (go accuracy) data were assessed using nonparametric Kruskal-Wallis tests and Bonferroni-corrected post hoc Mann-Whitney *U* tests. All tests were two-tailed, with the significance level (α) set at .05.

Structural and functional MRI data were acquired using 3T MRI scanners of different manufacturers (including GE Healthcare, Chicago, IL; Siemens, Munich, Germany; Philips, Amsterdam, Netherlands; Bruker, Billerica, MA). Details of the structural and functional neuroimaging procedures are provided in the Supplement. Image preprocessing was completed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Functional MRI data processing included manual origin setting, slice-time correction, realignment, and coregistration to the T1-weighted structural scan. A study-specific template was created for normalization using the DARTEL toolbox (26). The resultant flow fields were used to normalize the coregistered data to Montreal Neurological Institute space (27). Normalized images were smoothed using an 8-mm full width at half maximum Gaussian kernel.

Subject-specific regressors were created using onsets corresponding to the presentation of the go target, and duration corresponded to the latency between onset and response. These were convolved with the canonical hemodynamic response function to create explanatory variables for the following trials: successful stop (SS) trials, failed stop (FS) trials, successful go (SG) trials, missed trials, incorrect go trials, and early stop trials (i.e., responding before the appearance of the stop signal). The high-pass filter was set to 128 Hz, and potential residual autocorrelation was controlled for using an autoregressive function (1). Scans were checked manually and excluded if there was visual evidence of excessive motion.

First-level contrasts were generated for the following a priori comparisons: FS > SS (error with intention to stop), FS > SG (erroneous/unwanted vs. wanted response), and SS > SG (successful inhibition). These were taken forward to group-level random-effects analyses, specifically three one-way analyses of covariance exploring the main effect of group followed by post hoc *t* tests, and subsequent regression analyses to identify group-by-covariate interactions in the relationships between neural recruitment and behavioral performance measures (transformed SSRT and post-error slowing). Cumulative head motion (sum of volume-to-volume Euclidean distance) and study site (dummy variables) were included as nuisance regressors in the models to control for confounding effects of head movement and site. We explored group differences in neural recruitment and the relationship between neural and behavioral outcomes in three planned group comparisons:

- HCs versus developers: As neither of these groups reported DEBs at the time of the scan, differences between them in neural activity may be a potential marker of future vulnerability.
- HCs versus maintainers: This allowed comparison of a group who showed current and prolonged DEB with a healthy group.
- Recoverers versus maintainers: Both groups reported DEBs at the time of scan; thus, differences in neural activity should permit comparison between individuals displaying transient symptoms from individuals with more prolonged symptoms.

Only results that survive familywise error correction at $p < .05$ at a cluster height threshold of $p < .001$ were considered significant.

RESULTS

One-way analyses of variance and Kruskal-Wallis tests confirmed no differences between groups in age ($F_{3,168} = 1.396$, $p = .246$), puberty ($\chi^2_3 = 1.947$, $p = .583$), and IQ (verbal [$F_{3,168} = 0.926$, $p = .430$], performance [$F_{3,168} = 0.130$, $p = .942$]) (Table 1). Chi-square analyses revealed no differences between the groups in lifetime use of substances known to affect appetite (all $\chi^2_3 \leq 6.057$, $p \geq .109$) (Supplemental Table S3), except for lifetime hash use at follow-up ($\chi^2_3 = 9.521$, $p = .023$). No differences were observed in the proportion of individuals reporting binge eating and purging between recoverers and maintainers at baseline or between developers and maintainers at follow-up (all $U \geq 731.0$, $Z \geq -1.938$, $p \geq .053$) (Supplemental Table S1).

Group differences in BMI were present at baseline ($F_{3,171} = 5.013$, $p = .002$), driven by lower BMI *Z* scores in the developers compared with the recoverers ($t_{84} = -3.203$, $p = .002$) and maintainers ($t_{84} = -3.311$, $p = .001$), which survived Bonferroni correction. This was not due to differences in endorsement of food restriction among developers (77%) compared with either recoverers (79%) or maintainers (86%) ($\chi^2_2 = 1.080$, $p = .583$) (Supplemental Table S2). BMI *Z* scores were also lower in HCs compared with recoverers

Table 1. Demographic Information for the Final Matched Sample of Participants Who Responded at Both Time Points

	Group			
Time Point	HCs	Developers	Recoverers	Maintainers
T1 (14 Years of Age)				
Age, years	14.61 ± 0.36	14.49 ± 0.33	14.66 ± 0.44	14.57 ± 0.35
BMI *Z* score	0.25 ± 1.04	0.07 ± 0.88	0.67 ± 0.82	0.69 ± 0.83
PDS	16.16 ± 1.46	15.89 ± 2.10	15.65 ± 2.94	16.03 ± 2.17
Verbal IQ	106.88 ± 13.35	108.20 ± 11.24	108.08 ± 14.57	109.35 ± 13.16
Performance IQ	104.53 ± 15.50	104.80 ± 15.07	105.42 ± 14.80	106.44 ± 13.48
Anxiety[a]	0.38 ± 0.66	0.57 ± 0.98	0.77 ± 1.07	0.91 ± 1.31
Depression[a]	0.50 ± 0.62	0.46 ± 0.92	0.88 ± 1.03	0.97 ± 1.03
T2 (16 Years of Age)				
Age, years	16.46 ± 0.66	16.47 ± 0.52	16.51 ± 0.75	16.60 ± 0.80
BMI *Z* score	−0.09 ± 1.10	0.16 ± 1.06	0.58 ± 1.00	0.51 ± 0.99

Values are mean ± SD.
BMI, body mass index; HCs, healthy control subjects; PDS, Pubertal Development Scale.
[a]Development and Well-Being Assessment probability band scores for an anxiety or depressive disorder.

(t_{84} = −2.092, p = .039) and maintainers (t_{84} = −2.198, p = .031), though these findings did not survive Bonferroni correction. A trend toward a difference in anxiety (χ^2_3 = 6.508, p = .089) and depression (χ^2_3 = 7.297, p = .063) was also seen at baseline, driven by greater anxiety in the developers compared with HCs, (U = 668.0, Z = −2.536, p = .011), and greater depression in the maintainer group compared with the developer group (U = 651.0, Z = −2.579, p = .010). However, these did not survive Bonferroni correction. No other group comparisons were significant at an uncorrected level (all p > .053).

Stop Signal Task

Stop accuracy tended to converge around 40% accuracy (range: 28.7%–62.1%). One-way analyses of variance did not reveal any differences in behavioral performance between groups (Table 2).

A trend toward a main effect of group was observed on the contrast comparing FSs to SSs (FS > SS) in the right anterior cingulate cortex (ACC)/medial prefrontal cortex (PFC) (Table 3; Supplemental Figure S2). No main effect of group was observed on the contrasts comparing FSs with SGs (FS > SG) or SSs with SGs (SS > SG).

Group comparisons were further evaluated using post hoc *t* tests. The developers showed significantly greater recruitment during FS > SS compared with HCs in a cluster spanning the ACC bilaterally and compared with recoverers in three clusters: the caudate (bilaterally); the right inferior parietal lobe and middle and superior temporal gyrus; and the right superior and middle frontal gyrus (Figure 1, Table 4). No differences were observed among the maintainers, recoverers, and HCs.

Relationship Between Behavioral and Neural Performance

When exploring the relationship between neural responses and adaptive error-related behavior (i.e., slowing responses after committing an error on the previous trial), a group-by-covariate interaction was found between post-error slowing and activation in two clusters during failed compared with successful stop trials (one in the precuneus [bilaterally] and another in the insula, thalamus and superior temporal gyrus [bilaterally], left putamen, and caudate). The parameter estimates (cluster means) were extracted and plotted for further inspection (Figure 2). They revealed that during FS > SS, post-error slowing positively correlated with activity in the regions seen in HCs and developers, but negatively correlated with activity in recoverers and maintainers.

DISCUSSION

This study has prospectively identified potential neural correlates (biomarkers) associated with future onset of DEBs. It

Table 2. Stop Signal Task Behavioral Outcome Data for the Four Groups and Statistical Comparisons Between Groups

	Group				
Outcome	HCs	Developers	Recoverers	Maintainers	One-Way ANOVA
RT, ms	475.99 ± 83.75	477.10 ± 96.19	456.66 ± 73.02	465.87 ± 81.09	$F_{3,167}$ = 0.527, p = .664
Go Accuracy, %	92.8 ± 8.9	89.8 ± 12.9	90.7 ± 15.1	89.9 ± 11.5	$F_{3,167}$ = 0.548, p = .650
Stop Accuracy, %	42.4 ± 5.4	41.7 ± 6.0	41.5 ± 4.9	44.1 ± 5.2	$F_{3,167}$ = 0.673, p = .570
SSRT, ms	227.47 ± 101.60	227.07 ± 75.85	242.37 ± 64.32	241.73 ± 108.71	$F_{3,167}$ = 0.606, p = .612
SSD, ms	248.52 ± 158.55	250.03 ± 146.57	214.29 ± 112.13	224.14 ± 158.51	$F_{3,167}$ = 2.077, p = .105
Post-error Slowing	31.27 ± 60.43	28.42 ± 47.39	20.99 ± 52.88	16.78 ± 45.83	$F_{3,167}$ = 0.606, p = .612

Values are mean ± SD.
ANOVA, analysis of variance; HCs, healthy control subjects; RT, reaction time; SSD, stop signal delay; SSRT, stop signal reaction time.

Table 3. Peak Coordinates Emerging From the Trendwise Main Effect of Group Contrast on the One-Way Analysis of Covariance Comparing Neural Recruitment Between Groups During Failed Relative to Successful Inhibition, Covarying for Total Head Motion and Study Site

Peak-Level *p*(FWE)	*F*	*Z*	*k*	Coordinates of Peak Voxel, mm			Hemisphere	Location of Cluster Peak(s)
				x	y	z		
.094	9.72	4.36	122	20	42	10	Right	Anterior cingulate cortex

FWE, familywise error.

focused on inhibitory control, a core element of many models of ED [e.g., (7,8,28)]. When adolescents failed to inhibit their responses, those who developed binge eating/purging at 16 years of age showed greater recruitment of the ACC and medial PFC implicated in error processing and inhibitory control (29–32) than those who did not report these behaviors at 16 years of age (recoverers and HC), suggesting that increased medial PFC activity during failed inhibitory control precedes symptom development. Thus, elevated recruitment of medial PFC and ACC during failed inhibitory control may be a biomarker for future DEB. Importantly, while behavioral performance did not differ, the observation that group-by-covariate interactions differed between the groups indicates that the relationship between behavior and neural response is disrupted. Thus, adolescents who later become symptomatic show intact inhibitory control at a behavioral level, but differ in the neural response to failed inhibitory control.

It is surprising that there were no neural differences observed between HCs and recoverers or maintainers, given that the recoverers and maintainers were endorsing DEBs at the time of scanning. In this study, DEB was classified by self-report. As we did not have sufficient information regarding the frequency of the DEBs assessed, our DEB classification may span a range of symptom severities. It may be that the recoverers engaged in DEB infrequently and therefore may be more similar to HCs with regard to their overall eating behavior; however, this could not be formally assessed. Moreover, it is unknown if participants received treatment between the time points, i.e., it cannot be ascertained whether "recovery" was spontaneous. Future replications could explore whether neural differences are associated with differences in severity and evaluate whether the absence of aberrant neural activity could be a marker of symptom cessation.

An elevated medial PFC response in developers may reflect differences in several processes/mechanisms during failed inhibition, e.g., less fully developed inhibitory processing (4,30,33,34), poorer behavioral flexibility (33), enhanced error detection (31,35), or greater recruitment of attentional resources (36): the need to elucidate the role of these regions in behavioral responding has been highlighted (37). Group-by-covariate interactions assessed whether neural recruitment during failed inhibition was differentially associated with behavioral responding between the groups. In HCs, adaptive responding (greater post-error slowing) was associated with greater recruitment of the thalamus, dorsal striatum, and insula during failed inhibition. As the striatum has been implicated in reward processing and response selection (38) and the insula in self-regulation and emotional processing (39), this activation

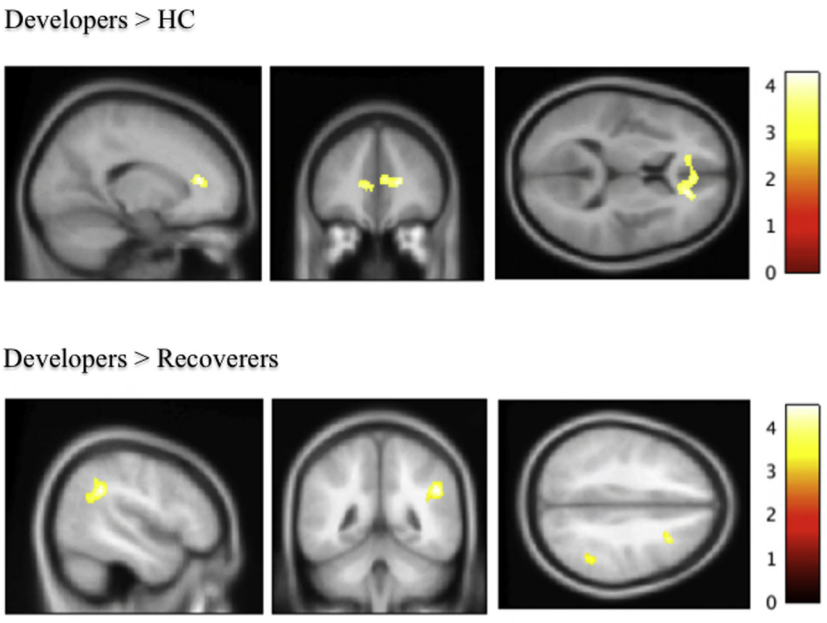

Figure 1. Statistical parametric maps resulting from post hoc *t* tests exploring regions that were more active during failed inhibition (compared with successful inhibition) in the developers compared with healthy control subjects (HCs) and the recoverers (i.e., the groups who were asymptomatic at 16 years of age). A cluster (height) threshold of $p = .001$ and clusterwise familywise error correction was applied (p[familywise error] $< .05$).

Table 4. Peak Coordinates of the Significant Clusters Emerging From the Post Hoc *t* Tests Comparing Neural Recruitment Between Groups During Failed Relative to Successful Inhibition

Cluster-Level *p*(FWE)	*k*	Coordinates of Cluster Peak(s), mm			Hemisphere	Location of Cluster Peak(s)
		x	y	z		
Developers > HCs						
.013	769	18	39	10	Right	Frontal lobe/anterior cingulate
		12	33	15	Right	Anterior cingulate
		6	44	12	Right	Anterior cingulate
Developers > Recoverers						
.012	792	9	3	15	Right	Caudate
		0	−2	15		
		16	−4	14	Right	Caudate (closest)
.015	744	48	−46	32	Right	Supramarginal gyrus, parietal lobe
		58	−57	22	Right	Superior temporal gyrus
		54	−64	26	Right	Middle temporal gyrus
.042	543	30	20	38	Right	Frontal lobe (closest: middle frontal gyrus)
		24	15	50	Right	Middle frontal gyrus
		24	26	57	Right	Superior frontal gyrus

A cluster (height) threshold of $p < .001$ and clusterwise FWE correction was applied (p[FWE] $< .05$).
FWE, familywise error; HC, healthy control subjects.

pattern may reflect the relationships between recruitment of evaluative (decision making) systems in response to failures and the subsequent deployment of an adaptive strategy (i.e., post-error slowing). While a similar relationship was observed in developers with respect to post-error slowing, maintainers and recoverers displayed the opposite. Specifically, greater slowing following failure to inhibit was associated with less error-related recruitment in symptomatic individuals: post-error slowing (an adaptive behavioral response strategy) is negatively associated with error responses in individuals who reported DEB at the time of scan, and positively associated in those who were not symptomatic at the time of scan. As similar networks are implicated in risky and affective decision making (40–42) and decision making under uncertainty (43), our findings suggest that while enhanced neural responses to errors in the ACC/medial PFC may be a marker of risk for future DEB, the presence of DEBs is associated with abnormal processing of errors (i.e., there is a disconnect between error-related brain activity and adaptive behavioral responding [post-error slowing] in symptomatic individuals), although no differences in the ability to respond adaptively were observed (44).

Our data are consistent with models implicating frontostriatal systems in the development/maintenance of EDs (7,45, 46). In addition, reduced recruitment of midline frontal regions has been reported in studies using the SST in individuals with restricting-type AN (47,48). Importantly, while the directionality of the findings is inconsistent with our data, the same regions

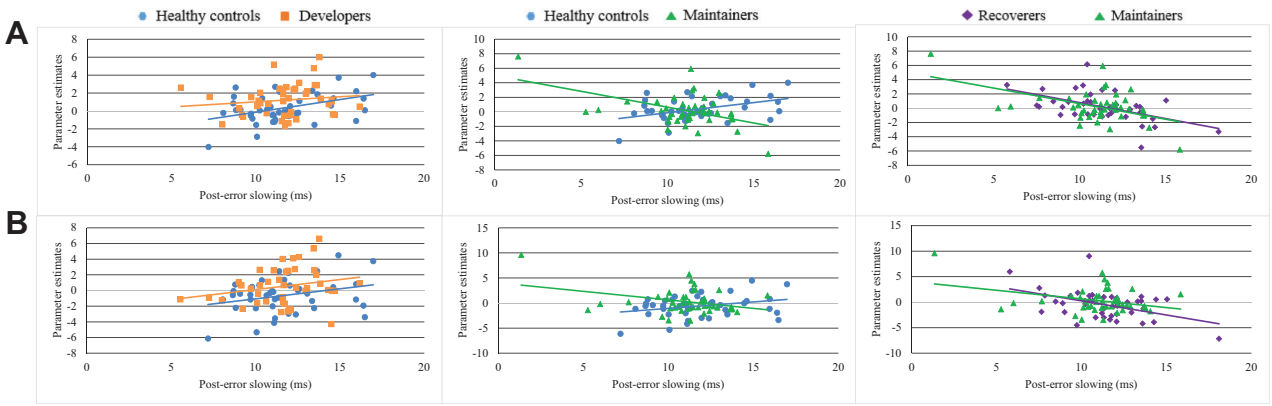

Figure 2. Regression models assessing the relationship between functional magnetic resonance imaging parameter estimates and behavioral data. Graphs plotting the parameter estimates for each cluster emerging from the main effect of group analysis for each regression model, illustrating group differences in parameter estimates from clusters in which there was a relationship between post-error slowing and relative activity during failed stops compared with successful stops (row **A** = bilateral precuneus; row **B** = bilateral insula, superior temporal gyrus and left thalamus, putamen and caudate). Three group comparisons were plotted (left to right: healthy control subjects [blue] vs. developers [orange], healthy control subjects [blue] vs. maintainers [green], recoverers [purple] vs. maintainers [green]).

are being implicated. It is of note that all previous neuroimaging studies using the SST to assess EDs/DEBs have only assessed individuals with restricting-type AN and not those who binge eat/purge, and they have differed in the contrasts explored (hard/easy vs. failed/successful). Moreover, our study explored the relationship between inhibitory control and transdiagnostic symptoms of EDs, rather than its relationship with a particular ED diagnosis. Thus, the inherent sample-based differences may contribute to the differences in directionality. However, rather than being viewed as opposing findings, this inconsistency may instead support spectrum models of EDs, which propose that EDs lie on a spectrum of inhibitory control with restricting-type AN at the overinhibited extremity and BN and BED at the impulsive extremity (8, 49). Our data, together with those of previous studies in restricting-type AN (47,48), may therefore suggest that this spectrum of inhibitory control may be reflected at a neural level, with restricting-type AN associated with reduced recruitment and binge eating/purging associated with increased recruitment of the medial PFC and ACC during error-related processing compared with matched HCs. This may indicate reduced efficiency (greater recruitment for equivalent performance) within the error-processing network in individuals who binge/purge compared with asymptomatic individuals. It may also be the overengagement of frontal/cingulate regions in those who subsequently develop binge/purge behaviors. Alternatively, these findings could reflect enhanced processing of errors as a function of augmented attentional processes, consistent with observations of greater sensitivity to rewards and punishment in individuals with EDs who binge and/or purge (50,51). It would be of interest for future research to discriminate between these hypotheses.

Similar regions have been implicated in studies of adolescents who binge/purge using other executive control tasks, though the directionality of findings has been inconsistent. Lock *et al.* (5) found that adolescents who reported binge eating and purging (including individuals with a diagnosis of either BN or anorexia nervosa binge/purge type showed greater activity in frontal and midline regions during successful inhibition (compared with successful responding) in a task assessing action restraint (the go/no-go task) compared with HCs. In contrast, Marsh *et al.* (6) found that adolescents with BN had reduced neural recruitment of these regions during the Simon task. However, while all these tasks require a rapid button-press response, the Simon task required a response on all trials (i.e., had no stop/no-go trials) and compared reaction time on congruent and incongruent trials. Differences in directionality between these studies may therefore be due to differences in the type of inhibitory control assessed.

There are some considerations regarding the method of participant categorization. First, presence or absence of DEBs was determined by self-report. There is a debate surrounding the optimal method of assessing DEBs in children and adolescents; however, we found that participants were forthcoming about their behaviors, with a greater prevalence of DEBs emerging from adolescent compared with parental reports (52). Second, participant groups were not random. However, the matching procedure is considered a strength of the study. Given the unequal sample sizes between the groups and the impact of pubertal stage, gender, age, and IQ on neural development and neuropsychological performance, participants within each group were matched at an individual level to reduce the possible influence of these variables while maintaining strong power. Third, data were not collected on medication taken at the time of scan, which could affect inhibitory control (53,54). Finally, this study is not able to determine the extent to which this potential neural biomarker is specific to the DEBs assessed or is a marker of ED vulnerability or impulsive behavior more generally. However, our findings accord with reports of altered error-related brain activity (recruitment and coupling of the dorsal ACC following negative feedback on a probabilistic reversal learning task) in individuals with early stage AN compared with HCs in the context of comparable behavioral performance (44). However, Geisler *et al.* (44) excluded participants who reported regular binge eating. Therefore, although our study differed from Geisler *et al.* in terms of the functional MRI task used and in terms of DEBs studied, the findings from these studies suggest that altered error-related neural recruitment may precede observable differences in behavior and may be a potential biomarker/endophenotype for ED vulnerability more generally.

We propose that impulsivity-related recruitment of medial PFC and ACC is related to core symptoms of EDs and may indicate future development of binge eating and purging. Our findings have implications for biomarker research, as this neural profile predated symptom development, and while behavior could not discriminate the groups before symptom development, this was possible with neuroimaging. Thus, until better behavioral metrics are developed, neuroimaging may continue to be an important tool for identifying markers of psychopathological risk.

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