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Neural activations are related to body-shape, anxiety, and outcomes in adolescent anorexia nervosa

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ABSTRACT

Anorexia nervosa (AN) is an illness that frequently begins during adolescence and involves weight loss. Two groups of adolescent girls (AN-A, weight-recovered following AN) and (HC-A, healthy comparison) completed a functional magnetic resonance imaging task involving social evaluations, allowing comparison of neural activations during self-evaluations, friend-evaluations, and perspective-taking self-evaluations. Although the two groups were not different in their whole-brain activations, anxiety and body shape concerns were correlated with neural activity in a priori regions of interest. A cluster in medial prefrontal cortex and the dorsal anterior cingulate correlated with the body shape questionnaire; subjects with more body shape concerns used this area less during self than friend evaluations. A cluster in medial prefrontal cortex and the cingulate also correlated with anxiety such that more anxiety was associated with engagement when disagreeing rather than agreeing with social terms during self-evaluations. This data suggests that differences in the utilization of frontal brain regions during social evaluations may contribute to both anxiety and body shape concerns in adolescents with AN. Clinical follow-up was obtained, allowing exploration of whether brain function early in course of disease relates to illness trajectory. The adolescents successful in recovery used the posterior cingulate and precuneus more for friend than self evaluations than the adolescents that remained ill, suggesting that neural differences related to social evaluations may provide clinical predictive value. Utilization of both MPFC and the precuneus during social and self evaluations may be a key biological component for achieving sustained weight-recovery in adolescents with AN.

1. Introduction

Anorexia nervosa (AN) involves altered perceptions about one's body shape and weight and an inability to maintain one's body weight, and typically begins in adolescence or young adulthood (Nagl et al., 2016). Differences in self-identity have been proposed as a core feature of this illness (Fairchild and Cooper, 2010; Stein and Corte, 2007), and neurobiological differences in midline cortical structures associated with self-perception have been observed repeatedly in adult women with eating disorders when thinking about themselves and others (McAdams et al., 2015, 2016; McAdams and Krawczyk, 2014). However, whether neural differences in self-perception also contribute to AN in adolescents has not been established. Additionally, the relationships between the neural differences in self-perception and specific clinical symptoms in AN is unknown.

Here, we consider these clinical questions by comparing the neural activations during self and other evaluations in adolescent girls with AN (AN-A) and healthy adolescent girls (HC-A) using the same functional magnetic resonance imaging (MRI) task we recently examined in adults with and recovered from AN (McAdams et al., 2016). This imaging task, the Social Identity-V2 task, involves reading and evaluating statements presented with different perspectives. Neurodevelopmental differences in the ability to consider oneself and others have been observed in adolescents compared to adults (Pfeifer et al., 2013, 2007, 2009); here we considered whether AN affects neural activations during

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perspective-taking and mentalization in adolescents.

We hypothesized that eating disorder (ED) clinical symptoms in adolescence would be related to neural activations in regions that differed in adults with AN because many adolescents with AN go on to be adults with AN. Thus, we also explored whether clinical outcomes following treatment of AN in adolescents could be related to neural activations, by collecting clinical follow-up from the AN-A subjects for a year after the scan, and dividing into recovered (AN-AR) and ill (AN-AI) groups based on the course of the disease. We then assessed whether any of the task-related neural activations, obtained soon after treatment, differed based on clinical outcome.

2. Methods

2.1. Participants

Subjects provided written informed consent to participate, approved by the UT Southwestern Institutional Review Board. A total of 42 adolescent girls (13–19 years) participated: 18 healthy comparison (HC-A) recruited from the community and 24 recently treated for AN (AN-A) recruited from both treatment centers and the community. All AN-A subjects met DSM- IV criteria, excluding amenorrhea, within prior year but were weight recovered at the scan to minimize the possibility of effects due to current starvation.

2.2. Clinical measures

Subjects aged 18–19 were interviewed using the Structured Clinical Interview for DSM-IV (First et al., 2002). Patient-participants aged 13–17 and their parents were interviewed using the Kiddie Schedule for Affective and Mood Disorders (Kaufman et al., 1997). The HC-A group, aged 13–19, were screened for psychiatric disorders, and excluded if there was any history of treatment for any mental illnesses. All AN-A participants had been in either a partial hospital and/or intensive outpatient program for AN during the prior 6 months. Treatment duration was defined as the total number of days of involvement in a specialty eating disorder treatment program, defined as an inpatient, residential, partial hospital, or intensive outpatient level of care, prior to the MRI scan.

All subjects completed a structured interview for current depression (Quick Inventory of Depressive Symptoms, QIDS-CR (Bernstein et al., 2010)), and anxiety (Structured Interview Guide for the Hamilton Anxiety Scale, SIGH-A (Shear et al., 2001)). The Wechsler Abbreviated Scale of Intelligence (WASI (Wechsler, 1999)) provided an estimate of intelligence. Self-report measures provided information about current eating symptoms (Eating Attitudes Test, EAT (Garner et al., 1982)) and body shape concerns (Body Shape Questionnaire, BSQ (Rosen et al., 1996)).

Both in-person office visits and phone calls to parents were utilized to determine clinical outcomes, with a minimum of twelve and up to forty-eight months of follow-up obtained after completing the MRI study for 19 of the 24 participants in the AN-A group; five were lost to follow-up. Variability in length of follow-up related to both availability of participants, and acquisition of funding for outcomes was received more than a year after many participants had completed the study. Subjects were designated as recovered if they had succeeded in sustaining weight-recovery and adequate control of eating disorder symptoms such that they remained at either an outpatient or no treatment level for the twelve months following completion of the study, and maintained work and school activities since completing the MRI scan. Subjects were designated as relapsed or ill if they had lost significant weight, or required return to a higher level of care (intensive outpatient, partial hospital, residential, or inpatient) for additional treatment within the first year after completing the MRI study.

2.3. Neuroimaging task, MRI acquisition and processing

The *Social Identity-V2* task (McAdams et al., 2016) involves reading and responding to statements related to thinking about oneself (*Self*, ex. “I believe I am deceitful”), one's friend (*Friend*, “I believe *my friend* is moody”), or what one's friend thinks of them (*Reflected*, “*My friend* believes I am proud”). In the *Friend* and *Reflected* conditions, the term friend was personalized with the actual name of a female friend. Each statement was presented above the terms *Agree* and *Disagree* for 4 s, with a response selected each trial, followed by a jittered fixation period of 4, 6, or 8 s. There were 48 statements in each of three runs; 16 statements for each condition resulting in a total duration of 8 min per run. All statements for each condition were sequential, and condition order pseudorandomized across runs. During each trial, each subject provided a rating of agreement using a hand-held button, providing behavioral data that included a reaction time and response (*Agree* or *Disagree*).

Images were acquired with a 3T Philips Achieva MRI scanner, using a 1-shot gradient T2*-weighted echoplanar (EPI) image sequence sensitive to blood oxygen level-dependent (BOLD) contrast with a repetition time (TR) of 2 s. For Social Identity-V2, the echo time (TE) was 35 ms, and the flip angle was 70°; volumes were composed of 36 axial slices (4 mm thick, no gap). Each slice was acquired with a 22.0 cm^2 field of view, a matrix size of 64×64 and a voxel size of $3.4 \times 3.4 \times 4$ mm. Functional images were acquired during 4 runs (3 for *Social Identity-V2,* each 480 s). High resolution MP-RAGE 3D T1-weighted images were acquired for anatomical localization with the following imaging parameters: TR = 2100 ms, TE = 3.7 ms; slice thickness of 1 mm with no gap, a 12° flip angle, and 1 mm^3 voxels.

Functional MRI task data were analyzed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience London, www.fil.ion.ucl.ac.uk/spm) run in Matlab 2012 (http://www.mathworks.com) and viewed in both SPM and xjview (http://www.alivelearn.net/xjview8/). Preprocessing began with motion-correction performed by aligning each image spatially to the first volume of acquisition, using least-squares minimization to determine the best-fit for a six-parameter, rigid-body spatial transformation. The realigned functional images were normalized to the MNI standard template, and spatially smoothed with a 6 mm full-width at half-maximum 3D Gaussian kernel. The voxel time-series was high pass filtered (128 s). An event-related design extracted the BOLD signal during the 4-s presentation of each statement or image and a general linear model created contrast images of each event (events: *Self-Agree, Self-Disagree, Friend-Agree, Friend-Disagree, Reflected-Agree, Reflected-Disagree*). Evoked activation was assessed using multiple regression analysis set as boxcar functions. Each regressor was convolved with a canonical hemodynamic response function (HRF) provided in SPM8 and entered into the modified general linear model (GLM). Parameter estimates (e.g. β values) were extracted from this GLM analysis for each regressor. The within-subject first level analysis evaluated the three a priori task contrasts (*Self* − *Friend, Self-Agree* − *Self-Disagree*, *Reflected* − *Self*) for each subject.

2.4. Group statistical comparisons

Demographic and clinical measures (Age, BMI, WASI, QIDS, SIGH-A, EAT, BSQ) were compared using two-tailed independent-sample t-tests (Criterion $p < 0.05$) and the behavioral measures (mean reaction time and percentage with agreement) were examined with a two-way mixed ANOVA examining both condition (*Self*, *Friend*, *Reflected*) and group (AN-A, HC-A). All statistical