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A neurophysiological marker of impaired preparation in an 11-year follow-up study of attention-deficit/hyperactivity disorder (ADHD)

Mirko Doehnert,[1,2,3,*] Daniel Brandeis,[1,4,5,*] Gudrun Schneider,[1] Renate Drechsler,[1] and Hans-Christoph Steinhausen[1,6,7]

[1]Department of Child and Adolescent Psychiatry, University of Zurich, Zurich, Switzerland; [2]Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, University of Leipzig, Leipzig, Germany; [3]LIFE–Leipzig Research Center for Civilization Diseases, Universität Leipzig, Leipzig, Germany; [4]Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland; [5]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany; [6]Aalborg Psychiatric Hospital, Aarhus University Hospital, Aarhus, Denmark; [7]Clinical Psychology and Epidemiology, Institute of Psychology, University of Basel, Basel, Switzerland

Background: This longitudinal electrophysiological study investigated the course of multiple impaired cognitive brain functions in attention-deficit/hyperactivity disorder (ADHD) from childhood to adulthood by comparing developmental trajectories of individuals with ADHD and typically developing controls. **Methods:** Subjects with ADHD (N = 11) and normal controls (N = 12) diagnosed in childhood [mean age ADHD/CTRL = 10.9 years [*SD* 1.72]/10.0 years (*SD* 1.03)] were followed up after 1.1 and 2.4 years, and as young adults [ADHD/CTRL: 21.9 years (*SD* 1.46)/21.1 years (*SD* 1.29)]. At all four times, event-related potential (ERP) maps were recorded during a cued continuous performance test (CPT). We focused on residual deficits as adults, and on developmental trajectories (time and time × -group effects) for CPT performance and attentional (Cue P300), preparatory (CNV: contingent negative variation) and inhibitory (NoGo P300) ERP components. **Results:** All ERP components developed without significant time × group interactions. Only the CNV remained reduced in the ADHD group, although 8/11 individuals no longer met a full ADHD diagnosis as adults. Cue P300 and NoGo P300 group differences became nonsignificant in early adulthood. The CNV parameters correlated with reaction time (RT) and RT-*SD*. Perceptual sensitivity improved and the groups' trajectories converged with development, while RT-*SD* continued to be elevated in adult ADHD subjects. **Conclusions:** Attentional and preparatory deficits in ADHD continue into adulthood, and the attenuated CNV appears to reflect a particularly stable ADHD marker. Although some deficit reductions may have gone undetected due to small sample size, the findings challenge those developmental lag models postulating that most ADHD-related deficits become negligible with brain maturation. **Keywords:** ADHD, developmental lag, CPT, CNV, RT-*SD*.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric disorder that often persists into adulthood, and continuing symptoms are common even in individuals who no longer qualify for a syndromatic diagnosis in adulthood (Barkley, Fischer, Smallish, & Fletcher, 2002; Biederman, Mick, & Faraone, 2000; Faraone, Biederman, & Mick, 2006). The clinical picture changes over time due to a marked decrease of hyperactivity along with an increase of symptoms like boredom, impatience, or restlessness, but attention problems persist (Newcorn, 2008). Also the increasing impact of comorbid conditions makes it difficult to distinguish the effects of ADHD from other clinical problems (Newcorn, 2008).

The majority of studies on adult ADHD report on clinically referred patients diagnosed as adults. As this group suffers from a variety of comorbidities with unspecific neuropsychological symptoms (e.g., Seidman, 2006, Seidman et al., 2004), it may not be typical for adults who were diagnosed with ADHD in childhood but no longer meet full diagnostic adult ADHD criteria.

Longitudinal studies focusing on the ADHD group diagnosed in childhood can provide additional insights into specific developmental aspects of the disorder, and distinguish persisting from compensated or normalized structures and functions.

Structural neuroimaging has already highlighted developmental aspects of ADHD by comparing the developmental growth curves of regional gray and white matter (Castellanos et al., 2002) or cortical thickness (Shaw et al., 2007). Developmental trajectories of ADHD subjects paralleled those of controls for most brain regions despite smaller volumes, suggesting that the fundamental development during late childhood and adolescence is essentially normal in ADHD. An exception from this pattern of persisting deviation was the normalization of the caudate nucleus volume by midadolescence, suggesting a relation with decreasing hyperactivity/

[*] Equally contributing first authors.

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impulsivity in ADHD. The leading hypothesis implicates a developmental delay in ADHD for some brain structures and functions, as maturation of cortical thickness is delayed in ADHD, with particularly prominent delays in frontal and temporal cortex regions, and with cortical thickness normalization associated with clinical remission of ADHD (Shaw, Gogtay, & Rapoport, 2010). Similarly, subcortical (striatal) volume normalization in ADHD with age and medication use has also been revealed through meta-analysis (Nakao, Radua, Rubia, & Mataix-Cols, 2011).

However, functional measures in attentional tasks relate more directly to the core symptoms of ADHD. Event-related potential (ERP) components provide particularly useful time-resolved measures of brain function. Studies using the cued continuous performance task with its embedded Go/NoGo task (CPT A-X or O-X, Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956) capture a sequence of attentional and preparatory brain processes initiated by the cue stimulus [indexed by Cue P300 and contingent negative variation (CNV)] which precede inhibitory control (indexed by NoGo P300; e.g., van Leeuwen et al., 1998). The typical development of these components illustrates the late maturation of these attentional processes (Jonkman, 2006; Valko et al., 2009).

In childhood ADHD, deficits of attentional orienting and resource allocation are indexed by a reduced Cue P300 (Banaschewski et al., 2003, 2004; van Leeuwen et al., 1998), while deficits of preparation and time processing underly the reduction of the subsequent CNV (Banaschewski et al., 2003; van Leeuwen et al., 1998). The few studies examining both components in adult ADHD subjects (McLoughlin et al., 2010; Valko et al., 2009) also found reductions compared with healthy controls. Furthermore, these deficits in adult subjects closely resemble findings in children with ADHD and suggest the possibility of developmentally persistent deficits. The deficits are presumably related to posterior attentional system (van Leeuwen et al., 1998), disturbed state regulation (Banaschewski et al., 2004) and subcortical generators (Halperin and Schulz, 2006; Valko et al., 2009).

One of the leading theories of ADHD assumes a core deficit of response inhibition (Barkley, 1997). Neurophysiological studies have focused on the inhibitory NoGo P300. Studies on childhood ADHD found reduced NoGo P300 activity (Banaschewski et al., 2004; Brandeis et al., 2002; Fallgatter et al., 2004) as well as studies on adult ADHD (Dhar, Been, Minderaa, & Althaus, 2010; Fallgatter et al., 2005). Our 3-year longitudinal results suggested that performance deficits and the delayed development of the NoGo P300 may support a developmental lag model for response inhibition (Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010). Source localization revealed NoGo activation in the prefrontal cortex (particularly the anterior cingulate cortex, ACC), consistent with other inhibitory tasks including the stop signal task (Bekker et al., 2005).

The development of CPT performance data from childhood into adulthood revealed persistent deficits, with increased reaction time (RT) and RT variability in adult ADHD subjects depending on their current ADHD status (Fischer, Barkley, Smallish, & Fletcher, 2005; Hinshaw, Carte, Fan, Jassy, & Owens, 2007; Halperin and Schulz, 2006, Halperin, Trampush, Miller, Marks, & Newcorn, 2008; Tucha et al., 2008; McLoughlin et al., 2010). While accuracy develops and becomes less sensitive to ADHD with development, the trajectories of signal detection measures (sensitivity and bias) in ADHD (van Leeuwen et al., 1998; Oades, 2000) remain to be explored.

Our longitudinal ERP study of these higher brain functions in ADHD had revealed both aspects of development lag and deviation during adolescence. Developmental lag contributed to inhibitory brain dysfunction (e.g., NoGo P300 maps and source localizations of younger control subjects resembled those of older ADHD subjects) but preparatory and attentional functions (reflected by the CNV and the Cue P300) were instead characterized by deviant developmental trajectories (Doehnert et al., 2010).

The present study addresses the lack of prospective long-term ERP studies of attentional, preparatory, and inhibitory brain functions in ADHD covering longer periods, particularly from childhood into adulthood. Instead of focusing only on inhibition deficits, we also investigated the developmental trajectories of the Cue P300 and the CNV, along with CPT performance.

Subjects were assessed four times during 11 years. Patterns of transient or persistent developmental delay versus developmental deviation as potential trajectories were analyzed.

Methods and materials

All subjects were recruited in Zurich from an epidemiologic field study (Steinhausen, Metzke, Meier, & Kannenberg, 1998), from self-help organizations for parents with hyperactive children, from regular schools, and from our clinic. The recruitment started in 1994.

Children with neurological disorders or with IQ < 80 had been excluded from the study. Stimulant medication treatment was suspended at least 48 hr prior to testing.

The four assessments consisted of the baseline (Time 1) and three follow-up examinations after approximately 1.1 years (Time 2), 2.4 years (Time 3), and 11 years (Time 4).

Participants

The original group selected for this study included 28 individuals with ADHD and 22 normal controls (CTRL; Doehnert et al., 2010). At Time 4 two subjects could not be tracked. All other former participants were contacted via mail to their parents' address. A

total of 11 young adults with a childhood diagnosis of ADHD (age range 19–24 years) and 12 normal controls (age range 18–23 years) agreed to participate in the present study. All participants gave informed, written consent and the study was approved by the local Ethics Committee.

The categorical diagnosis of ADHD in childhood was based on a structured interview conducted with at least one of the parents [Diagnostic Interview Schedule for Children (DISC) Ver. 2.3; Shaffer et al., 1993] at Time 1, conducted by trained undergraduate students according to DSM-III-R criteria, which was repeated at Time 3 to assess persistence.

Details regarding IQ testing and diagnosis have been fully reported in previous publications from this longitudinal study (Drechsler, Brandeis, Földényi, Imhof, & Steinhausen, 2005; Steinhausen, Drechsler, Földényi, Imhof, & Brandeis, 2003). The validation of diagnosis was based on information provided by board-certified clinicians, and by the multiple informant approach including the subjects and their parents in both groups.

Parents rated their child on the Child Behavior Checklist (CBCL; Achenbach, 1991) at Time 1, 2, and 3. At Time 4, current ADHD status (DSM-IV) was established by a German adaptation of the Wender–Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), an adult ADHD interview (Rosler et al., 2008). In addition, adult participants rated their current ADHD symptoms on a DSM-IV-based self-rating checklist for adults with ADHD (ADHS-SB; Rosler et al., 2004) and completed the Young Adult Self-Report (YASR; Achenbach, 1997). At time 4, parents completed the Young Adult Behavior Checklist (YABCL; Achenbach, 1997).

Group characteristics are shown in Table 1. The subjects with ADHD scored significantly higher than control subjects on CBCL attention problems scale and almost significantly at Time 4 on YABCL attention problems scale. The total score of the specific adult ADHD rating scale (ADHS-SB), the YASR attention problems scale and the total score of the WRAADDS showed significant differences between both groups at the last assessment. Their IQ was also significantly lower at first assessment, but neither age nor sex distribution showed significant differences between the two groups.

Three out of 11 individuals with a childhood diagnosis of ADHD continued to display full ADHD (persisters) according to the WRAADDS, whereas the remaining eight individuals fell below the categorical cut-off (remitters). When the adult remitters were compared with healthy controls on the WRAADDS total scores, the significant group differences remained, indicating substantial subclinical impairment in at least a subgroup of remitters ($t = 4.611$; $p < .001$).

To control for sampling bias, the baseline characteristics of the present ADHD sample ($N = 11$) were compared with those of the dropouts ($N = 17$) at Time 1. There were no significant difference for mean IQ (99.8 vs. 97.9), mean age (10.3 vs. 9.7 years), female to male gender ratio (1/10 vs. 2/16), or severity as measured by the CBCL attention problems subscale *T*-score (67.8 vs. 67.2). Thus, despite a considerable attrition rate the present sample still was representative of the original ADHD group.

ERP task

At all four assessment times event-related potential (ERP) maps were recorded during a validated cued Continuous Performance Test (CPT A-X; van Leeuwen et al., 1998). This CPT includes rare cued Go and NoGo conditions embedded in a vigilance task with frequent distractors to assess both attentional and inhibitory processes. The test consists of 400 letters presented for 150 ms with a SOA (stimulus onset asynchrony) of 1.65 s in a pseudorandomized order at the center of a computer monitor. The viewing distance to the monitor measured 120 cm at a vertical visual angle of approximately 0.5°. The cue letter *A* (at Time 4 letter *O*; e. g., Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008; Valko et al., 2009; McLoughlin et al., 2010) occurred with 20% probability (80 Cue stimuli), signaled a Go–NoGo task, and induced response preparation. Children pressed a mouse button with the index finger of their dominant hand as fast as possible every time the cue was followed directly by the letter X [A–X (or O-X) target sequence, 10% probability, 40 Go stimuli] but had to withhold responses to A-not-X (or O-not-X) sequences (NoGo trials, also 10%, 40 NoGo stimuli).

EEG recording

The EEG was recorded with electrodes (Ag/AgCl) from 32 channels using SynAmps amplifier (Neuroscan, El Paso, TX) with 256 Hz (at T4 with 500 Hz), filters set to 0.1–70 Hz and calibrated technical zero baselines. Impedances were below 10 kΩ. Caps used for the montage included the standard 10–20 system positions plus Fpz (recording reference), and two EOG electrodes. The EEG was bandpass filtered to 0.1–30 Hz (24 dB/Oct). After artifact rejection [using independent component analyses (ICA) to remove ocular artifacts plus automatic rejection of remaining artifacts], averaged stimulus-locked ERP map series were computed and transformed to the average reference. We used only correct trials for averaging. All ERP averages contained at least 20 accepted single trial EEG epochs.

To avoid distorting ERP topography, no baseline subtraction was applied (van Leeuwen et al., 1998). Amplitudes of the ERP maps were computed as global field power (GFP), the root mean square of all voltages in a map reflecting overall map strength (Lehmann and Skrandies, 1980) regardless of changing topographies. Microstates were determined by adaptive segmentation of the grand mean across both groups and all conditions (e.g. van Leeuwen et al., 1998;

Table 1 Group characteristics

	ADHD	CONTROLS	*t*/*p*
N (female)	11 (1)	12 (4)	n. s.
Age mean (*SD*)			
T1	10.93 (1.72)	10.04 (1.03)	n. s.
T2	12.15 (1.80)	11.18 (1.11)	n. s.
T3	13.44 (1.86)	12.41 (1.17)	n. s.
T4	21.91 (1.46)	21.12 (1.29)	n. s.
IQ (*SD*)			
T1	99.84 (9.77)	112.22 (14.77)	−2.39/.027
CBCL attention problems			
T-score (*SD*)			
T1	67.83 (4.98)	41.92 (4.91)	12.56/<.001
T2	63.07 (9.24)	45.18 (5.65)	5.13/<.001
T3	63.07 (7.44)	44.53 (6.23)	6.07/<.001
YABCL attention problems			
Raw data (*SD*)			
T4	4.70 (3.89)	1.60 (2.50)	2.12/.051
YASR attention problems			
Raw data (*SD*)			
T4	3.45 (1.37)	1.08 (1.08)	4.63/<.001
WRAADDS total score	22.60 (11.68)	5.82 (4.79)	4.23/.001
Persisters (*N* = 3)	37.6 (8.1)		
Remitters (*N* = 8)	16.1 (4.5)		
ADHD rating scale total score	15.00 (8.38)	6.67 (3.94)	3.10/.005

Lehmann et al., 1987). A P300 microstate (254–578 ms) was selected for brain mapping analysis. The mean CNV amplitude in the 1,000–1,600 ms interval in cue trials was computed as global field power (GFP). Automatic peak amplitude and latency detection was used to detect Cue P300 (selection criteria: start/end 300 ms/700 ms, channel Pz, positive polarity) and NoGo P300 (selection criteria: start/end 300 ms/500 ms, channel Cz, positive polarity) peaks.

Statistical analyses

To describe and compare the different developmental trajectories ERP analyses were based on repeated-measures time × group ANOVAs of mean GFP in a given microstate and conditions, followed by post hoc *t*-tests. To test specific topographic hypotheses *t*-maps were used. These were computed for the effects of both ADHD (ADHD minus control subjects) and development (younger minus older age, for instance, voltage at T1 minus voltage at T4). Supplementary ANOVAs of peak amplitudes and latencies (at Pz for the Cue P300, and at Cz for the NoGo P300) were also computed to examine contributions of developmental latency changes.

To clarify associations between neurophysiological and psychological data, Pearson's correlations were computed. Furthermore, we analyzed associations between neurophysiological variables and CPT measures with Pearson's correlations.

In addition, the smaller group of ADHD remitters was compared with the healthy controls to clarify how adult ADHD outcome affected the main results.

For CPT performance, repeated-measures analyses of variance (ANOVAs) of false alarms (commission errors), hits (total Go trials minus commission errors), reaction time (RT), and its standard deviation (RT-*SD*) were performed and followed by post hoc *t*-tests (nonparametric Mann–Whitney *U*-test for non-normally distributed data).

Furthermore, we also examined perceptual sensitivity (d'). This signal detection measure provides an index of performance accuracy independent of response bias or criterion (calculated by subtracting the *z*-transformed false alarm rate from the *z*-transformed hit rate, Stanislaw & Todorov, 1999).

Results

CPT performance

The development of CPT performance is shown in Figure 1. Hit rates increased with age, developmental trajectories tended to converge, and subjects with ADHD had lower hit rates than control subjects at the first two assessments (time: $F_{(3,19)} = 4.695$, $p = .013$; group by time: $F_{(3,19)} = 3.077$, $p = .052$; group: $F_{(1.21)} = 7.397$, $p = .013$; significant results for the subgroup of ADHD remitters: time: $F_{(3,16)} = 4.976$, $p = .013$; group by time: $F_{(3,16)} = 3.374$, $p = .045$; group: $F_{(1,18)} = 9.878$, $p = .006$). At the third and fourth assessment, the post hoc tests no longer revealed significant group differences.

False alarms (commission errors) appeared to decrease over time for subjects with ADHD from the first assessment, but there were no significant effects involving time. Although the mean number of false alarms appeared slightly larger for subjects with ADHD than for controls at all assessments, no significant main effect of group, and no significant post hoc group differences were found for the full group (time: $F_{(3,19)} = 1.478$, n.s.; group by time: $F_{(3,19)} < 1$, n.s.; group: $F_{(1.21)} = 2.944$, n.s.; despite significant result for the subgroup of ADHD remitters: group: $F_{(1,18)} = 5.357$, $p = .033$; Figure 1).

Signal detection sensitivity d' increased with age, particularly for the less sensitive ADHD group, resulting in converging trajectories (time: $F_{(3,19)} = 13.315$, $p < .001$, group by time: $F_{(3,19)} = 6.279$, $p = .004$, group: $F_{(1.21)} = 10.036$, $p = .005$; significant results for the subgroup of ADHD remitters: time: $F_{(3,16)} = 10.803$, $p < .001$; group by time: $F_{(3,16)} = 5.362$, $p = .010$; group: $F_{(1,18)} = 13.754$, $p = .002$). Response bias C also decreased with age but similarly for both groups, and bias was higher with ADHD (time: $F_{(3,19)} = 9.802$, $p < .001$; group by time: $F_{(3,19)} = 2.235$, $p = .117$, group: $F_{(1.21)} = 11.745$, $p = .003$; similarly for the ADHD remitters: time: $F_{(3,16)} = 7.834$, $p = .002$; group: $F_{(1,18)} = 12.797$, $p = .002$).

Reaction time decreased with age (time: $F_{(3,19)} = 43.087$, $p < .001$; for the ADHD remitters: $F_{(3,16)} = 43.750$, $p < .001$). Although subjects with

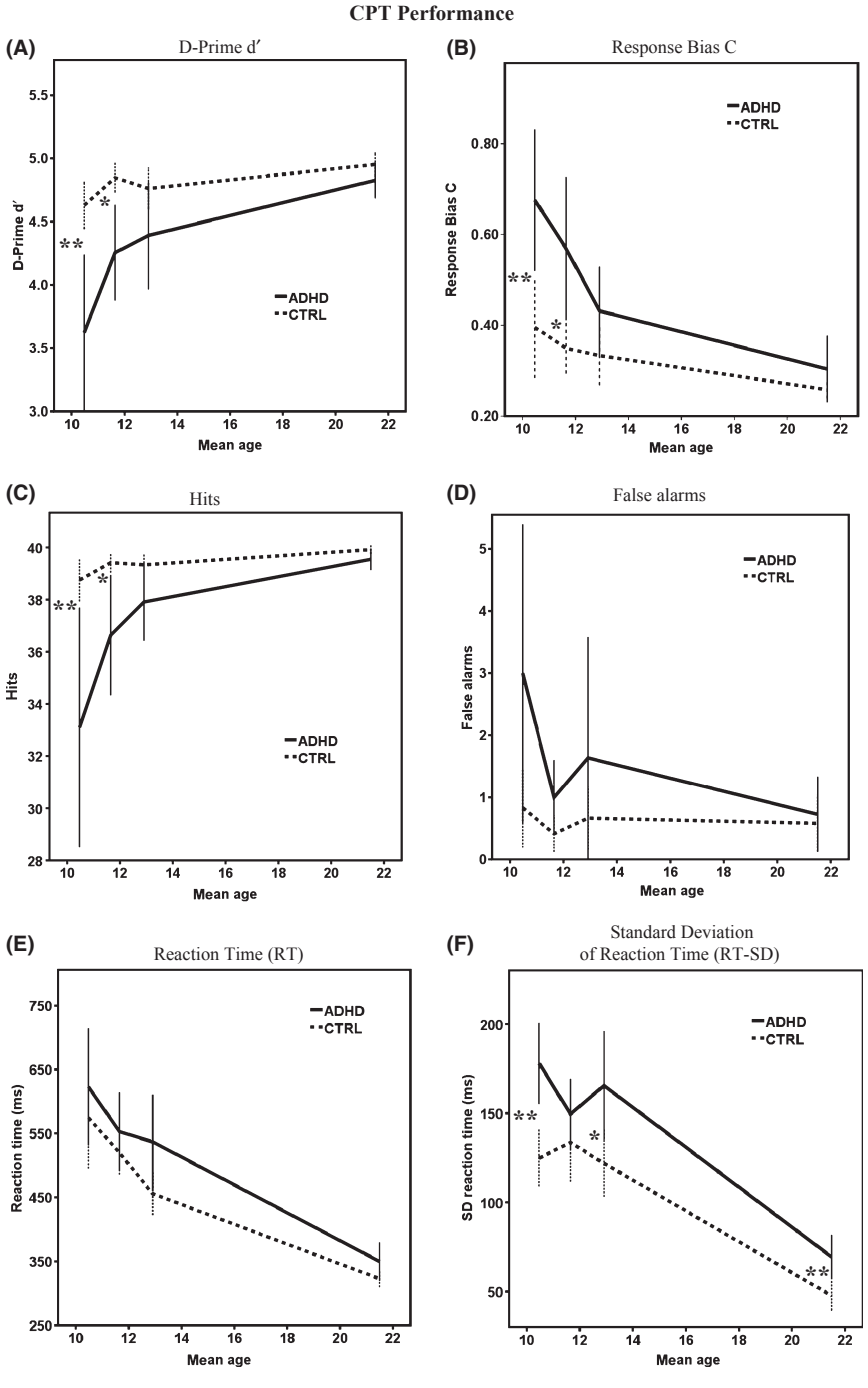

Figure 1 Continuous Performance Test (CPT) performance including post hoc *t*-tests (significance labeled in the figure with asterisks). *p < 0.05, **p < 0.01, error bars ±2 standard errors

ADHD appeared to respond slightly slower than control subjects, these differences were not significant in post hoc *t*-tests (group by time: $F_{(3,19)} < 1$, n.s.; group: $F_{(1.21)} = 2.816$, n.s.).

The RT-*SD* decreased with age (time: $F_{(3,19)} = 57.747$, $p < .001$; for the ADHD remitters: $F_{(3,16)} = 46.543$, $p < .001$). The RT-*SD* of subjects with ADHD showed a peak at Time 1 and 3 and became lowest at Time 4. The RT-*SD* of the controls peaked at Time 2 and became lowest at Time 4. Controls displayed significantly lower RT-*SD* than subjects with ADHD at Time 1, 2, and 4 in post hoc *t*-tests (group by time: $F_{(3,19)} = 2.118$, $p = .132$; group: $F_{(1.21)} = 11.956$, $p = .002$; significant result for the ADHD remitters: group: $F_{(1,18)} = 10.642$, $p = .004$).

Cue P300

Cue P300 GFP decreased over time (time: $F_{(3,19)} = 26.952$, $p < .001$; result for the subgroup of ADHD remitters: $F_{(3,16)} = 22.449$, $p < .001$). The shape of the developmental trajectories did not differ between diagnostic groups (group by time interaction: $F_{(3,19)} = 1.755$, n. s.), although subjects with ADHD had less Cue P300 activity than control subjects (group: $F_{(1,21)} = 9.17$, $p = .006$; result for

the ADHD remitters: $F_{(1,18)} = 6.643$, $p = .019$). Control subjects' GFP peaked at the second assessment. Post hoc *t*-tests showed group differences for Cue P300 GFP at the second and third assessments (Figure 2). The waveforms of Cue P300 at electrode Pz for both groups and all four assessments are depicted in Figure S1.

Analyses of topographic maps and t-maps, the Cue P300 peak latencies and amplitudes at Pz as well as analyses with the subsample of remitted ADHD subjects are reported in the supplementary material (Figure S2 and Table S1).

Contingent negative variation

The CNV decreased over time (time: $F_{(3,19)} = 4.012$, $p = .023$; result for the subgroup of ADHD remitters: $F_{(3,16)} = 4.672$, $p = .016$; Figure 2), while the developmental trajectories did not show differences between both diagnostic groups (group by time interaction: $F_{(3,19)} < 1$, n. s.). The ADHD group had less CNV GFP than control subjects (group: $F_{(1,21)} = 12.635$, $p = .002$; result for the ADHD remitters: $F_{(1,18)} = 12.787$, $p = .002$). Post hoc *t*-test revealed significant CNV GFP differences between both groups at all assessments. The CNV waveforms at Cz for both groups and all four assessments are depicted in Figure S1.

The ADHD effects illustrated by the t-maps were significant for the central negativity (area around Cz) at all assessments with right lateralization of the central effect in the t-maps for the fourth assessment. Subjects with ADHD had a marked developmental increase of midline and right frontal negativity after adolescence, whereas the CNV of control subjects kept relatively stable over time with a slight frontocentral effect at Time 4. Developmental effects between the third and fourth assessment were almost identical for both groups and were located frontally (Figure 3).

NoGo P300

Younger subjects had more NoGo P300 GFP than older ones (time: $F_{(3,19)} = 31.10$, $p < .001$; for the subgroup of ADHD remitters: $F_{(3,16)} = 25.268$, $p < .001$) and the diagnostic groups did not differ concerning developmental trajectories (group by time interaction: $F_{(3,19)} = 1.077$, n. s.). The ADHD subjects had less GFP than controls (group: $F_{(1,21)} = 6.66$, $p = .017$; for the ADHD remitters: $F_{(1,18)} = 7.149$, $p = .015$). These effects are illustrated along with the post hoc comparisons in Figure 2. Control subjects showed the highest NoGo P300 GFP at the third assessment. Post hoc *t*-test revealed significant GFP differences between both groups at the third assessment only.

The waveforms of the NoGo P300 at Cz for both groups and all four assessments are shown in Figure S1. Analyses of topographic maps and t-maps, analysis of NoGo P300 peak latencies and amplitudes at Cz as well as analysis of the subsample of remitted ADHD subjects are shown in Figure S3 and Table S2.

Correlations between psychological data, ERP data and CPT performance data

Exploratory correlations (without correction for multiple testing) were calculated between psychological data (Interview WRAADDS, Questionnaires YABCL and YASR) and ERP data (CNV GFP) as well as between ERP data and CPT performance measures (hits, false alarms, RT, RT-*SD*) at Time 4. Concerning ERP data we focused on the CNV as the only statistically stable marker. Analysis revealed that RT and RT-*SD* correlated significantly with CNV GFP ($r = -.440$, $p < .01$; $r = -.509$, $p < .01$). Correlations between the other variables were not significant.

Discussion

The present examination of cognitive processes from childhood to early adulthood revealed several stable differences between ADHD subjects and healthy controls. ADHD and control subjects showed no different developmental trajectories of the Cue P300 and NoGo P300 compared with healthy controls and the differences between both groups diminished in early adulthood. The developmental trajectory of the

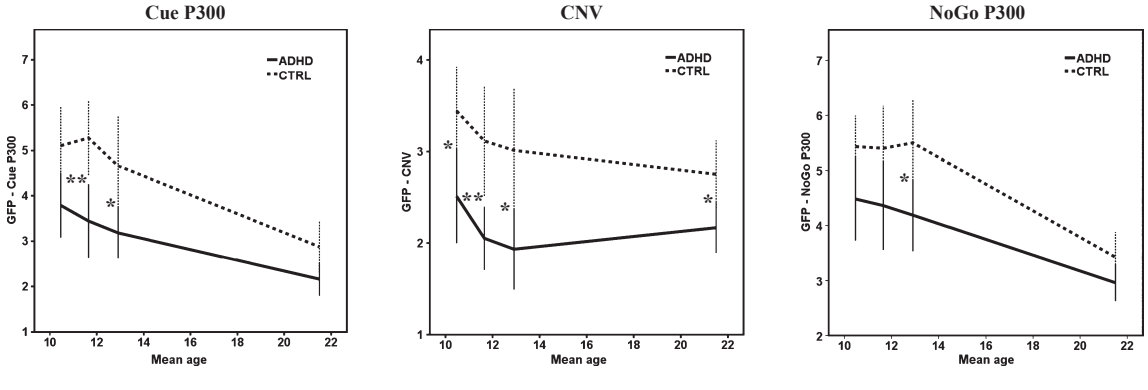

Figure 2 Cue P300, CNV, and NoGo P300 GFP. Post hoc *t*-tests: $*p < 0.05$, $**p < 0.01$, error bars ±2 standard errors

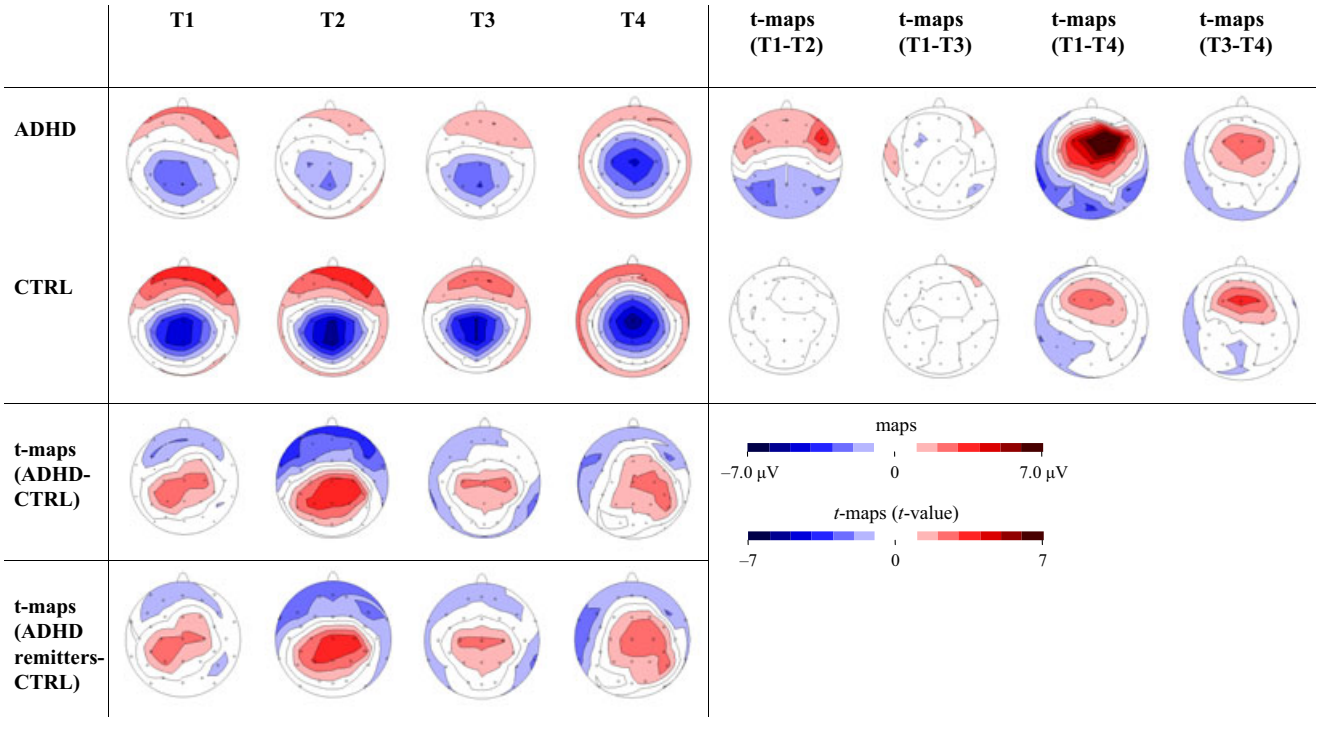

Figure 3 CNV (1000–1600 ms) topographic maps and *t*-maps for the differences between assessments and groups [ADHD and controls (CTRL)]. Group comparison in the last line represents the difference between healthy controls and remitted ADHD subjects [see online version for full-colour]

CNV in ADHD subjects paralleled the curve of healthy controls. Abnormalities in preparation and time processing represented by CNV remained detectable even in young adult ADHD subjects. These findings were even present for the subsample of subjects with remitted ADHD. Developmental lag implies that within a certain time window developmental trajectories are of normal shape but delayed. Either normal values are attained later, or ADHD subjects never outgrow the delay. Such a persistent developmental deviation could explain our CNV findings (Doehnert et al., 2010). The reduced CNV in ADHD at all four assessments along with the different topographies of the developmental and the ADHD effects contradicts those developmental lag models which imply that deficits become negligible with brain maturation.

Instead the findings extend our former CNV findings at the first three assessments until midadolescence (Doehnert et al., 2010) and demonstrate the continuity of differences into early adulthood at the individual level despite major late maturation effects in both groups.

Furthermore, younger controls' and ADHD children's CNV were not alike, which is not predicted from the developmental lag theory (although our design allows no firm conclusions regarding developmental lag in the youngest age group). Group differences were stable with increasing age, which makes it unlikely that a maturational lag contributes to these deficits. Attenuated or deviant development seems a better explanation for these results.

Thus, the CNV appears to be a robust and developmentally stable parameter of cognitive preparation and time processing that is attenuated in ADHD. In addition, it reflected subtle reduction in adults with subthreshold symptoms and may thus qualify as a potential endophenotype of ADHD (Tye, McLoughlin, Kuntsi, & Asherson, 2011). As endophenotypes are presumably more closely related to the genetic variations underlying ADHD than the clinical symptomatology, further research should analyze associations between diminished CNV amplitudes in ADHD and known risk polymorphisms of candidate genes. This 'imaging genetics' approach has already proven effective for other neuroimaging (Durston, 2010) and ERP (Baehne et al., 2009) measures.

Task performance in the cued CPT improved in both groups with age, but also remained partly impaired in adults with childhood ADHD due to their still increased RT-*SD*. Most of our adult ADHD subjects displayed only subthreshold symptoms which may have contributed to the smaller effects. The significant group effect on RT-*SD* is all the more remarkable, but in line with findings that increased variability is a particularly robust marker of ADHD (Klein, Wendling, Huettner, Ruder, & Peper, 2006; Steger et al., 2001). This variability has been related to impaired timing (Castellanos & Tannock, 2002), reduced energetic resources, and impaired state regulation in ADHD subjects (Sergeant, 2005) as well as to altered patterns of very low frequency oscillations of brain activity at rest (Sonuga-Barke & Castellanos, 2007; Tian et al., 2006). In genetic studies,

the association of higher reaction time variability and DRD4 (7-R allele absence) appears to be a consistent endophenotype (Kebir & Joober, 2011). These timing related deficits are manifestations of impaired temporal information processing proposed as a possible endophenotype of ADHD (Himpel et al., 2009; Tye et al., 2011).

The lack of performance deficits in adults with ADHD on error measures may reflect a shift toward timing related deficits and ceiling effects for errors, as already reported for other neuropsychological measures in ADHD during adolescence (Drechsler et al., 2005). The strong developmental increase of hit rates and speed with age correspond well with the literature (Posner & Rothbart, 2007). The findings are also partly consistent with a 20-year follow-up of CPT performance in ADHD individuals and controls (Fischer et al., 2005) who found that residual impairment depended on current ADHD status. The increase of sensitivity (d') with development reflects improving target discrimination and was more pronounced for the ADHD group. The convergence of the groups' sensitivity trajectories following an initial deficit in ADHD is consistent with the developmental lag hypothesis. The response bias trajectories did not converge but indicated that controls as well as older subjects used a more liberal decision criterion closer to the neutral point, where neither response is favored.

Some reduction of deficits in absolute terms was also apparent for other measures upon visual inspection, and may have missed significance due to low statistical power with our small sample size (despite the parallel reduction of standard deviations). Still, our findings demonstrate that significant trajectory convergence as well as residual deficits in adulthood could be detected in these small groups.

Our ADHD sample consists of grown up individuals who were diagnosed in childhood. They differ from fully symptomatic adult ADHD subjects, who often present inhibition deficits (e. g. McLoughlin et al., 2010). Most of the symptoms in our ADHD sample had improved and inhibition deficits decreased, possibly reflecting compensatory processes. Differences in the CNV and in performance variability may reflect more enduring brain mechanisms, while differences in the Cue P300 and NoGo P300 might be more associated with current disease status. These findings support the developmental ADHD model of Halperin and Schulz (2006) which distinguishes enduring subcortical dysfunctions associated with suboptimal state regulation (and thus RT-*SD*) from inhibitory deficits, which are more related to severity and persistence of ADHD, and which may decrease with compensation mediated by the development of the prefrontal cortex.

Attenuated CNV is not only a robust neurophysiological marker of ADHD but also an important target for neurofeedback treatment by self-regulation in Slow Cortical Potentials (SCP). Studies that investigated effects of SCP neurofeedback in ADHD showed encouraging results (Doehnert et al., 2008; Drechsler et al., 2007; Gevensleben, Holl, Albrecht, Schlamp, et al., 2009; Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Gevensleben et al., 2010; Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004; Wangler et al., 2010). The present finding supports the rationale that SCP neurofeedback in ADHD could improve the symptoms of ADHD by improving a developmentally stable core deficit. It also suggests that this rationale extends to young adults with mainly subthreshold symptoms of ADHD and a history of ADHD diagnosis in childhood.

Among the limitations of our study, the small sample sizes (which also required disregarding comorbidities) should be mentioned. Furthermore, the unequal intervals between the follow-up assessments limit the precision with which one can model late maturation in this longitudinal study. Nevertheless, our findings demonstrate a striking persistence of some behavioral and neural deficits in ADHD from adolescence to early adulthood. That subjects with childhood ADHD continued to show attentional and preparatory deficits is inconsistent with developmental lag models predicting that all deficits disappear with brain maturation. In particular, the persistent CNV attenuation suggests that this neural marker of preparation and time estimation which does not reflect the considerable remission of ADHD diagnoses is a possible endophenotype. Future studies in larger samples should explore whether distinct ADHD subtypes based on this endophenotype could have genetic underpinnings and profit from more individualized treatments during neurofeedback therapy.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Cue P300 peak latency and amplitude at Pz. Analysis of peak latencies and amplitudes at Pz indicated that latency decreased with development (main effect for time). Reduced amplitudes in the ADHD group were observed (but no notable effect for group, significant post hoc *t*-tests for T2). Control subjects' amplitudes peaked at the second assessment, which correspond to the typical nonlinear P300 development.

Table S2. NoGo P300 peak latency and amplitude at Cz. Analyses of peak latencies and amplitudes at Cz revealed decreasing peak latencies with development (time main effect) as well as significant group differences regarding peak amplitude (group main effect). Post hoc *t*-tests showed significant group differences for NoGo P300 amplitude at the first three assessments.

Figure S1. Waveforms of ERPs (CNV, Cue P300, NoGo P300) at all four assessments (T1–T4), which display group differences between ADHD subjects (red lines) and healthy controls (blue lines). Group differ-

ences became nonsignificant in adulthood except for the CNV.

Figure S2. Cue P300 (microstate 254–578 ms) – topographic maps, and *t*-maps; *t*-maps depict the differences between the different assessments and between both groups (attention-deficit/hyperactivity disorder [ADHD] and controls [CTRL]), respectively. The t-maps characterizing ADHD subjects (ADHD minus CTRL) and those characterizing younger subjects (younger minus older; T1 minus T4) showed roughly opposite polarity. The t-maps characterizing the differences between ADHD subjects and healthy controls showed reduced activity for ADHD subjects in left parietal areas at second and fourth assessment. At Time 1 this ADHD effect was localized in central areas.

Figure S3. NoGo P300 (microstate 254–578 ms) – topographic maps, and *t*-maps; *t*-maps depict the differences between the different assessments and between both groups (attention-deficit/hyperactivity disorder [ADHD] and controls [CTRL]), respectively. The NoGo-P3a topography developed from an 'immature' parietal toward the typical central positivity. This central positivity was already present at T1 for the control subjects but not before T3 for the ADHD group. The *t*-maps illustrate that the development of the NoGo P300 is particularly prominent and similar for both groups, with highly significant increases at frontocentral, and decreases at posterior electrodes. The *t*-maps characterizing the ADHD effect showed differences between ADHD and control subjects with age mainly at frontocentral sites that strongly resembles the developmental effects. At the fourth assessment, t-maps showed a left lateralization of this ADHD effect.

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Correspondence

Mirko Doehnert and Daniel Brandeis, Department of Child and Adolescent Psychiatry, University of Zurich, Neumünsterallee 9, CH-8032 Zurich, Switzerland; Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, University of Leipzig, Liebigstrasse 20a, D-04103, Germany; LIFE –Leipzig Research Center for Civilization Diseases, Universität Leipzig, Germany; Email: mirko.doehnert@uniklinik-leipzig.de or brandeis@kjpd.uzh.ch

Key points

- The leading hypothesis implicates a developmental delay in ADHD for some brain structures and functions. Doehnert et al. investigated cognitive brain activities longitudinally from childhood to early adulthood in ADHD subjects and healthy controls. Several electrophysiological measures of brain activity during a cued continuous performance test (CPT) were attenuated with childhood ADHD but followed similar developmental trajectories in both groups. Trajectory shapes differed only for performance sensitivity.
- Preparatory activity (CNV) in ADHD remained attenuated in adulthood, even for the subsample with partly remitted ADHD. Adult ADHD subjects also still exhibited increased reaction time variability (RT-*SD*). In contrast, neither attentional (Cue P300) nor inhibitory (NoGo P300) activity remained significantly attenuated in adulthood.
- The authors conclude that the persistent CNV reduction due to childhood ADHD is unlikely to reflect developmental lag and represents a possible endophenotype of impaired preparatory and time processing in ADHD. Larger studies should explore whether subtyping based on this potential ADHD endophenotype is useful for developing more individualized treatments such as neurofeedback training.

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