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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 adolescent cohort. Participants completed baseline assessments (questionnaires and a brain scan [functional magnetic resonance imaging, fMRI]) at age 14, and a follow-up assessment (questionnaires) at 16. 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 Controls (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 to Healthy Controls and Recoverers.

**Conclusion:** Greater recruitment of 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.
INTRODUCTION

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 to childhood and adulthood, attributed at least partly to heterochronous regional brain development (3), e.g., between the maturity of subcortical regions associated with arousal, and 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 (DEB). 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. 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., a sense of loss of control during binge eating episodes,
and attempts to regain control over weight or food intake through food restriction/purging, while simultaneously experiencing the inability 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 dys-control outside of eating contexts is common, suggesting 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 multi-national 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 (age 14), those who develop these behaviors later (at age 16) and individuals who do not report/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). A total of 2225 fourteen year olds [T1] were recruited from secondary schools at 8 sites (UK, Ireland, Germany and France). 1607 completed a follow-up assessment at ~16 years old [T2]. Participants were excluded from the IMAGEN study if they had any MRI contraindications, neurological/neurodevelopmental disorders, nutritional/metabolic diseases, certain historical/current medical conditions (e.g., congenital heart defects), IQ<70, or receiving treatment for schizophrenia/bipolar disorder (see 17). Participants in the present study were further excluded if they did not complete the diet, weight and shape element of the Development and Wellbeing Assessment (DAWBA) interview at both time-points, did not provide complete demographic data, or had inadequate/incomplete structural and functional (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 Controls” (HC), n=1265, [567 girls]). Due 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 intelligence quotient (IQ) (matching procedure outlined in Supplement A). Thus, a total sample of 172 participants comprised of 43 individuals (40 girls) from each group was analyzed.
( Supplement B ). A description of the endorsed DEBs is provided in supplementary files D and E.

4 Questionnaires

Disordered eating behavior, anxiety and depression were assessed using the DAWBA, 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) were used to indicate the presence of DEB. Due 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, their parent, and their teacher, were used to assess anxiety and depression. Pubertal stage was determined using self-reports on the Pubertal Developmental Scale (PDS; 19). The short form of the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV; 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 (ESPAD; 21).

Body Mass Index (BMI)

Height and weight were measured at both time-points to calculate 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 an fMRI stop signal task (SST). This reactive response inhibition task assesses action cancellation (23), and involves two concurrent tasks: a choice reaction time task (“go trials”: 80%, 400 trials) where participants must indicate the direction (left/right) of a presented arrow (“target”, 1000ms stimulus duration) using a button-press response, and a stop task where participants must inhibit their motor response (“stop trials”: 20%, 87 trials) when an unpredictable stop signal (upwards arrow, shown for 100-300ms) 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 50ms increments/decrements, range: 0-900ms, initial delay: 150ms) to ensure participants’ stop accuracy converges at approximately 50% correct inhibition. The inter-trial interval was 1800ms. Behavioral dependent variables from this task included the mean SSD, stop accuracy, mean reaction time on correct go trials (mean RT) and the stop signal reaction time (SSRT). SSRT reflects the latency of the stop process (24), calculated by subtracting mean SSD from mean RT (25).

Procedure

Neuroimaging and questionnaire data were obtained from adolescents at T1; follow-up questionnaires were completed online at T2. The DAWBA, PDS and ESPAD were completed on a computer. A researcher administered the WISC-IV, 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 ANOVAs. 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 accuracy data distribution was strongly negatively-skewed. Non-normally distributed demographic and task-based (go accuracy) data were assessed using non-parametric Kruskal-Wallis tests and Bonferroni-corrected post-hoc Mann-Whitney *U* tests. All tests were two-tailed, with the significance level set at *α*=0.05.

Structural and functional MRI data were acquired using 3 Tesla MRI scanners of different manufacturers (including General Electric, Siemens, Philips, Bruker). Details of the structural and functional neuroimaging procedures are provided in the supplementary files (supplement C). Image preprocessing was completed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). fMRI 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 Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL; 26). The resultant flow fields were used to normalize the coregistered data to MNI space (27). Normalized images were smoothed using an 8mm FWHM 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 128Hz, and potential residual autocorrelation was controlled for using an autoregressive function (AR(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: failed>successful inhibition (error with intention to stop: FS>SS), failed stop>successful go (erroneous/unwanted vs. wanted response: FS>SG), and successful stop>successful go (successful inhibition: SS>SG). These were taken forward to group-level random-effects analyses, specifically 3 one-way ANCOVAs 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:

- HC vs. 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;

- HC vs. Maintainers: This allowed comparison of a group who showed current and prolonged DEB with a healthy group;
• Recoverers vs. 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 which survive FWE correction at $p<0.05$ at a cluster height threshold of $p<0.001$ will be considered significant.

**RESULTS**

One-way ANOVAs and Kruskal-Wallis tests confirmed no differences between groups in age ($F(3,168)=1.396$, $p=0.246$), puberty ($\chi^2(3)=1.947$, $p=0.583$) and IQ (Verbal: $F(3,168)=0.926$, $p=0.430$; Performance: $F(3,168)=0.130$, $p=0.942$) (Table 1). Chi-squared analyses revealed no differences between the groups in lifetime use of substances known to affect appetite (all $\chi^2(3)\leq6.057$, $p\geq0.109$; Supplement F), except for lifetime hash use at follow-up ($\chi^2(3)=9.521$, $p=0.023$). 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 $U\geq731.0$, $z\geq-1.938$, $p\geq0.053$) (Supplement D).

Table 1

Group differences in BMI were present at baseline ($F(3,171)=5.013$, $p=0.002$), driven by lower BMI $z$-scores in the Developers compared to the Recoverers ($t(84)=-3.203$, $p=0.002$) and Maintainers ($t(84)=-3.311$, $p=0.001$), which survived Bonferroni correction. This was not due to differences in endorsement of food restriction amongst Developers (77%) compared to
either Recoverers (79%) or Maintainers (86%) ($\chi^2(2)=1.080$, $p=0.583$) (Supplement E). BMI
z-scores were also lower in HCs compared to Recoverers ($t(84)=-2.092$, $p=0.039$) and
Maintainers ($t(84)=-2.198$, $p=0.031$), though these findings did not survive Bonferroni
correction. A trend towards a difference in anxiety ($\chi^2(3)=6.508$, $p=0.089$) and depression ($\chi^2$
(3)=7.297, $p=0.063$) was also seen at baseline, driven by greater anxiety in the Developers
compared to HCs, ($U=668.0$, $z=-2.536$, $p=0.011$), and greater depression in the Maintainer
group compared to the Developer group ($U=651.0$, $z=-2.579$, $p=0.010$). However, these did
not survive Bonferroni correction. No other group comparisons were significant at an
uncorrected level (all $p>0.053$).

Stop signal task

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

Table 2

A trend towards a main effect of group was observed on the contrast comparing failed stops
to successful stops (FS>SS) in the right anterior cingulate cortex (ACC)/medial prefrontal
cortex (PFC) (Table 3, Supplement G). No main effect of group was observed on the
contrasts comparing failed stops to successful go (FS>SG) or successful stop to successful go
trials (SS>SG).
Group comparisons were further evaluated using post-hoc \( t \)-tests. The Developers showed significantly greater recruitment during FS>SS compared to HC in a cluster spanning the ACC bilaterally, and compared to Recoverers in three clusters: the caudate (bilaterally); the right inferior parietal lobe, middle and superior temporal gyrus; and the right superior and middle frontal gyrus (Figure 1, Table 4). No differences were observed between the Maintainers, Recoverers and HCs.

**Figure 1**

**Table 4**

**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 to successful stop trials (one in the precuneus (bilaterally), and another in the insula, thalamus and STG (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 HC and Developers, but negatively in Recoverers and Maintainers.

**Figure 2**
This study has prospectively identified potential neural correlates (biomarkers) associated with future onset of DEBs. It 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 age 16 showed greater recruitment of the anterior cingulate and medial PFC implicated in error processing and inhibitory control (29-32) than those who did not report these behaviors at age 16 (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 regards 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 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 was 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 ANR (47, 48). Importantly, while the directionality of the findings is inconsistent with our data, the same regions are being implicated. It is of note that all previous neuroimaging studies using the SST to assess EDs/DEBs have only assessed individuals with ANR and not those who binge eat/purge, and 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 ANR at the over-inhibited extremity and BN and BED at the impulsive extremity (8, 49). Our data, together with those of previous studies in ANR (47, 48), may therefore suggest that this spectrum of inhibitory control may be reflected at a neural level, with ANR associated with reduced recruitment and binge eating/purging associated with increased recruitment of the medial PFC and ACC during error-related processing compared to matched HCs. This may indicate reduced efficiency (greater recruitment for equivalent performance) within the error-processing network in individuals who binge/purge compared to asymptomatic individuals. It may also be the over-engagement 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 ANBP) showed greater activity in frontal and midline
regions during successful inhibition (compared to successful responding) in a task assessing
action restraint (the go/no-go task) compared to HC. In contrast, Marsh et al., (6) found
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. Firstly,
presence/absence of DEBs were determined by self-report. There is a debate surrounding the
optimal method of assessing DEBs in children and adolescents, however, we found
participants were forthcoming about their behaviors, with a greater prevalence of DEBs
emerging from adolescent compared to parental reports (53). Secondly, 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. Thirdly, data were not collected on medication
taken at the time of scan, which could affect inhibitory control (54, 55). Finally, this study is
not able to determine the extent to which this potential neural biomarker is specific to the
DEBs assessed, or 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 to HC 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.
(44) in terms of the fMRI task used and in terms of DEB 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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DISCLOSURES
Conflicts of interest
Dr. Banaschewski served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Lundbeck, Medice, Novartis, Shire. He received conference support or speaker’s fee by Lilly, Medice, Novartis and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships. Dr Barker has received funding for a PhD student and honoraria for teaching on scanner programming courses from General Electric Healthcare; he acts as a consultant for IXICO. Dr Walter received a speaker honorarium from Servier (2014). The other authors report no biomedical financial interests or potential conflicts of interest.

Previous presentation
Early versions of this work along with brief abstracts/summaries has been presented in poster format at the Forum for European Neuroscience Societies in Copenhagen, Denmark (2nd-6th July 2016) and at the European College for Neuropsychopharmacology (ECNP) Junior Scientists Workshop in Nice, France (12th-15th March 2015), and as oral presentations at the ECNP Congress in Amsterdam, the Netherlands (29th August – 1st September 2015) and the Academy for Eating Disorders International Conference on Eating Disorders in San Francisco, USA (5th-7th May 2016).
Table 1. Demographic information for the final matched sample of participants who responded at both time-points.

<table>
<thead>
<tr>
<th>Time-point</th>
<th>Measure</th>
<th>Group [Mean (SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HC</td>
</tr>
<tr>
<td>T1 (age 14 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>14.61 (0.36)</td>
<td>14.49 (0.33)</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.25 (1.04)</td>
<td>0.07 (0.88)</td>
</tr>
<tr>
<td>PDS</td>
<td>16.16 (1.46)</td>
<td>15.89 (2.10)</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>106.88 (13.35)</td>
<td>108.20 (11.24)</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>104.53 (15.50)</td>
<td>104.80 (15.07)</td>
</tr>
<tr>
<td>Anxiety*</td>
<td>0.38 (0.66)</td>
<td>0.57 (0.98)</td>
</tr>
<tr>
<td>Depression*</td>
<td>0.50 (0.62)</td>
<td>0.46 (0.92)</td>
</tr>
<tr>
<td>T2 (age 16 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>16.46 (0.66)</td>
<td>16.47 (0.52)</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>-0.09 (1.10)</td>
<td>0.16 (1.06)</td>
</tr>
</tbody>
</table>

* DAWBA probability band scores for an anxiety or depressive disorder.

PDS=Puberty Development Scale.
Table 2. SST behavioral outcome data for the four groups, and statistical comparisons between-groups.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group</th>
<th>One-Way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC</td>
<td>Developers</td>
</tr>
<tr>
<td>Mean RT (ms)</td>
<td>475.99 (83.75)</td>
<td>477.10 (96.19)</td>
</tr>
<tr>
<td>Go Accuracy (%)</td>
<td>92.8% (8.9%)</td>
<td>89.8% (12.9%)</td>
</tr>
<tr>
<td>Stop Accuracy (%)</td>
<td>42.4% (5.4%)</td>
<td>41.7% (6.0%)</td>
</tr>
<tr>
<td>SSRT</td>
<td>227.47 (101.60)</td>
<td>227.07 (75.85)</td>
</tr>
<tr>
<td>Mean SSD</td>
<td>248.52 (158.55)</td>
<td>250.03 (146.57)</td>
</tr>
<tr>
<td>Post-error slowing</td>
<td>31.27 (60.43)</td>
<td>28.42 (47.39)</td>
</tr>
</tbody>
</table>
Table 3. Peak coordinates emerging from the trend-wise main effect of group contrast on the one-way ANCOVA comparing neural recruitment between groups during failed relative to successful inhibition, covarying for total head motion and study site.

<table>
<thead>
<tr>
<th>Peak level</th>
<th>$F$</th>
<th>$z$</th>
<th>$k$</th>
<th>Coordinates of peak voxel (mm)</th>
<th>Hemisphere</th>
<th>Location of cluster peak(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$(FWE)</td>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
<td>$y$</td>
<td>$z$</td>
</tr>
<tr>
<td>0.094</td>
<td>9.72</td>
<td>4.36</td>
<td>122</td>
<td>20</td>
<td>42</td>
<td>10</td>
</tr>
</tbody>
</table>
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. A cluster (height) threshold of $p<0.001$ and cluster-wise family-wise error correction was applied ($p$(FWE)$<0.05$).

<table>
<thead>
<tr>
<th>Cluster-level $p$(FWE)</th>
<th>$k$</th>
<th>Coordinates of cluster peak(s) (mm)</th>
<th>Hemisphere</th>
<th>Location of cluster peak(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$x$ $y$ $z$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developers &gt; HC</td>
<td>0.013</td>
<td>769 18 39 10</td>
<td>Right</td>
<td>Frontal lobe/Anterior cingulate</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>33 15</td>
<td>Right</td>
<td>Anterior cingulate</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>44 12</td>
<td>Right</td>
<td>Anterior cingulate</td>
</tr>
<tr>
<td>Developers &gt; Recoverers</td>
<td>0.012</td>
<td>792 9 3 15</td>
<td>Right</td>
<td>Caudate</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>-2 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>-4 14</td>
<td>Right</td>
<td>Caudate (closest) Supramarginal gyrus,</td>
</tr>
<tr>
<td></td>
<td>0.015</td>
<td>744 48 -46 32</td>
<td>Right</td>
<td>Parietal lobe</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>-57 22</td>
<td>Right</td>
<td>Superior temporal gyrus</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>-64 26</td>
<td>Right</td>
<td>Middle temporal gyrus</td>
</tr>
<tr>
<td></td>
<td>0.042</td>
<td>543 30 20 38</td>
<td>Right</td>
<td>Frontal lobe (closest: middle frontal gyrus)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>15 50</td>
<td>Right</td>
<td>Middle frontal gyrus</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>26 57</td>
<td>Right</td>
<td>Superior frontal gyrus</td>
</tr>
</tbody>
</table>
Figure 1. Statistical parametric maps resulting from post-hoc \( t \)-tests exploring regions that were more active during failed inhibition (compared to successful inhibition) in the Developers compared to HCs and the Recoverers (i.e., the groups who were asymptomatic at age 16). A cluster (height) threshold of \( p=0.001 \) and cluster-wise family-wise error correction was applied \((p(FWE)<0.05)\).
Figure 2. Regression models assessing the relationship between fMRI 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 to successful stops (row (A) = bilateral precuneus; row (B) = bilateral insula, STG and left thalamus, putamen and caudate). Three group comparisons were plotted (left to right: HC (blue) vs. Developers (orange); HC (blue) vs. Maintainers (green); Recoverers (purple) vs. Maintainers (green)).