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CASE REPORT

Anterior cingulate activity in bulimia nervosa: A fMRI case study

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ABSTRACT. INTRODUCTION: *Eating disordered patients (EDp) who binge-eat appear to present impulse control deficits that influence treatment outcome. The present bulimia nervosa (BN) study tests the function of brain areas involved in top-down control of behavior, associated with the anterior cingulate cortex (ACC), at the individual level.* **METHODS:** *ACC activity was analyzed in two women with BN and one matched control with a reliable and simple cue imperative target paradigm for response anticipation and response conflict processing using an event-related functional magnetic resonance imaging (fMRI) design.* **RESULTS:** *Patients showed meaningful ACC patterns of activation, less recruitment for response anticipation, and abnormal for response conflict, when they had to suppress an inappropriate response.* **DISCUSSION:** *Preliminary evidence suggests a BN neurocognitive model of impaired executive control-related brain activity. Reliable fMRI paradigms may be clinically useful to determine ACC dysfunction in EDp, to inform treatment and track changes.*
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INTRODUCTION

Eating disordered patients (EDp) who binge-eat appear to present deficits in impulse control, which influence treatment outcome (1). A key brain neural substrate in implementing cognitive control of behavior is the anterior cingulate cortex (ACC). The ACC is involved in detecting conflict or errors when simultaneously faced with competing responses, and sending signals to prefrontal cortex (PFC) areas for greater top-down control to adjust subsequent behavior (2). By extension, it is thought that ACC may predict conflict/error likelihood, and prepare (3) and anticipate (4) upcoming responses by strategically allocating attentional processes to facilitate execution. The ACC is also proposed to implement control and response selection directly, given its dense projections to motor areas (5).

Despite the lack of neuroimaging studies aimed at targeting and testing ACC function with reliable tasks in EDp, there are data suggesting that they may present impaired ACC activity. At rest, anorexia nervosa (AN) patients in particular have been shown to exhibit reduced ACC activity (6, 7), even after treatment (8). On the other hand, specifically in response to emotionally relevant binge food stimuli, chronic anorectic and bulimic (9) as well as recovered AN patients (10) show greater ACC activation than controls after controlling for motivational feelings of hunger.

In support of the above indirect evidence about ACC dysfunction in EDp, additional facts already reviewed (11) are highlighted. Firstly, contrary to results in EDp, in healthy volunteers hunger is associated with increased ACC activity, and modulates neural activity during exposure to desired food images. Secondly, ACC dysfunction may underlie the lack of control in the domain of eating in EDp [e.g., binge eating/purging type of AN, bulimia nervosa (BN), binge eating disorder] given the ACC dense connections with the hypothalamus, which is involved in the metabolic regulation of eating. Additionally, ACC dysfunction is established as underlying symptoms that are common in EDp such as negative affect, interceptive awareness, and impulsivity (11). Finally, ACC impairment in the restricting subtype of AN may be explained by an underlying vulnerability that ultimately puts such individuals at increased risk of developing an eating disorder that does include binge eating and/or other impulsive behaviors (12). However, to further address whether there is a top-down control-related ACC dysfunction in EDp, it appears necessary to use reliable cognitive tasks that tap it across different conditions with stimuli unrelated to food/weight. Reliable tasks in concert with high spatial resolution functional

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magnetic resonance imaging (fMRI) may permit the identification of ACC deficits at the individual level. Additionally, we can explore whether these deficits are specific to certain cognitive functions, in order to better focus treatment objectives.

Thus, this case study of two women with BN and one matched control proposes a model of investigation which analyzes ACC activity in relation to response preparation, anticipation and conflict processing by using an fMRI event-related design. For that aim, we used a reliable cue imperative target paradigm to isolate ACC activity related to response anticipation and conflict. Impaired ACC activity in BN was hypothesized in all conditions.

MATERIALS AND METHODS

Participants

Three adult females, two BN patients from the Mount Sinai Eating and Weight Disorders Program and one healthy control participated in the fMRI study. Exclusion criteria were body mass index (BMI) <18.5, prior traumatic brain injury with loss of consciousness, pregnancy, acute intoxication, neurological disorders, seizure disorder, out-of-state residency, and all constraining factors for fMRI. In addition, participants reported to have at least 14 years of full-time education, be medication free, have eaten a light meal (e.g. a sandwich and a drink, though we did not control for total caloric intake) within the 3 hours prior to scanning and not to be hungry, and be on the follicular phase of their menstrual cycle (days 5, the case 1; 7, the control; and 10, the case 2). A signed informed consent approved by the Mount Sinai School of Medicine Institutional Review Board was obtained from each participant prior to the experiment. Participants were reimbursed for participation in the study.

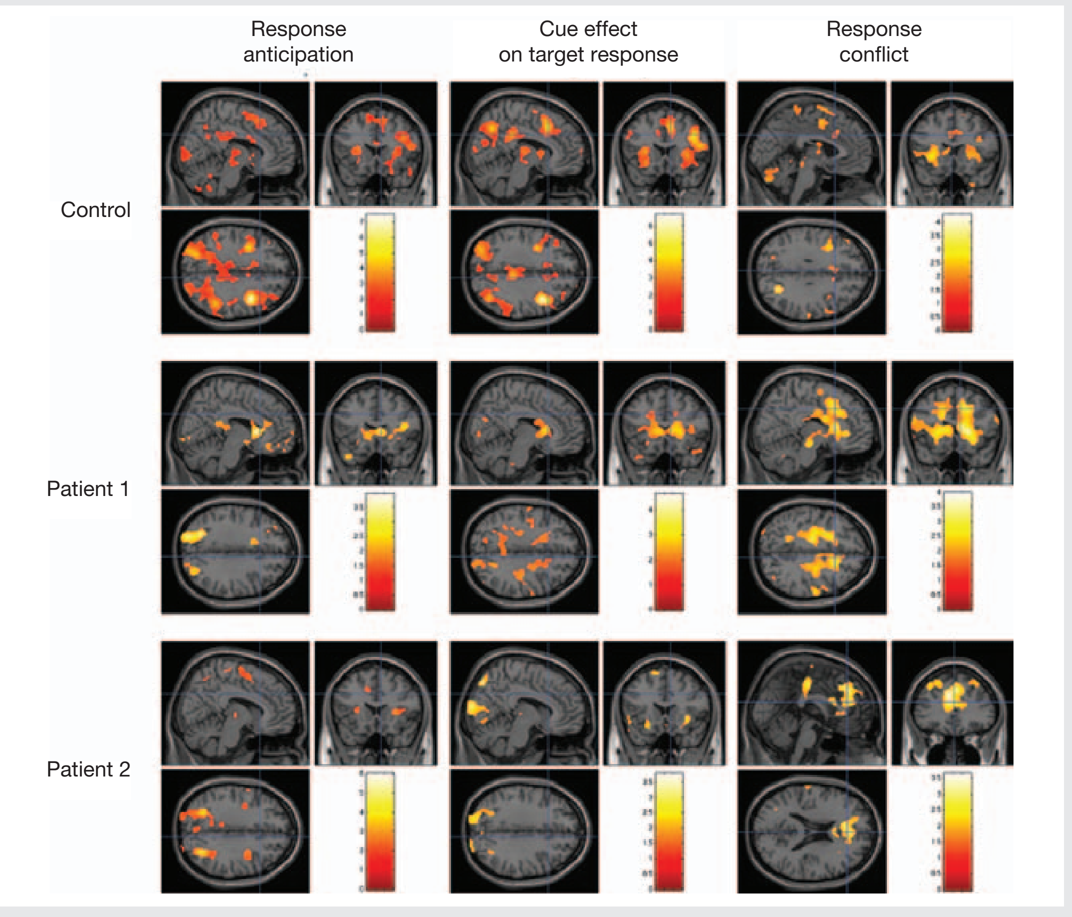

FIGURE 1
Brain activation associated with response anticipation and response conflict in one control subject and two patients.

TABLE 1
Blood oxygenation level-dependent (BOLD) signal in anterior cingulate (ACC) cortex between incongruent and congruent target conditions.

			MNI coordinates					
	Region	*BA*	*x*	*y*	*z*	*Voxel*	*Z*	*p*
Control 1	ACC	32	-4	16	30	107	2.35	0.01
Patient 1	ACC	32	13	16	27	710	3.09	0.001
Patient 2	ACC	32	-4	26	32	535	3.17	0.001

Measures and procedure

Each participant was informed about the study and gave their signed informed consent to participate. They provided demographic information and then completed self-report measures that have demonstrated sound psychometric properties (13-16). BMI was calculated from reported height and weight [BMI= weight (kg)/height (m2)]. The participants were later trained in the behavioral task (17) for 5 minutes before scanning (17).

Behavioral task

This new task was designed to tap a corticostriatal circuit by using principles of established go/no-go and flanker tasks. This task has reliably shown to activate ACC for different cognitive functions. It consisted of two cue conditions: no-cue and cue, subdivided into relax and ready cues (pair of triangles and pair of circles above and below a fixation cross, respectively) for the cue condition; and two target conditions: no-target and target, subdivided into targets with congruent and incongruent flankers for the target condition (an arrow flanked on both sides by either two arrows in the same direction or opposite direction, respectively). Participants were instructed to make a left or right hand response as quickly and accurately as possible to identify the correct direction of the center arrow from the horizontal row of arrows on the screen. The 16 trial combinations of 2 (cue, no cue) x 2 (target, no target) x 2 (congruent, incongruent flankers) x 2 (left, right hand response) were pseudorandomized across 8 runs of 32 trials. The intertrial interval was jittered with an average duration of 8 seconds. Each run lasted 288 seconds. The first and last 16 seconds of each run were resting periods.

RESULTS

The characteristics of the sample and results on the self-report measures and behavioral task are presented for descriptive purposes. Patients' age was 20 and 28 years, and BMI was 21.8 for both of them. The controls' age was 24 years and BMI was 26.4, within the overweight category. On the self-report measures (13-16), the two patients presented significantly higher scores reflecting in all cases more pathological attitudes and behaviors. On the behavioural task, the two patients presented shorter reaction times than the control on the conflict effect (determined by contrasts between the incongruent vs. the congruent target conditions), suggesting greater impulsivity (36.7 and 78.6 vs. 158.8 ms, respectively). However, on the cue effect (determined by contrasts between cued and no cued conditions), one of the patients presented a shorter reaction time while the other took longer than the control (30.8 and 97.8 vs. 45.4 ms, respectively). The percentages of accuracy in patients and the control were similar across all conditions, and in all cases the means were over 0.75.

fMRI contrasts between the ready vs. relax cue conditions, response anticipation effect, activated the fronto-parietal top-down control network (18) and the pre-supplementary motor area in the control subject (Fig. 1), as already seen in healthy volunteers (17). However, in the two patients, there was hypoactivation in these regions. The contrasts between the uncued vs. cued targets and ready vs. relax cued targets showed no significant activation in the patients, but the control showed activation in ACC and other PFC areas such as superior frontal gyrus and middle frontal gyrus (Fig. 1).

fMRI contrasts between the incongruent vs. congruent target conditions, response conflict effect, activated several regions associated with the executive control network in the control and the EDp, mostly the ACC and other PFC. However, the patients demonstrated prefrontal hyperactivation in comparison to a normative control, whose pattern of activation was representative of healthy volunteers (17). In particular, the ACC was over-activated in the patients in comparison to the control (Table 1) (Fig. 1).

DISCUSSION

This novel cognitive neuroscience hypothesis of ACC dysfunction in binge-eating women is consistent with the assumption that ACC dysfunction may underlie binge-eating behavior given the ACC dense connections with the hypothalamus, which is involved in the metabolic regulation of eating as previously outlined. It may also relate to other novel paradigms for cognitive deficits in AN related to implicit learning (19) and the processing of emotionally aversive stimuli (20), given the ACC connections with the striatum and amygdala respectively, which also project into the hypothalamus. However, low weight in AN patients may be a confound.

The present study shows abnormal ACC activation in BN during response anticipation and response conflict processing at the individual level. It appears that patients do not benefit from using the cues to prepare or anticipate upcoming competing responses, and thus, they show increased ACC and PFC recruitment whenever they process conflict, regardless of whether it is expected or not. Consequently, a neurocognitive model of ACC dysfunction is proposed for EDp who binge eat (11), in which the inefficient function of ACC and related areas will correlate with deficits at modulating the recruitment of cognitive control or implementing it, and will contribute to the maintenance and severity of the disorder. For instance, in our environment of food surplus, BN patients are frequently exposed to common conflicting binge-eating stimuli, and ACC hyperactivation, even in states of satiation, will undermine the flexible and effortful recruitment of ACC and related PFC areas for any situation that may require cognitive control leading to binge eating and/or other inappropriate automatic behavior. Likewise, the hypoactivation in the top-down control network related to response anticipation found in the two BN patients suggests an executive function deficit, as has been indirectly shown in women with severe obesity and binge eating by using another very reliable behavioral task (21) that also taps the ACC.

Despite limitations inherent with the case-study design, results seem to confirm the possibility to use this model in larger groups of cases to test if ACC impairment in BN patients in relation to response anticipation and response conflict correlate with binge eating severity. Most importantly, it offers a framework to test new hypotheses in broader samples of patients, and to identify the implications of specific dysfunctional regions within the ACC in EDp characterized by binge eating.

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