Tracking temporal response dynamics in the ventral striatum during social feedback in anorexia nervosa: A functional magnetic resonance imaging exploratory study

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Abstract

Objective: Research suggests abnormalities in reward-based processes in anorexia nervosa (AN). However, few studies have explored if such alterations might be associated with different temporal activation patterns. This study aims to characterize alterations in time-dependent processes in the ventral striatum (VS) during social feedback in AN using functional magnetic resonance imaging (fMRI). **Method:** 20 women with restrictive-subtype AN and 20 age-matched healthy controls (HC) underwent a social judgment experimental fMRI task. Temporal VS hemodynamic responses were extracted in SPM for each participant and each social condition (acceptance/rejection). **Results:** Compared with age-matched HC, patients with AN showed a significant time by group interaction of peak VS response throughout the task, with a progressive blunting of peak activation responses, accompanied by a progressive increase in baseline activity levels over time. **Discussion:** The results suggest an attenuated response pattern to repetitive social rejection in the VS in patients with AN, together with a difficulty in returning to baseline. The information obtained from this study will guide future, design-specific studies to further explore alterations temporal dynamics.

KEYWORDS

anorexia nervosa, functional magnetic resonance imaging, reward system, social reward, ventral striatum

1. INTRODUCTION

Anorexia nervosa (AN) is commonly associated with an impairment of social information processing, considered a vulnerability factor for the development and maintenance of the disorder (Treasure, Corfield & Cardi , 2012). Social responses in normal development are partly processed by the same mesocorticolimbic brain network involved in basic reward (Krach, 2010). Literature supports differences in reward processing in AN within regions of the reward circuit such as the ventral striatum (VS) (Zhu et al., 2012).

Our group conducted an fMRI experiment involving positive and negative social feedback in women with AN to evaluate brain reward responses to social stimuli (Via et al., 2015). While VS activation did not differ between groups in the whole-brain analysis, its activity during negative feedback was positively correlated with illness severity. The study did not evaluate temporal dynamics, and we hypothesized that time-dependent processes of VS responses after repetitive exposure to positive or negative feedback might have masked putative between-group differences. To further explore this question, the present study presents a secondary and exploratory analysis of the same data aiming to assess the temporal response of the VS to social feedback in individuals with AN. The information obtained from this study will guide future, design-specific studies.

Based on prior research (Kaye, Fudge, & Paulus, 2009; Wierenga et al., 2014), we hypothesized that patients with AN would demonstrate progressively attenuated VS activity to repeated acceptance feedback. As for the rejection condition, we posed two possible scenarios. Considering the role of the VS in regulating social distress and the heightened sensitivity to social rejection in AN (Cardi, Matteo, Corfield, & Treasure, 2013), we anticipated that the AN group would show a progressive increase (sensitization) in VS responses. Another possible outcome would be a blunted activity to repetitive negative feedback (habituation).

2. MATERIALS AND METHODS

2.1 Participants

Twenty women with AN, restricting subtype, according to DSM-IV-TR criteria (American Psychiatric Association, 2000) were recruited from the day patient program of the Bellvitge University Hospital Eating Disorders Unit (Barcelona) as described in Via et al. (2015). Diagnoses were conducted by experienced psychologists/psychiatrists (E.V., I.S., F.F-A.) using the Structured Clinical Interview for DSMI-IV Axis I Disorders (SCID) (First, 2007). Comorbid psychiatric disorders, neurological conditions and substance abuse except for nicotine were exclusion criteria. Twenty age-matched HC women were recruited from the same sociodemographic area. This screening was conducted by means of the General Health Questionnaire (GHC-28) (Artal & Pérez-Echeverría, 1986) and the SCID. Control women had no history of psychiatric or neurological conditions. The ethical committee of clinical research (CEIC) of the Bellvitge University Hospital approved the study protocol, which was in compliance with the national legislation and the principles expressed in the Declaration of Helsinki. All participants gave written informed consent after detailed description of the study.

2.2 Clinical variables

Current eating disorder symptoms were assessed using the self-reported Eating Disorder Inventory-2 (EDI-2) scale (Garner, 1991). Depressive and anxiety symptoms were measured by the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959).

2.3 Social judgment paradigm

The fMRI task used in the current study was a modification of the social judgment experiment originally reported in Davey et al. (2010). Briefly, participants were asked to participate in a multi-center study about the influence of first impressions. They were shown a face database containing 70 people's faces and asked to decide (Likert-type scale) whether they would like to meet them in person or not (acceptance/rejection). Additionally, each participant had a picture of themselves taken and was told that it would be sent and reciprocally scored by the other participants. Five days after this first assessment, participants underwent the fMRI social judgment task; they were shown 54 of the previously rated faces and were informed of acceptance (happy face symbol on the screen) or rejection (sad face symbol) feedback. Neutral faces formed the control condition and appeared when people supposedly could not be contacted. The database actually consisted of photographs selected from a larger public database (Martínez & Benavente, 1998), and the real nature of the study was disclosed at the end of the experiment.

2.4 Behavioral measures

After the scanning session, a 10-point Likert-type scale was used to evaluate the participants' subjective experience after each type of feedback. Participants' subjective experience when receiving each type of feedback was compared between groups and conditions using a 3x2 analysis of variance (ANOVA).

2.5 Clinical and sociodemographic analyses

Sociodemographic variables were compared between groups using a two-sample t-test. Additionally, two-sample t-tests were conducted to compare severity and psychological eating disorders features (EDI-2), anxiety (HARS) and depressive symptoms (HDRS) between groups. Analyses were performed in SPSS v22.0. Level of significance was set at $p<0.05$.

2.6 Imaging acquisition and preprocessing

Imaging data were collected with a 1.5-T Signal Excite system (General Electric Milwaukee, WI, USA) magnetic resonance equipped with an 8-channel phased array head coil and single-shot echoplanar imaging software. The functional sequence consisted of gradient recalled acquisition in the steady state (repetition time (RT) = 2,000 ms, echo time (TE) = 50 ms and pulse angle, 90^0) in a 24 cm field of view, 64 x 64 pixel matrix, slice thickness of 4 mm (inter-slice gap, 1.5 mm). Twenty-two interleaved sections, parallel to the anterior-posterior commissure line, were acquired to generate 216 whole-brain volumes (voxel size: 3.75 x 3.75 x 4). Four initial dummy volumes were excluded to allow the magnetization to reach equilibrium.

Data were processed on a personal computer equipped with Microsoft Windows operating system running Matlab 7.14 (The Math-Works, Inc.) and statistical parametric software version 8 (SPM 8). Within participants, time-series images were first slice-timing corrected to adjust for temporal differences in image acquisition. Thereafter, images were realigned to the mean image (6-parameter rigid body transformation), normalized (to the standard echoplanar imaging (EPI) template in SPM) and resliced to Montreal Neurological Institute (MNI) space, $2mm^3$, and smoothed using an 8 mm isotropic Gaussian filter. Normalized and smoothed images were routinely inspected for potential movement or artifacts (motion exclusion criteria being >2mm translational and >2° rotational movement). Criteria about movement parameters were met for all participants except one HC participant, who was excluded.

2.7 fMRI data processing and analysis

At first single-subject level of analysis, each stimulus duration was convolved with a canonical hemodynamic response function to model the acquired BOLD signal. The model was built using the finite impulse response analysis approach (FIR) in SPM. Temporal regressors were included in each first level general linear model (GLM) to model the temporal response of the VS along the social feedback stimulus and the entire duration of the task. We considered three phases of social feedback stimulus response (early response—2s after feedback presentation—, middle—2s to 4s—, and late response—4s to 6s—). Then, we also considered three periods of equal duration throughout the task (the 7,2-minute task was divided into three periods of 144 seconds—17 volumes—). Therefore, each one of the task conditions (acceptance, rejection and neutral) included 9 regressors corresponding to early-mid-late-feedback stimulus response phase for each of the three task periods (the total number of regressors was 27).

For the purpose of this study, only the acceptance and rejection conditions were carried into following analyses. Second level random-effects group analyses in SPM (a between-group t-test model) were used to extract VS temporal data for each one of the 9 modeled time points (e.g., early stimulus response phase for the first part of the task, early stimulus response phase for the mid part of the task, late stimulus response phase for the last part of the task, etc.), for each condition of interest (acceptance/rejection), using the SPM eigenvariate function. We used a VS mask created from a given set of coordinates (+/-9.9,-8; 8mm spheres) corresponding to the nucleus accumbens (Harrison et al., 2009).

2.8 fMRI statistical analysis

Single-subject VS temporal activation data obtained for each condition were transferred to a SPSS database. A first visual plotting of the data showed that the mean VS stimulus response at task response was an inverted u-shape, with the early and late responses to the stimuli (seconds 1-2 and 5-6) being the valleys of the u-shape and the middle response (seconds 3-4) being the peak.

We used an ANOVA model to analyze changes in both the maximum peak intensity and the valley points of this inverted-u along the three periods of the task. In a first 3x2 repeated measures ANOVA, the Peak Response at the three parts of the task was included as the within-group variable, and Group (AN patients, HC) as the between-group variable. In a second 3x2 repeated measures ANOVA, the sum of the two Valley Responses (seconds 0-2 and 4-6) at each one of the three parts of the task were included as the within-group variable, and Group (AN patients, HC) as the between-group variable. This was conducted separately for both conditions (acceptance/rejection)

3. RESULTS

3.1. Demographic variables and clinical behavioral assessments

There were no statistically significant differences in age, handedness or educational level between patients and controls. Mean EDI-2 scores, anxiety and depressive symptoms were significantly higher in the AN group. There were no interaction effects or between-group differences on the subjective experience after any type of feedback, and all of them liked more being accepted than rejected ($p<.001$) or receiving no feedback ($p<.001$).

3.2. Main analyses

3.2.1. Acceptance

Peak Response: There was a significant effect of time ($F(2,74)=6.84$, $p=.002$). The effect was driven by an increase in the peak of the VS response between the first and the third parts of the task ($F(1,37)=8.13$, $p=.007$), i.e. the mean intensity signal at the peak of the VS shape response was higher at the end of the task (after repetitive stimuli presentation) compared to the beginning. When stratifying by group, this effect was only significant in controls ($F(1,18)=5.36$, $p=.033$).

Valley Response: There were no significant effects.

(Figure 1 and Table 1).

3.2.2. Rejection

Peak Response: There was a significant effect of time by group ($F(2,74)=4.64$, $p=.013$). The interaction was driven by an increased peak response between the first and third parts of the task ($F(1,37)=9.66$, $p=.004$). When stratifying by group, this effect was only significant in controls ($F(1,18)=7.61$, $p=.013$)

Valley Response: There was a significant effect of time ($F(2,74)=4.01$, $p=.022$). The effect was driven by an increase of the valley response between the first and third parts of the task ($F(1,37)=6.01$, $p=.019$) and between the second and third parts of the task ($F(1,37)=4.14$, $p=.049$). When stratifying by group, this effect was only significant in the patient's group and comparing the first and third parts of the task (F(1,19)=4.87, p=.040).

The Rejection condition shows that patients present an increase in baseline activation throughout the task in addition to a progressively blunted peak response (Figure 1 and Table 1).

4. DISCUSSION

The evaluation of VS ventral striatum temporal dynamics in AN during social feedback evidenced few, but some differences, that should be tested in a future study designed to evaluate temporal dynamics in the VS. The most relevant result was found during rejection: AN participants showed a progressive flattening of VS peak response when exposed to repeated rejection, accompanied by a progressive increase in baseline activity levels.

Evidence of temporal patterns of striatal response in healthy population has shown a sustained striatal BOLD signal to salient stimuli (Delgado, 2007). The difficulty of returning to baseline levels and the flattening effect of the peak VS response observed in our AN group during social rejection might suggest a maladaptive response of the VS in this context and could be interpreted as a difficulty of the structure to flexibly adjust to challenging social scenarios, but should be taken with caution and considering the limitations of this exploratory study.

Several limitations warrant consideration. Given that the original task was not specifically designed to evaluate temporal information and the small sample, our results should be interpreted with caution. However, this fMRI approach might provide useful information about temporal neural activity in AN using a larger sample. Our study was limited to AN low-weight adult women with no comorbidities, so future research should explore a variety of populations. The study was conducted on a 1.5 Tesla magnet, which may have limited the ability to detect signal from certain regions. Future, design-specific studies focused in the temporal dynamics of brain activity should take into consideration these aspects.

CONFLICT OF INTEREST

The authors have no conflicts to declare.

ETHICS STATEMENT

The ethical committee of clinical research (CEIC) of the Bellvitge University Hospital approved the study protocol, which was in compliance with the national legislation and the principles expressed in the Declaration of Helsinki. All participants gave written informed consent after detailed description of the study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, EV and NC, upon reasonable request.

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Figure Legend

FIGURE 1. Within and between-group ventral striatum peak and valley activations along the task

For each condition (acceptance, rejection), the task was divided into three temporal periods. The mean ventral striatum (VS) stimulus activation response at each one of these periods was an inverted u-shape, being the valleys of the u-shape the first 2 seconds after feedback presentation ("early") and the last 2 seconds of feedback presentation ("late"), whereas the peak of the u-shape was the middle response (seconds 3 and 4, "middle"). For the rejection condition, a significant effect of time by group in the peak response is observed (patients are represented by a red line, HC by a blue line). Additionally, there is a significant effect of time in the valley response driven solely by the patients group (red line). The graphic representation of these results shows both a progressive lack of return to baseline levels in the patient group, as well as a progressive blunting of task shape response. For the acceptance condition, it is observed a significant effect of time, driven by the HC group, represented by a progressive increase in the peak response (blue line).