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# Functional dysconnectivity of cerebellum and attention networks in emotional dysregulation shared between attention deficit hyperactivity disorder and major depressive disorder: a multimodal imaging study

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## Abstract

**Background.** Emotional dysregulation (ED) is a common characteristic of both attention deficit hyperactivity disorder (ADHD) and major depressive disorder (MDD), especially in adolescents. However, whether ADHD and MDD may share the specific ED-related neural networks remains unknown.

**Methods.** In total, 43 adolescents with clinical ED (22 adolescents with ADHD and 21 with MDD) were recruited; in addition, 29 sex- and age-matched healthy controls (HCs) were included. Resting-state functional connectivity (RSFC) analysis, voxel-based morphometry, and diffusion tensor imaging analysis were performed for each patient. In addition, we determined the significant regions of interest in patients with ED due to ADHD and MDD as compared with HCs and tested their correlations with clinical rating scale scores.

**Results.** Compared with HCs, patients with ED had greater RSFC in the cerebellum and supramarginal gyrus (SMG), especially between vermis VI and the SMG in the attention networks, and lower RSFC between the right supplementary motor area and right lateral parietal area. Lower gray matter (GM) volume in the SMG was also found. RSFC was significantly correlated with clinical rating scale scores for all patients with ED due to ADHD or MDD. GM change was correlated with ED and MDD rating scale scores.

**Discussion.** The cerebellum and attention networks might play major roles in ED pathophysiology in adolescents with ADHD and MDD. Increased connectivity of the vermis to the SMG serves as a possible underlying neural network.

## Introduction

Attention deficit hyperactivity disorder (ADHD) and major depressive disorder (MDD) are prevalent (approximately 5%) among youth worldwide.[1,2] ADHD and MDD have different effects on patients: MDD causes depressive mood and loss of interest, whereas ADHD leads to an inability to sustain attention and modulate activity levels and impulsive actions.[3,4] Although ADHD is categorized as an externalizing disorder and MDD as an internalizing disorder, both disorders affect young people psychologically and socially and usually disrupt their personal and social functions.[2,5] In addition, ADHD and MDD are commonly comorbid in adolescents[6] and associated with increased risks of substance use problems and psychological disturbances.[7,8] Both disorders may interfere with attention maintenance and mood stability in the long term.[4] The confluence and interaction of various genetic and environmental risk factors lead to a spectrum of neurobiological vulnerabilities to ADHD and MDD.[9,10] In addition to the psychological feature of reward impairment, emotional dysregulation (ED) is common in adolescents with ADHD and MDD.[9,11]

Emotional regulation is defined as the ability to modify the emotional state and behaviors in response to environmental stimuli, and it has three major components: attention, appraisal, and response.[12,13] By contrast, ED is considered a failure to manage this ability. According to the Research Domain Criteria, ED serves as a transdiagnostic characteristic and appears in various disorders, such as ADHD, MDD, bipolar disorders, disruptive behavior disorders, and anxiety disorders.[14,15] Approximately, 11% of patients with ADHD and 5.6% of those with depression

exhibit clinical ED.[16] More specifically, ED has been described as one of the clinical core features associated with ADHD,[5,17] and considered a core or predictive factor of MDD.[6,18] However, the especially high co-occurrence of ED in pediatric mental disorders, including ADHD and MDD, causes difficulties in diagnosis and management.[9] Moreover, patients with ADHD or MDD who had a deficit in emotional regulation are 4 times more likely to complete suicide.[19] Therefore, investigating the role of ED in the psychopathology of ADHD and MDD is crucial.

In recent research, ED in pediatric ADHD and MDD has been a focus. However, studies have investigated ED in certain psychiatric disorders separately. Although some studies have addressed the shared etiology of ED in adolescents with ADHD and MDD, only clinical rating scales have been employed.[9] Functional magnetic resonance imaging (fMRI) analysis reveals that emotional regulation involves visual, attention, and default networks interacting.[20,21] Moreover, each process of emotional regulation activates different neural networks: attention requires the anterior insula and presupplementary motor area (pre-SMA); appraisal involves the premotor cortex, temporoparietal junction (TPJ), inferior parietal lobe, cingulate gyrus, and pre-SMA; and response requires the TPJ and ventrolateral prefrontal cortex (VLPFC).[12] Therefore, ED may cause dysfunction in any of these neural networks.

In a series of MRI studies with different analyses on children with clinical ED, children with ADHD had frontostriatal deficits, and MDD revealed cortical changes in the prefrontal cortex.[22] For ED in youth with comorbid mental disorders, high contributions came from the cerebellar, sensorimotor, and frontolimbic areas, as determined by task-based fMRI at initial recruitment.[14] Nevertheless, no study has focused on the underlying neural mechanism of ED in both adolescents with ADHD and adolescents with MDD through multimodal fMRI analyses. Therefore, the present study employed resting-state functional connectivity (RSFC), gray matter (GM) volume, and diffusion tensor imaging (DTI) to detect possible neural networks of ED shared in adolescents with externalizing disorders and internalizing disorders. We further hypothesized that shared mechanisms of ED in adolescents with ADHD and MDD lie in the prefrontal areas and attention networks.

## Methods

### Inclusion criteria for MDD and ADHD patients with ED and control groups

Adolescents who met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD (n = 22) or ADHD (n = 21) and had a child behavior checklist profile of deficient emotional self-regulation or severe dysregulation (over 1 standard deviation higher than the mean for the anxiety/depression, aggression, attention subscales, total T scores of CBCL-AAA subscale ≥180) were included as the study group. Age- and sex-matched healthy controls (HCs; n = 29) who did not have a DSM-5 diagnosis; first-degree relatives with histories of major psychiatric disorders; instances of pregnancy, breastfeeding, or severe physical diseases (ie epilepsy, stroke, or systemic lupus erythematosus); or unstable physical illnesses were enrolled as the control group. For all participants, demographic characteristics—namely, age, sex, and education—were recorded, and the following clinical assessments were conducted: CBCL-AAA; Montgomery-Åsberg Depression Rating Scale (MADRS); and Swanson, Nolan, and Pelham (SNAP-IV) rating scale. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study.

### MR image acquisition

Each subject received a T1-weighted MRI scan to confirm the absence of organic lesions in the brain. MR images were obtained using a 3T GE Discovery 750 (GE Medical Systems, Milwaukee, WI, USA) and were acquired in the axial plane using a high-resolution sequence (repetition time [TR] = 12.24 milliseconds; echo time [TE] = 5.18 milliseconds; field of view [FOV] = 256 × 256; matrix size = 256 × 256; number of excitations [NEX] = 1; inversion time [TI] = 450 milliseconds; and flip angle = 15°). In addition, resting-state functional images were collected using a gradient-echo T2* weighted sequence (TR/TE/Flip = 2500 milliseconds/30 milliseconds/90°). Forty-three contiguous horizontal slices, parallel to the inter-commissural plane (voxel size: 3.5 × 3.5 × 3.5 mm), were acquired interleaved. For DTI, images were acquired using a single-shot spin echo-echo plane sequence in alignment with the anterior-posterior commissural plane with the following parameters: TR = 9500 milliseconds, TE = 83 milliseconds, and flip angle = 90. The diffusion sensitizing gradients were applied along 13 noncollinear directions ($b = 1000$ seconds/mm$^2$), together with an acquisition without diffusion weighting ($b = 0$ seconds/mm$^2$). During functional runs, the subject was instructed to remain awake with his or her eyes open (1 run, each run 8 minutes and 20 seconds, 200 time points). The heads of the participants were supported using cushions, and all participants were provided earplugs (29-dB rating) for attenuating noise.

### Image preprocessing

For the RSFC, the data were preprocessed and analyzed using MATLAB R2019b (MathWorks, Natick, MA, USA) and SPM12 (The Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12). All functional images were slice-timing corrected and realigned to the first volume using a 6-parameter rigid-body transformation. The mean image generated was spatially normalized into standard stereotactic space, using the Montreal Neurological Institute (MNI) echo-planar imaging template. Computed transformation parameters were applied to all functional images, interpolated to isotropic voxels 2 mm in size, and the resulting images were smoothed using a 7-mm full-width at half-maximum isotropic Gaussian kernel. Preprocessing procedures also included outlier detection using Artifact Detection Tools implemented in the CONN toolbox (version 18.b).

For the voxel-based morphometry (VBM), data were processed using the VBM toolbox (http://dbm.neuro.uni-jena.de/vbm.html) in a statistical software package (SPM12; http://www.fil.ion.ucl.ac.uk/spm/). Then, preprocessing was undertaken: the T1-weighted images were checked and reoriented to anterior commissure as the coordinate origin. Data were first corrected for slice-dependent time shifts and then head movement through rigid-body affine of each volume to the first scan. They were bias-corrected and segmented into GM, white matter (WM), and cerebrospinal fluid; Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) create a template; DARTEL existing template; normalize to MNI space; spatial smoothing with 8-mm full-width at half-maximum Gaussian kernel.

For the DTI, the processing of DTI data was conducted with Tract-Based Spatial Statistics (TBSS) version 1.2 implemented in

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the FMRIB Software Library (FSL version 5.0, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl). First, DTI data were preprocessed to create fractional anisotropy (FA) maps. All images were corrected for the effects of head movement and eddy currents using FMRIB's Diffusion Toolbox in FSL. A brain mask was created from the b0 image by running the Brain Extraction Tool, and maps were calculated by fitting a tensor model to the raw diffusion data. Then, the resulting FA maps were further analyzed using TBSS. In general, FA maps of all subjects were aligned into a common (MNI-152 standard) space using the nonlinear registration tool FNIRT. The transformed FA images were averaged to create a mean FA image, and the tracts were thinned to create a mean FA skeleton that represents the centers of all tracts common to the group. The FA threshold was set at 0.2 to confine the analysis to WM. Each subject's FA image was projected onto this skeleton, and the resulting data were fed into voxelwise between-subject statistics.

### Statistical analysis

A correlation map was computed first by extracting average time-series images across all voxels in the regions of interest (ROIs) of the whole brain, and then the correlation of each pair of these regions was examined with Pearson's correlation coefficient. Fisher's *r*-to-*z* transformation was conducted to normalize the correlation coefficients into *z*-scores. Analysis of variance was used to test for the main group effect. Post hoc tests were performed. Statistical thresholds were set at *P*-values corrected by nonstationary cluster-level correction, with group differences in connectivity examined at significance thresholds that were false discovery rate-corrected to $P < .05$ at the individual seed level for RSFC and uncorrected $P < .05$ at the nonstationary cluster level for VBM.[23] The results from these analyses were used for selecting the significant connectivity in the RSFC from the CONN toolbox (based on the Harvard-Oxford structural atlases) and the ROIs from VBM analyses (in the MNI and Hospital coordinates) extracted with MarsBaR (version 0.44) in SPM.

For DTI analysis, the threshold for statistical significance was $P < .05$. The randomized tool in FSL was used to perform voxelwise statistical analysis with age, as a covariate was performed to explore regions of significant differences between the FA images of patients with ADHD or MDD and those of HCs. The contrast was computed using 500 permutations. The results were corrected for multiple comparisons using threshold-free cluster enhancement, which allowed us to avoid making an arbitrary choice of the cluster-forming threshold while preserving the sensitivity benefits of cluster-wise correction. The threshold for significance was set at $P < .05$. For regions of significant differences, FA values were extracted from each participant's FA image.

### Correlations between ROIs and clinical evaluations

To clarify the association between functional connectivity and GM volume with selected significant ROIs and clinical evaluations in both patients and HCs, partial correlation analyses for the effects of group, age, sex, and education level controlled were performed to investigate the correlations of functional connectivity and GM volume with CBCL-AAA, MADRS, and SNAP-IV scores in all groups. The correlations were considered significant at $P < .05$.

## Results

### Demographic and clinical characteristics

In total, 72 adolescents (22 patients with MDD, 21 patients with ADHD, and 29 HCs) were included in the analyses. The 22 adolescents in the MDD group had MADRS scores indicating clinical depression. The 21 adolescents in the ADHD group had SNAP-IV scores indicating clinical inattention, hyperactivity, and impulsiveness. The MDD and ADHD groups scored significantly higher than the HC group on the CBCL-AAA, representing clinical ED. There were no significant differences between the MDD or ADHD and HC groups in terms of sex or age (Table 1).

### ROI-based RSFC analyses: group comparisons

Both the MDD and ADHD groups had higher RSFC than did the HCs between the following ROIs: vermis VI and left inferior temporal gyrus near occipital cortex (toITG), vermis VI and right

**Table 1.** The Demographic Data of Patients with ED and Controls

| | Patients with ED (n = 43) | | Healthy controls | | | | |
|---|---|---|---|---|---|---|---|
| | ADHD (n = 21) | MDD (n = 22) | (n = 29) | *F* or $\chi^2$ | *P*-value | P1-val | P2-val |
| Baseline variables: mean (SD) | | | | | | | |
| Age | 14.29 (1.68) | 15.91 (1.80) | 15.24 (1.60) | 5.05 | .009 | .154 | .495 |
| Male | 15 | 4 | 13 | 12.34 | .002 | .145 | .136 |
| Education | 8.19 (1.54) | 9.77 (1.82) | 9.69 (1.67) | 6.21 | .003 | .008 | 1.000 |
| Med: RCS | 11 | 0 | – | – | – | – | – |
| Med: ATDs | 0 | 18 | – | – | – | – | – |
| Med: MS | 0 | 3 | – | – | – | – | – |
| MADRS | 9.24 (5.91) | 28.50 (8.72) | 1.28 (1.46) | 139.06 | <.001 | <.001 | <.001 |
| SNAP-IV | 46.67 (1.93) | 21.09 (5.73) | 8.10 (6.37) | 100.94 | <.001 | <.001 | <.001 |
| CBCL-AAA | 211.57 (23.67) | 201.23 (14.51) | 153.79 (5.20) | 102.90 | <.001 | <.001 | <.001 |

Abbreviations: ADHD, attention deficit hyperactivity disorder; CBCL-AAA, anxious/depressed, aggressive behavior, and attention problems scales of the child behavior checklist; ED, emotional dysregulation; HC, health control; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; Med: ATD, medicated with antidepressants; Med: MS, mediated with mood stabilizers; Med: RCS, medicated with Ritalin/Concerta/Strattera; PANSS, Positive and Negative Syndrome Scale; P1-val, *P*-value of post hoc analysis between ADHD and HC groups; P2-val, *P*-value of post hoc analysis between MDD and HC groups; SNAP-IV, Swanson, Nolan, and Pelham Questionnaire; SRS, Social Responsiveness Scale.

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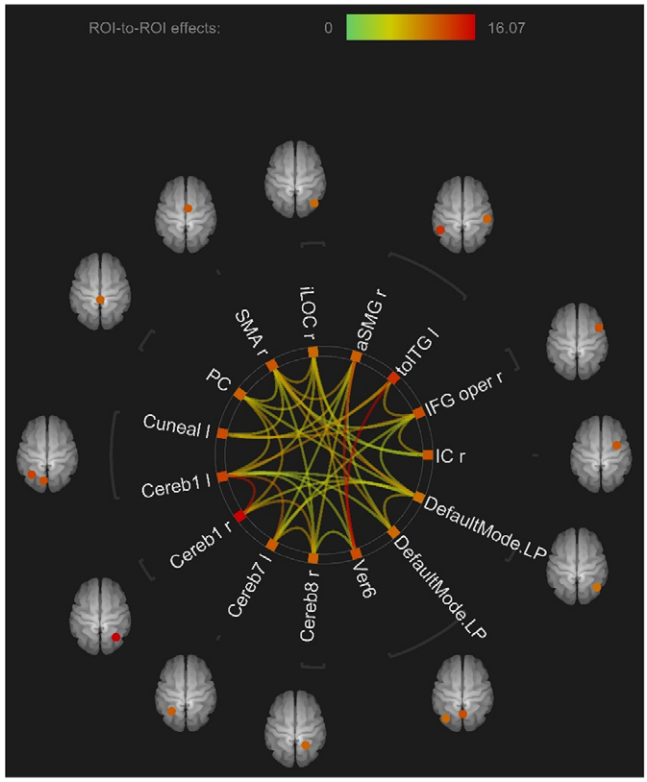


**Figure 1.** Functional connectivity of region of interest (ROI)-to-ROI analyses in patients with emotional dysregulation (ED) vs healthy controls. In ROI-to-ROI analyses of patients with ED group to control group increased resting-state functional connectivity (RSFC) in vermis VI-left inferior temporal gyrus near occipital cortex, vermis VI-right anterior supramarginal gyrus (aSMG), right aSMG-right supplementary motor area (SMA), right opercular inferior frontal gyrus (IFGoper)-right insular cortex, right IFGoper-left cuneus, posterior cingulate cortex-right inferior occipital cortex, right cerebellum lobe VIII-right cerebellum lobe I, and left cereb1-left cerebellum lobe VII were found; decreased RSFC in right SMA-right lateral parietal area (LP), right SMA-left LP.

anterior supramarginal gyrus (SMG), right anterior SMG and right supplementary motor area (SMA), right opercular inferior frontal gyrus (IFGoper) and right insular cortex (IC), right IFGoper and left cuneus, posterior cingulate cortex (PC) and right inferior occipital cortex (IOC), right cerebellum lobe VIII and right cerebellum lobe I, and left cerebellum lobe I and left cerebellum lobe VII. By contrast, lower RSFC was found for both the MDD and ADHD groups than for the HC group between the right SMA and bilateral lateral parietal areas (LPs; Figure 1 and Table 2).

### *Correlations between RSFC and clinical variables*

RSFC was significantly positively correlated with CBCL-AAA score in all higher RSFC brain areas and negatively correlated with CBCL-AAA score in all lower RSFC brain regions ($P < .05$). In addition, the RSFC between vermis VI and the left toITG and right anterior SMG was positively correlated with both MADRS and the SNAP-IV scores. The RSFC between the right SMA and right lateral parietal area (LP) was negatively correlated with both the MADRS and SNAP-IV scores. Respectively, the SNAP-IV score was positively correlated with the RSFC between the right anterior SMG and right SMA, right IFGoper and right IC, right cerebellum lobe VIII and right cerebellum lobe I, and left cerebellum lobe I and left cerebellum lobe VII; the MADRS score was correlated with the RSFC between the right SMA and the left LP, negatively, the right IFGoper and the left cuneus, and the PC and the right IOC, both positively (Table 3). In addition, the statistical significance of associations between the above RSFC and clinical symptoms remained consistent after *P*-value was revised to .05/3 (.0167) owing to the multiple-testing correction.

### *VBM analyses: group comparisons*

Lower GM volume in the right SMG was found in both the MDD and ADHD groups than in the HC group (Figure 2 and Table 2).

### *Correlations between gray matter volume change and clinical variables*

Decreased GM volume in the right SMG was significantly negatively correlated with CBCL-AAA and the SNAP-IV scores (Table 3). After the *P*-value was revised to .05/3 (.0167) owing to the multiple-testing correction, the significance of the correlation between the right SMG volume reduction and the SNAP-IV score disappeared, but the relationship between the right SMG volume reduction and the CBCL-AAA score remained significant.

### *DTI analyses: group comparisons*

The results of DTI analyses revealed no significant difference in FA values between the ADHD or MDD groups and the HC group.

## Discussion

In this study, ED in adolescents with ADHD or MDD shows distinct alterations in connectivity that can indicate different underlying network involvement. In addition, several shared neural connectivities involving the cerebellum, inferior frontal gyrus, and some attention networks regions of ED in ADHD and MDD were also found. Moreover, these differences in the RSFC of patients with ADHD and MDD with clinical ED were significantly correlated with not just an ED rating scale (CBCL-AAA), but also MDD and ADHD clinical rating scales (MADRS and SNAP-IV). Finally, yet importantly, connectivity with the right IFGoper and the right SMG in the ventral attention network was correlated with clinical rating scale scores for ED in this study, supporting our hypothesis. Thus, this study shows that neural networks with cerebellum and attention networks of ED are possibly shared in adolescents with ADHD and MDD.

### *Distinct neural networks involved in ED in adolescents with ADHD*

Functionally, increased RSFCs between the right SMG and right SMA, the right cerebellum VII and right cerebellum I, the left cerebellum VIII and left cerebellum I, and the right IFGoper and right IC were positively correlated with clinical ED and ADHD rating scale scores. Structurally, decreased GM volume in the right SMG was negatively correlated with clinical ED and ADHD rating scale scores.

For patients with ADHD, dysfunction in the frontoparietal, dorsal attention, motor, visual, or default mode network (DMN) is found.[24] Taking together, both increased RSFC and decreased GM volume involving right SMG were also correlated with ED in adolescents with ADHD in this study. This is consistent with previous neuroimaging studies, showing increased activation in the SMG and motor area in patients with ADHD performing

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**Table 2.** The Difference in Functional Connectivity Between Patients with ED and Controls

| Resting-state functional connectivity | Harvard-Oxford structural atlases | | | *F* | *P*-value[a] |
|---|---|---|---|---|---|
| | Vermis VI-left toITG | | | 16.07 | <.001 |
| | Vermis VI-right aSMG | | | 14.36 | <.001 |
| | Right aSMG-right SMA | | | 8.03 | .005 |
| | Right IFGoper-right IC | | | 6.73 | .010 |
| | Right IFGoper-left cuneus | | | 8.34 | .008 |
| | PC-right IOC | | | 6.17 | .010 |
| | Right cereb8-right cereb1 | | | 8.99 | .025 |
| | Left cereb1-left cereb7 | | | 10.52 | .008 |
| | Right SMA-right LP | | | 9.21 | .035 |
| | Right SMA-left LP | | | 8.07 | .035 |
| Voxel-based morphometry | MNI coordinates | | | *k* | *P*-value[a] |
| | *x* | *y* | *z* | | |
| Right SMG | 51 | −51 | 32 | 13.55 | .044 |

Abbreviations: aSMG, anterior supramarginal gyrus; cereb1, cerebellum lobe I; cereb7, cerebellum lobe VII; cereb8, cerebellum lobe VIII; ED, emotional dysregulation; IC, insular cortex; IOC, inferior occipital cortex; IFGoper, opercular inferior frontal gyrus; LP, lateral parietal area; MNI, Montreal Neurological Institute; PC, posterior cingulate gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; toITG, inferior temporal gyrus near occipital cortex.
[a]FDR-corrected to $P < .05$ at the seed level for resting-state functional connectivity; uncorrected $P < .05$ at the nonstationary cluster level for voxel-based morphometry.

**Table 3.** Correlation Between Functional Connectivity and Clinical Rating Scales Among Patients with ED and Controls

| Pearson correlation (*P*-value) | CBCL-AAA | MADRS | SNAP-IV |
|---|---|---|---|
| Resting-state functional connectivity | | | |
| Vermis VI-left toITG | 0.461 (<0.001*) | 0.275 (0.019*) | 0.528 (<0.001*) |
| Vermis VI-right aSMG | 0.416 (<0.001*) | 0.305 (0.009*) | 0.318 (0.007*) |
| Right aSMG-right SMA | 0.373 (0.001*) | 0.163 (0.172) | 0.401 (<0.001*) |
| Right IFGoper-right IC | 0.332 (0.004*) | 0.007 (0.954) | 0.428 (<0.001*) |
| Right IFGoper-left cuneus | 0.406 (<0.001*) | 0.370 (0.001*) | 0.203 (0.087) |
| PC-right IOC | 0.406 (<0.001*) | 0.333 (0.004*) | 0.192 (0.106) |
| Right cereb8-right cereb1 | 0.466 (<0.001*) | −0.014 (0.907) | 0.389 (<0.001*) |
| Left cereb1-left cereb7 | 0.372 (0.001*) | 0.230 (0.052) | 0.343 (0.003*) |
| Right SMA-right LP | −0.399 (<0.01*) | −0.352 (0.002*) | −0.293 (0.012*) |
| Right SMA-left LP | −0.278 (0.018*) | −0.396 (<0.001*) | −0.180 (0.131) |
| Voxel-based morphometry | | | |
| Right SMG | −0.387 (<0.001*) | −0.133 (0.265) | −0.277 (0.018*) |

Abbreviations: aSMG, anterior supramarginal gyrus; CBCL-AAA, anxious/depressed, aggressive behavior, and attention problems scales of the child behavior checklist; cereb1, cerebellum lobe I; cereb7, cerebellum lobe VII; cereb8, cerebellum lobe VIII; ED, emotional dysregulation; IC, insular cortex; IFGoper, opercular inferior frontal gyrus; IOC, inferior occipital cortex; LP, lateral parietal area; MADRS, Montgomery-Åsberg Depression Rating Scale; PC, posterior cingulate gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SNAP-IV, Swanson, Nolan, and Pelham Questionnaire; toITG, inferior temporal gyrus near occipital cortex.
*$P < .05$.

executive tasks such as attention deployment in emotional control.[24] In addition, thinner cortical thickness in SMG of ADHD adolescents is associated with inattention.[25,26] Thus, the functional and structural deficits in SMG of attention networks might cause dysfunction of attentional employment in the ED of ADHD adolescents. In addition, increased RSFC between the right SMG and right SMA that is in line with a study indicating increased variability of activation in the motor cortex in patients with ADHD is positively related to pre-SMA activation,[24] which might relate to the attention deployment in emotional control. Moreover, the increased RSFC in cerebellum VII and VIII with cerebellum I is positively correlated with ED in adolescents with ADHD in our study. These can be explained by cerebellar hemispheres VIIb and VIII being associated with the task-positive network and salience network, and ADHD impairs their connections with motor networks and DMN.[27] In addition, we also found increased RSFC between the right IFGoper and right IC, which can be related to the crucial role of the striatum-amygdala-media prefrontal cortical network in patients with ADHD and ED.[28] Patients with disruptive mood dysregulation disorder who present with clinical ED and ADHD might show dysfunction in the right paracentral lobule, superior parietal lobe, fusiform gyrus, and cerebellar culmen.[18]

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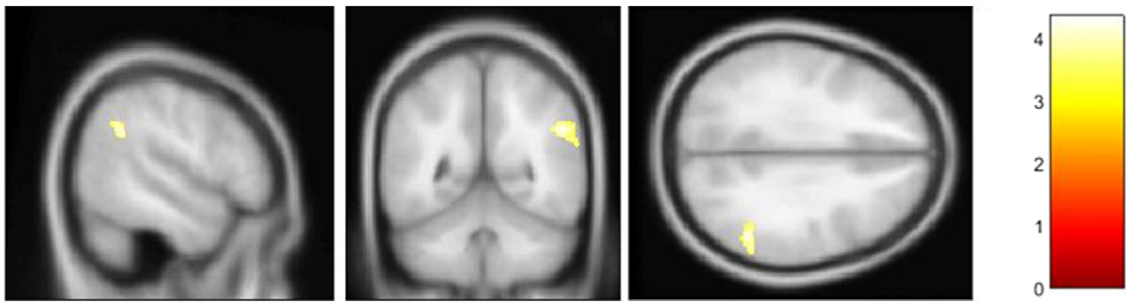


**Figure 2.** Gray matter (GM) volume difference of right supramarginal gyrus (SMG) in patients with emotional dysregulation (ED) vs healthy controls (HCs). In voxel-based morphometry analysis (HC > attention deficit hyperactivity disorder or major depressive disorder), decreased GM volume in the right SMG (MNI coordinates: *x*, *y*, *z* = 51, −51, 32) in patients with ED was found. The color bar indicates the GM difference (*z*-score) between groups.

Moreover, a structural study reveals that children with ED and ADHD have a lower GM volume in the prefrontal cortex and cerebellum and a lower FA in the right SMA and cerebellum compared with children without.[22] However, without the involvement of the amygdala, the findings might be explained by contrasting responses to stimuli in the reappraisal of patients with ED.[24] Thus, greater involvement of the neural networks in the cerebellum, SMG with the SMA, and prefrontal cortex with the IC may contribute to the ED of adolescents with ADHD.

### Distinct neural networks involved in ED in adolescents with MDD

Increased RSFCs between the right IFGoper and left cuneus, the PC, and right IOC were positively correlated with clinical ED and MDD rating scale scores, and decreased RSFC between the right SMG and left LP was negatively correlated with clinical ED and MDD rating scale scores.

The PC in the DMN is associated with the modulation of emotional and cognitive behavior.[29,30] In patients with MDD, failure to disengage negative memory processing for emotional context is shown by a decreased correlation between the angular gyrus and PC.[31] Weaker connectivity in the DMN is susceptible to ED, especially in internalizing disorders such as MDD.[32] It explains the connection between the PC in the DMN and the lateral occipital cortex in this study, and the occipital cortex might help the dorsal attention network to suppress irrelevant stimuli for attention maintenance in emotional control.[24] In this study, we also noted that the cuneus in the DMN was also connected with the IFGoper in VLPFC in the ED of adolescents with MDD. Previous fMRI studies have shown that reappraisal in emotional control processes involves the inferior frontal gyrus, SMA, parietal lobe, SMG,[12,21] and also the right VLPFC works as a core hub for response in emotional regulation.[12,33] In addition, involvement from the cuneus of DMN and lateral intraparietal sulcus to the prefrontal cortex is found in an attention study.[24] Since attention is fundamental to emotional control, the VLPFC is important for evaluating emotion regulation.[34] Therefore, the right VLPFC may be a therapeutic target for ED in patients with MDD.[35] To recapitulate, the DMN and VLPFC are crucial in ED in adolescents with MDD.

### Cerebellum in adolescents with ED in ADHD and MDD

The cerebellum is crucial for emotional control, and it can be attenuated by repetitive transcranial magnetic stimulation.[36,37] The vermis in the limbic cerebellum serves functions in affective processing, including emotional regulation.[38] In our study, vermis VI in the cerebellum was increasingly connected with the left toITG and SMG, and the connections were positively correlated with clinical ED, ADHD, and MDD scale scores. This suggests that the vermis is essential in adolescent ED in ADHD and MDD, supporting previous studies that negative emotional reaction arises from lesions and infarcts in the vermis.[38,39] In addition, functional connectivity between the right vermis and right premotor cortex is responsible for the affective disturbances of loneliness and isolation.[40] With our results and previous studies, it may explain the common comorbidity between ADHD and MDD in adolescents.[7] Moreover, the cerebellum is connected with the sensorimotor network, DMN, frontoparietal network, task-positive network, salience network, and motor and premotor areas.[27] ED is attributed not only to the cerebellum, but also to the sensorimotor and frontolimbic areas.[14] More specifically, vermis VI is associated with the premotor area in the sensorimotor network, cingulate cortex, frontoinsular cortex, and salience network in emotional control.[27,41] In addition, RSFC between the cerebellum and left toITG was positively correlated with clinical ED in patients with ADHD and MDD in our study. Because the inferior temporal gyrus responds to emotional stimuli in the initial phase of emotional processing,[41] emotional misrepresentations in recognition of human faces or voices in the inferior temporal gyrus may play an important role in ED psychopathology,[28] perhaps in the appraisal phase. Overall, the cerebellum is integral to emotional control.[36]

### Attention networks and associated networks in ED with ADHD and MDD

The IFGoper and SMG were correlated with clinical ED in adolescents with MDD and ADHD in the present study. The right IFGoper is a part of the VLPFC, and the TPJ includes the SMG, superior temporal gyrus, and angular gyrus. Moreover, attentional deployment is regulated by the dorsal and ventral attention networks. The dorsal attention network is composed of the lateral intraparietal sulcus and frontal eye fields, and the ventral attention network is constituted by the TPJ and IFG.[12,33] In addition, the inferior frontal junction in the IFG may serve as an interface between the dorsal and ventral attention networks.[33] The ventral attention network is anchored by the TPJ, SMG, IFGoper, and anterior insula, with a close relationship with the salience network and cingulo-opercular network.[24] Right VLPFC is associated with the integration of visually induced emotional processes, and thus dysfunction of the right VLPFC may induce ED.[42] In addition, the right TPJ is activated in an orientation attention task with the right lateral intraparietal sulcus.[33] In a nutshell, based on our findings and previous studies, right insula, SMG, VLPFC, and right TPJ may play important roles in emotion regulation, including attention

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deployment, appraisal, and response, among both adolescents with ADHD and those with MDD.[12] Therefore, the present study provides evidence for the connection between the cerebellum and attention networks in the ED of adolescents with MDD and ADHD.

## Limitations

First, patients enrolled in our study took medications during the study period, including during clinical assessment and fMRI. However, this study design is ethically appropriate for patients with severe ED, and it can provide natural data. Thus, the possible confounding effect of the medication needs further investigation. Second, the present study collected cross-sectional data. Therefore, further longitudinal design for investigating the prolonged effect of ED in brain functional and structural imaging of ADHD and MDD might be considered in the future. Third, we did not head-to-head compare the ROI of SMG in VBM with involved connectivity in RSFC with different atlas coordinates. Therefore, the interpretation of two coordinate systems should take with caution. Last, although the sample size of the study was small, this was the first study of ED to use multiple disorders and modes of analysis. Therefore, future research should adopt a similar design with larger recruitment to ensure the generalizability of any discovered mechanism.

## Conclusion

This study showed the shared neural networks and interactions between the cerebellum and attention networks in adolescents with clinical ED due to ADHD and MDD. Distinct connectivity in different functional networks for patients with ED in ADHD or MDD was found as well. Specifically, the TPJ and DMN play vital roles in the ED of ADHD and MDD patients, respectively, as evidenced by the functional connectivity and the GM volume. To sum up, this study provides the possible shared and distinct neural networks of clinical ED in adolescents with externalizing and internalizing disorders.

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