NeuroImage xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Weight restoration therapy rapidly reverses cortical thinning in anorexia nervosa: A longitudinal study

Fabio Bernardoni [a,1], Joseph A. King [a,1], Daniel Geisler [a], Elisa Stein [a], Charlotte Jaite [b], Dagmar Naetsch [a], Friederike I. Tam [a], Ilka Boehm [a], Maria Seidel [a], Veit Roessner [a], Stefan Ehrlich [a,c,d,*]

[a] Eating Disorder Services and Researech Center, Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany
[b] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Charité – Universitätsmedizin Berlin, Berlin, Germany
[c] MGH/MIT/HMS Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA
[d] Harvard Medical School, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

ARTICLE INFO

Article history:
Received 1 October 2015
Accepted 4 February 2016
Available online xxxx

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

ABSTRACT

Structural magnetic resonance imaging studies have documented reduced gray matter in acutely ill patients with anorexia nervosa to be at least partially reversible following weight restoration. However, few longitudinal studies exist and the underlying mechanisms of these structural changes are elusive. In particular, the relative speed and completeness of brain structure normalization during realimentation remain unknown. Here we report from a structural neuroimaging study including a sample of adolescent/young adult female patients with acute anorexia nervosa (n = 47), long-term recovered patients (n = 34), and healthy controls (n = 75). The majority of acutely ill patients were scanned longitudinally (n = 35): at the beginning of standardized weight restoration therapy and again after partial weight normalization (>10% body mass index increase). High-resolution structural images were processed and analyzed with the longitudinal stream of FreeSurfer software to test for changes in cortical thickness and volumes of select subcortical regions of interest. We found globally reduced cortical thickness in acutely ill patients to increase rapidly (0.06 mm/month) during brief weight restoration therapy (≈3 months). This significant increase was predicted by weight restoration alone and could not be ascribed to potentially mediating factors such as duration of illness, hydration status, or symptom improvements. By comparing cortical thickness in partially weight-restored patients with that measured in healthy controls, we confirmed that cortical thickness had normalized already at follow-up. This pattern of thinning in illness and rapid normalization during weight rehabilitation was largely mirrored in subcortical volumes. Together, our findings indicate that structural brain insults inflicted by starvation in anorexia nervosa may be reversed at a rate much faster than previously thought if interventions are successful before the disorder becomes chronic. This provides evidence drawing previously speculated mechanisms such as (de-)hydration and neurogenesis into question and suggests that neuronal and/or glial remodeling including changes in macromolecular content may underlie the gray matter alterations observed in anorexia nervosa.

Introduction

Anorexia nervosa (AN) is a serious eating disorder that usually begins during puberty in females and is characterized by a distorted body image and a relentless drive for thinness, despite extreme emaciation, typically by self-starvation. In attempt to understand this enigmatic illness, researchers have long sought clues in brain structure, as illustrated in several recent reviews (Van den Eynde et al., 2012; Seitz et al., 2014). Modern structural magnetic resonance imaging (sMRI) studies report substantial reductions of gray matter in acutely underweight AN patients (acAN), but it remains unclear whether such anomalies reflect regionally specific disturbances that might help explain disorder-defining psychopathology or merely generic, global consequences of malnutrition (Frank, 2015). Similarly, it remains unclear whether structural alterations in AN constitute premorbid traits or persisting "scars," as might be the case if they would still be evident following weight restoration (Kaye et al., 2013). More fundamentally, we lack understanding of the biological mechanisms underlying changes in brain structure associated with acute illness and weight rehabilitation. Longitudinal measurement during weight restoration therapy has the potential of being particularly informative to these open questions.

While earlier computed tomography studies (Dolan et al., 1988; Enzmann and Lane, 1977; Kohlmeyer et al., 1983) focused primarily

* Corresponding author at: Technische Universität Dresden, Faculty of Medicine, University Hospital C. G. Carus, Dresden, Department of Child and Adolescent Psychiatry, Translational Developmental Neuroscience Section, Fetscherstraße 74, 01307 Dresden, Germany. Fax: +49 351 458 5754.
E-mail address: stefan.ehrlich@tu-dresden.de (S. Ehrlich).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.neuroimage.2016.02.003
1053-8119/

on global measures and were limited in their ability to detect fine-grained structural differences in AN, several modern voxel-based morphometry (VBM) studies have emphasized local volume alterations (including both decreases and increases) in a range of functionally distinct regions across the brain and their possible association with disorder-specific symptoms (Brooks et al., 2011; Friederich et al., 2012; Gaudio et al., 2011; Mainz et al., 2012; Suchan et al., 2010). For example, Frank et al. (2013) found abnormally elevated volume in medial orbitofrontal and insular regions involved in taste reward in both acutely ill (acAN) and long-term weight-recovered patients (recAN). In contrast, using state-of-the-art surface-based morphometry which decomposes cortical gray matter volume into its constituent parts, cortical thickness (CT), and surface area, we recently found regionally unspecific thinning over virtually the entire cortical surface in a moderately large sample of predominately adolescent acAN patients (King et al., 2015). More recently, however, studies in acAN adults have reported reductions in CT and gyrification abnormalities to be more localized (Bär et al., 2015; Favaro et al., 2015). Longitudinal observation also has potential to clarify discrepancies such as these which may be due in part to differential neurodevelopmental trajectories in the age ranges of the investigated samples.

Although some studies have reported noteworthy persistence of structural brain abnormalities in recAN (Katzman et al., 1997; Mühlau et al., 2007), the majority of sMRI studies including our recent CT investigation have demonstrated at least partial normalization after long-term recovery (King et al., 2015; Wagner et al., 2006; for review, see Seitz et al., 2014). Critically, however, it is unknown how fast reversal occurs (months or years) and only few studies with heterogeneous samples have tracked brain structure in the same acAN patients longitudinally over the course of weight restoration (Roberto et al., 2011; Swayze et al., 2003), especially in typical adolescent cases (Castro-Fornieles et al., 2009; Mainz et al., 2012). Moreover, it is unknown whether changes in brain structure during recovery are related to changes in symptoms or merely weight gain. These are important questions because answers will shed light on the mechanisms underlying dynamic changes in brain structure.

Here, we use automated surface-based procedures implemented in FreeSurfer (http://surfer.nmr.mgh.harvard.edu; Dale et al., 1999; Fischl, Sereno, and Dale, 1999; Fischl, Sereno, Tootell, et al., 1999; Fischl and Dale, 2000) to estimate longitudinal changes in CT in a large unmedicated sample of adolescent and young adult female acAN patients (n = 35) receiving standardized weight restoration therapy. All acAN patients in the longitudinal sample underwent sMRI scanning within 96 h after beginning therapy (acAN-T1) to avoid early effects of realimentation and were re-scanned after partial weight restoration defined as a body mass index (BMI; kg/m^2) increase of at least 10% (acAN-T2). Building on our previous cross-sectional study (King et al., 2015), we supplement analyses of CT by exploring weight-gain-related changes in volume of select subcortical gray matter regions of interest (ROIs). To assess the relative speed and completeness of changes in brain structure attributable to increased BMI, statistical analysis involved fitting linear mixed models including both recAN (n = 34) and healthy control (n = 75) participants while accounting for age-related neurodevelopmental trajectories, which are known to be considerable across adolescence and young adulthood (Shaw et al., 2008; Tamnes et al., 2010; Wierenga et al., 2014). Additionally, we explored whether the changes in brain structure were mediated by improvements in psychiatric symptoms, hydration status, or duration of illness.

Materials and methods

Participants

The current sample consisted of 156 female volunteers: 47 acutely ill patients diagnosed with AN according to DSM-IV criteria (acAN; 12–23 years; mean age = 15.7, SD = 2.4), 34 recovered former AN patients (recAN; 17–28 years; mean age = 22.2, SD = 3.1) and 75 healthy control participants (HC; 12–28 years; mean age = 19.5; SD = 4.3). The study was approved by the Institutional Review Board of the Technische Universität Dresden (Germany) and all participants (or their legal guardians, if under 18 years old) gave written informed consent.

acAN patients were admitted to eating disorder programs at the Universitätsklinikum Carl Gustav Carus at the TU Dresden. Diagnosis was established according to the Structured Interview for Anorexia and Bulimia Nervosa (SIAB-EX; Fichter and Quadflieg, 2001), which requires BMI <10th age percentile (if younger than 15.5 years) and <17.5 (if older than 15.5 years). A total of 35 acAN patients (mean age at baseline: 15.5 ± 2.4 SD years old) completed all assessments at two time points (longitudinal sample): first within 96 h after beginning nutritional rehabilitation and a second time after a BMI increase (and maintenance) of at least 10% (minimum discharge criterion). We refer to acAN participants at the beginning of therapy as "acAN-T1" (baseline) and after achieving partial weight restoration as "acAN-T2" (follow-up).

A total of 29 acAN patients belonging to the longitudinal sample participated in our previous cross-sectional study (King et al., 2015), while an additional 6 longitudinal subjects were newly recruited for the current study. Single time point data from 12 acAN-T1 patients (11 from our previous study) were also included to improve statistical power in supplemental analyses designed to extend the results from our previous study of CT in AN (King et al., 2015; see Supplementary Methods online). These 12 patients could not be scanned longitudinally due to various reasons including psychotropic medication intake, therapy discontinuation, not yet having achieved partial weight restoration, other contraindications against scanning, and scanner scheduling problems.

To assess the relative speed and completeness of changes in CT in AN resulting from weight restoration, our sample also included single time point data from 34 recAN (all from our previous study) and 75 HC participants (69 from our previous study). To be considered "recovered," recAN participants had to 1) maintain a BMI >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 prior to the study. HCs were recruited through advertisement among middle school, high school, and university students and eating disorders were excluded using the SIAB-EX. We applied several additional exclusion criteria for all groups—most importantly, a history of bulimia nervosa or "regular" binge eating, psychotropic medications within 6 weeks prior to the study, substance abuse, and neurologic or medical conditions. Complete details regarding group inclusion and exclusion criteria are provided in the online Supplementary Methods.

Clinical measures

We assessed eating disorder-specific psychopathology with the Eating Disorders Inventory (EDI-2; Paul and Thiel, 2005), affective symptoms with the Beck Depression Inventory (BDI-II, Hautzinger et al., 2009), and general levels of psychopathology with the global severity index of the revised Symptom Checklist 90 (SCL-90-R; Franke, 2002) both at baseline and follow-up. IQ was estimated in acAN patients after they reached at least the 10th BMI age percentile with age-appropriate short versions of the Wechsler Adult Intelligence Scale (WIE; Von Aster et al., 2006) or the Wechsler Intelligence Scale for Children (HAWIK; Petermann and Petermann, 2008). Demographic and clinical study data were collected and managed using a secure, web-based electronic data capture tool [Research Electronic Data Capture (REDCap); http://www.project-redcap.org; Harris et al., 2009)]. Group differences in demographic and clinical variables were tested using scipy.stats software (http://www.scipy.org/).

Details on nutritional assessment of acAN patients, including measurements of urine-specific gravity to gauge hydration status (Baron et al., 2015) and serum leptin as an indicator of nutritional status (Föcker et al., 2011) are described in the Supplementary Methods.

Please cite this article as: Bernardoni, F., et al., Weight restoration therapy rapidly reverses cortical thinning in anorexia nervosa: A longitudinal study, NeuroImage (2016), http://dx.doi.org/10.1016/j.neuroimage.2016.02.003