Distinguishing Adolescents With ADHD From Their Unaffected Siblings and Healthy Comparison Subjects by Neural Activation Patterns During Response Inhibition

Daan van Rooij, M.Sc., Pieter J. Hoekstra, M.D., Ph.D., Maarten Mennes, Ph.D., Daniel von Rhein, M.Sc., Andrieke J.A.M. Thissen, M.Sc., Dirk Heslenfeld, Ph.D., Marcel P. Zwiers, Ph.D., Stephen V. Faraone, Ph.D., Jaap Oosterlaan, Ph.D., Barbara Franke, Ph.D., Nanda Rommelse, Ph.D., Jan K. Buitelaar, M.D., Ph.D., Catharina A. Hartman, Ph.D.

Objective: Dysfunctional response inhibition is a key executive function impairment in attention deficit hyperactivity disorder (ADHD). Still, behavioral response inhibition measures do not consistently differentiate affected from unaffected individuals. The authors therefore investigated neural correlates of response inhibition and the familial nature of these neural correlates.

Methods: Functional MRI measurements of neural activation during the stop-signal task and behavioral measures of response inhibition were obtained in adolescents and young adults with ADHD (N=185), their unaffected siblings (N=111), and healthy comparison subjects (N=124).

Results: Stop-signal task reaction times were longer and error rates were higher in participants with ADHD, but not in their unaffected siblings, while reaction time variability was higher in both groups than in comparison subjects. Relative to comparison subjects, participants with ADHD and unaffected siblings had neural hypoactivation in frontal-striatal and frontal-parietal networks, whereby activation in inferior frontal and temporal/parietal nodes in unaffected siblings was intermediate between levels of participants with ADHD and comparison subjects. Furthermore, neural activation in inferior frontal nodes correlated with stop-signal reaction times, and activation in both inferior frontal and temporal/parietal nodes correlated with ADHD severity.

Conclusions: Neural activation alterations in ADHD are more robust than behavioral response inhibition deficits and explain variance in response inhibition and ADHD severity. Although only affected participants with ADHD have deficient response inhibition, hypoactivation in inferior frontal and temporal-parietal nodes in unaffected siblings supports the familial nature of the underlying neural process. Activation deficits in these nodes may be useful as endophenotypes that extend beyond the affected individuals in the family.

Am J Psychiatry 2015; 172:674–683; doi: 10.1176/appi.ajp.2014.13121635

Response inhibition is assumed to be a key deficit underlying attention deficit hyperactivity disorder (ADHD) (1). However, a meta-analysis showed only medium effect sizes (g=0.62) for response inhibition deficits in ADHD (2), with large interindividual differences. Indeed, around half of individuals with ADHD have a response inhibition performance overlapping that of healthy comparison subjects (2). Similar behavioral task outcomes can be due to different neural mechanisms. For example, neural correlates of reversal learning performance differed between participants with severe mood dysregulation and those with pediatric bipolar disorder despite similar task performance (3). We therefore postulated that neural measures may be a more robust method than task performance to investigate the nature of response inhibition alterations in individuals with ADHD (4).

Neuroimaging research in healthy subjects has identified a core network of brain regions involved in response inhibition, including a frontal-striatal network (the inferior frontal gyrus, the presupplementary motor area, basal ganglia, and suprathalamic nucleus [5, 6]) and a frontal-parietal network (the inferior frontal, superior frontal, and temporal/parietal areas [7–9]). The inferior frontal gyrus, generally linked to salient cue detection (10), is thought to initiate the inhibition process, which is further executed by the presupplementary motor area and basal ganglia (11–13). Temporal/parietal and superior frontal nodes are thought to underlie the top-down direction of attentional resources during response inhibition (7, 14). Additionally, anterior cingulate areas are involved in error processing, as indicated by activation following failed response inhibition (15). While attention and

See related feature: **AJP Audio** *(online)*

error processing are not specific to response inhibition (16), deficits in these processes influence response inhibition performance (see, for instance, reference 17).

Children and adolescents with ADHD, when compared with healthy subjects, previously demonstrated hypoactivation in frontal and medial nodes of response inhibition networks (18–24), as well as in frontal-parietal nodes of the attentional networks (25, 26), indicating altered functionality in both inhibition and attentional processes. Literature on adults with ADHD showed inconsistent findings, with both hypoactivation (21, 22, 27) and hyperactivation (28, 29) reported in frontal-striatal and frontal-parietal areas.

Given these inconsistent previous findings, as well as relatively small study groups in earlier studies (4, 26), the first aim of our study was to investigate neural activation patterns underlying response inhibition in a large group of adolescents and young adults with and without ADHD. Reaction time on the stop-signal task was used as a behavioral index of response inhibition performance, reaction time variability as a measure of attention (16), and error rate as a measure of error processing (15). We expected hypoactivation in the frontal-striatal and frontal-parietal networks during both successful and failed response inhibition in individuals with ADHD (23, 30) and expected the degree of hypoactivation to be associated with ADHD severity. Inhibition-related activation in frontal areas was expected to correlate with stop-signal reaction times (5), activation of parietal nodes with reaction time variability (7), and error rates with anterior cingulate activation after failed inhibition (31).

As a second aim, we investigated the suitability of response inhibition as an ADHD endophenotype by comparing neural correlates of response inhibition in adolescents with ADHD, their unaffected siblings, and healthy comparison subjects. Endophenotypes are heritable markers more closely related to the genetic underpinnings of a disorder than the disorder itself (32), which may facilitate the search for causal genetic variants of a disorder (33). Assuming neural activation to be causally closer to the genetic factors underlying ADHD than task-outcome measures, we expected unaffected siblings to demonstrate neural hypoactivation in frontal-striatal nodes that was intermediate between the activation of the probands and the comparison subjects, even in the absence of behavioral deficits (34). Unaffected siblings may further be able to recruit alternative neural mechanisms to compensate for impaired response inhibition, which would show as hyperactivation outside of the response inhibition network, specifically in parietal areas (35–37).

METHOD

Participants

The participants were part of NeuroIMAGE (www.neuroimage.nl), the Dutch follow-up of the International Multicenter ADHD Genetics (IMAGE) study (38). Three groups were included: participants with ADHD (N=185), their unaffected siblings (N=111), and healthy comparison subjects (N=124); for demographic characteristics, see Table 1. Participants with ADHD had to have six or more hyperactive/impulsive and/or inattentive symptoms according to DSM-IV criteria; unaffected siblings and unrelated comparison subjects had to have fewer than two symptoms overall, based on a structured psychiatric interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children [39]) and Conners questionnaires (40). Comorbidity with oppositional defiant disorder or conduct disorder was allowed. Among participants with ADHD, 53.5% were currently using stimulant medication. IQ was lower and the proportion of females was smaller in the ADHD group than in the comparison group. Detailed recruitment and diagnostic information can be found in the main NeuroIMAGE design article (42); specifics regarding the current study group are available in the "Supplementary Methods" section of the data supplement accompanying the online version of this article.

Stop-Signal Task Acquisition and Analysis

The stop-signal task was used to operationalize response inhibition (43). The main outcome measure was the stop-signal reaction time. Reaction time variability and the number of commission and omission errors on go trials (errors) were other outcome measures (see online data supplement).

Familial relationships between participants with ADHD and their siblings were accounted for by using generalized estimating equation models. To test the unique effects of each task outcome measure, we investigated the effects of diagnostic group on stop-signal reaction time, reaction time variability, and errors in separate models, while correcting for the influence of the other measures. Age, gender, and IQ were added as covariates. Potential confounding effects of medication use or comorbid diagnoses within the probands on the stop-signal task measures were tested in separate analyses (see online data supplement).

fMRI Group Analysis

fMRI data were processed by using FSL FEAT (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain [FMRIB] software library, www.fmrib.ox.ac.uk/fsl; fMRI Expert Analysis Tool, version 6.0); information on fMRI acquisition and preprocessing can be found in the online data supplement. For single subject analysis, three first-level contrasts of interest were constructed: 1) successful stop-go and 2) failed stop-go trials, to isolate activation of successful and failed inhibition, respectively, by using go trial activity as an implicit baseline, and 3) a failed-successful stop contrast to model activation unique to the failed inhibition process.

For the between-group analysis, an F test contrast comparing the three diagnostic groups was subsequently applied to these contrast maps, separately for the successful stop-go, failed stop-go, and failed stop–successful stop contrasts. Age, gender, IQ, and scan site were added as covariates. To ensure robust cluster-level statistics, subsequent group-level correction for multiple comparisons was performed by using thresholds

TABLE 1. Characteristics and Stop-Signal Task Measures for Patients With ADHD, Their Unaffected Siblings, and Healthy Comparison Subjects[a]

Characteristic	ADHD (N=185)		Siblings (N=111)		Healthy Subjects (N=124)		Wald-χ^2	Cohen's d	Between-Group Effects
	N		N		N				
Male	129		48		55				
Female	56		63		69		28.1**	0.54	ADHD<sibs=healthy
Medication use	142		0		0		160.6**	1.57	ADHD>sibs=healthy
Comorbid oppositional defiant disorder[b]	55		4		0		67.7**	0.88	ADHD>sibs=healthy
Comorbid conduct disorder[b]	12		0		0		15.6**	0.39	ADHD>sibs=healthy
Comorbid reading disability[b]	34		11		11		7.3*	0.27	ADHD>healthy
	Mean	SD	Mean	SD	Mean	SD			
Number of ADHD symptoms[a]	12.9	3.1	1.3	3.4	0.6	1.5	242.7**	2.34	ADHD>sibs=healthy
Age (years)	17.3	3.2	17.3	4.0	16.5	3.3	1.6	0.13	
Estimated IQ[c]	95.3	16.8	102.4	15.9	107.1	14.5	38.2**	0.63	ADHD<sibs<healthy
Education (years)	12.8	2.1	12.8	2.2	13.5	1.9	6.4*	0.25	ADHD=sibs<healthy
	Range		Range		Range				
Age (years)	8–25		8–27		9–23				
IQ[c]	55–138		56–144		58–141				
	Mean	SD	Mean	SD	Mean	SD			
Stop-signal reaction time (ms)[d]	268.1	59.4	254.1	49.0	258.2	52.6	6.0*	0.24	ADHD>sibs=healthy
Reaction time variance (ms)[d]	112.0	38.3	93.2	36.7	82.2	30.8	30.0**	0.56	ADHD>sibs>healthy
Errors on go trials[d]	6.3	7.6	4.2	5.6	3.1	3.5	13.6**	0.37	ADHD>sibs=healthy

[a] ADHD diagnosis was based on K-SADS structured psychiatric interviews (39) and Conners questionnaires (40).
[b] Diagnosis was based on K-SADS structured psychiatric interviews (39).
[c] Estimated IQ was based on the block-design and vocabulary subtests of the Wechsler Intelligence Scale for Children (WISC) or Wechsler Adult Intelligence Scale (WAIS-III) (41).
[d] Task effects for the stop-signal task were derived from generalized estimate equation models, using a significance threshold of $p<0.05$ and correcting for familiality, gender, age, and IQ.
*$p<0.05$. ** $p<0.001$.

more stringent than FSL standard settings, with implementation of a z-statistic cluster thresholding of 2.6 and a family-wise-corrected significance threshold of $p<0.01$ (44).

Post hoc analysis of between-group differences was done by exporting beta values from all clusters (N=11) that reached significance in the diagnostic group F test. These were included in separate models, with correction for familial relations between participants. In probands, the relation between ADHD severity and neural activation was investigated by incorporating ADHD symptom count as a predictor in a separate set of analyses (see online data supplement).

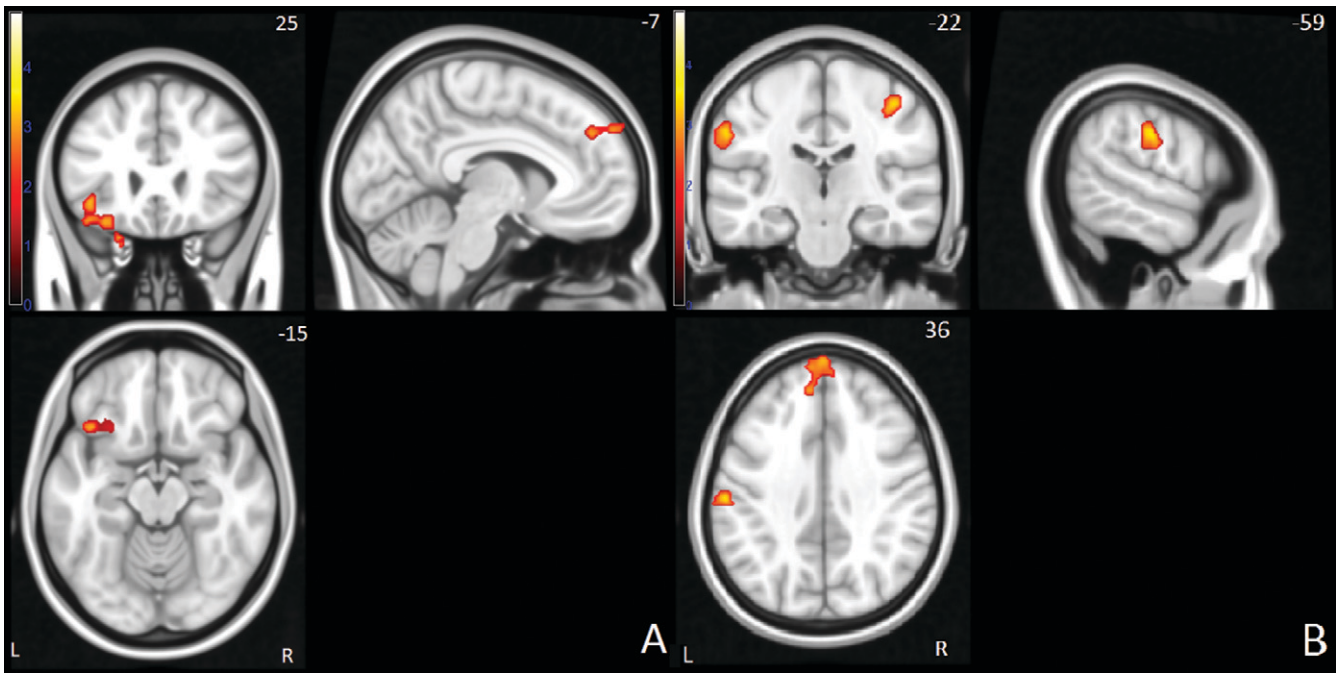
Associations between stop-signal task outcomes and neural activation measures in the clusters showing a group effect were subsequently investigated. We incorporated the exported beta values from significant clusters as dependent variables and added reaction time variability, stop-signal reaction time, and errors as predictors in the same model. Results of these analyses were assessed by using Bonferroni-Holm-corrected p values. Finally, a number of additional sensitivity analyses were run. That is, the probands with ADHD, unaffected siblings, and comparison subjects in our study were not matched a priori on demographic factors. Therefore, the potential confounding effects of several covariates were tested and additional sensitivity analyses were performed to investigate the robustness of the main diagnostic group effects (see online data supplement).

RESULTS

Task Outcome Measures

A main effect of diagnostic group on stop-signal reaction time (see Table 1) was found, indicating longer reaction times in participants with ADHD than in unaffected siblings ($\beta=-15.4$, $p=0.015$) and in comparison subjects ($\beta=-13.8$, $p=0.05$). Probands made significantly more errors on the go trials than unaffected siblings ($\beta=-1.8$, $p<0.013$) and comparison subjects ($\beta=-2.5$, $p<0.001$). Stop-signal reaction time and error rate did not differ between the latter two groups. Regarding reaction time variability, probands performed worse than their unaffected siblings ($\beta=-15.6$, $p<0.001$), who performed

FIGURE 1. Brain Activation Differences of Patients With ADHD or Their Unaffected Siblings From Healthy Comparison Subjects in Successful Stop-Go Trials of the Stop-Signal Task[a]



[a] A, frontal area; B, parietal area. Yellow hues correspond to higher signal in the comparison subjects. In bilateral views, the right side of the image corresponds to the right hemisphere of the brain.

worse than the comparison subjects ($\beta=-9.5$, $p<0.021$). No influences of age, gender, IQ, medication status, or comorbid diagnoses were found.

fMRI Task Activation

Activation maps for the successful stop-go, failed stop-go, and failed stop–successful stop contrasts across all participants are shown in Figure S1 in the online data supplement. In the successful stop condition we observed higher beta values in the bilateral inferior frontal cortex, as well as in the bilateral insula, right frontal pole and middle frontal gyrus, right thalamus and caudate nucleus, bilateral anterior and posterior cingulate, medial frontal gyrus, bilateral temporal/parietal junction and lateral occipital areas, left hippocampus, and cerebellum. Similar patterns were observed in the failed stop condition, with higher beta values in the left inferior frontal gyrus, insula, and caudate nucleus merged into one cluster. The failed stop condition showed additional activation in the left frontal pole and superior frontal area.

The failed–successful stop condition showed increased betas in the bilateral calcerine occipital cortex, anterior cingulate, presupplementary motor area, and left inferior frontal gyrus (see Table S1 in the online data supplement). Activation maps for the diagnostic groups as well as difference maps for the go condition are also reported in the online data supplement; although the comparison subjects showed higher activation in the medial frontal pole during go trials, this activation did not overlap with group contrasts of interest nor did it survive multiple-comparison corrections.

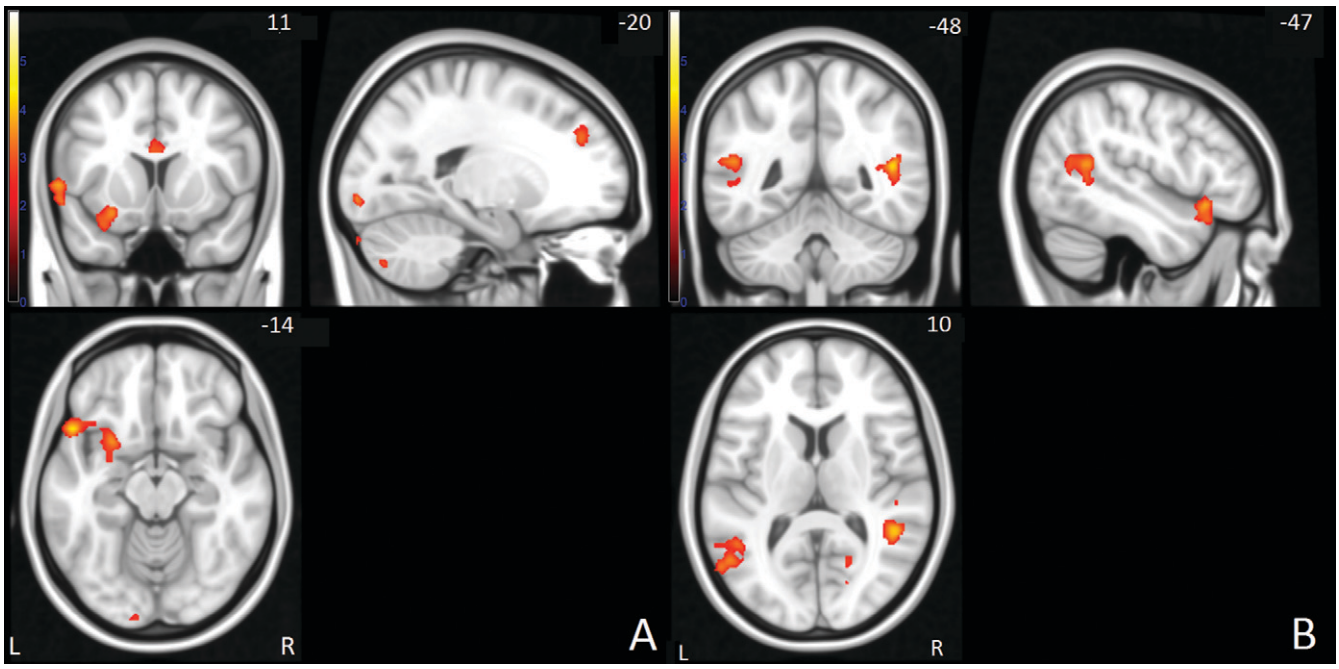
Group Differences in fMRI Task Activation

Between-group differences in neural activation for the successful stop-go condition were located in the left inferior frontal, superior frontal and anterior cingulate gyrus, left supramarginal gyrus, right postcentral gyrus, and right temporal/parietal junction (Figure 1). For the failed stop-go condition, between-group comparisons showed differences in the left inferior and superior frontal, anterior cingulate, left supramarginal, and bilateral temporal/parietal areas, as well as left cerebellum and right occipital areas (Figure 2). An overview of all overall group effects and differences between the three diagnostic groups is shown in Table 2.

For the successful stop condition, the siblings and probands showed less activation than the healthy comparison subjects in right temporal/parietal, left supramarginal, and right postcentral/supramarginal areas. In the left superior frontal and inferior frontal gyri, the probands showed less activation than both the siblings and comparison subjects, while the latter two did not differ (see also Figure S2 in the online data supplement).

In the failed stop condition, we observed levels of activation for siblings that were in between the levels observed for the probands and comparison subjects in bilateral temporal/parietal areas and the inferior frontal gyrus. In the anterior cingulate and left superior frontal gyri, probands and siblings showed similar levels of hypoactivation relative to the healthy comparison subjects. In the left supramarginal region, the siblings did not differ from the comparison subjects and showed higher activation than the probands (see also Figure S3 in the online data supplement).

FIGURE 2. Brain Activation Differences of Patients With ADHD or Their Unaffected Siblings From Healthy Comparison Subjects in Failed Stop-Go Trials of the Stop-Signal Task[a]



[a] A, frontal area; B, parietal area. Yellow hues correspond to higher signal in the comparison subjects. In bilateral views, the right side of the image corresponds to the right hemisphere of the brain.

Additionally, results from post hoc analyses relating neural activation to ADHD severity in the probands (Table 3) indicated significant negative correlations between ADHD symptom count and neural activation in the inferior frontal gyrus during both successful and failed stop conditions, as well as in the superior frontal and temporal/parietal gyrus during the failed stop condition.

The failed stop–successful stop contrast did not reveal any significant differences between diagnostic groups.

Associations of Stop-Signal Task Outcomes With fMRI Task Activation

Shorter reaction times on the stop-signal task were significantly associated with higher levels of activation in the left inferior frontal and left superior frontal gyrus during successful stops (Table S2 in the online data supplement). Reaction time variability and error rate were not associated with activation in any of the nodes. Post hoc analyses confirmed the significant relation between inferior frontal activation and reaction time when examined in probands with ADHD and healthy comparison subjects separately, while the relation between stop-signal reaction time and superior frontal activation held only in the comparison subjects (see online data supplement). We further investigated the distribution of task performance and neural activation across the three groups. To this end, we compared the percentage of participants with ADHD and siblings who scored above the 90th percentile of the scores for the comparison group (see online data supplement). This analysis showed that 12% of the ADHD probands and 7% of the siblings showed task outcome (stop-signal reaction time) above the 90th percentile of the comparison group, while the elevated neural activation values across the different nodes showed on average 22% of probands' and 19% of siblings' values were above the 90th percentile of the comparison group (see Table S5 in the online data supplement for the comparison of individual nodes). This indicates that the within-group distributions of scores of the probands and siblings differed from that of the healthy comparison subjects more strongly for the neural activation than for the behavioral task outcome measures.

Covariate Effects and Sensitivity Analyses

No significant effects of age, scanner site, and gender were found in any of the neural nodes, nor were there interactions between diagnostic group and these covariates. In the online data supplement we present the outcomes of additional sensitivity analyses, in which we reexamined the main contrasts of interest while strictly correcting for IQ, gender, scan site, medication status, familial relations, comorbid disorders, stop-signal reaction time performance, and Conners' scale scores. None of these factors significantly affected the reported main group differences in neural activation.

DISCUSSION

This study provides several new insights into the relation between response inhibition performance, related neural activation, and ADHD. First, we demonstrated slower stop-signal reaction times and higher error rates along with hypoactivation in both the frontal-striatal and frontal-parietal networks in

TABLE 2. Brain Regions Differing in Activation During the Stop-Signal Task Between Patients With ADHD, Their Unaffected Siblings, and Healthy Comparison Subjects

Task Condition and Brain Area[a]	Mean β[a]	SD[a]	Wald χ^{2}[b]	Cohen's d[b]	Peak Voxel (MNI[c])	BA[c]	Voxels in Cluster	Between-Group Effects[b]
Successful stop-go condition								
Inferior frontal gyrus, left	4.91	25.46	16.34***	0.40	−38, 20, −18	44, 47	371	Healthy=sibs>ADHD
Superior frontal gyrus, left	−2.87	37.46	16.25***	0.40	−2, 60, 38	8	245	Healthy=sibs>ADHD
Supramarginal gyrus, left	−7.50	31.47	9.91**	0.31	−58, −20, 34	2, 40	189	Healthy>sibs=ADHD
Postcentral gyrus, right	−17.59	31.10	11.28**	0.33	42, −24, 52	3, 4	134	Healthy>sibs=ADHD
Temporal-parietal junction, right	17.22	21.34	7.10*	0.26	48, −42, 14	41	95	Healthy>sibs=ADHD
Failed stop-go condition								
Inferior frontal gyrus, left	14.80	23.15	35.29***	0.61	−52, 18, −12	13, 44, 47	1064	Healthy>sibs>ADHD
Temporal-parietal junction, left	14.97	25.02	22.46***	0.48	−50, −50, −12	19, 22	811	Healthy>sibs>ADHD
Temporal-parietal junction, right	11.81	16.12	33.50***	0.59	48, −44, 14	13	368	Healthy>sibs>ADHD
Superior frontal gyrus, left	3.34	24.51	20.55***	0.46	−18, 42, 30	9	164	Healthy>sibs=ADHD
Anterior cingulate cortex, left/right	21.64	24.59	11.24**	0.33	−2, 12, 22	24	160	Healthy>sibs=ADHD
Supramarginal gyrus, left	16.44	30.61	10.57**	0.32	−58, −24, 26	40	151	Healthy=sibs>ADHD

[a] Activation clusters are derived from the F contrasts testing differences in task activation as a function of diagnostic group, including gender, IQ, age, and scan site as covariates. Correction for multiple comparisons was performed by using a cluster threshold of Z>2.3 and a significance threshold of p<0.05 corrected.
[b] Between-group effects and associated Wald χ^{2} values, p values, and Cohen's d reflect the specific diagnostic group in each region as derived from post hoc generalized estimating equation analyses, corrected for familial dependency between siblings as well as for covariates age, gender, IQ, and scan site.
[c] MNI=Montreal Neurological Institute x, y, z coordinates. BA=Brodmann area.
*p<0.05. **p<0.01. *** p<0.001.

adolescents and young adults with ADHD. Second, we showed that the level of hypoactivation in these networks correlated with both stop-signal reaction time and ADHD severity. Third, we provided novel evidence for similar hypoactivation patterns in unaffected siblings, in the absence of behavioral response inhibition deficits (19). Last, we showed that reaction time variability was higher in both probands with ADHD and unaffected siblings, suggesting a specific response inhibition deficit in ADHD and a broader cognitive impairment in both probands and siblings.

Over all groups, neural activation patterns during both successful and failed stop trials formed a network including the bilateral inferior frontal and superior frontal gyri, basal ganglia, and supramarginal areas. Activation in the inferior and superior frontal gyrus and basal ganglia nodes is in line with the response inhibition model proposed by Aron (5). On the other hand, activation in temporal and parietal nodes, areas previously linked to attentional redirection and task-set maintenance (45), likely reflects recruitment of attentional processes during response inhibition, in line with the models of Chambers et al. (7) and Simmonds et al. (9). The failed–successful stop contrast further revealed differential activation in visual areas, the anterior cingulate, and the inferior frontal cortex, consistent with previous findings, including a possible error processing component in anterior cingulate activation (45). Inferior frontal activation in this contrast may reflect recruitment of additional resources to the response inhibition network (5) or reflect more general cue updating after failed responses (10). These results indicate that response inhibition is realized by activation in a large number of nodes from both frontal-striatal and frontal-parietal networks.

Adolescents and young adults with ADHD and their unaffected siblings showed levels of hypoactivation during both successful and failed stop trials, with unaffected siblings generally showing levels of activation similar to those of the probands or intermediate between those of the comparison subjects and probands with ADHD. Hypoactivation patterns were distributed across left superior, inferior, and medial frontal as well as bilateral temporal/parietal nodes, indicating a general and familial neural dysfunction across a large number of nodes attributed to distinct neural networks. Our results thereby confirm many preliminary previous findings in smaller groups of children and adolescents (19–24, 46, 47), which taken together describe very similar hypoactivation patterns in frontal-striatal and frontal-parietal areas (26, 48). However, previous response inhibition studies in adults with ADHD demonstrated both neural hypo- and hyperactivation in the response inhibition networks (21, 22, 26, 48). Our results indicate no evidence for hyperactivation, nor any interaction between neural activation and age. This suggests that at least in young adults the neural alterations are qualitatively similar to those in adolescents with ADHD and resemble alterations reported in children.

Activation in inferior and superior frontal as well as temporal/parietal areas was associated with ADHD severity, suggesting that multiple neural mechanisms are affected in both ADHD probands, as previously proposed in a meta-analysis (26), and unaffected siblings. The hypoactivation in the left inferior and superior frontal gyrus were the only neural measures that correlated significantly with stop-signal reaction time length. This again fits relatively well with the model proposed by Aron (5), who indicated the inferior frontal area as the central node in the response inhibition process. Both models by Aron (5) and Chambers et al. (7) have additionally indicated the dorsolateral prefrontal cortex as critical for top-down executive control, which would be the most

TABLE 3. Associations Between Brain Activation and Number of Behavioral ADHD Symptoms in Patients With ADHD

	Effect of Number of ADHD Symptoms on Height of Neural Activation[a]			
Area	β	Wald χ^2	Cohen's d	p
Successful stop-go condition				
Inferior frontal gyrus, left	**−0.026**	**7.204**	**0.204**	**0.007**
Superior frontal gyrus, left	0.012	3.422	0.181	0.064
Supramarginal gyrus, left	0.008	1.088	0.102	0.297
Postcentral gyrus, right	−0.002	0.051	0.022	0.821
Temporal-parietal junction, right	−0.02	3.329	0.179	0.068
Failed stop-go condition				
Inferior frontal gyrus, left	**−0.025**	**5.564**	**0.232**	**0.018**
Temporal-parietal junction, left	−0.014	2.126	0.143	0.145
Temporal-parietal junction, right	**−0.027**	**4.142**	**0.2**	**0.042**
Superior frontal gyrus, left	**−0.02**	**4.384**	**0.205**	**0.036**
Anterior cingulate cortex, left/right	0.001	0.02	0.014	0.887
Supramarginal gyrus, left	−0.008	1.214	0.108	0.271

[a] Bolded values indicate significant effects. All measures were derived from a single generalized estimating equation model for familial dependency between siblings, as well as for the covariates age, gender, IQ, and scan site. A significance threshold of $\alpha<0.05$ was used.

likely explanation for the superior frontal hypoactivation in probands with ADHD in this area. However, since there was no condition manipulating attention or top-down control, these speculations cannot be directly derived from our data.

Hypoactivation in supramarginal and temporal/parietal regions of the probands with ADHD is also consistent with the models of Chambers et al. (7) and Simmonds et al. (9), which implicate these regions in attentional processes, which may influence the response inhibition process indirectly. These models are supported by evidence from transcranial magnetic stimulation studies showing attenuated attentional processing after parietal cortex stimulation (49). However, none of the task outcome measures were related to neural activation in the parietal nodes. Therefore, more research targeting the temporal/parietal areas is necessary to establish their causal role in response inhibition and ADHD. Lastly, hypoactivation in anterior cingulate areas during the failed inhibition trials in both probands with ADHD and siblings suggests an additional deficit in response to perceived errors (50). This appears consistent with the higher error rates found in probands with ADHD, although we found no direct association between error rates and anterior cingulate activation.

No group differences were found in the failed–successful stop contrast, indicating that there are no qualitative differences underlying inhibition failure between the diagnostic groups. Rather, the neurobiological nature of response inhibition deficits in ADHD is related to distributed hypoactivation in both frontal-striatal and frontal-parietal nodes during both task conditions.

The neural hypoactivation observed in unaffected siblings is largely in line with previous work (19) that showed similar patterns of hypoactivation in inferior frontal and parietal areas in the absence of behavioral deficits in unaffected siblings of probands with ADHD, though this previous work reported atypical activation in the right instead of left inferior frontal gyrus for siblings. The intermediate activation levels in inferior frontal and temporal/parietal nodes specifically fit with previous work addressing the heritable nature of inferior frontal activation (51). However, the predicted pattern of intermediate activation in siblings was present only during the failed stop condition, and it was not found in the superior frontal and supramarginal regions. Thus, although no direct evidence was found for differential activation between the successful and failed conditions, activation during the failed stop trials nonetheless appeared most sensitive in distinguishing probands with ADHD, unaffected siblings, and healthy comparison subjects.

The absence of behavioral response inhibition deficits in unaffected siblings is in contrast with previous behavioral literature (52), including evidence from our own sample at an earlier time (53). This current finding suggests that developmental factors are important in the investigation of familial patterns of response inhibition deficits, as unaffected siblings possibly show improved response inhibition performance during adolescence, while probands with ADHD do not (54).

Of note is that the effect sizes of behavioral versus neural measures suggest that the differences in neural activation during response inhibition between diagnostic groups are more robust than stop-signal reaction time differences. Comparisons of the distributions of behavioral and neural outcome measures likewise indicate that neural hypoactivation is also more consistently present than response inhibition deficits in probands with ADHD. The strong differences in reaction time variability between probands with ADHD, their unaffected siblings, and healthy comparison subjects have effect sizes comparable to those obtained from the neural measurements. These results confirm earlier studies regarding reaction time variability as an endophenotype for ADHD (55–57). An alternative interpretation of the neural hypoactivation found in probands with ADHD could be that the deficits in reaction time variability in both probands and their siblings are related to a general attentional deficit, mediated

by temporal/parietal hypoactivation. However, there was no significant correlation between neural activation in parietal areas and reaction time variability, which makes this interpretation less likely.

No direct evidence for compensatory neural activation in either subjects with ADHD or unaffected siblings was found. The finding of hypoactivation in unaffected siblings in the absence of behavioral response inhibition deficits or compensatory neural mechanisms warrants further attention. Additional research is needed to establish whether the siblings recruit compensatory resources that could not be detected with the current paradigm or whether the hypoactivation observed in siblings is unrelated to the response inhibition process or insufficient to cause behavioral deficits. Specifically, functional connectivity measures may offer additional insight into the possible recruitment of alternative neural resources in unaffected siblings.

To summarize the group differences, hypoactivation in inferior frontal, superior frontal, and temporal/parietal regions all independently explained variance in ADHD severity, with unaffected siblings showing intermediate patterns of hypoactivation in these areas during failed but not successful inhibition and in the absence of behavioral deficits. These findings support the familial nature of the response inhibition process in ADHD and suggest that the neural activation measures in these regions could be useful as possible endophenotypes for ADHD, although only the failed inhibition contrast showed a clear distinction between all three diagnostic groups.

It should further be noted that left rather than right inferior frontal activation distinguished our diagnostic groups. While we showed bilateral inferior activation patterns during response inhibition for all groups, no right-sided hypoactivation was observed in probands with ADHD. Previous studies in both healthy subjects and participants with ADHD have emphasized involvement of the right inferior frontal gyrus in response inhibition (5, 58), although studies have also demonstrated functional involvement of the left inferior frontal gyrus in the response inhibition process (59). We postulate that both inferior frontal nodes are involved in response inhibition and that lateralization may vary more between individuals than hitherto thought. This study strongly indicates that the left hemisphere should not be neglected and that future studies should be aimed at delineating the specific functional differences in response inhibition nodes between hemispheres.

The current study should be viewed in light of its strengths and limitations. A main strength was the large and well-documented sample. The unbalanced distributions of IQ and gender between diagnostic groups and scan sites were potential weaknesses of the current design.

To conclude, we demonstrated a distinction in neural activation patterns during response inhibition between adolescents with ADHD, their unaffected siblings, and healthy comparison subjects, indicating the familial nature of neural activation patterns underlying response inhibition in ADHD. Specifically, neural activation measures in superior frontal, inferior frontal, and temporal/parietal nodes of the response inhibition network showed hypoactivation patterns in line with the endophenotype model during failed but not successful response inhibition.

AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry, University Medical Center, University of Groningen, Groningen, the Netherlands; the Department of Cognitive Neuroscience, the Department of Psychiatry, and the Department of Human Genetics, Donders Institute for Brain, Cognition, and Behavior, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; Karakter Child and Adolescent Psychiatry University Center Nijmegen, Nijmegen, the Netherlands; the Department of Psychology, VU University Amsterdam, Amsterdam, the Netherlands; and the Department of Psychiatry and the Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, N.Y.

Address correspondence to Mr. van Rooij (d.vanrooij@fcdonders.ru.nl).

Drs. Buitelaar and Hartman contributed equally.

Supported by NIMH grant R01 MH-62873 (to Dr. Faraone), NWO Large Investment Grant 1750102007010 (to Dr. Buitelaar), and grants from Radboud University Nijmegen Medical Center, from University Medical Center Groningen and Accare, and from VU University Amsterdam.

The authors thank Roshan Cools for input and comments in the preparation of the manuscript and the Department of Pediatrics of the VU University Medical Center for the opportunity to use the mock scanner for preparation of the study participants.

Dr. Hoekstra has received advisory panel payments from Shire as well as an unrestricted research grant from Shire. In the past year, Dr. Faraone received income, travel expenses, and/or research support from and/or has been on an advisory board for Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, Neurovance, Impax, and NeuroLifeSciences and has received research support from the National Institutes of Health (NIH); his institution is seeking a patent for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD; in previous years, he received consulting fees or was on advisory boards or participated in continuing medical education programs sponsored by Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly; and he receives royalties from books published by Guilford Press and Oxford University Press. In the past 3 years, Dr. Oosterlaan has received an investigator-initiated grant from Shire Pharmaceuticals. In the past 3 years, Dr. Buitelaar has been a consultant to, member of an advisory board for, and/or speaker for Janssen Cilag, Eli Lilly, Bristol-Myers Squibb, Shering Plough, UCB, Shire, Novartis, and Servier; he is not an employee of any of these companies and not a stock shareholder of any of these companies; he has received no other financial or material support, including expert testimony, patents, and royalties. All other authors report no financial relationships with commercial interests.

Received Dec. 13, 2013; revisions received May 19, Oct. 22, and Oct. 27, 2014; accepted Nov. 3, 2014; published online Jan. 23, 2015.

REFERENCES

1. Alderson RM, Rapport MD, Kofler MJ: Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of the stop-signal paradigm. J Abnorm Child Psychol 2007; 35:745–758
2. Lipszyc J, Schachar R: Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. J Int Neuropsychol Soc 2010; 16:1064–1076
3. Adleman NE, Kayser R, Dickstein D, et al: Neural correlates of reversal learning in severe mood dysregulation and pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 2011; 50:1173–1185.e2
4. Cortese S, Kelly C, Chabernaud C, et al: Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry 2012; 169:1038–1055
5. Aron AR: From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. Biol Psychiatry 2011; 69:e55–e68

6. Aron AR, Durston S, Eagle DM, et al: Converging evidence for a fronto-basal-ganglia network for inhibitory control of action and cognition. J Neurosci 2007; 27:11860–11864
7. Chambers CD, Garavan H, Bellgrove MA: Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev 2009; 33:631–646
8. Garavan H, Hester R, Murphy K, et al: Individual differences in the functional neuroanatomy of inhibitory control. Brain Res 2006; 1105: 130–142
9. Simmonds DJ, Pekar JJ, Mostofsky SH: Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. Neuropsychologia 2008; 46:224–232
10. Hampshire A, Chamberlain SR, Monti MM, et al: The role of the right inferior frontal gyrus: inhibition and attentional control. Neuroimage 2010; 50:1313–1319
11. Zandbelt BB, Bloemendaal M, Hoogendam JM, et al: Transcranial magnetic stimulation and functional MRI reveal cortical and subcortical interactions during stop-signal response inhibition. J Cogn Neurosci 2013; 25:157–174
12. Swann NC, Cai W, Conner CR, et al: Roles for the pre-supplementary motor area and the right inferior frontal gyrus in stopping action: electrophysiological responses and functional and structural connectivity. Neuroimage 2012; 59:2860–2870
13. Cai W, George JS, Verbruggen F, et al: The role of the right pre-supplementary motor area in stopping action: two studies with event-related transcranial magnetic stimulation. J Neurophysiol 2012; 108:380–389
14. Fassbender C, Murphy K, Hester R, et al: The role of a right fronto-parietal network in cognitive control: common activations for "cues-to-attend" and response inhibition. J Psychophysiol 2006; 20: 286–296
15. van Meel CS, Heslenfeld DJ, Oosterlaan J, et al: Adaptive control deficits in attention-deficit/hyperactivity disorder (ADHD): the role of error processing. Psychiatry Res 2007; 151:211–220
16. Esterman M, Rosenberg MD, Noonan SK: Intrinsic fluctuations in sustained attention and distractor processing. J Neurosci 2014; 34: 1724–1730
17. Bekker EM, Overtoom CCE, Kooij JJS, et al: Disentangling deficits in adults with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2005; 62:1129–1136
18. Cubillo A, Halari R, Giampietro V, et al: Fronto-striatal underactivation during interference inhibition and attention allocation in grown up children with attention deficit/hyperactivity disorder and persistent symptoms. Psychiatry Res 2011; 193:17–27
19. Durston S, Mulder M, Casey BJ, et al: Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder. Biol Psychiatry 2006; 60:1062–1070
20. Rubia K, Smith AB, Brammer MJ, et al: Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. Am J Psychiatry 2005; 162:1067–1075
21. Mulligan RC, Knopik VS, Sweet LH, et al: Neural correlates of inhibitory control in adult attention deficit/hyperactivity disorder: evidence from the Milwaukee longitudinal sample. Psychiatry Res 2011; 194:119–129
22. Congdon E, Altshuler LL, Mumford JA, et al: Neural activation during response inhibition in adult attention-deficit/hyperactivity disorder: preliminary findings on the effects of medication and symptom severity. Psychiatry Res 2014; 222:17–28
23. Pliszka SR, Glahn DC, Semrud-Clikeman M, et al: Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. Am J Psychiatry 2006; 163:1052–1060
24. Epstein JN, Casey BJ, Tonev ST, et al: ADHD- and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD. J Child Psychol Psychiatry 2007; 48:899–913
25. Bush G: Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. Biol Psychiatry 2011; 69:1160–1167
26. Hart H, Radua J, Nakao T, et al: Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry 2013; 70:185–198
27. Cubillo A, Halari R, Ecker C, et al: Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood attention-deficit hyperactivity disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching. J Psychiatr Res 2010; 44:629–639
28. Dibbets P, Evers L, Hurks P, et al: Differences in feedback- and inhibition-related neural activity in adult ADHD. Brain Cogn 2009; 70:73–83
29. Schneider MF, Krick CM, Retz W, et al: Impairment of fronto-striatal and parietal cerebral networks correlates with attention deficit hyperactivity disorder (ADHD) psychopathology in adults—a functional magnetic resonance imaging (fMRI) study. Psychiatry Res 2010; 183:75–84
30. Rubia K, Cubillo A, Smith AB, et al: Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive-compulsive disorder. Hum Brain Mapp 2010; 31:287–299
31. Garavan H, Ross TJ, Murphy K, et al: Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. Neuroimage 2002; 17:1820–1829
32. Gottesman II, Gould TD: The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003; 160: 636–645
33. Glahn DC, Knowles EEM, McKay DR, et al: Arguments for the sake of endophenotypes: examining common misconceptions about the use of endophenotypes in psychiatric genetics. Am J Med Genet B Neuropsychiatr Genet 2014; 165B:122–130
34. Cannon TD, Keller MC: Endophenotypes in the genetic analyses of mental disorders. Annu Rev Clin Psychol 2006; 2:267–290
35. Fassbender C, Schweitzer JB: Is there evidence for neural compensation in attention deficit hyperactivity disorder? A review of the functional neuroimaging literature. Clin Psychol Rev 2006; 26: 445–465
36. Dillo W, Göke A, Prox-Vagedes V, et al: Neuronal correlates of ADHD in adults with evidence for compensation strategies—a functional MRI study with a Go/No-Go paradigm. Ger Med Sci 2010; 8:Doc09
37. Durston S, Tottenham NT, Thomas KM, et al: Differential patterns of striatal activation in young children with and without ADHD. Biol Psychiatry 2003; 53:871–878
38. Müller UC, Asherson P, Banaschewski T, et al: The impact of study design and diagnostic approach in a large multi-centre ADHD study, part 1: ADHD symptom patterns. BMC Psychiatry 2011; 11:54
39. Kaufman J, Birmaher B, Brent D, et al: Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36:980–988
40. Conners CK, Sitarenios G, Parker JD, et al: The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol 1998; 26:257–268
41. Wechsler D: WAIS-III Nederlandstalige bewerking: Technische handleiding. London, Psychological Corp, 2002
42. von Rhein D, Mennes M, van Ewijk H, et al: The NeuroIMAGE study: a prospective phenotypic, cognitive, genetic and MRI study in children with attention-deficit/hyperactivity disorder, design and descriptives. Eur Child Adolesc Psychiatry (Epub ahead of print, July 11, 2014)
43. Logan GD, Cowan WB, Davis KA: On the ability to inhibit simple and choice reaction time responses: a model and a method. J Exp Psychol Hum Percept Perform 1984; 10:276–291
44. Woo C-W, Krishnan A, Wager TD: Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. Neuroimage 2014; 91:412–419
45. Sharp DJ, Bonnelle V, De Boissezon X, et al: Distinct frontal systems for response inhibition, attentional capture, and error processing. Proc Natl Acad Sci USA 2010; 107:6106–6111

46. Suskauer SJ, Simmonds DJ, Fotedar S, et al: Functional magnetic resonance imaging evidence for abnormalities in response selection in attention deficit hyperactivity disorder: differences in activation associated with response inhibition but not habitual motor response. J Cogn Neurosci 2008; 20:478–493
47. Smith AB, Taylor E, Brammer M, et al: Task-specific hypoactivation in prefrontal and temporoparietal brain regions during motor inhibition and task switching in medication-naive children and adolescents with attention deficit hyperactivity disorder. Am J Psychiatry 2006; 163:1044–1051
48. Cubillo A, Halari R, Smith A, et al: A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 2012; 48:194–215
49. Chambers CD, Stokes MG, Janko NE, et al: Enhancement of visual selection during transient disruption of parietal cortex. Brain Res 2006; 1097:149–155
50. Schachar RJ, Chen S, Logan GD, et al: Evidence for an error monitoring deficit in attention deficit hyperactivity disorder. J Abnorm Child Psychol 2004; 32:285–293
51. Koten JW Jr, Wood G, Hagoort P, et al: Genetic contribution to variation in cognitive function: an FMRI study in twins. Science 2009; 323:1737–1740
52. Bidwell LC, Willcutt EG, Defries JC, et al: Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. Biol Psychiatry 2007; 62:991–998
53. Rommelse NNJ, Altink ME, Oosterlaan J, et al: Support for an independent familial segregation of executive and intelligence endophenotypes in ADHD families. Psychol Med 2008; 38:1595–1606
54. Thissen AJ, Luman M, Hartman C, et al: Attention-deficit/hyperactivity disorder (ADHD) and motor timing in adolescents and their parents: familial characteristics of reaction time variability vary with age. J Am Acad Child Adolesc Psychiatry 2014; 53:1010–1019, e4
55. Castellanos FX, Sonuga-Barke EJ, Scheres A, et al: Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. Biol Psychiatry 2005; 57:1416–1423
56. Klein C, Wendling K, Huettner P, et al: Intra-subject variability in attention-deficit hyperactivity disorder. Biol Psychiatry 2006; 60: 1088–1097
57. Kofler MJ, Rapport MD, Sarver DE, et al: Reaction time variability in ADHD: a meta-analytic review of 319 studies. Clin Psychol Rev 2013; 33:795–811
58. Rubia K, Smith AB, Brammer MJ, et al: Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage 2003; 20:351–358
59. Swick D, Ashley V, Turken AU: Left inferior frontal gyrus is critical for response inhibition. BMC Neurosci 2008; 9:102