

Variability in paralimbic dopamine signaling correlates with subjective responses to d-amphetamine

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## Supplementary Material

<b>PET Frame</b>	
<b>Acquisition Times (secs)</b>	
<b>Initial Protocol (n=12)</b>	<b>Revised Protocol (n=34)</b>
<b>Discovery LS</b>	<b>Discovery STE</b>
<b>Dynamic 1 (DY1)</b>	
0-15	0-15
15-30	15-30
30-45	30-45
45-60	45-60
60-75	60-75
75-90	75-90
90-105	90-105
105-120	105-120
120-150	120-150
150-180	150-180
180-210	180-210
210-240	210-240
240-270	240-270
270-300	270-300
300-360	300-360
360-420	360-420
420-480	420-480
480-540	480-540
540-600	540-600
600-750	600-660
750-900	660-810
900-1200	810-1100
1200-1500	1110-1410
1500-1800	1410-1710
1800-2400	1710-2310
2400-3000	2310-2910
3000-3600	2910-3510
	3510-4110
BREAK*	BREAK#
<b>Dynamic 2 (DY2)</b>	
1500 sec length	1500 sec length
1500 sec length	1500 sec length
BREAK*	BREAK#
<b>Dynamic 3 (DY3)</b>	
1800 sec length	1800 sec length
1800 sec length	1800 sec length

**Table S1. With the change in PET scanners, there was also a change in acquisition (frame) timing in the first dynamic (DY1) run. For neither protocol did the start timings of DY2 or DY3 significantly differ within subjects across placebo and dAMPH sessions (max  $t=1.78$ , min  $p=0.10$ ). Comparing the two acquisition protocol groups, Break 1 on dAMPH ( $t(44)=2.16$ ,  $p=0.037$ ), and Break 2 on placebo ( $t(44)=7.03$ ,  $p<0.001$ ) and dAMPH ( $t(44)=6.18$ ,  $p<0.001$ ) differed with longer breaks in the initial protocol subjects. Importantly, however, the variation in overall acquisition length between placebo and dAMPH sessions did not differ across protocols ( $t(44)=0.98$ ,  $p=0.33$ ; Initial Acquisition Protocol dAMPH – Placebo Scan Length:  $315\pm737$ ; Revised Protocol:  $134\pm476$ ).**

**\*Initial Acquisition Protocol:**

**Placebo:**

Break 1:  $1541\pm103$  sec, Break 2:  $2203\pm91$  sec

Mean Start Times for DY2:  $5141\pm103$  sec; DY3:  $10344\pm150$  sec

**dAMPH:**

Break 1:  $1716\pm49$  sec, Break 2:  $2343\pm97$  sec

Mean Start Times for DY2:  $5316\pm49$  sec; DY3:  $10658\pm122$  sec

**#Revised Acquisition Protocol:**

**Placebo:**

Break 1:  $1431\pm83$  sec, Break 2:  $1014\pm95$  sec

Mean Start Times for DY2:  $5541\pm83$  sec; DY3:  $9555\pm58$  sec

**dAMPH:**

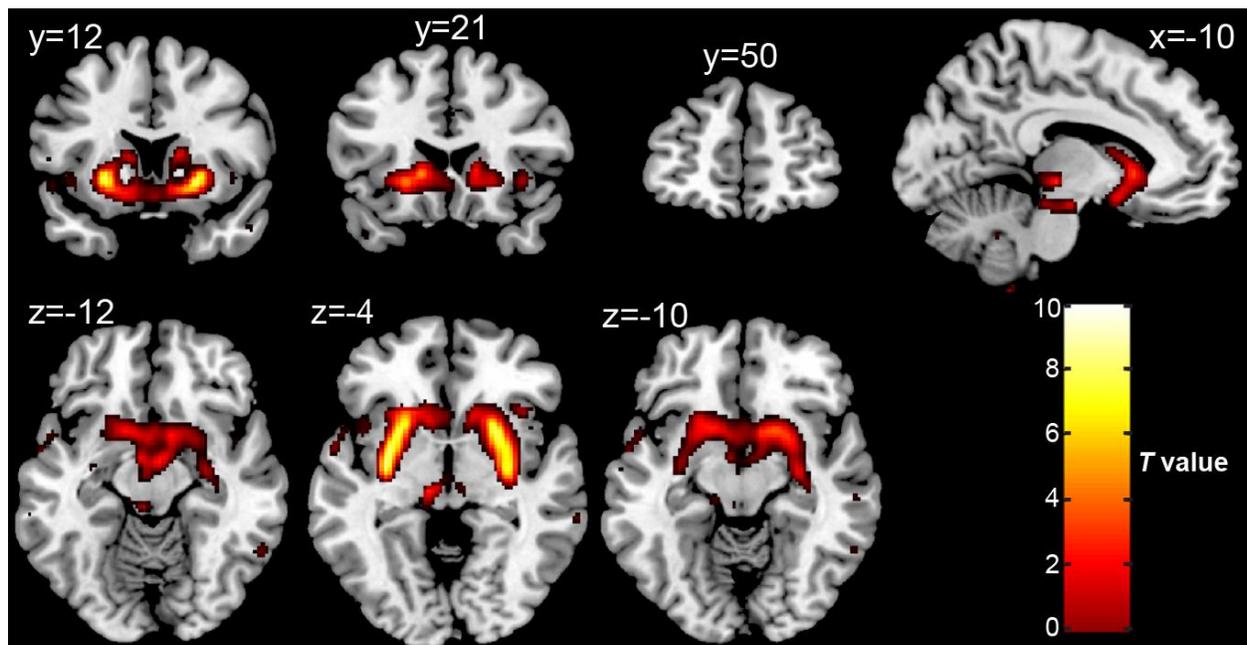
Break 1:  $1359\pm96$  sec, Break 2:  $1220\pm102$  sec

Mean Start Times for DY2:  $5469\pm96$  sec; DY3:  $9689\pm82$  sec

## Maximum DEQ Ratings in Responders versus Nonresponders

DEQ Subscale	Responders (n=35) Max Rating (mean±std dev; range; median)	Nonresponders (n=11) Max Rating (mean±std dev; range; median)	Group Difference (T, p)
All	0.457±0.181; 0.15 – 0.98; 0.44	0.028±0.028; 0.00 – 0.07; 0.02	13.50, <0.001
Feel	0.581±0.209; 0.20 – 0.99; 0.55	0.092±0.127; 0.00 – 0.38; 0.05	9.38, <0.001
Like	0.522±0.207; 0.13 – 0.98; 0.49	0.010±0.059; -0.14 – 0.10; 0.01	13.04, <0.001
High	0.468±0.249; 0.00 – 0.98; 0.48	0.037±0.063; 0.00 – 0.22; 0.02	9.34, <0.001
Want More	0.398±0.267; 0.01 – 0.98; 0.39	0.004±0.044; -0.11 – 0.08; 0.01	8.37, <0.001
% Female	37.1%	90.9%	$\chi^2=9.68, 0.002$

**Table S2. Responders reported higher Max DEQ ratings on all subscales relative to Nonresponders. DEQ<sub>All</sub> (average of 4 DEQ subscales) was used to differentiate Responders and Nonresponders (max DEQ<sub>All</sub> rating <0.10). There was a large amount of variability in DEQ ratings, for High and Want More in particular. In fact, some Responders had very low max Want More (6 were <0.10) and High ratings (3 < 0.10) while the lowest max Feel and Like ratings were 0.20 and 0.13, respectively in these subjects. Note that Responders and Nonresponders differed in the proportion of female subjects in each group.**

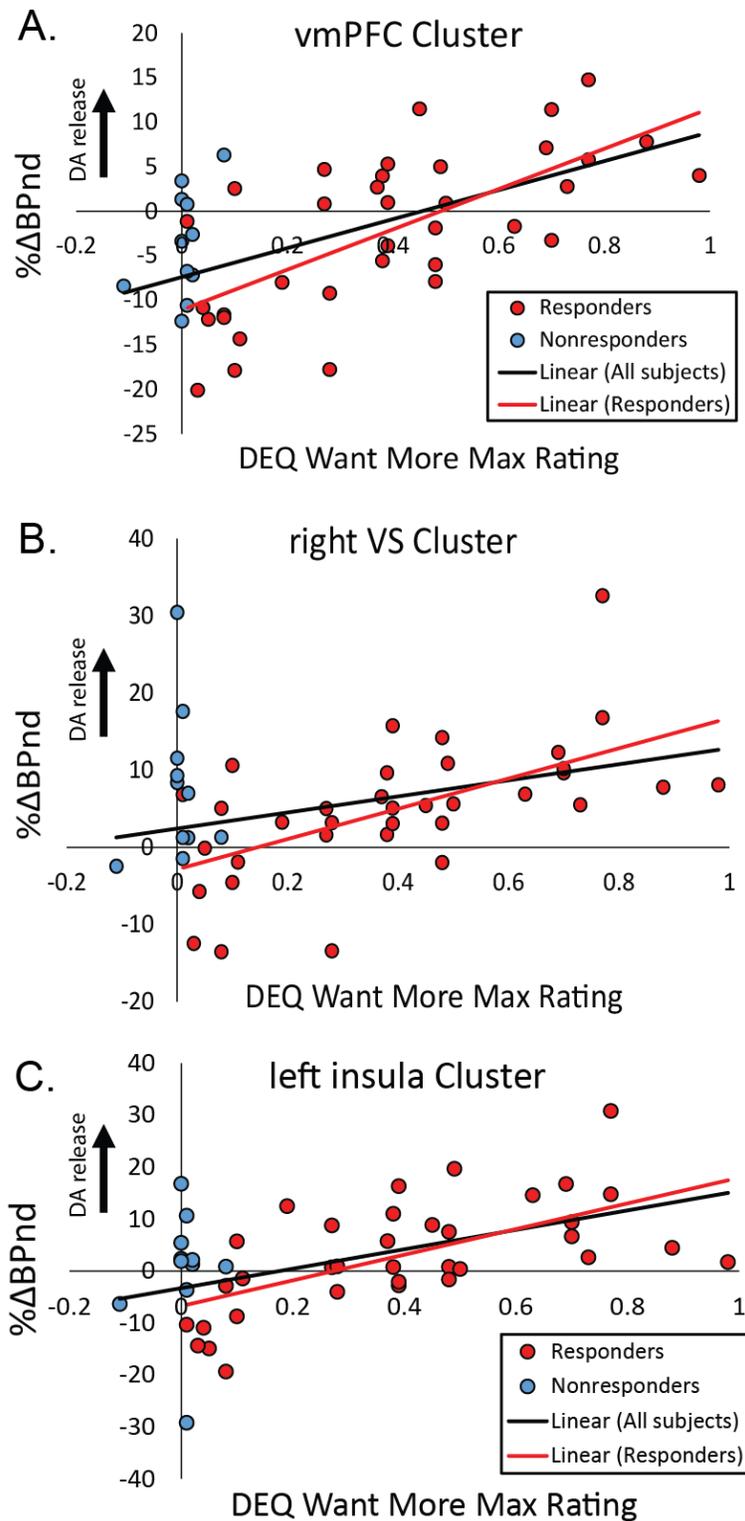


**Figure S1. Result of one-way T-test on %ΔBPnd data reveals areas showing elevated DA (positive %ΔBPnd) release in DEQ Responders. Note the presence of significant DA release in the striatum and ventral striatum in particular (y=12) as well as DA release occurring in the portions of the insula bilaterally (z=-4). However, no significant DA release was present in vmPFC (-10, 50, -10). p<0.005, uncorrected (20 voxel extent) used for visualization purposes.**

**Areas showing significant dAMPH-induced DA release (positive % $\Delta$ BPnd)**

Cluster Size (k)	Area	Peak MNI coordinates	Peak T value	
4874	Left Putamen	-28, 2, 0	9.99	
	Right Putamen	24, 10, -4	9.13	
	Midbrain		-5, -14, -15	6.99
			8, -20, -18	6.15
	Left Thalamus	-10, -22, -4	5.75	
	Left Caudate	-14, 20, 0	6.94	
	Right Hypothalamus	4, -6, -14	6.54	
	Left Hypothalamus	-4, -6, -14	5.63	
	Right Caudate	14, 20, 2	5.57	
	Ventral Striatum	-2, 8, -12	4.94	
	Medial Thalamus	-2, -8, 0	4.84	
	Right Amygdala	18, -2, -24	4.80	
	38	Left Amygdala	-16, -2, -26	4.56
	64	Right Insula	36, 22, -2	4.54
177	Left Superior Temporal Cortex/Temporal Pole	-58, 2, -6	4.40	
			-54, 8, -16	3.15
	Left Insula	-44, 10, -4	3.59	
225	Right Inferior Temporal Cortex/Fusiform Gyrus	42, -14, -36	4.29	
			38, -25, -28	4.12
			48, 0, -44	4.06
75	Left Inferior Temporal Cortex	-58, -44, -24	4.14	
			-58, -56, -20	3.87
74	Left Superior Temporal Cortex	-50, -30, 12	3.78	
			-55, -34, 18	3.51
51	Left Interior Temporal Cortex/Fusiform Gyrus	-38, -20, -32	3.64	
			-48, -20, -32	3.37

**Table S3. The table displays areas showing significant positive % $\Delta$ BPnd (DA release) in DEQ Responders via a One-way T-test in SPM8. Data are listed by cluster size and associated maximum T value for the T-test. Peak T coordinates from anatomical areas within large clusters and the associated T values from these areas are also reported. Note significant cortical % $\Delta$ BPnd was observed in temporal cortices and right and left insula only. A p threshold of <0.005, uncorrected, 20 voxel-extent was used to identify significant clusters.**



**Figure S2. Max DEQ<sub>want</sub> ratings are significantly correlated with % $\Delta$ BPnd in A) vmPFC ( $r=0.68$ ,  $p<0.001$  (Responders);  $r=0.57$ ,  $p<0.001$  (All subjects)), B) right VS ( $r=0.59$ ,  $p<0.001$  (Responders);  $r=0.33$ ,  $p=0.024$  (All subjects)), and C) left insula ( $r=0.62$ ,  $p<0.001$  (Responders);  $r=0.50$ ,  $p<0.001$  (All subjects)).**

**Data in DEQ Responders (n=35)**

Area (MNI coord at peak T value)	Baseline BPnd	dAMPH BPnd	% $\Delta$ BPnd	Significant $\Delta$ BPnd ( <i>T</i> , <i>p</i> )
Right VS (4, 6, -8)	7.96 $\pm$ 1.62	7.49 $\pm$ 1.63	5.89 $\pm$ 8.47	4.12, <0.001
vmPFC (-4, 42, -6)	0.706 $\pm$ 0.132	0.714 $\pm$ 0.141	-1.411 $\pm$ 8.55	-0.77, 0.45
Left Insula (-40, 2, 4)	2.24 $\pm$ 0.66	2.12 $\pm$ 0.62	4.58 $\pm$ 12.27	2.43, 0.020

**Data in DEQ Nonresponders (n=11)**

Area (MNI coord at peak T value)	Baseline BPnd	dAMPH BPnd	% $\Delta$ BPnd	Significant $\Delta$ BPnd ( <i>T</i> , <i>p</i> )
Right VS (4, 6, -8)	8.12 $\pm$ 1.04	7.28 $\pm$ 0.92	9.80 $\pm$ 9.65	3.33, 0.008
vmPFC (-4, 42, -6)	0.717 $\pm$ 0.120	0.731 $\pm$ 0.119	-2.20 $\pm$ 6.32	-0.964, 0.358
Left Insula (-40, 2, 4)	2.17 $\pm$ 0.77	2.03 $\pm$ 0.48	3.02 $\pm$ 14.38	1.31, 0.221

**Table S4. Data represent extracted mean BPnd and % $\Delta$ BPnd ( $\pm$  standard deviation) from clusters showing a significant relationship between % $\Delta$ BPnd and DEQ<sub>want</sub> ratings. Significant positive % $\Delta$ BPnd (DA release) was tested by performing a paired T-test on the BPnd values from the baseline and dAMPH scan day. Data are presented separated by DEQ Responders (who were used in the correlations) and DEQ Nonresponders (to test for generalizability of the observed effects). Note that on no BPnd or % $\Delta$ BPnd measure across these clusters did Responders and Nonresponders differ (max *T*=1.29, min *p*=0.205 for vmPFC % $\Delta$ BPnd cluster).**