Archival Report

Biological Psychiatry

Global Cortical Thinning in Acute Anorexia Nervosa Normalizes Following Long-Term Weight Restoration

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ABSTRACT

BACKGROUND: Anorexia nervosa (AN) is a serious eating disorder characterized by self-starvation, extreme weight loss, and alterations in brain structure. Structural magnetic resonance imaging studies have documented brain volume reductions in acute AN, but it is unclear whether they are 1) regionally specific, or 2) reversible following weight restoration. Here, we measured cortical thickness (CT) for the first time in AN.

METHODS: Structural magnetic resonance imaging data were acquired from adolescent and young adult female patients with acute AN ($n = 40$), recovered patients following long-term weight restoration ($n = 34$), and an equal number of age-matched healthy control subjects. Group differences in CT were tested with well-validated procedures implemented in FreeSurfer. The mediating role of clinical variables including body mass index and drive for thinness were explored. For completeness, we also used FreeSurfer's subcortical segmentation stream to test group differences in volumes of select gray matter regions of interest.

RESULTS: Vertex-wise analyses revealed significant thinning of over 85% of the cortical surface in patients with acute AN and CT normalization in recovered patients following long-term weight restoration, although normal age-related trajectories were absent in the disorder. This pattern of results was largely mirrored in subcortical volumes. We also observed a strong negative correlation between CT and drive for thinness in extrastriate regions involved in body perception.

CONCLUSIONS: Structural brain anomalies in AN as expressed in CT and subcortical volume are primarily the consequence of malnutrition and unlikely to reflect premorbid trait markers or permanent scars, but longitudinal data are needed.

Keywords: Anorexia nervosa, Cerebral cortex, Cortical thickness, FreeSurfer, MRI, Subcortical structures

http://dx.doi.org/10.1016/j.biopsych.2014.09.005

Anorexia nervosa (AN) is a life-threatening eating disorder that usually begins in adolescence in female individuals and is characterized by an intense fear of weight gain, despite severe emaciation, and a perpetual drive for thinness, typically by self-starvation. To elucidate the underlying neurobiology, researchers have long searched for clues in brain structure (1,2). In acute AN (acAN), reduction of brain mass is often readily visible in individual patients' brain scans and several structural magnetic resonance imaging (sMRI) studies have documented decreases in both gray and white matter volume (3–11). However, recent studies using voxel-based morphometry (VBM) have emphasized regionally specific differences (3,7–9,12,13), including volume increases (14–16) and their possible link to AN-specific clinical characteristics (17–20). Furthermore, while a number of studies have shown differences in acAN to normalize in weight-recovered AN patients (recAN) (7,21–23), others have reported persistence of structural alterations (11,12,24,25). Thus, important questions remain regarding 1) the regional specificity of structural brain anomalies in AN; and 2) whether they merely reflect state-related consequences of malnourishment or constitute disorder-defining traits (26,27).

Several factors may contribute to the lack of consistency in the sMRI literature on AN. First, study samples have generally been small ($n < 20$) and heterogeneous, sometimes also including individuals with bulimia nervosa. Also, group inclusion criteria have not been uniformly defined according to diagnostic standards across studies, and definitions of weight-recovered have varied. More critically, some studies have included patients receiving psychoactive medications, which may have a considerable effect on brain morphometry (28). Particularly relevant for the current study, the results of VBM methods can be highly dependent on registration strategies and normalization templates (29,30). In an attempt to gain new

SEE COMMENTARY ON PAGE 602

 ISSN: 0006-3223

insight, the current study employed an alternative approach for the first time in AN, surface-based morphometry (SBM), to measure cortical thickness (CT) in a comparatively large and medication-free sample of young acAN and recAN patients.

Whereas VBM provides generic measures of brain volume inferred indirectly from matter density, SBM utilizes geometric models of the cortical surface to partition its constituent surface area and CT components, which are thought to constitute genetically independent properties (31–33). Surface-based analysis, especially in the case of CT, has therefore been proposed to constitute a more biologically informative measure with particular sensitivity to structural changes both in health (34,35) and disease (36–40). CT has the added advantage of being a direct measure of gray matter expressed in millimeters.

Here, we use a well-validated, automated surface-based procedure to estimate CT (FreeSurfer; http://surfer.nmr.mgh.harvard.edu) (41–44) in adolescent and young acAN and recAN women and test for group differences relative to age-matched healthy control subjects (HC). We conducted both vertex-wise analyses of the entire cortical surface and confirmatory region of interest (ROI) comparisons based on the Desikan-Killiany atlas (45). Additionally, we exploited FreeSurfer's subcortical processing stream (46,47) to explore whether group differences and similarities were also evident in the volumes of select gray matter ROIs.

METHODS AND MATERIALS

Participants

The current sample consisted of 143 female volunteers: 40 acute patients diagnosed with AN according to DSM-IV criteria (12–23 years old), 34 recovered former AN patients (17–28 years old), and 69 healthy control participants (12–28 years old). The study was approved by the Institutional Review Board of the Technische Universität Dresden and all participants gave written informed consent (or their legal guardians, if under 18 years old).

acAN patients were admitted to eating disorder clinics at the departments of Child and Adolescent Psychiatry or Psychosomatic Medicine at the Universitätsklinikum Carl Gustav Carus in Dresden, Germany, and underwent magnetic resonance imaging (MRI) within 96 hours after beginning nutritional rehabilitation programs. Diagnosis was supported using the Structured Interview for Anorexia and Bulimia Nervosa (48), which requires body mass index (BMI) $<$10th age percentile (if younger than 15.5 years) and $<$17.5 (if older than 15.5 years). To be considered recovered, recAN subjects had to 1) maintain a BMI (kg/m^2) $>$18.5 (if older than 18 years) or $>$10th age percentile (if younger than 18 years); 2) menstruate; and 3) have not binged, purged, or engaged in restrictive eating patterns for at least 6 months before the study. Further details regarding the AN samples are provided in Table 1 and Supplement 1. HCs were recruited through advertisements among middle school, high school, and university students. To be included in the HC group, participants had to be of normal weight and eumenorrheic.

Information pertinent to exclusion criteria and possible confounding variables, including menstrual cycle and use of contraceptive medication, were obtained from all participants using the Structured Interview for Anorexia and Bulimia Nervosa interview (48), supplemented by our own semistructured interview. HC participants were excluded if they had any history of psychiatric illness, a lifetime BMI below the 10th age percentile (if younger than 18 years)/BMI below 18.5 kg/m^2 (if older than 18 years), or were currently obese (BMI over 97th age percentile if younger than 18 years; BMI over 30 kg/m^2 if older than 18 years). Participants of all groups were excluded if they had a history of any of the following diagnoses: organic brain syndrome, schizophrenia, substance dependence, psychosis not otherwise specified, bipolar disorder, bulimia nervosa, or binge-eating disorder. Further exclusion criteria for all participants were IQ $<$ 85; psychotropic medication within 4 weeks before the study; current substance abuse; inflammatory, neurologic, or metabolic illness; chronic medical or neurological illness that could affect appetite, eating behavior, or body weight; clinically relevant anemia; and pregnancy or breast feeding.

Clinical Measures

Eating disorder-specific psychopathology was assessed with the German version of the Eating Disorder Inventory-2 (EDI-2) (49). Depressive symptoms were explored using the German version of the Beck Depression Inventory-II (50). General levels of psychopathology were gauged with the global severity index of the Symptom Checklist-90 Revised (51). IQ was estimated with a short version of the German adaptation of the Wechsler Adult Intelligence Scale (Wechsler Intelligenztest für Erwachsene) (52) or a short version of the German adaptation of the Wechsler Intelligence Scale for Children (Hamburg-Wechsler-Intelligenztest für Kinder IV) (53) for participants aged 15 years or younger. Demographic and clinical study data were collected and managed using a secure, web-based electronic data capture tool (Research Electronic Data Capture; http://www.project-redcap.org) (54).

MRI Acquisition and Processing

All participants underwent MRI scanning between 8:00 AM and 9:00 AM following an overnight fast. High-resolution three-dimensional T1-weighted structural scans were acquired on a 3.0T scanner (Magnetom Trio; Siemens, Erlangen, Germany) using a magnetization prepared rapid acquisition gradient-echo sequence with the following parameters: 176 sagittal slices (1 mm thickness, no gap), repetition time = 1900 msec; echo time = 2.26 msec; flip angle = 9° voxel size = 1.0 × 1.0× 1.0 mm^3; field of view = 256 × 224 mm^2, bandwidth of 200 Hz/pixel. The data were registered, motion corrected, realigned, averaged, and analyzed in an automated manner with the FreeSurfer software suite (http://surfer.nmr.mgh.harvard.edu, version 5.1.0), a well-documented program for cortical surface reconstruction and volumetric segmentation (41–47). In the current study, we focused on estimations of CT and volumes of the following subcortical ROIs: accumbens, amygdala, caudate nucleus, cerebellum, hippocampus, pallidum, putamen, and thalamus. For details on the implementation of the surface-based and subcortical processing streams according to standard FreeSurfer procedures, see Supplement 1.