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Striatal dopamine type 2 receptor availability in anorexia nervosa

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ABSTRACT

The neurobiology of anorexia nervosa remains incompletely understood. Here we utilized PET imaging with the radiotracer [^{11}C]raclopride to measure striatal dopamine type 2 (D_2) receptor availability in patients with anorexia nervosa. 25 women with anorexia nervosa who were receiving treatment in an inpatient program participated, as well as 25 control subjects. Patients were scanned up to two times with the PET tracer [^{11}C]raclopride: once while underweight, and once upon weight restoration. Control subjects underwent one PET scan. In the primary analyses, there were no significant differences between underweight patients ($n=21$) and control subjects ($n=25$) in striatal D_2 receptor binding potential. Analysis of subregions (sensorimotor striatum, associative striatum, limbic striatum) did not reveal differences between groups. In patients completing both scans ($n=15$), there were no detectable changes in striatal D_2 receptor binding potential after weight restoration. In this sample, there were no differences in striatal D_2 receptor binding potential between patients with anorexia nervosa and control subjects. Weight restoration was not associated with a change in striatal D_2 receptor binding. These findings suggest that disturbances in reward processing in this disorder are not attributable to abnormal D_2 receptor characteristics, and that other reward-related neural targets may be of greater relevance.

1. Introduction

The neurobiology of anorexia nervosa (AN) is incompletely understood. Current theories regarding the neurobiology of this illness are wide-ranging, and include hypotheses relevant to the possible placement of AN within the "internalizing" spectrum of disorders, including mood disorders, anxiety disorders, and obsessive compulsive disorder (OCD) (Forbush et al., 2010), as well as hypotheses which suggest that brain reward systems may be altered in AN, thus altering motivation and responses towards food reward stimuli [reviewed in (Kaye et al., 2013)]. As the striatal dopamine (DA) system bears potential relevance to both conceptualizations of this illness, the current study sought to assess brain reward circuitry in AN through evaluation of striatal dopamine D_2 receptor levels (specifically, D_2 receptor availability for tracer binding) using Positron Emission Tomography (PET) neuroimaging with the radiotracer [^{11}C]raclopride.

The striatal D_2 receptor is one of five dopamine (DA) receptor subtypes in the brain, with high concentration in the striatum. Within the striatum, the D_2 receptor acts as a presynaptic autoreceptor, regulating the release, re-uptake, and synthesis of DA; postsynaptically, it is also present on medium spiny neurons regulating outflow tracts from the striatum (Beaulieu and Gainetdinov, 2011; Ford, 2014). The striatal D_2 receptor's role in reward processing has been considered in previous clinical studies. For example, studies of the striatal D_2 receptor in healthy human subjects have been performed using PET neuroreceptor neuroimaging with tracers such as [^{11}C]raclopride, which binds the D_2 family of receptors (including D_3 and D_4 receptors), indicating that striatal D_2 receptor availability (as measured by "binding potential") may influence preferences for rewards (Volkow et al., 1999; Volkow et al., 2002). Whether such findings might relate to clinical expression of the extreme avoidance of food reward seen in AN is as yet unknown. Additionally, the striatal DA system, and specifically the D_2 receptor, is thought to influence cognitive flexibility, a neurobiological dimension thought to be impaired in disorders including OCD (Klanker et al., 2013) and AN (Tchanturia et al., 2014; Treasure and Schmidt, 2013). Therefore, the striatal D_2 receptor may bear relevance to the behaviors of AN from a variety of

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neurobiological perspectives. Studies of the striatal D_2 receptor have also been conducted across a large range of mood, anxiety, and substance use disorders–disorders which are all of potential relevance to AN. While findings across mood and anxiety disorders have been somewhat discrepant (reviewed in the discussion), a large number of studies utilizing PET imaging techniques with [^{11}C]raclopride have been conducted in substance use disorders, demonstrating decreased striatal D_2 receptor availability in these conditions [reviewed in (Trifilieff and Martinez, 2014; Volkow et al., 2009)]. Similar findings of diminished striatal D_2 receptors have been seen in a smaller number of studies of obesity (de Weijer et al., 2011; Volkow et al., 2008; Wang et al., 2001), and a trend towards diminished striatal D_2 receptors was observed in a previous study in bulimia nervosa (Broft et al., 2012).

To our knowledge, only two published studies to date have evaluated striatal D_2 receptor availability in patients with AN compared to control subjects. Both of these studies evaluated patients recovered from AN: an earlier study reported increased D_2 receptor availability relative to control subjects in the anteroventral striatum, an area of the striatum particularly associated with reward salience (Frank et al., 2005), though a subsequent study reported no difference between recovered patients and control subjects in any striatal subregions (Bailer et al., 2013).

To our knowledge, no study of striatal D_2 receptor availability in AN has been conducted in an acutely underweight (non-recovered) population, and no study has been conducted in a longitudinal fashion, testing subjects before and after nutritional restoration. Here we utilized PET imaging with the radiotracer [^{11}C]raclopride to measure striatal D_2 receptor availability in patients with AN. In this study, we chose to examine a population of patients acutely underweight, who were in the early stages of undergoing inpatient treatment for AN. We also studied patients with AN at a second timepoint – i.e. once they had achieved weight restoration. This design allowed us to study acute illness, while also partially accounting for the confounder of acute malnutrition, in that (1) underweight patients had been acutely stabilized nutritionally, through the beginnings of participation in an inpatient program, and (2) a direct, within-subject comparison between D_2 findings in an underweight vs. weight-restored (non-malnourished) state was possible. On the basis of the previous published study in weight-restored patients with a history of AN, we hypothesized that we would find (1) increased striatal D_2 receptor availability in the striatum in acutely-underweight patients with AN, compared to control subjects and (2) a decrease in striatal D_2 receptor availability after weight restoration (reflecting normalization of receptors over the course of treatment).

2. Methods

The study was conducted at the Eating Disorders Research Unit of the New York State Psychiatric Institute/Columbia University Medical Center, as well as at Weill Cornell Medical College. The study was reviewed and approved by the New York State Psychiatric Institute/Columbia University IRB as well as the Weill Cornell Medical College IRB, and was registered with clinicaltrials.gov.

2.1. Calculation of sample size

Based on the effect sizes from PET studies of differences in D_2 receptor availability reported in individuals with substance abuse vs. controls (Martinez et al., 2004), and in PET studies of obese vs. normal weight individuals (Wang et al., 2001), we initially calculated that a sample size of 15 patients with AN and 15 control participants would provide sufficient (80%) power to detect a moderate (e.g. 15%) difference in D_2 receptor availability with $\alpha = 0.05$ (two-tailed). Based on (Martinez et al., 2004), and comparing a main effect of diagnosis on two independent means (control subjects' striatal D_2 receptor binding potential 4.13 ± 0.49; patients with cocaine use disorder: 3.58 ± 0.40): Cohen's $d = 1.23$, which suggests a minimum sample size of 12 patients/12 control subjects. Here, an initial sample size of 15 patients with AN and 15 control subjects was calculated to provide 90% power to detect a similar relative difference in striatal D_2 binding potential, or 80% power to detect a 12% difference (Faul F, 2009). A second scanner site was later introduced, due to the temporary closure of the primary site's PET center. At the time, we had recruited and scanned 11 patients with AN and 17 control subjects; we subsequently adjusted our planned sample size to recruit a similar number of subjects at each site, ultimately yielding a sample size of 50 subjects. In the cases of subjects with AN who completed both the baseline (underweight) and weight-restored scans, both scans were completed at the same scan site; therefore, scanner type was not confounded with baseline vs. follow-up imaging.

2.2. Recruitment and screening

Women seeking inpatient treatment for AN were recruited via self-referral and referral from clinicians; control participants responded to notices and advertising in local media. Subjects with both subtypes of AN (AN, restricting subtype, “AN-R” and AN, binge-purge subtype, “AN-BP”) were recruited. 17/25 of the control subjects presented here had been previously incorporated for comparison purposes in a concurrent PET imaging study evaluating the striatal D_2 receptor in patients with bulimia nervosa (Broft et al., 2012). During the subject's initial phone call to the clinic, potential participants were told about the study by a research coordinator, and information was collected from the subject after verbal consent was obtained. Following this telephone assessment, those participants who continued to be interested and eligible underwent a longer assessment, including (1) full psychiatric and medical assessment, including physical exam, (2) a complete blood count, basic metabolic panel, liver function tests, thyroid stimulating hormone, and serum pregnancy test, (3) urine toxicology, (4) electrocardiogram, (5) Structured Clinical Interview for DSM-IV (First, 1995), and the Eating Disorder Examination-12 (Fairburn, 1993).

2.3. Inclusion/exclusion

Participants were excluded if they met DSM-IV-TR criteria for current or past Axis I disorders, other than anorexia nervosa, for the patient group. Patients with AN were not excluded by the presence of mild or moderate depressive and anxiety symptoms; patients with severe anxiety and depressive symptoms requiring specialized treatment, such as medications, were not eligible. Patients who reported a diagnosis of current ADHD during the telephone assessment or in-person interview were excluded from the study. In addition, participants were excluded for the presence of (1) past histories of abuse or dependency on alcohol or other drugs (assessed by phone interview, in-person MD clinical interview, and urine drug screen on the screening day), (2) active suicidal ideation, (3) use of psychoactive medications in the 4 weeks prior to the study, other than nicotine patch and occasional sleep medications, (4) ongoing medical or neurological illness, (5) pregnancy, (6) exposure to radiation in the workplace, or nuclear medicine procedures during the previous year, and (7) presence of metallic implants that could be adversely affected by MRI procedures. Patients were eligible for inclusion in the second, post-weight restoration PET scan if they had achieved a minimum of 90% of ideal body weight according to Metropolitan Life Insurance