

Supplemental Information

Supplemental Methods

Datasets

Data was obtained from the International Study to Predict Optimized Treatment in ADHD (iSPOT-A) and the Limbic Maturational Changes in Young Adulthood (LIMCA) study. Both studies used the same experimental procedures, behavioral paradigms and scanner hardware.

Participant selection

Participants were screened for the completeness and quality of behavioral, neuroimaging and clinical data. To minimize the impact of head movements during scanning, subjects whose head motion measures exceed movement criterion (translational x, y, z, and rotational pitch, roll and yaw exceeds 1 voxel, mean framewise displacement greater 0.25mm, or max framewise displacement greater than 1mm) were excluded. Subjects whose Go accuracy was less than 80% and NoGo accuracy was less than 20%, were also excluded. This resulted in a final sample size of 27 children with ADHD and 30 TD children with matched age, gender and head movement.

MRI acquisition

MRI data was acquired using an 8-channel head coil in a 3T GE Signa HDx scanner (GE Healthcare, Milwaukee, Wisconsin). Functional MRI images were collected using echo planar imaging (EPI) sequence (TR=2500ms, TE=27.5ms, matrix=64x64, FOV=24cm, flip angle=90°). Structural MRI images were also acquired using a 3D spoiled gradient echo (SPGR) sequence (TR=8.3ms, TE=3.2ms, flip angle=11°, TI=500ms, NEX=1, ASSET=1.5).

PPI analysis

The gPPI model consisted of a physiological term (the time series of a seed), psychological terms (HRF convolved main effect of condition of interest, e.g. NoGo correct and NoGo error), and PPI terms (deconvolved raw time series of the seed multiplied by main effect of condition of interest, and then convolved with HRF). We conducted multiple gPPI analyses and, in each analysis, one of the five ROIs was used as a seed and the rest were used as targets. PPI term in each pair of seed-target ROIs on NoGo correct trials were extracted for further dimensional and categorical analyses.

Supplementary Results

Go/NoGo task performance (including participants with large head motion)

We examined group differences in task performance in the larger group of 82 participants (45 children with ADHD and 37 TD children), without excluding any children for head motion. In this larger group, children with ADHD showed marginally significant deficits in NoGo accuracy ($p=0.05$; effect size=0.42).

Replication of the relationship between task-evoked effective connectivity between rdACC and rVLPFC and NoGo task accuracy as well as inattention symptoms

We found that effective connectivity between rdACC (seed) and rVLPFC (target) was significantly and positively correlated with NoGo accuracy in the combined group ($r=0.43$, $p=0.001$) (**Supplemental Figure S3A**). Additional analysis using age, gender and head motion as potential confounds confirmed that rdACC-rVLPFC connectivity was the only significant predictor in the combined group ($p=0.0003$, **Supplemental Table S1**). Further analysis revealed the same significant correlation in the ADHD group ($r=0.47$, $p=0.01$, **Supplemental Figure S3B**) and in the TD group ($r=0.30$, $p=0.12$, **Supplemental Figure S3C**). These results held when age, gender and head motion were included as potential confounds (ADHD group: $p=0.004$; TD group: $p=0.19$; **Supplemental Table S1**).

We also found a significant and negative correlation between rdACC-rVLPFC effective connectivity and inattention scores from the ADHD rating scale in children with ADHD ($r=-0.50$, $p=0.007$, **Supplemental Figure S4**). This result held when age, gender and head motion were included as potential confounds ($p=0.004$, **Supplemental Table S2**).

Figure S1. Whole-brain GLM analysis revealed significantly greater activation in the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), frontal pole, anterior insula (AI), pre-supplementary motor area (preSMA), dorsal anterior cingulate cortex (dACC), striatum and posterior parietal cortex (PPC) on correct NoGo trials in both children with ADHD and TD children ($p < 0.01$, FDR corrected).

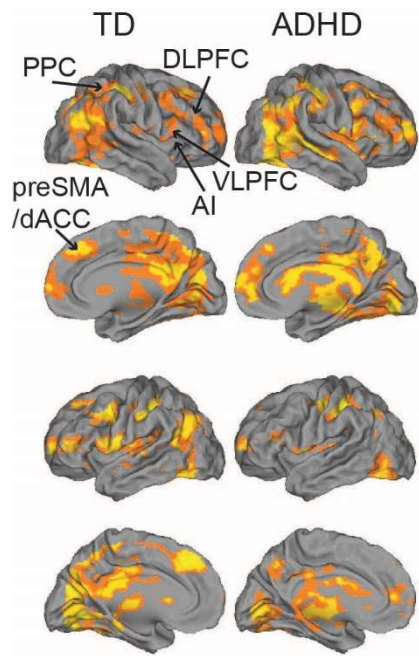


Figure S2. Whole-brain GLM analysis revealed significantly greater activation in anterior insula, pre-supplementary motor area/anterior cingulate cortex, ventrolateral prefrontal cortex and posterior parietal cortex on incorrect NoGo trials in TD children ($p < 0.01$, FDR corrected). No significant activation was detected in children with ADHD at this threshold.

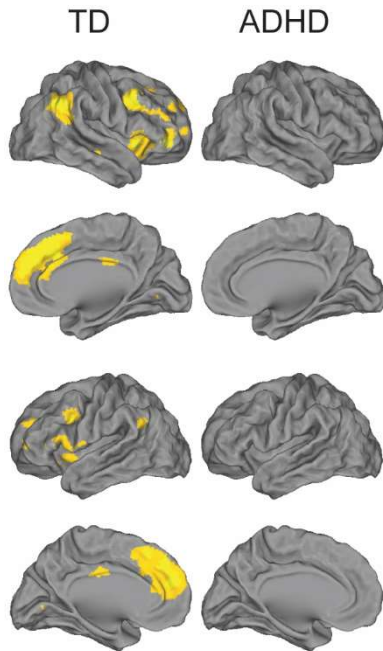


Figure S3. Whole-brain GLM analysis revealed greater activation on NoGo error trials in anterior insula, anterior cingulate cortex and pre-supplementary motor area in TD children than children with ADHD (activation height $p < 0.01$ and cluster $p < 0.05$). There was no significant difference in activation to NoGo correct trials between the two groups.

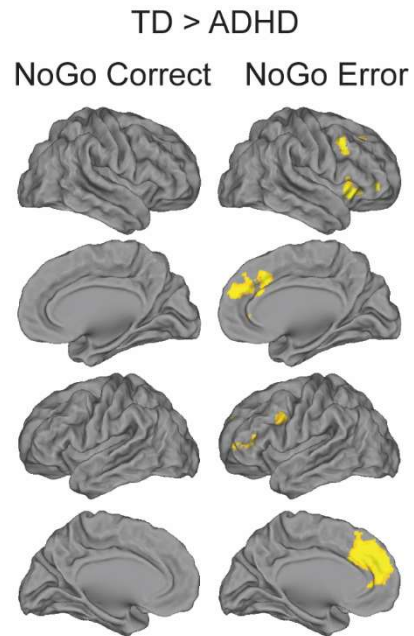


Figure S4. Task-evoked effective connectivity in the rdACC-rVLPFC (replication ROIs) was significantly correlated with NoGo accuracy in pooled data across the two groups (**A**) and in the ADHD group (**C**).

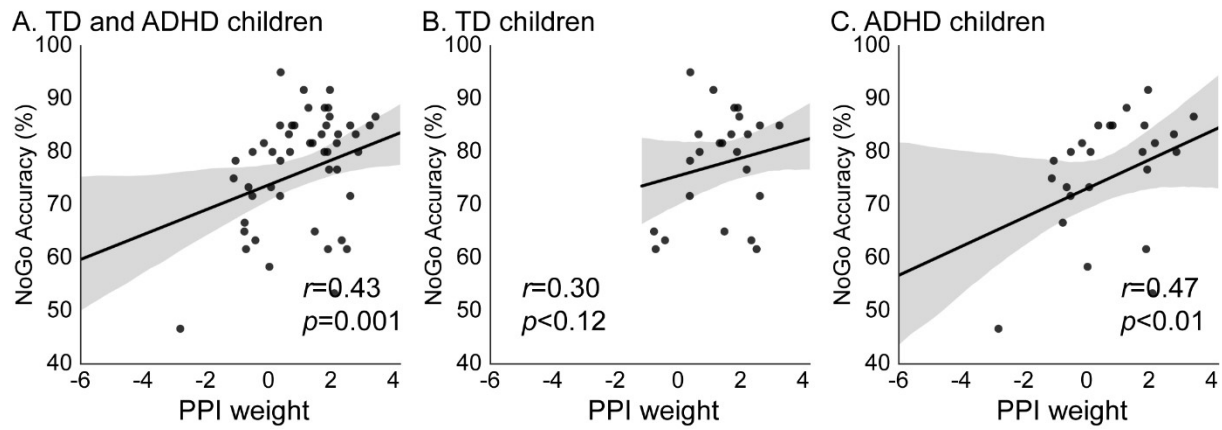


Figure S5. Task-evoked effective connectivity between rdACC and rVLPFC (replication ROIs) was significantly and negatively correlated with inattention symptoms in children with ADHD ($r=-0.50$, $p=0.007$).

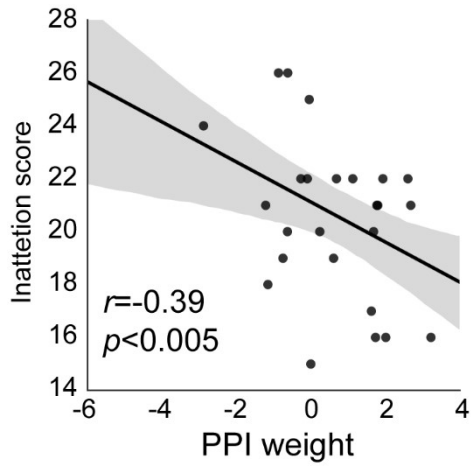


Table S1. Demographic and head motion statistics.

	<i>TD Controls (N=30)</i>	<i>ADHD (N=27)</i>	<i>p-value</i>
<i>Demographics</i>			
Age (years) 7-17 years old	13.65±2.47	13.95±2.62	0.67
Gender	8F/22M	6F/21M	0.94
<i>Head Motion</i>			
Range_X (mm)	0.38±0.27	0.34±0.25	0.52
Range_Y (mm)	0.37±0.22	0.40±0.23	0.65
Range_Z (mm)	0.79±0.43	0.71±0.41	0.44
Range_Pitch (mm)	0.67±0.39	0.70±0.37	0.75
Range_Roll (mm)	0.51±0.29	0.54±0.35	0.54
Range_Yaw (mm)	0.33±0.16	0.39±0.27	0.36
Frame-wise Displacement (mm)	0.09±0.05	0.07±0.04	0.30
<i>Task Performance</i>			
Go Accuracy (%)	96.04±4.87	94.26±5.95	0.23
NoGo Accuracy (%)	78.83±9.96	74.75±12.43	0.18
Go RT (ms)	329±66	336±71	0.70
NoGo Error RT (ms)	280±98	293±70	0.56

Table S2. Behavioral performance.

	<i>TD Controls (N=30)</i>	<i>ADHD (N=27)</i>	<i>p-value</i>
Go Accuracy (%)	96.04±4.87	94.26±5.95	0.23
NoGo Accuracy (%)	78.83±9.96	74.75±12.43	0.18
Go RT (ms)	329±66	336±71	0.70
NoGo Error RT (ms)	280±98	293±70	0.56

Table S3. Multiple linear regression analysis showed that psychophysiological interaction (PPI) between rdACC and rVLPFC (replication ROIs) on NoGo is the most robust predictor for NoGo Accuracy.

	<i>beta</i>	<i>t value</i>	<i>p value</i>
Control + ADHD			
rACC-rVLPFC PPI on NoGo	0.03	3.9	0.0003***
Gender	-0.03	-0.86	0.4
Age	0.01	1.82	0.08
Framewise displacement	-0.6	-1.58	0.12
Control			
rACC-rVLPFC PPI on NoGo	0.01	1.36	0.19
Gender	0.05	1.1	0.28
Age	-0.01	-0.76	0.45
Framewise displacement	-0.95	-2	0.06
ADHD			
rACC-rVLPFC PPI on NoGo	0.03	4.15	0.004***
Gender	-0.04	-1.69	0.33
Age	0.02	2.74	0.01
Framewise displacement	-0.24	-0.63	0.67

Table S4. Multiple linear regression analysis showed that psychophysiological interaction (PPI) between rdACC and rVLPFC (replication ROIs) was the most robust predictor of inattention symptoms in children with ADHD.

	<i>betas</i>	<i>t value</i>	<i>p value</i>
ADHD			
rACC-rVLPFC PPI on NoGo	-0.88	-3.23	0.004**
Gender	-1.21	-0.88	0.39
Age	-0.44	-1.7	0.11
Framewise displacement	-6.2	-0.35	0.73