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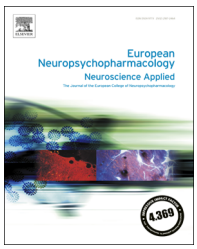

Neural response to catecholamine depletion in remitted bulimia nervosa: Relation to depression and relapse

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Abstract
Bulimia nervosa has been associated with a dysregulated catecholamine system. Nevertheless, the influence of this dysregulation on bulimic symptoms, on neural activity, and on the course of the illness is not clear yet. An instructive paradigm for directly investigating the relationship between catecholaminergic functioning and bulimia nervosa has involved the behavioral and neural responses to experimental catecholamine depletion. The purpose of this study was to examine the neural substrate of catecholaminergic dysfunction in bulimia nervosa and its relationship to relapse. In a randomized, double-blind and crossover study design, catecholamine depletion was achieved by using the oral administration of alpha-methyl-paratyrosine (AMPT) over 24 h in 18 remitted bulimic (rBN) and 22 healthy (HC) female participants. Cerebral blood flow (CBF) was measured using a pseudo continuous arterial spin labeling (pCASL) sequence. In a follow-up telephone interview, bulimic relapse was assessed. Following AMPT, rBN participants revealed an increased vigor reduction and CBF decreases in the pallidum and posterior midcingulate cortex (pMCC) relative to HC participants showing no CBF changes in these regions. These results indicated that the pallidum and the pMCC are the functional neural correlates of the dysregulated catecholamine system in bulimia nervosa. Bulimic relapse was associated with increased depressive symptoms and CBF reduction in the hippocampus/parahippocampal gyrus following catecholamine depletion. AMPT-induced increased CBF in

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this region predicted staying in remission. These findings demonstrated the importance of depressive symptoms and the stress system in the course of bulimia nervosa.

1. Introduction

Bulimia nervosa (BN) is a severe psychiatric disorder defined by recurrent binge eating episodes accompanied by inappropriate compensatory behavior like purging or excessive exercise. Understanding the pathophysiology of BN could guide the development of new and improved treatments for this disorder. Positron emission tomography (PET) and pharmacological challenge studies have implicated aberrant serotonin signaling in BN (Bailer and Kaye, 2011; Kaye, 2008). PET imaging revealed increased binding of the 5-HT_{1A} receptor tracer WAY100635 in ill and recovered BN (Kaye, 2008; Tiihonen et al., 2004), whereas the binding of the 5-HTT tracer 11C-McN5652 did not differ between recovered persons with BN and control participants (Bailer et al., 2007).

Acute tryptophan depletion was followed by increased sadness, body shape concerns, and subjective loss of control of eating in remitted BN (Smith et al., 1999). Monoamine systems interact in a reciprocal manner, such that aberrant serotonin functioning suggests alterations in catecholamine functioning in BN (Tremblay and Blier, 2006). Importantly, abnormal serotonin and dopamine functioning might contribute to different symptoms in BN, as demonstrated in major depression (MDD) (Homan et al., 2015). Whereas tryptophan depletion induced significantly more sadness, hopelessness, and depressed mood, catecholamine depletion induced lassitude, concentration difficulties, inactivity, and somatic anxiety in subjects with remitted MDD (Homan et al., 2015). Indeed, a central role has been proposed for the dopamine system in eating disorders (Frank, 2016): BN is related to a desensitized, and anorexia nervosa (AN) to a sensitized dopaminergic system (Frank, 2013). This thesis is supported by the finding that individuals with BN displayed a reduced activation of the ventral striatum and insula after unexpected delivery of a sucrose solution while participants with AN revealed increased activation in these regions (Frank et al., 2012, 2011). Further evidence for the implication of dopamine in the psychopathology of BN stems from the finding that higher frequency of binge eating is related to lower concentrations of the dopamine metabolite homovanillic acid in the cerebral spinal fluid (Jimerson et al., 1992). An experimental pharmacological challenge study with methylphenidate measuring the binding potential of the dopamine type 2 (D_2) receptor with PET revealed reduced dopamine reactivity in the striatum in individuals with BN (Broft et al., 2012), indicating a deficient dopamine activity, as suggested by Frank (2016). Importantly, experimental catecholamine depletion induced mild eating disorder symptoms, mild depressive symptoms and reward learning deficits in fully remitted bulimia nervosa (rBN) (Grob et al., 2012, 2015). These findings provide causative evidence for the exacerbating action of reduced dopamine activity on psychiatric symptoms linked to BN. Nevertheless, studies relating the behavioral effects of catecholamine depletion to measures of brain functioning are still missing. Therefore, in the present study, we focused on the functional neuroanatomical role of the dysfunctional dopamine system in BN and on its impact on relapse.

Based on our previous findings (Grob et al., 2012, 2015; Homan et al., 2015), we hypothesized that catecholamine depletion will induce lassitude, inactivity, mood and eating disorder symptoms in rBN participants and that this induction will be associated with reduced CBF in basal ganglia and insula in rBN relative to healthy control (HC) participants. In addition, we assumed that the dopamine-related dysfunction revealed by catecholamine depletion will be associated with later relapses in rBN participants.

By using a pseudo-continuous arterial spin labeled (pCASL) perfusion functional magnetic resonance imaging (fMRI) we aimed to examine the influence of catecholamine depletion on resting brain cerebral blood flow (CBF) in rBN and HC participants. This method provides a direct and absolute quantification of CBF, representing neural activity indirectly through the binding between blood flow and neural activity (Detre et al., 2012; Wang et al., 2011). Arterial spin labeling (ASL) fMRI methods are sensitive to assess different conditions of psychological stress (Wang et al., 2005). Moreover, pharmacological manipulation of the central dopamine system was found to influence CBF in dopamine-rich brain regions: A single dose of haloperidol was reported to increase CBF in the striatum, midcingulate cortex, and motor cortex, and decease CBF in the inferior temporal gyrus in healthy individuals (Handley et al., 2013). In addition, metoclopramide, a dopamine D_2 receptor antagonist, increased CBF in the pallidum, putamen, and thalamus and decreased CBF in the insula and anterior temporal lobes (Fernández-Seara et al., 2011). For investigating our hypotheses, we analyzed the perfusion imaging data using a region of interest (ROI) approach to assess specifically the effect of catecholamine depletion in the basal ganglia and insula. We furthermore conducted a voxel-wise analysis, as we may assume that cathecolamine depletion has a high likelihood to induce CBF alterations in brain regions beyond these ROIs.

2. Experimental procedures

2.1. Participants

Eighteen female participants in remission from BN (rBN), and 22 female healthy volunteers (HC) with no history of any psychiatric disorder and no major psychiatric condition in first-degree relatives participated in this study. We included only females in the study because previous studies had reported a higher prevalence of BN in women and had described gender differences in the pathogenesis of BN (Hoek and Hoeken, 2003; Hudson et al., 2007; Nagl et al., 2016; Weltzin et al., 2005). All rBN participants had previously met the DSM-IV criteria for BN, and had been in remission without any binge eating