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Effects of expectation on the brain metabolic responses to methylphenidate and to its placebo in non-drug abusing subjects

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The response to drugs is affected by expectation, which in turn is sensitive to prior drug experiences. Here, we evaluate the effects of expectation on the responses to intravenous methylphenidate (0.5 mg/kg) in fifteen subjects who had minimal experience with stimulant drugs. We used positron emission tomography to measure brain glucose metabolism, which we used as a marker of brain function and tested them under four randomized conditions (1) expecting placebo and receiving placebo; (2) expecting placebo and receiving methylphenidate; (3) expecting methylphenidate and receiving methylphenidate; (4) expecting methylphenidate and receiving placebo. We show that methylphenidate-induced decreases in striatum were greater when subjects expected to receive methylphenidate than when they were not expecting it. We also show that the subjects' expectations affected their responses to placebo. That is, when subjects expected to receive methylphenidate but received placebo there were significant increases in ventral cingulate gyrus (BA 25) and nucleus accumbens (regions involved with emotional reactivity and reward). The effect was largest in subjects who, because of experimental randomization, had not experienced methylphenidate. Because subjects were told that methylphenidate could be experienced as pleasant, unpleasant or devoid of subjective effects these results suggest the involvement of the ventral cingulate and of the nucleus accumbens in processing expectation for "uncertain drug effects". Thus, the state of expectation needs to be considered as a variable modulating the reinforcing and therapeutic effects of drugs even in subjects who have no prior experience with the drug.
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Introduction

Expectation and conditioning have been shown to modulate the reinforcing effects of drugs of abuse. For example, in drug abusers, the responses to a drug are more pleasurable when subjects expect to receive the drug than when they do not (Kirk et al., 1998). Also, the ability of drugs to increase dopamine (DA) in nucleus accumbens (NAc), an effect associated with their reinforcing value (Di Chiara and Imperato, 1988), is larger when animals are given cocaine in an environment where they had previously received it and therefore expected it than in an environment where they had not (Duvauchelle et al., 2000), or when animals self-administer cocaine than when administration is involuntary (Hemby et al., 1997). Similarly, cocaine-induced changes in regional brain metabolism, which is an indicator of brain function (Sokoloff et al., 1977), differ when animals self-administer cocaine from when administration is involuntary (Graham and Porrino, 1995) and when cocaine is given in a conditioned environment versus their home cage (Knapp et al., 2002).

We have shown that, in cocaine abusers, expectation enhanced the behavioral and the regional brain metabolic responses to intravenous methylphenidate (MP), which has a mechanism of action (blockade of the DA transporter) similar to cocaine (Volkow et al., 2003). We interpreted the enhancement of MP's effects by expectation as a reflection of conditioned responses related to subjects' chronic drug use. Because expectation is influenced by prior drug experiences, here, we investigate the effects of expectation on the brain responses to MP in non-drug abusing subjects to evaluate if this cognitive process affected drug responses in individuals with minimal drug experiences. For this purpose, we compared the response to expected versus unexpected MP. We also evaluated the effects of expectation independent of its interaction with the pharmacological effects of methylphenidate by testing subjects when they expected methylphenidate but received placebo and comparing this to their responses when they expected

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placebo and received placebo. Subjects were told that intravenous MP was perceived as rewarding by some individuals, aversive by others and as having no subjective effects by others (Volkow et al., 1999b). Brain responses were assessed using positron emission tomography (PET) and 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG), which were used to measure regional brain glucose metabolism. We used MP since it shares with cocaine the same primary site of action (both drugs block DA transporters (DAT) with similar potencies and rapid onset (Volkow et al., 1995)) and initial subjective effects (cocaine abusers report that intravenous MP feels similar to cocaine (Wang et al., 1997)), even though MP has lower abuse liability due to slower clearance in brain (Volkow et al., 1995). We hypothesized that expectation would activate striatum (including nucleus accumbens), orbitofrontal cortex and cingulate gyrus, which are DA-modulated brain regions involved with processing expectation, uncertainty and predictability of reward (Amiez et al., 2005; Berns et al., 2001; Tremblay and Schultz, 2000).

Methods

Subjects

We recruited and scanned 16 healthy male subjects (36 ± 7 years of age) who responded to an advertisement but report only on 15, since one of the scans for a subject had a technical problem. Subjects were excluded if they had a current or past history of drug abuse or dependence (except nicotine), a current or past history of other psychiatric diseases; past or present history of neurological, cardiovascular or endocrinological disease; history of head trauma with loss of consciousness greater than 30 min; and current medical illness. Subjects were also excluded if they had not had any prior exposure to illegal substances. Written informed consent was obtained for all subjects after complete description of the study and following the guidelines set by the Institutional Review Board at Brookhaven National Laboratory.

Scans

PET scans were acquired on a whole-body, high-resolution positron emission tomograph (Siemens/CTI ECAT HR+; with 4.6 × 4.6 × 4.2 mm resolution at center of field of view and 63 slices) in 3D dynamic acquisition mode using FDG. Details about the methods for positioning of subjects, catheterizations, transmission scans, and blood sampling and analysis are published elsewhere (Wang et al., 1993). Briefly, a 20-min emission scan was started 35 min after injection of 4–6 mCi of FDG. Arterialized blood sampling was used to measure FDG in plasma. During the study, subjects were positioned supine in the PET camera with their eyes open; the room was dimly lit, and noise was kept to a minimum except for the periodic evaluation of drug effects.

Subjects were scanned on 4 different days with FDG under the 4 conditions defined by the expectation-by-drug combinations: (1) expecting placebo and receiving placebo (PL–PL; this condition is used as *baseline*); (2) expecting placebo and receiving MP (PL–MP; *unexpected MP*); (3) expecting MP and receiving MP (MP–MP; *expected MP*); (4) expecting MP and receiving placebo (MP–PL; *expectation placebo condition*) (Fig. 1A). The order of the conditions was randomized across subjects. Placebo (3 cc of saline) or MP (0.5 mg/kg, i.v.) was injected over 60 s beginning 1 min prior to FDG injection. The plasma concentrations of MP were

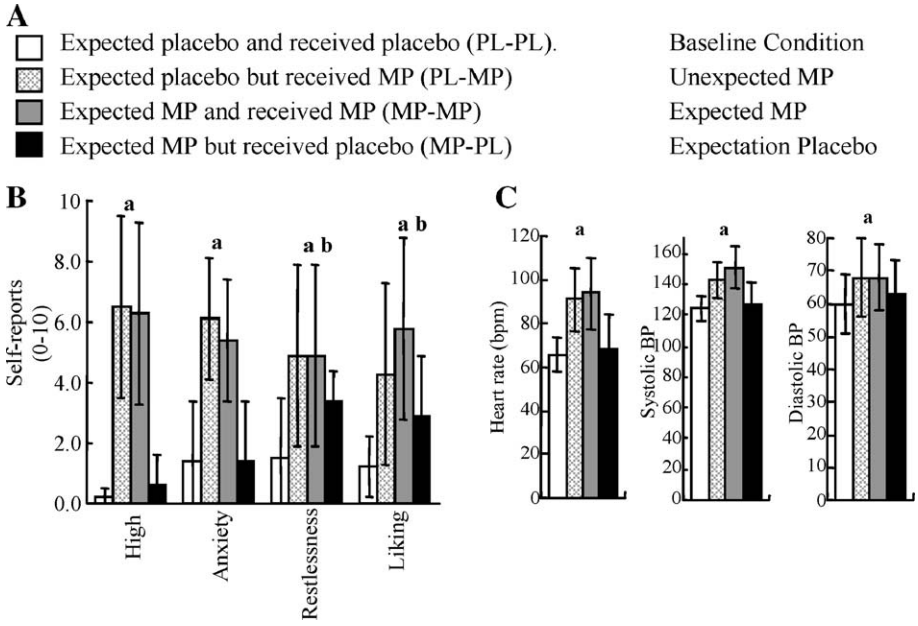

Fig. 1. (A) Experimental design and abbreviations used in figures (PL = placebo, MP = methylphenidate). Subjects were tested under 4 randomly assigned conditions: (1) Expected PL received PL (PL–PL), this is the baseline condition; (2) Expected PL but received MP (PL–MP), this is the unexpected MP condition; (3) Expected MP received MP (MP–MP), this is the expected MP condition and (4) Expected MP but received PL (MP–PL), this is the expectation placebo condition. (B) Self-reports of drug effects for the 4 conditions. MP (expected and unexpected) significantly increased self-reports for "high", "restlessness, "feel drug", and "drug liking" (post hoc *t* tests $P < 0.001$) when compared with the baseline condition. The expectation PL condition (MP–PL) induced significant increases in self-reports of "restlessness" and "drug liking" when compared with the baseline condition. (C) Cardiovascular measures for the 4 conditions. MP (unexpected and expected) significantly increased heart rate and systolic and diastolic blood pressure. [a]Repeated ANOVA, $df = 3,45$; $P < 0.001$. [b]Post hoc *t* test showing differences between PL–PL and MP–PL, $P < 0.05$.

measured prior to and at 10, 25, 40, and 54 min after MP using capillary GC/Mass spectrometry (Srinivas et al., 1991).

Instruction to subjects

Subjects were told that they would receive in a given experimental day either a placebo or intravenous MP. With regard to MP, they were told that MP is a stimulant drug used in the treatment of ADHD; that when MP is given for therapeutic purposes, it is given orally, but that in this study, they would receive MP intravenously. To keep the expectation neutral throughout the study (not affected by their sequential experiences with the interventions) and to inform them about MP effects (Volkow et al., 1999b), subjects were told that intravenous MP was perceived as rewarding by some individuals, aversive by others and as having no subjective effects by others. Subjects were also told that MP increases heart rate and blood pressure but that in some subjects it does not.

Behavioral and cardiovascular measures

Behavioral effects were evaluated using analog scales that assessed self-reports of "high", "anxiety", and "restlessness" (Wang et al., 1997) by responses from 0 (felt nothing) to 10 (felt intensely). These self-reports of drug effects have been shown to be reliable and consistent across studies and to predict administration of drugs in human subjects (Fischman and Foltin, 1991). Subjective ratings were recorded 5 min before placebo or MP and then every minute for the first 20 min and at 25, 30, 45, and 67 min after administration. At the end of the study, subjects were asked to rate "drug liking" on a 1 to 10 scale.

Heart rate and blood pressure were evaluated 5 min prior to placebo or MP and then continuously until the end of the procedure.

Analysis

The data were analyzed using Statistical Parametric Mapping (SPM) (Friston et al., 1995) both on the "absolute" and the "relative" (images normalized to the mean metabolic activity of all voxels within the brain) metabolic images. The SPM results were then corroborated with independently drawn regions of interest (ROI); that is, regions obtained using a template that was not guided by the coordinates obtained from the SPM. For the SPM analyses, the images of the metabolic measures were spatially normalized using the template provided in the SPM 99 package and subsequently smoothed with a 16-mm isotropic Gaussian kernel. Paired samples t tests were performed for the following 4 planned but non-orthogonal comparisons: MP when unexpected (PL–PL versus PL–MP) and MP when expected (PL–PL versus MP–MP); effects of drug expectation on MP (PL–MP versus MP–MP); and effects of drug expectation on placebo (PL–PL versus MP–PL). These sets of SPM comparisons were performed on the "absolute" and the "relative" images. Significance was set at $P < 0.005$ (uncorrected, 100 voxels), and the statistical maps were overlaid on an MRI structural image.

For the ROI, we used an automated ROI extraction method that is based on the standard brain template from the Talairach atlas (Talairach and Tournoux, 1988). First, to eliminate variations across individuals' brains, the FDG images were mapped into the Talairach brain using the spatial normalization package in SPM. The inverse mapping procedure was used to extract the Talairach coordinates of all voxels for a given anatomical region using the stereotaxic coordinates in the Talairach Daemon database (Collins et al., 1995; Lancaster et al., 1997, 2000). These anatomically defined ROIs were overlapped voxel by voxel onto the SPM normalized PET image. This automated ROI method had been validated by comparing the metabolic measures obtained with it versus those obtained with manually drawn ROIs from FDG images of 35 subjects (Ma et al., 2004). The correlations between the two methods were very high and ranged between $r = 0.86$ and $r = 0.99$, and the difference in the metabolic averages between both methods did not differ from 0.

This study used a 2×2 full factorial design with two factors A (expectation factor) and B (treatment factor) and with 2 levels for each factor A (expected PL, expected MP) and B (received PL, received MP). To assess if there was a main effect for treatment and a main effect for expectation and to evaluate their interaction, we used a two within factor repeated measure ANOVA. Post hoc t tests were used to assess for which of the conditions the differences were significant. Comparisons were made both on the "absolute" and the "relative" metabolic measures. For direct comparisons between two conditions (i.e., concentration of MP in plasma), we used paired t tests (two tail).

Pearson product moment correlations were used to assess the association between the regional metabolic changes and the behavioral changes induced by unexpected MP, expected MP and by expectation alone (MP–PL). Changes in metabolism for these 3 conditions were computed as the difference in metabolism with respect to the baseline condition (PL–PL). The correlations were done on the absolute metabolic measures. Because of the multiplicity of correlations, we set the level of significance to $P < 0.005$ when an association was obtained for only one of the conditions but to $P < 0.05$ when they were corroborated in more than one condition.

Results

Plasma MP concentrations and behavioral and cardiovascular measures

Plasma MP concentrations did not differ when MP was unexpected (PL–MP) from when MP was expected (MP–MP), and reached concentrations (respectively) of 164 ± 41 and 148 ± 28 ng/ml (at 10 min), of 112 ± 29 and 102 ± 15 ng/ml (at 25 min), of 88 ± 19 and 82 ± 15 (at 40 min), and 75 ± 14 and 73 ± 10 (at 54 min).

Peak behavioral effects after MP occurred 5–20 min after its administration. Repeated ANOVA on the behavioral measures (averaged scores between 5 and 20 min after placebo or MP, which is when peak effects were observed) revealed a significant treatment effect for self-reports of "high", "restlessness", "anxiety", and "drug liking" (obtained at end of study) ($P < 0.001$). Post hoc t tests ($df = 14$) revealed that MP (unexpected and expected) significantly increased self-reports of "high" ($t > 9.5$, $P < 0.0001$), "restlessness" ($t > 4.5$, $P < 0.0005$), anxiety ($t = 5.6$, $P < 0.0001$), and "drug liking" ($t > 4.0$, $P < 0.001$) when compared to the baseline condition (PL–PL) (Fig. 1B). There were no differences for the behavioral measures between expected and unexpected for the MP conditions.

For the placebo condition paired t tests revealed that the expectation condition (expecting MP but receiving placebo) significantly increased self-report of "restlessness" ($t = 3.1$, $P < 0.008$) and "drug liking" ($t = 2.7$, $P < 0.02$) when compared to the baseline condition (PL–PL) (Fig. 1B).

For the statistical comparison, we averaged the cardiovascular measures obtained 5–20 min after placebo or after MP (when the peak cardiovascular effects were observed after MP). There was a significant treatment effect for the cardiovascular measures. MP significantly ($P < 0.0001$) increased heart rate (Unexpected 45 ± 22% and Expected 44 ± 22%), systolic (Unexpected 19 ± 6% and Expected 22 ± 9%) and diastolic blood pressure (Unexpected 19 ± 15% and Expected 17 ± 16%). The expectation effect was not significant (Fig. 1C).

Effects of MP on regional brain metabolism

There was a significant treatment effect on whole brain glucose metabolism ($df = 1,14$, $F = 16.6$, $P < 0.001$), but the expectation effect was not significant. Post hoc t tests revealed that brain metabolism after MP was significantly higher than metabolism during the baseline condition (PL–PL) both when it was unexpected (4.7 ± 5 μmol/100g/min, 11 ± 10% increase; $t = 3.8$, $df = 14$, $P < 0.003$) and when expected (4.2 ± 6 μmol/100 g/min, 9 ± 14% increase $t = 2.6$, $df = 14$, $P < 0.03$). The increases in brain glucose metabolism induced by MP were not correlated with the concentration of MP in plasma for unexpected ($r = 0.16$, $df = 14$, $P = 0.58$) or expected MP ($r = 0.33$, $P = 0.22$).

SPM analysis of the absolute metabolic images corroborated a significant treatment effect. The largest MP-related increases both for unexpected and expected MP occurred in cerebellum (vermis and hemispheres), lateral orbitofrontal cortex (BA 11 and BA 47), thalamus, and mesencephalon. The analysis on the independently drawn ROIs on the absolute measures corroborated that the treatment effect was significant for cerebellum ($F = 30$, $P < 0.0001$), lateral orbitofrontal cortex (OFC) ($F = 19$, $P < 0.0006$), thalamus ($F = 29$, $P < 0.0001$), and mesencephalon ($F = 23$, $P < 0.0002$) (Fig. 2). The expectation effect was not significant.

SPM analysis on the normalized measures, which controls for MP-induced increases in global metabolism, also showed a significant treatment effect and revealed a similar pattern, though more restricted, than the pattern obtained by SPM on the absolute metabolic images. MP (unexpected and expected) induced significant "relative increases" in cerebellum (hemispheres and vermis) and lateral OFC (BA 47 and BA 11). MP also induced significant "relative" decreases in occipital cortex (BA 19) (Fig. 3, Table 1). In addition, expected MP also induced "relative increases" in right thalamus (mediodorsal nucleus) and "relative decreases" in left striatum. The ROI analysis of the relative measures corroborated that the treatment effect was significant for increases in cerebellum ($F = 23$, $df = 1,14$, $P < 0.0003$), lateral OFC ($F = 5$, $P < 0.05$) but were not corroborated for BA 19.

Comparison between unexpected and expected MP

SPM on the absolute metabolic images did not show differences between expected and unexpected MP. SPM comparisons of normalized images revealed greater decreases in the expected than the unexpected MP condition in the striatum (right: 180 pixels, x, y, z coordinates 20, 8, 8, $t = 4.82$, $P < 0.001$; left: 142 pixels, −18, 4, 4, $t = 4.03$, $P < 0.01$). The ROI analysis corroborated that MP-induced decreases in relative metabolism in striatum were greater for expected than for unexpected MP ($P < 0.05$) (Fig. 3B).

Expectation effects on the brain metabolic response to placebo (MP–PL)

The expectation placebo condition (MP–PL) increased whole brain metabolism when compared with the baseline condition (PL–PL), but this effect did not reach significance (1.6 ± 5 μmol/100/min, 6 ± 13% increase, $t = 1.5$, $P = 0.14$). SPM of the absolute metabolic images (not shown) revealed significant increases in BA 25 and posterior brain stem (mesencephalon and pons) ($P < 0.005$). These differences were corroborated by ROI, which showed significant increases in BA 25 (37.4 ± 5 versus 40.9 ± 5 μmol/100/min, $P < 0.01$), mesencephalon (30.8 ± 4 versus 33.3 ± 4 μmol/100/min, $P < 0.04$) and pons (29.6 ± 3 versus 22.8 ± 3 μmol/100/min, $P < 0.006$).

Analysis of the "relative" images revealed similar findings to those obtained with the "absolute" metabolic images. This analysis also showed significant increases in BA 25 and posterior brain stem and in addition showed increases in nucleus accumbens (Fig. 4A, Table 2). These differences were corroborated with ROI for BA 25, NAc, and brainstem (Fig. 4B, Table 2).

To assess if prior experience with MP affected the response of the expectation placebo condition (MP–PL), we compared the responses of the 6 subjects whose scans for this condition were performed prior to the conditions when they received MP to those of the 9 subjects whose scans for this condition were done after they had been exposed to one of the MP conditions. For both the absolute ($P < 0.05$) and relative ($P < 0.005$) metabolic images, a similar pattern of responses revealed that subjects who had not received MP had significantly higher activation in two brain regions than those that had received MP (BA 25 and NAc; see Fig. 5). These differences between the subjects were corroborated with ROI for BA 25, but the difference was not significant for NAc (Fig. 5).

Correlation between behavioral and regional brain metabolic measures

The pattern of correlations between MP-induced absolute metabolic regional changes and behavior were similar but stronger for unexpected MP (significance $P < 0.005$) than for expected MP (significant only at $P < 0.05$). For both unexpected and expected MP, "drug liking" was associated with increases in metabolism in dorsolateral prefrontal cortex, OFC and insula; "anxiety" with increases in OFC, insula, and cerebellum; and "restlessness" with increases in OFC, insula, occipital cortex (BA 19), and cerebellum (Table 3). In addition, for unexpected but not for expected MP, "drug liking" and "restlessness" were associated with increases in striatal metabolism.

The correlations between metabolism and behavior for the expectation placebo condition were not significant.

Discussion

Effects of MP on regional brain metabolism

Here, we show that intravenous MP produced significant increases in whole brain glucose metabolism (Unexpected 11% and Expected 9%). In a study done in cocaine abusers that used a

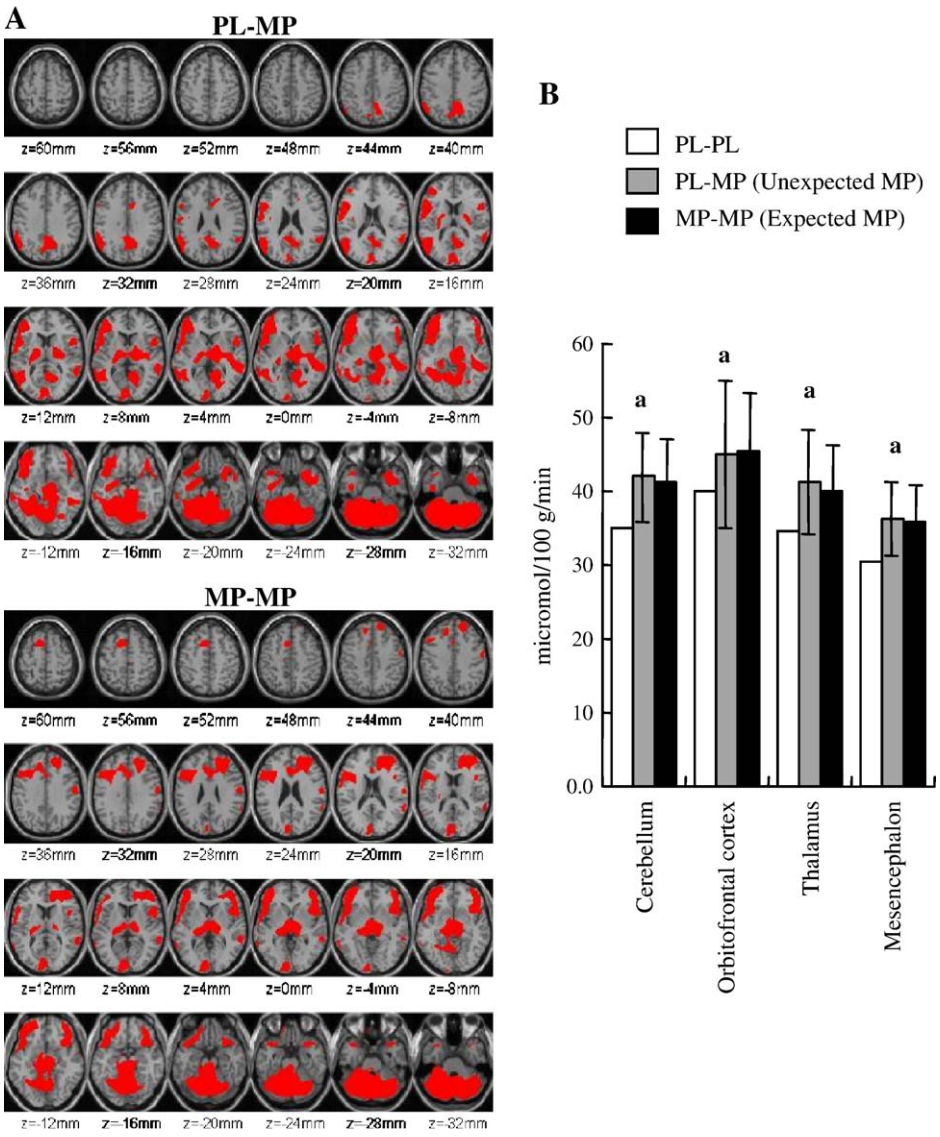

Fig. 2. (A) Brain maps obtained with SPM on the "absolute" metabolic images showing regions where unexpected MP (PL–MP) and expected MP (MP–MP) induced significant increases in metabolism when compared with the baseline condition (PL–PL). Significance corresponds to $P < 0.005$, threshold > 100 pixels. (B) Metabolic measures in cerebellum, lateral OFC, thalamus, and mesencephalon (micromol/100 g/min) obtained with ROI. Note the large increases in metabolism with MP both when it was expected and when it was unexpected. Repeated ANOVA was significant for these regions ($P < 0.001$). [a]Post hoc *t* test showing differences between PL–PL and unexpected and expected MP ($P < 0.005$). Abbreviations are as for Fig. 1.

similar design, we also reported significant increases in global brain metabolism after MP (Volkow et al., 2003), which indicates that intravenous MP increases the utilization of glucose by the brain. The largest metabolic increases with MP (unexpected or expected) occurred in cerebellum and in the lateral OFC followed by thalamus and mesencephalon.

Increases in cerebellar metabolism have been the most consistent finding in our studies assessing the effects of intravenous MP in controls and in cocaine abusers (Volkow et al., 1997, 1999a, 2003). DAT density in cerebellum is low, whereas norepinephrine transporter (NERT) density is high (Strazielle et al., 1999), and thus, blockade of NERT by MP (Patrick et al., 1987) is likely to contribute to the cerebellar increases. However, since metabolism predominantly reflects activity in the nerve terminals (Schwartz et al., 1979), cerebellar activation could also reflect downstream effects from DA stimulation of striatum via striatal–cerebellar projections (Houk and Wise, 1995). Indeed, DA D2 receptor levels in striatum predicted MP-induced increases in cerebellar metabolism (Volkow et al., 1997, 1999a). This would imply that DA modulates cerebellar activity even though the cerebellum receives minimal DA projection (McCulloch et al., 1982).

Large increases in metabolism with MP also occurred in the lateral OFC (BA 11 and BA 47) and this effect did not differ between expected and unexpected MP. In contrast, we had shown that in cocaine abusers MP-induced increases in lateral OFC were greater for unexpected than for expected MP (Volkow et al., 2003). This difference may reflect the fact that cocaine abusers are knowledgeable about the effects of stimulant drugs, which they experience as highly reinforcing. Thus, the greater activation of the lateral OFC in the cocaine abusers could be explained by receiving an unexpected reinforcing stimulus, since unpredictable stimuli induce stronger activation of OFC than predictable ones (Berns et

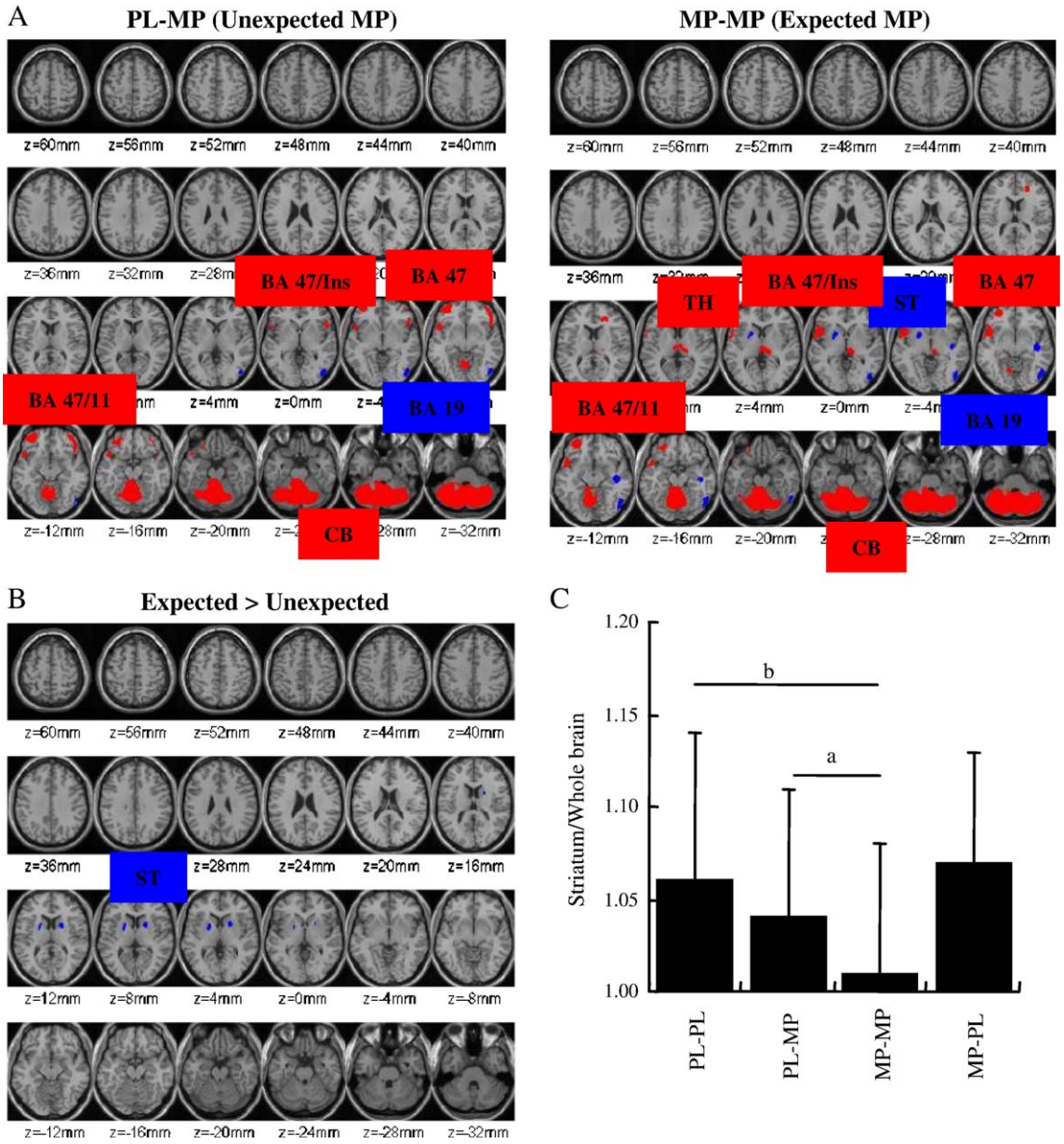

Fig. 3. (A) Brain maps obtained with SPM on the "relative" metabolic measures showing regions where unexpected MP (PL–MP) and expected MP (MP–MP) induced significant increases (red) and decreases (blue) in "relative metabolism" when compared with the baseline condition (PL–PL). Both MP conditions induced significant increases in cerebellum (vermis and hemispheres), lateral orbitofrontal cortex (BA 11 and BA 47) and significant decreases in occipital cortex (BA 19). In addition, expected MP increased relative metabolism in thalamus and decreased it in left striatum. Significance corresponds to $P < 0.005$, threshold > 100 pixels. (B) Brain maps obtained with SPM showing the regions were the MP-induced "relative" decreases were greater for expected than unexpected MP ($P < 0.005$, threshold > 100 pixels). (C) Regional "relative" metabolic measures obtained with ROI in striatum. Significance levels are for post hoc comparisons that differed between conditions $^{a}P = 0.05$, $^{b}P < 0.002$.

al., 2001). In non-drug abusing subjects, because of their minimal experience with stimulant drugs, both the expected and unexpected MP would result in unpredictable responses. Because the OFC receives direct DA (Oades and Halliday, 1987) and noradrenergic projections (Morecraft et al., 1992) and is also a main target of striato-thalamic projections (Morecraft et al., 1992), MP's blockade of both DAT and NERT is also likely to underlie its effects on the lateral OFC. Increases in metabolism with MP were confined to lateral OFC, whereas the medial OFC was one of the less sensitive areas to the effects of MP. This corroborates the distinctiveness of these two OFC regions (Kringelbach and Rolls, 2004), which differ in their neuroanatomical connections (Cavada et al., 2000) and function (Arana et al., 2003).

Effects of expectation on MP-induced changes in regional brain metabolism

The response to drugs reflects the interaction between pharmacological, conditioning and expectation effects (Mitchell et al., 1996; Robinson and Berridge, 1993). This makes the responses to drugs sensitive to prior drug experiences (Flaten et al., 1999). In this study, we showed no effect of expectation on MP's

Table 1
SPM results for the "normalized" metabolic images showing areas where MP induced significant changes in relative metabolic activity

	Cluster	x	y	z	t	P
Unexpected MP						
Increases						
1. Cerebellum	14222					
Left		−4	−64	−34	7.43	0.001
Right		40	−54	−38	5.66	0.001
2. L BA 11	679	−28	48	−16	5.14	0.001
3. R BA 11	479	40	56	−12	4.49	0.001
R BA 47		52	24	−8	4.24	0.001
4. L BA 47	239	−42	16	−14	3.62	0.001
Decreases						
1. Occipital (R BA 19)	129	48	−76	−4	3.68	0.001
Expected MP						
Increases						
1. Cerebellum	15473					
Left		−2	−54	−36	9.09	0.001
Right		36	−62	−30	10.12	0.001
2. L BA 11	323	−26	50	−16	5.85	0.001
3. L BA 47	441	−56	10	−2	5.24	0.001
4. R Thalamus (mediodorsal)	169	12	−24	8	3.78	0.001
Decreases						
1. Occipital (R BA 19)	410	50	−76	−8	3.51	0.002
2. L putamen	165	−20	8	−2	4.28	0.002

Significance for SPM was $P < 0.005$; cluster size > 100 pixels. Columns show under cluster the size of the area (number of pixels), the center of the cluster with respect to the x, y, z coordinates of the Talairach space, the magnitude of the effects (t values) and significance when MP was unexpected (PL–MP) and when it was expected (MP–MP).

Table 2
Areas where the expectation placebo condition (expected MP but received placebo) significantly increased relative metabolism when compared with the baseline condition (expected PL received PL)

Increases	Cluster	x	y	z	t	P
1. BA 25	768				5.41	0.001
Right		14	6	18		
Left		−12	4	−18		
R NAc		4	4	−10		
2. L BA 25	174	−24	20	−18	3.94	0.001
3. L brain stem	494	−4	−34	−26	4.54	0.001

Significance for SPM corresponded to $P < 0.005$; cluster size > 100 pixels. Columns show under cluster the size of the area (number of pixels), location of the center of the cluster with respect to the x, y, z coordinates of the Talairach space, magnitude of the effects (t values) and significance.

behavioral effects or on the absolute brain metabolic measures. However, we document a significant effect of expectation on MP-induced "relative decreases" in striatum, which were greater for expected than for unexpected MP. The effect of expectation in these non-drug abusing subjects differs from that which we observed in cocaine abusers in whom expectation enhanced MP's behavioral effects and enhanced MP-induced increases in thalamic and cerebellar metabolism (Volkow et al., 2003). Failure to see such an effect of expectation in non-drug abusing subjects suggests that the enhanced thalamic and cerebellar responses in cocaine abusers reflected conditioned responses. In addition, this suggests that the difference in MP-induced changes in striatum in non-drug abusing subjects reflects top–down modulation by expectation and not a conditioned response. Since MP increased absolute metabolism in all brain regions, we cannot rule out the possibility that a "relative decrease" in striatum could reflect less of an increase in absolute metabolism in this region than in the rest of the brain and thus less of a striatal response for expected than for unexpected MP. Indeed, greater activation in striatum has been reported for an unexpected than for an expected reward (juice) (McClure et al., 2003). However, the fact that MP was not necessarily perceived as a reward, and that it was the differences in "relative" but not in "absolute" striatal metabolism that differed between expected and unexpected MP suggests that the difference reflects an enhance-

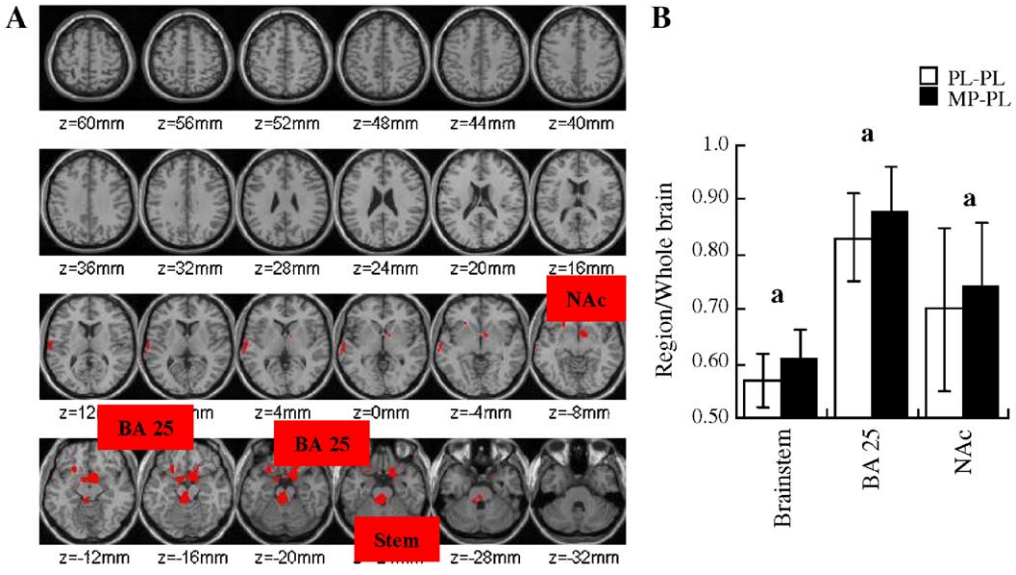

Fig. 4. (A) Brain SPM maps of the "relative" metabolic images showing regions where the expectation alone condition (expected MP but received placebo; MP–PL) induced significant increases when compared with the baseline condition (PL–PL). Expectation induced significant increases in right nucleus accumbens, ventral cingulate gyrus (BA 25), and posterior brain stem ($P < 0.005$, threshold > 100 pixels). (B) Regional "relative" metabolic measures obtained with ROI in brainstem, BA 25 and NAc. [a]Significance levels are for post hoc comparisons that differed between conditions, $P < 0.01$.

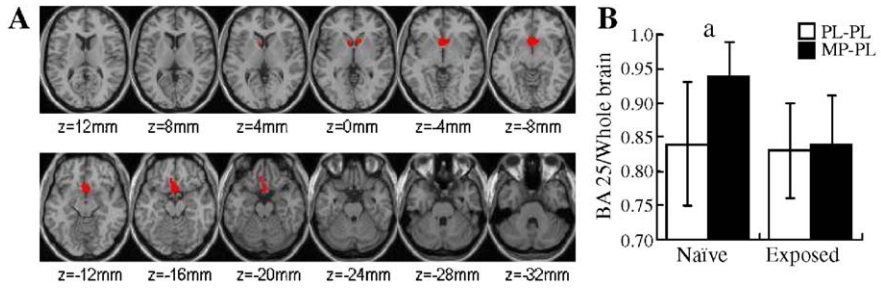

Fig. 5. (A) Brain SPM maps of the "relative" metabolic images showing regions where the effects of expectation on placebo (MP–PL versus PL–PL) were significantly greater in subjects who experienced the MP–PL condition prior to any of the conditions when they received MP and had therefore not experienced the effects of MP (naïve), versus those who experienced one of the conditions when MP was given prior to the MP–PL condition (exposed) ($P < 0.005$, threshold > 100 pixels). B. Regional "relative" metabolic measures obtained with ROI in BA 25, where ROI corroborated a significantly greater effect in the naïve than in the exposed subjects. Factorial repeated ANOVA showed significant differences in the effects of expectation to placebo between the two groups of subjects. [a]Post hoc t tests, $P < 0.01$.

ment by expectation of MP-induced inhibition of striatal activity. These results indicate that expectation can affect responses to a drug even in subjects who have not had prior experiences with it. They also provide a mechanism by which a drug such as MP, which is beneficial in the treatment of ADHD, is rarely perceived as reinforcing when used therapeutically but can have reinforcing effects when subjects abuse it with the expectation of getting "high" (Volkow and Swanson, 2003).

Effects of expectation on the response to placebo

In this study, we also document a significant effect of expectation when given with a placebo. Indeed, the effects of expectation on regional brain metabolism were more apparent when it was paired with the placebo (MP–PL) than when it was paired with MP (MP–MP). This may reflect the fact that in the latter condition the pharmacological effects of MP on brain metabolism, which were extensive, are likely to have hidden the response to expectation, which was much more localized. Expectation alone (expected MP but received placebo) resulted in increases in ventral CG (BA 25) and NAc. Others had documented the involvement of the ventral striatum and the ventral CG in the expectation of reward (Breiter et al., 2001; Ernst et al., 2004; Gottfried et al., 2003; Knutson et al., 2001; O'Doherty et al., 2002). In this study, the expectation of MP's effects were not necessarily that of a rewarding stimulus (subjects

Table 3
Significant correlations between metabolic changes and behavioral effects for expected and unexpected MP

	Unexpected MP (PL–MP)	Expected MP (MP–MP)
Drug liking	Lateral OFC	Lateral OFC
	BA 11 $r = 0.66$, $P < 0.008$	BA 11 $r = 0.60$, $P < 0.05$
	BA 47 $r = 0.72$, $P < 0.003$	BA 47 $r = 0.47$, $P < 0.05$
	Insula	Insula
	BA 13 $r = 0.73$, $P < 0.001$	BA 13 $r = 0.54$, $P < 0.05$
	Prefrontal cortex	Prefrontal cortex
	BA 10 $r = 0.77$ $P < 0.001$	BA 10 $r = 0.54$, $P < 0.05$
	BA 9 $r = 0.73$, $P < 0.002$	BA 9 $r = 0.60$, $P < 0.05$
	Striatum	
	Putamen $r = 0.76$, $P < 0.001$	
Anxiety	Lateral OFC	Lateral OFC
	BA 11/47 $r = 0.68$, $P < 0.003$	BA 11/47 $r = 0.51$, $P < 0.05$
	Insula	Insula
	BA 13 $r = 0.69$, $P < 0.004$	BA 13 $r = 0.47$, $P < 0.06$
	Cerebellum	Cerebellum
	$r = 0.68$, $P < 0.004$	$r = 0.58$, $P < 0.05$
Restlessness	Lateral OFC	Lateral OFC
	BA 11/47 $r = 0.78$, $P < 0.001$	BA 47 $r = 0.54$, $P < 0.05$
	Insula	Insula
	BA 13 $r = 0.69$, $P < 0.004$	BA 13 $r = 0.54$, $P < 0.05$
	Occipital cortex	Occipital cortex
	BA 19 $r = 0.73$, $P < 0.003$	BA 19 $r = 0.64$, $P < 0.01$
	Cerebellum	Cerebellum
	$r = 0.65$, $P < 0.008$	$r = 0.53$, $P < 0.05$
	Striatum	
	Caudate $r = 0.75$, $P < 0.001$	
High	NS	NS

were told that MP's effects were perceived as rewarding by some subjects, aversive by others, and neutral by some); these findings corroborate the involvement of the ventral CG and the NAc in expectation regardless of it being rewarding or not. Indeed, activation of the ventral CG has been reported with expectation to a wide variety of sensory stimuli (pleasant or unpleasant) (Koyama et al., 2005; Nitschke et al., 2006; O'Doherty et al., 2002; Petrovic et al., 2005; Ploghaus et al., 2003; Sarinopoulos et al., 2006; Wager et al., 2004).

The responses to a placebo, like those to a drug, are also influenced by expectation and conditioned responses (Haour, 2005). This makes the response to a placebo sensitive to prior experiences with the drug (Flaten et al., 1999). Because the subjects in this study had minimal or no experience with MP, their responses to the placebo were not due to conditioning but to their expectation of what MP should feel like and their uncertainty about it. In fact, the effects of expectation on the placebo were greatest in the subjects who experienced the placebo condition prior to the conditions when they were given MP; that is, in the subjects that were most uncertain about MP's effects. This suggests that the activation of NAc and BA 25 by the placebo reflects the uncertainty regarding the effects of a novel stimulus (in this case MP).

Dopamine and the effects of expectation

DA, which is involved in predicting reward and in the response to novelty and unexpectedness (Horvitz, 2000; Schultz, 1998), is likely to be involved in the activation by expectation of the NAc and the ventral CG and in the deactivation of the striatum. These brain regions receive direct as well as indirect projections from DA cells (Le Moal and Simon, 1991). The relevance of DA cells and of their projections regions in processing expectation for positive or negative outcomes has been documented by electrophysiological studies in laboratory animals (Hollerman et al., 1998; Schoenbaum et al., 1998; Schultz et al., 1997). Because DA cell firing at the time of an expected reward appears to be maximal for conditions of greatest uncertainty, DA cells have also been implicated in coding for the uncertainty of an event (Fiorillo et al., 2003). Imaging studies in humans have also corroborated the involvement of DA in expectation of drug reward (de la Fuente-Fernandez et al., 2002), and that of DA projection regions in expectation of positive or negative monetary outcomes (Breiter et al., 2001). Increases in DA in striatum have also been observed in patients with Parkinson's disease who expected to receive apomorphine but received placebo (de la Fuente-Fernandez et al., 2001; Kaasinen et al., 2004) and in healthy subjects who expected to receive caffeine but received a placebo (Kaasinen et al., 2004). DA circuits are therefore likely to be involved in the mechanism through which expectation affected the regional brain metabolic responses to MP and to placebo.

Correlations between regional metabolism and behavioral measures

The correlations between changes in regional metabolism and changes in behavior induced by MP showed overlap between the regions and the behaviors. Specifically, any one anatomical brain region correlated with more than one behavior and a given behavior correlated with more than one brain region. This highlights the relevance of broad regional networks in the subjective experiences from psychoactive drugs and supports the notion that the pattern of regional activation and not activation of a single region gives the specificity for a given subjective behavioral effect. The insula and the lateral OFC were the regions with the largest overlap with behavioral effects, manifested as an association with "drug liking", "anxiety", and "restlessness", which suggests their involvement in the subjective perception of the emotional responses to MP. Inasmuch as the OFC and the insula have widespread neuroanatomical connections with limbic brain regions, primary sensory areas, and regions involved with autonomic control, this puts them in a unique position to integrate emotional responses, and for interoceptive perception (Critchley et al., 2004; Kringelbach and Rolls, 2004). Indeed, the involvement of the OFC and the insula in emotional perception had been documented for painful stimuli (Craig et al., 2000).

Implications for imaging studies

To the extent that the regional brain metabolic responses to MP were influenced by the subject's expectations, one questions how the unique experimental conditions of imaging studies affect the pattern of brain responses being obtained. Indeed, imaging studies with somatosensory stimulation have shown the pattern of responses to an odor is influenced by the belief that the subjects had for the source of the smell; when they believed that it was "cheddar cheese" it induced a greater activation of the CG and the medial orbitofrontal cortex than when they believed it was "human odor" (de Araujo et al., 2005).

Study limitations

Brain metabolic responses measured with FDG-PET reflect the activity occurring over a 30-min period. Thus, the short-lived duration of some of MP's behavioral effects such as the "high" was likely lost amidst the metabolic responses. Here, we document an effect of expectation on MP regional brain metabolic effects but not on its behavioral effects. This could reflect the fact that we did not measure the relevant behaviors (i.e., tasks that involve the striatum), but it could also reflect that MP's consequences may not necessarily be consciously perceived and/or that the temporal course of the metabolic and the behavioral effects do not overlap.

The anatomical localization of the regions was based on the output from the SPM analysis and for the ROI on the coordinates from the Talairach space. However, the extent to which the measures accurately reflect metabolism in small areas such as the NAc and the BA 25 is limited by the relatively poor spatial resolution of the PET instrument.

This study reflects the effects of expectation on MP effects at baseline. The effects of expectation are likely to have differed had the subjects been studied while actively engaging in a task and also if we had manipulated the expectation the subjects had on how MP would affect their performance or experience (i.e., improve or decrease attention, enhance or decrease saliency of a stimulus).

In this study, we cannot rule out the possibility that some subjects realized that the information given to them was inaccurate, which would have weakened the effect of expectation. Specifically, after a subject was told he would receive MP but then experienced no effects, he may have started to suspect that he was

being deceived. However, the lack of a response to MP is unlikely to have aroused suspicion since subjects had been told that some individuals do not respond to MP. On the other hand a strong response to an "expected placebo" in a subject that received MP could have aroused suspicion. Since we did not question the subjects at the end of the experiment regarding their awareness of their having received placebo or MP, we cannot determine the extent to which they distrusted the instructions.

Summary

These results provide evidence that expectation effects are not just due to conditioned responses since they occur even in subjects with no prior experience with the drug. It also corroborates the involvement of the ventral CG (and provides evidence for the involvement of the NAc) in processing expectation for an uncertain event (new drug). Thus, the state of expectation needs to be considered as a variable modulating the reinforcing and therapeutic effects of drugs and of placebo even in naïve subjects. Expectation effects should also be considered in interpreting the pattern of regional brain responses reported by functional brain imaging studies.

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References

Amiez, C., Joseph, J.P., Procyk, E., 2005. Anterior cingulate error-related activity is modulated by predicted reward. Eur. J. Neurosci. 21, 3447–3452.

Arana, F.S., Parkinson, J.A., Hinton, E., Holland, A.J., Owen, A.M., Roberts, A.C., 2003. Dissociable contributions of the human amygdala and orbitofrontal cortex to incentive motivation and goal selection. J. Neurosci. 23, 9632–9638.

Berns, G.S., McClure, S.M., Pagnoni, G., Montague, P.R., 2001. Predictability modulates human brain response to reward. J. Neurosci. 21, 2793–2798.

Breiter, H.C., Aharon, I., Kahneman, D., Dale, A., Shizgal, P., 2001. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron 30, 619–639.

Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R.J., Reinoso-Suarez, F., 2000. The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb. Cortex 10, 220–242.

Collins, D.L., Holmes, C.J., Peters, T.M., Evans, A.C., 1995. Automatic 3-D model-based neuroanatomical segmentation. Hum. Brain Mapp. 3, 190–208.

Craig, A.D., Chen, K., Bandy, D., Reiman, E.M., 2000. Thermosensory activation of insular cortex. Nat. Neurosci. 3, 184–190.

Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nat. Neurosci. 7, 189–195.

de Araujo, I.E., Rolls, E.T., Velazco, M.I., Margot, C., Cayeux, I., 2005. Cognitive modulation of olfactory processing. Neuron 46, 671–679.

de la Fuente-Fernandez, R., Ruth, T.J., Sossi, V., Schulzer, M., Calne, D.B., Stoessl, A.J., 2001. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 293, 1164–1166.

de la Fuente-Fernandez, R., Phillips, A.G., Zamburlini, M., Sossi, V., Calne, D.B., Ruth, T.J., Stoessl, A.J., 2002. Dopamine release in human ventral striatum and expectation of reward. Behav. Brain Res. 136, 359–363.

Di Chiara, G., Imperato, A., 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. U. S. A. 85, 5274–5278.

Duvauchelle, C.L., Ikegami, A., Asami, S., Robens, J., Kressin, K., Castaneda, E., 2000. Effects of cocaine context on NAcc dopamine and behavioral activity after repeated intravenous cocaine administration. Brain Res. 862, 49–58.

Ernst, M., Nelson, E.E., McClure, E.B., Monk, C.S., Munson, S., Eshel, N., Zarahn, E., Leibenluft, E., Zametkin, A., Towbin, K., Blair, J., Charney, D., Pine, D.S., 2004. Choice selection and reward anticipation: an fMRI study. Neuropsychologia 42, 1585–1597.

Fiorillo, C.D., Tobler, P.N., Schultz, W., 2003. Discrete coding of reward probability and uncertainty by dopamine neurons. Science 299, 1898–1902.

Fischman, M.W., Foltin, R.W., 1991. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. Br. J. Addict. 86, 1563–1570.

Flaten, M.A., Simonsen, T., Olsen, H., 1999. Drug-related information generates placebo and nocebo responses that modify the drug response. Psychosom. Med. 61, 250–255.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.B., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.

Gottfried, J.A., O'Doherty, J., Dolan, R.J., 2003. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science 301, 1104–1107.

Graham, J., Porrino, L.J., 1995. Neuroanatomical substrates of cocaine self-administration. In: Hammer, R. (Ed.), Neurobiology of Cocaine. CRC Press, Boca Raton, FL, pp. 3–14.

Haour, F., 2005. Mechanisms of the placebo effect and of conditioning. Neuroimmunomodulation 12, 195–200.

Hemby, S.E., Co, C., Koves, T.R., Smith, J.E., Dworkin, S.I., 1997. Differences in extracellular dopamine concentrations in the nucleus accumbens during response-dependent and response-independent cocaine administration in the rat. Psychopharmacology (Berlin) 133, 7–16.

Hollerman, J.R., Tremblay, L., Schultz, W., 1998. Influence of reward expectation on behavior-related neuronal activity in primate striatum. J. Neurophysiol. 80, 947–963.

Horvitz, J.C., 2000. Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96, 651–656.

Houk, J.C., Wise, S.P., 1995. Distributed modular architectures linking basal ganglia, cerebellum, and cerebral cortex: their role in planning and controlling action. Cereb. Cortex 5, 95–110.

Kaasinen, V., Aalto, S., Nagren, K., Rinne, J.O., 2004. Expectation of caffeine induces dopaminergic responses in humans. Eur. J. Neurosci. 19, 2352–2356.

Kirk, J.M., Doty, P., De Wit, H., 1998. Effects of expectancies on subjective responses to oral delta9-tetrahydrocannabinol. Pharmacol. Biochem. Behav. 59, 287–293.

Knapp, C.M., Printseva, B., Cottam, N., Kornetsky, C., 2002. Effects of cue exposure on brain glucose utilization 8 days after repeated cocaine administration. Brain Res. 950, 119–126.

Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L., Hommer, D., 2001. Dissociation of reward anticipation and outcome with event-related fMRI. NeuroReport 12, 3683–3687.

Koyama, T., McHaffie, J.G., Laurienti, P.J., Coghill, R.C., 2005. The subjective experience of pain: where expectations become reality. Proc. Natl. Acad. Sci U. S. A. 102, 12950–12955.

Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog. Neurobiol. 72, 341–372.

Lancaster, J.L., Rainey, L.H., Summerlin, J.L., Freitas, C.S., Fox, P.T., Evans, A.E., Toga, A.W., Maziotta, J.C., 1997. Automated labeling of the human brain: a preliminary report on the development and evaluation of a forward-transform method. Hum. Brain Mapp. 5, 238–242.

Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., Kochunov, P.V., Nickerson, D., Mikiten, S.A., Fox, P.T., 2000. Automated Talairach Atlas labels for functional brain mapping. Hum. Brain Mapp. 10, 120–131.

Le Moal, M., Simon, H., 1991. Mesocorticolimbic dopaminergic network: functional and regulatory roles. Physiol. Rev. 71, 155–234.

Ma, Y., Volkow, N.D., Zhu, W., Rao, M., Wang, radhan., 2004. Automated region of interest (ROI) analysis for PET studies. Proceedings of the Organization for Human Brain Mapping 10th Annual Meeting, Budapest, CD-ROM: Methodology Section.

McClure, S.M., Berns, G.S., Montague, P.R., 2003. Temporal prediction errors in a passive learning task activate human striatum. Neuron 38, 339–346.

McCulloch, J., Savaki, H.E., McCulloch, M.C., Jehle, J., Sokoloff, L., 1982. The distribution of alterations in energy metabolism in the rat brain produced by apomorphine. Brain Res. 243, 67–80.

Mitchell, S.H., Laurent, C.L., De Wit, H., 1996. Interaction of expectancy and the pharmacological effects of d-amphetamine: subjective effects and self-administration. Psychopharmacology (Berlin) 125, 371–378.

Morecraft, R.J., Geula, C., Mesulam, M.M., 1992. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J. Comp. Neurol. 323, 341–358.

Nitschke, J.B., Sarinopoulos, I., Mackiewicz, K.L., Schaefer, H.S., Davidson, R.J., 2006. Functional neuroanatomy of aversion and its anticipation. NeuroImage 29, 106–116.

Oades, R.D., Halliday, G.M., 1987. Ventral tegmental (A10) system: neurobiology: 1. Anatomy and connectivity. Brain Res. 434, 117–165.

O'Doherty, J.P., Deichmann, R., Critchley, H.D., Dolan, R.J., 2002. Neural responses during anticipation of a primary taste reward. Neuron 33, 815–826.

Patrick, K.S., Caldwell, R.W., Ferris, R.M., Breese, G.R., 1987. Pharmacology of the enantiomers of threo-methylphenidate. J. Pharmacol. Exp. Ther. 241, 152–158.

Petrovic, P., Dietrich, T., Fransson, P., Andersson, J., Carlsson, K., Ingvar, M., 2005. Placebo in emotional processing-induced expectations of anxiety relief activate a generalized modulatory network. Neuron 46, 957–969.

Ploghaus, A., Becerra, L., Borras, C., Borsook, D., 2003. Neural circuitry underlying pain modulation: expectation, hypnosis, placebo. Trends Cogn. Sci. 7, 197–200.

Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Brain Res. Rev. 18, 247–291.

Sarinopoulos, I., Dixon, G.E., Short, S.J., Davidson, R.J., Nitschke, J.B., 2006. Brain mechanisms of expectation associated with insula and amygdala response to aversive taste: Implications for placebo. Brain Behav. Immun. 20, 120–132.

Schoenbaum, G., Chiba, A.A., Gallagher, M., 1998. Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nat. Neurosci. 1, 155–159.

Schultz, W., 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. 80, 1–27.

Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599.

Schwartz, W.J., Smith, C.B., Davidsen, L., Savaki, H., Sokoloff, L., Mata, M., Fink, D.J., Gainer, H., 1979. Metabolic mapping of functional activity in the hypothalamo-neurohypophysial system of the rat. Science 205, 723–725.

Sokoloff, L., Reivich, M., Kennedy, C., Des Rosiers, M.H., Patlak, C.S., Pettigrew, K.D., Sakurada, O., Shinohara, M., 1977. The [14C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J. Neurochem. 28, 897–916.

Srinivas, N.R., Hubbard, J.W., Quinn, D., Korchinski, E.D., Midha, K.K., 1991. Extensive and enantioselective presystemic metabolism of DL-threo-methylphenidate in humans. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 15, 213–220.

Strazielle, C., Lalonde, R., Hebert, C., Reader, T.A., 1999. Regional brain distribution of noradrenaline uptake sites, and of alpha1-alpha2- and beta-adrenergic receptors in PCD mutant mice: a quantitative autoradiographic study. Neuroscience 94, 287–304.

Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human BrainThieme Medical Publishers, New York.

Tremblay, L., Schultz, W., 2000. Reward-related neuronal activity during go-nogo task performance in primate orbitofrontal cortex. J. Neurophysiol. 83, 1864–1876.

Volkow, N.D., Swanson, J.M., 2003. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. Am. J. Psychiatry 160, 1909–1918.

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Angrist, B., Hitzemann, R., Lieberman, J., Pappas, N., 1997. Effects of methylphenidate on regional brain glucose metabolism in humans: relationship to dopamine D2 receptors. Am. J. Psychiatry 154, 50–55.

Volkow, N.D., Wang, G.J., Fowler, J.S., Hitzemann, R., Angrist, B., Gatley, S.J., Logan, J., Ding, Y.S., Pappas, N., 1999. Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. Am. J. Psychiatry 156, 19–26.

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., Gifford, A., Hitzemann, R., Ding, Y.S., Pappas, N., 1999. Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. Am. J. Psychiatry 156, 1440–1443.

Volkow, N.D., Ding, Y.S., Fowler, J.S., Wang, G.J., Logan, J., Gatley, J.S., Dewey, S., Ashby, C., Liebermann, J., Hitzemann, R., et al., 1995. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. Arch. Gen. Psychiatry 52, 456–463.

Volkow, N.D., Wang, G.J., Ma, Y., Fowler, J.S., Zhu, W., Maynard, L., Telang, F., Vaska, P., Ding, Y.S., Wong, C., Swanson, J.M., 2003. Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. J. Neurosci. 23, 11461–11468.

Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., Kosslyn, S.M., Rose, R.M., Cohen, J.D., 2004. Placebo-induced changes in fMRI in the anticipation and experience of pain. Science 303, 1162–1167.

Wang, G.J., Volkow, N.D., Roque, C.T., Cestaro, V.L., Hitzemann, R.J., Cantos, E.L., Levy, A.V., Dhawan, A.P., 1993. Functional importance of ventricular enlargement and cortical atrophy in healthy subjects and alcoholics as assessed with PET. MR imaging, and neuropsychologic testing. Radiology 186, 59–65.

Wang, G.J., Volkow, N.D., Hitzemann, R.J., Wong, C., Angrist, B., Burr, G., Pascani, K., Pappas, N., Lu, A., Cooper, T., Lieberman, J.A., 1997. Behavioral and cardiovascular effects of intravenous methylphenidate in normal subjects and cocaine abusers. Eur. Addict. Res. 3, 49–54.