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Increased event-related theta activity as a psychophysiological marker of comorbidity in children with tics and attention-deficit/hyperactivity disorders

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Objective: **The question as to whether coexisting tic disorder (TD) and attention-deficit/hyperactivity disorder (ADHD) in children represent a combination of two independent pathologies, a separate nosologic entity manifested by both tics and hyperactivity or a phenotype subgroup of one of the two major clinical forms has received increasing attention. The aim of the present study was to classify the TD+ADHD comorbidity in the neurocognitive domain and to elucidate the neurophysiological background of TD+ADHD coexistence by analyzing event-related electroencephalographic (EEG) oscillations in the theta (3–7.5 Hz) frequency band.**

Methods: **Event-related potentials were recorded at 10 electrodes in 53 children (9–13 years old) from four groups (healthy controls, TD-only, ADHD-only, and combined TD+ADHD patients), while they performed an auditory selective attention task requiring a button press to a predefined target. Event-related theta oscillations were analyzed by means of time–frequency decomposition (wavelet analysis) in two latency ranges—early (0–200 ms) and late (200–450 ms). The effects of psychopathology factors (TD and ADHD) and task variables (attended channel and stimulus task relevance) on early (ETR) and late (LTR) theta responses were evaluated statistically. Theta response measures were further correlated with psychopathology scores and spontaneous theta EEG activity.**

Results: **(1) The ETR was enhanced only in comorbid children and did not differ between the control, TD-only, and ADHD-only groups. (2) The LTR was larger in children with ADHD (ADHD-only and comorbid), but this effect was mediated by the spontaneous theta EEG activity. (3) The ETR was larger to attended stimuli at frontal–central electrodes contralateral to the side of attention, to the target stimulus type at frontal locations, and at the hemisphere contralateral to the side of the response. The functional reactivity and scalp distribution of ETRs were modulated by psychopathological factors.**

Conclusions: **In the neurocognitive domain, the TD+ADHD comorbidity can be identified as a unique nosologic entity. Both the spontaneous theta activity and late event-related theta oscillations appear as neurophysiological markers of the ADHD condition. In children, the early event-related theta oscillations may be associated with representations of relevant target features in working memory.**

Significance: **(1) A new model is proposed according to which TD+ADHD comorbidity can be classified at different levels (from neurobiological to cognitive). (2) The functional significance of stimulus-synchronized theta oscillations in children is described for the first time.**

Keywords: Attention-deficit/hyperactivity disorder; Tic disorder; Event-related theta oscillations; ERP; EEG; Memory and attention; Children

Introduction

Because of their prevalence and great social impact, hypermotor symptoms in children have been increasingly focused on in recent child psychiatric research (Buitelaar and Rothenberger, 2004). Hypermotor behavior is identified in attention-deficit/hyperactivity disorder (ADHD) and tic disorder (TD). The core clinical symptoms of ADHD are inattention, impulsivity, and general motor hyperactivity (e.g., Swanson et al., 1998). In contrast, though being a complex neuropsychiatric disturbance, TD is essentially characterized by multiple motor and/or phonic tics with fluctuating phenomenology (Rothenberger, 1991; Leckman et al., 1997; Leckman, 2002). Extensive literature has

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CWT, continuous Wavelet transform; EEG, electroencephalogram; ERP, event-related potential; ETR, early theta response; LTR, late theta response; NT–A, non-target–attended; NT–NA, non-target–non-attended; RT, reaction time; T–A, target–attended; TF, time–frequency; TD, tic disorder; T–NA, target–non-attended; TR, theta response.

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documented that in TD, comorbidity with ADHD ranges from 35 to 90% in different studies (average 52%, review: Spencer et al., 1998; Rothenberger and Banaschewski, 2005), while in ADHD patients, tic disorders are seen in 11–33% (MTA Coop. Group, 1999a,b; Kadesjo and Gillberg, 2001), both of which are much above the by-chance rate of combination. The overlap and relationships between these two psychiatric disturbances have been recognized as critical with respect to treatment choice and clinical consequences. Accordingly, the question as to whether coexisting TD and ADHD in children represent a combination of two independent pathologies (*additive model*), a separate nosologic entity manifested by both tics and ADHD (*interactive model*), or a phenotype subgroup of one of the two major clinical forms (*phenotype model*) has received increasing attention (Yordanova et al., 1996, 1997; Rothenberger et al., 2000; Moll et al., 2001).

At the level of clinical evaluation, previous epidemiologic and genetic studies have supplied evidence for each of the different models for TD+ADHD (e.g., Comings, 1995; Pauls et al., 1993; Spencer et al., 1998), which may at least partially stem from limitations imposed by symptom overlap. Therefore, to pursue the origins of comorbidity, the pathophysiological mechanisms underlying TD+ADHD coexistence need to be explored. At the neurophysiological level, motor processes in TD+ADHD have been examined by means of transcranial magnetic stimulation (TMS) and event-related brain potentials (ERPs). TMS application has supported the additive model by demonstrating that TD and ADHD may contribute independently to the excitability of the motor system in comorbid children (Moll et al., 2001). However, ERP studies have not yielded conclusive results (Dumais-Huber and Rothenberger, 1992; van der Meere et al., 1996; Yordanova et al., 1996, 1997). Analysis of slow negative potentials has shown that the preparatory motor cortical activation is similar between comorbid and TD-only group in support of the phenotype model (Yordanova et al., 1996). Further examination of the post-imperative negative variation has demonstrated that TD+ADHD may manifest itself as either a combined (additive model) or a unique (interactive model) psychopathology depending on motor response controllability (Yordanova et al., 1997). Thus, in TD+ADHD coexistence, two independent pathogenic sources may contribute to the inhibition/disinhibition mechanisms within the motor system (Moll et al., 2001), whereas the neurophysiological mechanisms subserving higher motor control may manifest deviations that do not result from a simple combination of TD- and ADHD-related deficits but may interact upon specific cognitive demands.

In this regard, analysis of external stimulus processing may provide important additional information about the neurocognitive background of TD+ADHD comorbidity. Previous ERP studies have demonstrated deviations in active stimulus processing during attention conditions in both TD-only (van de Wetering et al., 1985; van Woerkom et al., 1994; Oades et al., 1996) and ADHD-only children (Satterfield et al., 1990, 1994; Jonkman et al., 1997; Karayanidis et al., 2000; van der Stelt et al., 2001). In TD, ERP alterations have been attributed to difficulties in focusing, sustaining and allocating attention (Oades et al., 1996; Johannes et al., 2001), and to increased processing of non-relevant stimuli (van Woerkom et al., 1994). In ADHD, ERP variations are thought to reflect sustained and focused attention deficiency as well as problems of inhibition and working memory (Barkley, 1997; Tannock, 1998; Swanson et al., 1998). Despite the ERP evidence for specific changes of cognitive stimulus processing in pure TD and ADHD (Oades et al., 1996), in only one previous study, has stimulus processing been analyzed in combined TD+ADHD (Rothenberger et al., 2000). The results from an auditory attention task have shown that frontal and temporal mechanisms of stimulus selection may be similarly impaired in comorbid and ADHD-only children, but comparisons with pure TD have not been made. Thus, the mechanisms of cognitive stimulus evaluation in TD+ADHD need further examination.

In child psychiatric research, cognitive stimulus processing is conventionally explored by subtraction waveforms (e.g., Satterfield et al., 1990) or by ERP measures in the time domain (reviews: Tannock, 1998; Barry et al., 2003b, etc.). However, subtraction waveforms do not distinguish the source of differences and are prone to misinterpretations (van Boxtel, 2004). Likewise, a time domain ERP component may have a complex heterogeneous structure comprising several subcomponents that are completely or partially overlapped (Basar, 1980; Falkenstein et al., 1995). Such subcomponents may be functionally distinctive and may have specific frequency characteristics (delta, theta, alpha, gamma), but they remain undetected in the time domain ERPs (Basar, 1998; Kolev et al., 1997; Demiralp and Ademoglu, 2001; Yordanova et al., 2000, 2004). These EEG responses to external stimuli, called event-related oscillations or time–frequency ERP components, can be extracted by ERP decomposition in the time–frequency domain and can provide new refined information about neuroelectric dynamics of information processing (e.g., Basar, 1998; Kolev and Yordanova, 1997; Heinrich et al., 1999; Demiralp and Ademoglu, 2001; Makeig et al., 2004; Yordanova et al., 2004).

With this background, the main objective of the present study was to further classify the TD+ADHD comorbidity in the neurocognitive domain by (1) analysis of cognitive stimulus processing and (2) using time–frequency analysis of ERPs. As in the study of Rothenberger et al. (2000), here different models of TD+ADHD were tested in an auditory selective attention task, in which stimulus task relevance was varied on the base of internally guided spatial attention and physical stimulus features. Four groups of children (controls, TD-only, ADHD-only, and TD+ADHD) were studied with a balanced statistical design (Yordanova et al., 1996). The following specific goals were targeted.

(1) A main goal was to explore whether and how the processing of stimulus task relevance would depend on major psychopathology symptoms presented with TD, ADHD, and their combination. As a relevant analytic tool, stimulus-synchronized oscillations from the theta frequency range were used because of the following reasons: (a) time–frequency decomposition of ERPs from the current data set revealed that the ERPs contained prominent components from the theta (3–7.5 Hz) frequency band (see Results), which indicated that theta oscillations represented a most relevant EEG signal in this task. (b) Theta responses have been consistently associated with focused attention (Demiralp and Basar, 1992; Basar-Eroglu et al., 1992) and working memory processes (Yordanova and Kolev, 1996, 1997; 1998a,b; Kolev et al., 1997), thus appearing as an adequate correlate of cognitive stimulus evaluation. (c) Theta EEG frequency has been most frequently related with activations of frontal lobe networks (Basar et al., 2001; Sarnthein et al., 1998; von Stein and Sarnthein, 2000; Niedermeyer, 2001). Since frontal networks have been suggested to be differentially impaired in TD and ADHD, analysis of the theta frequency band would be especially appropriate to discriminate TD, ADHD, and TD+ADHD conditions.

(2) Another goal was to extend current views on the neurophysiological background of TD+ADHD by differentiating

neurobiological from neurocomputational deficits. This was done by analyzing the spontaneous EEG theta activity in parallel with event-related theta oscillations. Spontaneous EEG rhythms reflect the neurobiological organization of frequency-specific networks in the brain, whereas event-related oscillations reflect the reorganization of these networks in relation to event-specific computational demands (Basar, 1998; Yordanova and Kolev, 1998a,b). It is noteworthy that children with ADHD and other psychiatric disorders have larger spontaneous theta EEG activity than normal children (Clarke et al., 2001; for review, see Barry et al., 2003a). This implies that irrespective of specific processing demands, there exists a basic (unspecific) alteration of the neuroelectric signaling in these children (Niedermeyer and Naidu, 1997, 1998; Niedermeyer, 2001; Clarke et al., 2001). Thus, analysis of both the spontaneous and event-related theta activity would allow to assess whether the TD+ADHD comorbidity may be associated (a) with basic alterations of the neurobiological substrate, (b) with deficits emerging only upon specific processing demands, or (c) with both.

(3) A third goal of the present study was to shed further light on the functional significance of event-related theta responses. Despite the evidence for theta involvement in cognitive processes such as mental arithmetic, will, attention, episodic memory, memory gating, spatial learning, navigation, etc. (Basar et al., 2001; Klimesch, 1999; Kahana et al., 2001; Raghavachari et al., 2001; Caplan et al., 2003; etc.), the precise functional correlates of theta oscillations require further clarification. As stated earlier (Demiralp and Basar, 1992; Basar-Eroglu et al., 1992; Basar et al., 2001; Yordanova and Kolev, 1997; 1998a; Kolev et al., 1997), analysis of event-related EEG is expected to increase most substantially the understanding of theta functional significance (Kahana et al., 2001). The present study therefore aimed at refining the functional correlates of stimulus-synchronized theta oscillations elicited in an auditory selective attention task in children.

Methods

Subjects

Within the framework of a multilevel longitudinal study on central nervous regulatory mechanisms in child psychiatric disorders, a total of 56 boys participated in the experiment. Table 1 presents group characteristics of normal and psychopathological assessment. Children were matched for gender, age, and full-scale IQ. They belonged to four groups (healthy controls, TD-only, ADHD-only, and combined TD+ADHD patients, $n = 14$ each). Due to a large number of EEG artifacts, three subjects from the TD+ADHD group were excluded from further analyses. The entire study received prior approval by the local ethical review board. Informed consent was obtained from the children as well as the parents of each investigated child.

Subjects were totally unmedicated or drug-free for at least 4 weeks prior to the experiment. Healthy controls 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

Table 1
Psychiatric characteristics of children according to clinical group (mean values)

Group	1 Control $n = 14$	2 TD $n = 14$	3 ADHD $n = 14$	4 TD + ADHD $n = 11$	1 vs. 2 P	1 vs. 3 P	1 vs. 4 P	2 vs. 3 P	2 vs. 4 P	3 vs. 4 P
Age										
Mean (months)	137.2	139.4	139.7	138.5	NS	NS	NS	NS	NS	NS
±SD (months)	21.5	26.5	23.4	28.7						
SES (low = 1… high = 5)	3.0	2.8	2.9	3.1	NS	NS	NS	NS	NS	NS
IQ	105.7	103.2	99.0	103.2	NS	NS	NS	NS	NS	NS
CBCL T values										
Total	49.4	57.4	70.6	69.2	**	***	***	**	**	NS
Externalizing	50.8	58.6	74.9	71.1	NS	***	***	**	NS	NS
Internalizing	49.5	54.9	67.2	67.2	NS	***	***	**	**	NS
Attention	2.6	4.9	11.2	9.5	*	***	***	***	***	NS
Conners	3.4	7.2	20.0	18.8	NS	***	***	***	***	NS
TSSS score	–	11.1	–	7.8	–	–	–	–	NS	–
TSGS-Tic	–	3.1	–	3.1	–	–	–	–	NS	–
Leyton										
Total (“Yes”)	14.0	14.8	19.7	15.8	NS	NS	NS	NS	NS	NS
Resistance	11.4	14.7	18.6	11.6	NS	NS	NS	NS	NS	NS
Interference	11.3	15.1	25.9	13.1	NS	**	NS	NS	NS	NS
MFFT										
Time	238.0	182.0	148.0	169.0	NS	*	NS	NS	NS	NS
Errors	3.0	5.5	9.0	5.9	NS	***	NS	NS	NS	NS
Score	2.2	4.9	8.5	6.1	NS	***	NS	NS	NS	NS
CGAS (0–100)	87.1	62.5	45.0	57.0	***	***	***	**	NS	NS

TD, tic disorder; ADHD, attention-deficit/hyperactivity disorder; SES, socioeconomic status; CBCL, Child Behavior Checklist; TSSS, Tourette Syndrome Severity Scale; TSGS, Tourette Syndrome Global Scale; Leyton, Leyton inventory on obsessive–compulsive behavior; MFFT, Matching Familiar Figures Test; CGAS, Children’s Global Assessment Scale. Significance levels are given for pairwise comparisons between groups performed with Mann–Whitney U tests (two-tailed): *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; NS, not significant.

(314.01) and/or for chronic motor/vocal tic or Tourette disorder (307.22; 307.23). Patients with additional psychiatric comorbidity such as obsessive–compulsive disorder, dyslexia, etc. were excluded. Detailed information on psychopathology and level of social functioning according to the Children's Global Assessment Scale (CGAS, Shaffer et al., 1983) was gathered by clinical investigation (including a structured parent interview, several questionnaires, and neuropsychological testing) and pooled to yield best estimate based diagnoses by board-certified child psychiatrists.

For all children, the Child Behavior Checklist (CBCL, Achenbach and Edelbrock, 1983) was used as screening instrument 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). In addition, the Matching Familiar Figures Test (MFFT, Kagan and Kogan, 1970) was administered to assess cognitive impulse control, which is often a great problem in hyperkinetic children, while the child version of the Leyton Obsession Inventory (Berg et al., 1986) was used to evaluate additionally obsessive–compulsive behavior (Moll et al., 2000). Threshold scores used as exclusion criteria for the control group were >60 for CBCL Total, >8 for Conners questionnaire, and >20 for Leyton Inventory. Both control children and patients were excluded if their IQ was lower than 80. For 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). All subjects were right handed.

Subgroups

The examined patients presented with chronic multiple tics, ADHD, or a combination of tics and ADHD. There were two groups of TD patients, each corresponding to one of the two levels of hyperactivity as reflected by the Conners scores: TD-only (Conners = 0–11) and TD+ADHD (Conners = 18–30). ADHD-only patients (without TD) were selected in such a way that their Conners and CBCL attention scores would match those of the TD+ADHD children (Table 1). The table shows that (a) ADHD children from the pure and comorbid groups belong to the combined type, (b) the degrees of hyperactivity and inattention problems are similar for the ADHD-only and TD+ADHD groups, and (c) the severity of tic problems does not differ between TD-only and TD+ADHD groups.

Task procedure

In each of the two recording conditions, a total of 240 auditory stimuli were used. Two stimulus types were presented randomly to the left and right ear via headphones. The stimuli were non-target (1000 Hz, $n = 144$, $P = 0.6$) and target (1500 Hz, $n = 96$, $P = 0.4$) tones with a duration of 120 ms, rise/fall time of 10 ms, and intensity of 85 dB SPL. Interstimulus intervals varied randomly from 1150 to 1550 ms. Equal numbers of each stimulus type were presented to the left and right ear. In the first condition, subjects were instructed to press a button in response to the targets presented to the right, while in the second condition, the attended targets were the high tones presented to the left. Thus, there were four signal types in each series: target–attended (T–A, $n = 48$), target–non-attended (T–NA, $n = 48$), non-target–attended (NT–A, $n = 72$), and non-target–non-attended (NT–NA, $n = 72$). During the entire recording session, subjects kept their eyes open and responded with the right hand.

Data recording

EEG activity was recorded via Nihon Kohden Ag/AgCl cup electrodes (impedance kept below 3 kΩ) fixed to the scalp at F3, Fz, F4, C3, Cz, C4, P3, P4 locations according to the International 10/20 system and referred to the two mastoid electrodes, which were connected via a 10-kΩ resistor (voltage divider, cf., Nunez, 1981, pp. 191–193). Spontaneous EEG was registered also at Oz. Vertical and horizontal electro-oculograms (EOGs) were simultaneously recorded from electrodes above and below the right eye and at the outer canthi. Reaction time data were collected as behavioral measures. The EEG and EOG signals were amplified and filtered with cutoff frequencies of 0.03 and 70 Hz. Analysis epochs of 150 ms before and 1000 ms after stimulus onset were sampled with a frequency of 500 Hz.

Data analysis

EEG epochs contaminated with ocular or muscle artifacts were rejected, with only traces lower than 200 μV peak-to-peak being accepted. Next, slight horizontal and vertical eye movements preserved in the accepted trials were corrected by means of a linear regression method for EOG correction (Dumais-Huber and Rothenberger, 1992). To control strictly for sweep number effects, for each subject, 35–40 sweeps were randomly selected from artifact-free trials of each stimulus type and used for further analysis.

Spontaneous theta activity

The spontaneous theta EEG activity was evaluated for artifact-free EEG epochs of 20 s recorded, while the subjects were relaxing with closed eyes. The 20-s epoch was divided into 10 time windows of 2-s duration each. Each 2-s epoch was transformed to the frequency domain by means of Fast Fourier Transform (FFT). Afterwards, averaging in the frequency domain was performed to increase statistical validity of frequency domain measures. In individual spectra, peaks of frontal theta activity were detected between 4 and 7 Hz, without a clear group-dependent distribution of peak frequencies within this range. To account for these individual variations in theta peaks, theta power was measured for separate subbands (4–5 and 6–7 Hz) for each subject and electrode. Although these subbands are smaller than the broader theta range used for analysis of event-related theta oscillations (see below), this approach was chosen to provide for a more precise characterization of the spontaneous theta activity. Furthermore, in contrast to ADHD-only and tic patients (e.g., Clarke et al., 1998, 2001; Barry et al., 2003a), the spontaneous theta EEG of TD+ADHD children has not been sufficiently described so far. For technical reasons, the spontaneous EEG records were not done for 3 subjects from the control group, 3 subjects from the ADHD-only group, 4 subjects from the TD-only group, and 2 subjects from the comorbid group. Spontaneous EEG was thus analyzed in 11 controls, 10 TD-only, 11 ADHD-only, and 9 comorbid children.

Event-related theta activity

To analyze phase-locked theta oscillations individual averaged ERPs were obtained. To identify precisely the frequency content of time–frequency (TF) ERP components from the theta frequency

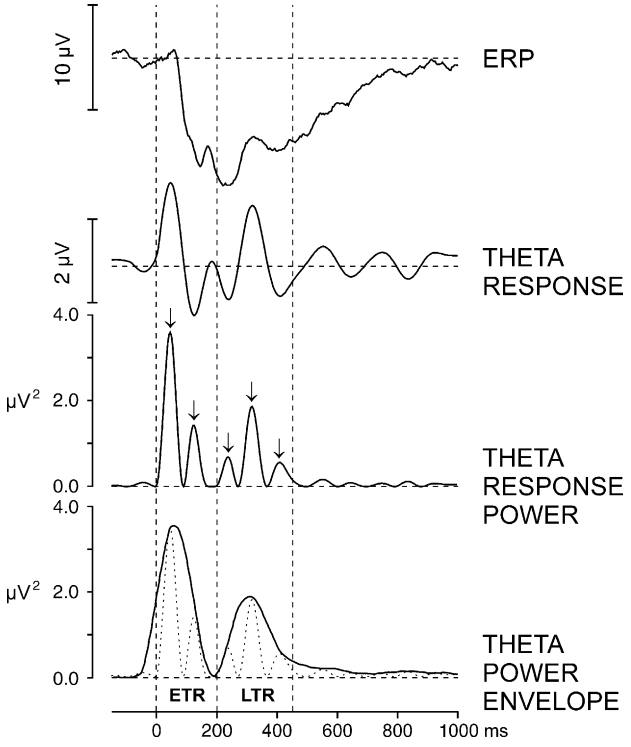

Fig. 1. Schematical illustration of methods. Event-related averaged potential (ERP), its time–frequency component in the theta (3–7.5 Hz) range (theta response), theta response power, and envelope of theta response power. Early (0–200 ms) and late (200–450 ms) theta responses are designated accordingly as ETR and LTR. Maximal power values (marked by arrows) are measured, averaged for each of the time windows of ETR and LTR and further subjected to statistical analyses. Envelopes of theta response power are used only for visualization. Positivity is upwards. Please note that the original ERPs of children contain large-amplitude slow components from the delta frequency (0.1–3 Hz) range. These large delta components overlap theta oscillations that are smaller in amplitude (compare the scales of ERP and theta response), which may obscure the expression of event-related theta activity in the wide-band ERP.

range, ERPs were decomposed in the TF domain. Decomposition was done by means of a continuous Wavelet transform (CWT, Mallat, 1999). TF representations were calculated by Morlet's wavelets as described previously (Tallon-Baudry et al., 1997; see also for similar application Yordanova et al., 2004). The analytical presentation of Morlet's wavelet $w(t, f)$ is:

$$w(t,f) = A\ \exp\left(-t^2/2\sigma_t^2\right)\exp(2i\pi f t)$$

where t is time, f is frequency, $A = (\sigma_t\sqrt{\pi})^{-1/2}$, σ_t is the wavelet duration, and $i = \sqrt{-1}$.

For TF plots, a ratio of $f_0/\sigma_f = 3.8$ was used, where f_0 is the central frequency and σ_f is the width of the Gaussian shape in the frequency domain. The choice of this f_0/σ_f ratio was oriented to a better identification of slower phase-locked components expected to be present in the ERP analysis epoch, since this ratio affects the shape of the Morlet wavelet by decreasing its decay. The analysis was performed in the frequency range 0.1–12 Hz with a central frequency at 0.1-Hz intervals. For different f_0, time and frequency resolutions were calculated as $2\sigma_t$ and $2\sigma_f$, respectively (Tallon-Baudry et al., 1997).

As illustrated in Fig. 1, time–frequency ERP components from the theta range were extracted in the time domain and squared to obtain post-stimulus theta response power. According to the observations (see Results), ERP theta components were enhanced in two latency ranges after stimulus–early (0–200 ms) and late (200–450 ms). Accordingly, as indicated in Fig. 1, the mean value of successive power maxima was measured for these two time windows to reflect the magnitude of phase-locked theta responses. To normalize data, these measures as well as those for the spontaneous theta activity were log10 transformed before statistical evaluation. For visualization, theta power envelopes were used (Fig. 1, bottom).

Statistical analysis

The analysis was a repeated measures analysis of variance (ANOVA) with two between-subjects factors: TD and ADHD. The levels of the TD factor were 'with TD' (TD+) comprising the TD-only and TD+ADHD groups vs. 'without TD' (TD−) comprising the Controls and ADHD-only groups. The levels of the ADHD factor were 'with ADHD' (ADHD+) comprising the ADHD-only and TD+ADHD groups vs. 'without ADHD' (ADHD−) comprising the Controls and TD-only groups. The within-subjects task variables were Attended channel (attended vs. non-attended) and Stimulus task relevance (target vs. non-target). Measures from 8 electrodes (F3, Fz, F4, C3, Cz, C4, P3, P4) formed the levels of the within-subjects Electrode factor.

In the present experimental design, the effects of Attended channel are confounded with those of Series sequence (first [attend-right] vs. second [attend-left]) and Side of stimulation (right vs. left). Therefore, as a first step, the effects of these variables were tested to control for a possible influence of each of these factors on group differences. These analyses revealed a main effect of series sequence and no effects of side of stimulation on ETR or LTR ($F(1,49) < 1.21$, $P > 0.28$). Thus, the final analysis design was TD × ADHD × Attended channel × Stimulus task relevance × Series sequence × Electrode. The complexity of this

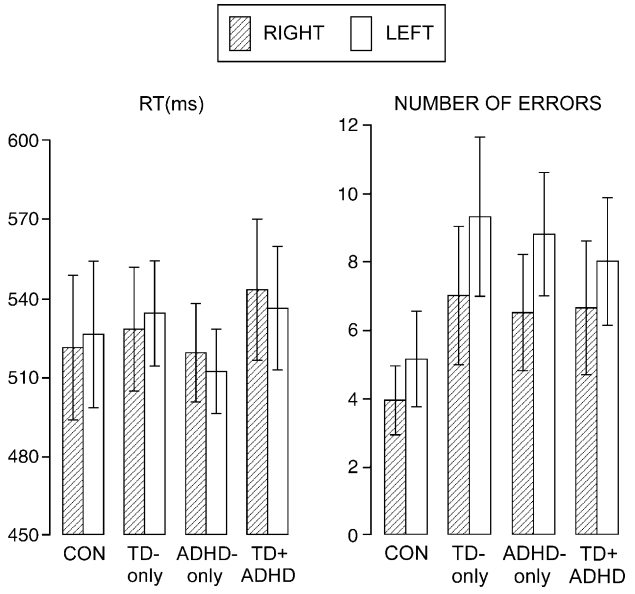

Fig. 2. Reaction time (RT, mean ± SD) and number of errors (mean ± SD) for different groups: CON—controls, TD—tic disorder, ADHD—attention-deficit/hyperactivity disorder, TD+ADHD-comorbid group, in the first (attend RIGHT) and second (attend LEFT) conditions.

design is not compromised by the relatively small number of subjects in each group because there were only two between-subjects variables (TD and ADHD), while the other factors were repeated-measures factors. Measures of theta power were analyzed separately for the early (0–200 ms) and late (200–450 ms) time windows. Significant interactions were tested as required by each particular result. For all ANOVAs, the degrees of freedom were corrected by using the Greenhouse–Geisser procedure. The original *df* and corrected probability values are presented in the results. Log10 transformed values of the spontaneous theta power within 4–5 and 6–7 Hz bands were subjected to a repeated measures analysis of variance TD × ADHD × Laterality (left [F3, C3, P3] vs. midline [Fz, Cz, Oz] vs. right [F4, C4, P4]) × Region (frontal [F3, Fz, F4] vs. central [C3, Cz, C4] vs. posterior [P3, Oz, P4]).

To test for the associations of theta response measures with clinical scores and spontaneous EEG theta activity, multiple regression analyses were carried out as described in the results. In these analyses, only subjects who had the spontaneous EEG analyzed (see above) were included.

Results

Behavioral data

All subjects performed the task accurately, with the percentage of errors (omission and commission) being less than 3%. Fig. 2 presents group means of RT and error rate. It is shown that there were no significant differences in RT among the four groups ($P > 0.5$), nor between the first (attend-right) and second (attend-left) conditions ($P > 0.5$). Yet, RT variability was lowest in the control group of children (TD × ADHD, $F(1,49) = 5.94$, $P < 0.05$). Error rate tended to be higher in patient groups and in the second experimental session, but neither of these differences reached a level of significance.

Spontaneous theta activity

The spontaneous 4–5 Hz EEG activity manifested a specific topographic distribution characterized by a predominance at midline anterior sites (laterality × region, $F(4,148) = 26.79$, $P < 0.001$). The spontaneous 4- to 5-Hz activity significantly depended on the ADHD variable, because at midline and right-hemisphere frontal–central electrodes, children with ADHD (ADHD-only and comorbid) had a larger 4- to 5-Hz spectral power than children without ADHD (controls and TD-only). This was verified by the significant interactions ADHD × region ($F(2,74) = 6.03$, $P < 0.005$) and ADHD × laterality ($F(2,74) = 5.32$, $P < 0.01$). The same trends were yielded for the 6- to 7-Hz activity. No main effect or interactions with the TD variable were found.

Time–frequency ERP analysis

Fig. 3 presents TF decomposition plots of ERPs of the control group and demonstrates that several TF components characterized the neuroelectric activity in the post-stimulus epoch: (1) as

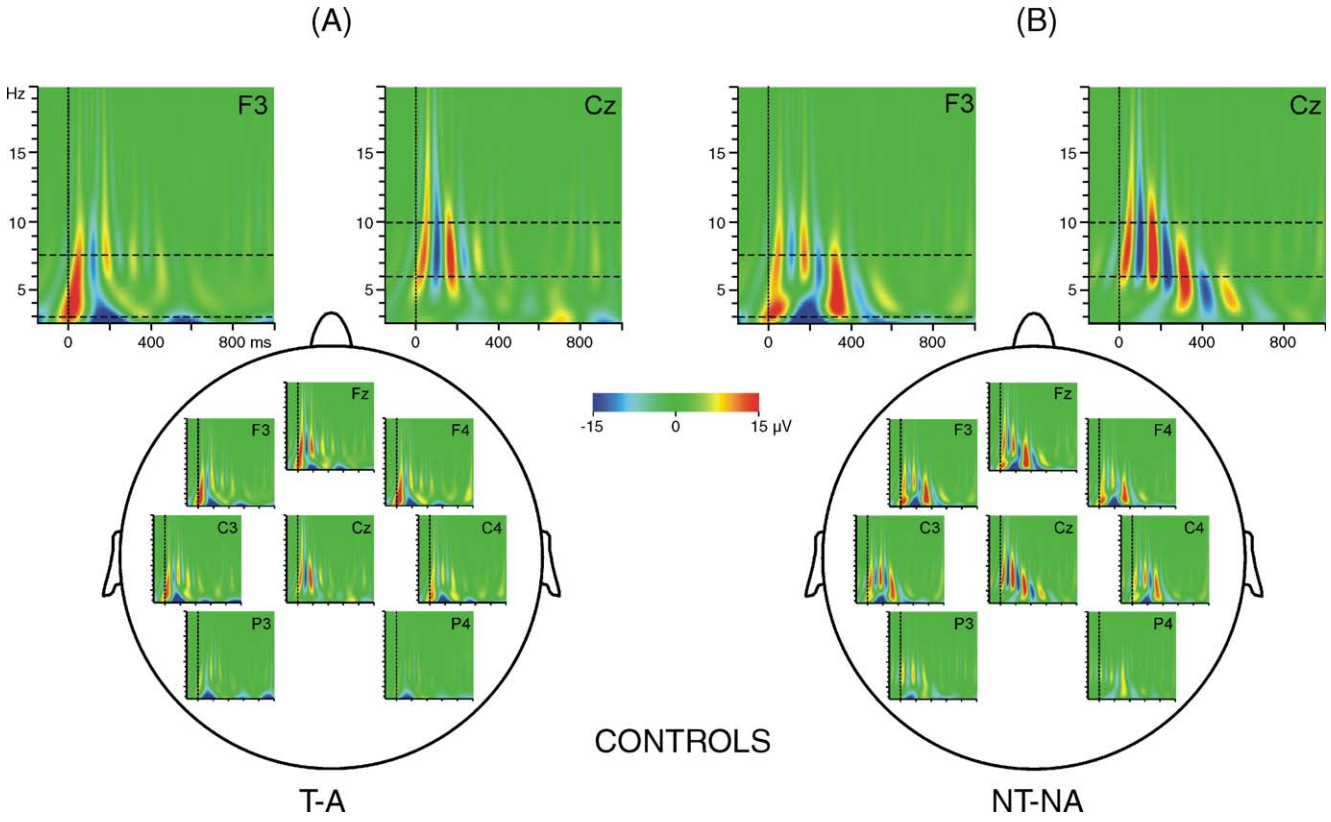

Fig. 3. Group mean time–frequency plots of wavelet-transformed ERPs for the control group: (A) target–attended stimulus condition (T–A). Early theta response within 0–200 ms is clearly seen. (B) Non-target–non-attended stimulus condition (NT–NA). Late theta response within 200–400 ms is clearly seen. Selected electrodes F3 and Cz for each stimulus condition are shown enlarged.

illustrated in Fig. 3A for T–A ERPs, a positive TF component from the theta (3–7.5 Hz) frequency range emerged in the first 0–200 ms after stimulus at anterior (bilateral fronto-central and midline frontal) locations. This TF component was most prominent for T–A ERPs but was also observed for other stimulus types. Because of its frequency content and early latency range of occurrence, this TF component was termed 'early theta response' (ETR). (2) Fig. 3B illustrates that a second TF component from approximately the same frequency band (3–7.5 Hz) emerged at fronto-central electrodes between 200 and 450 ms after stimulus (late theta response, LTR). Comparing Fig. 3A and Fig. 3B shows that the LTR was not generated after attended targets. It was especially enhanced after non-attended non-targets (NT–NA) and was much less evident after T–NA and NT–A stimulus types. (3) As shown in Figs. 3A–B, a TF component from the 6- to 10-Hz (theta-alpha) frequency band with a fronto-central midline maximum (Cz and Fz) was revealed within 200 ms after each stimulus type. (4) Other TF components from the delta (below 3 Hz) and higher (above 12 Hz) frequency bands were also detected, but they were not further analyzed in the present study.

Fig. 4 presents TF decomposition plots of grand average ERPs of four groups of children and demonstrates that early and late theta responses with the same frequency content were generated in each of the groups (controls, TD-only, ADHD-only, and TD+ADHD). As found for healthy controls, ETRs and LTRs of children with psychiatric disorders also characterized specific stimulus types.

Event-related theta activity

Early theta response (0–200 ms)

Scalp distribution. Fig. 5 presents the power envelopes of event-related theta activity in four groups of children and shows that the ETR had an anterior (frontal and central) distribution (electrode, $F(7,343) = 37.15$, $P < 0.001$). Unlike children without ADHD, children with ADHD tended to have

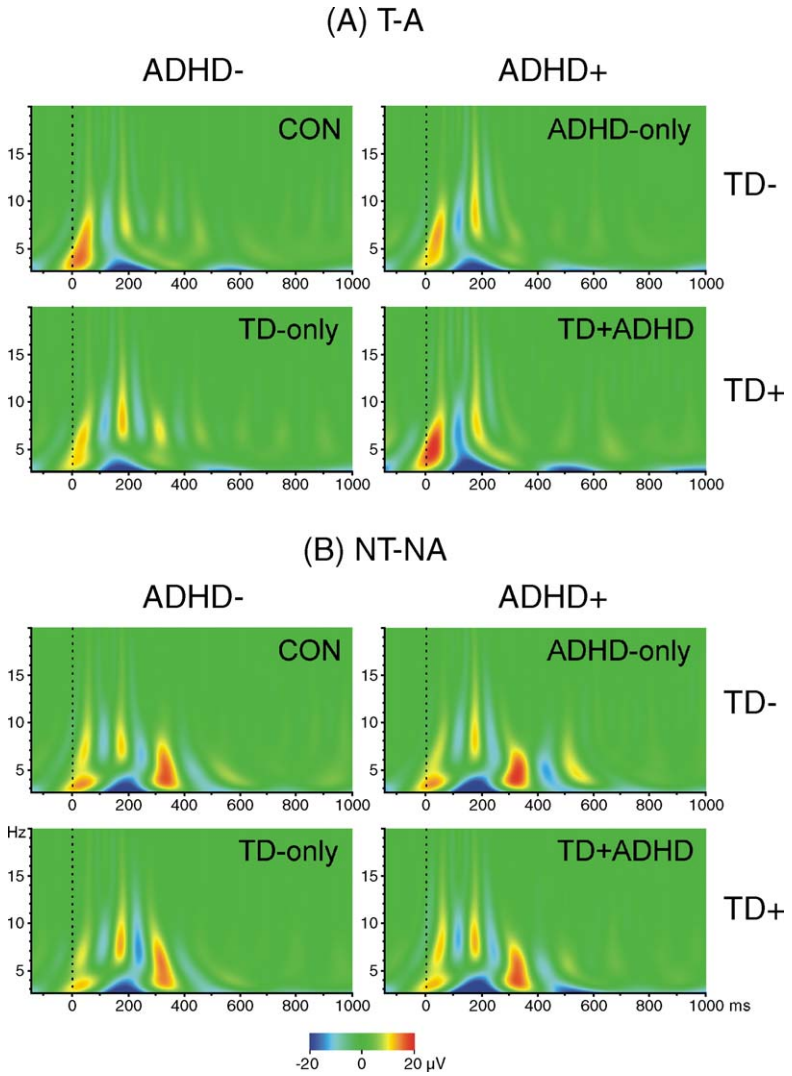

Fig. 4. The effect of ADHD and TD on the event-related activity presented in the time–frequency domain for (A) target–attended (T–A) and (B) non-target–non-attended (NT–NA) stimulus conditions at electrode F3. Groups are designated as in Fig. 2. Note the presence of significant activity around 5 Hz in the time window 200–450 ms in condition (B) which is lacking in panel A.

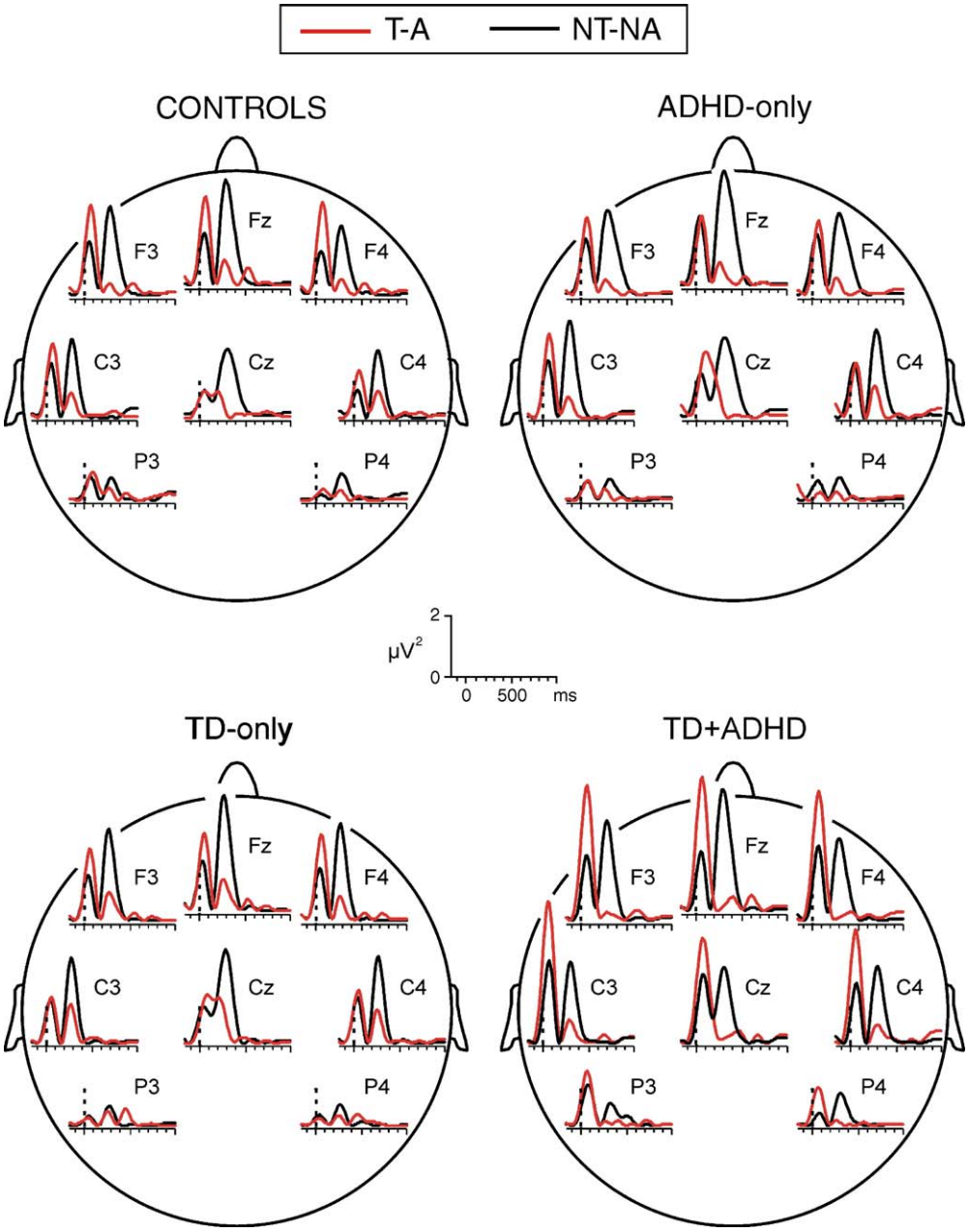

Fig. 5. Grand average time–frequency components from the scale 3–7.5 Hz (event-related theta power) for two stimulus conditions (T–A and NT–NA). Groups are designated as in Fig. 2. For clarity of illustration power envelopes are shown. The impression that the ETR starts before stimulus is due to envelope presentation (cf., Fig. 1).

an increased ETR at Cz (electrode × ADHD, $F(7,343) = 2.1$, $0.05 < P < 0.1$).

Task effects. No significant main effect of stimulus task relevance was obtained ($F(1,49) = 1.3$, $P > 0.3$), but there was a significant effect of the attended channel on the ETR ($F(1,49) = 4.79$, $P < 0.05$). Also, the ETR was larger in the first (attend-right) than in the second (attend-left) session (series sequence, $F(1,49) = 8.81$, $P < 0.005$), but this effect was strongly modulated by the attended channel at specific electrodes (sequence × attended channel × electrode, $F(7,343) = 3.52$, $P < 0.005$). Testing this interaction demonstrated that the ETR did not differ between attended and non-attended stimuli over the frontal–central electrodes ipsilateral to the attended side. However, over the frontal–central electrodes contralateral to the attended side, the ETR was enhanced to attended and was decreased to non-attended stimuli. Fig. 6A illustrates these effects and shows that in the first (attend-right) condition, the attend vs. non-attend difference was found only for the left-hemisphere electrodes (attended channel × electrode, $F(7,343) = 3.05$, $P < 0.05$). In the second (attend-left) condition, the attend vs. non-attend difference was found for the right-hemisphere electrodes (attended channel × electrode, $F(7,343) = 2.25$, $P < 0.05$).

Psychopathology effects. Each of the two psychopathology factors (TD and ADHD) was associated with larger ETRs (TD, $F(1,49) = 4.31$, $P < 0.05$; ADHD, $(1/49) = 5.14$, $P < 0.05$).

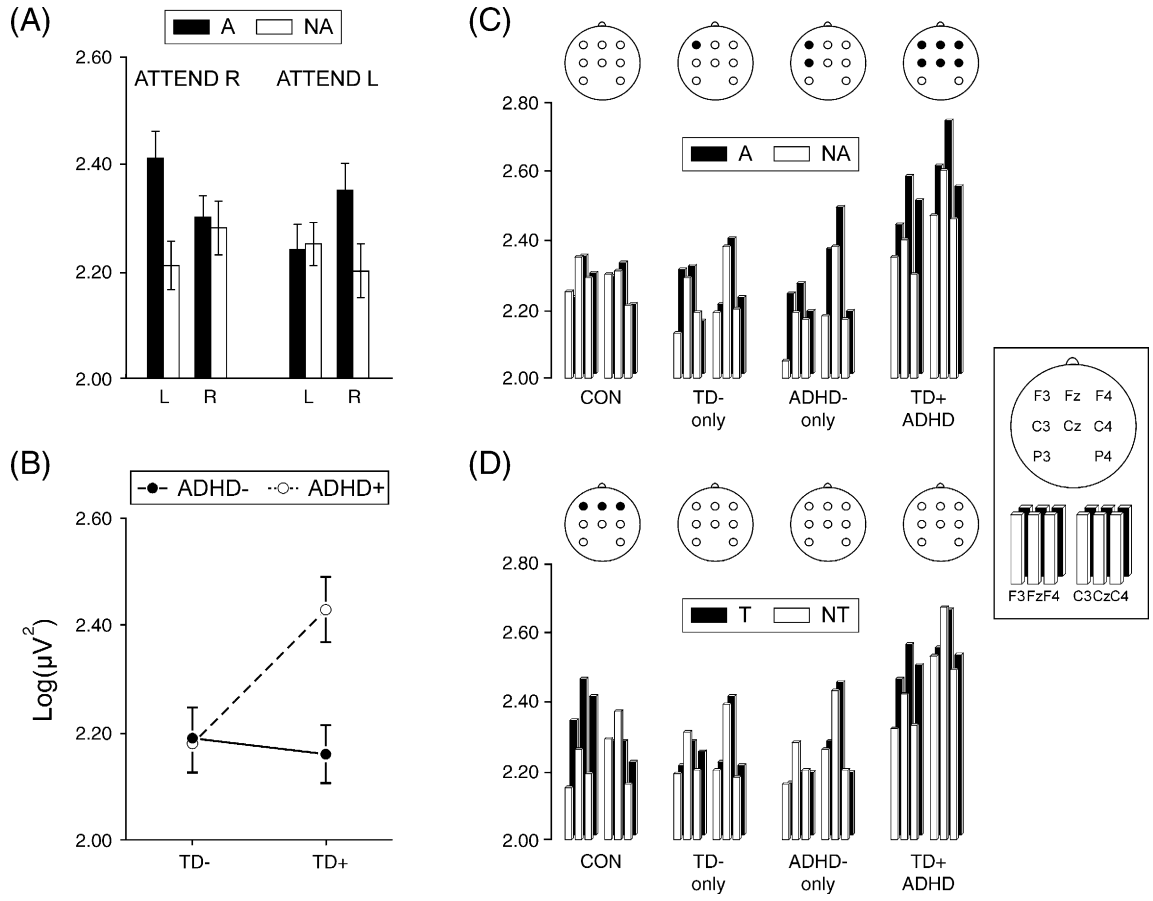

Fig. 6. Statistical evaluation of the early theta response power (logarithmic values). (A) ETR (mean values ± SE) across groups and fronto-central lateral electrodes. Effect of attended channel (A-attended, NA-non-attended) on ETR at left (L) and right (R) electrodes in two conditions (attend right and attend left). A significant attend vs. non-attend difference is seen only for the hemisphere contralateral to the attended side. (B) The effect of psychopathology factors (TD and ADHD) on ETR (mean values ± SE). A significantly larger ETR is seen only for the comorbid (TD + ADHD) group. (C) The effect of attended channel (A vs. NA) on ETR in four groups of children (designated as in Fig. 2) at six electrodes as they appear for each group: F3, Fz, F4, C3, Cz, C4. The order of electrodes is given in the legend. Significant A vs. NA differences ($P < 0.05$—black circles) for each electrode are additionally illustrated on the corresponding heads above each group values. (D) The effect of stimulus task relevance (T—target vs. NT—non-target) on ETR in four groups of children (designated as in Fig. 2) at six electrodes as they appear for each group: F3, Fz, F4, C3, Cz, C4. Significant T vs. NT differences for each electrode are additionally illustrated on the corresponding heads above each group values (as in panel C).

However, as indicated by the significant TD × ADHD interaction ($F(1,49) = 6.4$, $P < 0.01$), the psychopathology-related increase of the ETR resulted only from the comorbid children (TD+ADHD) (see Figs. 5 and 6B). Post hoc between group comparisons (Bonferroni corrected) showed that the ETR did not differ among controls, ADHD-only, and TD-only groups, but the ETR of comorbid (TD+ADHD) children was significantly larger than the ETR of each of these groups (for separate comparisons, $P < 0.05$, 0.015, and 0.01, respectively).

Importantly, ETR reactivity to task variables (attended channel and stimulus task relevance) depended on psychopathology. As illustrated graphically in Fig. 6C and indicated by the significant interaction TD × ADHD × attended channel × electrode ($F(7,343) = 2.48$, $P < 0.05$), the overall ETR increase to attended stimuli was produced by the pathology groups (TD-only, ADHD-only and TD+ADHD), because in the controls, no difference between attended and non-attended stimuli was found at any location (attended channel, $F(1,13) = 0.22$, $P = 0.65$; attended channel × electrode, $F(7,91) = 1.08$, $P > 0.3$). In contrast, attended stimuli elicited larger ETR at the left frontal site in the TD-only group (attended side × electrode, $F(7,91) = 2.4$, $P < 0.05$), at left frontal and central sites in the ADHD-only group (attended channel × electrode, $F(7,91) = 3.7$, $P < 0.05$), and at all frontal–central electrodes in the TD+ADHD group (attended channel, $F(1,10) = 5.48$, $P < 0.05$). Opposite to these effects, as shown in Fig. 6D, target-type stimuli produced a significant increase of ETR at frontal locations only in the controls (TD × ADHD × stimulus task relevance × electrode, $F(7,343) = 4.13$, $P < 0.005$; stimulus task relevance × electrode in the controls, $F(7,91) = 3.5$, $P < 0.01$), with no statistically reliable changes of ETR related with stimulus type found for the psychopathology groups ($P > 0.3$).

Late theta response (200–450 ms)

Scalp distribution. As illustrated in Fig. 5, the LTR had a clear maximum at midline frontal–central electrodes and decreased at bilateral central/frontal sites, where response power was significantly larger than that at parietal sites (electrode, $F(7,343) = 33.3$, $P < 0.001$).

Task effects. No significant main effect or interactions were obtained for series sequence. LTR power was significantly larger

for non-attended than for attended stimuli (attended channel, $F(1,49) = 14.37$, $P < 0.001$) and for non-target than for target stimulus type (stimulus task relevance, $F(1,49) = 6.96$, $P < 0.01$), mostly at anterior locations (stimulus task relevance × electrode, $F(7,343) = 3.34$, $P < 0.01$). However, Fig. 7A demonstrates that these task effects resulted from the specific increase of late theta power to non-targets in the non-attended channel (attended channel × stimulus task relevance, $F(1,49) = 7.91$, $P < 0.005$).

Psychopathology effects. Fig. 7B illustrates that the LTR was significantly larger in children with ADHD than without ADHD (ADHD, $F(1,49) = 3.92$; $P < 0.05$), whereas no effects of TD were found. Fig. 7C shows that in addition to the overall ADHD-related augmentation of the late theta power, ADHD+ children displayed a much more pronounced LTR increase to the attended non-targets (ADHD × attended channel × stimulus task relevance, $F(1,49) = 3.88$, $P < 0.05$).

Correlational analyses

With respect to event-related theta oscillations, a clear enhancing effect of ADHD was detected, which, for the ETR, was most prominent in the comorbid (TD+ADHD) group. The spontaneous theta EEG was also increased in ADHD+ children. To examine more precisely the origin of ADHD-related theta response enhancement, multiple regression analyses were performed. The dependent variables were early and late theta response power for T–A, NT–A, T–NA, and NT–NA at Fz and Cz, and the independent variables were subject's age, individual IQ scores, Conner's scores, CBCL scores, RT, and spontaneous EEG theta power. The independent variables were selected such as to include all factors such as age, cognitive status, psychopathology severity, hyperactivity, and response production, known to be related to theta EEG activity (e.g., Barry et al., 2003a; Niedermeyer and Naidu, 1998; Yordanova et al., 2004). Measures from only the 4–5 Hz subband of the spontaneous EEG were used because the effects of psychopathology, and topography factors were more prominent in comparison with the 6–7 Hz subband. The results of multiple regression analyses presented in Table 2 demonstrate that the ETR power at Cz was determined by CBCL-I scores such that ETR increased with severity of psychopathology. Late theta response at Fz, however, appeared strongly associated with the 4- to 5-Hz activity of the spontaneous EEG because the power of LTRs to T–A, T–NA, and NT–NA stimuli was predicted only by the spontaneous theta (4–5 Hz) power of the EEG. The LTR to NT–A was associated with two determinants, age and Conner's score such that the LTR decreased with age, and independently increased with the level of hyperactivity.

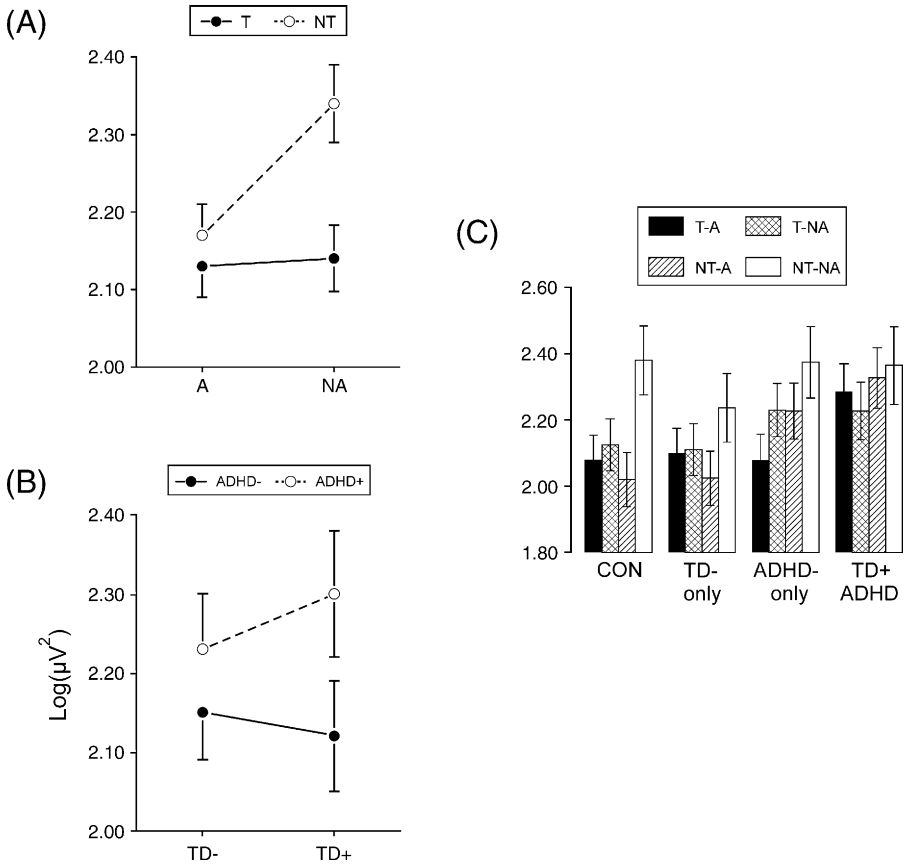

Fig. 7. Statistical evaluation of the late theta response power (logarithmic values). (A) Effects of attended channel (A vs. NA) and stimulus task relevance (T vs. NT) on LTR (mean values ± SE). A significant interaction of attended channel and stimulus task relevance is reflected by the increase of LTR only for NT–NA. (B) The effect of psychopathology factors (TD and ADHD) on LTR (mean values ± SE). A significant increase of LTR is seen for groups with ADHD (ADHD-only and TD + ADHD). (C) LTR (mean values ± SE) for four groups of children (designated as in Fig. 2) across all electrodes for four stimulus types (TA—target–attended, T–NA—target–non-attended, NT–A-non-target–attended, NT–NA-non-target–non-attended).

Table 2
Multiple regression analyses

Attend left										Attend right									
R	R^2	R^2 adj	*F*(1,40)	*P*	Predict	*B*	*ß*	*t*	*P*	*R*	R^2	R^2 adj	*F*(1,40)	*P*	Predict	*B*	*ß*	*t*	*P*
A. Early theta response (Cz)																			
T–A										T–A									
0.36	0.13	0.107	5.81	0.02	Const	1.41		3.58	0.001	0.454	0.206	0.185	10.12	0.003	Const	1.39		4.02	0.000
					CBCL-I	0.016	0.36	2.41	0.021						CBCL-I	0.018	0.454	3.2	0.003
NT–A										NT–A									
0.351	0.123	0.101	5.48	0.024	Const	1.5		3.75	0.024	0.536	0.288	0.269	15.74	0.000	Const	1.34		4.42	0.000
					CBCL-I	0.01	0.351	2.34							CBCL-I	0.02	0.536	3.97	0.000
T–NA										T–NA									
–	–	–	–	–	Const	–	–	–	–	0.339	0.115	0.092	5.07	0.03	Const	3.03	8.54	0.000	
					–	–	–	–							CBCL-T	0.013	0.339	2.25	0.03
NT–NA										NT–NA									
0.37	0.137	0.115	6.18	0.017	Const	1.34		3.14	0.017	0.332	0.11	0.087	4.82	0.034	Const	1.5		3.61	0.001
					CBCL-I	0.018	0.37	2.5							CBCL-I	0.015	0.332	2.2	0.034
B. Late theta response (Fz)																			
T–A										T–A									
0.406	0.165	0.144	7.71	0.008	Const	1.88		14.4	0.008	0.352	0.124	0.102	5.52	0.024	Const	1.78		11.25	0.000
					Sp theta	0.608	0.406	2.78							Sp theta	0.521	0.352	2.35	0.024
NT–A										NT–A									
0.485	0.236	0.216	12.03	0.001	Const	1.7		9.5	0.001	0.64	0.409	0.378	13.17	0.000	Const	3.73		10.42	0.000
					Sp theta	0.865	0.485	3.47							Age	0.012	−0.595	−4.75	0.000
															Conners	0.019	031	2.5	0.018
T–NA										T–NA									
0.558	0.312	0.294	17.67	0.000	Const	1.68		11.08	0.000	0.384	0.147	0.126	6.74	0.013	Const	1.94	11.63	0.000	
					Sp theta	0.887	0.558	4.2							Sp theta	0.604	0.384	2.6	0.013
NT–NA										NT–NA									
0.436	0.19	0.169	9.14	0.004	Const	2		11.15	0.004	0.334	0.112	0.09	4.91	0.033	Const	2.15	11.78	0.000	
					Sp theta	0.756	0.436	3.02							Sp theta	0.565	0.334	2.21	0.033

T–A, target–attended; NT–A, non-target–attended; T–NA, target–non-attended; NT–NA, non-target–non-attended; Sp theta, spontaneous (EEG) theta; CBCL-I, Child Behavior Checklist Internalizing; CBCL-T, Child Behavior Checklist Total. The number of subjects used in these analyses was 11 for controls, 10 for TD-only, 11 for ADHD-only, and 9 for TD+ADHD.

Discussion

In the following discussion, major results are interpreted in the context of two aspects: (1) models for TD+ADHD comorbidity (additive, interactive, and phenotype) and (2) functional correlates of event-related theta oscillations and cognitive stimulus processing in children.

Comorbidity of TD and ADHD: a specific nosology in the neurocognitive domain

The main pathology-related findings demonstrated that (1) spontaneous theta EEG activity was larger in boys with ADHD than without ADHD. This observation is in line with previous reports (Niedermeyer, 2001; Niedermeyer and Naidu, 1997, 1998; Chabot and Serfontein, 1996; Clarke et al., 2001). Also, the spontaneous theta did not differ between the comorbid and the ADHD-only group because the two groups manifested comparable hyperactivity and inattention scores (Table 1) known to affect specifically the spontaneous theta in ADHD subtypes (Clarke et al., 1998, 2001; Barry et al., 2003a; Magee et al., 2005). These results suggest that basic alterations in neuroelectric signaling accompany ADHD symptoms irrespective of their isolated or comorbid manifestation. (2) In contrast, the early theta response was specifically enhanced only in TD+ADHD and did not differ between the control, TD-only and ADHD-only groups. This ETR increase was not associated with the variations of the spontaneous theta EEG activity in comorbid children. (3) The late theta response was enhanced in children with ADHD, but this effect was mediated by the ADHD-related increase of the spontaneous theta EEG activity.

These results indicate that children with combined TD+ADHD manifest highly specific alterations in the processes of early selection of auditory task stimuli as reflected by the ETR. Moreover, these alterations are not generated by the neuroelectric state of theta frequency networks as reflected by the spontaneous EEG. Instead, they are confined to the active processes of early selection of auditory task stimuli. It is notable that neither the psychopathology scores nor the behavioral performance parameters were able to separate the comorbid from other psychopathology groups. In contrast, the neurophysiological examination of cognitive stimulus processing could identify the TD+ADHD comorbidity as a separate entity, thus supporting the interactive model for TD+ADHD in the neurocognitive domain.

Previous TMS findings, however, substantiate the additive model for TD+ADHD (Moll et al., 2001). Since TMS measures reflect the background state of motor system excitability, basic subcortical–cortical (striato-thalamo-cortical) loops controlling the output from the cortical motor system (e.g., Leckman, 2002) seem to be differentially impaired in TD and ADHD, and these impairments co-contribute separately in TD+ADHD comorbidity. Similarly, the regulation of another basic function, the sleep–wake cycle, has been found to be differentially altered in TD and ADHD, and, also consistent with the additive model, a combination of independent TD- and ADHD-related sleep disturbances was present in TD+ADHD (Kirov et al., submitted for publication). Likewise, the spontaneous theta EEG activity analyzed here reflects the background (passive) neuroelectric brain state and could also discriminate the TD and ADHD conditions but did not distinguish the comorbid group. However, as the present and previous ERP studies demonstrate, when active processing demands are imposed, TD+ADHD can be classified as either a phenotype expression of TD (Yordanova et al., 1996) or ADHD (Rothenberger et al., 2000) or as a unique nosology (Yordanova et al., 1997, present findings). Taken together, these results suggest that the TD+ADHD comorbidity can be specified at several different levels, ranging from a neurobiological basic level to a neurophysiological functional level. In TD+ADHD coexistence, basic cerebral functions such as the sleep–wake regulation, inhibitory control of the motor system, and cortical excitability, appear to be guided by independent TD- and ADHD-related pathogenic sources. Yet, any cognitive activation involving these basic functions may lead to a complex interplay of the separate pathogenic sources, which may result in highly specific neurocognitive modes of information processing in comorbid patients. It will be a matter of future research to identify the neural substrate of this interplay as well as the extent to which it may exclusively impair specific cognitive operations in TD+ADHD. This multilevel scheme of comorbidity interpretation may prove relevant for improving treatment strategies.

Functional correlates of event-related theta oscillations

The present methodological approach identified time–frequency components of the ERPs and showed that in an auditory selective attention task, oscillatory theta ERP responses were generated after each stimulus type, which is in line with previous studies of passive and active auditory ERPs in children (Yordanova and Kolev, 1996, 1997, 1998b). Also consistent with earlier reports (Demiralp and Basar, 1992; Basar-Eroglu et al., 1992; Yordanova and Kolev, 1998a,b), enhanced theta oscillations (1) emerged with different latencies according to stimulus task relevance and (2) depended differentially on task variables. It is to be noted that the temporal patterns of event-related theta activity were very similar across control and pathological groups (Figs. 4 and 5), thus forming stable early and late theta ERP components. More importantly, however, the elicitation of early and late theta oscillations manifested a consistent dependence on stimulus-specific processing. These observations validate that the ETR and LTR represent basic electrophysiological correlates of stimulus information processing whose elicitation is not deteriorated even by comorbid psychopathological conditions in children.

The early theta response: discriminating stimulus task relevance

In the currently employed task, stimuli with target features appeared from either a relevant or irrelevant location in space, and the to-be-responded stimulus had to be selected with regard to both side of appearance (location in space) and physical features.

Spatial target selection. Across groups, at frontal–central electrodes contralateral to the attended side, the ETR was enhanced for attended and suppressed for non-attended stimuli, but the ETR did not differ between attended and non-attended stimuli at ipsilateral electrodes (Fig. 6A). Hence, the theta oscillations generated in the first 200 ms after auditory stimulus may be functionally associated with attention gating processes aimed at increasing the distinction between spatially relevant and spatially irrelevant stimuli. This interpretation is substantiated by previously found associations between cortical oscillatory theta activity and spatial learning during a virtual maze navigation (Kahana et al.,

1999; Caplan et al., 2001, 2003). The sensitivity of event-related theta oscillations to the spatial relevance of incoming auditory information is reported here for the first time and indicates that in children, theta oscillations can play an important functional role for early auditory selection on the basis of relevant spatial characteristics.

Physical features selection. In the group of control subjects, the ETR at frontal scalp locations was significantly enhanced for the high (target) than for the low (non-target) tones, irrespective of their spatial relevance. This result suggests that the ETR of children is also involved with early target selection by discriminating stimulus physical characteristics. A previous developmental study of fast frequency (gamma band) ERPs has demonstrated that the selection of to-be-responded stimuli in 9–12 year-olds is primarily guided by physical stimulus characteristics (Yordanova et al., 2000, 2001, 2002). Oscillatory theta networks with a presumably frontal distribution also appear to take part in target selection according to physical stimulus properties, in addition to their role for discriminating spatial target characteristics.

Motor task relevance. Independently of the side of attention, attended stimuli produced larger ETRs at the left frontal location in TD-only children, at the left frontal and central locations in ADHD-only children, and at all frontal–central locations in comorbid children (Fig. 6C). As mentioned before, motor system inhibition has been found to be decreased in TD and ADHD and further reduced in an additive way in comorbid children (Moll et al., 2001). In view of these earlier results, and also regarding the fact that in the present experimental design, motor responses were produced with the right hand, increased ETR to attended stimuli in the pathology groups may originate from either an increased excitability of the motor cortex primarily contralateral to the responding hand, or from a stronger functional activation required to solve the motor task in a state of dysregulation between inhibition and facilitation processes. Notably, in healthy children, the ETR was observed to be overall larger at C3 than at C4 suggesting a greater reactivity of the motor cortical area contralateral to the responding hand (Yordanova et al., in preparation)—see also Fig. 6C. It may be assumed therefore that early theta responses at motor cortex electrodes are also linked with the motor task relevance of a target stimulus. Such a relationship appears more likely to be detected in the psychopathology groups as an attended channel effect possibly because of the deviations in their neuronal excitability.

In sum, the ETR results indicate that early stimulus-locked theta oscillations manifest functional sensitivity to spatial target characteristics, physical target characteristics, and also motor-related target features, all of which represent relevant target attributes. Further, ETR reactivity to each particular target feature occurred at specific electrodes. According to previous studies, phase-synchronized theta oscillations in humans are related to focused attention (Basar-Eroglu et al., 1992), integration of incoming sensory information with working memory (Yordanova and Kolev, 1998a) and working memory maintenance (Jensen and Tesche, 2002; Raghavachari et al., 2001; Rizzuto et al., 2003). Although not derived from a typical task for working memory, the present results support and further specify these observations by showing that event-related theta oscillations of the auditory task used here may reflect an attentional trace held in working memory, in which all dimensions for relevant stimulus (target) identification are represented. The distinct topographic effects found for specific target dimensions further imply that working memory representations (or their effective projections) are distributed in task-specific regions.

The functional involvement of the late theta response

Notably, a late theta response within 200–450 ms after the stimulus was detected mainly after task irrelevant stimuli, and the LTR was most prominent for the most irrelevant (i.e., non-attended non-target) tones. This late theta response cannot be simply linked with a no-go P3 (Falkenstein et al., 1995) because in addition to the non-attended non-target, two other stimulus types in this task required response inhibition as no-go stimuli (i.e., the non-attended target and attended non-target), but the LTR was enhanced only after non-attended non-targets. Previously, positive ERP deflections in the same latency range also have been observed after irrelevant standard tones in an auditory selective attention task (Alho et al., 1987). They have been interpreted as reflecting active inhibition of irrelevant information (Alho et al., 1987; Araki et al., 2005) or a temporary relaxation after identifying stimulus irrelevance (Alho et al., 1987). Current observations that the LTR is predicted by the power of the spontaneous EEG theta (4–5 Hz) activity (Table 2) points to the strong association between the background state of the theta system and event-related theta oscillations in the late post-stimulus period. Hence, the LTR may reflect a recovery of the ongoing theta EEG pattern occurring mainly after irrelevant stimuli as a transition from an active to a passive processing mode. Alternatively, if the LTR is associated with an active mechanism for irrelevant information processing, this mechanism appears to involve or strongly depend on the neurobiological state of theta networks in the brain. Further analyses are needed to specify LTR functional significance, which may provide a relevant tool to study the link between neurobiological and neurocomputational brain states.

Cognitive stimulus evaluation in children with TD and ADHD: theoretical implications

According to the previous discussion, the ETR appears associated with a complex multidimensional trace within working memory maintained to support relevant target identification. In this context, larger ETRs in comorbid children may reflect an inappropriately effortful (or compensatory) processing of stimulus task relevance, due to disinhibition deficits in motor as well as other cortical regions. Interestingly, this deviant tendency becomes stronger as a function of psychopathology severity (Table 2a). The ETR results further imply that a such a problem may be most topographically focused in TD-only, less focused in ADHD-only, and generalized in combined TD+ADHD disorder (Fig. 6C), which additionally supports the interactive model for TD+ADHD comorbidity in this case. In patient groups too, auditory stimulus selection seems to be modulated primarily by the spatial dimension, and to be further mediated by the motor cortical disinhibition, in contrast to healthy children.

The findings of the present study were derived from analysis of event-related theta oscillations in averaged ERPs. An important task for future research will be to extend these analyses to the level of single sweeps and establish the extent to which major psychopathology-related amplitude differences stem from single theta response variability or amplitude enhancement (Yordanova and Kolev, 1998a,b). Single-sweep analysis will also allow to assess

more precisely the relationship between the pathological deviations of the spontaneous EEG and the behavior of event-related oscillations (Yordanova and Kolev, 1998a,b). In addition, event-related theta oscillations can certainly be used to provide relevant information about cortical connectivity in psychopathology groups (Sarnthein et al., 1998). Replication of results with larger samples may be of use for the clinical relevance of both the spontaneous and event-related theta oscillations (Niedermeyer, 2001).

Conclusions

(1) In the neurocognitive domain of stimulus relevance processing, the TD+ADHD comorbidity can be identified as a unique nosologic entity. (2) Both the spontaneous theta activity and late event-related theta oscillations can be viewed as neurophysiological markers of the ADHD psychopathology condition. (3) It is suggested that the early theta oscillations are associated with multiple representations of relevant target features in working memory, whereas the late frontal–central theta oscillations are related to the processing of task-irrelevant information.

Acknowledgments

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