Localized Brain Volume and White Matter Integrity Alterations in Adolescent Anorexia Nervosa

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Objective: The neurobiological underpinnings of anorexia nervosa (AN) are poorly understood. In this study, we tested whether brain gray matter (GM) and white matter (WM) in adolescents with AN would show alterations comparable to those in adults. **Method:** We used magnetic resonance imaging to study GM and WM volume, and diffusion tensor imaging to assess fractional anisotropy for WM integrity in 19 adolescents with AN and 22 controls. **Results:** Individuals with AN showed greater left orbitofrontal, right insular, and bilateral temporal cortex GM, as well as temporal lobe WM volumes compared to controls. WM integrity in adolescents with AN was lower (lower fractional anisotropy) in fornix, posterior frontal, and parietal areas, but higher in anterior frontal, orbitofrontal, and temporal lobes. In individuals with AN, orbitofrontal GM volume correlated negatively with sweet taste pleasantness. An additional comparison of this study cohort with adult individuals with AN and healthy controls supported greater orbitofrontal cortex and insula volumes in AN across age groups. **Conclusions:** This study indicates larger orbitofrontal and insular GM volumes, as well as lower fornix WM integrity in adolescents with AN, similar to adults. The pattern of larger anteroventral GM and WM volume as well as WM integrity, but lower WM integrity in posterior frontal and parietal regions may indicate that developmental factors such as GM pruning and WM growth could contribute to brain alterations in AN. The negative correlation between taste pleasantness and orbitofrontal cortex volume in individuals with AN could contribute to food avoidance in this disorder. J. Am. Acad. Child Adolesc. Psychiatry, 2013;52(10):1066–1075. **Key Words:** anorexia nervosa, brain, gray matter, white matter

Anorexia nervosa (AN) is an eating disorder (ED) associated with intense fear of weight gain, and perception of being overweight despite often severe emaciation from self-driven food refusal.[1] It is the third most common chronic illness among adolescents,[2] with a mortality rate 12 times higher than the death rate associated with all causes of death for females 15 to 24 years old.[3] AN shows a difficult-to-disentangle interplay among neurobiological, psychological, and environmental factors,[4] and little is known about brain biomarkers in children and adolescents with AN.

In the past, functional brain imaging studies implicated the striatum, insula, anterior cingulate, amygdala, and orbitofrontal cortex (OFC) in AN, brain regions that contribute to taste and reward processing.[5,6] The mechanisms for those alterations remain unclear, but brain gray matter (GM) and white matter (WM) might underlie altered brain function and behavior.[7]

Most structural brain imaging studies in EDs come from adult samples, and a recent meta-analysis found the available data "inconclusive."[8] Early studies in youth and adults suggested lower total GM and WM volume,[9-12] whereas studies after recovery in adults found lower[13,14] or normal[15,16] total brain tissue volumes.[8] Studies in adult AN assessing regional volume differences indicated lower GM volumes in the insula, frontal operculum, occipital, medial temporal, and cingulate cortex, whereas 1 recent study found larger dorsolateral prefrontal GM volumes.[17-21] After long-term recovery, regional brain-tissue

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volumes in adults with an ED history were normal.[15] Very few brain structure studies in adolescent AN have been conducted.[8] One study in mostly adolescents found lower GM in the frontal, temporal, parietal, occipital, and cerebellar areas.[22] A study of adolescent AN[16] that found greater total GM compared to that in controls, but lower temporal, parietal, frontal, and cingulate cortex volumes, indicating that the rate of localized GM development could be different between groups.

Only some studies corrected for age or total intracranial volume (TIV), and the effects of comorbid diagnoses or medication were often not taken into account. Not taking TIV into account could miss group differences pertaining to the more static body size–related cranial vault, and comorbid anxiety and depression have been associated with GM alterations independent of an AN diagnosis.[23] Furthermore, nutritional status is associated with quickly occurring GM and WM changes.[24] After only 2 to 3 days of dehydration, GM and WM volumes are significantly lower, whereas hyperhydration is associated with higher GM and WM volumes.[24] All of those factors may contribute to inconsistent results across studies. Recently[25] we found, in adult AN in a nutritionally highly controlled environment and AN after long-term recovery, after correcting for TIV, medication use, and comorbidity, larger left orbitofrontal cortex gyrus rectus GM volumes that correlated with perceived taste pleasantness, as well as larger right insula volumes. Those results suggested that altered orbitofrontal and insula cortex volumes could be trait markers for AN related to altered reward function.[26-28]

Another brain imaging method, diffusion tensor imaging (DTI),[29] maps water diffusivity along WM axons, expressed as fractional anisotropy (FA)[30] and is considered to be a measure of axon integrity related to myelination, and density. A second measure, the apparent diffusion coefficient (ADC), measures water diffusivity at the voxel level, and higher ADC indicates dispersed water diffusion reflecting cell damage.[30] Commonly, high ADC reflecting cell disruption is associated with low axon integrity and FA. One study showed lower fimbria–fornix WM integrity that was related to trait anxiety[31] in adult AN compared to that in controls, whereas a study in mixed ill and recovered adult AN found lower FA in the posterior thalamic radiation.[32]

In this study, we tested the following hypotheses: first, that larger left orbitofrontal gyrus rectus as well as right insula volumes, associated with adult AN, are present in adolescents with AN; second, that orbitofrontal cortex volume predicts taste pleasantness perception in both individuals with AN and control adolescents; and third, that adolescents with AN have lower WM integrity in the fimbria fornix similar to that in our previous study in adults, which could point to altered reward-processing pathways.[33]

METHOD

Subjects

A total of 19 individuals with AN (17 restricting-type and 2 binge/purge-type) and 22 healthy control adolescent girls who were similar in age participated in the study. Individuals with AN were recruited from the Children's Hospital Colorado Eating Disorders Program. The study was approved by the Colorado Multiple Institutional Review Board. Individuals with AN were within 1 to 2 weeks of inpatient hospital treatment, were closely supervised, and followed the program meal plan to avoid acute effects of starvation and dehydration. Control adolescents were recruited through local advertisements. Participants were administered the Computerized Diagnostic Interview Schedule for Children (C-DISC) for *DSM-IV* diagnoses.[34] All participants were right-handed, without history of head trauma, neurological disease, or major medical illness.

In addition, we compared the adolescents in this study with the adult sample (AN: $n = 19$, age 23.1 ± 5.8 years; control individuals: $n = 24$, age 27.4 ± 6.3 years) from our previous study.[25]

Behavioral Measures

Study participants completed as described previously,[35] the following: the Eating Disorder Inventory–3 (EDI-3) for Drive for Thinness (DT), Bulimia (B), and Body Dissatisfaction (BD); the Temperament and Character Inventory (TCI) for Novelty Seeking (NS) and Harm Avoidance (HA); the Spielberger State and Trait Anxiety Inventory (STAI); the Children's Depression Inventory; the revised Sensitivity to Reward (SR) and Punishment (SP) Questionnaire (SPSRQ); and rating of 1 molar sucrose and a control solution (slightly salty, resembling saliva) for sweetness and pleasantness on 9-point Likert scales (0 = not sweet/pleasant at all to 9 = extremely sweet/pleasant).

Magnetic Resonance Imaging for GM and WM

Structural brain images were acquired on a GE Signa 3T scanner, axial, 3-dimensional, T-1 weighted magnetization–prepared rapid acquisition gradient echo (spoiled gradient recall [SPGR]; field-of-view 22 cm, flip angle 10°, slice thickness 1.2 mm, scan