ORIGINAL ARTICLE

Functional Brain Electrical Activity Mapping in Boys With Attention-Deficit/Hyperactivity Disorder

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Background: Symptoms of attention-deficit/hyperactivity disorder (ADHD) have been associated with frontal lobe deficits. We used a novel brain electrical imaging method to investigate rapid and continuous changes in brain activity during the continuous performance task (CPT) in normal boys and in boys with ADHD. The amplitude and latency topography of the steady-state visually evoked potential (SSVEP) were examined while subjects performed the "X" version of the CPT (CPT-X; the reference task) and the "A-X" version of the CPT (CPT-AX).

Methods: Seventeen boys meeting *DSM-III-R* criteria for ADHD and 17 age-matched controls participated in the study. Brain electrical activity was recorded from 64 scalp sites. During the reference task, subjects pressed a microswitch on the unpredictable appearance of the letter X. During the CPT-AX, subjects were required to press the microswitch on the appearance of the letter X only if an A had preceded it.

Results: In the interval between the appearances of the A and the X of the correct trials of the CPT-AX, control boys showed transient reductions in SSVEP latency at right prefrontal sites. By contrast, boys with ADHD showed no change or an increase in prefrontal SSVEP latency at right prefrontal sites.

Conclusion: Our results suggest increased speed of prefrontal neural processing in children without ADHD following a priming stimulus, and a deficit in such processes in children with ADHD.

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ATTENTION-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed psychiatric conditions of childhood, with an estimated incidence of 3% to 6%.[1] Attention-deficit/hyperactivity disorder is characterized by developmentally inappropriate levels of inattentiveness, impulsivity, and overactivity. Neuropsychological findings suggest that a failure to inhibit motor responses may constitute the primary deficit in ADHD.[2] Such findings have been interpreted in terms of prefrontal lobe deficits.[3-5]

Functional brain imaging studies have also pointed to prefrontal lobe abnormalities. Single photon emission computed tomographic studies in ADHD have demonstrated hypoperfusion of the central frontal lobes and caudate nucleus and reduced prefrontal blood flow in response to cognitive tasks.[6-8] In a positron emission tomographic (PET) study of adults with a history of ADHD, Zametkin et al[9] reported reduced increases in premotor and sensorimotor glucose metabolism when subjects performed an auditory continuous performance task (CPT). However, a subsequent study of teenagers with ADHD failed to statistically differentiate the ADHD group from the control group.[10]

Some of the disparate PET neuroimaging findings could be the result of several factors, such as small population size and different cognitive activation tasks, but one important feature could be the poor temporal resolution of the brain imaging methods used. ^{18}F-fluoro-2-deoxy-D-glucose PET has a temporal resolution of 40 minutes typically, while oxygen 15–labeled water enables a resolution of approximately 60 seconds.[11,12] By contrast, a cognitive activation task may make demands on compromised cortical regions for only certain brief intervals. Thus, PET imaging may only yield an averaged representation of cortical activity that may grossly underestimate important regional changes of a transient nature.

In evoked potential studies of ADHD, normal control subjects have demonstrated evoked potential differences between attended and nonattended stimuli,

SUBJECTS AND METHODS

The study was approved by the Human Experimentation Ethics Committee of Swinburne University of Technology, Melbourne, Australia, and by the Australian National Health and Medical Research Council Twin Registry. For each individual subject, informed consent was obtained from a parent.

SUBJECTS

All subjects who participated in this study were male, right-handed as assessed using the Edinburgh Inventory,[19] and had a full-scale IQ of at least 80 as estimated with the Wechsler Intelligence Scale for Children–Third Edition[20] using the Block Design and Vocabulary short form as recommended by Sattler.[21] Seventeen boys with ADHD (mean age, 129 months; age range, 88-168 months; mean IQ, 96; IQ range, 80-115) were diagnosed as having ADHD by pediatricians and met *DSM-III-R* criteria[22] for ADHD according to maternal and/or teacher reports obtained using the Australian Twin Behaviour Rating Scale (ATBRS).[23,24] Comorbidity with disruptive behavior and learning disorders was also assessed by the ATBRS. Twelve boys with ADHD (71%) met criteria for oppositional defiant disorder, 6 (35%) met criteria for conduct disorder, and 15 (88%) had a history of learning difficulties. The 15 subjects with ADHD who were being treated with stimulant medication remained medication free for at least 24 hours before their brain electrical activity recording. Seventeen healthy control subjects (mean age, 132 months; age range, 104-159 months; mean IQ, 111; IQ range, 88-152) were rated free of ADHD, disruptive behaviors, and learning difficulties according to maternal and teacher reports obtained using the ATBRS.

COGNITIVE TASKS

All subjects first performed a low-demand visual vigilance task, followed by the CPT-X (reference task) and the CPT-AX. In the reference task, subjects were required to press a microswitch on the unpredictable appearance of an X, while in the CPT-AX they were required to respond on the unpredictable appearance of an X that had been preceded by an A. In all tasks, the letters remained on the screen for 2 seconds and were followed by a blank screen for 1.5 seconds. The ratio of targets to nontargets was 1:4 and the task duration was 280 seconds. Reaction time was recorded to an accuracy of 1 millisecond. For all tasks, a correct response to a target was defined as one that occurred no less than 100 milliseconds and no more than 1.5 seconds after the appearance of the target (X or X preceded by an A). Any responses outside the "correct" time intervals were defined as errors of commission, or false alarms, while failure to respond in the correct interval was defined as an error of omission.

STIMULUS

The cognitive tasks were presented on a computer monitor. Each letter subtended a horizontal and vertical angle of approximately 1.0° when viewed by subjects from a fixed distance of 1.3 m. The stimulus used to evoke the SSVEP was a spatially diffuse 13-Hz sinusoidal flicker subtending a horizontal angle of 160° and a vertical angle of 90°, which was superimposed on the visual fields. This flicker was present throughout the task and special goggles enabled subjects to view the cognitive task and the sinusoidal flicker simultaneously.[25]

RECORDING

Brain electrical activity was recorded from 64 scalp sites that included all international 10-20 positions, with additional sites located midway between 10-20 locations. The specific locations of the recording sites have been previously described.[25] The average potential of both earlobes served as a reference and a nose electrode served as a ground. Brain electrical activity was amplified and bandpass filtered (3 dB down at 0.1 Hz and 30 Hz) before digitization to 12-bit accuracy at a rate of 200 Hz.

SIGNAL PROCESSING

The major features of the signal processing have been described.[25,26] Briefly, the SSVEP was determined from the 13-Hz Fourier coefficients evaluated over 10 stimulus cycles at the stimulus frequency of 13 Hz, thus yielding a temporal resolution of 0.77 seconds. The 10-cycle evaluation period was shifted 1 stimulus cycle and the coefficients were recalculated for this overlapping period. This process was continued until the entire 280 seconds of activity was analyzed. An identical procedure was applied to data recorded from all 64 recording sites.

whereas subjects with ADHD show smaller or nonsignificant evoked potential differences.[13] While evoked potential findings point to deficits in a range of attentional mechanisms in ADHD, it is more difficult to determine the neurophysiological and neuroanatomical substrates of the disorder from evoked potential recordings alone.

Previous work by 1 of us (R.B.S.) suggests that steady-state probe topography, a novel method using the steady-state visually evoked potential (SSVEP), offers the opportunity of high temporal resolution analysis of brain electrical correlates of extended tasks coupled with noise resistance.[14,15] We have reported strong cognitive task effects on the SSVEP when the eliciting stimulus comprises a uniform visual flicker superimposed on the computer monitor used to present the cognitive task. Increases in visual vigilance, for example, were associated with SSVEP amplitude reductions at occipitoparietal sites while a planning task yielded SSVEP amplitude reductions at prefrontal sites.[15] Findings yielded by this technique appear analogous to the regional reductions in alpha activity associated with cognitive tasks.[16] Such transient reductions in alpha activity have been used as indicators of increased regional activity,[16] and the corresponding reductions in SSVEP amplitude may also indicate increased regional activity.

In a steady-state probe topographic study of the A-X version of the CPT (CPT-AX), where subjects are required to make a response on the unpredictable appearance of the letter X if preceded by the letter A, it was found that the appearances of the A and X were as-

To assess the changes in the SSVEP associated with different components of the cognitive tasks, the following procedure was used. Ten-second epochs of SSVEP real and imaginary components centered on the appearance of a target were averaged, for all correct responses to the targets in both the reference task and CPT-AX. These complex time series were then averaged across the subject pool. The complex SSVEP time series was then expressed in terms of SSVEP amplitude and the phase difference between the visual sinusoidal stimulus and the SSVEP. Variations in the phase were expressed in terms of latency variations.

ARTIFACT DETECTION AND COMPENSATION

A specific advantage of the SSVEP is its relative noise and artifact insensitivity.[14] This is of special importance in a patient population with compromised impulse control and a limited ability to comply with the constraints of brain electrical activity recording. The electroencephalogram and SSVEP time series were subjected to several tests to ascertain whether the artifact levels had exceeded a predetermined threshold level. These tests have been described previously.[26]

STATISTICAL ANALYSES AND TOPOGRAPHIC MAPPING

Topographic maps of the difference between the mean values of amplitude and latency for correct responses in the reference task (CPT-X), and the time series for correct responses centered on the appearance of the target X in the A-X sequence of the CPT-AX, were produced using a spherical spline interpolation procedure.[27]

Statistical parametric mapping based on a multivariate permutation test using the Hotelling T^2 statistic was used to illustrate the topography of the statistical strength of the effect. The use of multivariate permutation tests to evaluate differences in event-related potential topography was first suggested by Blair and Karniski.[28,29] With the availability of inexpensive and powerful computers, these have become increasingly popular in the field of functional brain imaging as they are distribution free, require no assumptions about the underlying correlation structure of the data, and produce exact *P* values for any number of subjects and observations (time points and electrodes).[30]

In this study, a multivariate permutation test based on the Hotelling T^2 statistic was used to estimate the probability of falsely rejecting the null hypothesis (type I error) associated with task differences in the SSVEP amplitude and phase. Specifically, the multivariate permutation test was used to compare the SSVEP observed during the reference task with that of the CPT-AX. These tests were conducted at 3 points during the CPT-AX: at the appearance of the A, the disappearance of the A, and the appearance of the X. Thus, for each population, 192 (64 recording sites by 3 time points) null hypotheses were tested. It should be noted that the multivariate permutation test explicitly takes into account the correlation between SSVEP values at different recording sites and points in time and thus yields exact *P* values corrected for multiple comparisons.[30,31]

IQ SUBMATCHING

A Mann-Whitney *U* test was performed to compare IQ scores for the 2 groups. As the mean IQ of the ADHD group was significantly lower than that of the control group ($U_{17,17} = 72.5$; $P < .05$), we selected 2 subgroups of matched mean IQ that included all subjects with estimated IQs in the "average" range of 85 to 115 (control subgroup: mean IQ = 102, SD = 9.0, n = 12; ADHD subgroup: mean IQ = 99, SD = 8.6, n = 15; $U_{12,15} = 72.5$; $P > .3$) to determine whether the effects apparent in the entire groups persisted in the IQ-matched subgroups. The following procedure was adopted. The SSVEP amplitude and latency differences between the CPT-AX and the mean of the reference task were calculated for the entire control group (n = 17) and the entire ADHD group (n = 17). This procedure was repeated for the IQ-matched control subgroup (n = 12) and the IQ-matched ADHD subgroup (n = 15). This yielded 2 sets of SSVEP waveforms, 1 for the total control and ADHD populations, and 1 for the IQ-matched subgroups. The control group waveforms were subtracted from the ADHD group waveforms for both the entire groups and the IQ-matched subgroups. This yielded 2 sets of group difference waveforms, 1 for the entire group and 1 for the IQ-matched subgroups. The correlation coefficient between the total group difference waveforms and the IQ-matched difference waveforms was evaluated at each of the 64 recording sites.

A high correlation coefficient would mean that the differences apparent in the entire group are also apparent in the IQ-matched subgroups and the SSVEP differences between populations are unlikely to be a consequence of the differences in mean IQ.

sociated with transient reductions in prefrontal SSVEP amplitude and latency.[17]

While the amplitude reduction is consistent with increased regional activity, the latency reductions suggest increased neural information processing speed, possibly due to an increase in the efficiency of interactions between prefrontal neural networks. In light of our previous CPT findings and other studies suggesting CPT performance deficits in ADHD (for a review see Corkum and Siegel[18]), we undertook a steady-state probe topographic study of attentional processes in ADHD using the CPT-X (response on the unpredictable appearance of X) and CPT-AX. We reasoned that, when using the CPT-X as a reference task, the appearance of the A in the CPT-AX would act to prime attentional processes in anticipation of the possible appearance of a target X. We hypothesized that this priming effect would be apparent in the prefrontal region and that subjects with ADHD would demonstrate reduced prefrontal priming that would be most apparent in the interval between the appearances of the A and X.

RESULTS

BEHAVIORAL FINDINGS

Eight 1-way analyses of variance were performed to compare the task performance of the 2 groups (**Table**). The control group demonstrated faster reaction times than the ADHD group, although this difference was

Behavioral Responses for the Reference and CPT-AX Tasks*

	Reference Task				CPT-AX			
	Control (n = 17)	ADHD (n = 17)	$F_{1, 32}$	*P*	Control (n = 17)	ADHD (n = 17)	$F_{1, 32}$	*P*
Mean reaction time, ms	599 (115)	717 (194)	4.68	<.05	529 (119)	583 (153)	1.34	.13
Correct trials	19.9 (0.2)	19.1 (2.5)	1.87	.09	14.7 (0.6)	14.3 (0.9)	2.42	.07
Omission errors	0.1 (0.2)	0.9 (2.5)	1.87	.09	0.2 (0.5)	0.5 (0.8)	1.60	.11
Commission errors	0.5 (0.8)	1.8 (1.9)	6.17	<.01	1.1 (1.1)	2.6 (3.4)	2.91	<.05

*Data are given as mean (SD). CPT-AX indicates the A-X version of the continuous performance task; ADHD, attention-deficit/hyperactivity disorder.

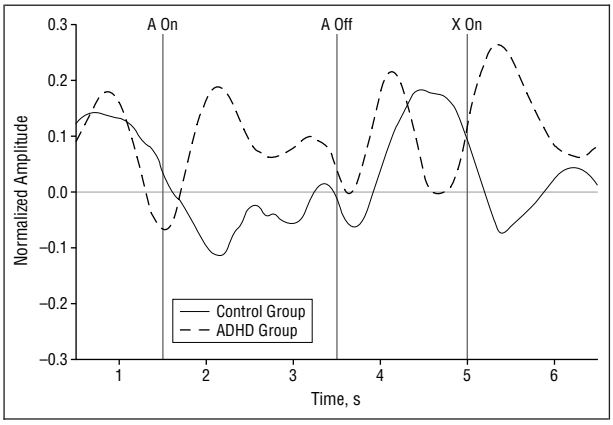

Figure 1. *Steady-state visually evoked potential (SSVEP) amplitude at a central prefrontal site (Fz, electrode 16) during the target sequence in the A-X version of the continuous performance task (CPT-AX) as a function of time in control subjects and subjects with attention-deficit/hyperactivity disorder (ADHD). The dotted horizontal line indicates the mean value of the SSVEP amplitude during the 10-second epoch centered on presentation of the target X in the reference task and is set to zero for both populations.*

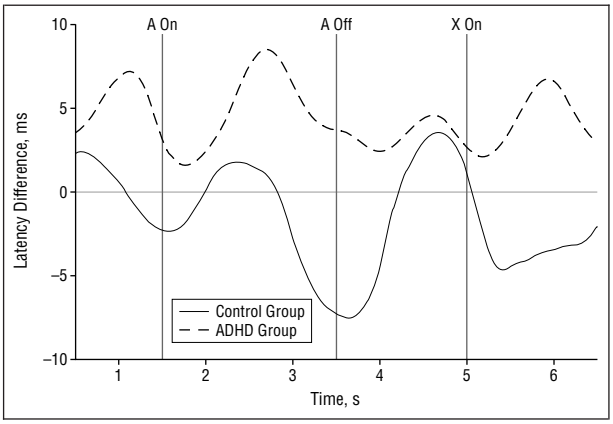

Figure 2. *Changes in steady-state visually evoked potential (SSVEP) latency at electrode 16 (Fz) in the A-X interval in the A-X version of the continuous performance task (CPT-AX), with respect to the mean latency during the reference task, in control subjects and subjects with attention-deficit/hyperactivity disorder (ADHD). The dotted horizontal line indicates the mean SSVEP latency during the 10-second epoch centered on presentation of the target X in the reference task and is set to zero for both populations.*

only significant for the reference task. More correct trials were averaged for the control group than for the ADHD group and the control group made fewer errors of omission than the ADHD group, but these differences were not significant. The ADHD group made significantly more errors of commission in both tasks.

BRAIN ELECTRICAL ACTIVITY

The SSVEP amplitude and latency demonstrated variations that were synchronized with the various components of the CPT-AX.

For controls, the SSVEP amplitude in the interval between the appearance and disappearance of the A was generally below the mean value for the reference task at a central prefrontal site (Fz). This suggests increased regional activity in this interval relative to the reference task (**Figure 1**). By contrast, subjects with ADHD demonstrated an increase in prefrontal SSVEP amplitude, suggesting reduced activation during this interval.

In control subjects, the appearances of the A and X, and more prominently the disappearance of the A, were associated with a reduction in SSVEP latency relative to the reference task at the same prefrontal site (**Figure 2**). By contrast, the ADHD group demonstrated an increase in SSVEP latency at this prefrontal site on the disappearance of the A.

IQ-MATCHED SUBGROUPS

The group difference SSVEP amplitude waveforms for the entire populations (solid line, **Figure 3**) and the IQ-matched subgroups (dashed line, Figure 3) are similar, with a corresponding correlation coefficient of 0.87. This similarity extends to the SSVEP latency waveforms (**Figure 4**), with a correlation coefficient of 0.83.

The SSVEP amplitude and latency waveforms were similar at all of the 64 recording sites (mean correlation coefficient for amplitude waveforms, 0.86; mean correlation coefficient for latency waveforms, 0.88), suggesting that the effects observed for the entire group are not a consequence of the differences in mean IQ between control and ADHD groups.

TOPOGRAPHIC DISTRIBUTIONS

In the control group (**Figure 5**), the points "A on," "A off," and "X on" were associated with reductions in SSVEP latency relative to the reference task mean, although these effects were only statistically significant at right prefrontal sites at the appearance ($P<.05$) and disappearance ($P<.005$) of the A. By contrast, in the ADHD group (**Figure 6**), there were increases in SSVEP latency at central and prefrontal sites although these changes did not reach statistical significance ($P>.05$).

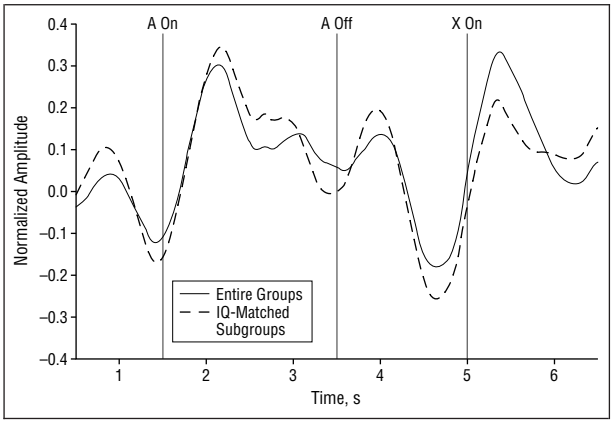

Figure 3. *Group differences in steady-state visually evoked potential (SSVEP) amplitude at electrode 16 (Fz) in the entire groups of 17 control subjects and 17 subjects with attention-deficit/hyperactivity disorder (ADHD) and the IQ-matched subgroups of 12 control subjects and 15 subjects with ADHD.*

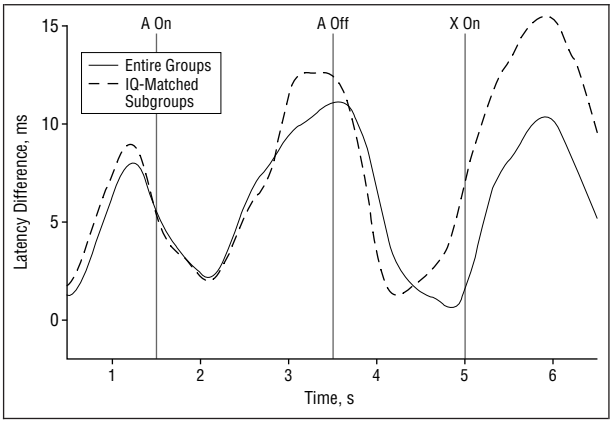

Figure 4. *Group differences in steady-state visually evoked potential (SSVEP) latency at electrode 16 (Fz) in the entire groups of 17 control subjects and 17 subjects with attention-deficit/hyperactivity disorder (ADHD) and the IQ-matched subgroups of 12 control subjects and 15 subjects with ADHD.*

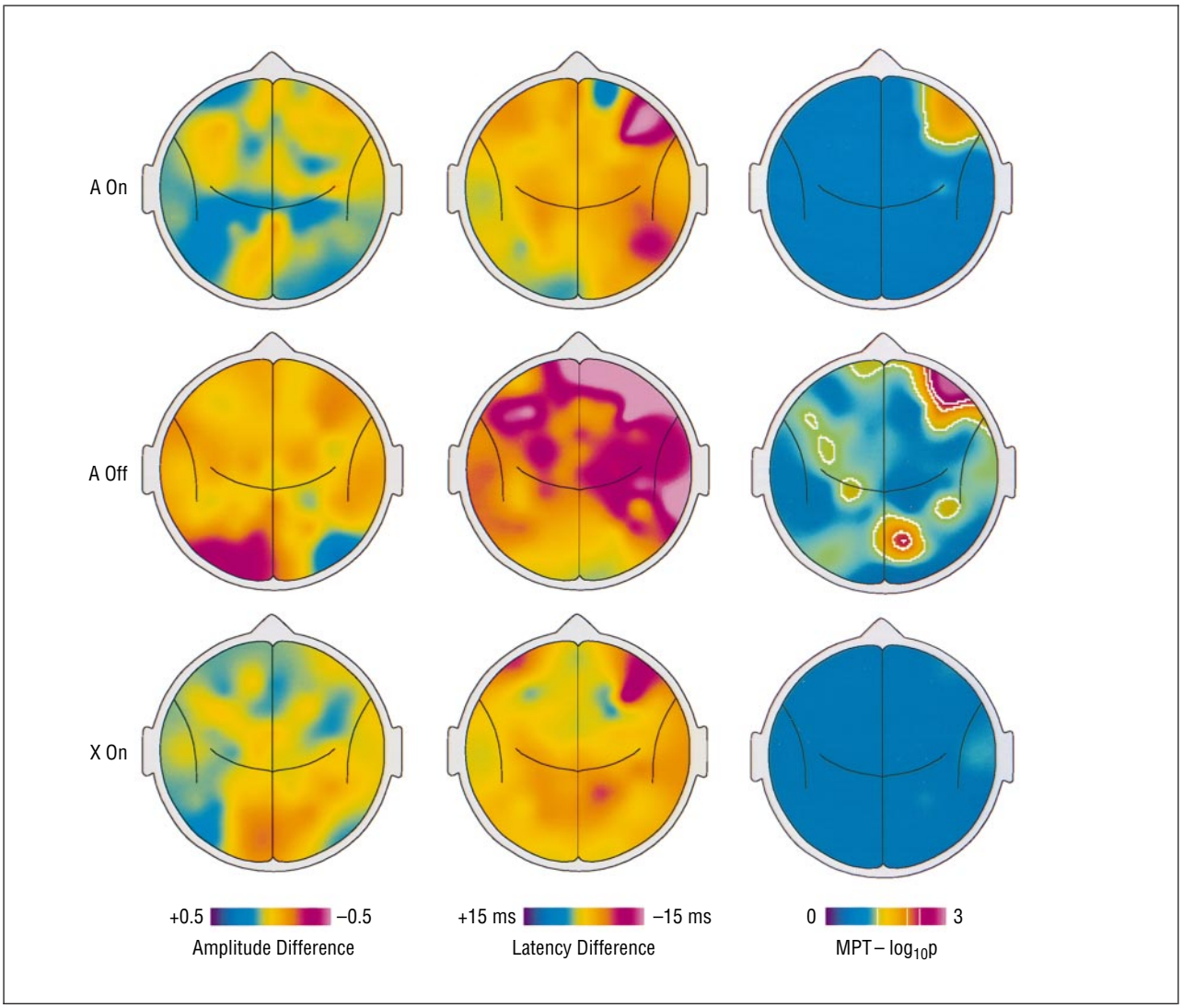

Figure 5. *Topographic distribution of steady-state visually evoked potential (SSVEP) amplitude (left column) and latency (center column) differences between the A-X version of the continuous performance task (CPT-AX) time series and the reference task mean for control subjects. The right column illustrates the logarithm of the type I error probability estimated from the multivariate permutation test (MPT) described in the "Statistical Analyses and Topographic Mapping" subsection. The contours correspond to* P *values of .05, .01, and .005. The SSVEP amplitude and latency and the logarithm of the probability are shown at the times of the appearance of the letter A (top row), the disappearance of the letter A (middle row), and the appearance of the letter X (bottom row).*

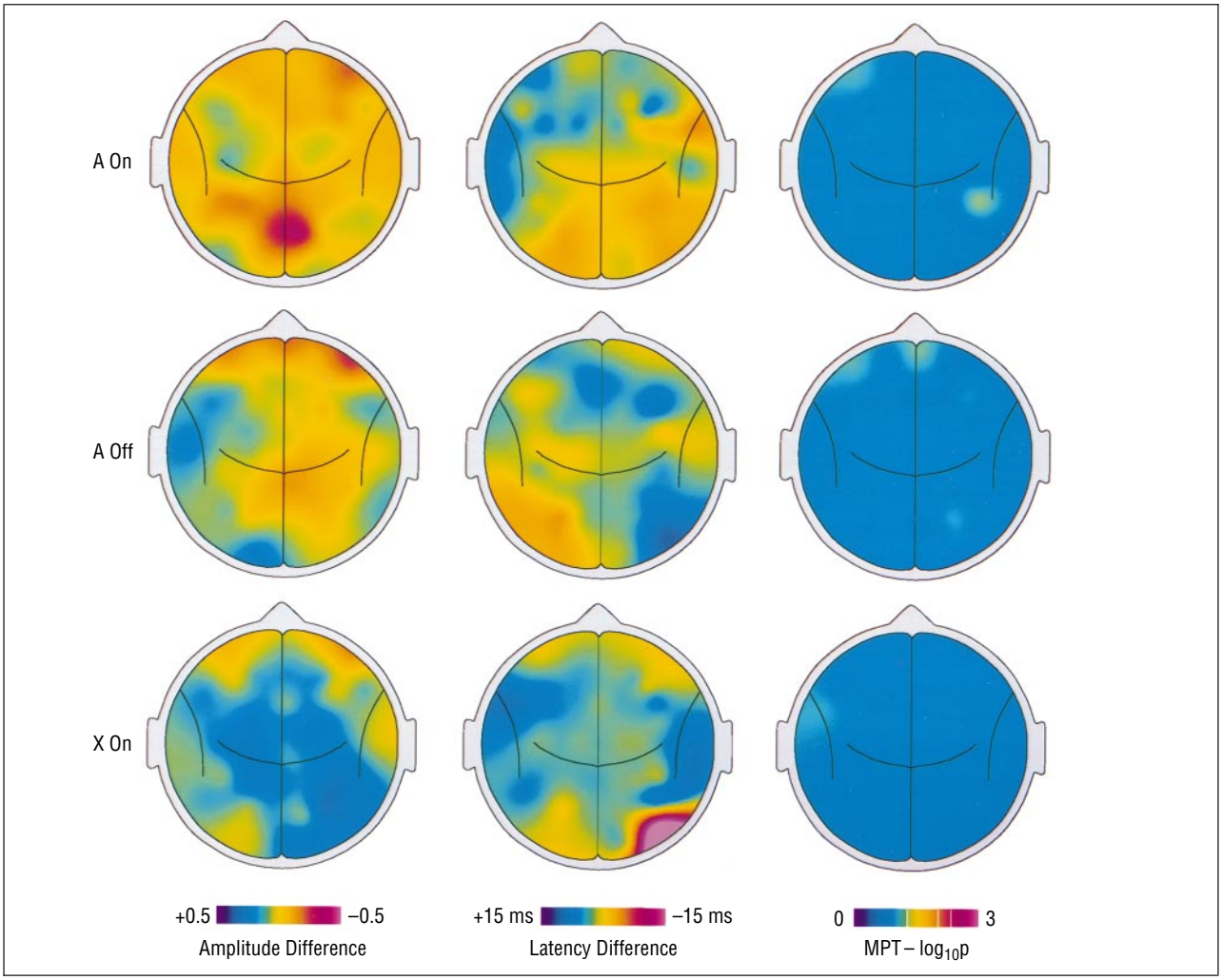

Figure 6. *Topographic distribution of steady-state visually evoked potential (SSVEP) amplitude differences, SSVEP latency differences, and probability for subjects with attention-deficit/hyperactivity disorder. All conventions are the same as those for Figure 5.*

COMMENT

For the first time, differences in SSVEP latency were observed between controls and subjects with ADHD at 3 critical points in time of the CPT-AX. Control subjects demonstrated an SSVEP latency reduction at right prefrontal sites coinciding with the appearances of the A and X and the disappearance of the A. We have previously suggested that such a latency reduction may reflect increased efficiency of coupling between prefrontal neural networks. Such an interpretation is consistent with our previous findings that faster responses in the CPT-AX were associated with larger prefrontal SSVEP latency reductions.[17] Compared with the prominent frontal SSVEP latency reductions observed in controls, subjects with ADHD showed only a slight right frontal latency reduction at the appearance of the A and latency increases at other frontal and temporal sites throughout the A-X interval.

A possible relationship between dopaminergic processes and SSVEP latency reductions in the A-X interval is suggested by the similarity of the SSVEP latency reduction topography and the primate neocortical dopaminergic distribution.[32] The possibility of such a relationship is strengthened by our finding of reduced or nonexistent frontal SSVEP latency reduction in subjects with ADHD, and long-standing evidence pointing to dopaminergic deficits underlying the symptoms of ADHD.[33,34]

These findings are unlikely to be a consequence of ADHD group deficits in performance as the SSVEP amplitude and latency for both the reference task and the CPT-AX were derived from only the correct trials, and the number of correct responses included in the analyses was similar for both groups. Furthermore, we do not believe that these findings are a consequence of the group difference in mean IQ as the differences were also apparent in mean IQ-matched subgroups.

Our ADHD sample manifested considerable comorbidity with other disruptive behavior disorders and learning difficulties, but this is typical of ADHD populations.[35-37] Relatively little is known about the effects of comorbidity on the type and severity of cognitive deficits found in children with ADHD. Some recent studies[37-39] have reported that deficits in performance on neuropsychological tasks by children with ADHD cannot be accounted for by the presence of psychiatric

comorbidity or learning difficulties. While the present study did not allow us to determine comorbidity effects on the electrophysiological and behavioral findings, we are currently undertaking a larger study that aims to examine this.

The failure of the ADHD group to demonstrate transient prefrontal SSVEP latency reductions at critical points in the CPT-AX suggests prefrontal deficits in ADHD. This is consistent with a range of neuropsychological and functional neuroimaging reports pointing to prefrontal deficits in ADHD. Although many neuropsychological tests point to prefrontal abnormalities, specific deficits in prefrontal processes mediating sustained attention also have been inferred from covert attention shift studies using the Posner paradigm.[40,41]

Our results are also consistent with those of a variety of functional neuroimaging studies[9,42] that have identified deficits in prefrontal activation in ADHD. In particular, we find some of the most prominent SSVEP differences between the control group and the ADHD group to be situated at right prefrontal recording sites, suggesting a specific role for the right prefrontal cortex in the CPT-AX. Such prefrontal lateralization is consistent with PET studies indicating preferential right prefrontal cortical activation in prolonged vigilance.[43] A preferential role for the right prefrontal cortex in planning and inhibitory motor control also has been recently reported by Rubia et al.[44] In a functional magnetic resonance imaging study of a "stop-task," where motor responses to a "go" stimulus had to be inhibited in 50% of the trials, pronounced activation was observed at the right dorsolateral prefrontal cortex and the right anterior cingulate in the population of 9 normal adults.

In summary, we suggest that steady-state probe topography may offer a useful neuroimaging modality to complement PET and functional magnetic resonance imaging in the investigations of the neurobiological substrate of ADHD. It should, however, be stressed that steady-state probe topography cannot match the high spatial resolution and 3-dimensional information available with PET and functional magnetic resonance imaging. This is especially important when considering the role of subcortical structures, such as the basal ganglia, in ADHD.

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