Eur Arch Psychiatry Clin Neurosci (2000) 250 : 101–110

ORIGINAL PAPER

Aribert Rothenberger · Tobias Banaschewski
Hartmut Heinrich · Gunther H. Moll
Martin H. Schmidt · Ben van't Klooster

Comorbidity in ADHD-children: effects of coexisting conduct disorder or tic disorder on event-related brain potentials in an auditory selective-attention task

Received: 10 May 1999 / Accepted: 3 January 2000

Abstract In children with attention-deficit hyperactivity disorder (ADHD) some deficits in auditory information processing seem to exist. Further, comorbidity of ADHD with conduct disorder (CD) and tic disorder (Tic) is quite common but not yet fully understood. Thus, we investigated the effects of these two disturbances, when combined with ADHD, on electrophysiological correlates of auditory information processing. An auditory selective-attention task was used, and temporal as well as frontal lobe sensitive event-related electrical brain activity indicators like mismatch negativity (MMN) and negative difference wave (Nd), as well as P300 were registered in four groups of children (healthy controls, ADHD-only, and combined ADHD + CD as well as ADHD + Tic; total number 42). Performance measures showed that ADHD + CD had a higher impact on errors and reaction times than ADHD + Tic. The MMN effect indicated that all ADHD groups showed lower MMN amplitudes compared to normals, but only the group with ADHD + CD suffered from a significant deficiency in automatic auditory information processing. Nd and P300 amplitudes showed no significant group differences. It may be assumed that neurodynamic sufficiency in ADHD-only and ADHD + Tic children seems to be similarly impaired while there might be a greater deficit in ADHD + CD.

Key words Attention-deficit hyperactivity disorder · Comorbidity · Frontal lobe · Auditory selective-attention · Mismatch negativity (MMN) · Negative difference wave (Nd) · Tic disorder · Conduct disorder

A. Rothenberger · G. H. Moll · M. H. Schmidt · B. van't Klooster
Central Institute of Mental Health,
Child and Adolescent Psychiatry, P.O. Box 122120,
D-68072 Mannheim, Germany

A. Rothenberger (✉) · T. Banaschewski · H. Heinrich
G. H. Moll
University of Göttingen, Child and Adolescent Psychiatry,
von-Siebold-Str. 5, D-37075 Göttingen, Germany
email: arothen@gwdg.de, Website: http://www.gwdg.de/~ukyk,
Tel.: 0049-551-396727; Fax: 0049-551-398120

Introduction

Children with attention-deficit hyperactivity disorder (ADHD) often suffer from additional disturbances such as conduct disorder, tic disorder, dyslexia, and emotional disorders (Rothenberger 1996, Jensen et al. 1997). Since disturbed central auditory information processing increases with comorbidity (Riccio et al. 1994), it seems necessary to investigate the effects of specific types of comorbidity on the auditory attentional abilities of ADHD children. To answer this question adequately we have to overcome the constraints of pure behaviorally oriented studies (where only the final product of information processing is measurable), and combine them with recordings of event-related potentials (ERP) which enable us to register electrical brain activity elicited by task stimuli before the behavioral response takes place.

Although sustained focusing on auditory stimuli at school is an important problem for ADHD children, only few ERP studies have used an auditory selective-attention task (Zambelli et al. 1977, Loiselle et al. 1980, Oades et al. 1996, Jonkman et al. 1997, Winsberg et al. 1997) to compare ADHD children with healthy controls. So far, comorbid ADHD groups were not investigated systematically in this respect. Only Klorman et al. (1990) evaluated the impact of methylphenidate on N1 in ADHD-aggressive compared to ADHD-only children using a combined auditory-visual task requiring little selective attention; no significant differences for auditory N1 amplitude were found.

In general, the results of ERP studies (including perfomance measures) indicated that hyperactive children may perform worse (lower hit percentages and more errors of commission) than healthy controls. At the psychophysiological level correlates of early attentional deficits (e.g., smaller amplitude of N1, Nd) in ADHD may be found (Jonkman 1997). Satterfield et al. (1988, 1990) performed several selective-attention tasks which required subjects to attend to targets in one sensory modality (visual or auditory) while ignoring both the other modality and non-

targets in the attended modality. They found lower ERP amplitudes in hyperactive children during information processing. The authors reported that this effect could be observed primarily at the frontal recording sites and was mainly related to the so-called Nd (Negative difference) wave. Satterfield et al. (1988) suggested that a deficit of information processing was present in hyperactive children.

Nevertheless, it is difficult to draw firm conclusions for early attentional effects in ADHD patients from these results since different diagnostic classification systems and different paradigms with varying interstimulus intervals were used, different ERP measures were studied, and examined subjects had different ages. Zambelli et al. (1977), for example, studied formerly hyperactive adolescents (mean age 14 years), whereas Satterfield et al. (1988, 1994) investigated six-year-old children, and the study of Jonkman et al. (1997) included seven- to thirteen-year-old children.

Since discrimination of stimuli – which seems to be poor in ADHD children and relevant for their behavioral problems (Satterfield et al. 1988) – may be influenced by comorbidity (Riccio et al. 1994), the aim of the present research was to test the impact of two clinically relevant comorbid disorders (conduct disorder, tic disorder) on ERP parameters of auditory attentional processes (mismatch negativity, negative-difference wave).

Mismatch negativity (MMN) was chosen as a marker for automatic cerebral discrimination of auditory stimuli (Näätänen 1990). The MMN is an ERP component which can be detected with respect to the differentiation of deviant stimuli in a sequence of standard stimuli and can be best registered when the subject tries to ignore the sensory channel. Therefore, the MMN has some functional relation to automatic information processing. MMN has a maximum amplitude at frontocentral leads. Dipole mapping has confirmed that MMN is generated bilaterally from both the frontal lobes and the supratemporal auditory cortex (Alho 1995; Giard et al. 1990; Hari et al. 1992; Näätänen & Alho 1995; Sams et al. 1991; Scherg et al. 1989; Serra et al. 1998; Tiitinen et al. 1993). Also, there is some evidence that frontal cortical lesions may influence the neuronal activity of this brain region and diminish the MMN[1]. It has been proposed that the supratemporal component reflects merely sensory specific memory and change-detection mechanisms, whereas the frontal component seems to be associated with the initiation of involuntary shifts of attention to changes in the environment (Alho et al. 1994; Alain et al. 1998; Näätänen 1990).

The *negative-difference wave* (Nd) represents the difference wave of two auditory brain potentials during information processing. It is induced when an auditory nontarget stimulus which is being heard in the attended channel elicits a larger cortical negativity than the same stimulus presented in the unattended channel. The Nd was chosen as an appropriate parameter to be examined since converging evidence points at its strong relation to frontal brain mechanisms of selective-attention control (Näätänen 1990, 1992; Woods 1990). Similar to the MMN the Nd displays anterior scalp distributions with maxima over the frontocentral und frontopolar brain areas (Hansen and Hillyard 1980). Current density maps (Giard et al. 1988, 1990) have also suggested that a deep frontal source contributes to the generation of the Nd. The Nd seems to be reduced in patients with dorsolateral frontal brain lesions (Knight et al. 1981).

Hence, on the basis of a known frontal lobe deficit in ADHD children (Rothenberger 1995) one may regard MMN[1] as a merely "indirect" and Nd as a "direct" psychophysiological marker of their frontal lobe functioning. Since conduct disorder may be an essential part of ADHD comorbidity, significant differences could be expected in both ERP parameters (MMN, Nd) not only for ADHD only but mainly for ADHD + CD in comparison with healthy controls. ADHD children with comorbid tic disorder (ADHD + Tic) are supposed to display little differences of electrical brain activity compared to ADHD-only with respect to those components, since there is some evidence that neurodynamics of psychophysiological parameters of frontal lobe functioning (e.g., post-imperative negative variation) is widely preserved not only in Tic-only children but also in Tic + ADHD comorbidity, while it is insufficient in ADHD-only children (Dumais-Huber and Rothenberger 1992, Yordanova et al. 1994, 1996, 1997). Therefore, the aim of the study was to disentangle the influence of tic-disorder and conduct disorder on auditory information processing in comorbid ADHD children registrating brain electrical activity while performing a selective attention task.

Methods and materials

Subjects

Within the framework of a multi-level longitudinal study on central nervous regulatory mechanisms and child psychiatric disorders, 42 male subjects participated in the experiment. They were subdivided into four groups of children matched for age and IQ, three groups including children with psychiatric disorders (ADHD only, ADHD with additional conduct disorder (CD), ADHD with additional chronic tic disorder (chronic motor/vocal tics or Tourette disorder) and one other group consisting of healthy controls (Table 1).

Subjects were included if they had normal intelligence and either never medicated or drug-free for at least four weeks before the experiment. Healthy controls (coming from the community and going through the same investigational procedure as the other groups) were devoid of child psychiatric disorders and gross neurological or other organic disorders.

Patients, most of them outpatients, fulfilled the DSM-III-R criteria (American Psychiatric Association 1987) for ADHD-only: 314.01; ADHD + CD: 314.01/312.9, and ADHD + Tic: 314.01/307.22 or 307.23. There were no children with the diagnosis of specific learning disabilities or other child psychiatric disorders (exclusionary criteria). Detailed information on psychopathology and level of social functioning gathered by clinical investigation (including a structured parent interview (Esser et al. 1989),

[1] Notice: Reduced MMN-amplitudes may reflect deficits at the level of the supratemporal cortex, either primarily developed at this site or indirectly influenced by frontal lobe disturbance or both.

several questionnaires, and neuropsychological testing (Rothenberger et al. 1994)) was pooled by experts according to the Children's Global Assessment Scale (CGAS, Shaffer et al. 1983).

For all children, the Child Behavior Checklist (CBCL, Achenbach and Edelbrock 1983) was used for child psychiatric symptoms based on parents' reports. The level of hyperactivity was assessed by the 10-item Conners parent questionnaire (Goyette et al. 1978). For ADHD + Tic children, additional parent and expert information was recorded with the Tourette Syndrome Global Scale (TSGS, Harcherik et al. 1984), and Tourette Syndrome Severity Scale (TSSS, Shapiro et al. 1988). The study was approved by the local ethics committee and informed consent by the parents as well as assent of the children was achieved.

Task procedure

Audiometric testing was done. All children had normal hearing. Prior to data acquisition, children performed some training sequences in order to assure comprehension and accomplishment of the task. Low (1000 Hz, non-targets) and high (1500 Hz, targets) tones (85 dB SPL) were presented pseudorandomly to the left and right ear separately (i.e., there were four stimuli, one at a time, with equal distribution on both sides for each tone, see Fig. 1). The subject had to attend to one ear only as indicated by preceding instructions: In a fixed order the subjects had to first attend to the right ear (block 1), and in a second series the left ear had to be attended to (block 2). A button-press response had to be given to each target tone presented on the attended side. Each block consisted of a total of 96 high tones and 144 low tones. The interstimulus interval varied randomly between 1100 ms and 1500 ms. Total stimulus duration was 120 ms, with a rise- and falltime of 10 msec each.

The frequency difference of the tones and the probability of the targets was chosen on the basis of pilot experiments with this paradigm to guarantee a sufficient number of artifact-free ERP epochs for averaging.

Behavioral measures

Response errors and reaction times (RT) for correct responses (to attended targets) were recorded. RTs were measured between 150 ms and 1250 ms poststimulus. The reaction time data are congruent with the "accepted" ERP sweeps to attended targets (epochs containing artifacts, omission or commission errors were not averaged for the ERP), i.e., only hits were used to control for similar performance between groups. RTs below 150 ms or exceeding 1250 ms were also considered as omission errors. The RTs for commission errors were not included.

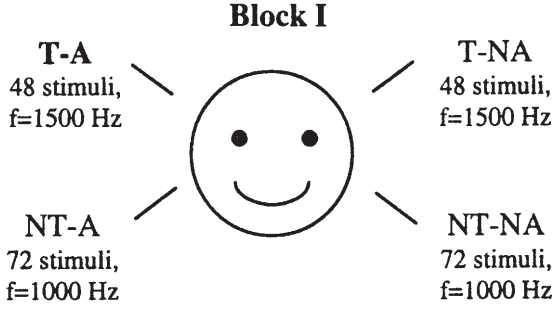


Fig. 1 In an auditory selective attention task children had to respond by button-press to higher tones (f = 1500 Hz, targets) on the right side (= attended side) during block 1. In block 2 the left side was the attended side. A total of 240 stimuli was delivered in each block. *T-A* target attended, *NT-A* non-target attended, *T-NA* target nonattended, *NT-NA* non-target nonattended)

Data recording

EEG activity was recorded via Nihon Kohden Ag/AgCl cup electrodes (electrode-to-skin impedance kept under 3 kOhms) fixed to the subject's scalp with Grass EC2 cream at locations F3, Fz, F4, C3, Cz, C4, P3, and P4 according to the International 10-20 system and referred to the two mastoid electrodes which were connected via a 10 kOhm resistor (voltage divider, cf. Nunez 1981, pp. 191–193). Vertical and horizontal EOG were simultaneously recorded from electrodes above and below the right eye and at the outer canthi. The EEG and EOG signals were amplified and filtered by a Nihon Kohden electroencephalograph (model 4321 G), with cutoff frequencies of 0.03 and 120 Hz for EEG channels, and 0.03 and 70 Hz for EOG channels. Signals were PCM-coded for storage on magnetic tapes. For further analysis, data were fed into a Compaq 386 computer equipped with an analog-to-digital converter (500 Hz sampling rate).

Data analysis

EEG sweeps that were heavily contaminated with ocular movements and muscle artifacts were rejected. In order to preserve as many sweeps as possible for data analysis, a step-wise control for artifacts was chosen. As a first step, a 150 μV EOG threshold was applied to exclude only grossly disturbed sweeps that could hardly be used even after an EOG-correction procedure. This rejection also involved the exclusion of EEG signals which were out of the amplifier range. Obviously, residual EOG-related EEG activity was not tackled by this conventional rejection method. Therefore, as a second step, an off-line regression-based EOG correction was performed in the time domain by assuming a linear model of EEG-EOG interaction (Dumais-Huber 1993). For precise control of ocular movement effects, correction factors were estimated separately in each block. They were then applied to the raw data of the corresponding block. The correction factors were calculated by the software OASYS 88.1 ("Ocular Artifact SYStem", Base-Line, SofAS-Software for Applied Science, Hessenplatz 3, D-60487 Frankfurt/M., Germany). All ERP channel averages contained a minimum of 50 trials (mean values over all conditions: healthy 113, ADHD-only 108, ADHD + CD 104, ADHD + Tic 97).

Measurement

The mean values of ERP amplitudes were measured automatically relative to a 150 msec prestimulus baseline using the following time windows: MMN: 100–200 ms; Nd: 180–430 ms; P3b: 400–600 ms. MMN was constructed by subtracting the nonattended non-target from the nonattended target. Nd was computed by subtracting the nonattended non-target from the attended non-target. In addition, P3b (for reasons of clarity difference wave of attended target minus attended non-target) was registered and measured as an "accompanying" ERP of the used paradigm to control for attended target effects in our task with high probability of targets. The time window was chosen to avoid confoundation with P3a and P2 effects. The measurements were performed at sites where the waveforms were prominently visible. For the MMN and the Nd waveforms, measurements were performed at six frontocentral leads (F3, Fz, F4, C3, Cz, C4), while the P3b was measured at two parietal leads (P3, P4).

Statistical analysis

To address the formulated questions, for ERP data repeated-measures analyses of variance (ANOVAs) with group (4) x lead (6 or 2) as factors were computed in which group membership served as the between-subjects factor. Analysis of performance data was done with Kruskal-Wallis analyses and Mann-Whitney U-tests. Bonferroni correction to the probability values was employed for the post hoc contrasts performed. In the analysis, effects of exper-

imental block were not taken into account. This was decided because the unbalanced presentation of attend-right and attend-left blocks makes it impossible to discriminate effects of time and tasks and order of attended side. Correlations between ERP and behavioral data were made with Spearman rank procedure.

Results

The sample of children with valid data for the selective-attention task consisted of 42 boys. Table 1 gives an overview of sample characteristics and the results of Kruskal-Wallis ANOVAs performed to inspect group differences. It is shown that the control group does not differ statistically from the patient groups on age, IQ, SES or handedness. The ADHD groups did not differ on Conners scores. Control children had lower aggression, delinquency and attention CBCL subscores than the ADHD children. In turn ADHD – only children had lower aggression, delinquency and attention scores than the ADHD + CD and ADHD + Tic groups. Also, the ADHD + Tic group had lower aggression scores than the ADHD + CD children, but did not differ significantly from the ADHD + CD group on delinquency and attention scales.

Performance measures

No group effects occurred for omission errors or mean reaction time (Table 2 a). Group effects were found in commission errors and for reaction-time variability (standard deviation). The results of the Kruskal-Wallis ANOVAs are shown in Table 2a. All three ADHD groups appeared to make more commission errors and have higher RTSDs (reaction time standard deviations) than the control subjects, while the three ADHD groups did not differ significantly from each other in these parameters. Upon closer inspection using Mann-Whitney U-tests, it turned out that the control group made fewer commission errors than each individual ADHD group. Except for the ADHD + Tic children, the same pattern was found for RTSD measures (Table 2 b). A distinction between the three types of false alarms (attended non-targets/nonattended targets/ non-targets) did not reveal significant group effects.

ERP measures

Mean values and standard deviations of ERP amplitudes for all groups and leads are listed in Table 3. For all ERP parameters, the amplitude values of the control group were significantly different from baseline amplitudes (MMN: $F(1,10) = 21.3$, $p = 0.001$; Nd: ($F(1,10) = 9.01$, $p = 0.013$), P3b: $F(1,10) = 11.25$, $p = 0.007$). This reflects a basis for good data quality.

MMN mean amplitude (100–200 ms): In Fig. 2 a the grand averages of MMN difference waves at midfrontal lead (Fz) are shown for all groups, pooled over blocks. Visual inspection shows reduced amplitude for ADHD + CD during the whole post-stimulus sweep length of 1000 msec while this is not the case for ADHD + Tic. At frontocentral leads, the MMN was visible as a small negative deflection in all groups. Compared to combined posterior electrodes ((P3+P4)/2) the mastoid electrodes showed a positive deflection during the MMN latency range (mean amplitude at mastoids (100–200 ms) = 0.90 μV), whereas the frontocentral electrode locations showed a negative deflection (mean amplitude at Fz (100–200 ms) = –1.11 μV); this indicates that the observed MMN is not superimposed by a N2b which is not, or only to a small amount, measurable at the mastoids (Sams et al. 1990). As seen in the group mean

Table 1 Group characteristics of selective-attention task sample. Kruskal-Wallis analyses of variance were performed over all four groups of subjects (Healthy controls, attention-deficit hyperactivity disorder (ADHD-only), ADHD with conduct disorder (ADHD + CD), ADHD with tic disorder (ADHD + Tic)) and over the three patient groups. (NS: non significant)

	Group				K-W groups 1–4 p (χ^2)	K-W groups 2–4 p (χ^2)
	1 Controls n = 11 x (sd)	2 ADHD-only n = 11 x (sd)	3 ADHD + CD n = 9 x (sd)	4 ADHD + Tic n = 11 x (sd)		
Age (yrs)	11.5 (2.1)	11.1 (2.3)	11.2 (1.1)	12.1 (2.5)	NS	–
IQ (PSB)	102.0 (11.8)	96.7 (11.8)	98.0 (9.6)	97.2 (12.3)	NS	–
SES (MEI) 1 = low ... 5 = high	2.8 (1.3)	2.7 (1.2)	2.7 (0.7)	2.8 (1.0)	NS	–
Conners	3.3 (2.8)	21.3 (3.3)	23.9 (4.1)	21.2 (4.2)	p < 0.001 (25.2)	NS
Aggression (CBCL)	5.4 (3.1)	10.6 (5.2)	25.4 (4.2)	18.8 (6.2)	p < 0.001 (29.3)	p < 0.001 (17.2)
Delinquency (CBCL)	1.9 (1.3)	2.5 (2.0)	7.0 (1.4)	4.9 (3.0)	p < 0.001 (19.2)	p < 0.005 (12.0)
Attention (CBCL)	2.7 (2.9)	9.3 (1.8)	12.6 (2.2)	12.4 (2.8)	p < 0.001 (28.0)	p < 0.005 (11.4)
Handedness (sum of 8 items)	35.0 (6.1)	33.2 (11.2)	36.8 (3.2)	33.7 (10.4)	NS	–

Note: CBCL attention scale scores and handedness scores were not used as inclusion or exclusion criterion, but are reported for descriptive purposes.
PSB Prüfsystem für Schule und Bildungsfragen; *SES* Socioeconomic status according to school/university level; *MEI* Mannheimer Elterninterview; *CBCL* Child behavior checklist

Table 2 Performance data from the selective-attention task, pooled over both experimental blocks (block 1: attend to the right ear; block 2: attend to the left ear), analyzed by two Kruskal-Wallis analyses of variance; one over all four groups of subjects (Healthy controls, attention-deficit hyperactivity disorder (ADHD-only), ADHD with conduct disorder (ADHD + CD), ADHD with tic disorder (ADHD + Tic)), and one over the three patient groups

	Group				K-W groups 1–4 p (χ^2)	K-W groups 2–4 p (χ^2)
	1 Controls n = 11 x (sd)	2 ADHD-only n = 11 x (sd)	3 ADHD + CD n = 9 x (sd)	4 ADHD + Tic n = 11 x (sd)		
Omission errors	1.0 (1.2)	2.1 (2.5)	4.4 (4.6)	3.1 (5.6)	NS	NS
Mean RT (ms)	510 (85)	534 (74)	542 (96)	504 (92)	NS	NS
Commission errors	1.3 (1.7)	3.7 (2.8)	5.0 (4.9)	3.4 (2.5)	p < 0.05 (9.9)	NS
SD RT (ms)	141 (24)	177 (34)	178 (34)	155 (47)	p < 0.1 (7.5)	NS

Further inspection results by Mann-Whitney U-tests (2-tailed p)

	Control vs ADHD-only (p (Z)	Control vs ADHD + CD p (Z)	Control vs ADHD + Tic p (Z)
Commission errors	p < 0.01 (–2.6)	p < 0.01 (–2.6)	p < 0.05 (–2.3)
SD RT	p < 0.05 (–2.3)	p < 0.05 (–2.4)	NS

Table 3 Mean values and standard deviations of ERP amplitudes (in microvolts, μV) (mismatch negativity (MMN), negative difference wave (Nd), P300 wave (P3b) for the groups (Healthy controls, attention-deficit hyperactivity disorder (ADHD-only), ADHD with conduct disorder (ADHD + CD), ADHD with tic disorder (ADHD + Tic) and leads (Frontal left (F3), middle (Fz), right (F4); central left (C3), middle (Cz), right (C4); parietal left (P3), right (P4)) investigated

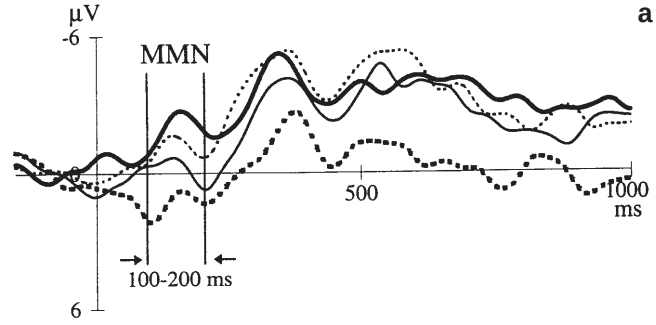
	MMN						Nd						P3b	
	F3	Fz	F4	C3	Cz	C4	F3	Fz	F4	C3	Cz	C4	P3	P4
Control	–2.1 (± 2.4)	–2.0 (± 2.1)	–2.4 (± 1.6)	–2.2 (± 1.1)	–1.9 (± 1.9)	–2.4 (± 1.1)	–2.0 (± 2.1)	–2.1 (± 2.0)	–1.8 (± 2.5)	–1.7 (± 2.2)	–1.6 (± 2.9)	–1.5 (± 2.5)	6.0 (± 5.7)	5.0 (± 4.8)
ADHD–only	–1.2 (± 1.7)	–0.2 (± 2.1)	–0.2 (± 2.0)	–1.4 (± 1.5)	–0.4 (± 1.9)	–0.5 (± 1.8)	–2.5 (± 1.9)	–2.7 (± 2.2)	–2.8 (± 1.3)	–2.1 (± 1.7)	–2.3 (± 1.9)	–2.0 (± 1.2)	4.6 (± 4.0)	3.4 (± 4.2)
ADHD + CD	0.5 (± 2.0)	0.9 (± 2.6)	0.6 (± 1.6)	–0.1 (± 1.3)	0.6 (± 2.4)	0.5 (± 1.9)	–1.6 (± 2.0)	–1.3 (± 2.3)	–0.8 (± 2.2)	–1.1 (± 1.7)	–0.8 (± 2.1)	–1.2 (± 1.9)	4.9 (± 2.2)	2.7 (± 2.3)
ADHD + Tic	–1.3 (± 3.4)	–1.2 (± 3.6)	–0.4 (± 2.7)	–1.0 (± 2.9)	–0.3 (± 3.1)	–0.5 (± 2.7)	–1.1 (± 2.1)	–2.2 (± 2.5)	–2.0 (± 2.1)	–0.8 (± 2.3)	–1.2 (± 3.2)	–1.2 (± 2.1)	5.7 (± 3.2)	4.4 (± 3.2)

values of the measured time window (100–200 ms) averaged over all six frontocentral leads (Controls: –2.2 μV, ADHD only: –0.6 μV, ADHD + CD: +0.5 μV, ADHD + Tic: –0.8 μV), a significant group difference of MMN mean amplitude towards less negative values for all ADHD groups as compared to normals ($F(3,38) = 2.8$, $p < 0.05$) is observed (Fig. 2b). Contrasts between controls and patient groups revealed that only the ADHD + CD group had a significantly smaller MMN ($F(1,18) = 12.01$, $p = 0.01$) while ADHD-only and ADHD + Tic tended to show smaller MMN amplitudes ($F(1,20) = 4.90$, $p = 0.13$ and $F(1,20) = 1.87$, $p = 0.57$, respectively). In direct comparison, the ADHD + CD group did not differ significantly from the other two ADHD groups.

Since the ERP curve of ADHD + CD children (compared to the other groups) showed a lower amplitude even after the time window of the MMN, we performed a post hoc analysis of variance for the later ERP interval between 450–800 ms (slow negative wave SNW, mean values in μV: healthy –2.2, ADHD-only –2.1, ADHD + CD + 0.9, ADHD + Tic –2.2) and found also a significant group effect ($F(3,38) = 3.81$, $p = 0.02$). Contrasts between groups revealed that only the ADHD + CD group showed a significantly smaller amplitude compared to healthy controls, ADHD-only and ADHD + Tic, respectively, p's < 0.01).

Finally, we controlled post hoc for ERP effects during the attended condition but no significant group differences could be found for MMN nor for SNW.

Nd mean amplitude (180–430 ms): Fig. 3 shows the grand average Nd difference waves at midfrontal site (Fz), pooled over blocks. At frontocentral electrode positions,



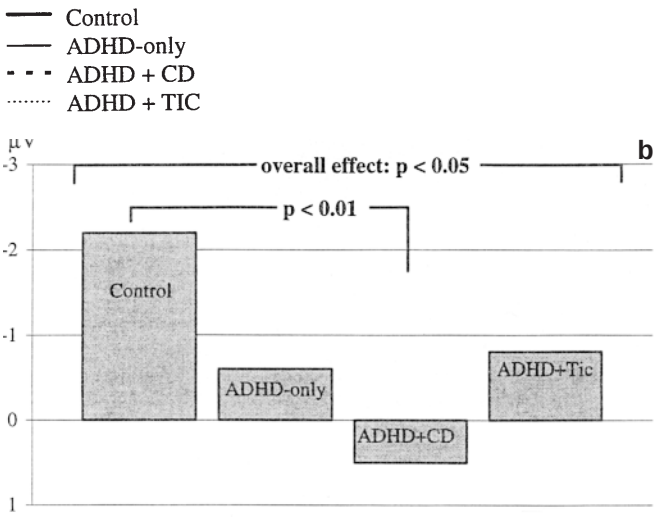


Fig. 2 a Difference waveforms at Fz (Target Nonattended Non-Target Nonattended) for four groups of children[a] to inspect the MMN. ERPs are pooled over blocks. ADHD + CD children show the lowest amplitudes during the whole sweep length.
[a] Healthy controls, attention-deficit hyperactivity disorder (ADHD-only), ADHD with conduct disorder (ADHD + CD), ADHD with tic disorder (ADHD + Tic)

Fig. 2 b MMN mean amplitude effect for four groups of children[a]. Group mean values averaged over all six frontocentral leads (F3, Fz, F4, C3, Cz, C4).
[a] Healthy controls, attention-deficit hyperactivity disorder (ADHD-only), ADHD with conduct disorder (ADHD + CD), ADHD with tic disorder (ADHD + Tic)

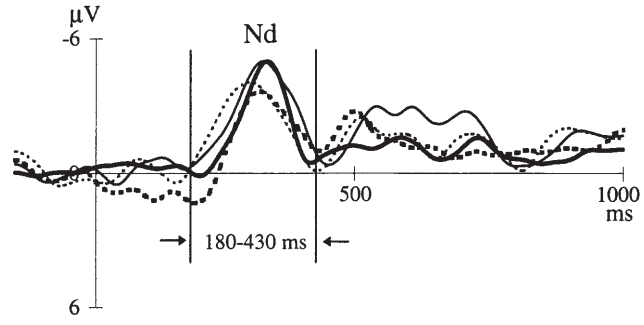


Fig. 3 Difference waveforms at Fz (Non-Target Attended Non-Target Nonattended) for four groups of children[a] to inspect the Nd. ERPs are pooled over blocks. No significant differences.
[a] Healthy controls, attention-deficit hyperactivity disorder (ADHD-only), ADHD with conduct disorder (ADHD + CD), ADHD with tic disorder (ADHD + Tic)

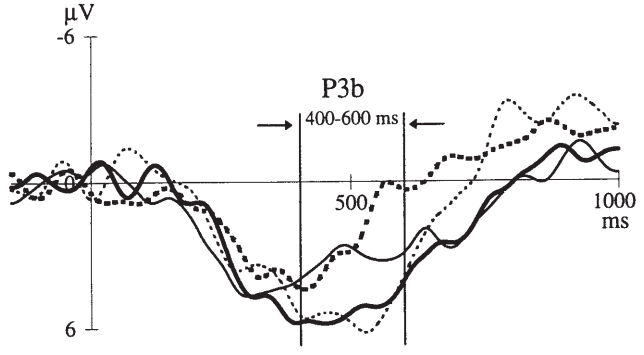


Fig. 4 Difference waveforms at P4 (Target Attended/Non-Target Attended) for four groups of children[a] to inspect the P3b. ERPs are pooled over blocks. No significant differences.
[a] Healthy controls, attention-deficit hyperactivity disorder (ADHD-only), ADHD with conduct disorder (ADHD + CD), ADHD with tic disorder (ADHD + Tic)

the Nd was seen as large negative deflection reaching its maximum amplitude around 300 ms. Although the Nd amplitudes for ADHD + CD are somewhat smaller compared to the other groups, no significant group effect on the mean Nd amplitude was found, nor effects of leads.

P3b mean amplitude (400–600 ms): In Fig. 4 grand average P3b difference waves at right parietal (P4) lead are shown, pooled over blocks. For reasons of clarity it was decided to present the attended target minus the attended non-target difference waveform. This difference wave gives a good impression of the clear P3b target effect. In the right parietal location, a large positive wave can be seen, with a peak latency of about 450 ms. Upon visual inspection, the curve seems to be reduced in amplitude for ADHD and ADHD + CD, but not for ADHD + Tic. However, no significant group or lead effects were found in P3b mean amplitude.

Correlations of ERP and performance

There was no significant correlation between ERP parameters (amplitudes of MMN, Nd, P3b) and behavioral parameters (RT, RTSD to hits).

Discussion

The aim of the present work was to study brain electrical correlates of associated psychopathology in ADHD children by means of an auditory selective-attention task. The main question was whether, compared to normals and the two other ADHD groups (ADHD-only, ADHD + Tic), the combination of ADHD + CD would affect frontal lobe sensitive ERPs more strongly, probably in parallel with deficits in performance.

Performance effects

As has been reported in other studies (Jonkman 1997), ADHD-only children made more commission errors than controls. This holds also for the comorbid groups (with the highest values for ADHD + CD) and underlines the known reduced cognitive impulse control in ADHD. It should be noted that ADHD + Tic did not make more commission errors than the ADHD-only group. This is consistent with Schuerholz et al. (1998) who reported that ADHD-only presented significantly greater commission errors compared to ADHD + Tic. ADHD groups did not make significantly more omission errors than controls and did not differ with respect to their mean reaction times to targets (hits). This is in agreement with previous findings (in the auditory modality) by Satterfield et al. (1988, 1990) and Jonkman et al. (1997) – indicating that, in a stimulating situation like the one provided in our selective-attention task, motivational problems are less likely to occur.

However, the standard deviations of reaction times were larger for the ADHD-only and ADHD + CD groups, but not for the ADHD + Tic patients. Like in Schuerholz et al. (1998), there was no significant difference between ADHD-only and ADHD + Tic. This is in line with our earlier research, and may reflect that, in ADHD patients, comorbidity of CD versus tic disorder has a different impact on behavioral control, i.e., more disturbing when CD is the comorbid factor, (Rothenberger et al. 1994, Yordanova et al. 1996, 1997). The higher variability of reaction times in the two other groups (ADHD-only and ADHD + CD) could be caused by shifts of attentional level. The fact that mean reaction times do not differ from controls suggests that those two groups of ADHD children are able to compensate temporary “lapses” of inattention, while ADHD + Tic subjects show a more stable performance.

ERP effects

MMN

The focus of our study was on early temporal and frontal lobe sensitive brain electrical effects of auditory information processing in ADHD comorbidity. Task manipulations detected a significant overall effect to lower MMN amplitude in the ADHD groups compared to normals. As a limitation of our study design, one might argue that there was a relatively high deviant rate of 40% which might have hampered the development of a ”true” MMN. However, the polarity inversion of the mastoids (as test for a ”true” MMN) could clearly be stated in the investigated sample.

In a post hoc pair-wise contrast a significantly lower MMN amplitude was seen in ADHD + CD compared to controls, while there was only a tendency in the same direction for both ADHD-only and ADHD + Tic. The two latter groups showed similar values for MMN amplitude except for Fz, where ADHD + Tic showed a higher amplitude. Thus, taken together with our earlier research on frontal lobe sensitive executive functions and post-imperative negative variation (Rothenberger et al. 1994, Yordanova et al. 1997) performance and MMN data support the suggestion that tic children, even with coexisting ADHD, seem to be at least as efficient with respect to these kinds of neurodynamics and neuropsychological tasks as children with ADHD-only. Therefore, they may be quite successful to activate frontal lobe neuronal resources to regulate their behavior. The reported MMN effects may indicate that mainly ADHD + CD suffer from a deficiency in early auditory information processing (“disturbed automatic deviancy detector”) at the level of the auditory cortex, which might have been influenced by known frontal lobe deficits in ADHD children (Rothenberger 1995). The latter is supported by the fact that dorsolateral prefrontal damage results in a reduction of MMN amplitude (Alho et al. 1994; Alain et al. 1998).

In an earlier report using an active auditory odd-ball task, Winsberg et al. (1993) found a decreased MMN in six ADHD children compared to five controls. However, after augmenting this sample to 14 ADHD children and 14 healthy controls, their recent data (Winsberg et al. 1997) did not confirm these initial observations. Two aspects seem to be responsible for this result. First, a high interindividual variability (behaviorally and psychophysiologically) in ADHD children exists which might explain many of the deviating ERP results in this group of patients. Especially, research problems posed by comorbidity factors in ADHD were not addressed satisfactorily. Second, although the MMN can be elicited by deviant stimuli in active (attend) and passive (ignore) conditions, MMN is best observed in ignore conditions (Näätänen 1990) as used in our study. Thereby overlap with N2b (which is related to voluntary attention) can be avoided. The polarity inversion at the mastoids was a further indication that the MMN was not superimposed by a N2b which is not, or only to a small amount, measurable at the mastoids (Sams et al. 1990). Thus, it could be understandable that we found no differences for the attended condition and the comparison of 12 ADHD children and 12 healthy controls by Oades et al. (1996), using a binaural three-tone (differing in pitch and rarity) odd-ball paradigm without ignore condition, also did not find significant differences in MMN amplitude. Furthermore, ERP

data may be influenced by general developmental processes. Since there were no age effects in this study and the MMN amplitude seems to remain similar within the age range of 5–15 years (Csépe et al. 1992), developmental effects are unlikely to play a role for our results.

A tendency for reduced MMN amplitude was found by Schreiber et al. (1992) in children at risk for schizophrenia. They used a selective-listening task which also incorporated a passive condition. Furthermore, pitch MMN amplitude in a passive non-attend situation was significantly attenuated in dysphasic children when compared to normals (Korpilahti and Lang 1994), and preliminary ERP results in 4 1/2 year-old children, using a passive auditory odd-ball task, showed that hyperactive children exhibited a lower MMN amplitude than normal controls (Rothenberger 1995). Hence, this ERP variable may explain certain aspects (attention deficit of automatic auditory discrimination) of ADHD symptomatology but it is not disorder-specific and seems to represent merely a risk factor for additional psychopathology as may be derived from the significant reduction of MMN in the ADHD + CD group.

Whether the reduced SNW found in our ADHD + CD sample is a sequential effect of the reduced earlier MMN remains to be answered. The differences between both variables concerning post hoc pairwise group contrasts and lead effects make it likely that at least some other influences may be involved. Nevertheless, this observation suggests that later auditory information processing in this group of children may also be disturbed.

Nd

In contrast to similar studies in children of the same age range (Schreiber et al. 1992, Jonkman et al. 1997), the examined groups did not differ in Nd amplitude. While the earlier work suggested that some groups of children with psychiatric risks and/or symptomatology show an unspecific deficit in frontal lobe functioning, our finding is not supportive to the notion of a deficient automatic interchannel stimulus preference in the auditory modality as a sign of decreased frontal lobe activity manifested by smaller Nd amplitude to standard stimuli. Influences of group selection and task design (e.g., easy vs. difficult discrimination of stimuli) may explain these differences at least partly, as it is known from Nd studies in healthy persons by Alho et al. (1986). Further studies with larger group sizes are warranted.

P3b

Similar to other studies (Jonkman 1997, Winsberg et al. 1997), P3b amplitude as a measure for a later intrachannel selection process was not significantly different between groups, i.e., there seem to be no relevant differences in P3b amplitude when ADHD and control groups perform comparably. In summary, the deficit in performance found in our study may be attributed merely to deficient information processing preceding the P3b since target processing was not abnormal.

Correlation of ERP and peformance

There were no significant correlations between electrical brain activity and performance. Concerning reaction time measures, there were differences between normals and ADHD groups only for RTSD but not for mean reaction time. This finding is well in line with the theory of a deficit in response inhibition for ADHD (Sergeant 1995, Barkley 1997, Casey et al. 1997) and can hardly be related to deficits of auditory information processing at the level of the auditory cortex as revealed by ERP. Thus, as stated by Satterfield et al. (1988) and Karayanidis et al. (1997), differences may exist for psychophysiological indices of attention in the absence of overt behavioral differences. The possible discrepancy between brain electrical and behavioral data is also supported by Klorman et al. (1990) who reported comparable methylphenidate effects on N1 amplitude for tones for accurate as well as for inaccurate performing ADHD children. Also, Jonkman (1997, page 69) found no significant correlation between processing negativity and the percentage of hits of the ADHD group.

Conclusion

In an auditory selective-attention task, comorbid subgroups of ADHD children showed (besides increased commission errors and higher intraindividual variabilities of reaction times) psychophysiological signs of deficiencies in early stages of information processing reflected by MMN, which were most prominent in ADHD + CD.

Although in our study there were no significant group differences for auditory information processing reflected by Nd and P3b, data of other studies demonstrate differences between ADHD and healthy children (overview in Jonkman 1997) and suggest that further research is warranted in this complex field. The aspect of comorbidity should be given particular consideration, since different associated psychopathology (e.g., CD versus Tic) may influence brain dynamics and performance of ADHD in a different manner, suggesting more problems when CD is the comorbid factor, while there seems to be little negative influence by Tic. Thus, clarification of comorbidity issues seems to be important for the development of differentiated and individualized treatment strategies for child psychiatric patients.

Acknowledgements We are grateful to Gisela Janzer, Angela Nassal, Verena Heinrich and Wolfgang Woerner for their assistance at different steps of data acquisition and preparation. This work was supported by a grant of the German Research Society (Deutsche Forschungsgemeinschaft, SFB 258/E2, University of Heidelberg) and a post-doctoral fellowship to Ben van't Klooster by the European Union (BIOPHYRIS)

References

Achenbach TM, Edelbrock C (1983) Manual for the Child Behavior Checklist and Revised Child Behavior Profile. Burlington VT, University of Vermont, Dept of Psychiatry

Alain C, Woods DC, Knight RT (1998) A distributed cortical network for auditory sensory memory in humans. Brain Research 23, 812 : 23–37

Alho K (1994) Lesions of frontal cortex diminish auditory mismatch negativity. Electroencephalographie and Clinical Neurophysiology 91 : 353–362

Alho K, Sams M, Paavilainen P (1986) Small pitch separation and the selective-attention effect on the ERP. Psychophysiology 23 : 189–197

American Psychiatric Association (1987) Diagnostic and Statistical Manual III (revised). American Psychiatric Association, Washington

Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychology Bulletin 121 : 65–94

Casey BJ, Castellanos FX, Giedd JN, Marsch WL, Hamburger SD, Schubert AB, Vauss YC, Vaituzis AC, Dickstein DP, Safratti SE, Rapoport JL (1997) Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 36 : 374–383

Csépe V, Dieckmann B, Hoke M, Ross B (1992) MMN to pitch change of acoustic stimuli in preschool and schoolage children. EPIC X (International Conference on Event-Related Potentials of the Brain), Eger (Hungary)

Dumais-Huber C (1993) Electrical brain acitivity and stimulus control: a study on the regulatory processes of the frontal cortex in psychiatric disordered children. Doctoral Thesis, University of Heidelberg, Germany

Dumais-Huber C, Rothenberger A (1992) Psychophysiological correlates of orienting, anticipation and contingency changes in children with psychiatric disorders. Journal of Psychophysiology 6 : 225–239

Esser G, Blanz B, Geisel B, Laucht M (1989) Mannheimer Elterninterview. Strukturiertes Interview zur Erfassung von kinderpsychiatrischen Auffälligkeiten. Belz Test, Weinheim, pp 7–10

Giard MH, Perrin F, Pernier J, Bouchet P (1990) Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. Psychophysiology 27 : 627–640

Giard MH, Perrin F, Pernier J, Bouchet P (1990) Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. Psychophysiology 27 : 627–640

Giard MH, Perrin F, Pernier J, Peronnet F (1988) Several attention-related waveforms in auditory areas: a topographic study. Electroencephalography and Clinical Neurophysiology 69 : 371–384

Goyette CH, Conners CK, Ulrich RF (1978) Normative data on revised Conners Parent and Teacher Rating Scales. Journal of Abnormal Child Psychology 6 : 221–236

Hansen JC, Hillyard SA (1980) Endogenous brain potentials associated with selective auditory attention. Electroencephalography and Clinical Neurophysiology 49 : 277–290

Harcherik DF, Leckman J, Detlor J, Cohen DJ (1984) A new instrument for clinical studies of Tourette's syndrome. Journal of the American Academy of Child and Adolescent Psychiatry 23 : 153–160

Hari R, Rif J, Tiihonen J, Sams M (1992) Neuromagnetic mismatch fields to single and paired tones. Electroencephalography and Clinical Neurophysiology 82 : 152–154

Jensen PS, Martin D, Cantwell DP (1997) Comorbidity in ADHD: implications for research, practice and DSM-V. Journal of the American Academy of Child and Adolescent Psychiatry 36 : 1065–1079

Jonkman LM (1997) Effects of methylphenidate on brain activity and behavior of children with Attention-Deficit Hyperactivity Disorder. Post-doctoral Thesis, University of Utrecht, The Netherlands

Jonkman LM, Kemner C, Verbaten MN, Koelega HS, Camfferman G, van der Gaag RJ, Buitelaar JK, van Engeland H (1997) Event-related potentials and performance of attention-deficit hyperactivity disorder children and normal controls in auditory and visual selective attention tasks. Biological Psychiatry 41 : 690–702

Karayanidis F, Robaey P, Bourassa M, Geoffroy G, Pelletier G (1997) ERPs indicate differences in visual attention between attention deficit hyperactivity disorder and control boys in the abscence of performance differences. Psychophysiology, SPR Abstracts : S 50

Klorman R, Brumaghim JT, Salzman LF, Strauss J, Borgstedt AD, McBride MC, Loeb S (1990) Effects of methylphenidate on processing negativities in patients with attention-deficit hyperactivity disorder. Psychophysiology 27 : 328–337

Klorman R, Salzman LF, Bauer LO, Coons HW, Borgstedt AD, Halpers WI (1983) Effects of two doses of methylphenidate on cross-situational and borderline hyperactive children's evoked potential. Electroencephalography and Clinical Neurophysiology 56 : 169–185

Klorman R, Salzman LF, Pass HL, Borgstedt AD, Dainer, KB (1979) Effect of methylphenidate on hyperactive children's evoked responses during passive and active attention. Psychophysiology 16 : 23–29

Knight RT, Hillyard SA, Woods D, Neville HJ (1981) The effects of frontal cortex lesions on event-related potentials during auditory selective attention. Electroencephalography and Clinical Neurophysiology 52 : 571–582

Korpilahti P, Lang HA (1994) Auditory ERP components and mismatch negativity in dysphasic children. Electroencephalography and Clinical Neurophysiology 91 : 256–264

Leeuwen van T, Brandeis T, Overtoom CCE, Pascual-Marqui RD, Klooster van't B, Rothenberger A, Sergeant JA, Steinhausen Hch (1998) The continous performance test revisited with neuroelectric mapping: impaired orienting in children with attention deficits. Brain and Behavior Research 94 : 97–110

Loiselle D, Stamm JS, Maitinsky S, Whipple SC (1980) Evoked potential and behavioral signs of attentive dysfunctions in hyperactive boys. Psychophysiology 17 : 193–201

Näätänen R (1990) The role of attention in auditory information processing as revealed by event-related potentials and other measures of cognitive function. Behavior and Brain Sciences 13 : 201–288

Näätänen R (1992) Attention and Brain Function. Lawrence Erlbaum Associates, New Jersey

Näätänen, R & Alho, K (1995) Generators of electrical and magnetic mismatch responses in humans. Brain Topography 7 : 315–320

Oades RD, Dittmann-Balcar A, Schepker R, Eggers C, Zerbin D (1996) Auditory event-related potentials (ERPs) and mismatch negativity (MMN) in healthy children and those with attention-deficit or tourette/tic symptoms. Biological Psychology 43 : 163–185

Riccio CA, Hynd GW, Cohen MJ, Hall J, Molt L (1994) Comorbidity of central auditory processing disorder and attention-deficit hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 33 : 6

Rothenberger A (1995) Electrical brain activity in children with hyperkinetic syndrome: evidence of frontal cortical dysfunction. In: Sergeant J (ed) European Approaches to Hyperkinetic Disorder. Trümpi, Zürich, pp 255–270

Rothenberger A (1996) Tourette-Syndrom und assoziierte neuropsychiatrische Auffälligkeiten. Zeitschrift für Klinische Psychologie 25 : 259–279

Rothenberger A, Woerner W, Dumais-Huber C, Moll GH, Röhrkohl N, Yordanova J (1994) Welche Bedeutung haben Merkmale des Hyperkinetischen Syndroms bei Kindern mit Tic-Störungen? In: Todt H., Heinicke D (eds), Aktuelle Neuropädiatrie 1993. Ciba-Geigy Verlag, Wehr

Sams M, Aulanko R, Aaltonen O, Näätänen R (1990) Event-related potentials to infrequent changes in synthesized phonetic stimuli. Journal of Cognitive Neuroscience 2:344–347

Sams M, Kaukoranta E, Hamalainen M, Näätänen R (1991) Cortical activity elicited by changes in auditory stimuli: different sources for the magnetic N100 and mismatch responses. Psychophysiology 28:21–29

Satterfield HJ, Schell AM, Nicholas TW, Backs RW (1988) Topographic study of auditory event-related potentials in normal boys and boys with attention deficit disorder with hyperactivity. Psychophysiology 25:591–606

Satterfield JH, Schell AM, Nicholas T (1994) Preferential neural processing of attended stimuli in attention-deficit hyperactivity disorder and normal boys. Psychophysiology 31:1–10

Satterfield JH, Schell AM, Nicholas TW, Satterfield BT, Freese TH (1990) Ontogeny of selective attention effects on event-related potentials in attention-deficit hyperactivity disorder and normal boys. Biological Psychiatry 28:879–903

Scherg M, Vajsar J, Picton TW (1989) A source analysis of the late human auditory evoked potentials. Journal of Cognitive Neuroscience 1:336–355

Schreiber H., Stolz-Born G, Kornhuber HH, Born J (1992) Event related potential correlates of impaired selective attention in children at high risk for schizophrenia. Biological Psychiatry 32:634–651

Schuerholz LJ, Singer HS, Denkla MB (1998) Gender study of neuropsychological and neuromotor function in children with Tourette syndrome with and without attention-deficit hyperactivity disorder. Journal of Child Neurology 13:277–282

Sergeant JA (ed) (1995) Eunethydis. European Approaches to Hyperkinetic Disorder. Trümpi, Zürich

Serra JM, Giard MH, Yago E, Alhok K, Escera C (1998) Bilateral contribution from frontal lobes to MMN. International Journal of Psychophysiology 30:236–237

Shaffer D, Gould MS, Brasic I, Ambrosini P, Fisher P, Bird H, Aluwahlia S (1983) A Children's Global Assessment Scale (CGAS). Archives of General Psychiatry 40:1128–1231

Shapiro AK, Shapiro ES, Young JG, Feinberg TE (1988) Gilles de la Tourette Syndrome, 2nd ed. Raven Press, New York

Tiitinen H, Alho K, Huotilainen M, Ilmoniemi RJ, Simola J, Näätänen R (1993) Tonotopic auditory cortex and the magnetoencephalographic (MEG) equivalent of the mismatch negativity. Psychophysiology 30(5):537–540

Winsberg BG, Javitt DC, Shanahan-Silipo G (1997) Electrophysiological indices of information processing in methylphenidate responders. Biological Psychiatry 42:434–445

Winsberg BG, Javitt DC, Shanahan-Silipo G, Doneshka P (1993) Mismatch negativity in hyperactive children: effects of methylphenidate. Psychopharmacology Bulletin 29:229–233

Woods DL (1990) The physiological basis of selective attention: implications of event-related potential studies. In: Rohrbaugh JW, Parasuraman R, Johnson R jr (eds) Event-related Potentials: Basic Issues and Applications. Oxford University Press, New York, pp 178–209

Yordanova J, Dumais-Huber C, Rothenberger A (1996) Coexistence of tics and hyperactivity in children: no additive effect at the psychophysiological level. International Journal of Psychophysiology 21:121–133

Yordanova J, Dumais-Huber C, Rothenberger A, Woerner W (1997) Frontocortical activity in children with comorbidity of tic disorder and attention-deficit hyperactivity disorder. Biological Psychiatry 41:585–594

Yordanova J, Rothenberger A, Moll G, Heinrich H (1994) Auditory selective attention in children with tic disorder. Poster presented at the Seventh International Swiss Brain Mapping Meeting, Zürich, March 11–12

Zambelli AJ, Stamm JS, Maitinsky S, Loiselle DL (1977) Auditory evoked potentials and selective attention in formerly hyperactive adolescent boys. American Journal of Psychiatry 134:742–747