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Sources of Auditory Selective Attention and the Effects of Methylphenidate in Children with Attention-Deficit/Hyperactivity Disorder

Chantal Kemner, Lisa M. Jonkman, J. Leon Kenemans, Koen B.E. Böcker, Marinus N. Verbaten, and Herman van Engeland

Background: The aim of this study was to determine 1) whether abnormal auditory selective attention in children with attention-deficit/hyperactivity disorder (ADHD), as reflected in the processing negativity (PN) of the event-related potential, is related to impaired frontal functioning; and 2) how methylphenidate (MPH) affects attentional functioning in ADHD.

Methods: Sources of electrical brain activity were estimated in healthy control children, in ADHD children without medication, and in children with ADHD during a placebo-controlled medication trial involving MPH.

Results: The source models showed that the PN is generated in the auditory cortex. Children with ADHD showed less activity related to selective attention in this brain region. Administration of MPH resulted in more frontally located sources.

Conclusions: The results showed no evidence for an important role of the frontal cortex in abnormalities in selective attention in children with ADHD. Also, the data did not indicate that MPH normalizes brain activity in these children.

Key Words: Attention-deficit/hyperactivity disorder, methylphenidate, processing negativity, selective attention, auditory, source

Abnormal patterns of electrical brain activity (event-related potentials [ERPs]) are often found in children with attention-deficit/hyperactivity disorder (ADHD) during the performance of selective attention tasks, especially activity reflecting the selective processing of a specific channel of information, the processing negativity (PN) (e.g., Barry et al 2003; Jonkman et al 1997a). Studies of normal control subjects show that the selective processing of an auditory channel modulates the activity of both the auditory cortex and frontal areas (Dien et al 1997; Lipschutz et al 2002). Impaired functioning of the frontal-striatal circuitry is often associated with ADHD symptomatology (Barry et al 2003; Swanson et al 1998; Tannock 1998); however, it is not clear whether the abnormalities seen in studies of selective attention are indeed related to abnormal functioning in frontal areas. In the above-mentioned ERP studies, there was no identification of the source of abnormal brain activity, such as can be done by brain source analysis.

Brain source analysis can also be used to study the role of methylphenidate (MPH) in attentional processing in ADHD. Methylphenidate is currently the most effective treatment for the symptoms of ADHD, but its mechanism of action is not yet known. The fact that MPH affects dopaminergic functioning might indicate that it influences frontal functioning in children with ADHD. It is important to know whether MPH ameliorates an existing deficit or whether it activates compensatory mechanisms.

From the Department of Child and Adolescent Psychiatry (CK, HvE), University Medical Center Utrecht, Utrecht; Department of Neurocognition (LMJ), Faculty of Psychology, Maastricht University, Maastricht; Department of Psychopharmacology (JLK, KBEB, MNV), Faculty of Pharmacy, Utrecht University, and the Rudolf Magnus Institute for Neurosciences (CK, JLK, KBEB, HvE), Utrecht, The Netherlands.

Address reprint requests to Chantal Kemner, Ph.D., University Medical Center Utrecht, B01.324, Department of Child and Adolescent Psychiatry, Heidelberglaan 100, Utrecht 3514 CX, The Netherlands.

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Methods and Materials

Healthy control children ($n = 18$, all boys) and children with ADHD ($n = 18$, two girls) were matched for age (mean 10.0 and 10.6 years, respectively) and intelligence quotient (IQ) (mean 102.6 and 93.9, respectively). There was no significant difference in mean age or IQ between the groups. Informed consent was obtained from the parents of all children, and the study was approved of by the Medical Ethics Committee of the University Medical Center Utrecht. All children completed an auditory selective attention task in which standard and deviant tones were presented pseudorandomly to either the left or the right ear (80% and 20%, respectively). Stimulus type was defined by frequency (1000 or 1100 Hz) and balanced over subjects. In total, 300 stimuli were presented (duration 50 msec, sound pressure level 95 dB). The interstimulus interval was randomized between 1750 and 2150 msec. The child had to press a button when the deviant tone in the to-be-attended ear was heard. The children with ADHD were also tested in two later sessions, 1 week apart, after treatment with either placebo or 15 mg MPH, which were administered in a double-blind manner. The electroencephalogram was recorded during the task from 31 tin electrodes attached with an electrocap according to the 10–20 system. Sampling with 256 Hz started 100 msec before stimulus onset and lasted 1 sec. Data for the midline electrodes and a more extensive description of the methods and subject selection have been previously published (Jonkman et al 1997a, 1997b).

Here we present the results of dipole source localization analyses, based on the whole electrode set. Source models were determined with brain electrical source analysis (BESA) with a four-shell ellipsoidal model of the head (Scherg and von Cramon 1985). First, a dipole pair was fitted to the average group data with locations constrained to mirror symmetry. If the variance not explained by the model (residual variance [RV]) was more than 10%, an additional symmetrical dipole pair was added. Thereafter, the group models were fitted to the individual potential distributions of each subject, with an energy restriction of 20%, at the lowest peak in the RV curve in the scoring window (Kenemans et al 2002). Scoring windows were 50–175 msec for N1, 110–250 msec for P2, and 200–400 msec for PN. The data of subjects for whom the RV was greater than 30% were excluded from further analysis, as were the data of subjects with unstable

Figure 1. Dipole configurations for the N1 (control subjects, light blue; attention-deficit/hyperactivity (ADHD) subjects, pink) and P2 (control subjects, dark blue; ADHD subjects, red).

or anatomically or physiologically implausible solutions. Six orientation parameters (x , y , z values for both the left and right hemisphere), three location parameters (x , y , z , values, because the location was mirror symmetrical), and two moment values were determined for each subject. Group differences (control children [$n = 17$] vs. ADHD children [$n = 16$], and ADHD children treated with either placebo [$n = 13$] or MPH [$n = 15$]) in these parameters were determined with independent t tests. To compensate for the increased possibility of type 1 errors due to the large number of tests, a significance level of $p < .01$ was used for the location and orientation tests. Because Jonkman et al (1997a) found an amplitude difference of the PN between control and ADHD children, a less conservative p value of .05 was chosen for the moment values of this comparison.

First, source models for the early auditory peaks N1 and P2 were fitted for the standards in the nonattended channel in the nonmedication condition to test the reliability of the source modeling procedure in children, especially the children with ADHD. Second, to test for the effect of selective attention,

difference waves were computed by subtracting the ERP to standards in the unattended channel from those in the attended channel and modeling the peak of the resulting difference wave (or PN) at 300 msec in the averaged data.

Results

N1 and P2

A tangential dipole was found for N1 (dipole fitted at 100 msec) and a radial dipole for P2 (dipole fitted at 175 msec), with an RV less than 10% in both the control and the ADHD groups. Statistical analysis of the location, orientation, and moment parameters showed no differences between the groups, either for N1 or P2 (Figure 1).

PN: Control-ADHD Comparison

With a symmetrical dipole pair, a solution was found with an RV of less than 10% in the control group and an RV of 15% in the ADHD group. The inclusion of a second dipole pair did not result

Figure 2. Dipole configurations of PN for control (green), attention-deficit/hyperactivity (ADHD) (purple), ADHD-placebo (dark pink), and ADHD-methylphenidate (orange) conditions.

in a stable solution in the ADHD group. Statistical analysis showed significant group differences for the y-location [$t(31) = 3.42, p < .01$], which indicates that PN sources were located more anteriorly in the ADHD group (Figure 2).

The right dipole moment differed between the groups [$t(31) = 2.39, p < .05$], being larger in the control group than in the ADHD group (45.7 vs. 30.8). The group difference in the left dipole (46.7 vs. 35.7, control vs. ADHD group) did not reach significance.

PN: Placebo–MPh Comparison

A stable solution for the PN source was found with an RV of less than 10% in the MPh condition and 25% in the placebo condition. Inclusion of an additional dipole pair did not result in a stable solution in the placebo condition. A significant difference between the placebo and MPh conditions was found for the y-locations of the left dipole [$t(26) = -3.41, p < .01$], which indicates a more frontal location in the MPh condition (Figure 2).

The PN data from the ADHD group (compared with the control group) and the placebo group were less reliable because the initial source model had an RV greater than 10%. Therefore, the control group and the MPh group (both with an RV less than 10%) were compared directly as an additional test to determine the effect of MPh on PN. The groups had a different y-location [$t(30) = -6.1, p < .001$], which indicates that the source location was more frontal in the ADHD children treated with MPh than in the control group (Figure 2).

Discussion

It was possible to model the early ERP peaks N1 and P2 in both control children and children with ADHD by a tangential and a radial dipole solution, which are thought to reflect activity from primary and secondary auditory cortex (Albrecht et al 2000; Ponton et al 2000). The parameters of N1 and P2 to nonattended standards were not different between the groups, which indicates the integrity of early auditory processes in nonattended stimuli in children with ADHD, in accordance with most of the literature (Barry et al 2003).

Activation related to selective attention (i.e., PN) was modeled reliably in the normal control group, with a source originating in the auditory sensory cortex. Children with ADHD showed more anteriorly located sources, but the location of these sources was still within the auditory sensory cortex. It has to be noted, though, that any conclusions with respect to the children with ADHD can only be made tentatively because the dipole solution did not reach the RV criterion for a reliable solution, probably because of the lack of power of the signal. The dipole moment was smaller in the children with ADHD (though significantly so only for the right dipole). These results indicate that auditory cortical activity is modulated less in children with ADHD than in control children during performance of a selective auditory task. It has been suggested often that the frontostriatal circuit, which is important in executive functions, such as selective attention, is functioning abnormally in children with ADHD (see, e.g., Tan-

nock 1998); however, the data do not support an important role for abnormal frontal functioning in children with ADHD in the selective attention task as used in the present study.

The source of PN activity was located more anteriorly in children with ADHD treated with MPh than in children with ADHD treated with placebo or in control children. This indicates that MPh does not normalize the brain activity related to selective attention in children with ADHD, but rather that it influences other sources of activity. It is difficult to speculate on the brain structure influenced by MPh. The locus of the dipole source in the MPh condition might reflect (additional) activity in a different part of the auditory cortex or activity related to motor activity (Ilic et al 2003; Moll et al 2003). To conclude, there is no clear evidence found that the frontal cortex has an important role in abnormalities in auditory selective attention in children with ADHD or that MPh normalizes brain activity in these children.

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