Familial Vulnerability to ADHD Affects Activity in the Cerebellum in Addition to the Prefrontal Systems

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ABSTRACT

Objective: Familial vulnerability to attention-deficit/hyperactivity disorder (ADHD) has been shown to be related to atypical prefrontal activity during cognitive control tasks. However, ADHD is associated with deficits in the cerebellum as well as deficits in frontostriatal circuitry and associated cognitive control. In this study, we investigated whether cerebellar systems are sensitive to familial risk for ADHD in addition to frontostriatal circuitry. Method: We used an event-related, rapid mixed-trial functional magnetic resonance imaging design. The paradigm was a variation on a go/no-go task, with expected (go) and unexpected (no-go) events at expected and unexpected times. A total of 36 male children and adolescents completed the study, including 12 sibling pairs discordant for ADHD and 12 matched controls. Results: Children and adolescents with ADHD were less accurate on unexpected events than control subjects. Performance by unaffected siblings was intermediate, between that of children and adolescents with ADHD and controls. Functional neuroimaging results showed dissociation between activation in the cerebellum and anterior cingulate cortex: Activity in the anterior cingulate cortex was decreased for subjects with ADHD and their unaffected siblings compared with controls for manipulations of stimulus type (no-go trials), but not timing. In contrast, cerebellar activity was decreased for subjects with ADHD and their unaffected siblings for manipulations of timing, but not stimulus type. Conclusions: These findings suggest that activity in both the prefrontal cortex and cerebellum is sensitive to familial vulnerability to ADHD. Unaffected siblings of individuals with ADHD show deficits similar to affected probands in prefrontal areas for unexpected events and in cerebellum for events at unexpected times. J. Am. Acad. Child Adolesc. Psychiatry, 2008;47(1):68–75. Key Words: attention-deficit/hyperactivity disorder, functional magnetic resonance imaging, familial vulnerability, cerebellum, prefrontal cortex.

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder in which familial effects are estimated to explain up to 70% of the phenotypic variance. Evidence from family, twin, and adoption studies shows that family members of individuals with ADHD are at increased risk for developing the disorder. For example, full siblings of individuals with ADHD have a three- to fivefold increased chance of developing ADHD. Although association studies have implicated a large number of candidate genes in ADHD, their relative contributions are not yet understood. Behavioral defined phenotypes, such as ADHD, are complex and are likely to be affected by multiple genes as well as gene–gene and gene–environment interactions. Investigating intermediate phenotypes can be useful to reduce the complexity
in etiology and genetic background.4,5 Deficits at the neuronal level may serve as intermediate phenotypes and may therefore be useful in investigating familial risk for ADHD.1

In ADHD, obvious candidates as neuronal intermediate phenotypes are deficits in frontostriatal circuitry and cognitive control. Cognitive control can be defined as the ability to control behavior in a constantly changing environment by inhibiting inappropriate thoughts or actions in favor of more appropriate ones. Behaviorally, individuals with ADHD perform worse than matched controls on tasks that probe cognitive control (for meta-analysis, see Oosterlaan et al.6; for review, see Sergeant et al.7). Functional magnetic resonance imaging (MRI) studies have shown decreased neural activity in frontostriatal areas in the context of cognitive control tasks, and reductions in volume have been shown in these areas in morphological MRI studies.8-10

We previously showed that changes in frontostriatal functioning may be a potentially useful intermediate phenotype for ADHD, as we showed that individuals at familial risk for ADHD activated frontostriatal regions less than typically developing controls during a cognitive control task.11 In this study, subjects with ADHD, their unaffected siblings, and controls participated in a go/no-go task in the context of a functional MRI study. Behaviorally, individuals with ADHD had lower accuracy on the most challenging no-go trials, whereas performance by siblings was no different from that of controls. However, activation in prefrontal areas was decreased for both subjects with ADHD and their unaffected siblings, suggesting that these regions are sensitive to familial vulnerability to ADHD.11 In a second study, we used this observation to directly investigate the effect of genotype on frontostriatal measures. Here, dopamine transporter (DAT1) genotype effects were found on striatal activity for individuals at familial risk for ADHD (affected and unaffected siblings), but not controls, implicating this region in translating familial risk into a neurobiological substrate.12a We found similar evidence of ADHD candidate gene effects on frontostriatal regions using anatomical MRI.12 Here, DAT1 genotype affected caudate volume, whereas a much-studied polymorphism in the dopamine-4 receptor gene affected prefrontal gray matter volume.

The cerebellum has been increasingly implicated in ADHD, both in morphological studies and in studies of time estimation.13-22 To date, two studies have suggested indirectly that the cerebellum may be less sensitive to familial risk for ADHD than frontostriatal areas. In a study of effects of familial risk on brain anatomy, we found that, whereas cortical gray matter was decreased in both boys with ADHD and their unaffected siblings, a reduction in cerebellar volume was only present in siblings with ADHD but not their unaffected counterparts.17 Furthermore, in our study of DAT1 gene effects on brain activation, the only other region where activity was influenced by genotype was the cerebellar vermis. There was no interaction between genotype and familial risk, suggesting that this effect is independent of familial risk for ADHD.12a Taken together, these results suggest that deficits in the cerebellum may be related more to the ADHD phenotype than to a familial risk for the disorder.

Recently, we investigated the effects of ADHD on frontocerebellar and frontostriatal regions during expectancy violation.23 Subjects with ADHD showed diminished activation in cerebellum during violations of stimulus timing and diminished ventral prefrontal cortex and anterior cingulated activity to violations in stimulus timing and identity. In the present study, we investigated whether cerebellar systems are sensitive to the familial risk for ADHD in certain contexts, in addition to frontostriatal circuits. Subjects with ADHD, their unaffected siblings and matched, typically developing control subjects participated in a functional MRI study, using a variation of a go/no-go paradigm where the predictability of stimulus type and stimulus timing was manipulated: expected and unexpected events (go and no-go trials) were presented at expected or unexpected times. We hypothesized that prefrontal regions would be sensitive to familial vulnerability for ADHD, as previously shown.11 Both subjects with ADHD and their unaffected siblings were hypothesized to show less activation in prefrontal regions less during violations of stimulus type. In contrast, we hypothesized that the cerebellum would not show sensitivity to familial vulnerability to ADHD. We expected unaffected siblings to show activation similar to that of controls to violations of stimulus timing in contrast to the diminished activation in the cerebellum of subjects with ADHD.23
METHODS

Participants

A total of 36 male children and adolescents participated in the present study. Demographic information is listed in Table 1. Controls were matched to subjects with ADHD and their unaffected siblings for age, sex, IQ, hand preference, and socioeconomic status, operationalized as the number of years of parental schooling.

Subjects were recruited through the Department of Child and Adolescent Psychiatry at the University Medical Center Utrecht in the Netherlands (sibling pairs) and local schools (controls). Twelve male children and adolescents with ADHD, their unaffected full siblings, and 12 matched, typically developing control subjects were included. Eight of 36 subjects had previously participated in another functional MRI study at our laboratory (four subjects with ADHD and their unaffected counterparts). Furthermore, data for 24 subjects (12 subjects with ADHD and 12 controls) were also included in the previous study in which we investigated the effects of expectancy violations in two samples of subjects with and without ADHD. In the present study, data from discordant siblings of subjects with ADHD were included to investigate the familial effects of ADHD on the cerebellum. Subjects with major physical or neurological illness, learning disabilities, or IQ <70 were excluded. Neurological illness and learning disabilities were assessed based on report from the primary clinician, chart review, and parental report. All of the subjects participated in a standardized IQ assessment using the WISC-III or WISC-Revised, and a parent participated in a semistructured interview session to confirm or disconfirm clinical psychiatric diagnosis using the Diagnostic Interview Schedule for Children (DISC-P). A full DISC interview was administered for all subjects. ADHD subjects were required to have received a clinical diagnosis of ADHD from our department and to meet DSM-IV criteria for ADHD, as assessed by DISC interview. Furthermore, they were required to have no comorbid disorders other than oppositional defiant disorder. Siblings and control subjects were excluded if they met DSM-IV criteria for any psychiatric diagnosis, as assessed by DISC interview. In addition, Child Behavior Checklist scores were obtained to ascertain the presence of ADHD-related symptoms in siblings and control subjects.

Subjects on short-acting medication for ADHD discontinued treatment for a minimum of 24 hours before the scan. After a full description of the study, informed assent/consent was obtained from all of the subjects and their parents before study participation commenced. Before the MRI scan, participants were acclimated to the scanning environment using an MRI simulator located in our laboratory. All of the procedures were conducted in accordance with guidelines established by the Dutch Central Committee on Research involving Human Subjects.

Behavioral Paradigm

Subjects were asked to perform a visual target detection task by pressing a single response button with their right index finger whenever a target stimulus was presented. The task was a variation of a go/no-go task, in which the temporal predictability of events was manipulated, in addition to the predictability of the type of the stimulus (i.e., no-go versus go-stimuli). Two subjects with ADHD and their unaffected siblings and three control subjects performed a slightly different version of the task, without trials at unexpected times. Therefore, analyses of the timing manipulation include 10 subjects with ADHD, 10 unaffected siblings, and 9 control subjects. Group effects were comparable for both versions of the task. The task was designed to build up the expectancy of an event occurring (the frequent and predictable go-trial). Subjects were required to adjust their behavior when that prediction was violated (i.e., inhibit a prepotent button press on no-go trials or press the button at an unexpected time on unpredictable go trials). The task was presented in the context of a computer game, where subjects were asked to “help feed a hungry little mouse as much cheese as possible.” The target stimulus was a cartoon drawing of a piece of cheese, whereas the unexpected stimulus was a cartoon drawing of a cat. During the interstimulus interval, a mouse hole remained on the screen, briefly opening to reveal one of the experimental stimuli in a continuous stream of trials.
The task involved five blocks of 72 trials (360 trials total). On the majority of trials (67% of 360 = 240 trials), the target stimulus (cheese) was presented at the expected time (every 4 seconds). On the remainder of the trials (33% of 360 = 120 trials), unpredictable trials (30 of each type) were presented: an unexpected stimulus at the expected time (cheese at 2 seconds; temporally unpredictable go-trial); an unexpected target stimulus at an unexpected time (cheese at 2 seconds; temporally unpredictable go-trial); and an unexpected stimulus at the unexpected time (cheese at 2 seconds; temporally unpredictable no-go trial). A fourth unpredictable trial type, in which no stimulus was presented at the predictable time (a nontrial) was also included to help prevent subjects learning any pattern other than that of the predictable go trials. Trial types were mixed pseudorandomly in equal numbers throughout each block. The stimuli were presented for 500 milliseconds, with an interstimulus interval of either 1500 or 3500 milliseconds.

### Analysis of Behavioral Data
All of the behavioral data were analyzed using the SPSS statistical package (version 14.0, SPSS Inc., Chicago). Accuracy scores were calculated as the percentage of hits to targets (predictable and unpredictable go trials) and correct omissions to nontargets (no-go trials) relative to the total number of trials of each type. Mean reaction times were calculated for the condition for which a response was required (i.e., expected stimulus at the expected or unexpected time). Differences between groups were investigated using analysis of variance techniques with post hoc t tests, using Tukey’s honestly significant difference test.

#### Image Acquisition
MR images were acquired on a 1.5-T Philips Allegra MR scanner (Philips Medical Systems, Best, the Netherlands). Functional MRI scans consisted of a navigated three-dimensional PRESTO pulse sequence (TE [echo time] 11 milliseconds, TR [recovery time] 21.74 milliseconds, flip angle 9.0°, matrix 64 × 64 × 36, FOV [field of view] 256 × 256 × 144 mm, voxel size 4 mm isotropic, and scan duration 2.0 seconds per 36-slice volume), covering the whole brain. Anatomical T1-weighted three-dimensional fast field echo scans with 170 1.2-mm contiguous coronal slices of the whole head (TE 4.6 milliseconds, TR 30 milliseconds, flip angle 30 degrees, FOV 256 mm, in-plane voxel size 1 × 1 mm) were also acquired. An FA30 scan with contrast more similar to the T1-weighted scans was also acquired to aid in the alignment of PRESTO images to the template (TE 11 milliseconds, TR 1.74 milliseconds, flip angle 30 degrees, matrix 64 × 64 × 36, FOV 256 × 256 × 144 mm, voxel size 4 mm isotropic).

#### Image Analysis
Data were analyzed using a random effects model in Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London). For the analyses, functional MR images were realigned and normalized to a standard stereotactic space (Montreal Neurological Institute template). Estimated motion parameters were examined on a subject-by-subject basis to ensure that the amount of motion did not exceed the size of one voxel.

At the first level, six event types were defined (expected and unexpected stimuli at expected and unexpected times, the omission of an event and incorrect trials). These included four effects of interest (correct trials for expected and unexpected stimuli at expected and unexpected times). Events were time-locked to the stimulus by a canonical synthetic hemodynamic response function and its first-order temporal derivative. At the second level, three separate analyses were conducted. Only correct trials were included in the analyses.

First, one-sample t tests were performed for control subjects. Three conditions of interest were investigated, all of which compared unpredictable events that required subjects to adapt their behavior to predictable events (expected stimulus at unexpected time [temporally unpredictable go trial]; unexpected stimulus at expected time [temporally predictable no-go trial]; unexpected stimulus at unexpected time [temporally unpredictable no-go trial]). An uncorrected threshold of p < .005, with a minimum extent of 10 voxels was used in each case. This analysis was conducted to allow the definition of functional regions of interest (ROIs) for comparisons with other groups.

Second, an ROI analysis was performed to investigate differences between controls, subjects with ADHD, and unaffected siblings in regions of a priori interest. Three regions were functionally defined from one-sample t tests for control subjects (Table 2), using the MarsBaR package: The anterior cingulate gyrus (ACG) and inferior frontal gyrus were defined from the manipulation of the stimulus type and the inferior cerebellum from the manipulation of timing. Subjects who differed in activation level by more than 2 SDs for any ROI were defined as outliers. ROI analyses were performed with and

### TABLE 2

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### Unexpected stimulus, expected time
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*Note: p < .005; minimum extent = 10 voxels; t > 3.36. Bold type indicates regions of a priori interest. MRI = magnetic resonance imaging; IFG = inferior frontal gyrus; R = right; L = left; ACG = anterior cingulate gyrus; MFG = middle frontal gyrus; FG = fusiform gyrus; STG = superior temporal gyrus; LG = lingual gyrus; Med = medial; SFG = superior frontal gyrus; IPL = inferior parietal lobule.*
without one outlier in the ADHD group. For each ROI, signal change per subject was extracted from the Statistical Parametric Mapping software contrast files. Individual average values for ROIs represent intrasubject differences between activation for the condition of interest minus the control condition (expected event at expected time). The SPSS statistical package (version 14.0) was used to analyze between-group differences with analysis of variance techniques and post hoc t tests, using Tukey’s honestly significant difference test. Power analyses were performed to determine the effect size of the observed differences.

Finally, whole-brain differences between subjects with ADHD and controls and siblings without ADHD and controls were investigated using exploratory two-sample t tests for the same three conditions of interest. An uncorrected threshold of $p < .005$, with a minimum extent of 10 voxels was used.28 The results of the whole-brain two-sample t test comparing subjects with ADHD to controls was included in an earlier article23 and is shown again here to allow for a direct comparison to the results for unaffected siblings.

RESULTS

Subjects with ADHD had significantly higher scores on ADHD symptoms compared with their unaffected siblings and matched controls, according to both Child Behavior Checklist scales and the DISC interview. There were no significant differences between unaffected siblings and matched controls (Table 1).

Behavioral Results

Accuracy. There were significant differences between groups in accuracy for manipulations of stimulus type (unexpected stimuli at the expected and unexpected time; $F_{2,33} = 4.51; p = .019$) and for manipulations of timing (expected and unexpected stimuli at the unexpected time; $F_{2,26} = 3.64; p = .04$; Fig. 1). For stimulus manipulations, accuracy was significantly lower for subjects with ADHD than for control subjects ($54 \pm 22\%$ for ADHD, $78 \pm 18\%$ for controls; $p = .026$). Differences between unaffected siblings and control subjects reached trend level ($57 \pm 24\%$ for unaffected siblings; $p = .051$).

For timing manipulations, accuracy was significantly lower for subjects with ADHD than control subjects ($78 \pm 11\%$ for ADHD, $92 \pm 8\%$ for controls; $p = .049$). Differences between unaffected siblings and control subjects reached trend level ($80 \pm 14\%$ for unaffected siblings; $p = .092$). There were no differences in performance between subjects with ADHD and unaffected siblings.

Reaction Time. There were no differences in reaction time between groups ($F < 0.71; p > .5$). All of the subjects were faster for expected than unexpected go trials (459.1 milliseconds versus 533.8 milliseconds; $t_{28} = -13.1; p < .001$).

Functional MRI Results

One-Sample t Tests for Control Subjects. Results for control subjects are summarized in Table 2. Regions in prefrontal cortex, including the inferior frontal gyrus and ACG (extending into superior frontal gyrus), were activated for unexpected stimuli at the expected and unexpected times. Inferior cerebellum was activated for presentations of expected stimuli at the unexpected time. These data were included in a previous study.23

ROI Analysis. Between-group differences in the right inferior frontal gyrus, ACG, and cerebellum were investigated using an ROI approach. ACG activation differed between groups for the manipulation of stimulus type, but not stimulus timing ($F_{2,32} = 3.67; p = .037$; effect size $\eta = .187$ for stimulus type; $F_{2,26} = 1.21; p = .314$; effect size $\eta = .097$ for stimulus timing; Fig. 2). In contrast, activation in the cerebellum differed

![Fig. 1](Accuracy for stimulus and timing manipulations are sensitive to familial risk for attention-deficit/hyperactivity disorder (ADHD). *Significant at $p < .04$.)
between groups for the manipulation of stimulus timing, but not stimulus type ($F_{2,26} = 8.38; \rho = .002; \text{effect size } \eta^2 = .375$ for timing; $F_{2,32} = .856; \rho = .434; \text{effect size } \eta^2 = .098$ for stimulus type; Fig. 2). Differences in IFG did not reach significance for any comparison.

For manipulations of stimulus type, activation in ACG was significantly decreased for subjects with ADHD compared with controls ($-4.37 \pm 1.65; \rho = .032$). When one outlier in the ADHD group was included in the analyses, between-group differences no longer reached significance ($F_{2,32} = 1.42; \rho = .256$). Differences between unaffected siblings and controls and between affected and unaffected siblings did not reach significance.

For manipulations of stimulus timing, activation in the cerebellum was decreased for both subjects with ADHD and their unaffected siblings compared to controls ($-10.51 \pm 2.87; \rho = .003$ for ADHD versus controls and $8.27 \pm 2.80; \rho = .018$ for siblings versus controls). There were no differences between unaffected siblings and the subjects with ADHD.

Two-Sample $t$ Tests. Exploratory, whole-brain $t$ tests were used to investigate differences between groups. For the manipulation of stimulus type, activation in an area in the lateral prefrontal cortex was attenuated for subjects with ADHD compared with control subjects (Talairach: $-36, 47, 9; t = 4.01; df = 22; \rho < .005$; minimum extent = 10 voxels). For siblings, activation in the ACG was attenuated compared with control subjects (Talairach: $24, 25, 32; t = 4.43; df = 22; \rho < .005$; minimum extent = 10 voxels). This effect was not significant for subjects with ADHD, although present at subthreshold
level (Talairach: 20, 21, 32; \(t = 3.49; df = 22; p < .005\); minimum extent = five voxels).

For the manipulation of stimulus timing, activity in the inferior cerebellum was attenuated for subjects with ADHD compared with control subjects (ADHD: Talairach: \(-16, -56, -41; t = 4.50; df = 17; p < .005\); minimum extent = 10 voxels). For unaffected siblings compared with control subjects, decreased activity in the cerebellum did not exceed subthreshold level (siblings: Talairach: 32, -48, -31; \(t = 3.63; df = 17; p < .005\); minimum extent = five voxels).

**DISCUSSION**

In this study, we investigated whether cerebellar systems are sensitive to the familial risk for ADHD in certain contexts in addition to frontostriatal circuits. Behaviorally, we found evidence of effects of familial vulnerability to ADHD on unexpected events and expected events at unexpected times: In both cases, accuracy was decreased for both subjects with ADHD compared with control subjects and intermediate for the unaffected siblings of subjects with ADHD. Functional neuroimaging showed less activity in critical brain areas, associated with both types of unpredictable events for both groups. Furthermore, attenuations in activation were context specific. During stimulus manipulations (no-go trials), both subjects with ADHD and their unaffected siblings showed decreased activity in the ACG and prefrontal areas, whereas during timing manipulations, both groups showed decreased activation in the inferior cerebellum. These results suggest that cerebellar regions are sensitive to familial vulnerability to ADHD in certain contexts, in addition to prefrontal systems.

The finding that the cerebellum was sensitive to familial risk for ADHD was unexpected. Based on earlier findings, we had hypothesized that deficits in the cerebellum would be specific to ADHD because we had found that decreases in the cerebellar volume were only present in siblings with ADHD but not their unaffected counterparts.\(^17\) Furthermore, in a study of DAT1 gene effects on brain activation, there was an interaction between vulnerability to ADHD and genotype for activity in the striatum, but not the cerebellum.\(^12a\)

However, in the present study, we found that activation in the cerebellum was sensitive to familial vulnerability to ADHD in certain contexts because both siblings with and without ADHD showed decreased activation in this region to events at unexpected times.

For controls, the ACG was active for unexpected events (no-go trials) and the cerebellum was active for events at the unexpected time, whereas activity in these regions was decreased for subjects with ADHD. However, we found no evidence of decreased activation in the inferior frontal gyrus for subjects with ADHD, likely related to diminished power to detect differences between groups as a result of fewer no-go trials in comparison to previous studies using go/no-go paradigms (e.g., see Durston et al.\(^11\)).

There are some important limitations to our study. First, although subjects with ADHD were either not taking medication or discontinued treatment 24 hours before undergoing the functional MRI scan, most were not stimulant naive. As such, we cannot rule out that some of the observed changes in brain activation were due to long-term effects of stimulant medication. However, recent evidence suggests that long-term effects of stimulant medication on brain activity patterns are small, if present at all.\(^30,31\) Furthermore, the unaffected siblings in this study had never taken stimulants, suggesting that changes shared by both groups are unlikely to be fully explained by stimulant treatment. Second, as we were careful to include only truly discordant sibling pairs in the study, the sample size is relatively small. With larger groups, statistical power would have been greater and our findings would likely have appeared stronger. As such, we cannot be certain that null findings in the present study are not due to low power. However, effect sizes (0.19–0.38) in ROIs (ACG and cerebellum) suggest that these findings are fairly robust. Certainly, in a previous study that included both subjects with ADHD and controls from this study, as well as an independent sample, differences between controls and ADHD were found in both these regions in both samples.\(^23\) Third, we used group averages rather than investigated differences at an individual level. As such, we cannot rule out that differences in activation between groups could be related to increased anatomical variability in the ADHD and unaffected sibling samples rather than functional differences. Finally, here we investigated full siblings of individuals with ADHD. Because the familial relatedness is similar (approximately 50%) for all of the sibling pairs in this study, we cannot estimate the heritability of phenotypic measures based on these individuals.
data. Future studies including both monozygotic and dizygotic twins will be better able to address this issue.

In sum, the present study suggests that activity in both the prefrontal cortex and cerebellum is sensitive to familial vulnerability to ADHD. Accuracy was lower for unexpected events (no-go trials) and expected events at unexpected times for subjects with ADHD compared with control subjects and intermediate for their unaffected siblings. Furthermore, unaffected siblings of individuals with ADHD showed decreased activity in prefrontal areas for unexpected events and in cerebellum for events at unexpected times, similar to their affected counterparts.

Disclosure: Dr. Eke van den Ban is on the advisory board of Eli Lilly Pharmaceuticals. The other authors report no conflicts of interest.

REFERENCES