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# Compensatory brain activation in children with attention deficit/hyperactivity disorder during a simplified Go/No-go task

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**Abstract** Given that a number of recent studies have shown attenuated brain activation in prefrontal regions in children with ADHD, it has been recognized as a disorder in executive function. However, fewer studies have focused exclusively on the compensatory brain activation in ADHD. The present study objective was to investigate the compensatory brain activation patterns during response inhibition (RI) processing in ADHD children. In this study, 15 ADHD children and 15 sex-, age-, and IQ-matched control children were scanned with a 3-T MRI equipment while performing a simplified letter Go/No-go task. The results showed more brain activation in the ADHD group compared with the control group, whereas the accuracy and reaction time of behavioral performance were the same. Children with ADHD did not activate the normal RI brain circuits, which are thought to be predominantly located in the right middle/inferior frontal gyrus (BA46/44), right inferior parietal regions (BA40), and pre-SMA(BA6), but instead, activated brain regions, such as the left inferior frontal cortex, the right inferior temporal cortex, the right precentral gyrus, the left postcentral gyrus, the inferior occipital cortex, the middle occipital cortex, the right calcarine, the right hippocampus, the right midbrain, and the cerebellum. Our conclusion is that children with ADHD tend to compensatorily use more posterior and diffusive brain regions to sustain normal RI function.

**Keywords** Response inhibition · ADHD · fMRI · Compensatory brain activation

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder and characterized by attention problems and hyperactivity with symptoms starting in childhood. Response inhibition (RI) plays a central role in the neural pathological mechanism of ADHD (Barkley 1997). The cessation of inappropriate thoughts and behaviors is a tool commonly used in daily human life to control and regulate actions. Top-down attention largely depends on the executive control of flexible shifts in the attention process, which is primarily based on normal functioning RI (Ghatan et al. 1998). To date, many studies have been conducted to show that the neural correlates of RI are located in the right inferior frontal gyrus (RIFG), the supplementary motor area (SMA), the pre-supplementary motor area (pre-SMA), the subthalamic nucleus (STN), and the caudate nucleus (Booth et al. 2005; Mostofsky and Simmonds 2008; Simmonds et al. 2008). In several studies, the classical Go/No-go task or Stop signal task was employed to evoke the activation of brain inhibition circuits (Picton et al. 2007; Verbruggen and Logan 2009), but in contrast to the control group, less activation was observed in some key brain regions of ADHD individuals (Booth et al. 2005; Durston et al. 2003). This result

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suggested that the brain regions, which generate inhibition function, are underactive in ADHD patients and these patients perform poorly in normal inhibition function, thus presenting the ADHD core symptoms of inattention and/or impulsiveness (Smith et al. 2006; Tamm et al. 2004).

Other studies have revealed reduced RI in ADHD patients, reflecting both increased rate of commission and omission errors as well as increased reaction time (RT) variability (Gomez-Guerrero et al. 2011; Vaurio et al. 2009). These neuropsychological measures provided only an estimate of compromised RI in ADHD patients because the actual brain activity has not been analyzed. During the past few years, a number of studies suggested that ADHD might be caused by a neurotransmitter system impairment (Nikolas et al. 2010; Roman et al. 2004) that explains a resulting loss of brain activation during RI. The dysfunction of some key neural circuits for RI could lead to apparent disinhibition of behaviors in the context of fast-changing environments (Agam et al. 2010), which might provide a better understanding of RI deficits in ADHD. Neuroimaging studies which identified abnormalities in the key brain pathways of RI (Martin et al. 2006; Mostofsky and Simmonds 2008) could extend our present knowledge of ADHD, and particularly functional magnetic resonance imaging (fMRI) has the unique power to reveal aberrant brain activity without hurting the human body (Smith et al. 2006; Suskauer et al. 2008; Tamm et al. 2004; Vaidya et al. 2005).

RI is a fundamental function in the human brain, which employs many brain regions to achieve the flexibility necessary to orchestrate constantly changing behaviors. Most of the fMRI data of ADHD patients demonstrated that there are some key brain regions in the 'prefrontal-parietal-striatal-cerebellum' pathway that were hypoactivated (Durston et al. 2003; Schulz et al. 2005), though others found hyperactivation in the 'dorsal lateral prefrontal cortex' and 'parietal cortex' (Fassbender and Schweitzer 2006). The authors explained these phenomena as 'compensatory activation', but the compensatory phenomenon and its characteristics in ADHD have not been systematically studied thus far. In the present study, we focused on how brain activation could be affected and whether the compensatory phenomenon existed, and as a result, we could provide a meaningful way to understand the compensatory strategy used by children with ADHD. However, in some cases, even though the children with ADHD employ brain compensatory strategies, they are unable to maintain normal function. A previous study also reported about compensatory brain activation (Suskauer et al. 2008), but RI performance was in their experimental design a post hoc variable. To our knowledge, this study is the first to investigate the compensatory brain activation patterns in ADHD children with RI function as a priori independent variable.

## Materials and methods

### Participants and clinical assessment procedure

The study sample comprised 15 children with ADHD (ADHD group) and 15 typically developing children (control group). The clinical assessment procedure consisted of structured interviews, excluding other mental diseases, evaluation of a detailed medical history, and a health check to eliminate the possibility of organic or nervous system diseases including (1) physical, psychiatric, and neurological evaluation by a team of two certified and experienced developmental and behavioral pediatricians and one child psychiatrist; (2) Wechsler Intelligence Scale for Children-Revised (WISC-R) test to determine the IQs of all subjects (Wechsler 1991). All structural MRI images of the children have been normal. Inclusion criteria for all participants were: (1) age 8–12 years; (2) right-handedness; (3) IQ $>$ 85; (4) following instructions well during pre-practice; and (5) head rotational and translational movement was $<$2 mm during MRI scanning. Exclusion criteria were: (1) any axis I psychiatric disease except ADHD; (2) a neurological disease based on clinical examination; (3) any metal device implanted in the body; or (4) claustrophobia. For the ADHD group, all children were diagnosed based on (1) DSM-IV criteria (American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4th edition) 1 (Association 1994); and (2) SNAP-IV (revision of the Swanson, Nolan, and Pelham questionnaire) (Gau et al. 2008) to scale the ADHD symptom scores (Swanson et al. 2001). Twelve of the ADHD patients never took any psychiatric medication and three of them were treated with Ritalin, but they stopped taking it more than 4 weeks before the test. Table 1 shows that there was no statistical difference between the two groups in terms of age, gender, handedness, or IQ. This study began in June 2009 and ended in June 2010. The ADHD children were collected from the outpatient clinic of the Department of Developmental and Behavioral Pediatrics at SCMC. The matched control group was recruited from a primary school to participate in the present experiment. All of them and their parents knew that they would be paid a certain amount of money for their participation.

### Instruments

#### *The simplified Go/No-go task paradigm*

A simplified Go/No-go task paradigm was used to tap brain activation during RI, which was similar to that in the study of Altshuler et al. (2005).

Stimuli were generated on a computer and projected to a screen mounted above the subject's head. The simplified

**Table 1** Demographic and behavioral performance data

| | ADHD [$n = 15$, mean (SD)] | CONTROL [$n = 15$, mean (SD)] |
|---|---|---|
| Age (years) | 9.82 (1.13) | 9.91 (1.67) |
| Gender | 8M/7F | 8M/7F |
| Handedness | $R = 15$ | $R = 15$ |
| Type | PI = 12 | N/A |
| | $C = 3$ | |
| IQ | 100.24 (12.45) | 102.58 (10.11) |
| SNAP-IV | IA: 2.23 (0.59) | IA: 0.54 (0.11)* |
| | HI: 2.01 (0.45) | HI: 0.23 (0.05)* |
| Accuracy (%) | 96.05 (22.11) | 96.14 (20.23) |
| CER (%) | 2.24 (0.51) | 2.17 (0.49) |
| OER (%) | 1.97 (0.33) | 1.95 (0.42) |
| RT (ms) | 497.3 (99.5) | 492.8 (87.6) |

*ADHD* attention deficit/hyperactivity disorder, *CONTROL* control, *R* right-handed, *L* left-handed, *PI* predominantly inattention subtype, *C* combined subtype, *N/A* not applicable, *SNAP-IV* revision of the Swanson, Nolan and Pelham Questionnaire, *IA* inattention symptom scores, *HI* hyperactivity/impulsiveness scores, *CER* commission errors rate, *OER* omission errors rate, *RT* reaction time

* $P < 0.05$

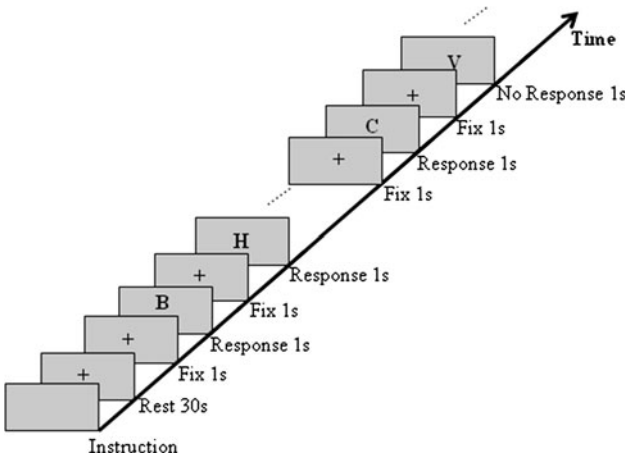


**Fig. 1** Scheme of the time series for the Go/No-go test. After the test introduction the participants had 30 s rest. Then the Go/No-go task included ten alternating Go and No-go blocks. In each block, the *letters* were presented 13 times as stimuli for 1 s following fixation for 1 s each *letter*, with an interval of 30 s between the blocks

Go/No-go task included ten alternating Go and No-go blocks. For each block, the letters were presented as stimuli for 1 s for each letter following fixation for 1 s, 13 times, and with an interval of 30 s between blocks (Fig. 1). During the No-go block, the letter 'V' was pseudo-randomly distributed among the other letters. The percentage of 'V' letters in the No-go block was 50%. All children were instructed to press a button for all letters in the go blocks and not to press it for the 'V' in No-go blocks and following these instructions as fast as possible. Before the experiment, a short practice run of 26 trials was completed by each child to ensure that they understood the task instructions. Children's response and reaction time (RT) were recorded by the computer.

### *fMRI scanning and data acquisition*

Functional scans were acquired with a 3.0 T Tim Trio system (Siemens Medical Systems Erlangen, Germany) using a 12-channel head coil at the Shanghai Key Laboratory of Magnetic Resonance, East Normal University. The pulse sequence was a T2*-sensitive ultrafast multi slice echo planar imaging (EPI) sequence sensitive to blood-oxygen-level-dependent (BOLD) contrast. Thirty-two transverse slices of functional images that covered the whole brain were acquired with TR = 2,000 ms, TE = 30 ms, flip angle 90°, matrix size = 64 × 64, slice thickness = 3 mm, field of view = 220 $mm^2$. The spatial resolution was 3.4 × 3.4 × 3.0 mm.

### *Data analysis*

Data were analyzed using Statistical Parametric Mapping software (SPM8, Welcome Department of Imaging Neuroscience, London, UK). First, all functional scans were realigned to correct the interscan movements with a rigid body transformation of rotation and flexion parameters. All the children with head movement (regardless of rotation or flexion) exceeding 2 mm were excluded from further analysis. Next, the functional images were spatially normalized to Montreal Neurological Institute (MNI)-labeled space (Evans et al. 1993), resulting in a voxel size of 2 × 2 × 2 mm. A Gaussian kernel with 6-mm full-width at half-maximum was applied to smooth images spatially. A 'random effects model' was employed to identify the brain activation associated with the RI. The parameter estimate process was performed using the best least-square fit of the adjusted data to model the experimental state. T statistical parametric maps were applied for each contrast in hemodynamic changes. Height threshold was set at $P < 0.001(t = 3.33)$, uncorrected for multiple comparisons. Only clusters above ten continuous voxels were used for further image analysis. The activation associated with the No-go blocks minus the Go blocks was used to elicit the brain activation map during the RI process. A one-sample $t$ test was implemented to compare the mean blood-oxygenation-level-dependent (BOLD) response within each group of No-go blocks and then compared with Go blocks. Then, two sample tests were used to compare the BOLD response to RI between the groups. Pearson's correlation analysis was used to explore whether there was a correlation between ADHD symptom

scores (as determined by SNAP-IV) or task performance and the amplitude of BOLD signals in any brain region.

The parents of all children provided written informed consent, and the study was approved by the ethics research committee of Shanghai Children's Medical Center (SCMC).

## Results

There were no significant differences between the ADHD group and control group with regard to the accuracy, rate of error commission, or response time (RT) of behavioral performance during the simplified Go/No-go task (Table 1). Regarding the neurons, the ADHD group showed diffuse activation in comparison to the control group in the temporal and posterior brain regions, such as the left inferior frontal cortex, the right inferior temporal cortex, the right precentral gyrus, the left postcentral gyrus, the inferior occipital cortex, the middle occipital cortex, the right calcarine, the right hippocampus, the right midbrain, and the cerebellum (Table 2; Fig. 2). Occipital brain regions were particularly activated broadly. In the ADHD group, the areas positively activated to No-go versus Go blocks included the right inferior temporal cortex, the right precentral gyrus, the left postcentral gyrus, the inferior occipital cortex, the middle occipital cortex, the right calcarine, the right hippocampus, and the cerebellum. In the control group, there was no positive activation to No-go versus Go blocks ($P < 0.001$ for multiple comparisons uncorrected, cluster size threshold >10) during the simplified Go/No-go task, but the right hippocampus and the right lateral frontal cortex (BA47) showed subthreshold activation (cluster size = 4 and 8, respectively). Correlation analysis revealed no positive or negative correlation between ADHD symptom scores (as determined by SNAP-IV) or accuracy on Go/No-go tasks and activation in any brain region.

## Discussion

In our present study, we used the simplified letter Go/No-go paradigm, which requires low cognitive effort, to elicit possible activation of RI-related brain regions. The task was so easy that most of the ADHD children could do it as well as control children, in terms of behavioral performance. However, their brain activation maps were completely different and the ADHD children were more likely to use a compensatory strategy for maintaining normal RI function that is in agreement with other reports (Dillo et al. 2010; Rubia et al. 2005; Simmonds et al. 2007).

In the previous studies, compensatory brain activation was described in patients with ADHD, but this phenomenon has not been aimed to be systematically investigated.

In the present study, compensatory brain activation of ADHD children was analyzed by diminishing a potential compensatory activation in the control group to the greatest extent possible. Theoretically, compensatory strategies used by children with ADHD depends on many factors, including the nature and difficulty of the task paradigm (Drager et al. 2004) and the RI capacity of the children (Hoeft et al. 2007), which is known to be lower in children with ADHD than in unaffected children (Swanson et al. 2010).

Hence, we sought to identify a task paradigm with a difficulty level such that the unaffected children would employ normal neural circuits, whereas the ADHD children would have to use compensatory neural circuits to cope with it. The key issue is the selection of a suitable task

**Table 2** Brain activation: ADHD versus control

| Region | Brodmann's area | MNI | | | *T* value | Cluster size ($mm^3$) | *P* | $P_{FWE}$-corrected |
|---|---|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | | | |
| R temporal inf. | BA37 | 44 | −64 | −8 | 5.72 | 280 | 0.000 | 0.000 |
| R midbrain | | 4 | −12 | −14 | 5.48 | 96 | 0.000 | 0.000 |
| R precentral | BA4/6 | 34 | 0 | 28 | 4.94 | 91 | 0.000 | 0.000 |
| R calcarine | BA18/31 | 32 | −60 | 12 | 4.71 | 58 | 0.000 | 0.000 |
| R occipital inf. | BA18 | 32 | −74 | −2 | 4.62 | 191 | 0.000 | 0.000 |
| L occipital mid. | BA18/19/39 | −32 | −76 | 12 | 4.54 | 283 | 0.000 | 0.000 |
| R cerebellum Vermis_1_2 | | 4 | −40 | −22 | 4.52 | 31 | 0.001 | 0.010 |
| L cerebellum Crus2 | | 2 | −80 | −30 | 4.42 | 55 | 0.000 | 0.000 |
| L postcentral | BA4 | −54 | −4 | 16 | 4.28 | 16 | 0.001 | 0.009 |
| L frontal inf. tri. | BA46 | −48 | 34 | 18 | 4.27 | 18 | 0.001 | 0.042 |
| R hippocampus | | 32 | −28 | −8 | 4.16 | 38 | 0.001 | 0.004 |
| R occipital mid. | BA18/31 | 28 | −90 | 14 | 4.06 | 46 | 0.000 | 0.001 |
| L occipital inf. | BA18/19 | −40 | −84 | −12 | 3.94 | 17 | 0.000 | 0.045 |

*L* left, *R* right, *Mid* middle, *Post* posterior, *Sup* superior, *Inf* inferior, *Tri* triangular part

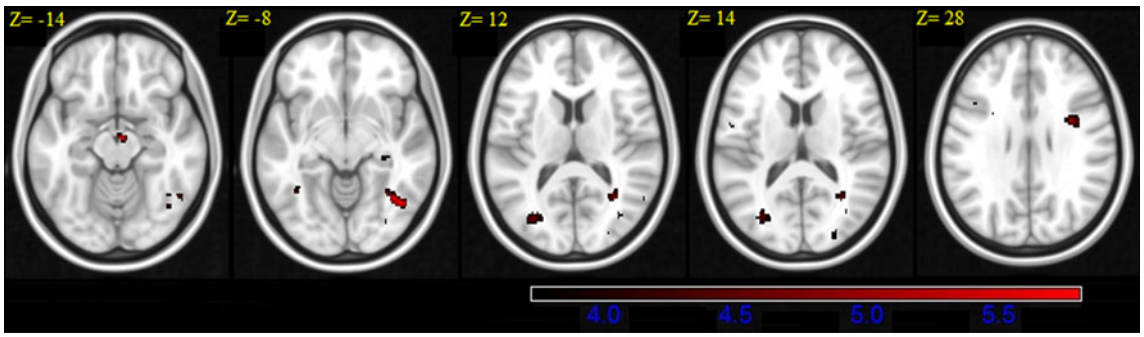


**Fig. 2** Statistical activation maps (No-go minus Go contrast) for ADHD group versus control group, showing more posterior and diffuse activation. The resulting SPM T maps of two sample *t* test between ADHD and control group were superimposed on the 1 × 1 × 1 mm MNI 152 standard template. *Z* indicates the coordinate in the MNI space

paradigm of minimal difficulty in order to tap defective brain regions of children with ADHD so that ADHD children would be more likely to use a compensatory strategy while control children would not.

Other studies showed that RI was compromised in ADHD children in terms of behavioral performance and brain activation patterns (Booth et al. 2005; Willcutt et al. 2005). Most of these studies used RI task paradigms with higher working memory load or cognitive demand, and even at the behavioral performance level, the ADHD group performed worse than the control group (Lipszyc and Schachar 2010). In this sense, there must have been some difficulties with the study design. First, if the task paradigm was difficult, not only the ADHD patients but also the control group might use the compensatory strategy, which could result in different activation maps (Simmonds et al. 2008). In such a case, it would be difficult to identify which brain regions were normal activated and which were merely compensatorily activated. These results would lead then to a mistaken understanding of the brain activation of RI and compensatory brain activation in both the ADHD and control groups. Second, if a block design is used, some brain activation retrieved from this experiment would merely reflect unevenly distributed behavioral performance (Vloet et al. 2010).

Our design allowed us to discriminate control children from ADHD children: the former, using normal RI circuits, would effortlessly manipulate the task, whereas the latter, using compensatory neural circuits due to compromised RI circuits, would manipulate the task successfully, but with more effort (Vaurio et al. 2009).

Our study showed that the task paradigm was so easy for the control group that almost no brain activation was observed during the No-go process that resulted in a lack of frontostriatal BOLD signal and is in agreement with the literature (van den Heuvel et al. 2003). For this reason, the sub threshold activation analysis was included within this study. We found the right hippocampus and the right lateral frontal cortex (BA47) showed sub threshold activation (cluster size = 4 and 8, respectively), which partly replicated the study outcome in the control group as described by Altshuler et al. (2005). This result was also in line with other studies, which demonstrated that the simple and low cognitive demand task paradigm might lead to little activation in the brain but still allow for good behavioral performance (Mostofsky et al. 2003).

Previous studies based on the hypothesis that ADHD is caused by a dysfunctional neurotransmitter system and, therefore, focused on deactivated brain regions as compared with the control (Smith et al. 2006). Very few studies paid attention to the brain regions that were more activated in the ADHD group than in the control that in fact has been described (Vaidya et al. 1998). Brain activation in the ADHD group showed more diffuse patterns, which were similar to those observed in very young children (Tsujii et al. 2009). The present study verified this phenomenon. Compared with the control group, the brain activation pattern in the ADHD group was more diffuse and posterior, and these results support the developmental delay hypothesis regarding the pathogenesis of ADHD (Yochman et al. 2006). The present study showed that, compared to the control group, the ADHD group displayed greater activation in the brain regions of the left inferior frontal cortex, the right inferior temporal cortex, the right precentral gyrus, the left postcentral gyrus, the inferior occipital cortex, the middle occipital cortex, the right calcarine, the right hippocampus, the right midbrain, and the cerebellum. Most notably, because we used the very simplified Go/No-go task paradigm, the control group generally showed no brain activation during the RI process due to the need for only minimal cognitive effort. Therefore, the present study results demonstrated no hypoactivation in the ADHD group as compared to the control group. We explain this as a ceiling effect, which created optimal conditions for us to observe and understand compensatory brain activation in children with ADHD.

Despite that some ADHD children can rely on the RI neural pathways with simple tasks and succeed in the

performance of compensatory behavior, with increasing task difficulty; this success of obtaining compensation will become difficult. In addition, not only the RI neural pathway can be successful but we cannot exclude other important compensatory neurological loop compensations. Other neurological circuits might be a reward function circuit, working memory circuit, etc. and may lead to barriers of the children's ADHD symptoms. We utilized the advantage of a block design to collect more salient BOLD signal changes during the No-go versus Go process (Passarotti et al. 2010). However, some authors have argued that it would involve several neural processes simultaneously. For example, comparison of the No-go block with the Go block could involve not only the RI process but also response preparation and the response selection process (Bush et al. 1998) that would make our results difficult to interpret. The results obtained could be derived from multineural pathways as opposed to pure RI pathways. Fortunately, the apparent compensatory activation in ADHD children did not exist in control children in our present study. Thus, our results still appropriately discriminated the neural response in ADHD children from that of control children, which reflected at least partially in the differential RI neural pathway observed. Another limitation of the present study is the small sample size (15 vs. 15). Most of the children with ADHD using the simplified letter Go/No-go task in the present study showed compensatory activation, whereas the control children did not; the certainty of this conclusion warrants future studies employing a larger sample population.

## Conclusions

In contrast with the control group, the ADHD group tended to activate more posterior parts of the brain: vision-related brain regions (right inferior temporal cortex, inferior occipital cortex, middle occipital cortex, and right calcarine), the right hippocampus, the right midbrain, and the cerebellum. This compensatory strategy might be effective as an attempt to cope with a simple RI task.

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