A Thalamocorticostriatal Dopamine Network for Psychostimulant-Enhanced Human Cognitive Flexibility

Supplemental Information

Supplementary Methods

Screening and Eligibility

Before admission into the positron emission tomography (PET) phase of the study, all participants were given a physical exam to assess for contraindications for study participation. Participants completed a psychiatric interview to rule out Axis I psychiatric history. Participants were excluded if they had any history of substance abuse, current tobacco use, alcohol intake greater than 8 ounces of whiskey or equivalent per week, use of psychostimulants (excluding caffeine) more than twice in the participant's lifetime or at all in past 6 months, any psychotropic medication for the past 6 months other than occasional use of benzodiazepines for sleep, history of psychiatric illness, significant medical condition, or any condition which would interfere with magnetic resonance imaging (MRI) or PET studies (e.g., extreme obesity, claustrophobia, cochlear implant, metal fragments in eyes, cardiac pacemaker, neural stimulator, and metallic body inclusions or other metal implanted in the body which may interfere with MRI scanning, pregnancy, or anemia). Urine drug screens were performed to test for the presence of amphetamine (d-AMPH), cocaine, marijuana, PCP, opiates, benzodiazepines, and barbiturates.

Task-Switching

All participants completed a classic task switching paradigm (1). A single digit 1, 2, 3, 4, 6, 7, 8, or 9 appeared within one cell of a 2 x 2 grid (Figure S1). If the digit appeared in one of the two cells on the top row, participants made a magnitude judgment. If the digit appeared in one of

the two cells on the bottom row, participants made a parity (odd-even) judgment. On magnitude trials, participants pressed a button to indicate if the digit displayed was less than 5 (left button) or greater than 5 (right button). On odd-even trials, participants pressed a button to indicate if the digit displayed was odd (left button) or even (right button). Trials where response times were shorter than 100 ms or longer than 3000 ms were removed from all analyses. Accuracy and mean reaction times reported include all trials. Switch cost calculations are based on correct trials only.

PET Imaging

Baseline binding of [^{18}F]fallypride is also influenced by endogenous dopamine (DA) levels, and thus provides a metric of receptor availability, rather than absolute receptor density. However, receptor availability has proven a highly useful measure in quantifying individual differences in DA functioning, and indeed in some ways may be a more relevant variable than receptor density examined in isolation (as only available receptors can be engaged at a given point in time). In addition, [^{18}F]fallypride has been found to be sensitive to endogenous DA release (2; 3), particularly in the striatum, making it an ideal ligand for use in conjunction with a dual scan strategy that allows assessment of both baseline receptor availability and individual differences in induced DA release.

Test-retest reliability for this PET radioligand, [^{18}F]fallypride, in the regions identified in our manuscript (frontal cortex, parietal cortex, thalamus, striatum) is very high. This has been demonstrated in prior manuscripts by other groups (e.g., 4; 5). There is evidence for very little 2-week test-retest variability in the caudate (3.8% +/– .7), thalamus (6.1% +/– 1.3), and frontal cortex (6.7% +/– 1.8) and high intraclass correlations in caudate (.98), thalamus (.91) and frontal cortex (.95) (5; Table 2). Similarly, test-retest error in parietal cortex is very low (2.6%)

suggesting it is quite reliable (4). Thus, our measures of non-displaceable binding potential (BP_{ND}) are highly stable. Critically, prior test-retest data show that for these regions, receptor availability is slightly higher in the second session compared to the first. This is inconsistent with the possibility that the observed reduction in [^{18}F]fallypride BP_{ND} is due to a repetition effect, rather than administration of .43 mg/kg of d-AMPH.

Magnetic Resonance Imaging

MRI scans of the brain were performed using thin section inversion prepared T1-weighted spoiled gradient recalled sequences [IR SPGR, echo time (TE) = 3.6, repetition time (TR) = 18.9, TI = 400, 24 cm field of view] in the sagittal (slice thickness 1.2 mm) and coronal (slice thickness 1.4 mm) planes. In addition, fast spin echo axial spin density weighted (TE = 19, TR = 5000, 3 mm thick) and T2-weighted (TE = 106, TR = 5000, 3 mm thick) scans were obtained to ensure that participants did not have any structural abnormalities.

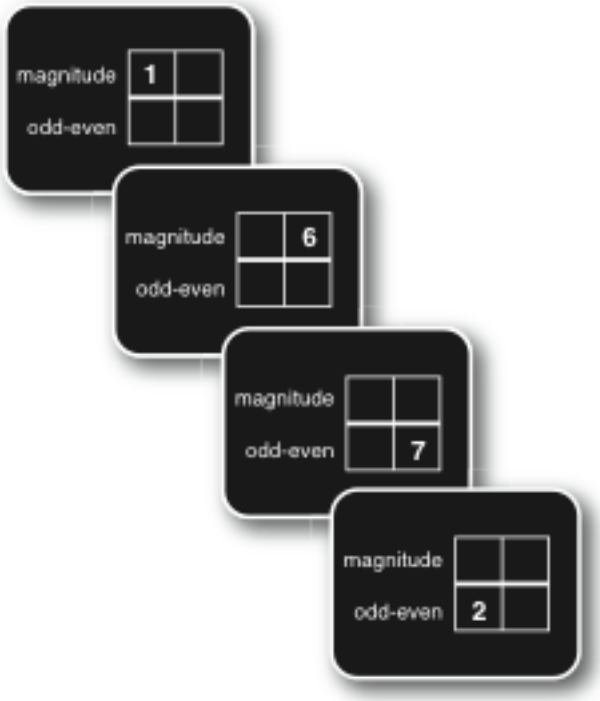

Figure S1. Task switching paradigm sample trials. Responses indicated whether digits were greater than or less than 5 on the top row and odd or even on the bottom row. The clockwise sequence with predictable switches repeated throughout the experiment.

Table S1. Localization of relations between amphetamine-induced cognitive flexibility and dopamine binding potential and release.

Region	R	A	S	Z	Voxels
Baseline D2 BP_{ND}					
R Middle Frontal Gyrus	40	34	26	4.80	103
L Thalamus	–12	–18	6	4.24	41
L Postcentral Gyrus	–60	–14	18	3.89	55
R Inferior Parietal Lobule	56	–18	38	3.66	44
Dopamine Release					
R Caudate	8	26	–6	3.89	32
R Inferior Frontal Gyrus	32	18	–14	3.74	32

BP_{ND}, binding potential, non-displaceable; L, left; R, right. Column labels R, A, S indicate Montreal Neurological Institute coordinates for right/left, anterior/posterior, and superior/ inferior, respectively.

Supplementary Results

Task-Switching Response-to-Stimulus Intervals (RSIs)

Half of the trials had an RSI of 150 ms and the other half of the trials had an RSI of 600 ms. These RSIs were blocked. Examination of the two RSI used in the present task revealed that the size of the d-AMPH reduction in switch cost did not differ for the 150 ms RSI (100 ms, SD = 13) and the 600 ms RSI (76 ms, SD = 20), $t_{39} = 1.34$, $p = .18$. Thus, average d-AMPH reduction in switch cost across the task is used for all analyses.

Quantification of Behavioral Repetition Effect in Subsample that Completed PET Imaging

We attempted to reach all subjects for follow-up to quantify the size of the behavioral task repetition effect in the same sample who completed the PET scans. Ten subjects responded to our request and completed two sessions separated by the same number of days as their original two sessions. This follow-up was conducted 4–5 years after the tasks were completed the first time, so it is unlikely that any initial exposure to the task carried over across this interval. Within this subset of ten subjects there was a non-significant reduction in switch costs across the two sessions (mean = 31 ms), $t_9 = .67$, $p = .52$. In contrast, the reduction in switch costs from d-AMPH were statistically significant even in this small sample (mean = 67 ms), $t_9 = 4.07$, $p < .003$.

Control Sample Results and Analysis of Additional Covariates in PET Sample

In a separate sample of 10 healthy young adults (ages 21–30) who performed the task twice but did not receive d-AMPH or undergo PET imaging, we examined both reaction time change and reduction in switch cost over approximately two weeks (range 13–18 days). Although there

was a small reduction (mean = 46 ms, SD = 75 ms) in switch cost over the two weeks, $t_9 = 1.97$, $p = .08$, this effect was no longer significant when controlling for reaction time change, $t_9 = –.90$, $p = .39$.

In the primary sample of 40 healthy adults who completed PET imaging (reported in the main text), the switch cost reduction after d-AMPH is not reduced by controlling for differences in overall reaction time between the placebo and d-AMPH sessions suggesting that the cognitive benefit of d-AMPH is more than a simple motor benefit from either the drug or repetition. In follow-up analyses of the primary PET dataset, we included mean reaction time change and number of days between sessions as additional covariates in the regression models. Including these covariates (with scanner, age, and sex) does not eliminate the relationships between switch cost under d-AMPH and thalamic and cortical receptors ($p < .001$) or caudate DA release ($p < .01$).

Supplemental References

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