Research Paper

Intact value-based decision-making during intertemporal choice in women with remitted anorexia nervosa? An fMRI study

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Background: Extreme restrictive food choice in anorexia nervosa is thought to reflect excessive self-control and/or abnormal reward sensitivity. Studies using intertemporal choice paradigms have suggested an increased capacity to delay reward in anorexia nervosa, and this may explain an unusual ability to resist immediate temptation and override hunger in the long-term pursuit of thinness. It remains unclear, however, whether altered delay discounting in anorexia nervosa constitutes a state effect of acute illness or a trait marker observable after recovery. **Methods:** We repeated the analysis from our previous fMRI investigation of intertemporal choice in acutely underweight patients with anorexia nervosa in a sample of weight-recovered women with anorexia nervosa (n = 36) and age-matched healthy controls (n = 36) who participated in the same study protocol. Follow-up analyses explored functional connectivity separately in both the weight-recovered/healthy controls sample and the acute/healthy controls sample. **Results:** In contrast to our previous findings in acutely underweight patients with anorexia nervosa, we found no differences between weight-recovered patients with anorexia nervosa and healthy controls at either behavioural or neural levels. New analysis of data from the acute/healthy controls sample revealed increased coupling between dorsal anterior cingulate cortex and posterior brain regions as a function of decision difficulty, supporting the hypothesis of altered neural efficiency in the underweight state. **Limitations:** This was a cross-sectional study, and the results may be task-specific. **Conclusion:** Although our results underlined previous demonstrations of divergent temporal reward discounting in acutely underweight patients with anorexia nervosa, we found no evidence of alteration in patients with weight-recovered anorexia nervosa. Together, these findings suggest that impaired value-based decision-making may not constitute a defining trait variable or "scar" of the disorder.

Introduction

Although many people have difficulty avoiding temptation from unhealthy foods and sticking to a nutritious diet, people with anorexia nervosa seem to resist hunger and restrict caloric intake with relative ease. This unusual ability is often assumed to reflect an excessive (self-destructive) amount of self-control (defined as the capacity to inhibit inappropriate or undesired responses in the pursuit of long-term goals[1]), and/or a generalized reward sensitivity,[2–4] both of which may contribute to maintenance of the disorder.[5]

To understand the seemingly exaggerated self-control and paradoxical reward-related decision-making in anorexia nervosa, studies have employed delay-discounting (or "intertemporal choice") paradigms.[6] Delay-discounting tasks require participants to make a series of decisions between small rewards (typically monetary) given immediately (or relatively soon) and larger ones delivered later; these tasks enable researchers to estimate the rate at which the subjective value of a reward decreases over time (i.e., temporal reward discounting). The discounting rate is thought to gauge impulsivity,[7] such that a greater preference for more immediate rewards (i.e., steeper discounting) is often assumed to reflect a relative lack of self-control and vice versa. For example, steeper discounting has been observed in disorders characterized by deficient impulse control[8] and is less steep as a function of self-control development.[9] Consistent with the clinical presentation of anorexia nervosa suggestive of excessive self-control, 4 studies of acutely underweight patients have reported decreased (i.e., less steep) discounting relative to healthy controls.[9–12] However, these findings were in predominantly chronic adult samples, and intertemporal choice

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can be highly dependent on task-specific variables.[13,14] Furthermore, altered discounting is not universal in anorexia nervosa.[6,14,15] For example, using a task with a demonstrated ability to discriminate between age groups known to differ in self-control,[16] we found no group differences in discounting rates in 2 independent adolescent acutely underweight samples relative to healthy controls.[17,18] Suggesting that an increased capacity to delay reward may reflect a state-related effect of acute undernutrition, 1 study in short-term weight-recovered anorexia nervosa[11] and 2 studies in long-term weight-recovered anorexia nervosa found no behavioural evidence of altered discounting.[17,19]

Functional MRI (fMRI) studies indicate that temporal reward discounting involves 2 primary neurocognitive processes: value-dependent processing and executive decision-making.[20,21] Value-dependent processing involves encoding the subjective value of rewards, and it activates regions that include the ventral striatum and ventromedial prefrontal cortex. Executive decision-making involves the actual choice based on comparisons between options and activates regions that include the lateral prefrontal cortex and posterior parietal cortex.[22,23] To date, only 3 fMRI studies have investigated temporal reward discounting in anorexia nervosa. Decker and colleagues[11] found that activation in reward-related cingulostriatal circuitry in adults with acute anorexia nervosa was decreased relative to healthy controls before treatment and increased after short-term weight recovery. In contrast, we found no differences in valuation circuitry in adolescents with acute anorexia nervosa, but reduced lateral prefrontal cortex and posterior parietal cortex activation, suggestive of altered decision-making efficiency.[18] This hypothesis was supported by consistently faster choice behaviour and decreased activation for difficult decisions in the dorsal anterior cingulate cortex (dACC), a region recruited to overcome cognitive conflicts.[24] In long-term weight-recovered patients, Wierenga and colleagues[19] found abnormal insensitivity to metabolic state (hunger, satiety) in reward valuation networks and elevated activation in executive control regions. These partially discordant results may be due to differences in study design, patient cohorts and analysis strategies.

Given the importance of distinguishing between state and trait factors associated with anorexia nervosa,[25,26] we sought to clarify whether divergent behavioural and/or neural correlates of delay discounting in anorexia nervosa are characteristic only of acute undernutrition (state marker), as suggested by previous studies,[9–12,18] or may also be present in long-term weight-recovered women with a history of anorexia nervosa (trait marker). To this end, we repeated our previous analysis focused on acutely underweight patients with anorexia nervosa[18] in a sample of weight-recovered women and age-matched healthy controls who participated in the same study protocol. To follow up on the results, we carried out separate additional investigations of functional connectivity using data from the weight-recovered/healthy controls sample at the focus of the current analyses and at the focus of the original acutely underweight/healthy controls sample.[18]

Methods

Participants and assessments

A total of 135 female volunteers participated in our greater fMRI study of delay discounting, which took place between March 2013 and July 2016: 34 acutely underweight patients with anorexia nervosa (age 12–22 yr), 39 long-term weight-recovered patients with anorexia nervosa (age 15–27 yr) and 62 healthy controls (age 12–27 yr). The study was approved by the institutional review board of the Technische Universität Dresden, and all participants (or their legal guardians) gave written informed consent.

In an attempt to disentangle trait from state factors while minimizing potentially confounding effects of (neuro)development, our study was designed to conduct separate (but identical) analyses in separate age-matched case–control samples of acutely underweight patients with anorexia nervosa versus healthy controls (King and colleagues[18]) and long-term weight-recovered patients with anorexia nervosa versus healthy controls (the current investigation). To be included in the current analyses, weight-recovered participants had to have previously met DSM-IV diagnostic criteria for anorexia nervosa and maintain a body mass index (BMI) above 18.5 kg/m^2 (or BMI > 10th percentile if age < 18 yr); menstruate; and have not binged, purged or engaged in significant restrictive eating behaviour for at least 6 months. To be included in the healthy controls group, participants had to be in the same age range as the weight-recovered sample, have a normal body weight (BMI 18.5–24.9 kg/m^2 or > 10th percentile if age < 18 yr); be eumenorrhoeic; and have no history of psychiatric illness (n = 42). Weight-recovered patients were individually age-matched to healthy controls using an automated search algorithm for optimal pairs.[27] Data for 9 participants (3 weight-recovered, 6 healthy controls) were excluded because of abnormal choice behaviour in the prescan calibration session (discounting rates > 3 standard deviations [SD] from the sample mean) or the fMRI experiment (> 10% invalid trials, defined below; 3 weight-recovered participants, 4 healthy controls) or because of scanner artifacts (2 healthy controls), resulting in a final sample of 36 in each group.

The behavioural data for 14 weight-recovered participants collected during the prescan calibration task had already been included in our behavioural pilot.[17] The behavioural and imaging data from 14 healthy controls were already included in our fMRI investigation focused on acute anorexia nervosa.[18] The current investigation, focused on long-term weight-recovered anorexia, also includes a follow-up functional connectivity analysis (described below) in the original acutely underweight/healthy controls sample.[18] A full description of this sample can be found in Appendix 1, available at jpn.ca/180252-a1.

The diagnostic procedures and inclusion and exclusion criteria used in the current investigation were identical to those used in our previous analyses.[17,18] We obtained pertinent information, including potential confounding variables (e.g., medication, comorbidities), using the SIAB-EX[28] structured interview, supplemented with our own semi-structured interview.

Comorbid psychiatric diagnoses in weight-recovered participants were taken from medical records and confirmed by an experienced psychiatrist after careful chart review, including consideration of medical and psychiatric history in addition to psychiatric screening instruments (detailed below). Participants completed the Eating Disorder Inventory–2[29] and the Beck Depression Inventory II.[30] We estimated IQ using short versions of the Wechsler Intelligence Scale for Children[31] or the Wechsler Adult Intelligence Scale.[32] We computed BMI SD scores[33,34] to provide an age-corrected index.

Study data were managed using Research Electronic Data Capture.[35]

Task

Participants performed the same 2-part intertemporal choice task used in our previous fMRI analysis in acutely underweight patients with anorexia nervosa.[18] They first performed a prescan calibration session, which included 50 choices between a fixed small immediate reward (€20; "smaller sooner," SS) or a larger amount to be paid after a delay (10, 30, 60, 120 or 180 days; "larger later," LL). Based on these choices, we estimated the individual discount parameter k as a metric of self-control and adapted the amounts and delays of rewards in the main fMRI task accordingly (Appendix 1). Participants performed the main fMRI task (Fig. 1) immediately after the calibration session. Before the main task began, participants were informed about the amount of the SS reward (fixed value between €5 and €15), which was determined based on the individual k value. Pairs of amounts and delays of rewards were calculated in advance and presented randomly across the task (for sample pairs, see Appendix 1, Table S1). The 5 delays in the main fMRI task were the same as in the calibration session. To encourage realistic choices, participants were told that 1 of their decisions would be randomly selected, and they would receive the reward either immediately after scanning (for an SS choice) or later by bank transfer (for an LL choice).

Behavioural data analysis

Behavioural data analysis was analogue to that in our previous analyses[17,18] and originally described by Ripke and colleagues.[16] For group comparison of the k parameter (2-sample t test), we used log-transformed values because they better fit a normal distribution. We gauged decision quality during the main fMRI task by analyzing response consistency, defined as the frequency at which the alternative with the higher subjective value was chosen. We computed area under the curve (AUC) as a consistency metric, which is higher for more consistent participants (i.e., always choosing the reward with the higher subjective value results in an AUC of 1; complete randomness of choices would yield an AUC of 0.5). We carried out group comparison of AUC (2-sample t test) with rank-transformed values, because they were not normally distributed. Decisions for a reward whose subjective value was lower than half of the alternative option and trials without a response were regarded as invalid and excluded (mean ± SD 3.4 ± 6.8 trials). An additional behavioural measure was mean reaction time on valid trials of the main fMRI session. We analyzed reaction-time data using a 2 (chosen reward: SS v. LL) × 2 (group: weight-recovered participants v. healthy controls) repeated-measures analysis of variance (ANOVA).

Image acquisition, processing and analysis

Image acquisition and preprocessing was analogue to that of King and colleagues[18] (Appendix 1). Importantly, in contrast to the only other fMRI study of delay discounting in long-term weight-recovered anorexia nervosa, which focused on the influence of metabolic state (hunger, satiety),[19] we controlled

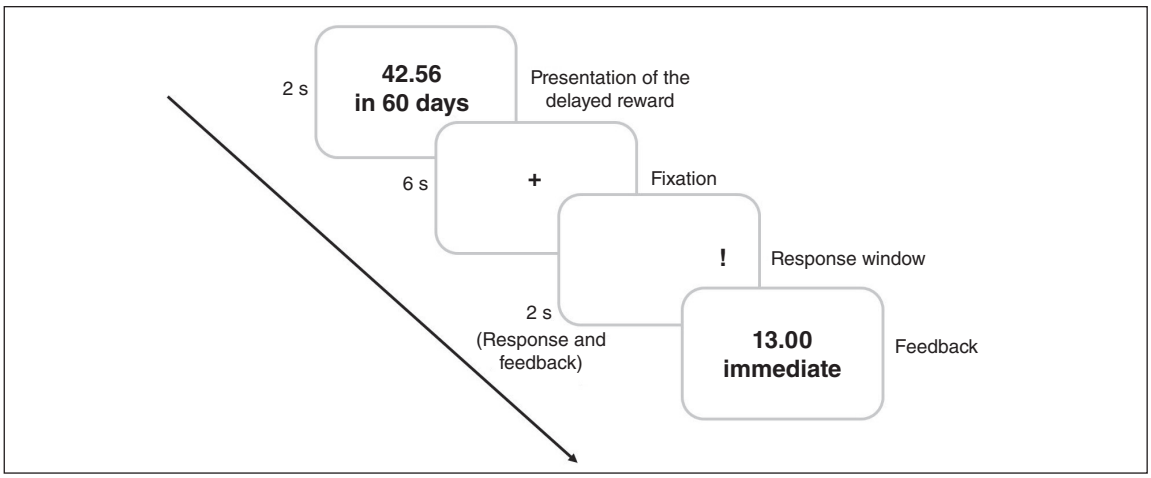

Fig. 1: Intertemporal choice task. Each of the 90 trials of the main task performed during functional MRI began with the presentation of the larger later (LL) amount and the respective delay (2 s), followed by a fixation period (6 s) and a response window (2 s). During the response window, an exclamation mark presented on the left or right side of the screen indicated which button was mapped to the LL amount for that trial. Decisions for the delayed reward (LL) were mapped to the right button in half of the trials and the left button in the other half. Each trial ended with feedback confirming the decision, followed by a jittered interval with an average duration of 7 s.

for potential group differences by scanning all participants between 0800 h and 0900 h following an overnight fast. First-level statistical analysis was based on a least squares estimation using a generalized linear model. As in King and colleagues,[18] the primary model consisted of the following regressors: (i) onsets of the delayed rewards; (ii) the subjective value of the delayed reward as a parametric modulator of (i); (iii) onsets of the response/feedback phase; (iv) invalid trials; and (v) the 6 realignment parameters/outlier volumes as nuisance regressors. In this model, regressor i was assumed to capture activity associated with executive decision-making, and regressor ii reflected correlation of this activity with subjective value. All events (0 duration) were modelled using the canonical synthetic hemodynamic response function. To confirm expected activation patterns in regions associated with decision-making (lateral prefrontal cortex and posterior parietal cortex) and valuation (ventral striatum and ventromedial prefrontal cortex), we first ran 2 independent 1-sample *t* tests corresponding to regressors i and ii, respectively. Our main analyses tested for group differences between weight-recovered participants and healthy controls in these processes with 2 corresponding 2-sample *t* tests. As in King and colleagues,[18] we also explored potential group differences in value-dependent processing by estimating an additional generalized linear model with separate regressors for SS and LL decisions followed by a 2-sample *t* test of the SS versus LL contrast.

Also as in King and colleagues,[18] we estimated an additional generalized linear model designed to identify activation associated with decision difficulty. As in several other studies (see Koffarnus and colleagues[36]), we defined decisions as "hard" if the ratio between the immediate reward/subjective value of the delayed reward was close to the individual indifference point (i.e., ratio close to 1; between the 25th and 75th percentile); we defined all other decisions as "easy" (i.e., ratio far from 1; beyond the 25th or 75th percentile; Appendix 1). We inspected both the main effect of decision difficulty (hard > easy; 1-sample *t* test) and potential group differences (hard > easy; 2-sample *t* test) in both an exploratory whole-brain search and a targeted analysis restricted to the dACC volume, in which we previously observed a group × difficulty interaction.[18]

To control for false positives, we performed family-wise error (FWE) correction for multiple comparisons using 3DClustSim (http://afni.nimh.nih.gov/afni; "fixed" version, compiled June 2017). Specifically, we used the program to run 10 000 Monte Carlo simulations to estimate the cluster size above which the false positive probability was below a given α level ($\alpha_{FWE} = 0.05$) for a given cluster-defining threshold ($p < 0.005$), corresponding to a combined threshold of $p_{FWE} < 0.05$. Based on our previous findings of a group difference in dACC activation associated with decision difficulty,[18] we also computed small-volume-corrected (SVC) thresholds ($p_{FWE,SVC} < 0.05$) using 3dClustSim to assess effects in this region of interest in the current weight-recovered/healthy controls sample.

The decision difficulty analysis described above revealed a main effect (hard > easy) in a region of the dACC overlapping the one in which we had previously observed a group × difficulty interaction in acutely underweight anorexia nervosa[18] and was consistent with previous studies,[35] but we found no group difference between weight-recovered particiopants with anorexia and healthy controls (see Results). Nevertheless, to test for potential group differences in connectivity between this and other brain regions as a function of decision difficulty, we carried out a generalized psychophysiological interaction analysis (gPPI; Appendix 1).[37] Based on the finding of no group differences (see Results), we carried out a follow-up gPPI analysis in the acutely underweight/healthy controls sample from our previous analysis[18] (Appendix 1, Table S2). The seeds for the 2 gPPIs were all voxels belonging to the respective clusters (hard > easy) in the dACC observed in the weight-recovered/healthy controls sample (main effect of difficulty; $x = 6$, $y = 20$, $z = 46$; 321 voxels) and the acutely underweight/healthy controls sample (group × difficulty interaction; $x = -10$, $y = 30$, $z = 28$; 580 voxels) at an uncorrected voxelwise threshold of $p < 0.005$.

Additional analysis designed to specify the results of whole-brain analysis in the dACC region of interest was carried out by extracting mean β parameter estimates as described in Appendix 1.

Results

Behavioural results

Demographic and clinical characteristics are summarized in Table 1. Weight-recovered participants with anorexia nervosa did not differ from healthy controls in terms of age, IQ, or current BMI, but they did show elevated eating disorder and depressive symptoms.

In line with our previous behavioural findings of no group difference as assessed by the discount rate k_{17}, the weight-recovered group (mean ± SD 0.006 ± 0.006) did not differ from the healthy controls group (mean ± SD 0.007 ± 0.006; $T_{70} = 0.9$; p = NS; Fig. 2A).

Confirming that adaptation of the main experiment to produce an equal number of decisions for SS and LL rewards was successful, we found that the number of valid decisions for SS rewards (mean ± SD 42.9 ± 5.9) did not differ from that for LL rewards (mean ± SD 43.7 ± 6.9; $F_{1,70} = 0.3$; p = NS). Importantly, the groups did not differ either in the ratio of valid SS:LL decisions ($F_{1,70} = 0.9$; p = NS) or generally in the number of valid choices ($F_{1,70} = 0.5$; p = NS). As expected from our fMRI investigation,[18] reaction times for valid decisions were generally faster for LL rewards (639 ms) relative to SS rewards (723 ms; $F_{1,70} = 176.1$; $p < 0.001$). However, contrary to the between-group differences indicative of consistently faster decision-making in acutely underweight patients with anorexia nervosa,[18] weight-recovered participants did not differ from healthy controls, either in this respect ($F_{1,70} = 0.2$; p = NS) or generally for decision-making speed ($F_{1,70} = 1.5$; p = NS).

Regarding the consistency at which participants chose rewards with a higher subjective value, AUC values estimated

in weight-recovered participants (mean ± SD 0.94 ± 0.05) did not differ from those in healthy controls (mean ± SD 0.95 ± 0.05; $T_{70} = 1.5$; p = NS; Fig. 2B).

fMRI results

One-sample t tests inspecting the main effects of value-dependent processing and executive decision-making confirmed expected activation patterns (Appendix 1, Fig. S1 and Fig. S2). More importantly, in contrast to our previous findings of decreased frontoparietal activation in acutely underweight anorexia nervosa,[18] a 2-sample t test revealed no significant differences between participants with weight-recovered anorexia nervosa and healthy controls in the analysis targeting executive decision-making. Similarly, we found no significant group differences in the main parametric analysis targeting value-dependent processing or in an exploratory analysis of the basic SS versus LL contrast.

We suggested that reduced frontoparietal activation in acutely underweight anorexia nervosa might reflect altered neural efficiency of decision-making.[18] This interpretation was supported by consistently faster choice behaviour in the patient group and decreased activation for hard versus easy decisions in the dACC, a region involved in resolving conflict between competing decisions.[24] In the current comparison of participants with weight-recovered anorexia nervosa versus healthy controls, no group activation differences associated with decision difficulty were evident. However, in line with previous intertemporal choice studies,[36] a main effect of hard > easy activation was present in a region of dACC that overlapped the one in which we previously found acutely underweight participants with anorexia nervosa to show a blunted response to difficult decisions (Fig. 3; Appendix 1, Fig. S3).[18] Because the lack of a difference between weight-recovered participants with anorexia nervosa and healthy controls in mean dACC activation does not preclude potential group differences in functional connectivity, we carried out a between-group gPPI analysis in which decision difficulty (hard > easy) served as the psychological variable and dACC activity served as the physiologic variable. Results again revealed no significant group differences. Motivated by this null finding in weight-recovered participants with anorexia nervosa — as well as by the question posed from our previous findings in acutely underweight participants as to whether neural connections between affected brain regions might be altered[38] — we carried out an analogue gPPI analysis with data from the original acutely underweight/healthy controls sample.[18] Results indicated increased coupling as a function of decision difficulty (hard > easy) in acutely underweight participants with anorexia nervosa (relative to healthy controls) with a broad region spanning from the right postcentral gyrus across the inferior parietal lobule and sensorimotor cortex into the middle temporal cortex (peak $x = 64$, $y = 52$, $z = 12$; $T = 4.13$; 1513 voxels; Fig. 4).

Table 1: Demographic variables and clinical measures*

Variable	Recovered	Healthy controls	t	p value
Age, yr	22.2 ± 3.3	21.2 ± 3.4	1.3	0.2
IQ	110.2 ± 9.1	110.6 ± 8.3	0.2	0.8
Minimum lifetime BMI, kg/m^2	14.2 ± 1.5	20.0 ± 1.6	16.0	< 0.001
Current BMI, kg/m^2	21.1 ± 1.9	21.6 ± 1.8	1.2	0.2
Current BMI-SDS	–0.39 ± 0.6	–1.3 ± 0.6	1.7	0.08
Duration of illness, mo	35.3 ± 23.4	—	—	—
Duration of recovery, mo	57.4 ± 40.8	—	—	—
BDI-II score	3.1 ± 5.2	0.55 ± 1.3	2.8	< 0.01
EDI-2 total score	173.1 ± 56.1	147.8 ± 38.8	2.2	< 0.05
Drive for thinness†	20.3 ± 9.3	14.9 ± 7.9	2.6	< 0.05
Body dissatisfaction†	31.5 ± 12.2	25.4 ± 10.4	2.2	< 0.05
Bulimia†	11.2 ± 4.4	11.3 ± 4.1	0.1	0.9

BDI-II = Beck Depression Inventory-II; BMI = body mass index; BMI-SDS = body mass index standard deviation score; EDI-2 = Eating Disorder Inventory-2; SSRI = selective serotonin reuptake inhibitor.
*Findings are shown as mean ± standard deviation for each variable. Of the participants with weight-recovered anorexia nervosa (recovered), 26 (72.2%) were predominantly of the restrictive subtype and 10 (27.8%) were predominantly of the binge/purge subtype during acute illness, as ascertained using the SIAB-EX[28] interview. Of the weight-recovered participants, 10 had a history of 1 or more formal comorbid psychiatric diagnoses (9 major depression, 4 anxiety disorder, 1 obsessive–compulsive disorder), including 2 who had active comorbid diagnoses (both major depression) and were taking SSRIs at the time of participation.
†Subscales of EDI-2.

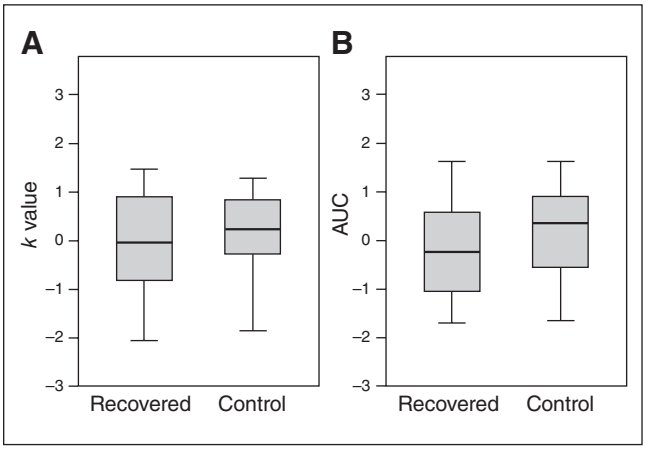

Fig. 2: Main behavioural results. (A) Logarithmized and z-standardized k values estimated from choice behaviour during the prescan calibration session for patients with weight-recovered anorexia nervosa (recovered) and healthy controls. (B) Rank-transformed and z-standardized area under the curve (AUC) values estimated from choice behaviour during the main task for the recovered and control groups.

Discussion

In contrast to our previous findings in acutely underweight patients with anorexia nervosa using the same analysis procedures,[18] the current analyses did not detect any group differences between weight-recovered patients with anorexia nervosa and healthy controls, on either a

behavioural or neural level. Specifically, whereas acutely underweight patients with anorexia nervosa showed faster and more consistent choice behaviour, decreased frontoparietal activation associated with decision-making and abnormally decreased dACC activation for difficult decisions relative to healthy controls,[18] no analyses in the current weight-recovered/healthy controls sample (including an analysis of functional connectivity, which was not conducted in our original analyses of acute anorexia nervosa) revealed any significant group differences. Interestingly, however, a main effect of decision difficulty (hard > easy) was evident in the same region of the dACC previously identified in acutely underweight patients with anorexia nervosa,[18] and new analysis of data from our acutely underweight/healthy controls sample revealed increased coupling between this region with a widespread region located predominantly in the right inferior parietal and sensorimotor cortex in patients during hard versus easy decisions. Assuming that more coordinated interregional brain activity reflects more efficient (and less costly) use of neural resources,[38] increased connectivity between the dACC and posterior cortex during difficult decisions dovetails with our previous findings, which gave rise to the hypothesis of altered neural efficiency in patients with acute anorexia nervosa.[18] Accordingly, a relative decrease in frontoparietal activation during decision-making (as observed in King and colleagues[18]) and more synchronous processing during difficult decisions (as observed in the new gPPI analysis in our acute/healthy controls sample) may be a consequence of the habitual tendency to execute control and restraint that is characteristic of the disorder. Together, these findings underline previous studies that demonstrated altered behavioural[9,10,12] and neural[11,18] correlates of delay discounting in acutely underweight patients with anorexia nervosa and provide novel support suggesting that impairments in value-based decision-making (as assessed with the intertemporal choice paradigm) may not be significantly pronounced in the disorder following weight recovery.[11,17,19]

An important question in the study of cognitive-behavioural disturbances in anorexia nervosa is whether deviations relative to healthy individuals reflect state-related consequences of starvation, chronic sequelae ("scars") or causal (or predisposing) trait factors.[25,26] While characterizing premorbid

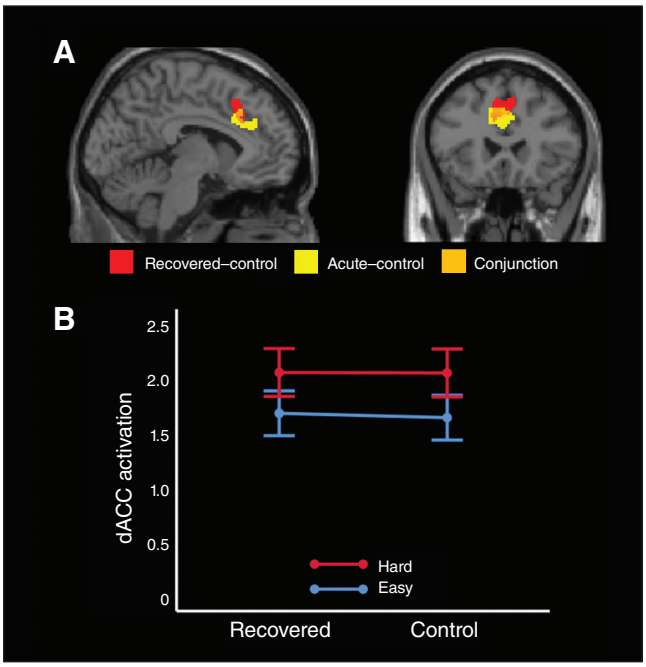

Fig. 3: Activation of the dorsal anterior cingulate cortex (dACC) during difficult decisions. (A) Regions of the dACC showing greater activation as a function of decision difficulty (hard > easy) in the weight-recovered anorexia nervosa/healthy control sample from the current analyses (red region; main effect of decision difficulty; $x = 6$, $y = 20$, $z = 46$; $t = 3.63$; 321 voxels), and decreased hard v. easy activation in patients with acute anorexia nervosa relative to healthy controls from our previous analyses[18] (yellow region; group × decision difficulty interaction; $x = -10$, $y = 30$, $z = 28$; $t = 3.58$; 580 voxels). Findings are shown at a voxel-wise threshold of $p < 0.005$ to illustrate their overlap (orange region; 92 voxels; $p_{FWE,SVC} < 0.05$). No other significant main effects or interactions were evident in the recovered/control or acute/control comparisons at this statistical threshold. (B) Mean dACC activation for the recovered and healthy control groups on trials with hard and easy decisions (β estimates ± standard error of the mean). A group × difficulty repeated-measures analysis of variance of the β estimates confirmed that while activation was increased in this region for hard v. easy trials ($F_{1,70} = 11.0$; $p < 0.001$), group activation levels did not generally differ ($F_{1,70} = 0.006$; p = NS), and no interaction was evident ($F_{1,70} = 0.023$; p = NS). For qualitative comparisons with the acute sample, age-adjusted dACC activation is shown for all study participants in Appendix 1, Fig. S3. FWE = family-wise error; NS = not significant; SVC = small-volume corrected.

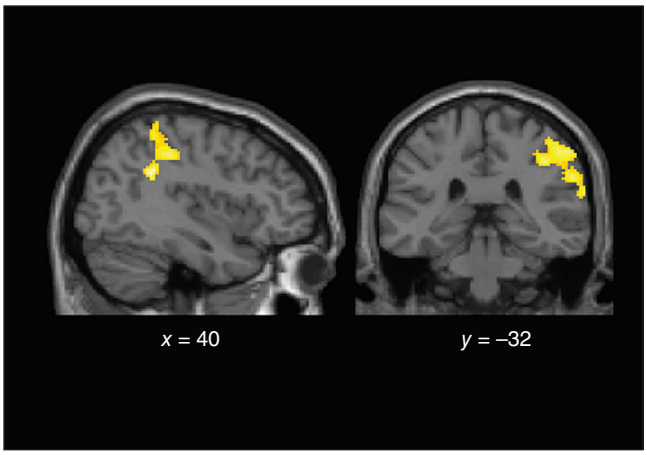

Fig. 4: Altered functional connectivity of the dorsal anterior cingulate cortex (dACC) during difficult decisions in patients with acute anorexia nervosa. Results $p_{FWE} < 0.05$, t map) of a generalized psychophysiological interaction analysis of dACC connectivity as a function of decision difficulty (hard > easy) indicating greater coupling with a broad region of the inferior parietal lobule and somatosensory cortex in patients with acute anorexia nervosa relative to healthy controls, as determined by a new analysis of the data originally analyzed in King and colleagues.[18] Note that no group differences in dACC functional connectivity were detected in an analogue analysis of the data from the weight-recovered anorexia-nervosa/healthy control sample at the focus of the current article. FWE = family-wise error.

traits is difficult, studying weight-recovered patients with anorexia nervosa has added potential for helping distinguish between cause and effect by reducing the confounding influence of acute undernutrition. To date, however, relatively few studies within the broader domain of value-based decision-making have focused on weight-recovered patients with anorexia nervosa. Some behavioural studies have suggested persistent impairments in weight-recovered patients,[39,40] but others found no differences relative to healthy controls.[41,42] Recent reviews concluded that while impairments on a range of tasks (including delay discounting) are pronounced in acutely underweight patients with anorexia nervosa, and that adults may be more affected than adolescents, reward-related decision-making seems to be less disturbed in weight-recovered patients with anorexia nervosa.[43,44] The current (null) findings in weight-recovered participants are generally supportive of this conclusion when considered in conjunction with the group differences previously observed in acutely underweight patients with anorexia nervosa[18] using the same task.

Functional neuroimaging studies of simple reward processing and cognitive control have documented persistent alterations in weight-recovered patients with anorexia nervosa,[4,45,46] but few fMRI studies in the domain of reward-related decision-making (other than delay discounting studies discussed below) have focused on this population. Similar to the current findings of no group differences in dACC function in weight-recovered patients with anorexia nervosa, Ritschel and colleagues[47] found (in contrast to acutely underweight patients[48,49]) no group differences in dACC response to negative feedback in a decision-making task that required participants to adapt choice behaviour to changing reward contingencies.

Most previous studies of intertemporal choice in acutely underweight patients with anorexia nervosa have found discounting rates to be less steep in acutely underweight patients than in healthy controls.[6,9–12] However, longitudinal observation suggests that differences in discounting behaviour may not be detectable after short-term weight recovery,[11,17] and the current study is now the third to find no behavioural group differences in long-term weight-recovered anorexia nervosa.[17,19] Nonetheless, in contrast to the lack of group differences in hemodynamic activity observed in the current study, previous studies in both short- and long-term weight-recovered anorexia nervosa found increased activation regions associated with reward processing[11] and executive decision-making.[19] Although these divergent results may be attributable to differences in patient cohorts, and task designs and analysis strategies may produce substantial differences in behaviour and brain activation,[13] the current findings obtained in a comparatively larger sample suggest that neither delay discounting behaviour nor its neural basis may be a significant marker of value-based decision-making in anorexia nervosa following long-term weight recovery. The underlying neurobiological mechanism remains unclear, but future studies might test whether such dynamic cognitive changes across recovery correlate with changes in brain structure.[50]

Limitations

Although the current behavioural (null) results replicate our previous findings in a largely independent weight-recovered sample[17] and are compatible with those from previous fMRI studies in both short- and long-term weight-recovered anorexia nervosa,[11,19] one noteworthy limitation of the present study is how difficult it is to interpret fMRI (null) results. The lack of group activation differences was surprising given the persistence of anorexia nervosa symptoms, cognitive rigidity,[51] and personality characteristics such as perfectionism and low impulsivity,[52,53] as well as previous findings of altered activation in a range of tasks,[45,46] including delay discounting,[11,19] and even at rest.[54,55] Although we found no evidence of alterations in weight-recovered participants with anorexia relative to healthy controls, it is important to keep in mind that activation may vary significantly between paradigms,[13,14] and the observed null effect may be task-specific. For example, although our task distinguished between individuals who differed in impulsivity,[16,56] the fact that it was designed to elicit equally frequent choices for immediate and delayed rewards may have masked our ability to detect subtle group differences. Another speculative explanation for the absence of group differences in brain function in the current weight-recovered/healthy controls sample might be that potential scar effects were not detectable in our relatively young sample with a relatively short duration of illness (Table 1) or normalization of brain structure following weight recovery.[57] Other possibilities we cannot rule out may be sampling error or insufficient statistical power. Although sufficient power can be reasonably assumed on the basis of previous findings of group differences in smaller samples (including our own) with the same task,[11,18,19] the absence of evidence for group differences between weight-recovered participants with anorexia and healthy controls should not be misinterpreted as proof that value-based decision-making is necessarily "normal" following long-term weight recovery. Finally, although a major strength of the current investigation is its qualitative comparability to our previous analyses in acutely underweight patients with anorexia nervosa,[18] quantitative comparisons are methodologically questionable given the considerable age difference between our weight-recovered/healthy controls sample (mean age: 21–22 years) and our acutely underweight/healthy controls sample (mean age 15–16 yr). To circumvent this limitation, future research should include longitudinal observation.

Conclusion

In contrast to our previous findings in acutely underweight patients with anorexia nervosa,[18] the current analyses in long-term weight-recovered patients with anorexia nervosa found no group differences in either behavioural or neural correlates of intertemporal choice. These results suggest that altered value-based decision-making in anorexia nervosa[11,43,44,49] may not constitute a significant trait factor or "scar" of the disorder. Further research is needed to substantiate this conclusion, ideally using other task variants[14]

(which might include disorder-relevant stimuli) and through longitudinal observation. Nonetheless, we believe the take-home message of the current work — suggesting that the neural substrate of value-based decision-making may not be significantly impaired following recovery from anorexia nervosa — is an encouraging one that can be integrated into therapeutic interventions, including psychoeducation that builds on neuroscientific research.[58–60]

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