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Striatal Dopamine D2/3 Receptor-Mediated Neurotransmission in Major Depression: Implications for Anhedonia, Anxiety and Treatment Response

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Abstract

Dopamine (DA) neurotransmission within the brain's reward circuit has been implicated in the pathophysiology of depression and in both, cognitive and pharmacological mechanisms of treatment response. Still, a direct relationship between measures of DA neurotransmission and reward-related deficits in patients with depression has not been demonstrated. To gain insight into the symptom-specific alterations in the DA system in patients with depression, we used positron emission tomography (PET) and the $D_{2/3}$ receptor-selective radiotracer [^{11}C]raclopride in twenty-

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CONFLICTS OF INTEREST

The authors have no interests to disclose that are or might be perceived to be in conflict with the work reported in this study.

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three non-smoking un-medicated Major Depressive Disorder (MDD) patients and sixteen healthy controls (HC). We investigated the relationship between $D_{2/3}$ receptor availability and baseline measures of depression severity, anxiety, anhedonia, and cognitive and pharmacological mechanisms of treatment response. We found that, compared to controls, patients with depression showed greater $D_{2/3}$ receptor availability in several striatal regions, including the bilateral ventral pallidum/nucleus accumbens (vPAL/NAc), and the right ventral caudate and putamen. In the depressed sample, $D_{2/3}$ receptor availability in the caudal portion of the ventral striatum (NAc/vPAL) correlated with higher anxiety symptoms, whereas $D_{2/3}$ receptor availability in the rostral area of the ventral striatum correlated negatively with the severity of motivational anhedonia. Finally, MDD non-remitters showed greater baseline anxiety, greater $D_{2/3}$ availability in the NAc/vPAL, and greater placebo-induced DA release in the bilateral NAc. Our results demonstrate abnormally high $D_{2/3}$ receptor availability in the ventral striatum of patients with MDD, which seem to be associated with comorbid anxiety symptoms and lack of response to antidepressants.

Keywords

Depression; Anhedonia; Anxiety; Dopamine; PET; Treatment Response

INTRODUCTION

Multiple lines of evidence have implicated dopamine (DA) dysregulation with the brain's reward neural circuit in the pathophysiology and treatment of depression. A direct relationship between striatal DA receptor availability and reward related deficits and their contribution to treatment response in patients with depression has not been investigated yet.

Clinically, DA dysregulations in depression have been linked to anhedonia (Nestler and Carlezon, 2006), one of the two cardinal symptoms of Major Depressive Disorder (MDD). Initially, the DA deficiency hypothesis of anhedonia (Wise, 1980) was thought to be related to reductions in the subjective experience of pleasure (consummatory anhedonia). However, this conceptualization has been largely abandoned in favor of a pivotal role of DA in the motivation to pursue meaningful rewards (motivational anhedonia) (Berridge and Robinson, 2003; Salamone, 2007). In humans, current evidence suggests that blunted processing of incentive salience, incentive motivation, and reinforcement learning might precede depressive symptoms. However, when these abnormalities are worsened by recurrences and emerge coupled with abnormalities in regions implicated in coding the hedonic value of stimuli, these disruptions might lead to more tenuous anticipatory reward-related associations, and ultimately anhedonic symptoms (Whitton et al., 2015).

From the treatment perspective, pharmacological enhancement of DA signaling with DA agonists, such as bromocriptine or pramipexole (Bouras and Bridges, 1982; Cassano et al., 2005; Shopsin and Gershon, 1978) and DA transporter (DAT) inhibitors, such as amineptine and bupropion, exhibit varying degrees of antidepressant effects (Stahl et al., 2004). Deep brain stimulation affecting the nucleus accumbens (NAc)—a key region implicated in reward processing— has also demonstrated evidence of sustained efficacy in patients diagnosed with treatment-resistant depression in an open trial (Bewernick et al., 2012).

Furthermore, previous evidence suggests that current first-line pharmacotherapies (e.g., SSRIs) do not adequately address motivational and reward-processing deficits in depression (Dunlop and Nemeroff, 2007; McCabe et al., 2009; McCabe et al., 2010; Price and Hotopf, 2009), and that anhedonia is generally a predictor of poor treatment response (Spijker et al., 2001).

DA has also been associated with the formation of placebo-induced positive expectations and subsequent treatment responses in clinical trials, introducing variability and confounding the interpretation of potential drug effects (Enck et al., 2013). It has been shown that the strength of beliefs of improvement directly modulate dopamine release in patients with Parkison's Disease (de la Fuente-Fernandez et al., 2001), and in the context pain (Scott et al., 2007, 2008). Broadly, expectations are fundamental in all emotional processes, and allow an individual to interact with an upcoming emotional or motivational situation before it actually occurs (Petrovic et al., 2005). The neural correlates of expectations have been shown in several functional neuroimaging studies of emotion in general and of reward processing specifically (Ernst et al., 2004; Knutson et al., 2001a; Knutson et al., 2001b). Overall, the dopaminergic system seems to be involved in the complex interaction among the pathophysiology of MDD, the mechanisms of action of some antidepressant treatments and the patients' expectations of improvement, all of which contribute to treatment response variability.

Human *in vivo* neuroimaging studies in depressed samples have aimed to clarified these questions. Studies using ^{123}I-iodobenzamide single-photon emission computed tomography ([^{123}I]-IBZM SPECT) initially reported increased binding of striatal D_2 receptors compared to controls (D'Haenen H and Bossuyt, 1994; Shah et al., 1997), which were thought to reflect either an up-regulation of D2/3 receptors, increased affinity of the receptor for the radioligand, decreased synaptic dopamine concentrations or potentially a combination of these mechanisms (Dunlop and Nemeroff, 2007). These initial findings were followed by a number of negative (Ebert et al., 1996; Hirvonen et al., 2011; Klimke et al., 1999; Montgomery et al., 2007; Parsey et al., 2001; Yang et al., 2008) or even opposite (Busto et al., 2009) studies using ^{123}I-IBZM SPECT or [^{11}C]-raclopride positron emission tomography (PET).

Some of the inconsistencies described above might be explained by the lack of approaches that specifically investigate DA-related symptoms of depression, such as anhedonia, and their relationship with sub-regions within the basal ganglia (e.g NAc). Here we used positron emission tomography (PET) and the $D_{2/3}$ selective radiotracer [^{11}C]raclopride to examine the relationships among $D_{2/3}$ receptor availability, symptoms of anhedonia, and the response to antidepressants and placebo treatments. For this purpose, we utilized a design identical to one recently utilized to examine endogenous opioid mechanisms of the placebo response in MDD (Peciña et al., 2015). In the present report, we also aimed to dissect the motivational and consummatory components of the overall anhedonia construct (Treadway and Zald, 2011), using two different self-reported questionnaires: the Apathy Evaluation Scale (motivational anhedonia) (Marin et al., 1991) and the Snaith-Hamilton Pleasure Scale (SHAPS) (consummatory anhedonia) (Snaith et al., 1995). We hypothesized that in patients with MDD, primary DA function deficits within the ventral striatum (e.g. a presynaptic

reduction in function) would result in observable, compensatory up-regulation of striatal $D_{2/3}$, lower placebo-induced DA release, and greater motivational (but not consummatory) anhedonia. Secondly, it was expected that higher motivational anhedonia scores would be linked to poor clinical response to both open-label antidepressant medication and a placebo intervention designed to increase positive expectations of improvement.

EXPERIMENTAL PROCEDURES

1. Subject Characterization

Sixteen healthy controls (HC, females= 9) and twenty-six patients meeting DSM-5 criteria for moderate-severe MDD (females=10), aged 18 to 56 years (HC=40±8.7, MDD=37±13.8, mean ± SD), were recruited through local advertisement. In addition to completing physical and neurological examinations, study participants were screened using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). For the MDD group, inclusion criteria included the diagnosis of MDD, 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) scores >12 and excluded suicidal ideation, comorbid psychiatric conditions (except for anxiety disorders), the use of psychotropic agents or recreational drugs, left-handedness and pregnancy. Average disease duration (current episode – disease onset age) was 11.5 years (Range: 0–44 y). Subjects were not taking any psychotropic medications at the time of the study for at least 6 months, except for occasional use of sleep aids (frequency of less than 2 per week), and none for at least a week prior to the study. Additional information about lifetime exposure to antidepressant medication is reported in Supplemental Table 1. Of interest, we found no significant differences in baseline $D_{2/3}$ binding potential between those previously exposed to antidepressant medication (including one subject with previous exposure to aripiprazole), and those who were antidepressant naïve. Three patients with MDD were currently smokers, and were excluded from the analyses because of the documented relationship between smoking status and DA receptor availability measures. Drug abuse or dependence history were not collected, but drug test were performed before each scanning procedures and negative results were require for participation in the study. None of the participants had taken antidepressant medications for at least 6 months prior to enrollment in the study. Written informed consent was obtained and all of the procedures were approved by the University of Michigan Investigational Review Board for Human Subject Use and the Radioactive Drug Research Committee. Data were collected and stored using Research Electronic Data Capture (REDCap) (Harris et al., 2009).

2. Trial Design

After the initial screening, MDD patients entered a clinical trial, which has been described in detail elsewhere (Pecina et al., 2015). The study had two phases, a 2-week placebo single-blind RCT and a 10-week open-label flexible-dose antidepressant treatment. This study had been specifically designed to investigate changes in opioid (Pecina et al., 2015) and dopamine receptor availability in response of expectations of mood improvement in patients with MDD (“the placebo effect”), as well as the role of inter-individual variability in receptor availability in the response to open-label antidepressant treatments. All subjects in

this study (n=23) were also studied with [^{11}C]carfentanil, a μ-opioid receptor radiotracer, as previously described (Pecina et al., 2015) (Fig.1).

2.1. Placebo Phase—During the first phase, subjects were randomized to (1) 1-week "active" oral placebo treatment (2 pills/day), with expectations that it represented a fast-acting antidepressant agent ("active" placebo condition), or (2) 1-week "inactive" oral placebo with disclosure that it was an inactive control ("inactive" placebo condition). After a 3-day "washout" period without pills, participants were crossed over into the group to which they were not previously assigned. After each placebo week, participants underwent a PET scanning session. As a challenge to induce endogenous DA system activation and to determine acute placebo effects, the PET session following the 1-week "active" oral placebo included the administration of an i.v. "active" placebo. This consisted of 1mL of 0.9% isotonic saline introduced i.v. every 4 minutes during 20 minutes, starting at minute 42 and lasting for 15 seconds each time. Subjects were aware that the study drug was to be administered through a computer-generated human voice recording, followed by a second-by-second count of the infusion timing (15 seconds). No i.v. placebo followed the "inactive" placebo condition. The post-inactive PET scan was considered a baseline condition. While open-label placebos have been associated with symptom relief under expectations of improvement (Kaptchuk et al., 2010), and could potentially lead to changes in DA neurotransmission, this has not been the case when placebos are administered in the absence of such expectations, and therefore no changes in DA binding should be expected under such manipulations. Reductions in the *in vivo* availability of receptors after an acute neurotransmitter releasing challenge (i.e., placebo administration) are thought to reflect processes, such as competition between radiotracer and endogenous ligand, associated with neurotransmitter release (Narendran and Martinez, 2008).

Clinical Assessments during the Placebo Phase: Depression symptoms were assessed using the Quick Inventory of Depressive Symptomatology (QIDS-SR16) (Rush et al., 2003) at pre- (baseline) and post-each placebo treatment. A single measure of sustained placebo response was created by subtracting the changes in QIDS-SR16 reductions from "active" and "inactive" placebo treatments [(QIDS-SR16 pre - post) "active" placebo—(QIDS-SR16 pre - post) "inactive" placebo]. In addition, patients' impression of depression severity (PIDS) ratings ("*from 0 to 100 how depressed do you feel now*?) were acquired every 4 minutes during the 2 PET scans, in the presence and absence of the i.v. placebo. Acute, i.v. placebo responses were assessed by the subtraction $PIDS_{\text{no i.v.}} - PIDS_{\text{active i.v.}}$

2.2. Antidepressant Phase—Following the placebo phases and the two PET sessions, participants were invited to participate in an un-blinded 10-week open-label trial with an FDA-approved antidepressant, in most cases citalopram (starting at 20 mg/day and up to 40 mg/day in 92% of cases). Two patients who did not tolerate citalopram switched to another antidepressant (duloxetine 60 mg/day or bupropion 150 mg/day) at week 4. Two patients with a prior history of non-response to citalopram were treated with an alternative antidepressant (mirtazapine 30 mg/day and fluoxetine 20 mg/day respectively).

Clinical Assessments during the Antidepressant Phase: At screening and during each clinical visit, participants' depressive symptoms were assessed using the QIDS-SR16 (Rush et al., 2003). At screening and immediately before (week 0) and after the trials (week 10) we collected information regarding: anxiety levels (Generalized Anxiety Disorder: GAD-7), consummatory anhedonia (SHAPS) and motivational anhedonia (AES) (Fig.1). Remission rates were established using the QIDS-SR16 (<5) and changes in the clinical assessments in response to the antidepressant treatment were examined against the remission rates, after controlling for baseline severity, using ANCOVA models.

3. Neuroimaging Methods

Immediately after each 1-week of placebo treatment, participants were positioned in the PET scanner gantry (Siemens HR^+, Knoxville, Tennessee) and 2 i.v. (antecubital) lines were placed. A light forehead restraint was used to eliminate intrascan head movement. Four 90 min PET scanning sessions, with and without i.v. placebo administration, were completed, but only those two using [^{11}C] raclopride are reported here. Images were acquired in 3-dimensional mode (reconstructed full-width/half-maximum resolution, approximately 5.5 mm in plane and 5.0 mm axially), with the septa retracted and scatter correction. [^{11}C] Raclopride was synthesized at high specific activity by the reaction of *O*-desmethyl raclopride with [^{11}C] methyl triflate. 15.0 ± 2.2 (mean ± SD) mCi were administered in each of the imaging procedures, with a mass of raclopride of 0.20 ± 0.15 (mean ± SD) μg per scan. Fifty percent of the radiotracer dose was administered as an initial bolus and the remaining 50% by continuous infusion for the remainder of the study to more rapidly achieve steady-state levels. For each study, 21 sets of dynamic scans were acquired with an increasing duration (four 30-second frames, three 1-minute frames, two 2.5-minute frames, eight 5-minute frames, and four 10-minute frames). Images were reconstructed using iterative algorithms (brain mode; Fourier rebinding algorithm with ordered-subsets expectation maximization, 4 iterations, and 16 subsets; no smoothing) into a 128×128-pixel matrix in a 28.8-cm-diameter field of view. Attenuation correction was performed through a 6-minute transmission scan (Ge^{68} source) obtained before the PET study and with iterative reconstruction of the blank/transmission data, followed by segmentation of the attenuation image. Small head motions during PET were corrected by an automated computer algorithm for each subject before analysis, and the images were co-registered with the same software (Minoshima et al., 1993). Time points were then decay corrected during reconstruction of the PET data. Image data were then transformed on a voxel-by-voxel basis into 2 sets of parametric maps, a tracer transport measure (K_1 ratio) and a receptor-related measure (non-displaceable binding potential, BP_{ND}, or receptor availability *in vivo)* (Innis et al., 2007). To avoid the need for arterial blood sampling, these measures were calculated using a modified Logan graphical analysis (Logan et al., 1996), using the cerebellum as reference region. Using the bolus-continuous infusion protocol described above, the slope of the Logan plot becomes linear ~5 min post-tracer administration and is proportional to the receptor concentration divided by its affinity for the radiotracer [BP_{ND} + 1, or (f_2Bmax/K_d) +1] (Mintun et al., 1984). Bmax is the receptor concentration and K_d, the receptor-ligand dissociation constant. The term f_2 refers to the concentration of free radiotracer in the extracellular fluid and is considered to represent a constant and very small value.

Anatomical MRI studies were acquired on a 3-T scanner (Philips Achieva, Best, Netherlands). A high resolution structural image was obtained for anatomic normalization using a T1-weighted, gradient echo (MPRAGE) sequence (220 slices, slice thickness = 1mm, echo time = 4.6 msec, repetition time = 9.8 msec, flip angle = 8°, field of view =240 mm2).

3.1 Data Analysis—All preprocessing and data analyses were performed using the SPM8 toolbox (Wellcome Department of Cognitive Neurology, University College, London, England) for Matlab (MathWorks, Natick, Massachusetts). For each experimental period, the anatomical MRI was coregistered to the K_1 PET image and then warped to Montreal Neurological Institute (MNI) space using the voxel-based morphometry (VBM) toolbox. The resulting deformation fields were used to warp the PET images to MNI space. To compensate for small residual anatomic variations across subjects and to improve signal-to-noise ratios, the warped PET images were smoothed with a 6-mm^3 Gaussian kernel.

Group analyses of PET images were performed with mass univariate general linear models. Due to raclopride's specific binding in the striatum, no global normalization was applied to the data, and therefore the calculations presented herein are based on absolute BP_{ND} (f_2 Bmax/*K*d) estimates (Carson et al., 1997). A mask was applied so that only regions with specific $D_{2/3}$ receptor binding were included in the analyses (voxels with BP_{ND} >0.1) (Wager et al., 2007). Baseline (inactive placebo condition) and subtraction analyses (inactive-active placebo condition) were performed on $D_{2/3}$ receptor images to assess main effects of the placebo intervention. For each analysis, 1-sample, 2-tailed *t* values were calculated for each voxel. A bilateral nucleus accumbens region of interest (ROI) map was created using the Harvard Oxford subcortical atlas in FSL (Jenkinson et al., 2012). Regional BP_{ND} values were obtained by applying this ROI to the individual parametric [^{11}C]raclopride images. We used MarsBaR (Brett et al., 2002) to extract average NAc BP values for quantification of regional changes in BP_{ND}, graphing and determination of correlation coefficients. Other regions within the striatum outside of the NAc were considered significant at $p<0.05$ FWE-corrected voxel-wise (Friston et al., 1994). FWE-corrected individual parametric maps were also extracted for quantification of regional changes in BP_{ND}, graphing and determination of correlation coefficients. Measures of $D_{2/3}$ availability *in vivo* (Innis et al., 2007) at baseline, and the reductions in BP_{ND} during i.v. placebo administration (reflecting activation of dopamine neurotransmission) were then related to the clinical measures and placebo and antidepressant responses. Because of our interest in three different clinical domains: anhedonia (SHAPS and AES), overall depression (QIDS-16SR) and anxiety scores (GAD-7), and one measure of subjective expectations of improvement, Pearson/Spearman correlations between clinical measures and DA baseline binding and release measures were considered significant at $p<0.0125$ after Bonferroni correction ($p<0.05/4$). All statistical analyses were controlled by age and QIDS-16SR scores. Additional nuisance variable for each particular analysis are described in the results section.

RESULTS

Clinical Measures of depression, anxiety, motivational and consummatory anhedonia and treatment response

Average clinical depression [QIDS-16SR (mean ± SD): 16 ± 5], anhedonia (SHAPS: 29.4 ± 9.6; AES: 5.88 ± 3.67) and anxiety (GAD-7: 10.05 ± 5.1) scores were computed. QIDS-16SR and SHAPS scores were significantly correlated, and so were SHAPS and AES scores (for all $r>0.5$, $p<0.05$). Anxiety scores were not significantly correlated with measures of depression severity or anhedonia. There were no significant sex effects on any of the clinical measures used (QIDS-16SR, HDRS, SHAPS, AES and GAD-7). Baseline measures of depression severity, anxiety, consummatory and motivational anhedonia were not significantly correlated with depression symptom improvement in response to i.v. or oral placebo (changes in PIDS or QIDS-16RS respectively) or 10 weeks of antidepressant medication treatment (changes in QIDS-16RS, GAD-7, SHAPS and AES scores).

Expectations of improvement were not correlated with depression severity, anxiety, consummatory anhedonia, or apathy scores, nor with the improvement of these symptoms in response to i.v. or oral placebo (changes in PIDS or QIDS-16RS respectively) or 10 weeks of antidepressant treatment (changes in QIDS-16RS, GAD-7, SHAPS and AES).

Effect of MDD diagnosis on $D_{2/3}$ BP_{ND}

We first examined the effect of group (healthy controls versus MDD) on baseline $D_{2/3}$ BP_{ND}. Mean $D_{2/3}$ receptor BP_{ND} in several regions within the striatum was significantly higher in subjects with MDD compared to the healthy control group [MNI coordinates: bilateral NAc/ventral pallidum (vPAL): −14, 6, 6 and 12, 2 −8; right ventral caudate (vCAU): 18, 8, 8; right putamen (PUT): 30, −16, −6; for all regions $p < 0.05$ FWE-corr., K>10 voxels, Fig. 2]. No effects were observed for the opposite contrast.

Baseline D2/3 BP_{ND} and Depression, Anxiety, Anhedonia Symptoms and Expectations of Improvement

Within the MDD sample, we examined the relationship between $D_{2/3}$ BP_{ND} in the NAc bilateral ROIs and the regions that resulted significant in the analysis above, and symptoms of anhedonia, as well as overall depression and anxiety severity. Considering our interest in three different clinical domains and the subjective expectations of improvement, these correlations were deemed significant at $p<0.0125$, after Bonferroni correction. Each model included the variable of interest and age as a nuisance variable. We found a significant positive correlation between $D_{2/3}$ receptor availability in the left NAc/vPAL (−14, 6, 6) and GAD-7 scores ($r=0.54$, $p=0.01$) (Fig. 2). We also found a negative correlation between $D_{2/3}$ receptor availability in the NAc ROI bilaterally and AES scores ($r=-0.5$, $p=0.01$) (Fig. 3). These results remain significant after controlling for AES scores and GAD-7 scores respectively. We found no significant association between baseline measures of $D_{2/3}$ receptor availability and SHAPS consummatory anhedonia scores or overall depression severity (QIDS-16SR scores).

Patient's expectations of recovery were positively correlated with baseline $D_{2/3}$ BP_{ND} in the NAc bilaterally (p=0.046, p=0.05), although these effects did not survive Bonferroni correction.

Placebo-induced changes in $D_{2/3}$ BP_{ND} and the clinical responses to Placebo and Antidepressants

The administration of the i.v. placebo, compared to no administration, resulted in significant activation of DA neurotransmission (acute reductions in BP_{ND}) in the bilateral NAc ROI (mean change=0.08, SD=0.15, t=2.5, p=0.02). Placebo-induced changes in BP_{ND} were not significantly correlated with the participant's levels of expectations of improvement or the i.v. or oral response to placebo or 10 weeks of antidepressant treatment.

Effect of Remission Group on Clinical Measures, Striatal $D_{2/3}$ BP_{ND}, Placebo-induced $\Delta D_{2/3}$ BP_{ND}

Based on the evidence provided above we conducted an exploratory analysis to examine whether remitters, compared to non-remitters, showed significant differences in baseline $D_{2/3}$ receptor availability or placebo-induced DA release. GAD-7 scores at baseline, but no other clinical measures, were significantly higher in non-remitters [GAD-7 $_{\text{remitters}}$: (mean ± SD) 5.43 ± 5.1; GAD-7 $_{\text{non-remitters}}$: 12.6 ± 3.1; F=11.14, p=0.005], therefore the following analyses were controlled by baseline QIDS-16SR, GAD-7 scores and age (Fig. 4).

MDD remitters (QIDS-16SR<5, n=7), compared to non-remitters (n=9), showed significantly greater clinical responses to placebo (decreases in QIDS-16SR after one week of placebo pills) [ΔQIDS-16SR $_{\text{remitters}}$: (mean ± SD) 5 ± 5; ΔQIDS $_{\text{non-remitters}}$: −2.7 ± 5; F=9, p=0.012]. As previously described in a larger sample (Pecina et al., 2015), the response to one week of placebo was significantly correlated to the response to 10 weeks of antidepressants (r=0.7, p=0.003).

Non-remitters, compared to remitters, had significantly higher baseline $D_{2/3}$ BP_{ND} in the left NAC/vPAL (NAC/vPAL $_{\text{remitters}}$: 1.5 ± 0.23; NAC/vPAL $_{\text{non-remitters}}$: 2 ± 0.1; F=7, p=0.02). Unexpectedly, MDD non-remitters, compared to remitters, also showed significantly greater DA activation in the NAc bilaterally in response to the i.v. placebo (ΔNAc $_{\text{remitters}}$: 0.01 ± 0.03; ΔNAc $_{\text{non-remitters}}$: 0.15 ± 0.03; F=6.8, p= 0.02) (Fig. 4).

DISCUSSION

In this study, we aimed to identify *in vivo* DA receptor availability differences in patients with MDD compared to healthy controls, as well as to relate measures of DA function to depression severity, anxiety, motivational and consummatory anhedonia, and the response to placebo and SSRI treatment. We found that compared to controls, patients with MDD showed greater DA $D_{2/3}$ receptor availability in several regions within the striatum, including the NAc/vPAL bilaterally, the right vCAU, and the right PUT. In the MDD patient sample, DA $D_{2/3}$ BP_{ND} measures in the NAc/vPAL were significantly correlated with higher anxiety symptoms, as measured by higher baseline GAD-7 scores. The NAc ROI DA $D_{2/3}$ BP_{ND} measures, bilaterally, correlated negatively with the severity of the patient's apathy scores and at a trend level with the subject's levels of expectations of improvement with the

"active" placebo treatment. Furthermore, the administration of the "active" placebo, compared to the "inactive" placebo, was associated with greater DA release in the ventral striatum. Finally, compared to MDD remitters, the non-remitter patients showed significantly greater baseline GAD-7 scores and DA $D_{2/3}$ availability in the NAc/vPAL. Non-remitters also showed greater placebo-induced DA release in the NAc bilaterally compared to remitters.

The existence of DA deficits in patients with MDD remains controversial. As summarized in the introduction, *in vivo* neuroimaging studies using [^{123}I]-iodobenzamide single-photon emission computed tomography ([^{123}I]-IBZM SPECT) or [^{11}C]-raclopride positron emission tomography (PET) have reported increased (D'Haenen H and Bossuyt, 1994; Meyer et al., 2006; Shah et al., 1997), no change (Ebert et al., 1996; Hirvonen et al., 2011; Klimke et al., 1999; Montgomery et al., 2007; Parsey et al., 2001; Yang et al., 2008) or even decreased (Busto et al., 2009) binding to striatal DA $D_{2/3}$ receptors, compared to controls. A number of potential confounders can explain these differences (e.g. medication status, heterogeneity of MDD, differences in neuroimaging methods). Still, the hypothesis that DA deficits in depression resulting in up-regulation of DA receptor sites remains plausible and is supported by the results presented here. We show that increments in baseline DA $D_{2/3}$ BP_{ND} in the more caudal portion of the NAc were associated with higher anxiety levels in MDD patients. These effects are consistent with the notion that caudal ventromedial striatal regions, which receive inputs from several "limbic" brain regions, including the amygdala and anterior cingulate cortex (Fudge et al., 2004; Russchen et al., 1985; Shammah-Lagnado et al., 2001), are involved in fear generation. In fact, preclinical evidence suggests that fear generation requires simultaneous stimulation of D1 and D2 receptors at caudal sites of the NAc (Richard and Berridge, 2011). On the contrary, the rostral ventral striatum is known to be a substrate for goal-directed behaviors based on its inputs from multiple brain regions mediating motivation and reward (Haber et al., 2000). We found a negative association between motivational, but not consummatory, anhedonia, and DA $D_{2/3}$ receptor binding in the ventral striatum. Extensive animal literature has elegantly related the DA system to incentive salience ("wanting") through the mesolimbic DA projections (Berridge and Robinson, 1998; Pecina et al., 2003), and the opioid system (and others, such as cannabinoid and GABA systems) to the hedonic impact of reward ("liking"), through what has been defined as the hedonic hotspots (e.g. the NAc rostrodorsal medial shell) (Pecina and Berridge, 2005). We originally hypothesized that higher $D_{2/3}$ BP_{ND} in the NAc will be associated with higher apathy scores, consistently with a lower DA tone. A negative relationship, as observed here, might potentially be explained by the paradoxical positive incentive effects of higher anxiety levels. For example, it has been shown that corticotropin-releasing factor (CRF), a neuropeptide released in response to acute stressors and other arousing environmental stimuli, acts in the NAc of naive mice to increase DA release through co-activation of the receptors CRFR1 and CRFR2 (Lemos et al., 2012). Furthermore, CRF injections in NAc shell have shown to amplify positive motivation for cued rewards, in particular by magnifying incentive salience (Pecina et al., 2006).

The administration of i.v. placebo in the context of a therapeutic agent was associated with increased DA neurotransmission in the NAc. Placebo treatments in humans were initially hypothesized to be associated with the activity of mesolimbic DA cells during reward

anticipation and their capacity to adapt to environmental information (Fields, 2004; Irizarry and Licinio, 2005). This hypothesis was first confirmed in patients with Parkinson's disease (de la Fuente-Fernandez et al., 2002) and subsequently during placebo analgesia experiments (Scott et al., 2008). Furthermore, our group demonstrated that NAc BOLD signal during monetary reward anticipation was correlated with placebo-induced DA release as measured with PET (Scott et al., 2007). In our sample, DA release during placebo administration was not associated with the improvement of depressive symptoms after the i.v. or the oral placebo (changes in PIDS or QIDS-16RS) nor 10 weeks of antidepressant treatment (changes in QIDS-16RS, GAD-7, SHAPS and Apathy scores). On the contrary, and in a previously published study, we have shown that endogenous opioid mediated neurotransmission during placebo administration in a sample that included the volunteers whose data is reported here, was associated with both, improvement of depressive symptoms in response to 1 week of placebo treatment and 10 weeks of antidepressant treatment (changes in QIDS-16RS), and explained up to 43% of the variance in the response to the antidepressants (Pecina et al., 2015). This evidence supports a greater role of the opioid system in the actual "effectiveness" of the placebo, whereas the dopamine system might be involved in processing the "saliency" of the treatment itself or learning of the reward experience, as it has been supported extensively by the preclinical literature (Berridge and Robinson, 1998; Pecina and Berridge, 2005; Pecina et al., 2003).

Studies investigating the relationship between baseline $D_{2/3}$ binding measures and response to antidepressant treatment have revealed conflicting results. Ebert *et al* showed that 150 mg of amitriptyline/daily for three weeks led to a decrease in IBZM binding to DA D_2 receptors in five treatment responders, while it remained unchanged in non-responders (Ebert et al., 1996). Kimke *et al* also demonstrated increased striatal IBZM binding in responders to a selective serotonin reuptake inhibitor (SSRI), but instead binding was decreased in non-responders (Klimke et al., 1999). Contrary, striatal IBZM binding was significantly lower in patients who responded to a selective serotonin reuptake inhibitor (SSRI) compared to non-responders and control subjects (Klimke et al., 1999). Finally, Hirvonen *et al* found that fluoxetine, but not psychotherapy, increased [^{11}C]raclopride binding in the thalamus, but not within the striatum, although this increase was not correlated with clinical improvement (Hirvonen et al., 2011). Here we found that compared to MDD remitters, MDD non-remitters showed significantly greater baseline DA $D_{2/3}$ receptors in the NAc/vPAL area. These results are consistent with previous evidence, where age-corrected baseline IBZM binding in the striatum was significantly lower in treatment responders than in depressed non-responders and control subjects (Klimke et al., 1999). In that study there was a significant linear correlation between treatment response and change of D2 receptor binding during treatment in the basal ganglia. We also showed that non-remitter MDD patients showed significantly higher GAD-7 scores and greater placebo-induce DA release. This increased dopaminergic responsiveness may again be explained by the paradoxical effect of high CRF levels in patients with higher anxiety which might result in greater DA release(Lemos et al., 2012). It is also well documented that MDD patients with high anxiety symptoms are less likely to respond to antidepressant treatment (Davidson et al., 2002) and that concomitant use of anxiolytics/hypnotics is a significant predictor of treatment resistance in older adults with depression (Bosworth et al., 2002).

Our results point to baseline DA striatal abnormalities in patients with MDD which seem to be positively associated to symptoms of anxiety (NAc/vPAL) and negatively associated with motivational anhedonia (NAc). Furthermore, this work supports the existence of a DA-mediated endophenotype of lack of remission in response to SSRI treatment in depressed patients with high levels of anxiety, which will need to be confirmed in larger samples. While not directly linked to clinical improvement on subjective depression severity measures, the i.v. placebo intervention was associated with increased DA release in the ventral striatum, which was greater in MDD non-remitters, and might be attributed to the saliency of the stimuli. The results from this study, in addition to clarifying pathophysiological mechanisms associated with MDD, a heterogenous diagnostic cluster, could potentially be used to stratify patients who might initially benefit from 2nd line treatment options or augmentation pharmacotherapy targeting DA mechanisms. Increasingly personalized treatment decisions may reduce the overall lack of response to first line antidepressant treatments as well as to improve overall outcomes for MDD, a frequent and disabling disease process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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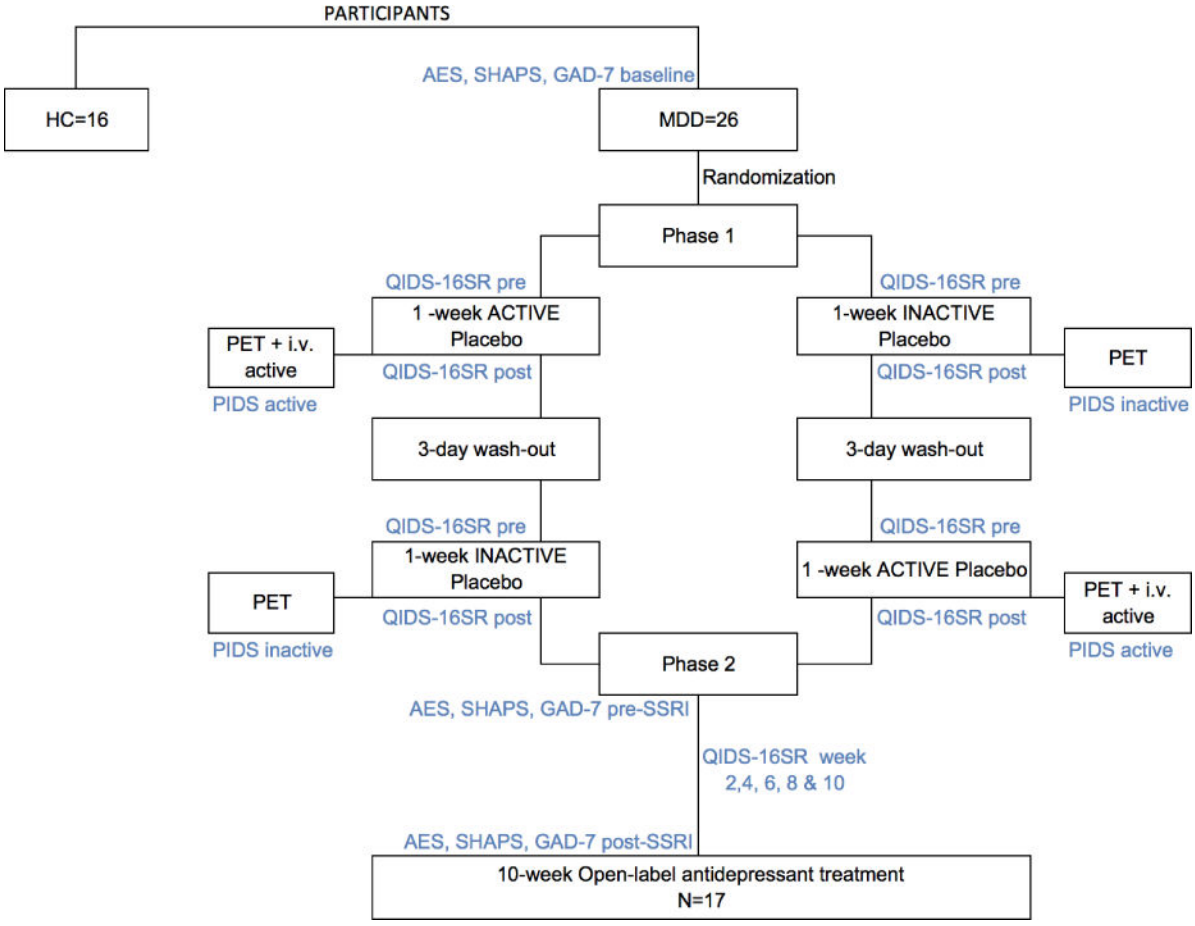

Figure 1. Experimental Design

Abbreviations: PET: Positron Emission Tomography; i.v.: intravenous; QIDS-16SR: Quick Inventory of Depression Symptomatology; PIDS: Patient's Impression of Depression Severity; HRDS: Hamilton Rating Depression Scale; Snaith: Snaith-Hamilton Pleasure Scale; NEO-PI-R: NEO Personality Inventory Revised.

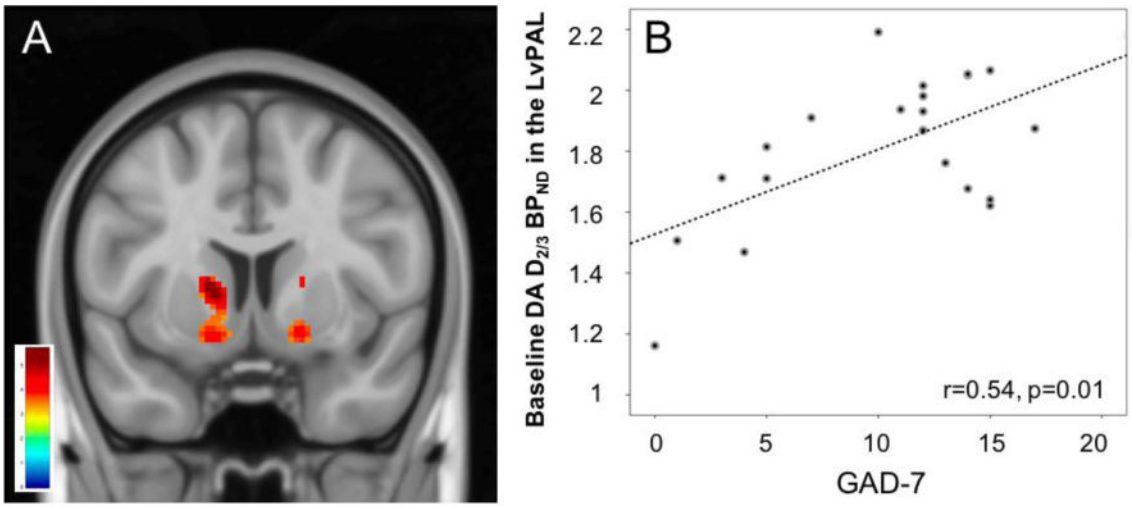

Figure 2. Group effect on striatal $D_{2/3}$ receptor availability at baseline (MDD>HC)

A) MDD patients had greater $D_{2/3}$ receptor binding in the ventral striatum, including the left nucleus accumbens/ventral pallidum (NAc/vPAL) and the left ventral caudate (vCAU), which are thought to reflect either an up-regulation of $D_{2/3}$ receptors, increased affinity of the receptor for the radioligand or a decreased synaptic dopamine concentration ($p<0.05$ FWE-corr, displayed at $p<0.001$). B) Correlation between GAD-7 anxiety scores and measures of baseline $D_{2/3}$ receptor availability in the left NAc/vPAL.

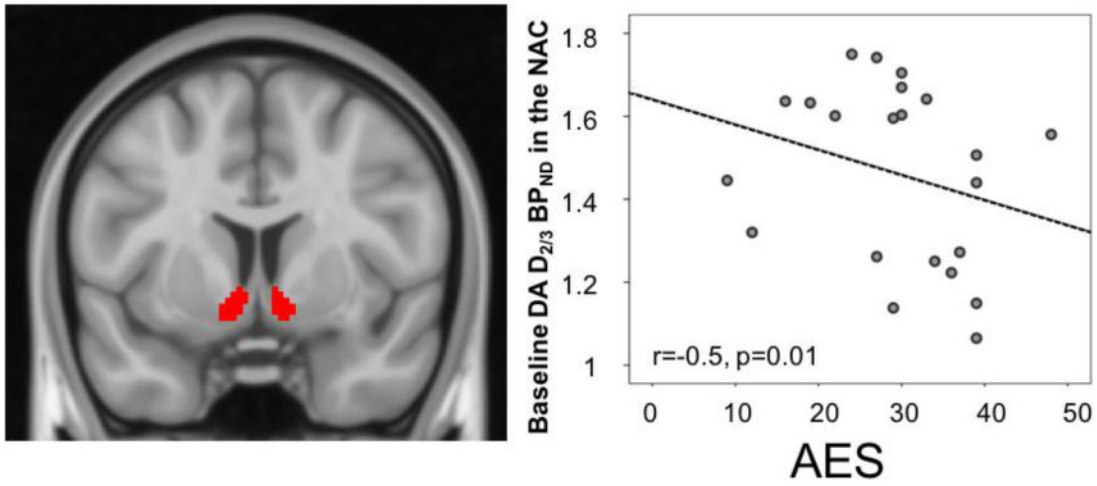

Figure 3.

Baseline D2/3 receptor availability in nucleus accumbens region of interest (ROI) (left) correlation with AES apathy scores (right).

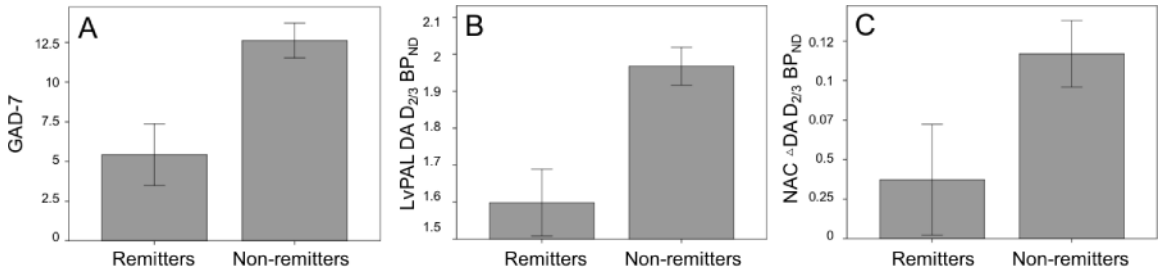

Figure 4. Univariate analysis of the effect of remission on

GAD-7 scores (A), baseline measures of DA $D_{2/3}$ BP_{ND} (B) and placebo-induced changes in DA $D_{2/3}$ BP_{ND} (C), after controlling for age, GAD-7 and baseline QIDS-16SR (B & C) (for all, $p<0.05$).