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BRIEF REPORT

Dopaminergic Activity and Altered Reward Modulation in Anorexia Nervosa—Insight from Multimodal Imaging

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ABSTRACT

Objective: Individuals with anorexia nervosa (AN) have anxious and inhibited temperaments with high concern for consequences. Studies using either positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) suggest involvement of the middle and dorsal caudate (DC) in individuals recovered (REC) from AN. For example, dopamine (DA) D2/D3 receptor binding in the middle caudate and DC was associated with anxiety and harm avoidance, and blood-oxygen-level-dependent (BOLD) response in the DC was positively related to trait anxiety. It has not been shown yet whether BOLD response in individuals REC from AN was related to DA function.

Methods: Post-hoc correlation analyses between the PET and fMRI studies by correlating D2/D3 binding in striatal regions and BOLD signal in the anteroventral striatum (AVS) and DC for wins and losses respectively in 12 individuals REC from AN.

Results: Individuals REC from AN with the greatest BOLD response in the DC in a monetary choice task had higher middle caudate D2/D3 binding, and greater anxiety and/or harm avoidance.

Discussion: Though preliminary, these findings suggest that increased dorsal striatal D2/D3 binding is associated with enhanced cognitive response to feedback, potentially related to anxious anticipation of consequences. © 2016 Wiley Periodicals, Inc.

Keywords: anorexia nervosa; dopamine; reward

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Introduction

It is well established that individuals with anorexia nervosa (AN) are anhedonic and find little in life that is rewarding aside from the pursuit of weight loss. Research indicates that individuals with AN are relatively consistent in demonstrating anxious, inhibited, and constrained temperaments with high concern for consequences.[1] Such traits suggest that disturbances of reward or pleasure,[2,3] coupled with alterations in the neurocircuitry that supports inhibition and cognitive control, underlie AN behavior. Recent studies suggest that altered striatal dopamine (DA) function may contribute to the behavioural pathology of AN, even though the results particularly regarding the involvement of the DA D2/D3 receptor are somewhat inconsistent whether in the ill state of the illness or in different stages of recovery.[4–6]

Recent research on approach–avoidance responding has begun to examine the association between behavioural inhibition and approach behaviour, as it is mediated by neural circuits that respond to rewards.[7] While preclinical literature shows D2 function may be related to indirect pathway and aversive inhibited response, e.g. risk aversive rats having greater striatal D2 expression,[8] the ability to look at this in humans in vivo is limited. For one thing, each modality of imaging studies provides a very narrow insight into brain activity, therefore the combination of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) offers a better understanding of molecular mechanisms associated with brain function.

We performed several studies in a cohort of individuals who had recovered (REC) from AN, allowing us to extrapolate trait related dysfunction in the absence of confounding effects of malnutrition, that are suggesting an indirect pathway dysfunction in AN. First, a study using [11C]raclopride and PET showed that individuals REC from AN had increased binding of DA D2/D3 receptors in the anteroventral striatum (AVS) relative to control women (CW).[4,5] Furthermore, [11C]raclopride

FIGURE 1. Correlation between [^{11}C]raclopride BP$_{ND}$ in the middle caudate and Spielberger Trait Anxiety (graph A); correlation between Spielberger Trait Anxiety and % (expressed as x/100) fMRI signal change in the dorsal caudate in response to losses (graph B); correlation between % fMRI signal change in the dorsal caudate and [^{11}C]raclopride BP$_{ND}$ in the middle caudate in response to losses (graph C) and wins (graph D); graph 1A and 1B have been added to show additional (unpublished) and previous findings, respectively.
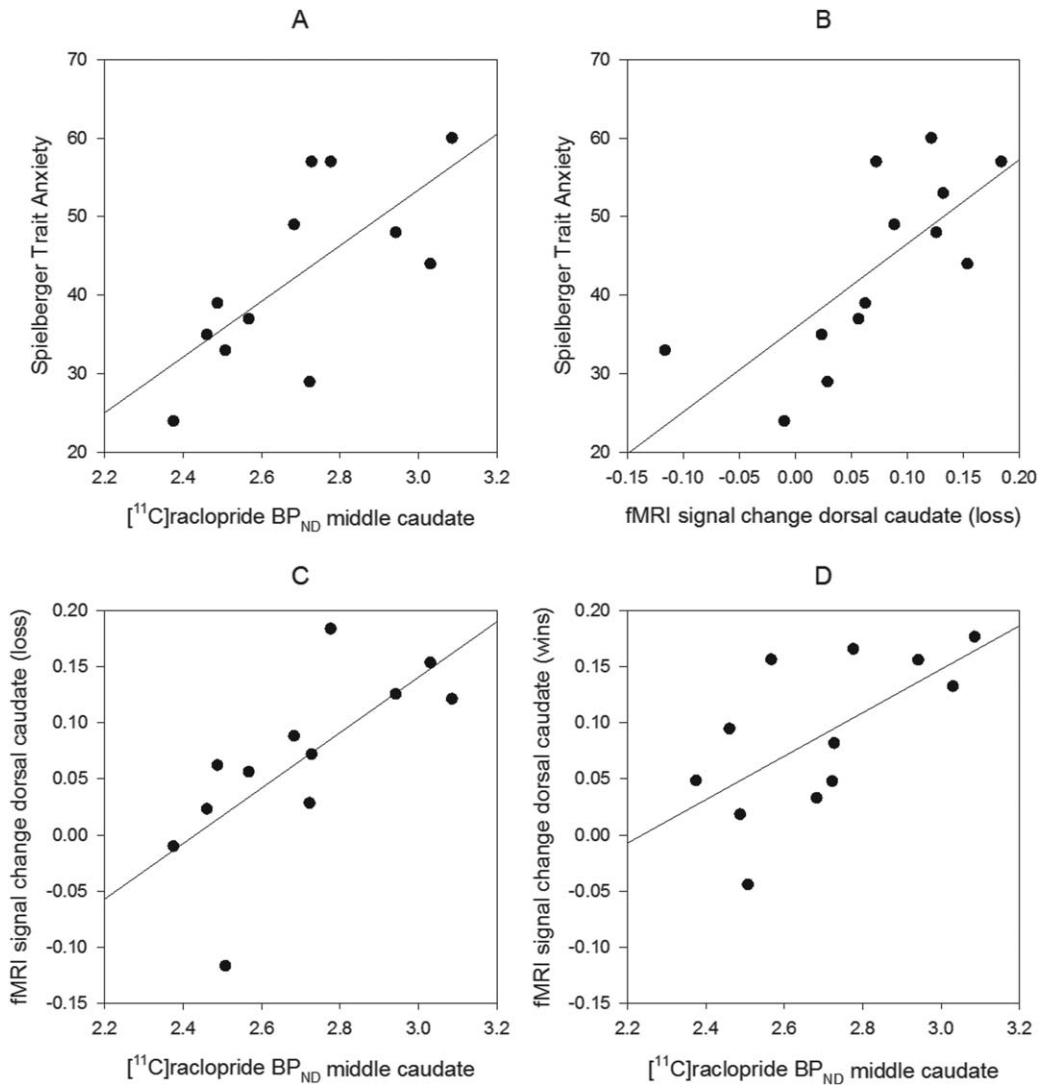
binding potential [BP$_{\text{Nondisplaceable (ND)}}$] in the dorsal caudate (DC) was associated with harm avoidance,[4,5] a measure of anxiety in individuals REC from AN and trait anxiety showed a positive relationship with [^{11}C]raclopride BP$_{ND}$ in the middle caudate ($r = 0.70$; $P = 0.01$) (Fig. 1A) and AVS ($r = 0.75$; $P = 0.01$) (unpublished data, and included here for illustration of correlations of [^{11}C]raclopride BP$_{ND}$ with anxiety measures, other than harm avoidance). Second, in a fMRI study using a monetary choice task[9] known to activate the striatum, individuals REC from AN[3] failed to show a differential AVS response to positive and negative monetary feedback compared to healthy CW. Individuals REC from AN showed greater BOLD response in the DC than CW. Only individuals REC from AN

showed a significant positive relationship between trait anxiety and the percentage change in hemodynamic signal in the DC during either wins ($r = 0.56$, $P = 0.04$) or losses ($r = 0.73$, $P = 0.005$) (Fig. 1B). With a limited amount of overlapping PET and fMRI data in AN as aforementioned, do such correlations imply that PET [^{11}C]raclopride BP$_{ND}$ might be related to the BOLD response to monetary choice in the DC of individuals REC from AN?

Methods

We ran post-hoc correlation analyses between the PET and fMRI studies by correlating baseline [^{11}C]raclopride BP$_{ND}$ in the AVS, DC, middle caudate, ventral and dorsal

putamen and BOLD signal in the AVS and DC for wins and losses respectively in twelve female individuals REC from AN (age: 27 ± 7; BMI: 20.3 ± 2 kg/m^2) who participated in both studies [12 out of 13 subjects of the Wagner et al.[3] study had also participated in the [^{11}C]raclopride PET studies; [^{11}C]raclopride PET data of all 12 were included in our previous report[4] and 3 thereof were also included in our earlier study[5]]. All 12 individuals REC from AN were non-smokers, right-handed and were not on any psychoactive medication at the time of study and had not used any psychoactive medication in the 3 months prior to the study. None of them met diagnosis of alcohol or drug abuse or dependence in the 3 months prior to the study as determined by self-report, psychiatric interviews and urine toxicology screen. Lifetime history of other Axis I disorders were major depressive disorder ($n = 8$), bipolar II disorder ($n = 1$), posttraumatic stress disorder ($n = 2$), social phobia ($n = 1$), panic disorder ($n = 1$), obsessive compulsive disorder (OCD) ($n = 3$), all of which were in full remission. Only two individuals REC from AN had a current mild specific phobia and mild OCD respectively.

All subjects were scanned on the same ECAT HR+ PET scanner (CTI PET systems, Knoxville, TN) in three-dimensional (3D) imaging mode during the first 10 days of the follicular phase of the menstrual cycle. After slow bolus intravenous injection of [11C]raclopride, dynamic emission scanning was performed over 60 minutes, as described previously.[5,10] Regions of Interest (ROIs) were hand drawn on the coregistered MR images, blind to subjects' diagnosis and applied to the dynamic PET data to generate time-activity curves, as described by Drevets et al.[10] : AVS, dorsal and middle caudate (the caudate head in the 3–5 image planes situated between the DC and AVS regions), dorsal and ventral putamen, and cerebellum (as a reference region).[4,5,10] A Reference Tissue Model[11] was applied for the imaging data analysis of [11C]raclopride, which has been shown to be an appropriate and robust model for quantifying [11C]raclopride BP$_{ND}$.[4,5,10]

Functional imaging data were collected with a 3-T Signa scanner (GE Medical Systems) using a one-shot reverse spiral pulse sequence[12] with an echo time of 26 msec and a repetition time of 2,000 msec (one full volume scan acquired every 2 sec); 30 oblique axial slices were acquired with an in-plane resolution of 64×64 with 3.125 mm^2 pixels and a slice thickness of 3.2 mm, with a field of view of 200 mm^2. Seven functional volumes were acquired per trial (further details on the guessing game paradigm, ROI delineation, fMRI data processing and analysis are outlined by Wagner et al.[3]).

Results

Individuals REC from AN showed a positive relationship between [^{11}C]raclopride BP$_{ND}$ in the middle caudate and the BOLD signal in the DC in response to losses ($r = 0.71$, $P = 0.01$) (**Fig. 1C**) or wins ($r = 0.64$, $P = 0.03$) (**Fig. 1D**), but not for the AVS (losses $r = 0.32$, ns; wins $r = -0.019$, ns). Correlations failed to reach statistical significance for [^{11}C]raclopride BP$_{ND}$ in the other four PET regions (AVS, DC, ventral and dorsal putamen) and the BOLD signal in response to both wins and losses in the AVS and DC. In summary, DA D2/D3 receptor binding in the middle caudate in individuals REC from AN was positively associated with the BOLD response to both wins and losses, whereas no such associations were found in the AVS. Only 6 healthy CW overlapped for both studies, so a comparison to CW was not possible.

Discussion

Other studies have found that measures of DA release tend to be associated with AVS activation in healthy controls (see Ref. 13). Moreover, AVS DA release in controls is often associated with positive emotions.[10] Despite a small sample, our exploratory data suggest that individuals REC from AN with the greatest BOLD response in the DC had higher levels of DA D2/D3 receptor BP$_{ND}$ in the middle caudate, and greater anxiety and/or harm avoidance. In light of our previous finding of positive correlations between harm avoidance and [^{11}C]raclopride BP$_{ND}$[4,5] in the DC in individuals REC from AN, these findings suggest that increased dorsal striatal DA D2/D3 receptor BP$_{ND}$ is associated with enhanced cognitive response to feedback in individuals REC from AN, potentially related to anxious anticipation of consequences. Individuals REC from AN may have an imbalance between ventral limbic and dorsal executive processes: ventral limbic-striatal circuitry may be inhibited by "hyperactive" inputs from dorsal executive processes. This theory is supported by recent animal studies showing that risk-averse rats[8] exhibited greater D2 mRNA expression in the DC and by human imaging data indicating that DC DA D$_2$/D$_3$ receptor availability is positively correlated with inhibition-related fMRI activation in frontostriatal neural circuitry in healthy controls.[14] Our recent study[15] supports the possibility that food-induced DA release in the DC stimulates anxiety in AN. So if individuals with AN experience endogenous DA release as anxiogenic, rather than hedonic, it may explain their pursuit of starvation from a clinical standpoint, as they may find food restriction is an effective means of reducing anxiety. This exploratory study has several limitations that include a very

small sample size with multiple comparisons therefore the need for replication in a larger sample, as well as a comparison to healthy controls. Why the BOLD response in the DC correlated with DA D2/D3 receptor BP_{ND} in the middle caudate only, but not in the DC, will have to be further explored in a larger sample. Although our data suggest that DA activity is implicated in functional brain responses within the striatal complex, we can only speculate about the direction of the relationship. DA release has been shown to affect the magnitude of the striatal BOLD signal,[16,17] but alternative possibilities have been discussed. The striatal BOLD response might mediate DA activity in midbrain by phasically inhibiting GABAergic neurons in pallidum that tonically inhibit the midbrain.[18] On this view, DA release results from rather than causes striatal BOLD activity. A third possibility is that there is a reciprocal relationship between these two directions of influence in that DA release affects the BOLD signal in as much as the opposite is true. The fact that we have not assessed DA release per se in our study, but DA D2/D3 receptor binding at baseline further limits interpretations of directionality. We have included only individuals REC from AN and hence have no information about similar or different findings in the ill state of the illness.

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