◆ Human Brain Mapping 32:800–811 (2011) ◆

Pramipexole Modulates the Neural Network of Reward Anticipation

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Abstract: Pramipexole is widely prescribed to treat Parkinson's disease. It has been found to cause impulse control disorders such as pathological gambling. To examine how pramipexole modulates the network of reward anticipation, we carried out a pharmacological functional magnetic resonance imaging study with a double-blind, within-subject design. During the anticipation of monetary rewards, pramipexole increased the activity of the nucleus accumbens (NAcc), enhanced the interaction between the NAcc and the anterior insula, but weakened the interaction between the NAcc and the prefrontal cortex. These results suggest that pramipexole may exaggerate incentive and affective responses to possible rewards, but reduce the top-down control of impulses, leading to an increase in impulsive behaviors. This imbalance between the prefrontal-striatum connectivity and the insula-striatum connectivity may represent the neural mechanism of pathological gambling caused by pramipexole. *Hum Brain Mapp 32:800–811, 2011.* © 2010 Wiley-Liss, Inc.

Key words: reward anticipation; pramipexole; nucleus accumbens; prefrontal cortex; insula; fMRI; functional connectivity

INTRODUCTION

Pramipexole is a dopamine D2/D3 receptor agonist which is widely prescribed to treat Parkinson's disease, targeting the dopamine deficit in the nigrostriatal pathway [Bennett and Piercey, 1999]. Pramipexole and other dopamine agonists have been reported to cause pathological gambling, an impulse control disorder creating serious life problems for afflicted individuals [Dodd et al., 2005; Weintraub et al., 2006]. For example, Dodd et al. [2005] observed that seven of 11 Parkinson's disease patients had developed pathological gambling within 1–3 months of achieving 4.5–7 mg pramipexole per day in therapy. This change in behavior suggests a distortion of reward processing which is mediated by the ventral striatum (including the nucleus accumbens, NAcc) and its interactions with other cortical and subcortical structures (Camara et al., 2009; Fehr and Camerer, 2007; Knutson and Greer, 2008]. Pramipexole may either change the way in which individuals weigh possible rewards (reward anticipation), experience reward outcomes (reward consummation), or both. During reward consummation, healthy adults receiving moderate doses of pramipexole (0.5 mg) showed a decreased NAcc activity in response to unexpected high wins in a lottery game [Riba et al., 2008]. The hypoactive pattern under pramipexole was similar to that observed in pathological gamblers [Reuter et al., 2005]. It was reasoned

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: DFG; Contract grant number: SFB 779, project A5; Contract grant sponsors: China Scholarship Council, La Marato TV3 foundation.

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Received for publication 11 January 2010; Accepted 8 March 2010
DOI: 10.1002/hbm.21067
Published online 9 June 2010 in Wiley Online Library (wileyonlinelibrary.com).

that pramipexole-treated individuals tended to seek higher rewards and make risky choices [Riba et al., 2008] to overcome the blunted NAcc response. With respect to reward anticipation, however, it remains unclear whether and how pramipexole may impact neural and cognitive processes. In the present study, we will examine how pramipexole modulates the network of reward anticipation using functional magnetic resonance imaging (fMRI). This study may help us to understand the neural mechanisms of pathological gambling caused by pramipexole.

The anticipation of monetary [Galvan et al., 2005; Knutson et al., 2000, 2001], taste [O'Doherty et al., 2002], and social rewards [Izuma et al., 2008; Spreckelmeyer et al., 2009] is subserved by a network of subcortical and cortical structures, including the NAcc, the supplementary motor cortex, the orbitofrontal cortex, the anterior cingulate cortex, and the insular cortex. Among these regions, the NAcc plays a primary role and discriminates between different levels of possible rewards. It is more activated for cues signaling potential rewards than for cues signaling no reward and activation is stronger for larger than smaller potential rewards [the incentive effect, see Galvan et al., 2005; Knutson et al., 2001].

Recent studies further linked the incentive effect to dopamine release in the ventral striatum. Knutson and coworkers proposed that released NAcc dopamine may change the postsynaptic membrane polarity by activating dopamine D1 receptors and engaging metabolic processes which eventually increase the local blood oxygen level dependent (BOLD) signal [Bjork et al., 2004; Knutson and Gibbs, 2007]. This hypothesis is supported by the observation that NAcc activity was correlated with NAcc dopamine release during reward anticipation [Schott et al., 2008]. According to this hypothesis, the NAcc activity in response to possible rewards may be regulated by dopamine autoreceptors D2 and D3, which can inhibit dopamine synthesis and/or release [Elsworth and Roth, 1997]. Administration of dopamine D2/D3 receptor agonists (e.g. pramipexole and amphetamine) may decrease NAcc dopamine release and reduce the incentive effect, while administration of dopamine receptor antagonists (e.g. olanzapine) may increase the NAcc dopamine release and amplify the incentive effect [Knutson and Gibbs, 2007]. However, these predictions seem inconsistent with existing findings. The D2 receptor agonist amphetamine (0.25 mg/kg) decreased the NAcc activation during the anticipation of monetary reward but did not affect the NAcc activation during the anticipation of no reward [Knutson et al., 2004]. The D2/D4 receptor antagonist olanzapine (5 mg) did not affect the NAcc activation during the anticipation of monetary reward but increased the NAcc activation during the anticipation of no reward [Abler et al., 2007]. In both cases, the incentive effects were reduced in the NAcc. Inconsistencies between theoretical predictions and empirical observations may result from the multiple effects of amphetamine which affects dopamine release as well as dopamine uptake [Schmitz et al., 2001; see Discussion]. Different dosages in different studies may also contribute to the inconsistencies in the literature [Lynch, 1991; Pugsley et al., 1995]. If pramipexole decreases the NAcc dopamine release as amphetamine does, we may observe a reduced NAcc activity during the anticipation of monetary reward. We may also obtain a reduced NAcc activity during the anticipation of no reward, if the effect of pramipexole shows up regardless of reward type. We will test this hypothesis in the current study.

Although the NAcc undoubtedly is a major relay for reward processing, it needs to be kept in mind that this structure is intimately linked with other cortical and subcortical regions. To gain a more complete picture of drug-induced changes of reward processing, the assessment of changes in the connectivity of the NAcc might be important. Previous studies have shown that the prefrontal cortex and the insular cortex are consistently activated during reward anticipation (for a meta-analysis, see Knutson and Greer, 2008]. The prefrontal cortex is assumed to control impulsive behavior and is deemed important for emotion regulation during decision making [Casey et al., 2008; Ernst et al., 2006; McClure et al., 2004]. Individuals who reported themselves as tending to continue previously rewarded behaviors (vs. impulsive behaviors) showed stronger white matter fiber connections between the striatum and frontal regions including the SMA and the orbitofrontal cortex [Cohen et al., 2009]. The insular cortex is associated with the general processing of emotions [Britton et al., 2006; Phillips et al., 1997; Takahashi et al., 2008] and has been shown to be functionally connected with the NAcc after reward delivery [Camara et al., 2008]. Moreover, insula activity correlates with the positive arousal experienced by individuals [Samanez-Larkin et al., 2007]. An imbalance between the prefrontal-striatal circuitry and the insula-striatal circuitry may thus lead to impulsive behaviors and suboptimal choices. For example, adolescents, who have a functionally mature limbic system but an immature prefrontal control system, have been characterized by risk-taking behaviors [Casey et al., 2008; see also, Galvan et al., 2006; Van Leijenhorst et al., 2010]. Pramipexole may cause a similar imbalance between different striatum-related circuitries by changing the strength of interregional interaction which in turn might be related to pathological gambling. We will test this hypothesis with a functional connectivity approach.

To test these hypotheses, we employed a double-blind, within-subject cross-over design in conjunction with the monetary incentive delay task [the MID task, Knutson et al., 2000; Fig. 1]. In the MID task, participants are asked to press a button whenever a white square appears. Before the square, they see a cue, which indicates the potential reward of a trial (reward anticipation). After the square, they see a feedback, which indicates the obtained reward of the trial (reward consummation). Each participant was tested twice in two separate sessions, once under pramipexole and once under placebo. To investigate the functional connections between the NAcc and other

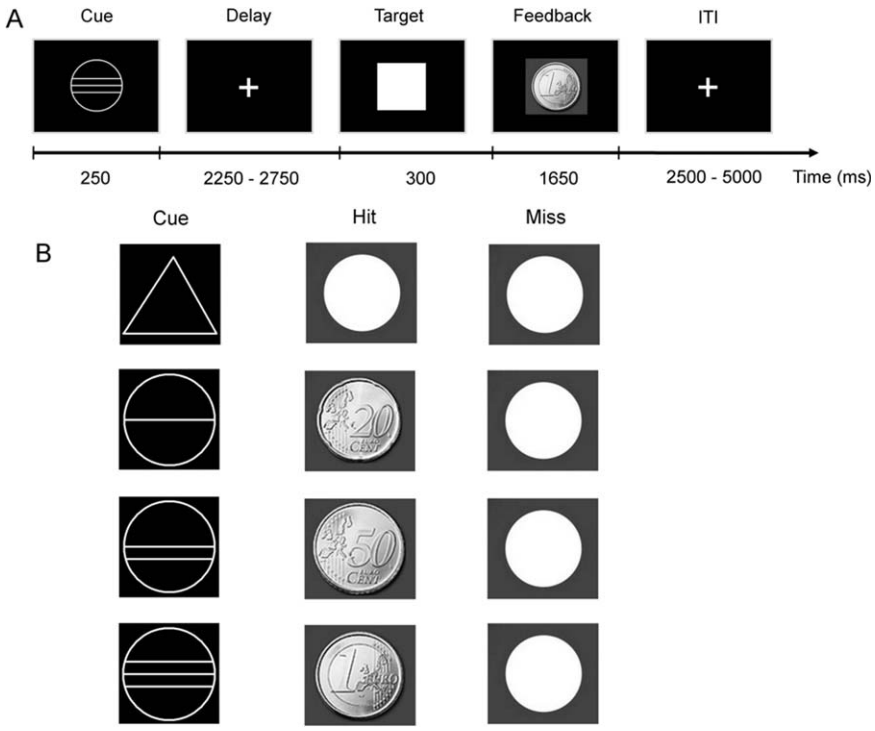

Figure 1.

(**A**) Timing of a single trial of the monetary incentive delay task. (**B**) Four types of cues (left) indicate different levels of potential rewards (middle). If participants exceed a response deadline for the button press to the target (miss) they get no reward (right).

cortical and subcortical regions, we used the "beta series correlation" method proposed by Rissman et al. [2004]. Unlike other connectivity techniques (e.g. psychophysiological interactions), this method has been developed to model the interregional interactions during distinct stages of a cognitive task (e.g. reward anticipation vs. consummation). This approach is implemented on the basis of the general linear model (GLM), using separate covariates to model hemodynamic responses of a particular stage in each single trial and giving rise to series of parametric estimates (beta values) for each stage. If two regions interact within a network, their beta series should be strongly correlated.

METHOD

All procedures had been cleared by the ethical review board of the University of Magdeburg. Experiments were carried out according to the declaration of Helsinki.

Participants

Only male subjects were included in this study to avoid problems that could arise with unknown pregnancies in female volunteers. Sixteen male volunteers (mean age 25 years, range: 21–28 years) participated in this study. They were right-handed and had normal or corrected-to-normal vision. None of them had a history of neurological or psychiatric disorder. All of them gave written informed consent and were paid according to their performance in the MID task (see below).

Design and Drugs

This study was carried out according to a double-blind randomized crossover design. Participants received pramipexole and placebo in two different sessions, which were separated by at least one week. In each session, participants received 20 mg domperidone in a nonblind fashion to antagonize potential nausea induced by pramipexole. At the same time, they received 0.5 mg pramipexole or placebo in a double-blind fashion according to a randomization table. The dose of pramipexole used in this study was similar to that used in a previous pharmacological-fMRI study of our lab [Riba et al., 2008] but less than that used in patients with Parkinson's disease (4.5–7 mg per day). Seven of them received pramipexole in the first session and the rest in the second session. The scanning started 2 h after the medication administration. After scanning, participants completed a questionnaire about their feelings. None of them reported nausea in the pramipexole session.

Stimuli and Task

In the MID task [Knutson et al., 2000; Fig. 1], participants are told that they will be paid according to their performances. They are asked to press a button as fast as possible whenever a white square appears on the screen. The target square is preceded by a cue, which indicates the potential monetary reward. On trials cued by a circle (66 trials), participants can earn money if they respond before the target disappears (response deadline). On trials cued by a triangle (22 trials), they will get no money even if they answer the target in time. There were three levels of potential rewards (22 trials each), which were indicated by the number of horizontal lines in the circle: 0.20 € (one horizontal line), 0.50 € (two horizontal lines), and 1.00 € (three horizontal lines). The target square is followed by a feedback indicating the reward obtained by displaying pictures of coins (0.20 €, 0.50 €, or 1.00 €). If participants exceed the response deadline or if the trial is cued by the triangle, a coin-sized white circle appears. The cue is presented for 250 ms and the cue-target interval varies between 2,250 and 2,750 ms. The feedback starts 300 ms after target onset and lasts for 1,650 ms. The duration of the target is adjusted for each participant according to his reaction times in a practice session to achieve an approximate hit rate of 66%. Trial sequence is pseudorandomized with intertrial intervals varying between 2,500 and 5,000 ms.

fMRI Data Acquisition

Data were collected in a neuro-optimized 1.5-T GE Signa Horizon LX scanner with a standard quadrature head coil. Functional images were obtained using a T2*-weighted echo planar imaging (EPI) sequence, with 2,000-ms time repetition, 35-ms time echo, and 80° flip angle. Each functional image consisted of 23 axial slices, with 64 × 64 matrix, 200 mm × 200 mm field of view (FOV), 5-mm thickness, 1-mm slice gap, and 3.125 mm × 3.125 mm in-plane resolution. Structural images were obtained using a T1-weighted 3D SPGR sequence. Each structural image consisted of 124 contiguous slices, with 256 × 256 matrix, 200 cm × 200 cm FOV, and 1.5-mm thickness.

fMRI Data Analysis

Data were analyzed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm). The first five volumes were discarded because of equilibration effects. Functional images were first phase-shifted with reference to the middle slice to correct differences in slice acquisition time. They were then realigned with a least squares approach and a rigid body spatial transformation to remove movement artifacts. Estimated movement parameters (six parameters per image: x, y, z, pitch, roll, and yaw) were involved in statistical analyses to minimize signal-correlated motion effects. Realigned images were normalized to the MNI-T1 template (resampled to 2 × 2 × 2 mm^3 voxel) by matching gray matter to a gray matter reference and white matter to a white matter reference [Ashburner and Friston, 2005]. Normalized images were smoothed with a Gaussian kernel of 8 mm full-width half-maximum and filtered with a high-pass filter of 128 s.

We carried out two statistical analyses, i.e. the standard univariate analysis and the functional connectivity analysis

Standard univariate analysis

The standard univariate analysis was performed to examine whether the NAcc was more activated for reward than no-reward cues or for pramipexole than placebo. Hemodynamic responses were modeled on the basis of a GLM with a canonical hemodynamic response function. The following events were specified and time-locked to their onsets: four types of cues (0 €, 0.20 €, 0.50 €, and 1.00 €), two types of targets (hit and miss), and five types of feedback (white circles in no-reward trials, 0.20 € coins, 0.50 € coins, 1.00 € coins, white circles in missed trials). For hits, reaction times were included as parametric modulators to account for trial-specific effects. Classical parameter estimation was applied with a one-lag autoregressive model to whiten temporal noise to correct the probability (P) of a false-positive voxel on the subject level. With the subject-level correction, there is no need for further correction on the group level [Smith et al., 2007]. Thus, we report uncorrected P values in group-level statistics. We analyzed both the cue and the feedback stages. We concentrated on the cue stage in the present communication. The result of the feedback stage is shown as Supporting Information (Supporting Information Fig. S1). For the cue stage, we first tested the effect of cue separately for placebo and pramipexole. For each participant, a contrast map was calculated by comparing reward (0.20 €, 0.50 €, and 1.00 €) and no-reward cues (0 €) in each medication condition. The contrast maps were entered into two one-sample t-tests (random effect) on the group level. Resulting maps were considered at $P < 0.001$ (uncorrected) with a minimum cluster of 20 voxels. Then we tested the main effects of cue (reward > no-reward cues) and medication (pramipexole > placebo). For each participant, eight contrast maps were calculated by comparing each condition with signal baseline. The contrast maps were entered into a flexible factorial test (random effect) on the group level with two factors, i.e. cue (four levels) and medication (two levels). The main effect of cue was considered at $P < 0.001$ (uncorrected) with a minimum cluster size of 20 voxels. The main effect of medication was considered at $P < 0.01$ (uncorrected) with a minimum cluster size of 20 voxels. The latter threshold was relatively liberal because of the subtle medication effect.

The whole brain analysis was followed by a region-of-interest (ROI) analysis. The bilateral NAcc ROIs were defined on the atlas of Anatomical Automatic Labeling [AAL, Tzourio-Mazoyer et al., 2002] according to Mawlawi

et al. [2001] and Martinez et al. [2003]. For each participant, the percentages of signal change were extracted from the eight conditions and averaged within each ROI for each condition. The values of percent signal changes were entered into a repeated-measures ANOVA with three factors: cue (0 € vs. 0.20 € vs. 0.50 € vs. 1.00 €), medication (pramipexole vs. placebo), and hemisphere (left vs. right). Results were considered with Bonferroni correction.

Functional connectivity analysis

The functional connectivity analysis was performed to examine how the interactions between the NAcc and other regions were changed by pramipexole during reward anticipation. This approach is based on the hypothesis that if two regions interact within a network, their activity patterns should be strongly correlated [Rissman et al., 2004]. This analysis was implemented on the basis of another GLM using separate covariates to model hemodynamic responses of a particular stage (cue) in each single trial. For each participant, parameter estimates (beta values) of cues were extracted to form a set of cue-specific beta series. We analyzed both the left and the right NAcc. We concentrated on the left NAcc in the present communication. The result of the right NAcc is shown as Supporting Information (Supporting Information Fig. S2). Beta series of the left NAcc ROI were averaged across voxels within the critical region and correlated with beta series of every other voxel in the whole brain. We first tested the connectivity patterns separately for reward and no-reward cues and separately for placebo and pramipexole. In this step, we did not distinguish between the cues of 0.20 €, 0.50 €, and 1.00 €. Four maps of correlation coefficients were calculated for each participant. All correlation maps were normalized using an arc-hyperbolic tangent transform for further statistical inference. Normalized maps were entered into four one-sample t tests (random effect) on the group level. Resulting maps were considered at $P < 0.001$ (uncorrected) with a minimum cluster of 20 voxels. The resulting map showed regions correlated with the left NAcc in beta series and were inferred to be functionally connected with the left NAcc in a particular condition. Then we tested the main effects of medication (pramipexole > placebo, placebo > pramipexole) and cue (reward > no-reward cues, no-reward > reward cues). In this step the cues of 0.20 €, 0.50 €, and 1.00 € were treated separately in beta correlation. Eight maps of correlation coefficients were calculated for each participant. All correlation maps were normalized by using an arc-hyperbolic tangent transform for further statistical inference. Normalized maps were entered into a flexible factorial test (random effect) on the group level with two factors, i.e. medication (two levels) and cue (four levels). Both main effects were considered at $P < 0.001$ (uncorrected) with a minimum cluster of 20 voxels.

The whole brain analysis was followed by a ROI analysis. Functional ROIs were defined as spheres with 4-mm radius in the medial superior frontal gyrus (coordinates in MNI: 0, 46, 34) and the right anterior insula (40, 22, 2). The coordinates were from the flexible factorial test. For each participant, the normalized correlation coefficients (r) were extracted from the eight correlation maps and averaged within each ROI for each condition. The normalized r values were entered into a repeated-measures ANOVA with two factors: medication (pramipexole vs. placebo) and cue (0 € vs. 0.20 € vs. 0.50 € vs. 1.00 €). Results were considered with Bonferroni correction.

Behavioral Data Analysis

The percentage of responses within the response deadline (hit rate) was calculated for each participant in each condition. The hit rates were first entered into a repeated-measures ANOVA with two factors, medication (placebo vs. pramipexole) and cue (0 € vs. 0.20 € vs. 0.50 € vs. 1.00 €), to test whether behavioral responses were modulated by medication or cue. They were then entered into another ANOVA with two factors, Session (first vs. second) and cue, to test whether participants were more accurate in their second than first sessions (practice effect).

RESULTS

Behavioral Results

Under placebo, percentages of responses within the response deadline were 61% (SE = 6%) for 0 €, 81% (4%) for 0.20 €, 79% (4%) for 0.50 €, and 85% (4%) for 1.00 €. Under pramipexole, hit rates were 56% (SE = 4%) for 0 €, 79% (3%) for 0.20 €, 80% (2%) for 0.50 €, and 86% (2%) for 1.00 €. There was a main effect of Cue ($F(3,45) = 29.73$, $P < 0.001$) but neither a main effect of medication nor an interaction between medication and cue ($F < 1$). Participants were more accurate for reward than no-reward cues (1.00 € vs. 0 €, 0.50 € vs. 0 €, and 0.20 € vs. 0 €: $P < 0.001$, pair-wise, Bonferroni corrected). In the first session, hit rates were 60% (5%) for 0 €, 81% (4%) for 0.20 €, 81% (3%) for 0.05 €, and 86% (3%) for 1.00 €. In the second session, hit rates were 57% (5%) for 0 €, 79% (3%) for 0.20 €, 79% (3%) for 0.50 €, and 85% (2%) for 1.00 €. No effect of session or interaction between session and cue was obtained ($F < 1$), indicating that participants were equally accurate in the two sessions.

Standard Univariate Results

Table I and Figure 2 show regions more activated for reward than no-reward cues in different medication conditions. The NAcc was anatomically defined and marked with a black outline in the figures. As revealed by the one-sample t tests, the bilateral NAcc were more activated for reward than no-reward cues under both placebo and pramipexole (Fig. 2A). In both medication conditions, the

TABLE I. Regions more activated for reward than no-reward cues

			Placebo					Pramipexole				
Region	BA	H	*x*	*y*	*z*	*t*	Size	*x*	*y*	*z*	*t*	Size
Nucleus accumbens/caudate nucleus		L	−2	8	−10	4.53	962	−4	8	−10	5.98	962
		R	18	8	−12	8.12	994	8	4	−10	5.95	994
Putamen/pallidum		L	−20	2	−10	7.24	1302	−24	8	−8	8.08	1302
		R	14	0	−4	7.91	1344	−22	−4	12	6.80	1344
Insula		L	−32	6	4	5.19	109	−32	0	4	4.44	1858
		R	32	14	6	4.39	33	26	28	2	3.99	1770
Supplementary motor area	6	R	12	−6	64	5.69	2371	10	0	54	7.55	2147
Anterior cingulate cortex	32	L	−8	46	12	6.12	321	−8	42	12	4.58	45
Middle cingulate cortex	24/32	L						−10	18	38	4.14	25
		R	8	4	34	4.65	33					
Superior frontal gyrus	9	L	−24	34	38	4.42	66					
Middle frontal gyrus	46	L	−36	40	16	4.05	50	−42	50	6	5.01	45
		R	40	44	32	5.71	21					
Inferior frontal gyrus	44/45	L	−38	38	8	5.17	50	−62	6	8	4.30	30
		R	50	8	28	5.26	75					
Precentral gyrus	6/4	L	−34	−24	62	7.25	3526	−54	−2	26	4.23	3526
		R	32	−16	56	7.68	3381	30	−12	68	4.95	238
Postcentral gyrus	4/3	L	−54	−4	22	5.55	3892	−52	−10	30	8.03	3892
		R						42	−32	54	4.31	83
Rolandic operculum		L	−50	−10	12	5.55	405					
		R	48	−26	22	6.07	284	48	−12	12	5.34	81
Superior temporal gyrus	42	L	−48	−40	12	5.84	44					
		R	56	−38	20	4.32	284					
Middle temporal gyrus	21/20/37	L	−66	−24	−10	5.80	104	−54	−14	−20	4.47	22
		R						46	−70	8	4.45	27
Inferior temporal gyrus	20/37	R	52	−46	−24	7.44	2827	54	−62	−4	4.83	55
Superior parietal lobule	7	L						−22	−60	56	5.01	79
Inferior parietal lobule	40	L	−40	−48	44	4.56	44	−38	−40	34	5.47	167
Precuneus	7	L						−12	−68	44	5.30	257
Superior occipital gyrus	7	R	22	−66	38	7.36	2222					
Middle occipital gyrus	18/19	L						−32	−68	36	4.81	40
		R						32	−88	8	4.70	46
Inferior occipital gyrus	18/19	L	−28	−92	−12	6.05	1148	−42	−74	−12	5.54	52
		R	28	−92	−12	7.82	503	36	−92	−2	4.04	46
Calcarine	17/18	L						−12	−66	12	5.35	78
		R	8	−70	16	5.18	77	18	−98	−6	5.07	69
Cuneus		L						−12	−72	28	6.26	257
Midbrain		6	−24	−4	5.16	1057	4	−20	−2	6.03	1100	
Cerebellum		L	−16	−68	−46	4.42	22	−2	−58	−24	6.66	2422
		R	4	−72	−36	6.20	1795	4	−74	−44	7.49	

BA, Brodmann area; H, hemisphere; coordinates in MNI; *t*, statistic values; L, left; R, right; Size, number of voxels.

bilateral NAcc were coactivated with a distributed set of brain structures including putamen/pallidum, insula, supplementary motor area, anterior and middle cingulate cortex, middle and inferior frontal gyrus, pre- and postcentral gyrus, Rolandic operculum, middle and inferior temporal gyrus, inferior parietal lobule, inferior occipital gyrus, midbrain, and cerebellum. Specifically, activations of the superior frontal gyrus, superior temporal gyrus, and superior occipital gyrus were only observed under placebo, whereas activations of the superior parietal lobule, middle occipital gyrus and cuneus were only observed under pramipexole. In addition to the main effect of cue in the bilateral NAcc (left: $t = 4.73$, $P < 0.001$; right: $t = 4.17$, $P < 0.001$), the flexible factorial test revealed a main effect of medication (Fig. 2B). The bilateral NAcc were more activated under pramipexole than under placebo (left: $t = 2.35$, $P < 0.01$; right: $t = 2.95$, $P < 0.01$). Although being subtle, the medication effect in the NAcc was confirmed by the independent ROI analysis (Fig. 2C). With the percentage of signal change extracted from the NAcc, we observed a main effect of medication (F (1, 15) = 4.85, $P < 0.05$), indicating that the NAcc was more activated under pramipexole than under placebo. In addition, a main effect of cue (F (3, 45) = 22.43, $P < 0.001$) was obtained,

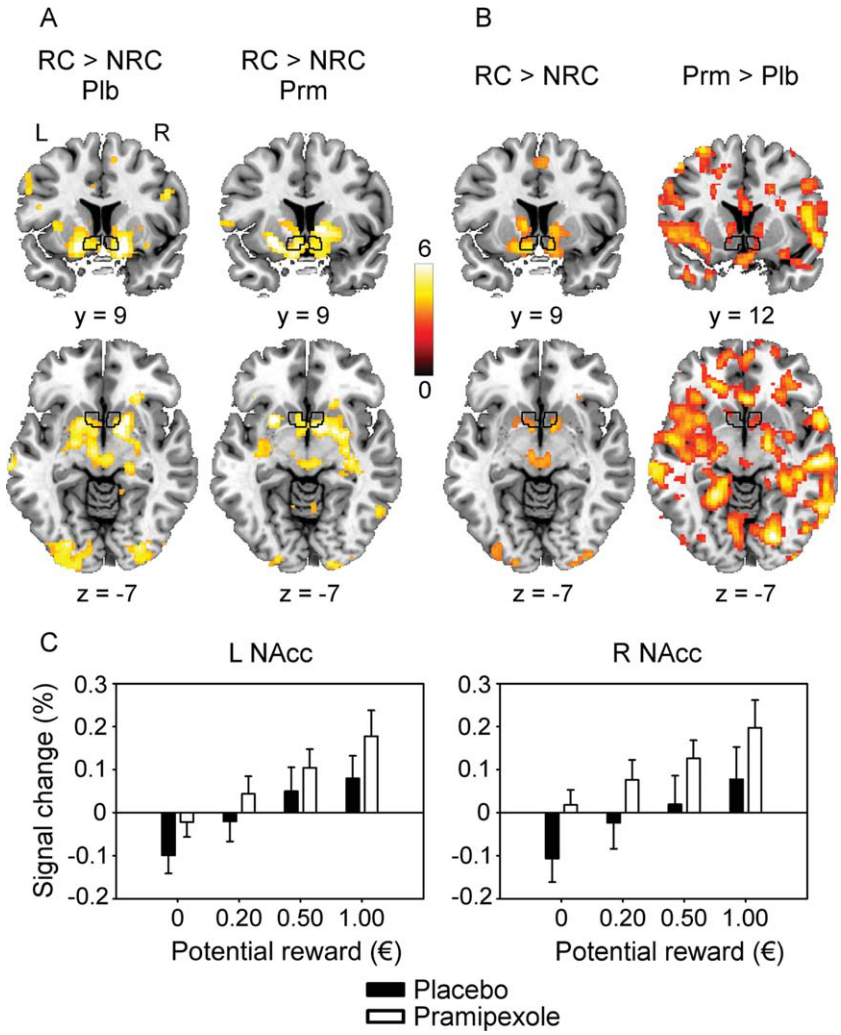

Figure 2.

Activations in the NAcc (marked by a black outline) during reward anticipation. (**A**) Activity larger for reward than no-reward cues (RC > NRC) under placebo (Plb) or under pramipexole (Prm). (**B**) Activity larger for reward than no-reward cues (RC > NRC) across medication conditions and activity larger under pramipexole than under placebo (Prm > Plb) across cues. Color scale indicates *t* values. Coordinates in MNI; L, left; R, right. (**C**) Percentage of signal change in the bilateral NAcc during reward anticipation under placebo (black) and pramipexole (white). Bars show means and error bars indicate standard errors.

indicating that the NAcc showed greater activations for potential rewards than no reward (1.00 € vs. 0 €, 0.50 € vs. 0 €, and 0.20 € vs. 0 €: $P < 0.05$, pair-wise, Bonferroni corrected), and for larger than smaller potential rewards (1.00 € vs. 0.50 €, 1.00 € vs. 0.20 €, and 0.50 € vs. 0.20 €: $P < 0.05$). There was no interaction between medication and cue ($F < 1$) or any effect of hemisphere ($P > 0.29$).

Functional Connectivity Results

Figure 3A shows regions interacting with the left NAcc in different cue and medication conditions. For both reward and no-reward cues, the left NAcc showed stronger connections with the prefrontal cortex (PFC) under placebo but stronger connections with the insula (especially in the right hemisphere) under pramipexole. The visual inspection was supported by the flexible factorial test (Fig. 3B and Table II). The connectivity between the left NAcc and the bilateral insula was stronger under pramipexole than under placebo, whereas the connectivity between the left NAcc and the medial superior frontal gyrus/anterior cingulate cortex (mSFG/ACC), medial orbitofrontal cortex (mOFC), supplementary motor area/middle cingulate cortex (SMA/MCC), superior frontal gyrus (SFG), and inferior frontal gyrus (IFG) was stronger under placebo than pramipexole. There was no significant difference between reward and no-reward cues in either direction. Figure 3C illustrates the normalized correlation

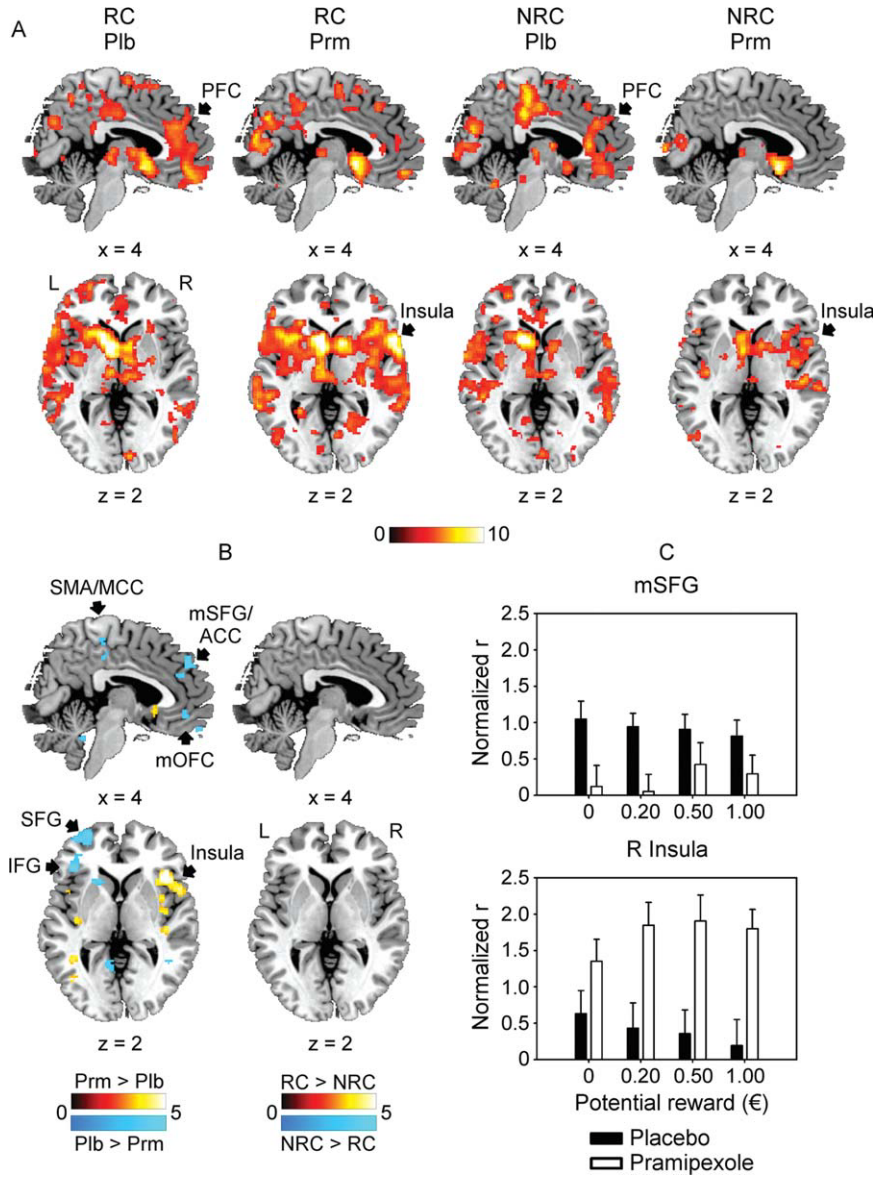

Figure 3.

Functional connectivity between the left NAcc and other areas during reward anticipation. (**A**) For both reward (RC) and no-reward cues (NRC), the NAcc showed more connections with the prefrontal cortex (PFC) under placebo (Plb) but more connections with the insula under pramipexole (Prm). (**B**) The NAcc-connectivity was stronger under pramipexole than under placebo (Prm > Plb) in the Insula. The NAcc-connectivity was stronger under placebo than under pramipexole (Plb > Prm) in prefrontal regions such as the medial superior frontal gyrus/anterior cingulate cortex (mSFG/ACC), supplementary motor area/middle cingulate cortex (SMA/MCC), medial orbitofrontal cortex (mOFC), superior frontal gyrus (SFG), and inferior frontal gyrus (IFG). There was no significant difference in functional connectivity between reward and no-reward cues (neither for RC > NRC nor for NRC > RC). Color scale indicates t values. Coordinates in MNI; L, left; R, right. (**C**) Normalized correlation coefficients (*r*) in the mSFG and the right insula during reward anticipation under placebo (black) and pramipexole (white). Bars show means and error bars indicate standard errors.

coefficients (*r*) in each condition for the mSFG and the right anterior insula. For the mSFG, we obtained a main effect of medication (F (1, 15) = 12.78, $P < 0.01$), indicating that the NAcc-mSFG correlation was stronger under placebo than under pramipexole. For the right anterior insula, we obtained another main effect of medication (F (1, 15) = 29.52, $P < 0.001$), indicating that the NAcc-insula correlation was stronger under pramipexole than under placebo. There was no main effect of Cue ($F < 1$) or interaction between medication and cue ($P > 0.24$) in either ROI.

TABLE II. NAcc-connectivity stronger under pramipexole than under placebo or that stronger under placebo than under pramipexole

Region	BA	H	*x*	*y*	*z*	*t*	Size
		Pramipexole > placebo					
Insula		L	−44	10	−4	3.97	27
		R	40	22	2	6.22	367
Nucleus accumbens		R	6	16	−2	4.06	41
Middle frontal gyrus	46	R	30	32	26	5.32	122
Superior ortitofrontal cortex	11	R	16	46	−22	4.40	31
Superior temporal gyrus	21/22	R	42	−24	2	4.23	29
Middle occipital gyrus	37	L	−40	−66	4	3.98	42
Calcarine	17	R	10	−80	14	4.38	20
Thalamus		R	16	−20	12	3.70	21
Cerebellum		L	−34	−48	−24	5.42	121
		R	44	−72	−40	5.52	64
		Placebo > pramipexole					
Medial superior frontal gyrus	9	L/R	0	46	34	4.32	156
Anterior cingulate cortex	32	L/R	0	38	26	4.18	
Middle cingulate cortex	23	L/R	0	−32	40	4.31	54
Supplementary motor area	4	R	8	−28	54	4.24	146
Superior frontal gyrus	11	L	−30	58	4	5.27	426
	6	R	16	10	50	4.58	397
Middle frontal gyrus	46	L	−40	16	42	4.46	37
Inferior frontal gyrus	45	L	−40	30	2	5.25	119
	6	R	50	6	22	5.60	350
Medial orbitofrontal cortex	11	L/R	12	40	−12	4.69	242
Rectus	11	R	6	56	−22	4.48	99
Precentral gyrus	3	R	40	−22	54	4.30	27
Postcentral gyrus	4	L	−46	−16	50	5.03	156
		R	20	−36	72	4.46	38
Superior parietal gyrus	7	L	−30	−72	52	4.40	24
Inferior parietal gyrus	40/39	L	−40	−58	46	5.51	308
		R	54	−44	50	4.61	40
Supramarginal gyrus	40	L	−56	−24	28	4.62	70
Superior temporal gyrus	41	R	50	−28	18	3.97	40
Middle temporal pole	20	R	40	8	−38	4.42	57
Inferior temporal gyrus	37	L	−60	−56	−10	4.13	46
	20	R	54	−14	−28	5.21	139
Fusiform gyrus	20	L	−28	−26	−28	4.37	92
	19	R	34	−70	−8	4.73	55
Middle occipital gyrus	19	R	48	−78	10	6.45	111
Inferior occipital gyrus	19	R	32	−86	−18	4.21	43
Cuneus	19	L	−4	−88	30	4.47	88
	18	R	18	−92	12	4.04	29
Caudate		L	−18	18	8	4.87	155
Cerebellum		L	−2	−46	−28	4.65	81

BA, Brodmann area; H, hemisphere; coordinates in MNI; *t*, statistic values; L, left; R, right; Size, number of voxels.

DISCUSSION

In this study, we found that pramipexole modulated the network of reward anticipation by changing the local activity of the NAcc, and by altering its connectivity with cortical regions. Consistent with previous studies [Galvan et al., 2005; Knutson et al., 2001], we observed the incentive effect of the NAcc during reward anticipation. Under placebo and pramipexole the NAcc showed more activation for potential rewards than no reward, and for larger than smaller potential rewards. Pramipexole increased the NAcc activity during the anticipation of monetary reward and during the anticipation of no reward. In addition, we found a shift in connectivity patterns regarding prefrontal-striatal circuitry and insula-striatal circuits: Specifically, the NAcc showed strong connections with the medial superior frontal gyrus (mSFG), medial orbitofrontal cortex (mOFC), supplementary motor area (SMA), anterior and middle cingulate cortex (ACC and MCC), superior and inferior frontal gyrus (SFG and IFG) under placebo. By

contrast, NAcc's connections with these frontal regions decreased under pramipexole. Instead, enhanced connectivity with the anterior insula was observed.

Our observation that pramipexole increased rather than decreased the NAcc activation during reward anticipation, seems inconsistent with the prediction of Knutson and Gibbs [2007] and also with previous observations regarding the effect of amphetamine in a rather similar paradigm [Knutson et al., 2004]. The current pattern of results is, however, consistent with predictions that follow from the tonic-phasic dopamine hypothesis proposed by Grace [2000] and Bilder et al. [2004]. This hypothesis assumes that dopamine dynamics in the striatum are driven by the interactions of phasic and tonic dopamine release. Phasic dopamine release is triggered by exogenous stimuli (e.g, reward cues). The transiently released dopamine is rapidly removed from the synaptic cleft via reuptake processes and is unlikely to influence extracellular dopamine levels. By contrast, tonic dopamine release is regulated by glutamatergic projections from the prefrontal cortex. The slowly but constantly released dopamine determines the general level of extracellular dopamine and therefore sets the rather stable baseline level of dopamine receptor stimulation. Alterations in tonic dopamine release may induce homeostatic processes that serve to restore the original stable level of dopamine receptor stimulation. In the current case, pramipexole may modulate the NAcc dopamine release via both processes. On the one hand, pramipexole may reduce phasic dopamine release by activating dopamine autoreceptors D2/D3. On the other hand, it may change tonic dopamine release by affecting prefrontal-striatum glutamatergic projections. It has been reported that the stimulation of cortical dopamine D2 receptors may directly inhibit the activity of glutamate neurons in the prefrontal cortex and subsequently the activity of dopamine neurons in the NAcc, eventually leading to a decrease in extracellular dopamine level [Beyer and Steketee, 2000; Del Arco and Mora, 2005]. To compensate the change in dopamine receptor stimulation, the amplitude of dopamine efflux is increased. The effect of pramipexole on phasic processes may be overridden by the effect of pramipexole on tonic processes, resulting in the increased NAcc activity during reward anticipation. The increased NAcc activity may reflect exaggerated incentive responses to possible rewards, and could be followed by impulsive behaviors and suboptimal choices [Kuhnen and Knutson, 2005].

Differences between the current results and the findings for amphetamine [Knutson et al., 2004] may originate from the multiple effects of amphetamine. Amphetamine can not only activate dopamine D2 receptors but can also bind to dopamine transporters inhibiting dopamine uptake [Schmitz et al., 2001]. Consequently, released dopamine cannot be removed from the synaptic cleft immediately, leading to an increase in extracellular dopamine level. In this case, the amplitude of dopamine efflux may be decreased to restore the initial stable level of dopamine receptor stimulation. In line with this assumption, previous studies reported that the amount of dopamine released per pulse can be significantly reduced by amphetamine [Schmitz et al., 2001]. The decreased NAcc dopamine release may underlie the reduced NAcc activity observed by Knutson et al. [2004][1].

An important and novel finding of this study is that pramipexole changed connectivity patterns of the NAcc. Under pramipexole, prefrontal regions such as the mSFG, mOFC, SMA, ACC, MCC, SFG, and IFG were less positively correlated with the NAcc. This weakened connectivity between the NAcc and the prefrontal cortex suggests that top-down executive control of impulsive decisions, usually ascribed to the medial prefrontal cortex [Bechara, 2005; Cohen et al., 2009; McClure et al., 2004], may be impaired under pramipexole. The enhanced connectivity between the NAcc and the anterior insula, on the other hand, may amplify emotional influences on decision making. Such an imbalanced network may lead to an overestimation of potential rewards but to an underestimation of possible risks. This change in connectivity patterns might thus contribute the tendency of pramipexole treated patients to develop pathological gambling and other impulse-control disorders. It is interesting to note that similar ideas have been proposed to interpret the increased occurrence of risky behaviors in adolescents [Casey et al., 2008; Ernst et al., 2005; Van Leijenhorst et al., 2010]. Casey et al. [2008] proposed that decision making in adolescents is biased by limbic regions (e.g. NAcc) rather than prefrontal regions because the NAcc development precedes the prefrontal development. During adolescence, the functionally more mature limbic system has a great sensitivity to upcoming rewards, while the immature prefrontal system cannot guide appropriate estimations of risky choices. In the face of emotionally salient stimuli such as money, adolescents showed more activations in the NAcc and the anterior insula [Van Leijenhorst et al., 2010], but less focal activation in the prefrontal cortex [Galvan et al., 2006], as compared to young adults who have a fully mature prefrontal control system. A similar antagonistic interplay of limbic and prefrontal regions has also been proposed to underlie intertemporal choice behavior. Although activity in limbic regions is driven by smaller but immediately available rewards, choices for larger but delayed rewards engage prefrontal areas [McClure et al., 2004].

In conclusion, we found that pramipexole modulates the network of reward anticipation by increasing the local activity of the NAcc, enhancing the insula-striatal connectivity, and weakening the prefrontal-striatal connectivity. These

[1]We also analyzed the impact of pramipexole during reward outcome. Pramipexole increased the NAcc activity in response to obtained rewards, although the main effect of Medication only reached significance in the right hemisphere (see Supp. Info. Fig. S2). This result seems inconsistent with that of Riba et al. [2008], in which pramipexole decreased the NAcc activity in response to unexpected high wins. This inconsistency may come from the difference in expectancy during reward consummation. The magnitude of reward is predictable in the current MID task (as indicated by the preceding cue) but not in the gambling task used by Riba et al. [2008]. It is unclear, however, how the NAcc activity is modulated by the interaction of pramipexole and expectancy and further studies are needed to investigate this issue.

alternations may reflect exaggerated incentive and affective responses to possible rewards and insufficient top-down control of impulsive choices. This imbalanced network of reward anticipation may underlie impulse control disorders, especially pathological gambling, observed in patients with Parkinson treated by pramipexole and other dopaminergic agonists.

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