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Amphetamine Modulates Human Incentive Processing

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Summary

Research suggests that psychostimulants can physiologically alter dopamine kinetics in the ventral striatum (VS) and psychologically enhance mood and attention. Using event-related functional magnetic resonance imaging (fMRI), we conducted a within-subject, double-blind, placebo (PLAC)-controlled study of the effects of oral dextroamphetamine (AMPH, 0.25 mg/kg) treatment on brain activity and affect during incentive processing. In two counterbalanced scanning sessions 60–180 min after ingesting AMPH or PLAC, 8 healthy volunteers played a game involving anticipation and receipt of monetary gains and losses. Group and volume of interest analyses suggested that by enhancing tonic over phasic activation, AMPH treatment "equalized" levels of VS activity and positive arousal during anticipation of both gain and loss. These findings suggest that therapeutic effects of amphetamine on incentive processing may involve reducing the difference between anticipation of gains and losses.

Introduction

The capacity of functional magnetic resonance imaging (fMRI) to resolve the activity in small subcortical regions in real time has advanced the study of incentive processing. Incentive processing refers to an organism's response to both appetitive and aversive incentives over time, including both anticipatory and consummatory phases (Craig, 1918). By combining event-related fMRI designs with different incentives ranging from juice to money, several laboratories have now been able to replicate functional dissociations in neural substrates associated with the anticipation and outcomes of appetitive incentives. For instance, in the case of monetary incentives, our laboratory has repeatedly observed activation of the ventral striatum (VS) of the subcortex during anticipation of gains versus nongains but activation of the mesial prefrontal cortex (MPFC) in response to gain versus nongain outcomes. These patterns of activation are not as evident during processing of losses (Knutson et al., 2001b, 2003). Similar dissociations have been observed during anticipation and consumption of pleasant versus unpleasant primary taste stimuli (O'Doherty et al., 2002).

A number of studies have also sought to characterize the effects of pharmacological incentives in humans using fMRI, including characterization of brain responses to injections of cocaine (Breiter et al., 1997), nicotine (Stein et al., 1998), and opiates (Sell et al., 1997). While fMRI does not directly provide information about changes in neurochemistry, it can provide temporally sensitive profiles of changes in oxygen utilization that can be modeled as a function of pharmacokinetics (Bloom et al., 1999). These studies suggest that injection of drugs of abuse often activates regions of the striatum and prefrontal cortex that overlap with regions that are commonly recruited by nonpharmacological incentives (Breiter et al., 2001; Breiter and Rosen, 1999).

In the context of pharmacotherapy, pharmacological agents are often not administered intravenously to evoke acute hedonic reactions, but rather orally, with the intent of tonically modulating ongoing affective and cognitive processing. For instance, the indirect dopamine agonist dextroamphetamine (AMPH) was historically utilized as a means of sustaining fighter pilots' vigilance and mood on long missions (Caldwell et al., 1995). Similarly, in the case of attention deficit hyperactivity disorder (ADHD), AMPH is widely prescribed to enhance and prolong attention and mood, particularly in situations that require sustained concentration and motivation. Even in healthy adults with no psychiatric diagnosis, administration of moderate doses of oral AMPH (e.g., 10–20 mg) can enhance attention and positive mood up to as much as 150 min after administration (de Wit et al., 2002; Wachtel and de Wit, 1999).

The goal of the present study was to examine the effects of oral AMPH administration on neural and affective responses to incentives. To this end, we utilized an event-related fMRI probe called the monetary incentive delay (MID) task, which was designed to elicit neural and affective responses to quantifiable incentives (Knutson et al., 2000). During the MID task, subjects are cued to anticipate potential monetary gains and losses and then respond to a rapidly presented target to either acquire the gains or avoid the losses. Previous research using this task suggests that while anticipation of gains elicits VS activity, gain outcomes elicit MPFC activity (Knutson et al., 2001b, 2003). Additionally, gain anticipation elicits increased positive aroused affect, which is correlated with VS activity (Bjork et al., 2004; Knutson et al., 2001a).

Additional research suggests both physiological and psychological hypotheses regarding AMPH's potential effects. Physiologically, comparative studies indicate that AMPH blunts phasic dopamine release (by agonizing D2 autoreceptors with elevated DA levels) while enhancing tonic availability (by blocking reuptake) in the VS (Schmitz et al., 2001). Thus, if fMRI's blood oxygen level-dependent response (hereafter, "activation") indexes

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postsynaptic changes in local field potentials (Logothetis et al., 2001), AMPH treatment might be expected to blunt the magnitude but prolong the length of ventral striatal (VS) activations commonly observed during anticipation of gain (Knutson et al., 2001a).

Psychologically, comparative studies suggest that direct infusion of AMPH into the VS increases expression of both conditioned and unconditioned appetitive behaviors (Burgdorf et al., 2001; Taylor and Robbins, 1984; Wyvell and Berridge, 2000). Similarly, human pharmacological studies suggest that moderate doses of oral AMPH can alter mood and attention (Wachtel and de Wit, 1999) in a manner that could be characterized as increased positive and aroused mood, or "positive arousal" (Watson et al., 1999). Thus, AMPH might increase positive arousal in response to incentive cues. However, it is not clear whether modulation of positive arousal would occur only during approach toward gains or also during avoidance of losses (Ikemoto and Panksepp, 1999).

Results

Behavior

Performance

Because the MID task was designed to probe affect and neural activity while controlling for behavioral performance, we predicted no significant effects of treatment, order, or condition on performance. As predicted, a 2 (drug) $\times$ 2 (dose order) $\times$ 2 (valence) $\times$ 4 (magnitude) repeated measures ANOVA on hit rate revealed no significant main effects or interactions. These findings suggested that subjects performed similarly during scans 1 and 2 and that performance was not significantly modulated by drug treatment or dose order. Across all trial types, average performance approximated the targeted 66% hit rate (mean = 66%, SD = 10%). A 2 (drug) $\times$ 2 (dose order) repeated measures ANOVA on total monetary earnings also revealed no significant main effects or interactions of drug treatment or dose order. Thus, because subjects consistently performed at maximum capacity, performance did not differ across scan sessions, incentive conditions, or drug treatment conditions.

Affect

Our research suggests that equal magnitudes of anticipated gains and losses elicit similar levels of self-reported arousal (B. Knutson et al., submitted). However, because prior findings also suggest that VS activity correlates most robustly with *positive arousal* during anticipation of gains (Bjork et al., 2004), we predicted that AMPH treatment would specifically modulate the experience of positive but not negative arousal during anticipation of large incentives. 2 (drug) $\times$ 2 (dose order) $\times$ 2 (valence) $\times$ 4 (magnitude) repeated measures ANOVAs revealed significant main effects of valence and magnitude on affective reactions to cues (i.e., "happy," "unhappy," "fearful"), qualified by significant interactions of magnitude by valence (all $p < .001$). As in prior research, subjects had more positive reactions ("happy" and "excited") to +$1.00 and +$5.00 cues relative to +$0.00 cues as well as more negative reactions ("unhappy" and "fearful") to −$1.00 and −$5.00 cues relative to −$0.00 cues. However, while there were also significant main effects of valence and magnitude on "excited" reactions to cues, these were qualified by the predicted higher-order interaction of valence, magnitude, and drug treatment [$F(3,18) = 3.74$, $p < .05$]. Paired comparisons of ratings under AMPH versus PLAC treatment revealed that AMPH-treated subjects reported a nonsignficant trend toward reporting less excitement in response to +$5.00 cues [$t(7) = 1.91$, $p < .10$] but more excitement in response to −$5.00 cues [$t(7) = 2.39$, $p < .05$]. There were no significant main effects or interactions of dose order on any other affective reactions to cues. Thus, AMPH appeared to exert an "equalizing" influence on incentive cue-elicited positive arousal, such that treated subjects felt similar levels of excitement during anticipation of both positive and negative large-magnitude incentives (see Figure 1).

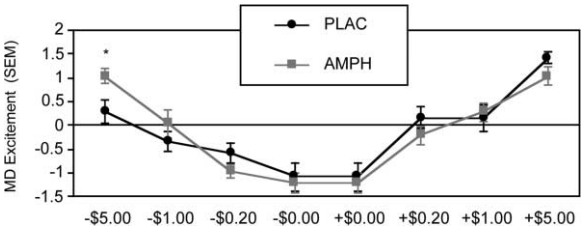

Figure 1. Positive Arousal by Drug Treatment

Effects of AMPH versus PLAC treatment on positive arousal (*$p < .05$).

Brain Activity

Statistical Maps

Using a voxel-based analysis, we examined the replicability of prior findings of NAcc and medial caudate activation during anticipation of gain versus nongain as well as MPFC, posterior cingulate, and parietal activation in response to gain versus nongain outcomes under PLAC treatment. Additionally, we examined whether AMPH treatment would alter either qualitative (i.e., localization) or quantitative (i.e., intensity) aspects of these activation patterns.

Gain versus Nongain Anticipation. Under PLAC treatment, gain versus nongain anticipation replicated prior findings, activating the bilateral NAcc, bilateral medial caudate, right putamen, and right anterior insula. In addition, the left superior frontal gyrus was significantly activated. Similar regions were activated under AMPH treatment, but not as extensively. Subcortical activations again included the left NAcc, the right medial caudate, and the left putamen. Cortically, the left inferior frontal gyrus was significantly activated. These findings suggest that the VS was activated under both PLAC and AMPH treatment, but less robustly under AMPH treatment (see Table 1).

Loss versus Nonloss Anticipation. Under PLAC treatment, loss versus nonloss anticipation deactivated the left MPFC and bilateral posterior cingulate. Under AMPH treatment, loss versus nonloss anticipation activated the left NAcc, left medial caudate, and left anterior insula, but deactivated the bilateral MPFC and left posterior cingulate. Thus, regions of deactivation were similar for PLAC and AMPH treatment, with some additional

Table 1. Gain versus Nongain Anticipation Contrast by Treatment

Drug	Region	Talairach Coordinates (RAS)			Z Value
Placebo	L sup frontal gyrus	−27	56	−6	4.96
	R anterior insula	30	19	1	4.52
	L NAcc	−15	11	0	7.52
	R NAcc	15	19	0	5.88
	L medial caudate	−8	11	4	7.48
	R medial caudate	11	11	4	6.81
	L head caudate	−15	7	12	6.03
	R putamen	19	7	−2	5.79
Amphetamine	L IFG	−44	29	12	4.40
	L NAcc	−12	10	0	5.55
	L medial caudate	−8	0	9	4.41
	R medial caudate	11	3	8	4.62
	L putamen	−22	6	4	5.51
	R putamen	27	6	−3	5.44

$p < 0.00001$, uncorrected.

subcortical activation foci apparent under AMPH treatment (see Table 2).

Gain Hit versus Miss Outcome. Under PLAC treatment, gain hit versus miss outcomes activated the posterior cingulate, replicating prior findings, but did not significantly activate MPFC (although an MPFC focus was evident at a lower significance threshold of $Z = 4.22$ at TC −8, 41, 4). In addition, the bilateral NAcc, right medial caudate, and left sublenticular extended amygdala (SLEA) were activated. Under AMPH treatment, the left MPFC and posterior cingulate were significantly activated, as well as the left NAcc. Thus, in addition to replicating prior findings under PLAC treatment, similar regions were activated under AMPH treatment, suggesting that AMPH did not diminish activation elicited by gain outcomes (see Table 3).

Loss Hit versus Miss Outcome. Under PLAC treatment, loss avoidance hit versus miss outcomes activated the right putamen and the bilateral superior temporal gyri. Under AMPH treatment, no significant activation foci were apparent (see Table 4).

Volume of Interest Analysis: Peak Activation

Based on prior research, we explored whether AMPH treatment might specifically modulate NAcc activation during anticipation of gains, or MPFC activation in response to gain outcomes. Thus, we directly compared peak activation (i.e., signal at lag = 6 s) in VOIs centered in foci previously activated by gain versus nongain anticipation (NAcc) or gain versus nongain outcomes (MPFC) (Knutson et al., 2003).

NAcc (Foci: ±11, 12, −2). For the right NAcc, a 2 (drug) × 2 (dose order) × 2 (valence) × 4 (magnitude) MANOVA revealed significant main effects of magnitude [$F(3,18) = 16.00$, $p < .001$] and drug [$F(1,6) = 62.30$, $p < .001$] on activation, qualified by interactions of valence × magnitude [$F(3,18) = 11.12$, $p < .001$], dose order × drug [$F(1,6) = 27.01$, $p < .005$], and the predicted interaction of valence × magnitude × drug [$F(3,18) = 2.86$, $p < .05$]. Pairwise comparisons of AMPH and PLAC treatment revealed that AMPH treatment elicited significantly reduced activation at the +$5.00 level [$t(7) = 3.85$, $p < .01$], significantly increased activation at the −$1.00 level [$t(7) = 3.46$, $p < .05$], and a nonsignificant trend toward increased activation at the −$5.00 level [$t(7) = 1.82$, $p < .10$]. For the left NAcc, the same analysis revealed significant main effects of magnitude [$F(3,18) = 27.72$, $p < .001$] and valence [$F(1,6) = 6.87$, $p < .05$] on activation, qualified by an interaction of magnitude × valence [$F(3,18) = 5.32$, $p < .01$], but no interaction with drug treatment status. Pairwise comparisons for the left NAcc VOI did not reveal significant differences between AMPH and PLAC treatment at any incentive level. Thus, prior findings of an interaction of valence and magnitude on right NAcc activation replicated but were additionally modulated by drug treatment status, such that AMPH treatment appeared to "equalize" activation during an-

Table 2. Loss versus Nonloss Anticipation Contrast by Treatment

Drug	Region	Talairach Coordinates (RAS)			Z Value
Placebo	*L mesial PFC*	*−8*	*44*	*−6*	*−4.59*
	L posterior cingulate	*−4*	*−56*	*27*	*−5.87*
	R posterior cingulate	*1*	*−56*	*24*	*−6.46*
Amphetamine	*L mesial PFC*	*0*	*61*	*−3*	*−5.20*
	R mesial PFC	*8*	*57*	*−6*	*−4.98*
	L posterior cingulate	*0*	*−59*	*23*	*−5.37*
	L insula	−30	18	12	4.42
	L NAcc	−12	10	0	5.55
	L medial caudate	−8	0	9	4.41
	R tail caudate	11	−5	20	4.76

Italicized text indicates deactivations.
$p < 0.00001$, uncorrected.

Table 3. Gain Hit versus Miss Outcome Contrast by Treatment

Drug	Region	Talairach Coordinates (RAS)			Z Value
Placebo	L NAcc	−8	8	−3	5.65
	R NAcc	8	16	0	4.80
	R head caudate	8	15	8	4.66
	L SLEA	−11	0	−7	4.41
	R medial caudate	4	0	8	4.88
Amphetamine	L mesial PFC	0	48	−7	5.56
	L NAcc	−8	7	−6	4.94
	L posterior cingulate	−51	24	24	4.85

$p < 0.00001$, uncorrected.

ticipation of large positive and negative incentives (see Figure 2).

MPFC (Foci: ±4, 50, −6). Analyses were conducted separately for gain and loss trials in order to directly compare hit and miss outcomes for each after controlling for anticipation. For right MPFC during gain trials, a 2 (drug) × 2 (dose order) × 2 (outcome) × 4 (magnitude) MANOVA revealed a significant main effect of outcome [$F(1,6) = 8.57$, $p < .05$], qualified by an interaction of magnitude × outcome [$F(3,18) = 5.41$, $p < .01$]. For loss trials, there was only a significant main effect of magnitude [$F(3,18) = 4.50$, $p < .05$]. Similarly, for left MPFC activation during gain trials, a significant main effect of outcome [$F(1,6) = 6.34$, $p < .05$] was qualified by an interaction of magnitude × outcome [$F(3,18) = 5.55$, $p < .01$], but for loss trials there was only a main effect of outcome [$F(1,6) = 9.35$, $p < .05$]. Thus, the previously observed activation of right MPFC for increasing gain outcomes was replicated in this sample, but neither dose order nor drug treatment significantly qualified this effect (see Figure 3).

Volume of Interest Analysis: Time Course

To determine whether AMPH treatment might have modulated the shape of the hemodynamic response function in the VS, we extracted and compared activation time courses from the right NAcc for trial types that showed maximal differences (i.e., ±$5.00 and ±$0.00 "hit" trials). Right NAcc VOI data for +$5.00 gain trials were subjected to a 2 (AMPH versus PLAC treatment) × 9 (epoch) ANOVA, which revealed a significant main effect of epoch [$F(8,56) = 7.39$, $p < .001$], qualified by a significant interaction of drug treatment × epoch [$F(8,56) = 3.37$, $p < .005$], but no main effect of drug treatment. This result indicated that while right NAcc activation during high-incentive trials differed at specific time points as a function of drug treatment, activity did not differ overall, suggesting that AMPH treatment modulated the shape of the hemodynamic response function in this region rather than merely blunting overall activation across the trial. To further examine this possibility, data across high- and low-incentive trial types were compared across drug treatment groups at predicted time points with paired t tests ($p < .05$, uncorrected).

While PLAC and AMPH treatment did not significantly differ from each other at any time point during +$0.00 trials, they did significantly differ during +$5.00 trials at time points 4 [6 s; $t(7) = 3.85$, $p < .01$] and 5 [8 s; $t(7) = 3.81$, $p < .01$] and showed a nonsignificant trend toward a difference in the opposite direction at time point 8 [14 s; $t(7) = 2.11$, $p < .08$]. Within PLAC treatment, activation during +$5.00 versus +$0.00 hit trials differed at time points 3 [4 s; $t(7) = 3.12$, $p < .05$], 4 [6 s; $t(7) = 6.89$, $p < .001$], 5 [8 s; $t(7) = 5.51$, $p < .001$], and 7 in the opposite direction [12 s; $t(7) = -2.47$, $p < .05$], whereas within AMPH treatment, activation differed between +$5.00 and +$0.00 trials at time points 3 [4 s; $t(7) = 4.21$, $p < .01$] and 4 [6 s; $t(7) = 4.19$, $p < .05$], but not at later time points. A 2 (drug) × 2 (time point) repeated measures ANOVA on activation for +$5.00 trials at time points 4 and 7 confirmed a crossover interaction [$F(1,7) = 7.27$, $p < .05$], suggesting that these differences were not merely due to temporal correlation in the signal. Thus, while these results suggest that AMPH treatment may have blunted peak NAcc activity during anticipation (i.e., time point 4; 6 s), they also are also not inconsistent with the hypothesis that AMPH treatment may have prolonged NAcc activity at later time points (i.e., time point 7; 12 s) (see Figure 4).

Similar analyses of potential loss trials did not reveal significant differences between PLAC and AMPH during −$5.00 trials. However, within PLAC treatment, comparison of −$5.00 versus −$0.00 time courses revealed significant differences at time point 5 [8 s; $t(7) = 2.72$, $p < .05$], and in the opposite direction at time points 7 and 8 [12 and 14 s; $t(7) = -2.97$, $p < .05$, and $t(7) = -2.85$, $p < .05$]. On the other hand, within AMPH treatment, comparison of −$5.00 versus −$0.00 time courses revealed a significant difference only at time point 3 [4 s; $t(7) = 2.80$, $p < .05$]. Thus, AMPH treatment did not blunt and may have potentiated activity in the right NAcc during loss anticipation.

Table 4. Loss Hit versus Miss Outcome Contrast by Treatment

Drug	Region	Talairach Coordinates (RAS)			Z Value
Placebo	R putamen	30	−18	8	4.47
	L sup temp gyrus	−60	−15	8	5.99
	R sup temp gyrus	57	−4	8	4.87
Amphetamine	N/A				

$p < 0.00001$, uncorrected.

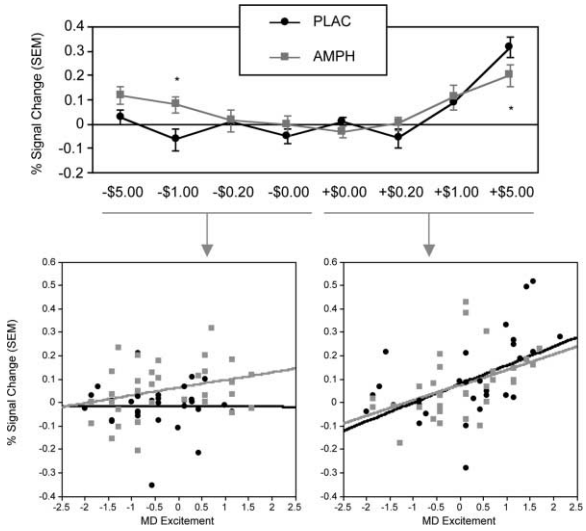

Figure 2. Right NAcc Peak Anticipatory Activation and Correlations with Positive Arousal

Right NAcc peak activation during incentive anticipation by condition and drug treatment and plotted versus excitement (mean-deviated) across all cue conditions and subjects (lag = 6 s, *$p < .05$, AMPH versus PLAC).

Brain/Affect Correlations

Analyses suggested that both right NAcc activation and self-rated positive arousal (e.g., "excitement") showed significant interactions with drug treatment status. To further examine how AMPH treatment might have altered the relationship between NAcc activation and positive arousal, we conducted four multiple regressions examining whether NAcc activation correlated with gain and loss cue-elicited excitement under PLAC and AMPH treatment. Across subjects and trial types for gain trials, right NAcc activation significantly correlated with cue-elicited excitement under both PLAC ($\beta = .52$, $p < .01$) and AMPH ($\beta = .48$, $p < .01$) treatment (see Figure 3). However, in the case of loss anticipation, right NAcc activation showed a nonsignificant trend toward correlating with excitement under AMPH ($\beta = .30$, $p < .10$) but not PLAC ($\beta = -.01$, n.s.) treatment (see Figure 3). Statistical comparison of the correlation between NAcc activation and excitement during loss trials indicated a significant difference between AMPH and PLAC treatment (Fisher's $Z = 1.94$, $p < .05$, one-tailed). Thus, AMPH treatment may have partially reinstated a positive association between NAcc activation and excitement during loss anticipation (see Figure 2).

Discussion

While researchers have separately examined how either pharmacological or psychological incentives alter brain activity, this is the first study to utilize an event-related design to examine their combined influence. The findings provide some evidence that AMPH modulates both physiological and psychological aspects of incentive processing in humans. In the context of a monetary incentive delay task, the effects of AMPH on brain activity were most evident in the ventral striatum (VS) and were associated with psychological changes in affect.

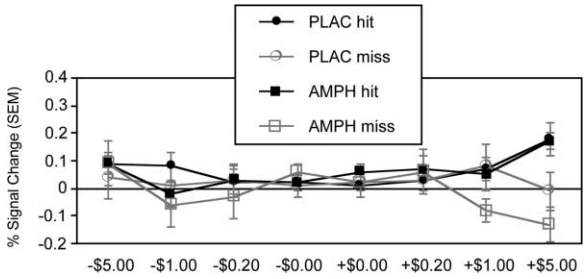

Figure 3. Right MPFC Peak Outcome Activation

Right MPFC peak activation in response to hit and miss outcomes by condition and drug treatment (lag = 6 s).

Physiologically, time course analyses suggested that relative to PLAC, AMPH treatment blunted the peak magnitude but appeared to extend the duration of VS activation during anticipation of gains. These findings are consistent with comparative data suggesting that while AMPH treatment reduces the magnitude of phasic DA release in the VS, it can also increase availability of tonic DA (Schmitz et al., 2001). Although fMRI measures changes in blood oxygenation rather than neurochemistry, these findings are consistent with the hypothesis that VS activation during anticipation of gain might partially index dopaminergic modulation of postsynaptic activity (Schultz, 2002). In this study, AMPH did not diminish peak brain activation in other regions (e.g., the MPFC), suggesting a local rather than global modulatory effect. Additionally, during anticipation of loss, which did not elicit significant VS activation under PLAC treatment, AMPH treatment appeared to augment VS activity. Psychological findings complemented these physiological effects.

Psychologically, as in prior studies, subjects reported experiencing maximum positive arousal (e.g., excitement) during anticipation of gains, and large gains in particular. Further, under both PLAC and AMPH treatment, VS activation was associated with gain cue-elicited positive arousal. Under PLAC treatment, anticipation of losses did not elicit significant VS activation or positive arousal, and VS activity and positive arousal were not significantly correlated. However, under AMPH treatment, anticipation of loss elicited increased VS activation and positive arousal, and the association between VS activation and positive arousal was partially reintroduced. Notably, this affective modulation was specific to positive arousal (e.g., excitement) but did not occur in the case of other affective states, including negative arousal (e.g., fearfulness).

Together, these findings provide further support for the hypothesis that activation in a region of the VS (i.e., right NAcc) is associated with increased positive aroused affect (Drevets et al., 2001; Knutson et al., 2001a). While positive arousal is most likely to occur during anticipation of acquiring gains, it may also occur to a lesser extent during anticipation of avoiding losses. In the case of potential loss, AMPH treatment appeared to potentiate right NAcc activity, which may have augmented positive arousal, and thus facilitated reframing

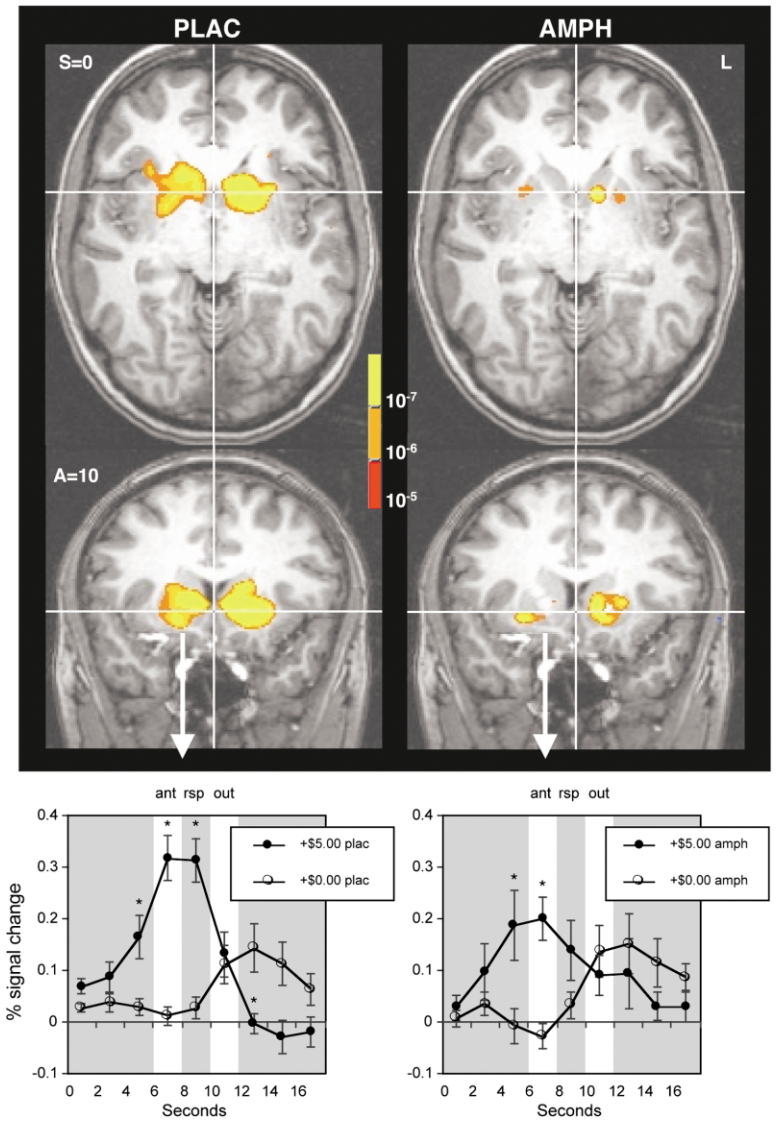

Figure 4. Gain versus Nongain Activation Maps and Right NAcc Time Courses by Drug Treatment

Effects of AMPH versus PLAC treatment on gain versus nongain anticipation contrast maps and right NAcc activation time courses ($n = 8$, within-subjects). Abbreviations: ant, anticipation; rsp, response; out, outcome. *$p < .05$ +$5.00 versus +$0.00.

of potential losses as potential gains of safety. This account is consistent with the "safety-seeking" hypothesis, which predicts that aversive events should only elicit NAcc activity to the extent that animals believe that they can escape (i.e., anticipate a positive outcome) (Ikemoto and Panksepp, 1999), and can be contrasted with accounts that predict equivalent NAcc recruitment during preparation for any behavioral response, whether appetitive or aversive (Young et al., 1998).

Beyond specific regions of interest, activation maps indicated that while foci did not qualitatively shift as a function of AMPH treatment, different foci did show distinct quantitative changes in activation levels. While striatal activation was blunted during gain anticipation, striatal activation was instead augmented during loss anticipation under AMPH treatment. In response to incentive outcomes, MPFC activation appeared to be similar or even augmented to gain hit versus miss outcomes under AMPH treatment. The potential of AMPH to potentiate the MPFC's discrimination between gain hit and miss outcomes deserves further study in a larger sample. Together, these findings suggest that not all activations were blunted by AMPH treatment, as might be predicted by a global hypoperfusion account. Future studies might utilize perfusion scans to ensure that global changes in perfusion do not alter task-induced activations. Because the limits of the scanning range precluded visualization of brain activity above the top of the corpus callosum, more dorsal cortical motor regions also deserve future exploration (Bush et al., 2002; Knutson et al., 2000).

In other fMRI studies utilizing block designs, investigators have reported increases in neural activation due to AMPH treatment in amygdala, prefrontal cortex, and motor cortex (Hariri et al., 2002; Mattay et al., 2000; Uftring et al., 2001). However, in the present study, during anticipation of large gains, AMPH treatment reduced rather than increased VS peak activation. Part of this apparent discrepancy may have to do with the event-related nature of the present experiment's design. If AMPH blunts activation magnitude but extends activation length, this could have the effect of blunting phasic

activations observed in event-related designs while enhancing tonic activations observed in block designs. Once characterized, tonic effects could be modeled in event-related as well as in block designs. In addition, most of the activation enhancements observed in prior studies were cortical while the peak blunting observed in this study occurred subcortically, where reuptake mechanisms are more prevalent, and thus subject to AMPH blockade (Garris and Wightman, 1994). Finally, prior studies may not have controlled for variation in behavioral performance, which often changes as a function of AMPH treatment (Salmeron and Stein, 2002), but which was controlled for in this paradigm (i.e., hit rate). Notably, in one fMRI study, when investigators did control for behavioral pace in a finger-tapping task, they did not observe significant differences in motor cortex activation as a function of stimulant treatment (Rao et al., 2000).

The current experiment has some limitations including small sample size, which may limit generalizability; oral administration of AMPH, which is more susceptible than other administration routes to individual differences in pharmacokinetics; assessment during AMPH peak blood concentration but not peak euphoric effects, such that synergistic psychological effects might not be maximized; experimenter administration, which might elicit different psychological effects than self-administration; and reliance upon fMRI indices of blood oxygenation, which do not yield specific information about neurochemistry. Additionally, future research might examine dose-response effects of AMPH, which have been well documented in the comparative literature (Cador et al., 1991). However, this study also features a number of notable strengths that include a counterbalanced within-subjects protocol; double-blind administration and placebo control; strict quality assurance to rule out intersession discrepancies due to motion and performance; event-related design, which confers real-time temporal resolution of changes in oxygenation; and use of a validated fMRI probe, which has been shown to parametrically activate the VS and reliably elicit affect in healthy subjects. Thus, this initial study lays a foundation for future work that utilizes event-related fMRI to investigate the combined effects of pharmacological and psychological manipulations in specific brain regions.

The present findings have a number of implications. Physiologically, they suggest that AMPH treatment may modulate endogenous VS activity during anticipation of incentives in a manner consistent with comparative studies, by accentuating tonic rather than phasic components (Schultz, 2002). In the context of fMRI methods, medications that influence dopamine kinetics may partially obscure endogenous activity in dopamine terminal fields if traditional modeling techniques are used. Thus, researchers may benefit from combining event-related probes with volume of interest analyses in fMRI studies of psychostimulant action. Psychologically, the findings suggest that AMPH treatment may also promote tonic VS activity during anticipation of loss, which might facilitate increased positive arousal and concomitant affective reframing of potential loss as potential gain. In this manner, agents that enhance dopaminergic tone in the VS may help organisms to maintain motivation, even in the face of adversity.

Experimental Procedures

Eight healthy volunteers (2 women, right-handed, age 20–40) participated in the study. Prior to the study, volunteers were screened for physical disorders (including neurological damage and abnormal cardiac function) via a physical exam. Absence of mental disorders as well as substance abuse was confirmed via a psychiatric diagnostic interview (APA, 1998). All subjects gave written informed consent, and the protocol was approved by the Institutional Review Board of the National Institutes of Mental Health.

150–165 min prior to scanning, each subject ingested either AMPH (0.25 mg/kg, per oral) or placebo (PLAC) in a double-blind, counterbalanced procedure. Timing of testing was based on pharmacokinetic data indicating that blood levels of orally administered AMPH peak 60–180 min after drug administration. Repeated testing sessions always occurred not less than 3 days and not more than 60 days apart. Prior to the second session, subjects received whichever treatment they had not received during their first session.

Before entering the scanner, subjects completed a practice version of the MID task and were subsequently tested on their explicit knowledge of the meaning of each incentive cue (see below). This practice task both minimized later learning effects and provided an estimate of mean reaction time for individually standardizing task difficulty in the scanner. Subjects were also shown the cash that they could earn by performing the task successfully in the scanner. All subjects correctly believed that they would receive cash at the end of the experiment. Once in the scanner, anatomical and functional scans were collected. Subjects engaged in two 10 min sessions of the MID task during functional scan acquisition. Following the final session, subjects retrospectively rated how they felt when they saw each of the seven cues on 4-point Likert scales indexing cue-elicited affect (e.g., "happy" and "excited," as well as "unhappy" and "fearful").

Monetary Incentive Delay Task

Each of the two memory incentive delay (MID) task sessions consisted of 72 trials lasting 6 s each, yielding a total of 144 trials. During each trial, subjects saw one of eight cue shapes (cue; 250 ms), fixated on a crosshair as they waited a variable interval (delay; 2000–2500 ms), and then responded to a solid white target square that appeared for a variable length of time (target; 160–260 ms) with a button press. Depending on the preceding incentive cue, subjects could gain or avoid losing money by pressing the button during target presentation. Feedback (feedback; 1650 ms) that followed the target's disappearance notified subjects whether they had won or lost money during that trial and indicated their cumulative total at that point. Subjects were instructed to respond on all trials. Task difficulty, based on reaction times collected during the practice session prior to scanning, was set such that each subject would succeed on approximately 66% of his or her target responses. This practice assured control for potential drug treatment influences on success across repeated testing sessions. fMRI volume acquisitions were time-locked to the offset of each cue as well as the onset of feedback presentation and thus were acquired during anticipatory delay periods as well as feedback presentation periods (Knutson et al., 2003).

Cues signaled potential gain outcomes ($n = 54$, denoted by open circles), potential loss outcomes ($n = 54$; denoted by open squares), or no monetary outcome ($n = 36$; denoted by open triangles). Gain cues signaled the possibility of gaining \$0.20 ($n = 18$; a circle with one horizontal line), \$1.00 ($n = 18$; a circle with two horizontal lines), or \$5.00 ($n = 18$; a circle with three horizontal lines). Similarly, loss cues signaled the possibility of losing \$0.20 ($n = 18$; a square with one horizontal line), \$1.00 ($n = 18$; a square with two horizontal lines), or \$5.00 ($n = 18$; a square with three horizontal lines) (Knutson et al., 2001a). Trial types were pseudorandomly ordered within each session, and different pseudorandom orders were used for repeated sessions.

fMRI Acquisition

Imaging was performed using a 3.0 T General Electric MRI scanner and a standard quadrature head coil. Twenty-four 2.0 mm thick slices (in-plane resolution 3.75 × 3.75 mm) starting at the midpons and extending upwards to the top of the corpus callosum were axially acquired with no interslice gap. This plane of acquisition and voxel size provided enhanced spatial resolution of subcortical regions of interest (e.g., the NAcc) and anterior orbital frontal cortex at the expense of acquiring data from the top of the head and bottom of the cerebellum. Functional scans were acquired using a T2*-sensitive gradient echo sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip = 90°, and number of volumes = 432. Structural scans were acquired using a T1-weighted magnetization-prepared rapid gradient echo sequence (TI = 725; TE = 1.4; TR = 5.0; TD = 1400; flip = 6°), which facilitated subsequent coregistration and localization of functional data.

fMRI Analysis

Analyses focused both on changes in blood oxygen level-dependent contrast (or "activation") that occurred during anticipatory delay periods as well as on activations that occurred during outcome periods. All analyses were conducted using Analysis of Functional Neural Images (AFNI) software (Cox, 1996). For preprocessing, voxel activation time series were interpolated to correct for nonsimultaneous slice acquisition within each volume (using sinc interpolation and the most inferior slice as a reference), concatenated across both task sessions, corrected for three-dimensional motion (using the third volume of the first session as a reference), subjected to slight spatial blurring to increase the signal to noise ratio (4 mm FWHM), and bandpass filtered to remove the influence of nonlinear trends unrelated to the task frequency (i.e., <6 and >90 s). Visual inspection of motion correction estimates confirmed that no participant's head moved more than 2 mm in any dimension from one volume acquisition to the next. Two other volunteers had violated this criterion on one of the two scanning sessions and so were excluded from further analyses, leaving a total of 8 subjects. Paired comparisons of movement estimate standard deviations in the *x*, *y*, and *z* planes assured that remaining subjects did not significantly differ under AMPH versus PLAC treatment.

Preprocessed time series data for each individual were analyzed with multiple regression (Neter et al., 1996) to verify activation of relevant reward-processing regions during treatment with both AMPH and PLAC. The regression model consisted of a set of six orthogonal regressors of interest, six regressors describing residual motion, and six regressors modeling baseline, linear, and quadratic trends for each of the two experimental sessions. Regressors of interest contrasted: (1) anticipation versus the rest of the trial; (2) anticipation of gain versus nongain outcome; (3) anticipation of loss versus nonloss outcome; (4) outcomes versus the rest of the trial; (5) "hit" versus "miss" outcomes on potential gain trials; and (6) "hit" versus "miss" outcomes on potential loss trials. Regressors of interest were convolved with a γ-variate function that modeled a prototypical hemodynamic response prior to inclusion in the regression model (Cohen, 1997). Maps of t statistics for these regressors of interest were transformed into Z scores, coregistered with structural maps, spatially normalized by warping to Talairach space, slightly spatially smoothed (FWHM = 2 mm) to minimize the effects of anatomical variability, resampled at 2 mm cubic, and combined into a group map using a meta-analytic formula (average Z*sqrt(n)). Analyses focused on subcortical and prefrontal regions comprising less than a quarter of the brain's total gray matter volume (i.e., ~140 of 560 ml; Knutson et al., 2001c). Thus, based on a voxel volume of .028 ml, the activation threshold was set at Z = 4.4, ($p < .00001$, two-tailed, uncorrected) to correct for 5000 comparisons in the search volume ($p < .05$, two-tailed, corrected).

Once activation of predicted structures was verified, 6 mm diameter spherical volumes of interest (VOIs) were constructed and centered upon foci identified in prior research using the MID task. These foci included the nucleus accumbens (NAcc, TC: 11, 12, −2) and mesial prefrontal cortex (MPFC, TC: 4, 50, −6) (Knutson et al., 2003). The a priori foci fell near (i.e., <4 mm in all planes) to VS and MPFC foci observed in the present study for PLAC and AMPH thresholds (the same analyses on post hoc VOIs derived from the present data set's foci yielded similar, but weaker, findings). Utilization of a standard volume ensured that equal amounts of data were extracted for each subject in each condition, and visual inspection confirmed that VOIs encompassed only gray matter for each individual subject. To compare peak event-related activation across different incentive conditions, activation time courses were extracted from each VOI and averaged at 6 s (anticipation) and 10 s (outcome) lags for each trial type within each individual. Averaged activation values for right NAcc and right MPFC VOIs were then analyzed with within-subjects 2 (drug: AMPH versus placebo) × 2 (dose order: first versus second visit) × 2 (valence: gain versus loss) × 2 (outcome: hit versus miss) × 4 (magnitude: 0.00, 0.20, 1.00, 5.00) repeated measures analyses of variance (ANOVAs, hypothesized interaction p's < 0.05, two-tailed). For gain anticipation, we predicted a significant interaction of drug, valence, and magnitude (but not dose order) on NAcc activation. For gain outcomes, we predicted a significant interaction of drug, valence, magnitude, and outcome (but not dose order) on MPFC activation. Paired t tests were used to decompose interactions and test for differences at predicted time points ($p < 0.05$, two-tailed). To examine the NAcc hemodynamic response function under AMPH versus PLAC treatment, we compared activation at each of the nine acquisitions during and following the cue presentation during each of the +$5.00, −$5.00, +$0.00, and −$0.00 trials. These trial types were selected because anticipatory activation changes most robustly under high incentive conditions (Knutson et al., 2001a).

Performance

Percentage of hits and hit reaction times on each trial type were averaged for each individual and subjected to repeated measures within-subjects 2 (drug) × 2 (dose order) × 2 (valence) × 4 (magnitude) ANOVAs. We predicted no significant effects of any variable on performance, since the practice task was designed to enable investigators to control for performance such that subjects performed at ceiling across conditions during scanning. In the event of a significant interaction, paired t tests were used to compare differences among trial types ($p < 0.05$, two-tailed, uncorrected).

Affect

Positive and negative aroused affect were assessed with retrospective ratings of "happiness," "excitement," "unhappiness," and "fearfulness" in reaction to the presentation of each cue. Ratings were mean-corrected for each descriptor across cue types within subjects to minimize response bias. Recent evidence suggests that such retrospective cue-elicited ratings are highly correlated with online probes acquired during actual play ($r > .50$), which show robust test-retest reliability ($r > .70$; B. Knutson et al., submitted). Mean-corrected ratings for each cue type were then subjected to repeated measures within-subjects 2 (drug) × 2 (dose order) × 2 (valence) × 4 (magnitude) ANOVAs. In accord with prior findings, we predicted a significant drug × valence × magnitude (but not dose order) interaction on adjectives most indicative of positive arousal (e.g., "excitement"), but not on other adjectives (Bjork et al., 2004). In the event of a significant interaction, paired t tests were used to compare differences within trial types across drug conditions ($p < 0.05$, two-tailed, uncorrected).

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