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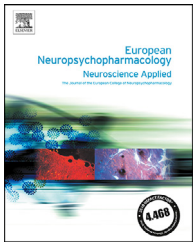

Attention deficit hyperactivity disorder: Last in, first out - delayed brain maturation with an accelerated decline?

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Abstract
While early neurodevelopmental processes during the emergence of ADHD in childhood received considerable attention, the neurobiological mechanisms that underlie the changes in ADHD in adulthood remain largely unaddressed. We wanted to delineate neurodevelopmental changes in adult ADHD using an electrophysiological measure, the fronto-central NoGo P3 event-related potential (ERP), which is an important neurophysiological index of brain functioning in ADHD, and biomarker for response inhibition and aging. ERPs were obtained from 45 ADHD and 41 healthy subjects using a 128-channel BioSemi recording-system, applying emotionally-valenced and neutral stimuli in a response inhibition task. Our results indicated that ADHD subjects manifested delayed developmental P3-trajectory in young-adulthood as compared to controls; they also showed P3 reduction across all emotional valences, and the reduction was most pronounced at younger ages. The differences in P3 diminished by mid-adulthood, and started to increase again at more advanced ages. Thus, similar to structural-MRI indices, developmental brain differences in the fronto-central NoGo P3 in ADHD largely normalize in young-adulthood. However, a reduction of P3 occurs again starting from mid-adulthood. As the fronto-central NoGo P3 reflects the functioning of the frontal areas (which show delayed maturation in ADHD), our findings are consistent with the ''last in, first out'' hypothesis, which refers to a mirroring pattern of brain development and aging, and posits that brain regions that develop relatively late degenerate relatively early with age. Thus, ADHD may not only be associated with delayed neurodevelopment, but also with a premature age-related deterioration, at least in some measures of electrophysiological functioning.

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1. Introduction

While early neurodevelopmental alterations during the emergence of ADHD in childhood received considerable attention in the literature (Shaw et al., 2006; Spronk et al., 2008; Vaidya, 2012), the neurobiological mechanisms that underlie the changes in ADHD in adulthood remain largely unaddressed. With respect to early neurodevelopmental processes, longitudinal structural-MRI data indicate that children with ADHD undergo delayed maturation in many brain regions, especially in the frontal cortex (Gogtay et al., 2002; Shaw et al., 2007). A significant portion of this maturational delay, however, is being made up by the beginning of young-adulthood (Shaw et al., 2007). A large cross-sectional investigation of structural-MRI data - termed as 'mega-analysis' by the authors (Hoogman et al., 2017) - of 1723 ADHD and 1523 control subjects (age range=4-63years) provided strong support for the "brain maturation delay theory for ADHD". Since it is conceivable that - through brain plasticity or experience-dependent synaptic reinforcement (Casey et al., 2005; Whitford et al., 2007) - these changes in brain morphology during childhood and adolescence induce functional alterations, it would be important to investigate post-adolescent neurophysiological changes in ADHD as compared to healthy individuals. In terms of functional brain alterations, a recently published comprehensive overview of developmental trajectories of ADHD over the lifespan (Franke et al., 2018) identified one small, longitudinal EEG study (Doehnert et al., 2013) which reported that only ERP impairments related to response preparation were associated with ADHD in adulthood. However, the study was small (ADHD $n = 11$/control $n = 12$) and the follow-up of subjects (children with a mean age=10.9 years) did not extend beyond young adulthood (mean age=21.9 years).

An important electrophysiological marker of brain functioning in ADHD is the fronto-central P3 ERP, a positive-going potential between approximately 300 to 450 msec post-stimulus, which is widely viewed as a measure of behavioral response inhibition (BRI) (Fallgatter et al., 2005; Knezevic and Marinkovic, 2017; Randall and Smith, 2011), and of aging (Rossini et al., 2007). It is typically observed after NoGo trials in response inhibition paradigms, and may reflect the activity of multiple cortical locations, including the frontal cortex, pre-supplementary motor area, the cingulate regions and the inferior parietal lobe (Albert et al., 2013; Tamm et al., 2002; Vara et al., 2014). BRI is a core executive function (EF); its impairment leads to behavior dyscontrol, distractibility and deficits in sustained attention, which are considered to be key features of ADHD (Wodka et al., 2007). Diminished ability to suppress inappropriate prepotent responses to stimuli has been observed in ADHD (Lipszyc and Schachar, 2010; Wodka et al., 2007), which has been viewed by some authors as a "disorder of deficient self-regulation"(DSR) (Barkley, 1997). BRI undergoes a prolonged maturation: in typically developing (TD) subjects, its development starts at the age of 6 years, and lasts at least until the age of 20 years (Jonkman, 2006; Tamm et al., 2002).

In line with the developmental changes of BRI, P3 also shows a protracted developmental path in TD children. It cannot yet be observed in 6-7-year old children (while it is present in 9-10 year olds), which has been interpreted as a sign of immature response inhibition processing in early childhood (Jonkman, 2006). Another study also found that the NoGo P3 develops relatively late, around age 10 (Okazaki et al., 2004). A systematic review by van Dinteren et al. 2014 identified a quadratic trajectory from childhood to old ages for the fronto-central P3 amplitude: a steady increase from preschool-age until a maximum at around the third-decade; and a subsequent plateau, followed by a decline from the fifth-decade.

As two important sources of the fronto-central P3 are the frontal cortex and the cingulate areas, and its amplitude correlates with the frontal gray matter volume (Ford et al., 2004), a parallel can be drawn between the gradual increase of P3 amplitude with age and the prolonged development of the frontal cortex. Importantly, the NoGo P3, as a neural marker of BRI, exhibits altered development in ADHD: diminished NoGo P3 is consistently reported in ADHD as compared to TD children between 7 and 14-years of age (Fallgatter et al., 2004; Fallgatter et al., 2005; Wiersema et al., 2006).

Prior studies of NoGo P3 ERP almost exclusively used BRI tasks which ignored affective contexts, and did not examine whether BRI is affected by the stimuli's emotional valence (see, e.g., Albert et al. for an exception in healthy subjects (Albert et al., 2013)). These studies considered EFs as purely cognitive skills (Tsermentseli and Poland, 2016). However, more recent theoretical models of EFs make a distinction between cool cognitive EFs (i.e., primarily those encompassed in the earlier conceptualization, such as attention, working memory, planning and inhibition) and "hot" EFs which involve emotions and motivation (Zelazo and Carlson, 2012). This theoretical framework has crucial implications for the developmental research in ADHD because current conceptualizations consider Deficient Emotional Self-Regulation (DESR) as a core feature of ADHD (Barkley, 1997; Castellanos et al., 2006; Surman et al., 2013). Nonetheless, we are not aware of any developmental data on the P3 ERP in ADHD during adulthood that were obtained in an emotional response inhibition task.

To fill in the above knowledge gaps, in the current study we focused on the fronto-central P3 ERP to investigate the neurobiological underpinnings of developmental changes in ADHD during adulthood. Using a quadratic regression modeling approach, we wanted (a) to delineate the developmental trajectory of P3 ERP in ADHD as compared to healthy controls; and (b) to examine whether the developmental changes are associated with changes in response inhibition. We adopted an emotional response inhibition paradigm based on a Go/NoGo task using emotionally-valenced and neutral pictures from the International Affective Picture System (IAPS) (Lang et al., 2008).

2. Experimental procedures

2.1. Study sample

Patients who met DSM-IV criteria for adult ADHD (mean age=30.4years, range:18-59years) and had no history of neurological illness were recruited for the study at the Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary, which provides outpatient service for patients with adult

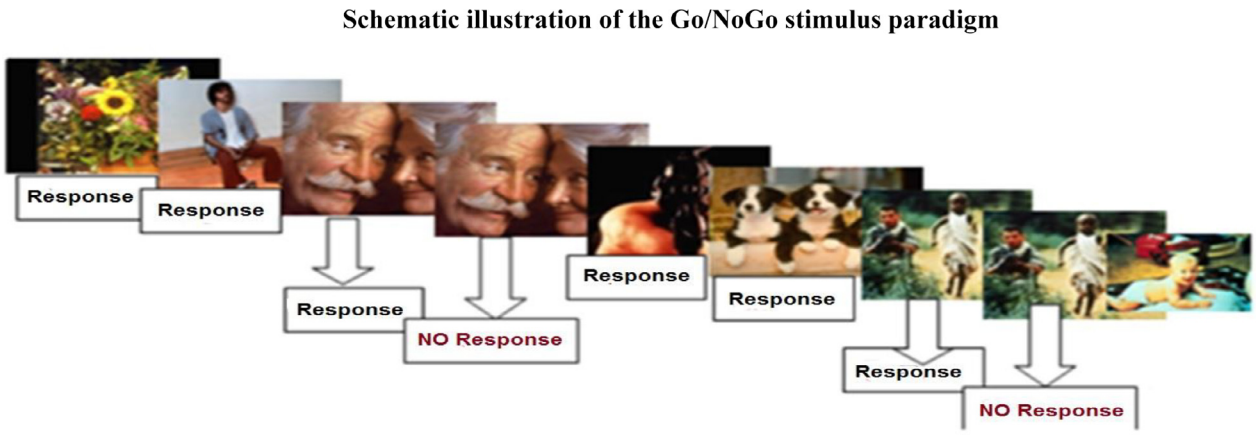

Fig. 1 Task and procedure. Stimuli were presented centrally every 1400 msec for 800 msec (inter-stimulus-interval = 600 msec). Subjects were asked to push a button as soon as possible upon the appearance of the stimulus pictures (Go trials); they were, however, asked to withhold response in case a picture was repeated (NoGo trials). 240 stimuli were shown in two blocks. The probability of Go and NoGo trials was 0.85 and 0.15, respectively.

ADHD. All included patients fulfilled the DSM-IV criteria for the combined subtype of ADHD (i.e., had >6 symptoms of the total of 9 symptoms of Inattention and Hyperactivity/Impulsivity, respectively). Recruitment was done by staff of the outpatient clinic. Diagnosis was confirmed through semi-structured interview by the treating physician. Healthy controls (HC) were recruited from the community through friends and acquaintances of the staff of the University. HCs had a mean age of 31.3years (range:18–59years), and had no history of psychiatric disease or current psychiatric comorbidity. They were individually matched to patients on age (±5years), gender and education level. Additional exclusion criteria for participants in the control group were any present or past neurological disorder and history of head injury with loss of consciousness. The study complied with the ethical standards of the Declaration of Helsinki, and received approval from the local Ethical Committee. All participants gave written Informed Consent for the study.

2.2. Description of measures

The Conners' Adult ADHD Rating Scale (CAARS;66-item version) was used to characterize ADHD symptom severity across core psychopathological domains of ADHD: Inattention, Hyperactivity, Impulsivity and Problems with Self-Concept (Conners, 1999; Erhardt et al., 1999). The Adult Self-Report Scale symptom Checklist (Adler et al., 2006) was used to delineate ADHD symptoms and to establish ADHD subtype. The total score on the Symptom Check List 90R(SCL-90R), a self-report scale was used to measure the severity on general domains of psychopathology (Derogatis, 1994). The scale was designed primarily to assess symptom patterns in a broad spectrum of populations, ranging from non-patient healthy subjects to individuals with psychiatric disorders (Derogatis and Cleary, 1977). The scale was administered by study personnel including psychologists and research assistants trained in its administration.

2.3. Stimuli and procedure

Participants were seated in a dimly lit room, approximately 100 cm from the monitor. The International Affective Picture System (IAPS) (Lang et al., 2008), a set of images with neutral, positive, and negative valences, were used as stimuli, and presented in random sequence using the Presentation 13.0 software (Neurobehavioral Systems, Inc., Albany, Calif.). The stimuli were presented centrally every 1400 msec for 800 msec (interstimulus-interval=600 msec). A total of 480 stimuli were presented in two blocks, each consisting of 240 stimuli. Subjects were asked to push a button as soon as possible upon appearance of the pictures (Go trials); they were asked to withhold response if a picture was repeated (NoGo trials). The probability of Go and NoGo trials was 0.85 and 0.15, respectively. The stimulus task and procedure are illustrated in Fig. 1.

2.4. EEG recording and pre-processing

High-density EEGs were recorded using a 128-channel BioSemi ActiveTwo system with an average reference, at a digitization rate of 1024 Hz, applying a band-pass filter of 0.5–70 Hz. We applied a standard BioSemi 128-electrode headcap system (online source: http://www.biosemi.com/pics/cap_128_layout_medium.jpg). Data were stored and analyzed off-line using the Electromagnetic Source Signal Imaging (EMSE) Suite as well as the Statistical Analysis System (SAS 9.4) software. EEG was re-referenced off-line to the common average potential and filtered between 0.5 and 70 Hz using zero-phase shiftforward and reverse IIR Butterworth-filter. Additionally, the signal was filtered using the 48–52 Hz Parks-McClellan stop-band Notch filter. The notch filter was used to remove any potential electric-interference from the 50 Hz line. Artifacts due to blinks and eye movements were removed manually and with the electrooculography artifact removal procedure. Epoch selection for the analyses was conducted manually, as well as applying automatic artifact rejection criteria. Stimulus-locked data were segmented into epochs of 1000 msec, including 200 msec before stimulus and 800 msec after stimulus. Segments with activity exceeding ±100 μV were excluded from further analysis. The threshold cut-off was 50 for the required minimum number of usable segments for the ERP analyses. Only correct trials were included in the current analyses. The stimulus-locked segments were baseline-corrected using a 200 msec pre-response window, and averaged to obtain the ERP-waveforms for each subject and each emotional valence.

2.5. Statistical analyses

2.5.1. Behavioral data

We used Analysis of Covariance with repeated-measures (rANCOVA) to investigate behavioral data, including commission-error rates

Table 1 Basic descriptive statistics of the study population.

Characteristics	ADHD ($n=45$)	Healthy Control ($n=41$)	Test statistic[a]	p-value
Categorical variables (%)			Chi-square test	
Male	71.1%	75.6%	0.2	0.64
Education level (high school graduate)	40%	46.3%	1.2	0.56
Continuous variables: mean (SD)			ANOVA (F)	
Age (years)	30.4 (10.9)	31.3 (11.4)	0.2	0.69
Conners Adult ADHD Rating Scale (CAARS)				
Total score	121.6 (23.6)	50.3 (25.7)	165.1	<0.0001
CAARS Subscales: Inattention/Memory Problem	24.5 (6.6)	8.5 (6.6)	116.8	<0.0001
Hyperactivity/Restlessness	20.2 (6.4)	11.1 (5.7)	43.8	<0.0001
Impulsivity/Emot. Lability	18.2 (7.3)	8.8 (4.5)	45.1	<0.0001
Problems with Self-Concept	10.8 (5.0)	4.2 (4.2)	39.1	<0.0001

[a] ANOVA for continuous variables, Chi^{2-}test for categorical variables.

and reaction times. Commission-error rate (%) and reaction time (RT, msec) were applied in separate analyses as dependent variables. Study group (ADHD, HC; used as a between-subjects factor and emotional valence (positive, negative, neutral;, used as a within-subject factor) were the independent variables. Age was applied as a continuous regressor. In order to examine potential non-linear changes over time, age was included in the analysis both as a linear and a quadratic term. Interaction between study group, emotional valence and age were also tested.

2.5.2. ERP measures

Based on literature, the definition of frontal P3 component time-window included the post-stimulus epoch of 300-450 msec (Knezevic and Marinkovic, 2017). Similar to our earlier work (DeSanctis et al., 2013), the statistical analyses were based on random-regression hierarchical linear modeling (HLM; (Bryk A.S. and Raudenbush S.W., 1992; Gibbons et al., 1988)). Repeated measurements of the ERP amplitude (in microvolts) in the frontal regions for the P3 ERP (region of interest included electrode Fz and the adjacent electrodes surrounding Fz) in the component time-window served as dependent variable. Study group (between-subjects factor), and emotional valence (within-subject factor) were the principal independent variables of interest. Time (sampling point in the component window, relative to stimulus onset) was also included in the analysis as a within-subject factor. A first-order autoregressive moving average correlation matrix among the sampling points was specified in the HLM model. Gender served as a covariate. Similar to the analyses of behavioral data, age was used as a continuous regressor. Interaction between study group, emotional valence and age (used in linear and quadratic form) was investigated in the HLM. The interaction effect between group and age tested whether the study groups had a different developmental trajectory with age.

3. Results

3.1. Demographic characteristics

Patients with ADHD ($N=45$) and HCs ($N=41$) had no significant difference in age (Table 1). The proportion of males was somewhat higher (75.6%) among the HC than among the ADHD subjects (71.1%); the difference was not significant. There was no significant difference in the education level, with more than 40% of the sample in both groups attaining college or higher education. The two groups significantly differed on CAARS psychopathological symptom dimensions: as expected, patients had higher severity on all symptom dimensions. The patient sample met the criteria for the ADHD combined subtype.

Among the ADHD patients, 12(26.6%) of the 45 patients had comorbidity according to DSM-IV. In the majority of cases (10[22.2%] of 45), comorbidities fell in the affective categories. Specifically, affective comorbidities included 8 cases with depression in their medical history, while dysthymia and bipolar disorder occurred in 1 patient, respectively. Additional comorbidities were obsessive-compulsive disorder in one patient, and substance (cannabis) use in one patient. Approximately half of the 45 patients ($n=23$, 51.1%) received stimulant medication. Patients taking stimulant treatment were off medication for at least 24 h before testing.

3.2. Behavioral measures

With respect to commission-errors, the analysis indicated a significant main effect of group ($F_{1,85}=4.72$, $p=0.032$), and a significant linear (but no quadratic) effect of age on the commission-error rates ($F_{1,85}=8.75$, $p=0.0041$). Post-hoc analyses showed that ADHD patients made more commission-errors than HCs, and that the commission-error rate decreased with age. The main effect of emotional valence, and its interaction with group and age were not significant ($p > 0.1$ for all respective terms in the rANCOVA analyses). The developmental trajectory of commission-error rates, determined on the basis of the linear regression estimates, is shown in Fig. 2 (top). To delineate the above results in terms of the observed data, we dichotomized the study groups into young-adult ($\leq$30years) and middle-aged (>30years) groups, and provided summary statistics for both age groups (Table 2, left). In the ADHD group, among the middle-aged subjects the proportion of commission-errors was significantly ($p < 0.05$) reduced for all three emotional valences as compared to the younger subjects. Among the HCs, the reduction was significant only for the neutral stimuli.

The analysis of RTs showed a linear main effect of age ($F_{1,85} = 13.7$, $p=0.0004$), with no quadratic or interaction effects. Post-hoc analyses indicated that in both study groups RTs increased with age. The estimated RT trajec-

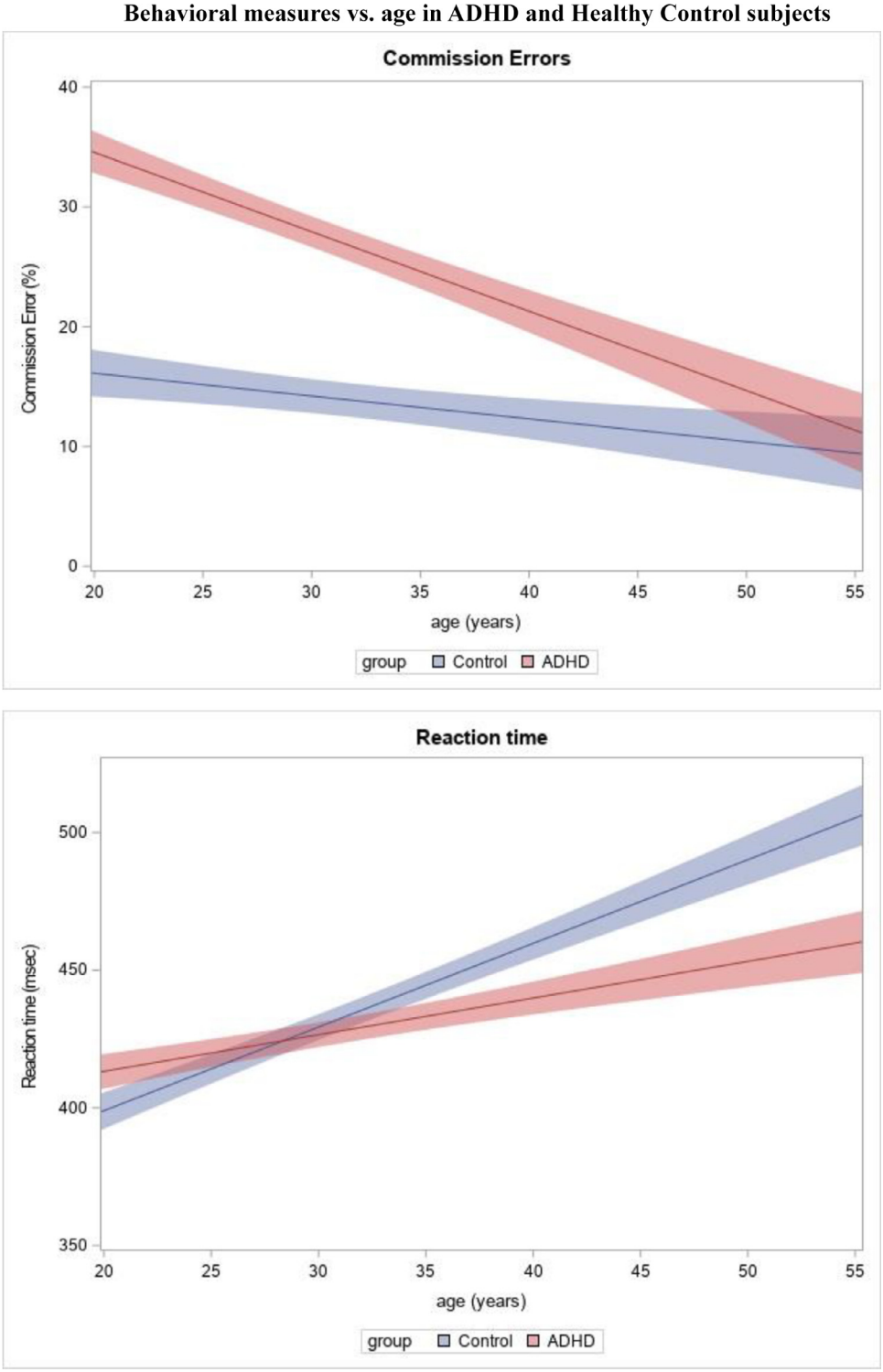

Fig. 2 Commission-error rate (top panel) and reaction time (bottom panel) as a function of age in the ADHD and the healthy control group, determined on the basis of the linear regression estimates obtained from the repeated measures ANCOVA model. The shaded bands depict the standard error of the estimates. For commission-errors, the analysis indicated a significant ($p = 0.032$) global effect of group, with a higher error rate among ADHD subjects irrespective of emotional valence; and a significant ($p = 0.0041$) reduction of error rate with age. The main effect of emotional valence, and its interaction with group and age were not significant. For reaction time, the analysis showed a significant ($p = 0.0004$) linear age main effect, indicating increased reaction times with age in both groups. The difference in reaction time between the two groups was not significant, and the age-related changes did not show a significant interaction with emotional valence or study group.

Table 2 Commission error rates and reaction times by age group among ADHD and healthy control (HC) subjects[a].

Study groups by age	Commission Error (%) mean (SE)			Reaction Time (msec) mean (SE)		
	POS	NEU	NEG	POS	NEU	NEG
ADHD ≤30 yrs $N=28$	37% (4)	38% (3)	36% (4)	416.1 (13.4)	410.5 (12.8)	426.7 (13.8)
ADHD >30 yrs $N=17$	18% (5)	22% (4)	18% (5)	444.2 (16.8)	435.0 (16.2)	447.8 (17.4)
Diff. (≤30 vs. >30 yrs)	19% (6)	16% (6)	18% (6)	−27.4 (2.14)	−24.5 (2.06)	−21.1 (2.2)
F, p[b]	9.11, **0.0043**	6.24, **0.0164**	8.72, **0.0051**	1.62, 0.2095	1.42, 0.2406	0.90, 0.3490
Control≤30 yrs $N=27$	20% (3)	19% (2)	17% (2)	413.4 (9.8)	410.2(10.1)	416.9 (10.8)
Control >30 yrs $N=14$	15% (4)	8% (3)	9% (4)	470.5 (13.6)	467.1(14.0)	477.9 (14.9)
Diff. (<30 vs. >30 yrs)	5% (5)	11% (4)	8% (5)	−57.1 (16.8)	−56.9(1.73)	−61 (1.84)
F, p[b]	0.74, 0.3949	7.07, **0.0113**	2.65, 0.1114	11.51, **0.0016**	10.82, **0.0021**	10.99, **0.0020**

[a] Study groups (ADHD, HC) were dichotomized by age (≤30 years [young adults] vs. >30 years [middle-aged subjects]).
[b] ANOVA was applied for both study groups to examine differences in commission errors rates and reaction times between the two age groups (young adults vs. middle aged subjects). The analyses were conducted separately for the positive, neutral and negative stimuli. Error rate (%) and reaction time was applied as dependent variable. Age group (≤30 years vs. >30 years) was used as an independent variable. Significant ($p<0.05$) differences between age groups are highlighted.

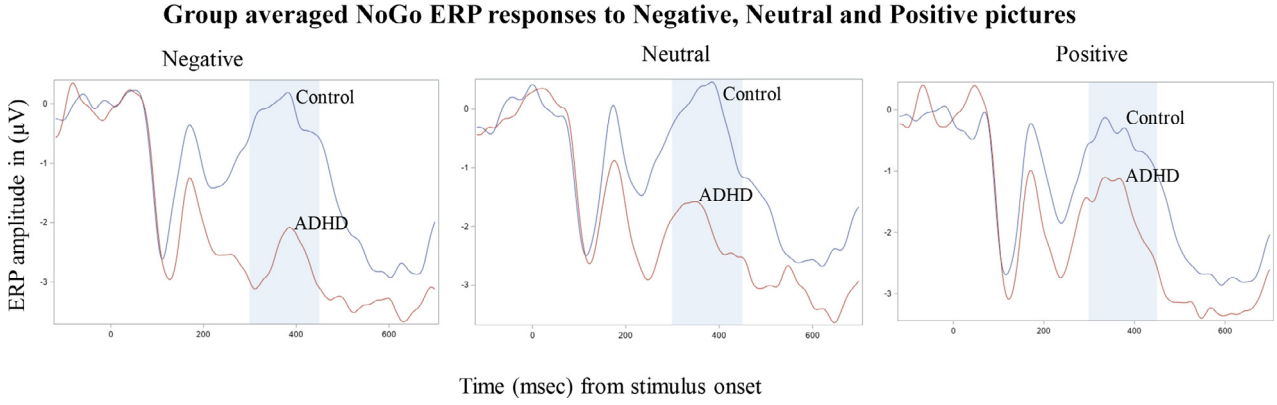

Fig. 3 Group averaged NoGo ERP responses to negative, neutral and positive pictures in the emotional NoGo paradigm, broken down by study group (ADHD, Control). Shaded areas indicate the time window of interest for the P3 ERP component. As shown by the Figure, the P3 component was preceded by a large negative-going wave, the frontal N2, which shifted the component downward (i.e., in negative direction). Random-regression Hierarchical linear model (HLM) analyses showed a significantly diminished P3 amplitude in the ADHD group for each of the three emotional valences (negative $p=0.0043$; neutral $p=0.038$; positive $p=0.023$).

tory with age, determined on the basis of the regression estimates, is shown in Fig. 2(bottom). Similar to the commission-errors, we also characterized the above findings in terms of the observed data by subdividing the study groups into young-adult and middle-aged subgroups (Table 2, right). By mid-adulthood, the RTs increased numerically in both the ADHD and the HC group for all emotional valences. The increase, however, obtained statistical significance only for the HCs.

3.3. P3 amplitude: group difference and developmental trajectories

Group-averaged NoGo ERPs to negative, neutral and positive pictures are shown in Fig. 3 separately for both study groups. The time window of interest for the P3 component is marked as a shaded area. As shown by the figure, the P3 component was shifted in negative direction by a preceding large negative-going wave, the frontal N2, which is typically enhanced in visual tasks(Folstein and Van Petten C., 2008; Zordan et al., 2008), especially under experimental conditions that involve considerable conflict processing effort(Donkers and van Boxtel, 2004; Gajewski et al., 2008; Nieuwenhuis et al., 2003). HLM analysis indicated a main effect of group with a larger P3 among the controls ($F_{1,85}=6.15$, $p=0.015$), and an interaction between group and emotional valence ($F_{1,85}=4.04$, $p=0.019$). The two-way interaction of group with the linear or with the quadratic effect of age on the P3 amplitude was also significant (linear $F_{1,85}=5.08$, $p=0.027$, quadratic $F_{1,85}=5.24$, $p=0.0247$). The three-way interaction of age by group by emotional valence was not significant ($p>0.1$).

Post-hoc analysis of the interaction between group and emotional valence showed a significantly lower P3 amplitude in the ADHD group for the negative pictures as compared to the positive ($t=-3.44$, df=85, $p=0.0009$) or neutral ones ($t=-2.40$, df=85, $p=0.0187$). The difference between positive and neutral pictures did not reach significance ($t=-1.62$, df=85, $p=0.11$). In the HC group, there were no differences by emotional valence ($p>0.1$ in all pairwise comparisons). Post-hoc analysis of the interaction of group with the linear and the quadratic effects of age revealed that in the ADHD group both the linear

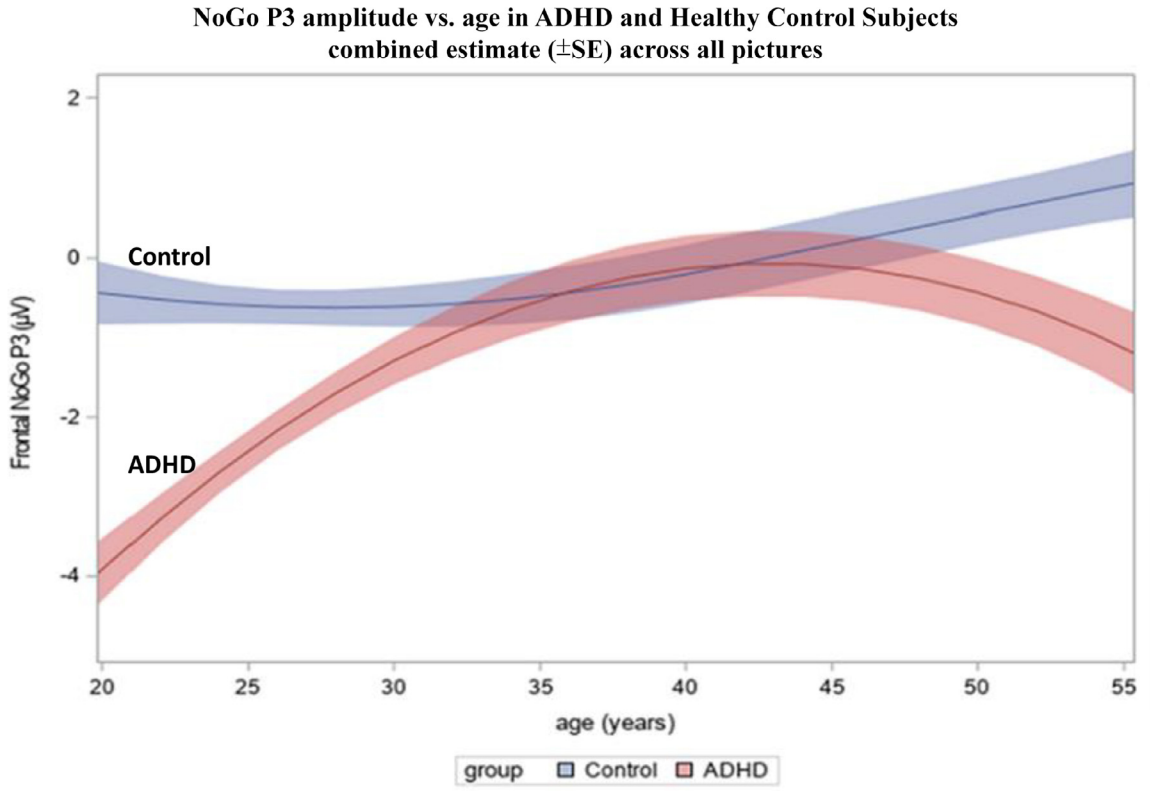

Fig. 4 NoGo P3 amplitude as a function of age in the ADHD and healthy control (HC) groups combined for all stimulus pictures. HLM analysis indicated a main effect of group ($F_{1,85} = 6.15$, $p = 0.015$), and an interaction of group with both the linear and the quadratic effect of age on the P3 amplitude (linear $F_{1,85} = 5.08$, $p = 0.027$, quadratic $F_{1,85} = 5.24$, $p = 0.0247$). In the HC group neither the linear nor the quadratic regression effects obtained significance, indicating no systematic change in P3 amplitude with age. In the ADHD group, both the linear and the quadratic effect was significant ($p < 0.05$), indicating a curvilinear relationship with age. The displayed trajectories represent the estimated regression functions of P3 amplitude with age based jointly on the linear and quadratic terms from the HLM. The shaded bands depict the standard error of the estimates.

and the quadratic effects reached significance (linear effect $t = 2.47$, df = 85, $p = 0.0156$); quadratic effect $t = -2.23$, df = 85, $p = 0.0286$), indicating a curvilinear relationship of P3 amplitude with age. In the HC group, neither the linear nor the quadratic effect was significant ($p > 0.1$), indicating no systematic change in P3 amplitude with age.

Fig. 4 shows the regression estimates for the NoGo P3 amplitude as a function of age (i.e., the estimated quadratic regression functions), combined across all stimulus pictures. The developmental path of the P3 amplitude was markedly different in patients and controls: patients with ADHD evidenced a significant amplitude reduction at younger ages as compared to HCs. The amplitude reduction diminished and lost significance by mid-adulthood, but then started to increase again at higher ages. Even though HCs exhibited a slight increase with age, the above mentioned group differences were primarily driven by the substantially more pronounced age-related changes in the ADHD group.

3.4. Subsidiary analyses

In subsidiary analyses, we investigated whether the inclusion of clinically relevant covariates, such as the severity of psychopathology, comorbidities and medication status, had an impact on our principal electrophysiological findings. For the severity of psychopathology we used the total score on the CAARS scale, while a dichotomous variable was applied for the use of stimulant medication (yes/no) and comorbidities. Our results are shown in Online Table 1. The rows of the Table depict the results of the addition of the covariates. The table shows that the group effect and the linear and quadratic interaction terms remained similar to those obtained from the analyses with no covariate in the model. Specifically, after the introduction of the covariates in the analyses, there was no change in terms of statistical significance with respect to the group effect and the linear and quadratic age interactions. Furthermore, the covariate-effects did not obtain statistical significance in the analyses. We also investigated whether there was a difference in the severity of psychopathology in the ADHD sample between the young-adult and middle-aged subgroups. The ANOVA analyses indicated no difference in the CAARS total score ($F_{1,44} = 0.12$, $p = 0.73$): the mean total score was 120.6(SD = 24.1) and 123.2(SD = 23.4) in the young-adult and middle-aged subgroup, respectively. Furthermore, the two subgroups did not differ in any of the CAARS subscales ($p > 0.1$ in all analyses).

4. Discussion

Our principal findings suggest that patients with ADHD manifest a delayed developmental trajectory of the fronto-central NoGo P3 in young-adulthood relative to HCs. In general, the developmental trajectory of P3 was markedly different in the patients and controls. While patients with ADHD showed a significant P3 reduction across all emotional valences, the reduction was the most pronounced at younger ages. The age difference in P3 diminished by mid-adulthood; this diminution effect, however, was limited to a certain age range, beyond which the difference started to increase again at higher ages.

Concerning the diminution of P3 alteration in ADHD with age, our findings parallel the results of several MRI studies that examined age-related changes. For example, a large longitudinal study in 223 ADHD and 223 normally-developing children showed that the peak of cortical-thickness maturation was delayed in ADHD by an average of 3 years; in frontal and temporal areas, the maturation was delayed by up to 5 years (Shaw et al., 2007). A recent longitudinal study by the same research-group extended the previous findings by demonstrating that the maturation of cortical surface area was also delayed in children with ADHD (Shaw et al., 2012). Data on potential developmental changes in adulthood were yielded by two MRI meta-analyses (Frodl and Skokauskas, 2012; Nakao et al., 2011), which included cross-sectional data from children and adults (from separate studies). These meta-analyses provided consistent evidence that the age-related alterations in structural-MRI measures diminish in adult ADHD. A recently published structural-MRI study (Onnink et al., 2014) which examined volumetric measures in a large cross-sectional sample of adult ADHD patients concluded that "developmental brain differences in ADHD largely normalize in adulthood" (Onnink et al., 2014).

Consistent with the above MRI data, our results suggest that a normalization of developmental brain differences in ADHD in adulthood may also occur in terms of neurophysiological measures. As the volume of the frontal cortex was shown to correlate with the P3 amplitude (Ford et al., 2004), this finding is in line with the assumption of delayed developmental maturation of the frontal cortex in ADHD. Furthermore, this P3 age-effect is consistent, at least in part, with Halperin and Schulz's (H-S) neurodevelopmental model of ADHD persistence (Halperin and Schulz, 2006), which suggests that partially distinct neural and cognitive mechanisms are involved in the cause of and recovery from ADHD.

The model assumes that the degree to which the development of the prefrontal cortex is able to compensate for early neural deficits accounts for the improvement of symptoms frequently seen in ADHD with age. We investigated the improvement of a core executive function in ADHD, the BRI, in relation with age, as indexed by the commission-errors. We found that both study groups exhibited better performance with increasing age in terms of commission-errors, but the improvement was more pronounced in the ADHD sample. Additionally, we found a prolongation of RTs with age in both groups, which, in contrast to the commission-errors, was more substantial among HCs.

While partially consistent with the H-S model, the finding that the P3 diminution effect was restricted to a certain age range points beyond the compensatory processes considered in the model. In particular, with respect to the neurodevelopmental time course of P3 we found a decline of P3 amplitude in the ADHD group, which started from mid-adulthood. As the fronto-central NoGo P3 is considered to reflect the functioning of the frontal areas (which show a delayed maturation in ADHD), our findings are consistent with the ''last in, first out'' hypothesis (Douaud et al., 2014; Raz, 2005), which refers to a mirroring pattern of development and aging of the human brain. As stated by (Douaud et al., 2014), "the sequence of events associated with brain decline should present itself in reverse order to the series of events related to brain development, with brain regions thought to develop relatively late - at both ontogenetic and phylogenetic level – also degenerating relatively early" (Hill et al., 2010; Raz et al., 2005; Reisberg et al., 2002). Hence, our findings raise the possibility that ADHD – at least in patients whose symptoms persist into adulthood - may not only be associated with a delayed neuro-developmental trajectory, but also with a premature age-related deterioration, at least in some areas of neurophysiological functioning.

Although impairment of "hot executive" functions was postulated as a key deficit in ADHD (Barkley, 1997; Surman et al., 2013), previous studies used emotionally-neutral stimuli in NoGo BRI tasks to investigate the fronto-central P3 (e.g.,(Fallgatter et al., 2004; Fallgatter et al., 2005; Wiersema et al., 2006)). In the current study, applying emotionally-neutral as well as valenced stimuli, we detected a significant group by emotional valence interaction, which revealed an effect of emotional valence in the ADHD group: the P3 reduction was significantly greater for negative than for neutral or positive stimuli. Among HCs, we found no overall difference by emotional valence across all ages.

The reduction of P3 in ADHD and the modulation of the P3 reduction by negative emotional valence may reflect the impairment of hot EFs. These findings can be interpreted in the context of cognitive-energetic model (CEM) (Sergeant, 2005), which postulates that ADHD causes defects across three levels of hierarchy, including attention at level 1 (with computational aspects and motor output); energetic pools at level 2 (effort, arousal and activation); and, the executive/management system (level 3). We assume that the overall reduction of P3 in ADHD is associated with a top level deficit in executive/inhibitory control (which would be linked to impairments in "cool" EFs). In light of the evidence that the P3 amplitude decreases with increased arousal (Polich, 2007), we think that the additional P3 reduction in ADHD by negative stimuli may be viewed as linked to the alterations in the energetic pool, including arousal (at level 2 in the CEM).

According to the low arousal theory of the disorder (Barry et al., 2003a; Barry et al., 2003b), ADHD patients are characterized by hypo-arousal, which has been shown to be associated with a relative up-regulation of the phasic arousal-response (Sikstrom and Soderlund, 2007). This may lead to hypersensitivity to emotionally-salient environmental stimuli, such as the negative pictures in our study. The behavioral finding that commission-error rates are

not higher for negative than for neutral or positive stimuli (despite increased arousal) may be linked to processes manifested at level 1 in the CEM. Specifically, the motor output may be preferentially blocked by negative stimuli, since the presentation of such stimuli - that capture attention and are associated with longer-lasting effects (Morriss et al., 2013) - may cause a momentary freeze in motor responding (as would be expected from the "fight, flight, freeze" theory (Kalanthroff et al., 2013; Pereira et al., 2010)). This would decrease the likelihood of button-press responses in the NoGo trials, leading to a maladaptive "improvement" in commission-errors. This latter effect may be present, at least in part, in healthy individuals because evidence indicates a lack of emotional interference by negative stimuli with respect to commission-errors in GoNoGo tasks (Littman and Takacs, 2017).

Several issues and study limitations merit comment. First, the response inhibition task we used involves a working memory (WM) component, as it requires a "same" vs. "different" decision based on the immediately preceding stimulus. It is therefore conceivable that WM alterations presented a confound in our investigation. Further studies that systematically manipulate the WM demand in the task are needed to clarify this issue. Second, the possibility of premature deterioration in patients with ADHD in certain electrophysiological indices of functioning, such as the age-related P3 reduction, may be seen at variance with some of the earlier findings. For example, the aforementioned mega-analysis of structural-MRI data indicated a later onset of volume decrease in the nucleus accumbens and putamen in the ADHD as compared to the control group (Hoogman et al., 2017). However, one has to keep in mind that various cortical and subcortical brain regions have different developmental trajectories (Coupe et al., 2017; Franke et al., 2018; Storsve et al., 2014).Third, our study included only adults with ADHD, and therefore did not cover the critical developmental trajectory from adolescence to adulthood. Furthermore, it was cross-sectional, which raises the issue of potential confounding in terms of causal relationships and possible age-cohort effects. However, our goal was not to identify causal associations, but to describe developmental trajectories with age. Since we continuously sampled an age-range rather than using distinct age-cohorts, and applied a regression approach, the age-cohort effects seem less likely. Nonetheless, we concur with the conclusions of a recent review of lifespan changes in ADHD that "a severe lack of knowledge on lifespan aspects in ADHD still exists", and large-scale research efforts would be essential to overcome the "knowledge gaps through appropriately granular longitudinal studies" (Franke et al., 2018).

Finally, approximately half of the patients received stimulant medication, and about one-fourth had comorbidities. However, the inclusion of medication and comorbidity status in the analyses did not influence the principal results. Finally, since we focused on adult patients, whose symptom severity met the diagnostic criteria (i.e., their ADHD persisted), our results pertain to this group of patients. Hence, our findings may not generalize to patients whose symptoms do not reach the diagnostic threshold in adulthood. These patients may evidence a more complete and earlier narrowing of the age-developmental gap than those who remain symptomatic in adulthood, and should be examined in future studies.

5. Conclusions

Consistent with MRI data, our results suggest that a normalization of developmental brain differences in ADHD in adulthood may also occur in terms of neurophysiological measures. However, with respect to the neurodevelopmental time course of P3, we identified a decline in ADHD, which starts from mid-adulthood. Since the fronto-central NoGo P3 reflects the functioning of the frontal areas (which undergo delayed maturation in ADHD), this finding is consistent with the "last in, first out" hypothesis (Douaud et al., 2014; Raz, 2005), which refers to a mirroring pattern of development and aging of the human brain. Hence, our results raise the possibility that ADHD may not only be associated with a delayed neuro-developmental trajectory, but also with a premature age-related deterioration, at least in some areas of neurophysiological functioning.

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Contributors

Authors Kakuszi, Czobor and Bitter designed study. Author Kakuszi performed the data collection and preprocessing of the EEG data under the supervision of authors Bitter and Czobor. Authors Kakuszi and Czobor managed the literature searches and analyses. Author Szuromi participated in the clinical data collection. Authors Czobor and Kakuszi undertook the statistical analysis. Authors Kakuszi and Czobor wrote the first draft of the manuscript. All authors contributed to the interpretation of the findings, and have approved the final manuscript.

Conflict of interest

Authors B. Kakuszi, B. Szuromi, I. Bitter and P. Czobor declare that they have no conflict of interest with regard to this study.

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Supplementary materials

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