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Functional MR to Localize Sustained Visual Attention Activation in Patients with Attention Deficit Hyperactivity Disorder: A Pilot Study

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PURPOSE: To evaluate brain cortical activation in patients with attention deficit hyperactivity disorder (ADHD) and to provide an initial comparison between activated regions in ADHD subjects and those previously localized in an unaffected population. **METHODS:** Ten patients with ADHD underwent imaging with a functional blood oxygen level–dependent MR technique during sustained visual vigilance. Pixel activation was inspected visually and statistical group analysis was performed. **RESULTS:** Activation was seen over the bilateral middle frontal gyri, the superior parietal lobules, and the inferior parietal lobules. The predominant activity occurred in the right middle frontal gyrus. Application of an additional statistical constraint revealed significant activity in the right inferior and left superior parietal lobules. **CONCLUSION:** ADHD patients effectively tolerated the necessary MR imaging constraints despite their difficulty with confinement and immobility. Single-section functional MR imaging revealed activation in brain regions known to be involved in the maintenance of attention in healthy subjects responding to auditory, tactile, or visual stimulation; additional areas of activity that were identified may represent true abnormal regions in the affected population or artifacts.

Index terms: Brain, magnetic resonance; Magnetic resonance, functional

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Attention deficit hyperactivity disorder (ADHD) is prevalent in 3% to 9% of children; it is often diagnosed in early childhood, with functional disturbances initially evident during the school years (1). Similar difficulties frequently persist through adolescence and into adulthood. Patients report easy distractibility, failure to complete tasks, and a sense of restlessness. In particular, they can be expected to have detectable trouble maintaining focus relative to unaffected persons. Empirically, many patients respond to pharmacologic stimulant therapy with improved function (2). ADHD patients thus represent an intriguing group for observation of cortical activation during tests of attention. As no underlying neurologic mechanism has been identified to explain this disorder, evaluation of cortical activity offers potential insight into the involved areas of the brain and the mechanisms of the disorder. Such study may also provide objective methods for patient examination and therapeutic guidance.

Our study was designed to evaluate cortical activation in a population of patients with ADHD. Further, it provides an initial comparison between identified areas of activation in ADHD subjects and those previously distinguished in an unaffected population.

Materials and Methods

Subjects

Ten patients (seven male and three female) ranging in age from 14 to 51 years were included in the study. In all patients, a primary diagnosis of ADHD had been made by

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psychiatrists and psychologists specializing in evaluation and treatment of that disorder. Diagnostic criteria for ADHD as established by the *Diagnostic and Statistical Manual of Mental Disorders–IV* were applied, meaning that six of nine symptoms of maladaptive inattention or hyperactivity-impulsivity were present without other identifiable psychosis or mood disorder. The presence of some symptoms before the age of 7 was necessary. Subtypes of ADHD were not specified. Magnetic resonance (MR) imaging was performed before the start of pharmacologic therapy. Patients were excluded if they had received any previous medication for this disorder. All patients volunteered and gave written informed consent to undergo investigational imaging. No sedation was used.

Functional MR Imaging

Studies were performed on a standard 1. 5-T unit capable of 10 mT/m gradients using a technique reported previously (3). The patient's head was positioned centrally within a circularly polarized head coil and fixed with padding. The forehead was additionally fixed with tape to maximize the subject's awareness of small movements in an attempt to minimize voluntary head motion.

Three-dimensional imaging data of the patient's head were then generated to allow anatomic correlation. Sagittal 3-D Fourier transform (3DFT) fast low-angle shot (FLASH) images were obtained with parameters of 17/6/1 (repetition time/echo time/excitation), a 20° flip angle, a 256 × 192 matrix, a 256-mm field of view, and a 128-mm slab with 64 partitions. A midsagittal reconstruction was used to delineate a line connecting the superior third of the anterior commissure with the inferior third of the posterior commissure (the AC-PC line). This line was then used to align construction of a proportional coordinate grid system for comparative stereotactic division of brain parenchyma (4). An axial T1-weighted standard spin-echo image was obtained at the anatomic level of functional acquisition.

Functional blood oxygen level–dependent imaging was then performed with data collection in an axial plane parallel and 40 mm (±4) superior to the AC-PC line (3, 5). A two-dimensional Fourier transform (2DFT) FLASH sequence (67/40/1, 25° flip angle, 128 × 128 matrix, 256-mm field of view, 8.6 seconds acquisition time) was used. An initial dummy set of 10 iterations at rest were run and then discarded to achieve steady-state equilibrium of magnetization and to acclimate the subject to the noise from the gradient generation. Subsequent paired sets of 10 iterations each were run. The first control set of 10 images ran with the patient at rest and was immediately followed by a second stimulation set of 10 with the patient performing a task. Up to three repeat image sets were obtained if obvious motion degradation was observed. Rest was defined as a relaxed patient with eyes closed. The task required sustained visual vigilance on a dim 5-mm spot of light projected to a screen hung over the opening of the magnet bore. The light emanated as a computer-generated image that was then rear-projected through a video projector to the screen. The screen could be seen easily by means of an angled mirror positioned onto the head coil above the subject's eyes. The task included momentary dimming of the spot for 1 second at random intervals and for a random number of times (range, 4 to 40) over the course of each data set. Subjects were requested to concentrate on the light in order to accurately observe the number of times it dimmed during the task. Count accuracy was variably checked by verbal communication with the patient. This was not done uniformly, as jaw motion encouraged head motion. As such, no correlations with count accuracy were attempted.

Image Processing

An initial image subtraction was performed. For each pair of data sets, the mean pixel intensities from the 10 images at rest were subtracted from the mean pixel intensities during the task for each coordinate. Subtracted images were then reviewed for motion degradation. Images were motion corrected by interpolation with a translational and rotational subvoxel reregistration (6). No correction for motion into or out of the axial plane was attempted. For complete analysis, a one-tailed nonparametric Mann-Whitney test was applied to compare each pixel location between rest and task (3). Pixels with statistically significant change at the $P = .05$ or greater level were considered activated. For visual inspection, a centroid linkage algorithm was then applied to identify activated pixels with a minimum of seven contiguous activated neighboring pixels (3). Activated pixels without such directly opposed activation were no longer displayed. Pixels fulfilling the algorithm criteria were then superimposed on the corresponding axial anatomic section and displayed as cluster images. These were then used to guide a semiautomated segmentation algorithm for removal of extradural structures and obvious superficial cortical veins. Postsegmentation cluster images were used for manual scoring of anatomic areas with activation.

Group Analysis

Data for this patient cohort were grouped for further evaluation. For each patient, a single rest/task experiment was selected that represented the fewest motion artifacts and the clearest clustering of activation over brain parenchyma. Analysis was then directed toward data within boxes defined by the Talairach grid system registered to the anatomic images. The grid was again modified to present uniform box size by splitting the distance between the anterior and posterior commissures into only two divisions, and only using the 38 boxes previously seen to include at least 70% brain parenchyma (3). Each box was assigned a score based on the proportion of activated pixels within it, for the entire cohort, and those scores were then normalized to the number of pixels within the head. The normalized scores for each box were then compared with the grand mean of all boxes in all subjects through analysis of variance (ANOVA). Statistical significance was assigned to any box with relatively increased activation

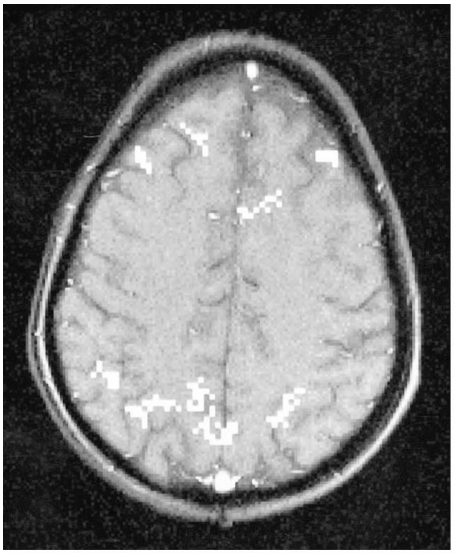
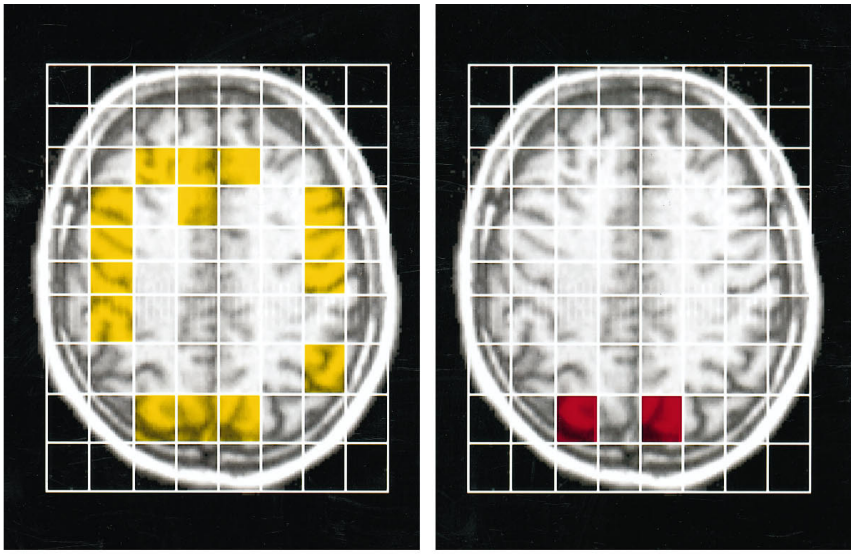


Fig 1. Representative image for visual analysis is a T1-weighted axial section 40 mm superior to the commissural line from an ADHD patient. Pixels from the same patient defined as activated and following a cluster analysis are superimposed.



A B

Fig 2. Group analysis summation. A representative T1-weighted axial image with superimposed Talairach grid is shown.

A, Boxes shaded in yellow are those in which pixel activation was greater than the grand mean.

B, Boxes shaded in red are those with activation significantly different from the whole by ANOVA testing.

over the grand mean with a *P* value of less than .05. Boxes with activation above the grand mean were tallied and compared with those identified in a healthy population and obtained with similar techniques (3).

Results

All patients with newly diagnosed ADHD who agreed to imaging were able to complete the study before the start of their therapy. The total scan time was approximately 1 hour for each patient.

Figure 1 shows an example of a cluster image used to guide segmentation and visual analyses. The Table shows activation within indicated compartments as identified by visual inspection. Activity was seen bilaterally in the frontal and parietal cortex, including the superior and middle frontal gyri, as well as in the superior and inferior parietal lobules. Occasional activity was noted in the precentral or postcentral gyri, while the predominate activity was in the right middle frontal gyrus. Figure 2 shows the Talairach grid as applied here and the results of statistical evaluation. Activation greater than the grand mean was seen over the bilateral middle frontal gyri, the superior parietal lobules, and the inferior parietal lobules. Application of an additional statistical constraint revealed activity in the right inferior and left superior parietal lobules.

Activation within compartments as indicated by visual inspection

Location	Percentage of Subjects with Activation	
	Right	Left
Superior frontal gyrus	30	10
Middle frontal gyrus	80	50
Precentral gyrus	20	10
Postcentral gyrus	20	0
Superior parietal lobule	50	40
Inferior parietal lobule	50	50

Note.—Data are inclusive of all repetitions and of all section positions obtained (36 to 44 mm superior to the AC-PC line). No additional weighting is given for degree of activity in an area.

Discussion

Our study showed cortical activation predominantly in the right middle frontal gyrus during sustained visual vigilance in patients with ADHD. Additional, less dominant activation was seen in the left middle frontal gyrus and in bilateral superior and inferior parietal lobules. Two methods for postprocessing pixel activation were used for analysis. In the first, a linkage algorithm was applied to detect areas in which activated pixels occurred in clusters. Given the known close physical approximation of functionally related neurons in human brain archi-

tecture, one would anticipate that activation would occur in such clusters rather than in widely dispersed patterns. In the latter technique, a Talairach grid was applied to generate a standard coordinate space and to delineate groups of activated pixels contained within the grid boxes. This permitted comparison of activation among the boxes in the ADHD cohort and among boxes at the same position between the ADHD and unaffected cohorts. The identified areas have previously been noted during performance of a similar task in healthy subjects both with positron emission tomography (PET) (5) and with functional MR imaging (3). Identification of these areas supports the reproducibility of MR studies in the localization of functional cortical activity and its potential application to the study of psychiatric disorders.

Because patients with ADHD frequently have difficulty sitting still, let alone remaining within a head coil within a magnet bore for upward of 1 hour, their success in tolerating the constraints of MR imaging was notable. This suggests that functional MR imaging may well be a plausible tool for continued study of cortical activation patterns in such patients on a clinical 1.5-T system. It is hoped that such evaluation will serve to help identify parenchymal areas involved in ADHD, allowing more objective assessment of these patients and of the effects of different therapeutic approaches.

Previous imaging studies of ADHD patients have focused on volumetric analysis of brain or on global perfusion. The volumetric analyses focused on the corpus callosum (7–9) or basal ganglia (10, 11), areas not included in the sections selected for this work. The mild right-sided dominance of frontal activation seen here partially correlates with the diminished metabolism seen on the left in previous investigations of global perfusion. Studies using single-photon emission tomography of the brain with a perfusion tracer have shown a relative decrease in activity in the left frontal and parietal regions (12). PET studies with fludeoxyglucose F 18 (FDG) performed during an auditory attention task showed a global decrease in metabolism in adults with ADHD and a regional decrease principally involving the left premotor and superior prefrontal cortices (13). Similar techniques applied to teenagers with ADHD showed no apparent difference in global metabolism; however, the left anterior frontal cortex again displayed diminished metabolism (14). Further, consistent identification of activity in the right middle frontal gyrus during visual attention tasks corresponds with earlier FDG-PET findings in which increased metabolism was seen in the right middle prefrontal cortex during auditory discrimination tasks (15). This suggests localization of generic attention pathways to this region. Finally, the degree of metabolism was directly related to the success of discrimination, suggesting a functional role for this area in sustaining attention (15).

A comparison can be made between the results obtained here and those reported in an unmatched cohort of unaffected subjects (3). Several anatomic boxes with activity greater than the grand mean in the ADHD subjects were not seen in the data from the unaffected subjects. These were in the right middle frontal, left middle frontal, left precentral, and left inferior parietal areas. These areas may represent true additional loci of activation in the ADHD population and may relate to the mechanism of the disorder, or to attempted compensation for it. Alternatively, these areas may represent a variety of false-positive artifacts, most frequently, motion effects (16). Clarification must await study of larger cohorts with improved motion control paradigms. Of interest, the current results also showed an even greater number of boxes with concordant areas of activation between the two cohorts using the same attention task and functional MR acquisition. Activation was seen bilaterally in the middle frontal gyri as well as in bilateral superior parietal and right inferior parietal lobules, with overall dominance in the right middle frontal gyri. Thus, given the sample size and the described variability, the observed cortical activation between the two populations appears more similar than different.

Caution should be maintained when attempting to generalize these results, as they were derived from a relatively small sampling and represent only an initial indication of cortical activation in ADHD patients. For example, a comparison of visual tabulation and statistical grouping showed some variation. Visual analysis showed activation in most patients in the right middle frontal gyri (Table), and grouped data analysis revealed concordant activity above the grand mean in many of the boxes over that region (Fig 2A). However, application of an additional statistical constraint failed to identify an anatomic box within this area of highly significant activity (Fig 2B). This appar-

ent discordance most likely resulted from spatial variation in the exact position of the right middle frontal gyrus among these patients that was not adequately compensated for by application of the Talairach grid system. Similarly, although significant activation was identified in the left superior parietal lobule in the group analysis (Fig 2B), only a large minority of patients was noted to have activation there after visual review (Table). This may reflect a nearly exact positional superimposition among that minority. Additional studies with a larger population should clarify such discrepancies.

Functional MR imaging and the task paradigm applied here have some limitations. This study ultimately relied on the initial PET studies done by Pardo et al (5) to identify a region of brain for selection of axial sections. Given the complexity of brain function, a more optimal MR technique would allow data collection from the whole brain. Echo-planar acquisition may permit this and can then be used for more global localization. Further, although this task of visual vigilance allowed comparison with previous work, it may not be ideal for identifying ADHD patients. Although these patients appeared similar to unaffected subjects in terms of cortical activation, each was sufficiently dysfunctional to have sought professional help; furthermore, they met diagnostic criteria, were judged to warrant intervention by their psychologists and psychiatrists, and began medical therapy within days after imaging. Conceivably, then, the task was too simple and subjects managed temporarily to overcome their deficit. A more complex test specifically designed to better discriminate ADHD will be necessary. Such complex multitask attention paradigms will require whole-brain image acquisition.

In summary, we have presented a preliminary view of a small ADHD cohort studied with functional MR imaging at a single-section position with the use of basic motion correction. Our findings showed activation in brain regions known to be involved in the maintenance of human attention in many studies of healthy subjects during auditory, tactile, or visual stimulation. Additional areas of activity were also identified, which may represent true abnormal regions in the affected population or artifacts. Further work will require a larger cohort, whole-brain imaging, and better motion controls to distinguish among these possibilities.

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