Brain hyperactivation related to working memory in medication-naive boys with non-comorbid ADHD

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Introduction:

Attention deficit hyperactivity disorder (ADHD) is characterized by developmentally inappropriate symptoms of inattention, impulsiveness, and hyperactivity that arise in childhood and often persist into adolescence and adulthood.[1] Previous studies have proposed that among executive functions, working memory is one of the most consistently reported deficits and is a crucial cognitive process that is implicated in theoretical models of ADHD.[2] Furthermore, categorical judgments about objects are essential parts of performance in working memory tasks. A new variant of the traditional n-back task, named the categorical n-back task (CN-BT), has been designed as a complex visual-object working memory paradigm comprising stringent attention focusing, active memory encoding, and cognitive categorical judgment. This CN-BT paradigm maximizes demands for executive reasoning while holding memory demands constant, and is more sensitive in detecting impairments in the executive domain of working memory.[3] The current study aimed to assess altered brain activation related to the CN-BT in medication-naive male children and adolescents with non-comorbid ADHD compared with normally developing healthy controls by functional MRI. The results demonstrate specific functional cerebral patterns subtending working memory-related processes in ADHD, which may underlie the pathophysiology and the expression of clinical symptoms.

Subjects and Methods:

The study was approved by the local ethical committee and written informed consent was obtained from all subjects. The Structural Clinical Interview for DSM-IV patient edition was used to establish diagnosis for ADHD. A total of 33 drug-naive, right-handed male children and adolescents with ADHD (mean age 9.9±2.4 years) and 27 right-handed, healthy control males (mean age 10.9±2.7 years) were recruited. The present CN-BT involved 57 commercially available color drawings of inanimate objects and animals, which were presented consecutively and in random order. Small crosses were pseudo-randomly intermixed with the picture stimuli to provide a fixation point and an irregularity of timing. A drawing of a panda served as the n-back target. When the panda was presented, the subject was required to press a button with his/her right thumb only if at least two drawings prior to the panda belonged to the category of animals; alternatively, he/she was required to press a button with the left thumb for any other combinations of stimuli preceding the panda.[3] The subjects viewed the visual stimuli through a mirror attached to a head coil. Each run consisted of 124 stimuli (25% pandas, 23% other animals, 22% non-animals, and 30% crosses). Each stimulus of animals and non-animals lasted 500 ms, each stimulus of 18 crosses lasted 6 s, and each stimulus of 19 crosses lasted 4 s to provide time for the participants to press the button. In total, each run lasted 227.5 s. The fMRI sensitized to changes in BOLD signal levels was obtained via a GE-EPI sequence (TR/TE=2000/30msec, flip angle=90°, slice thickness=5mm without gap, 30 axial slices, 114 volumes in each run resulting in a total scan time of 228s) via a Seimens 3T MRI system. Head translation movement of all participants was < 2 mm and rotation was < 2°. A general linear model (GLM) statistical analysis was performed in SPM8, and an event-related model was used in the present GLM analysis. The responses to panda stimuli preceded by at least two consecutive animal stimuli were modeled in SPM8 as correct categorical n-back responses. Using this model, a single contrast image was generated for each participant with a fixed-effects model, representing the difference between correct categorical n-back responses and baseline trials, which was then employed for group analyses using a random-effects model. For group statistical analysis, single-sample t tests were separately used for the ADHD and control groups to identify areas of significant activation during correct categorical n-back responses compared with the baseline trials. Two-sample t tests were used to identify areas showing significant differences in activation between ADHD patients and controls. Significant activation was defined according to a cluster-level threshold of $P<0.05$ using family-wise error (FWE) correction for multiple comparisons.

Results:

There was no significant difference between the two groups in the percent of correct responses in the CN-BT ($P=0.724$), whereas the ADHD patients showed a significantly shorter reaction time to correct responses ($P=0.038$). During the CN-BT, both ADHD patients and controls showed significant positive and negative activation by the correct responses, mainly in the sensory-motor pathways and the striato-cerebellum circuit (Figure 1). Compared with the controls, the ADHD patients showed significantly higher activation in the right globus pallidus (Talairach: 18,-2,-4, 45 voxels), left globus pallidus (Talairach: -16,-3,-2, 55 voxels) and the right hippocampus (Talairach: 30,-9,-12, 139 voxels) ($P<0.05$, FWE corrected).

Conclusion:

To our knowledge, the exploration of working memory-related brain activation using the CN-BT has not been previously reported in children and adolescents with ADHD. And the present study was more sensitive in terms of functional brain imaging than the behavioral data, as our findings are consistent with the results of several other ADHD imaging studies, in which functional differences were found despite no significant differences in behavioral performance in a working memory task.[4] In addition to having activation within the sensory-motor pathways and the striato-cerebellum circuit similar to that of healthy controls with related visual-object and action cognitive strategies, the ADHD patients also showed task-negative activation in the fronto-cingulate-parietal network involved in working memory. Recent studies have found that top-down control of working memory indeed results in both an enhancement of relevant information and a suppression of irrelevant information, and the amount of top-down modulation is related to individual working memory performance.[5] The dysfunction of top-down modulation seems to lead to the excessive processing of irrelevant information and that is in turn detrimental to working memory. Therefore, in the present study, the higher activation of the bilateral globus pallidus and right hippocampus in ADHD patients compared to healthy controls revealed an important role in the pathophysiology of ADHD related to working memory.

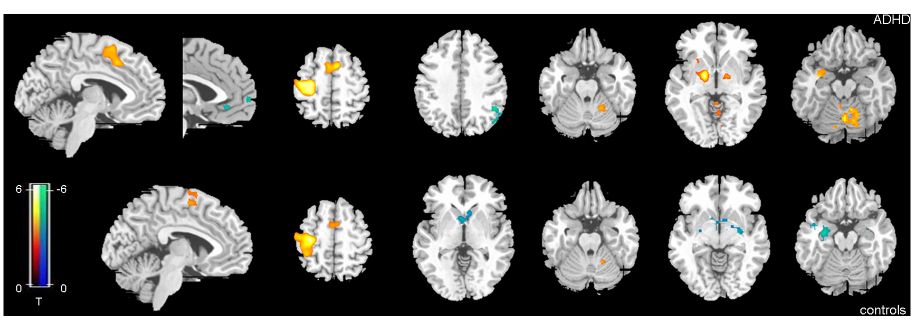

Figure 1. Brain regions of significantly positive (warm color) and negative (cool color) activation by the correct responses during performance of the categorical n-back task in ADHD patients and healthy controls.

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