Role of Pulvinar-Cortical Functional Brain Pathways in Attention-Deficit/Hyperactivity Disorder

To the Editor:

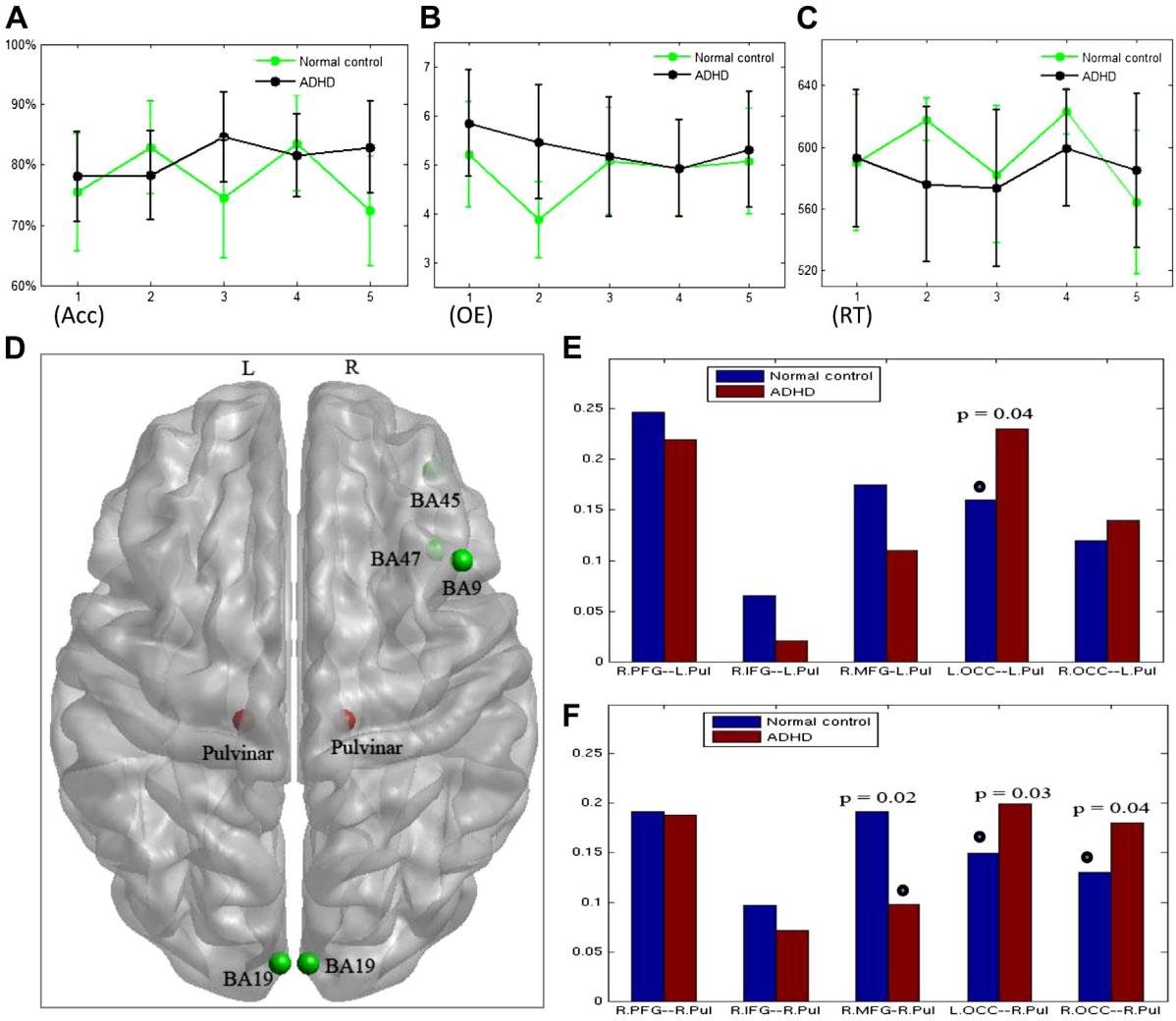
We are grateful for Dr. Shaw's comments[1] on our original research article.[2] Dr. Shaw highlighted the importance of the role of the thalamus and its brain connections in attention-deficit/hyperactivity disorder (ADHD) and indicated that the original study advanced the field by placing the pulvinar nuclei of the thalamus at the center of dysfunctional attentional networks in ADHD.[1] Since the publication of this research article, we have received e-mails from renowned scientists in this research field, such as Dr. Joseph A. Sergeant, who have asked for further results on the time-on-task (TOT) change of functional magnetic resonance imaging (fMRI) task performance and its relation to pulvinar-cortical connectivity during the fMRI task. This Letter to Editor aims at answering these very important questions by providing quantitative measurements of functional pulvinar-cortical connectivity in the fMRI data collected in the same study sample of the original article[2] and their relations to TOT performance changes and diagnostic measurements.

The visual sustained attention task implemented in our study consisted of 5 task blocks interleaved by 5 resting blocks. From each subject, we calculated the percentage of correct responses (Acc), the number of omission errors (OE), and the average reaction time (RT) as 3 performance measurements in each of the 5 task blocks. For each performance measurement, a least squares linear regression line was estimated through the 5 time points (task blocks), and the slope, r, was taken as the measurement of TOT. For between-group comparison of the TOT change of each performance measurement, the Student t test of r was carried out. The results showed that none of the 3 measurements presented significant between-group differences for TOT changes (Acc-TOT, $p = .872$; OE-TOT, $p = .698$; RT-TOT, $p = .191$). In addition, we investigated between-group differences of the nonparametric TOT distributions of the performance measurements using the Mann-Whitney U test. None of the 3 measurements presented significant between-group differences for TOT changes (Acc-TOT, $p = .491$; OE-TOT, $p = .780$; RT-TOT, $p = .963$; Figure 1A-C).

To quantitatively assess pulvinar-cortical functional connectivity (FC), 2 seed regions from the bilateral pulvinar nuclei, which were defined in the original article, were used (origins [±14, −26, 8]; radius 4 mm). Five spherical target regions-of-interest (ROIs; radius 5 mm), selected according to the results of the voxel-wise FC analysis in the original research article, were located at the right prefrontal gyrus (40, 22, 4; Brodmann area [BA] 47), right inferior frontal gyrus (39, 44, −14; BA 45), right middle frontal gyrus (47, 19, 45; BA 9), and bilateral occipital lobes (±4, −94, 14; BA 19). Figure 1D shows the anatomic locations of the seed and target ROIs. In each preprocessed fMRI datum, we calculated the Pearson correlation coefficients, R, of the average time series from each seed-target pair, after controlling for the effects of gender, age, and IQ. For between-group comparisons of the FC measurements of the 10 seed-target pairs, the Student t test of the R values was carried out, with false discovery rate correction for multiple comparisons. The results showed that 4 of the 10 FC pairs were significantly different between groups (detailed in Figure 1E, F).

In the last step, we calculated the Pearson correlations among the measurements of TOT, FC, and the 3 *DSM-IV* diagnostic indices (inattentive, hyperactive/impulsive, and total) in the ADHD group. False discovery rate was applied for multiple comparison corrections. We found that the measurements of the Acc-TOT significantly and positively correlated with bilateral occipital-right pulvinar FC measurements ($p = .018$ for left occipital-right pulvinar; $p = .033$ for right occipital-right pulvinar). The ADHD inattentive indices were significantly and negatively correlated with the Acc-TOT ($p = .020$) and RT-TOT ($p = .049$) measurements but significantly and positively correlated with the left occipital-right pulvinar FC measurements ($p = .011$). In addition, the ADHD hyperactive/impulsive indices were significantly and negatively correlated with the right prefrontal-left pulvinar FC measurements ($p = .020$).

FIGURE 1 A–C, Between-group comparisons of time-on-task changes of functional magnetic resonance imaging task performance measurements show no significant differences between groups; D, locations of regions of interest for functional connectivity analyses, where the 2 red spheres are seed regions of interest from bilateral pulvinar nuclei and the 5 green spheres are target regions of interest from right frontal lobe and bilateral occipital cortices; E, F, between-group comparisons of functional connectivity analyses running from the left and right pulvinar, respectively. Note: Acc = accuracy; ADHD = attention-deficit/hyperactivity disorder; BA = Brodmann area; L = left; L.OCC = left occipital lobe; L.Pul = left pulvinar; OE = omission errors; R = right; R.IFG = right inferior frontal gyrus; R.MFG = right middle frontal gyrus; R.OCC = right occipital lobe; R.PFG = right prefrontal gyrus; R.Pul = right pulvinar; RT = reaction time.



In summary, the quantitative investigations of this study showed significant impairment of functional communications of the occipital-pulvinar and pulvinar-prefrontal pathways during sustained visual attention processing. Functional impairments of these cortical-pulvinar brain pathways significantly affect the timely changing patterns of visual attention performance and correlate with inattentive/hyperactive symptoms in children with ADHD. Together with the original research article, we suggest that the occipital-pulvinar-frontal functional brain pathways may underlie the inattentiveness and hyperactivity/impulsivity in children with ADHD and may have the potential to be an intermediate phenotype of the disorder. To test this hypothesis, future works should focus on refined assessments of

the structural and functional connections between subregions (medial and lateral) of the pulvinar and cortices and their relations to the behavioral and clinical symptoms in children with ADHD, their normal siblings, and independent control children.

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