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Altered Habenula to Locus Coeruleus Functional Connectivity in Past Anorexia Nervosa Suggests Correlation with Suicidality: A Pilot Study

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Abstract

Purpose: Despite anorexia nervosa having the highest mortality rate of mental illnesses, little is known regarding the brain mechanisms involved. Given that lack of interest for food in anorexic patients is related to alterations in the reward system, we tested the hypothesis that patients with past anorexia nervosa (pAN) have altered resting state functional connectivity (RSFC) between the habenula (a major component of the reward system) and its targets.

Methods: RSFC between the habenula and major targets (locus coeruleus, median and dorsal raphe nuclei, substantia nigra, and ventral tegmental area) was studied in 14 psychiatric inpatients with pAN and 14 psychiatric inpatient controls (PC, never-anorexic patients in same clinic, matched for comorbidities). Next, we tested possible correlations between RSFC and suicidal ideation, depression, and anxiety as determined by self-report questionnaires.

Results: Left habenula/locus coeruleus RSFC was lower in pAN patients compared to PC. The left habenula/locus coeruleus RSFC was positively correlated with suicidal ideation (past two months) in pAN patients but not in controls.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study., and the Baylor IRB approved the study.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conclusions: pAN patients showed long lasting alterations in habenular connectivity. This may have clinical implications, possibly including future evaluation of the habenula as a therapeutic target and the need to carefully monitor suicidality in pAN patients.

No level of evidence: basic science.

Keywords

habenula; resting state functional connectivity; anorexia nervosa; suicide; reward circuitry

1. Introduction

Anorexia nervosa (AN) affects 0.9% of American women and 0.3% of American men in their lifetimes, has the highest mortality rate of all mental illnesses, and 20% of AN deaths are suicides [1]. These patients also have a high incidence of comorbid mental illnesses: 33–50% with mood disorders and ~50% with anxiety spectrum disorders [2]. The neural correlates of the disorder have been an active field of study for several years. The general current view is that brain regions involved in the reward circuit, including frontal cortex, insula, and striatal regions are implicated in AN pathophysiology. Thus, it is likely that reward/punishment signals are important in AN [3]. In addition, resting state functional connectivity (RSFC) have implicated the default mode network [4,5], the dorsal anterior cingulate cortex [6], and precuneus [7,6] as likely players in AN. In addition, advances in understanding of the brain circuitry possibly associated with AN and with other eating disorders have resulted in the testing of promising neuromodulatory techniques such as transcranial magnetic stimulation [8].

The habenula (Hb) is a small, bilateral midbrain structure that receives input from frontal and basal ganglia regions. The lateral Hb primary targets include the dorsal and median raphe nuclei, locus coeruleus (LC), substantia nigra, and ventral tegmental area. When reward is less than expected, lateral Hb activity increases, suggesting the Hb has a major role in learning from undesirable events [9]. Patients with AN learn best from punishment, or undesirable events [10]. We therefore hypothesized that the Hb could play a role in AN. Hb activation affects downstream neurotransmitter systems that are involved in altered reward (dopamine), mood (serotonin), and anxiety/stress (norepinephrine). The hedonic reward of food may be altered in patients with AN, and Hb functional connectivity may contribute to this process [11]. The prediction error (difference between expected and obtained reward, signaled by the Hb), which is critically important for survival as it allows for reward-based learning, is altered in AN patients [12], and sensitivity to reward and punishment are extremely important features of AN [13]. Furthermore, conditions frequently comorbid with AN such as depression, anxiety, and substance abuse, may also be affected by Hb function. Taken together, the literature suggests the Hb may play a role in AN.

To our knowledge, previous studies have not investigated a possible role of the Hb in AN, except for our work on cancer cachexia/anorexia, which showed altered habenular connectivity in those patients [11]. This study aimed to determine RSFC alterations between the Hb and its major targets in pAN. We hypothesized that pAN patients may continue to have altered brain connectivity, and that such alterations may be clinically relevant. We were

also interested in whether such connectivity alterations correlate with levels of suicide ideation, depression, and anxiety, which are highly comorbid with AN.

2. Material and Methods

2.1 Participants.

The McNair Initiative for Neuroscience Discovery – Menninger/Baylor (MIND-MB) is a study collecting clinical, imaging, and genetics data of psychiatric patients (N=423 at the time of this study) at the Menninger Clinic (Houston, TX) to identify biomarkers of psychiatric illness. Patients mainly presented with depressive, bipolar, substance use, anxiety, and personality disorders, with over 80% having comorbid conditions. Further description of the MIND-MB cohort and citations for the clinical instruments used can be found elsewhere [14]. We used this dataset to select 28 adult psychiatric inpatients: 14 pAN patients and 14 psychiatric controls (PC) (Table 1). The Institutional Review Board approved procedures and participants gave signed, informed consent. Psychiatric inpatients were recruited for this study and informed consent was obtained from patients only after their clinician determined they were suitable to consent.

The Structured Clinical Interview for DSM-IV (we used DSM-IV because the parent project started before DSM5 was available and we did not want to change parameters during data collection) Axis I Disorders (SCID-I) defines AN as defined having an intense fear of becoming overweight, low body-image, the absence of three or more consecutive menstrual cycles and the refusal to maintain minimally healthy weight. This study considered patients having these characteristics prior to their admittance to the Menninger Clinic (N=12). Additionally, 2 patients with an intense fear of becoming overweight, low body-image, and absence of three or more consecutive menstrual cycles were included as pAN; however, they maintained a healthy weight prior to their acceptance to the clinic. pAN (N=14) and PC (N=14) groups were created to have no (or minimal) differences for comorbid disorders as defined by SCID-I, SCID-II, suicide ideation, sex, and age. Fifty-seven percent of pAN patients presented with anxiety disorders and 100% with mood disorders. For correlations between dimensional symptoms and imaging parameters, we used the PHQ-9 (depression), GAD-7 (anxiety), and Columbia-Suicide Severity Rating Scale (suicide ideation). We believe the study of pAN is of interest because it has been shown that even after recovery from AN, former patients show a harm avoidant and perfectionist personality. These personality traits make pAN a possibly high risk group, which is often overlooked in terms of research [15].

2.2 Imaging.

Imaging was performed only for research purposes. Once the clinician associated to a patient gave her or his approval, patients were approached to participate in the study. Brain imaging was thus performed as close to admission as possible, usually with 4–5 days. A 3T Siemens Trio MR scanner at the Baylor College of Medicine Core for Advanced Magnetic Resonance Imaging in Houston, TX was used. Participants underwent a structural MPRAGE (4.5 min, 2.66 ms echo time (TE), 1200 ms repetition time (TR), 12° flip angle, 256×256 matrix, 160 1×1×1 mm voxels, axial slices) and resting state echo planar imaging (EPI) scan

(5 min, 40 ms TE, 2 s TR, 90° flip angle, 3.4×3.4×4 mm voxels). Images were realigned to the first image in the time series, slice-time corrected, segmented, normalized to the MNI EPI template, functionally normalized, and outliers detected using the Artifact Detection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/) within the CONN Functional Connectivity Toolbox.

2.3 RSFC analysis.

Hb targets were selected as *a priori* regions of interest (ROIs): Dorsal and median raphe nuclei, LC, substantia nigra compacta, and ventral tegmental area. Hb ROIs (images were resampled to 3×3×3 mm) were created manually using Statistical Parametric Mapping (SPM) 8 software for individual patients. The Hb coordinates were individually hand-picked by one investigator, while a second investigator did a sub-sample of the Hb coordinates and obtained the same findings. This strategy to pick individual habenula ROIs (Fig. 1A left panel) was used before in our lab and resulted in RSFC between the habenula and the rest of the brain that highly resembles that obtained by other group [16,17].

Using the MNI atlas, other ROIs were defined in the software AFNI. Noise was removed using band-pass filtering and linear regression using the anatomical component correction (aCompCor) method. After preprocessing, first-level analysis was performed using CONN v15.b. Variables of no interest in the general linear model (GLM) were cerebral spinal fluid, white matter, and realignment/scrubbing. The BOLD time series was extracted from the habenula seed and correlated with the BOLD time-series signal of the target seeds to obtain Pearson's Correlations. Functional connectivity values were then calculated as bivariate Fisher's z-transformed correlation coefficients for left/right Hb to each ROI.

2.4 Statistical analyses.

RSFC between left and right Hb to the dorsal raphe nucleus, median raphe nucleus, LC, substantia nigra (right and left combined), and ventral tegmental area (right and left combined) were studied using t-tests to compare pAN and PC (these are ten comparisons, therefore we used a $p=0.05/10=0.005$ as "statistically significant"). No additional covariates were included as there were no significant differences between pAN and PC in diagnostic comorbidity, sex, or age (Table 1). Note that the lack of differences was actually forced by choosing 14 PC that would match the comorbidities of the 14 pAN studied patients.

RSFC was also tested between the Hb and all other brain regions in the Automatic Anatomical Labeling (AAL) atlas in an explorative analysis (N=116 regions).

Suicidal ideation (lifetime and past 2 months), depression (past 2 weeks), and anxiety (past 2 weeks) assessments were obtained within 17 days of admittance to the clinic (mean = 4 days) using the Columbia Suicide Severity Rating Scale and Patient Health Questionnaire modules 7 and 9. Correlations were assessed between the values for significant RSFC results and values for the above clinical measures. No multiple comparison corrections were used for correlations, so correlations (and in fact this whole manuscript, as stated in the title) should be regarded as pilot.

3. Results

Left Hb/LC RSFC was significantly lower in pAN than in PC ($p=0.0042$) (Fig. 1B). Other RSFC studied were not significantly different between pAN and PC.

A positive correlation was found between the Left Hb/LC RSFC and suicide ideation in the past 2 months ($p=0.037$) in the pAN sample (Fig. 1C). The correlation with lifetime ideation in the pAN sample was nearly significant ($p=0.061$).

In the exploratory analysis, eight connections were different between pAN and PC. These RSFC were right Hb/rolandic operculum ($p=0.037$), and left Hb/left supplemental motor area ($p=0.014$), /right parahippocampus ($p=0.009$), /left amygdala ($p=0.039$), /right occipital inferior gyrus ($p=0.025$), /left cerebellum 3 ($p=0.041$), /right cerebellum 10 ($p=0.003$), and /vermis 1 and 2 ($p=0.001$). These are highly preliminary, as 116 regions were studied and no multiple comparison corrections were used.

4. Discussion

The Hb/LC RSFC was lower in patients with pAN when compared to PC. The LC is the main producer of norepinephrine, a neurotransmitter affecting stress, attention span, sleep, and memory [18]. Increased levels of norepinephrine can lead to feelings of anxiety, irritation, and insomnia whereas decreased levels of norepinephrine can cause a shortened attention span and a lack of energy. As these symptoms are correlated with depression and suicide ideation severity, altered Hb/LC signaling could cause abnormal levels of norepinephrine and be associated with suicidal tendencies in pAN [18]. Accordingly, we found a positive correlation between Hb/LC RSFC and suicide ideation over the past two months, with a possible correlation for lifetime suicide ideation. However, no correlation was found on PC, making this finding a pAN-specific effect.

In the whole-brain exploratory analysis, eight additional connections were found with the most significant being between the left Hb and the right parahippocampus, right cerebellum 10, and the vermis 1 and 2. Due to multiple comparisons, these data are highly exploratory. Parahippocampus connectivity has been seen to be altered in patients with current AN when viewing images of themselves, suggesting that the parahippocampus may play a role in body image in AN [19]. Our data would suggest that the habenula, probably through the negative prediction error, may influence that relationship. The cerebellum has been shown to affect the regulation of emotions and people's eating patterns, indicating that the connections of the right cerebellum 10 and vermis 1 and 2 may be worth further exploration.

The main comparison consisted of psychiatric inpatients with and without pAN, instead of between patients with pAN and healthy controls. This allowed for us to control for effects of comorbid diagnoses and created, in our view, a more representative sample than in the traditional imaging approach of comparing to a narrowly defined sample to healthy controls: there were no differences in comorbidities between pAN and PC suggesting RSFC differences were not affected by comorbidities.

Paradoxically, pAN showed lower Hb/LC RSFC than PC, but the higher the connectivity, the stronger the suicide ideation in pAN only. We hypothesize that Hb/LC RSFC increases in pAN patients may be part of a neural feedback mechanism that on one hand may have helped regularize some AN symptoms, while on the other hand may correlate with an increase in suicide ideation. Since there was no correlation between Hb/LC RSFC and suicide ideation in PC, we hypothesize that the appearance of such correlation in pAN is a sub-product of either anorexia, or anorexia recovery. Interestingly, in our exploratory results we showed increased left Hb/right parahippocampus RSFC in pAN as compared to PC. We have shown before that increases in this connectivity are associated with suicide ideation [20], which suggests that the RSFC between left Hb and LC and between left Hb and parahippocampus may be associated. The correlation could, of course, be a false positive, and replication is necessary before assigning possible clinical importance to the finding. The complexity of the system highlights the necessity of performing this type of experiment using different kinds of populations for comparison.

There are possible clinical implications for this work. In the short term, implementing enhanced clinical follow up with pAN patients to specifically check on suicidal ideation even after symptoms of AN are no longer present would be easy to implement in many clinics. In the longer term, our results argue that habenular activity may be a therapeutic target for AN, and for suicide ideation in pAN. Given small size, deep brain location, and scarcity of specific activity modulators, the habenula is a very hard target for medications. However, several strategies could be employed, from pharmacological such as nicotinic and opioid receptor blocker combinations [16], or neuromodulatory techniques such as focused ultrasound [21].

The main limitation of this study was sample size. However, among the few RSFC studies of pAN or AN, most reports used between 10 and 20 participants per group, with only one study with 35 participants per group. Additionally, the Hb is composed of medial and lateral nuclei, each having different connectivity and functions. As the 3T MRI has inadequate resolution to differentiate between medial and lateral Hb, these RSFC results cannot be attributed to a specific Hb region. Despite Hb functional imaging being difficult due to its small size, our RSFC data for the Hb are consistent with that published by another group [17]. When all patients were used (N>400), we found many similarities between our data and that from Ely et al: Hb RSFC was highest with the thalamus and high with the ventral tegmental area, substantia nigra (left higher than right), parahippocampal gyrus (left higher than right), and anterior and posterior cingulate [16,17]. Both studies found negative connectivity between Hb and occipital gyrus, lingual gyrus, and cuneus. Another limitation is that we used only 5 minutes of resting state, while a longer time may be better. In addition, we classify patients as “past AN” or not based on results from DSM-IV, but we had no detailed information about exactly when each patient had AN, what treatment (if any) they followed, or how severe was it in terms of malnutrition. Finally, RSFC is a correlational measure and no causal conclusions should be made.

Future studies should use larger sample sizes and further explore other regions involved in reward or suicidality. Further studies of the Hb should occur to determine if it could be studied as a possible therapeutic target for pAN. Finally, the hypothesized compensatory

mechanism suggests that pAN patients with higher Hb/LC RSFC may be the most vulnerable to suicide deation. Additional studies should determine whether this population needs to be monitored for suicidality even after remission.

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Figure 1: Habenular resting state functional connectivity (RSFC) in psychiatric inpatients with past AN. A. Indicates location of seed placement for the left habenula (Hb, manually located). B. Resting state functional connectivity for Hb to LC ($p = 0.0042$). C. Correlation between monthly suicide ideation and left Hb to LC RSFC ($p = 0.037$).

Table 1:

Demographics and Clinical Characteristics

Demographic	Psych. Controls (n = 14)	Past Anorexic (n = 14)	P-value
Gender (Men/Women)	(1/13)	(1/13)	1
Age (Mean)	35	32	0.52
Major Depressive Disorder	11	10	0.83
Bipolar	3	4	0.71
Anxiety Disorders	8	8	1
Suicidality	4	7	0.37
Substance Abuse	11	10	0.83
Personality Disorders	9	10	0.82

Patient mean age and total number of comorbid psychiatric disorders between patients with past anorexia nervosa and psychiatric controls. Major depressive disorder includes single and recurring major depressive disorder. Bipolar includes bipolar disorder 1, 2, and other. Anxiety disorders includes generalized anxiety disorder, post-traumatic stress disorder, social phobia, agoraphobia, and anxiety not otherwise specified. Substance abuse includes alcohol abuse and dependence and substance abuse and dependence. Personality disorders include avoidant personality disorder, obsessive-compulsive personality disorder, schizotypal personality disorder, narcissistic personality disorder, borderline personality disorder, and antisocial personality disorder. P-values were determined by a Chi-squared test between the groups (except for age, t-test) with a significant value set at p is less than 0.05.