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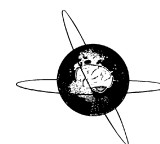
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# Electrophysiological correlates of improved executive function following EEG neurofeedback in adult attention deficit hyperactivity disorder



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## HIGHLIGHTS

- Go/NoGo task performance improved after a single-session of neurofeedback aimed at downregulating the alpha-rhythm.
- The amplitudes of both N1 and P3 event-related potentials were enhanced post-neurofeedback.
- Improvement of executive function correlated with enhanced P3 amplitude in adult ADHD patients.

## ABSTRACT

**Objective:** Event-related potentials (ERPs) are reported to be altered in relation to cognitive processing deficits in attention deficit hyperactivity disorder (ADHD). However, this evidence is mostly limited to cross-sectional data. The current study utilized neurofeedback (NFB) as a neuromodulatory tool to examine the ERP correlates of attentional and inhibitory processes in adult ADHD using a single-session, within-subject design.

**Methods:** We recorded high-density EEG in 25 adult ADHD patients and 22 neurotypical controls during a Go/NoGo task, before and after a 30-minute NFB session designed to down-regulate the alpha (8–12 Hz) rhythm.

**Results:** At baseline, ADHD patients demonstrated impaired Go/NoGo performance compared to controls, while Go-P3 amplitude inversely correlated with ADHD-associated symptomatology in childhood. Post NFB, task performance improved in both groups, significantly enhancing stimulus detectability (*d-prime*) and reducing reaction time variability, while increasing N1 and P3 ERP component amplitudes. Specifically for ADHD patients, the pre-to-post enhancement in Go-P3 amplitude correlated with measures of improved executive function, i.e., enhanced *d-prime*, reduced omission errors and reduced reaction time variability.

**Conclusions:** A single-session of alpha down-regulation NFB was able to reverse the abnormal neurocognitive signatures of adult ADHD during a Go/NoGo task.

**Significance:** The study demonstrates for the first time the beneficial neurobehavioral effect of a single NFB session in adult ADHD, and reinforces the notion that ERPs could serve as useful diagnostic/prognostic markers of executive dysfunction.

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## 1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a frequent neurodevelopmental disorder characterized by symptoms of inattention, impulsivity and hyperactivity, persisting in adulthood in

40–60% of cases, with major impacts on social and professional outcomes (Biederman and Faraone, 2005, Magnin and Maurs, 2017, Sibley et al., 2017). In adults with ADHD, although international guidelines recommend pharmacotherapy as a first line treatment (Hinshaw and Arnold, 2015), several non-pharmacological interventions, such as neurofeedback (NFB), have been developed to meet the demand of many patients who are unwilling or unable to take medication. Over the last decade, NFB has become popular as an innovative intervention for ADHD especially in children, with increased evidence of long-term clinical benefits (Arns et al., 2017, Enriquez-Geppert et al., 2019, Gevensleben et al., 2010, Gevensleben et al., 2009, Niv, 2013, Razoki, 2018, Van Doren et al., 2018). NFB consists of measuring a specific parameter of brain activity, which is presented in real-time to the participant via visual or auditory feedback; the participant's goal consists of modifying this parameter, thus enabling self-regulation of his/her own brain activity (Luft, 2014, Ros et al., 2013, Sitaram et al., 2017). Standard EEG NFB protocols employed in ADHD include the reduction of the theta/beta ratio, the upregulation of sensorimotor rhythm (SMR), and the bidirectional regulation of Slow Cortical Potential (SCP), all potentially involved in reducing inattentive and hyperactive/impulsive symptoms (Arns et al., 2017, Enriquez-Geppert et al., 2019).

While many studies have addressed the behavioral and clinical effects of NFB, evidence is still lacking on the neuronal mechanisms actually modulated by NFB interventions. In this study, we asked whether the neurophysiological correlates of ADHD may be linked to any pre- to post-NFB changes in electrocortical activity during a response inhibition task. For the latter, we used a classic Go/NoGo task which requires participants to respond to a frequent “Go” stimulus while withholding their response to an infrequent “NoGo” stimulus. Attentional performance is then measured by the number of correct stimulus detections in the Go trials, while inhibition performance is reflected by the number of correct response omissions in the NoGo trials. In parallel, the recording of event-related potentials (ERPs) during such a paradigm is able to reveal the different neural processes involved in stimulus perception, sustained attention and response inhibition. Namely, the early parieto-occipital P1 and N1 exogenous components reflect perceptual gating and attentional selection (Dering and Donaldson, 2016, Hillyard and Anllo-Vento, 1998), whereas the later fronto-central N2 and P3 endogenous components are related to processes involving stimulus discrimination, conflict monitoring, and response inhibition (Albert et al., 2013, Hong et al., 2017, Huster et al., 2013). Numerous studies have examined the Go/NoGo ERPs in ADHD, mainly in children, in search for a reliable biomarker of the disorder. Abnormalities of cue-P3 and NoGo-P3 were constantly reported, compatible with deficits in attention orienting and inhibitory control (Baijot et al., 2013, Doehner et al., 2010, Tye et al., 2014, Valko et al., 2009). According to a recent meta-analysis, ADHD individuals show a significant reduction of the P3 component, although there is a high heterogeneity in effect sizes (see Kaiser et al., 2020 for a review).

The existing studies addressing the effect of NFB on ERP components in ADHD patients have used multi-session NFB interventions employing either theta/beta ratio, SCP or SMR protocols (Arns et al., 2012, Bluschke et al., 2016, Gevensleben et al., 2014, Heinrich et al., 2004, Krepel et al., 2020, Kropotov et al., 2005, Mayer et al., 2016). Consistent behavioral improvements were reported in the domain of hyperactivity, impulsivity and attention (Arns et al., 2012, Gevensleben et al., 2010, Krepel et al., 2020, Kropotov et al., 2005, Micoulaud-Franchi et al., 2014, Ryoo and Son, 2015, Van Doren et al., 2018), in parallel with an enhancement of neurophysiological responses linked to cognitive control, especially the P3 component (Arns et al., 2012, Bluschke et al., 2016, Graczyk et al., 2014, Kropotov et al., 2005, Zioga et al., 2019). We

recently undertook a novel EEG-NFB study in adult ADHD patients that involved single training session of alpha-band down regulation (Deiber et al., 2020), a protocol that has previously been shown to alter cortical excitatory/inhibitory balance (Ros et al., 2010). Compatible with previous work (Klimesch et al., 2007, Mathewson et al., 2011), we uncovered a negative correlation between changes in alpha-band amplitude and improved attention as well as cortical inhibition, representing a promising avenue for linking NFB-based EEG biomarkers to improvements in ADHD symptomatology (Lenartowicz et al., 2018, Ros et al., 2014b, Selten et al., 2018). Specifically, ADHD patients showed reduced baseline and task-related alpha power compared to control subjects. Interestingly, while both groups were able to reduce their alpha amplitude during NFB, ADHD patients demonstrated an alpha amplitude enhancement post-NFB, which was associated with a reduction in inhibition errors. This suggests that NFB may induce spectral normalization of the EEG after only 30 minutes of training. In the present study, we extend the analysis specifically to the ERPs recorded during the Go/NoGo task of the same cohort, investigating whether any ERP components were affected by the NFB procedure, and their association with changes in task performance. Finally, we also sought to examine the putative relationship between abnormal amplitude/latency of ERP components and baseline ADHD severity (Mueller et al., 2010, Smith et al., 2003, Yamamuro et al., 2016), with the intention of reinforcing valid neurophysiological biomarkers of the disorder.

## 2. Material and Methods

### 2.1. Participants

This section has been partly described elsewhere (Deiber et al., 2020).

“Twenty-five adult patients with ADHD (13 female, mean age: 33.9, SD: 10.9) were recruited in a specialized center for the assessment, treatment and care of patients suffering from ADHD at the Department of Psychiatry of the University Hospitals of Geneva. At the time of recruitment (usually several months after the initial contact with our center), 10 patients were unmedicated, 10 were taking methylphenidate, 2 atomoxetine, 1 antiepileptic, 1 benzodiazepine, 1 neuroleptic. Patients with comorbid psychiatric conditions were excluded. Twenty-two healthy adults (Controls, 14 female, mean age: 31.1, SD: 7.4) were additionally recruited through announcements in the general population. Mean age between groups did not differ significantly (unpaired t-test,  $t = 0.996$ ,  $p = 0.325$ ). Prior to the study, written informed consent was obtained from each participant. The study was approved by the Research Ethic Committee of the Republic and Canton of Geneva [project number 2017–01029]” (Deiber et al., 2020).

“During a first clinical visit, patients and controls underwent three clinical questionnaires: (i) the ADHD Child Evaluation for Adults (ACE +), a semi-structured interview developed to support healthcare practitioners in the assessment and diagnosis of adults with ADHD (freely available at: <https://www.psychology-services.uk.com/adhd.htm>), (ii) the French version of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II, First et al., 1997) and (iii) the French version of the Diagnostic Interview for Genetic Studies (DIGS, mood disorder parts only, Preisig et al., 1999)” (Deiber et al., 2020). Additionally, all participants completed a number of standardized self-questionnaires to assess ADHD symptomatology. The Adult ADHD Self-Report Scale (ASRS v1.1) evaluates in 18 questions current ADHD symptoms in adolescents and adults (Kessler et al., 2005). The Wender-Utah Rating Scale (WURS), short version (25 items), completes the ASRS to evaluate ADHD symptoms during childhood (Ward et al., 1993).

The Barratt Impulsiveness Scale (BIS-11) explores 3 dimensions of impulsiveness: attentional, motor and nonplanning (Patton et al., 1995). The test scores relative to ADHD evaluation are reported in Table 1.

“Exclusion criteria included: history of head injury with loss of consciousness, epilepsy or stroke, non-neurological conditions susceptible to impair brain function (e.g., cancer or cardiovascular disease), and other current psychiatric disorders based on the above mentioned semi-structured interviews: major depressive disorder, bipolar disorder, anxiety disorders, personality disorder, and substance use disorders. All patients treated with psychostimulants stopped their medication 24 h before the experimental visit. Among the 25 patients, 18 were of the combined presentation, 6 of the predominantly inattentive presentation, and 1 of the predominantly hyperactive-impulsive presentation.” (Deiber et al., 2020).

## 2.2. EEG acquisition

This section has been partly described elsewhere (Deiber et al., 2020).

The experiment, designed to evaluate the effect of 30-minute NFB session on EEG at rest with eyes opened (EO) and during performance of a Continuous Performance Task (CPT), is described in Fig. 1. In the present study, we focused on the CPT tasks recorded before (CPT1) and after (CPT2) the 30-minute session of NFB. The CPT consisted in the sequential presentation of 16 letters for 200 ms (A, B, C, D, E, F, H, L, M, N, O, T, V, X, Y, Z). “The subjects were asked to press the left mouse button when any letter except the target letter ‘X’ appeared. There was a total of 240 trials, with 75% Go trials and 25% NoGo trials. The maximal response window was of 600 ms, with a varying intertrial interval (800, 900 or 1000 ms).” (Deiber et al., 2020).

“EEG was recorded continuously using 64 Ag/AgCl electrode cap according to the 10–20 international system, with a sampling rate of 500 Hz. The ground electrode was placed on the scalp at a site equidistant between Fpz and Fz, and the reference electrode at CPz. Bipolar derivations Fp1–M1 and AF7–AF8 were used for detecting vertical and horizontal eye movements, respectively. Electrical signals were amplified using the eego mylab system (ANT Neuro, Netherlands), and all electrode impedances were kept below 5 kΩ. For offline analyses, EEG signals were re-referenced to common-average reference.” (Deiber et al., 2020). Letter stimuli and response presses were automatically documented with markers in the continuous EEG file, which were used off-line to segment the continuous EEG data into epochs time-locked to letter onset.

EEG analysis was conducted with Brain Vision Analyzer 2 software (Brain Products GmbH). The Ocular Correction Independent Component Analysis (ICA) module was used for correction of ver-

tical and horizontal ocular artifacts, including automatic detection from Fp1–M1 and AF7–AF8 derivations respectively, and application of the ICA procedure (Jung et al., 2000). The EEG was segmented per letter type (Go, NoGo) into epochs of 1100 ms, starting 100 ms before letter onset. Epochs with voltage steps above 50 μV or peak-to-peak signal deflection exceeding 180 μV within 200 ms intervals were automatically rejected. The number of analyzed trials considering only correct responses after artifact rejection was as follows: CPT1, Go condition: ADHD: 171 ± 9.2, Controls: 174.6 ± 8.4; NoGo condition: ADHD: 43.1 ± 9.4, Controls: 47.9 ± 7.3. CPT2, Go condition: ADHD: 172.8 ± 10.3, Controls: 177.1 ± 5.9; NoGo condition: ADHD: 42.5 ± 7.3, Controls: 49.8 ± 7.6. There was no significant group difference in the number of trials analyzed, except for the CPT2, NoGo condition, where ADHD had less correct trials than Controls. In order to test whether the different number of trials could be a confounding factor in the CPT2, NoGo condition, the number of trials analyzed between the groups was matched by randomly excluding trials from the analysis in control participants. The manipulation had a negligible effect on the resulting ERPs and statistical conclusions were unaffected.

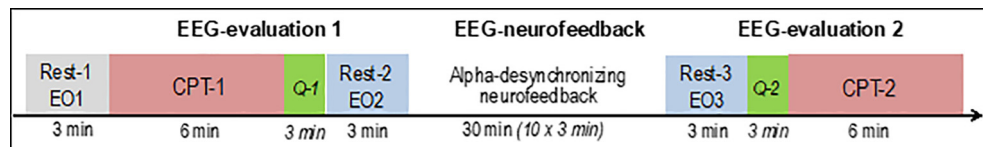
## 2.3. Neurofeedback procedure

The EEG NFB training protocol is fully described elsewhere (Ros et al., 2013), and summarized in the CRED-nf checklist (Ros et al., 2020). “Briefly, an additional electrode, bridging with the Pz sensor of the 64-channel cap, was specifically used for NFB, using a Pro-Comp + amplifier interfacing with EEGer 4.2 NFB software (EEG Spectrum Systems, CA). Separate ground and reference electrodes were placed at on the right and left earlobe, respectively. Pz was selected as the electrode overlying the posterior parietal cortex, whose metabolic changes have been previously linked to EEG alpha rhythm modulation (Laufs et al., 2006). All participants interacted with a ‘SpaceRace’ game where they received continuous visual feedback in the form of a moving spaceship and a dynamic bar graph whose height was inversely proportional to real-time alpha amplitude fluctuations. Participants were told that the spaceship would move forward whenever they were ‘in-the-zone’ of their target brain activity (i.e., alpha lower than threshold), and that it would stop when they were ‘out-of-the-zone’ (i.e., alpha higher than threshold). The aim of the training was to use the feedback they received during the game to learn to keep the spaceship traveling through space. For the purpose of online NFB training, the EEG signal was infinite impulse response band-pass filtered to extract alpha (8–12 Hz) with an epoch size of 0.5 s. Participants were rewarded upon suppression of their absolute alpha amplitude. For each participant, the reward threshold was initially set so that their alpha amplitude would fluctuate below the initial 3-min baseline average approximately 60% of the time (i.e., they

**Table 1**

Mean scores and standard deviations (between brackets) for the ADHD questionnaires in ADHD patients (N = 25) and healthy controls (N = 22), and one way-ANOVA results. ACE+: ADHD Child Evaluation for Adults, ASRS: ADHD Self-Report Scale, WURS: Wender-Utah Rating Scale, BIS: Barratt Impulsiveness Scale. All F values have (1, 45) degrees of freedom. \* corrected for multiple comparisons.

| Tests                     | ADHD          | Controls      | F ANOVA | p-value* |
|---------------------------|---------------|---------------|---------|----------|
| ACE+: Child_attention     | 7.92 (1.65)   | 0.05 (0.21)   | 488.86  | < 0.001  |
| ACE+: Adult_attention     | 8 (1.61)      | 0.09 (0.43)   | 500.48  | < 0.001  |
| ACE+: Child_hyperactivity | 6.16 (2.9)    | 0.23 (0.87)   | 85.33   | < 0.001  |
| ACE+: Adult_hyperactivity | 6.36 (2.77)   | 0.23 (0.68)   | 102.29  | < 0.001  |
| ASRS Attention            | 26.2 (4.96)   | 10.5 (4.09)   | 137.77  | < 0.001  |
| ASRS Hyperactivity        | 21.28 (6.76)  | 9.39 (5.22)   | 44.70   | < 0.001  |
| WURS                      | 51.57 (17.85) | 18.10 (13.15) | 52.30   | < 0.001  |
| BIS: Attentional          | 22.48 (3.86)  | 14.45 (2.56)  | 68.57   | < 0.001  |
| BIS: Motor                | 25.2 (5.79)   | 18.91 (2.35)  | 22.70   | < 0.001  |
| BIS: Planification        | 30.07 (3.86)  | 20.57 (4.02)  | 68.15   | < 0.001  |
| BIS: Total                | 77.75 (11.17) | 53.94 (7.45)  | 71.75   | < 0.001  |



**Fig. 1.** Timeline of the experimental procedure. EO: eyes opened; CPT: continuous performance task; Q: self-rated questionnaires (Spielberger's and Thayer's). From [Deiber et al. \(2020\)](#).

received negative feedback about 40% of the time). To ensure that all participants received comparable frequencies of reward, we readjusted their reward thresholds to meet the desired ratio, when they achieved disproportionately higher (>80%) or lower (<40%) rates of reward during feedback. The entire NFB session was divided into ten 3-min training periods with a short break (10 s) after each period. During the breaks, the scores for the preceding periods were displayed." ([Deiber et al., 2020](#)).

## 2.4. Data analysis

### 2.4.1. Identification of event-related potentials (ERPs)

ERPs were obtained separately in response to Go letters and NoGo letter "X" by stimulus-locked averaging of the signal with a 100 ms pre-stimulus baseline correction and a 0.1 to 30 Hz band-pass filter (-48 dB/octave). The main exogenous (P1 and N1) and endogenous (N2 and P3) ERP components were analyzed for correct responses only at their peak amplitude in time windows and location sites determined from the grand average waveforms ([Luck, 2014, Woltering et al., 2013](#)). The early perceptual P1 and N1 were scored at parieto-occipital site PO8 as the most positive deflection between 60 and 140 ms post-stimulus and the most negative peak deflection between 110 and 210 ms, respectively. The N2 was scored as the largest peak negative deflection with a fronto-central topography (average across values at Fz and FCz) between 160 and 360 ms after stimulus onset. The P3 was identified centrally on Cz within 290 and 610 ms post stimulus.

### 2.4.2. Statistical analysis of ERPs

For each component, a repeated-measures ANOVA was conducted with *Condition* (Go, NoGo) and *Time* (CPT1, CPT2) as within-subject factors, and *Group* (ADHD, Controls) as between-subject factor, to evaluate statistical differences of ERP latency and amplitude. Huynh-Feldt correction for non-sphericity was applied when appropriate. The alpha significance threshold was set at  $p < 0.05$ , following the Benjamini-Hochberg correction for multiple comparisons ([Benjamini and Hochberg, 1995](#)). Partial eta squared values ( $\eta^2$ ) were computed to determine effect size ( $\eta^2 = 0.01$  corresponds to a small effect,  $\eta^2 = 0.10$  to a medium effect, and  $\eta^2 = 0.25$  to a large effect ([Vacha-Haase and Thompson, 2004](#)). Post hoc analysis used paired t-tests with  $p < 0.05$  as significance threshold after Benjamini-Hochberg correction for multiple comparisons.

### 2.4.3. Performance at CPT

"Errors included omissions (missed targets) and commissions (responses to non-targets, or false alarms). D-prime was defined by the ratio between hits (correct responses) and commissions (false alarms), providing a measure of stimulus discriminability. Reaction time (RT) corresponded to the time interval between stimulus onset and mouse button press. RT variability (SD RT, i.e. RT standard deviation) and RT coefficient of variation (CV RT, i.e. RT standard deviation / RT mean) were also examined. A repeated-measures ANOVA with *Time* (CPT1, CPT2) as within-subject, and *Group* (ADHD, Controls) as between-subject factors was used to evaluate statistical differences of performance

between time and group. Huynh-Feldt correction for non-sphericity was applied when appropriate. Post hoc analysis used paired t-tests with  $p < 0.05$  as significance threshold after Bonferroni correction for multiple comparisons." ([Deiber et al., 2020](#)).

### 2.4.4. Correlation analysis between NFB-related modulation of ERP components and CPT performance

To examine the relation between within-subject modulations of endogenous N2 and P3 components and behavioral performance following NFB training, the following Spearman correlations were computed within each group: CPT2 - CPT1 differences of the latency and amplitude of N2 and P3 versus CPT2 - CPT1 differences of RT, SD RT, CV RT, d-prime, omission errors, commission errors. Significance level was set at  $p < 0.05$ , using the Benjamini-Hochberg correction for multiple comparisons ([Benjamini and Hochberg, 1995](#)).

### 2.4.5. Correlation analysis between baseline performance, ERP components and ADHD clinical scores

The Spearman correlation analyses were conducted in the ADHD group between each clinical test and (i) the performance metrics at CPT1, (ii) the N2 and P3 amplitude obtained at CPT1. Significance level was set at  $p < 0.05$ , using the Benjamini-Hochberg correction for multiple comparisons.

All statistical analyses were conducted with SPSS 25.

## 3. Results

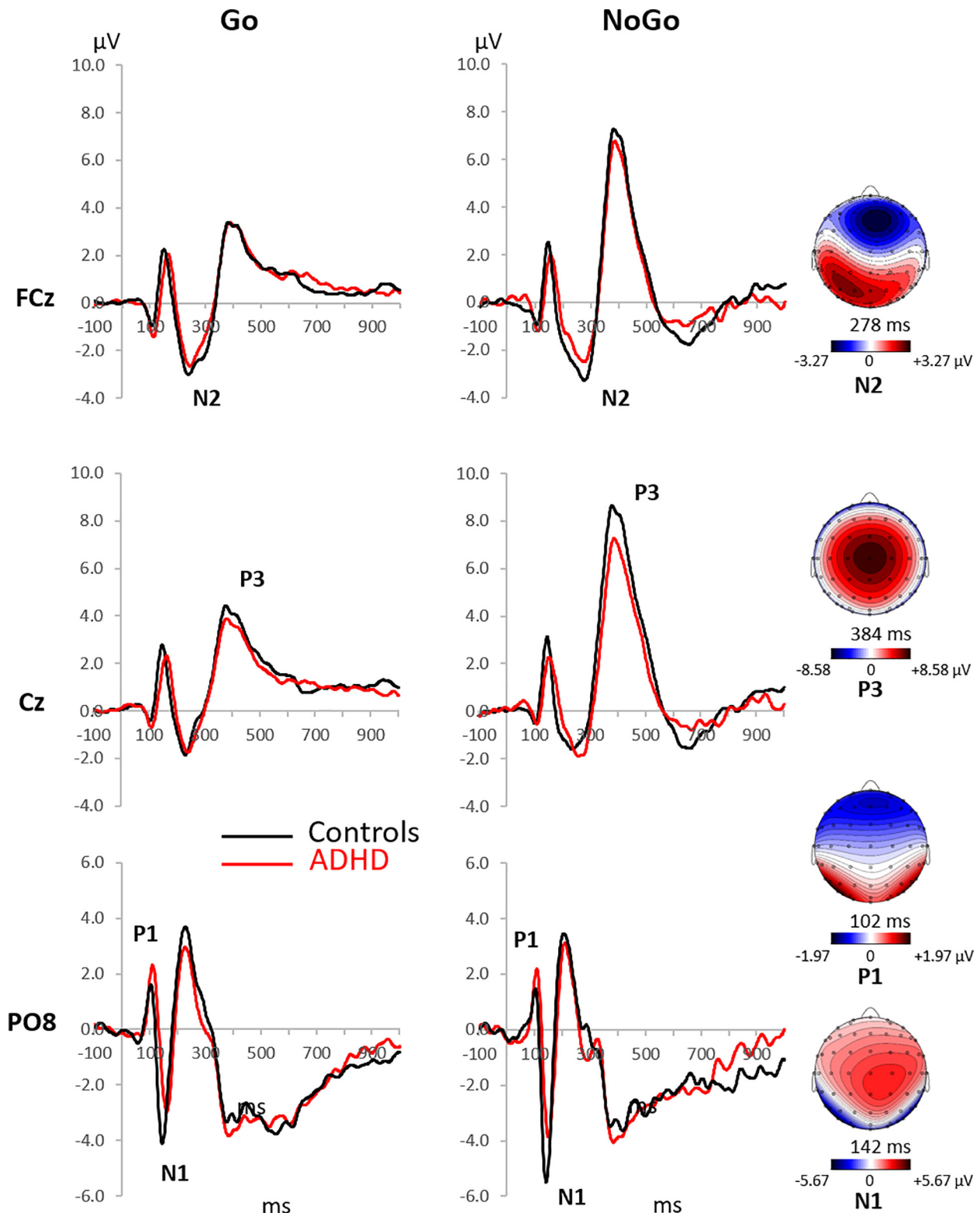
### 3.1. ERPs related to Go and NoGo stimuli in ADHD patients vs. Controls

The latencies and amplitudes of the 4 ERP components, as well as the repeated-measures ANOVA results, are presented in [Supplementary Material](#) (Tables S1 and S2). [Fig. 2](#) illustrates the averaged ERP waveforms in CPT1 obtained in each group for Go and NoGo conditions. Despite attenuated ERP amplitudes in ADHD patients, we did not identify a significant group effect either on latency or on amplitude on the main P1, N1, N2 and P3 components (Benjamini-Hochberg corrected).

A significant condition effect was observed on P1 ( $p < 0.01$ ) and N1 ( $p < 0.001$ ) latencies (Table S1), as well as on N1 ( $p < 0.001$ ) and P3 ( $p < 0.001$ ) amplitudes (Table S2, [Fig. 3](#)). P1 and N1 latencies were shorter in the NoGo compared with the Go condition (post hoc pairwise NoGo vs. Go corrected for multiple comparisons, P1: difference = 4.02 ms,  $p < 0.01$ , N1: difference = 5.67 ms,  $p < 0.001$ ). N1 and P3 amplitudes were larger in the NoGo compared with the Go condition (post hoc pairwise NoGo vs. Go corrected for multiple comparisons, N1: difference = 1.16  $\mu$ V,  $p < 0.001$ , P3: difference = 4.33  $\mu$ V,  $p < 0.001$ ).

### 3.2. Relationship of baseline ERPs and performance with ADHD severity

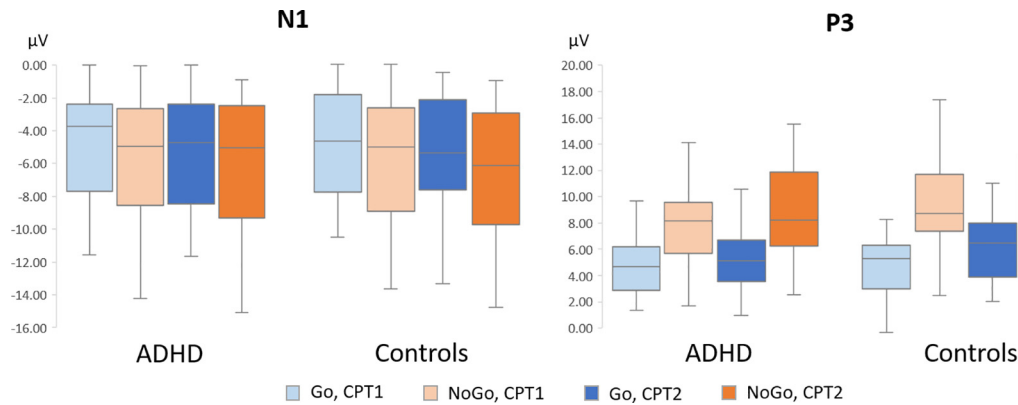
In an exploratory analysis step, the Go-P3 amplitude correlated significantly with several ADHD scores as follows: larger P3 amplitudes predicted lower ADHD childhood scores (WURS,



**Fig. 2.** Grand averaged ERP waveforms in CPT1 over fronto-central, central and parieto-occipital electrodes for the ADHD and healthy controls in the Go and NoGo conditions. Right panel: Topoplots of each component, illustrated for control subjects, CPT1, Go condition (P1, N1) and NoGo condition (N2, P3). ADHD: attention deficit hyperactivity disorder; CPT: continuous performance task; ERP: event-related potential; CPT1: CPT task recorded before the 30-minute session of NFB; NFB: neurofeedback.

Spearman's  $Rho = -0.514$ ;  $p < 0.01$ ), motor impulsivity scores (BIS motor, Spearman's  $Rho = -0.521$ ;  $p < 0.01$ ) and total impulsivity scores (BIS total, Spearman's  $Rho = -0.438$ ;  $p < 0.05$ ). After correction for multiple comparisons, only the correlation with the WURS remained significant at  $p < 0.05$ .

Regarding performance, the RT standard deviation (SD RT) and RT coefficient of variation (CV RT) correlated positively with ADHD childhood scores (WURS; SD RT:  $Rho = 0.481$ ;  $p < 0.05$ ; CV RT:  $Rho = 0.553$ ;  $p < 0.01$ ), but these correlations did not survive correction for multiple comparisons.



**Fig. 3.** Plots of N1 and P3 amplitude across both groups (ADHD, Controls), conditions (Go, NoGo) and times (CPT1, CPT2). Horizontal lines represent median amplitude, with boxes representing interquartile ranges and whiskers extending to minimum and maximum values. ADHD: attention deficit hyperactivity disorder; CPT: continuous performance task; CPT1: CPT task recorded before the 30-minute session of NFB; CPT2: CPT task recorded after the 30-minute session of NFB; NFB: neurofeedback.

### 3.3. ERPs related to Go and NoGo stimuli, pre- and post-NFB

Here we investigated changes in ERP amplitudes *before* (pre) versus *after* (post) a single session of NFB (Fig. 4). Importantly, a significant time effect was present on N1 ( $p < 0.001$ ) and P3 ( $p < 0.001$ ) amplitudes (Table S2, Fig. 3), yielded by larger values post- as compared to pre-NFB (post-hoc pairwise T2 vs. T1 corrected for multiple comparisons, N1: difference =  $0.76 \mu\text{V}$ ,  $p < 0.001$ , P3: difference =  $1.02 \mu\text{V}$ ,  $p < 0.001$ ).

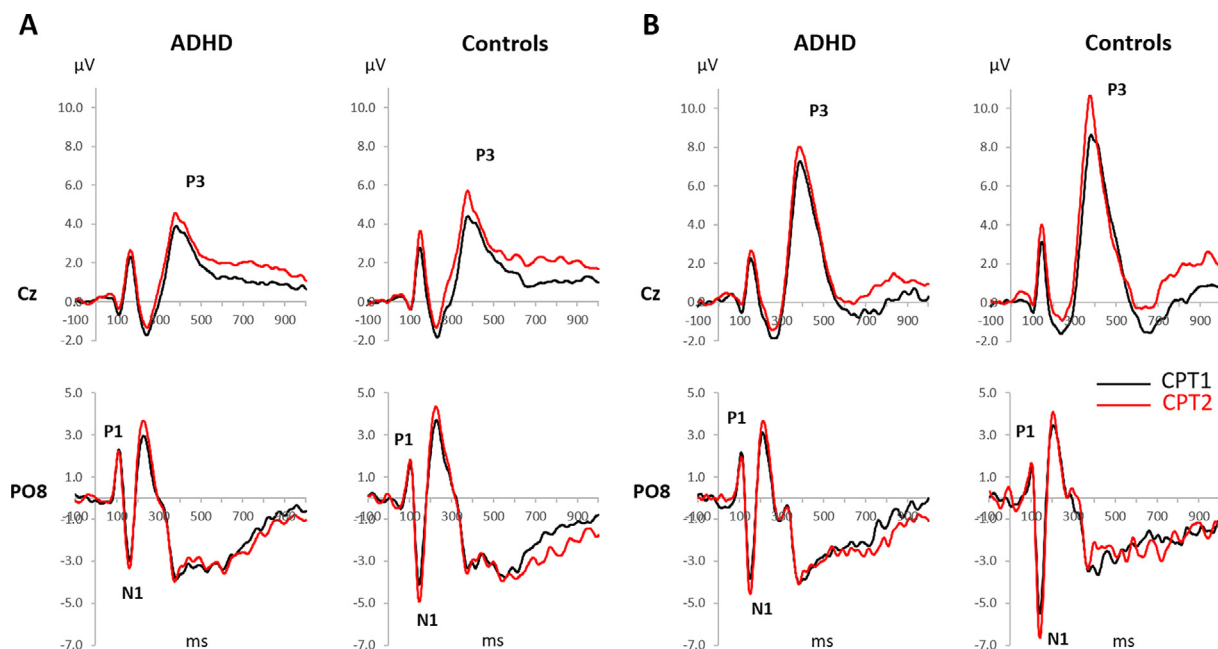
### 3.4. CPT performance pre- and post-NFB

The behavioral results are fully described in the initial publication by (Deiber et al., 2020). A significant group effect was observed on the following CPT parameters: omission ( $F_{(1,45)} = 10.40$ ,  $p < 0.01$ ), commission ( $F_{(1,45)} = 12.83$ ,  $p < 0.001$ ), d-prime ( $F_{(1,45)} = 25.50$ ,  $p < 0.001$ ), SD RT ( $F_{(1,45)} = 16.23$ ,  $p < 0.001$ ), CV RT ( $F_{(1,45)} = 27.09$ ,  $p < 0.001$ ). This shows that, com-

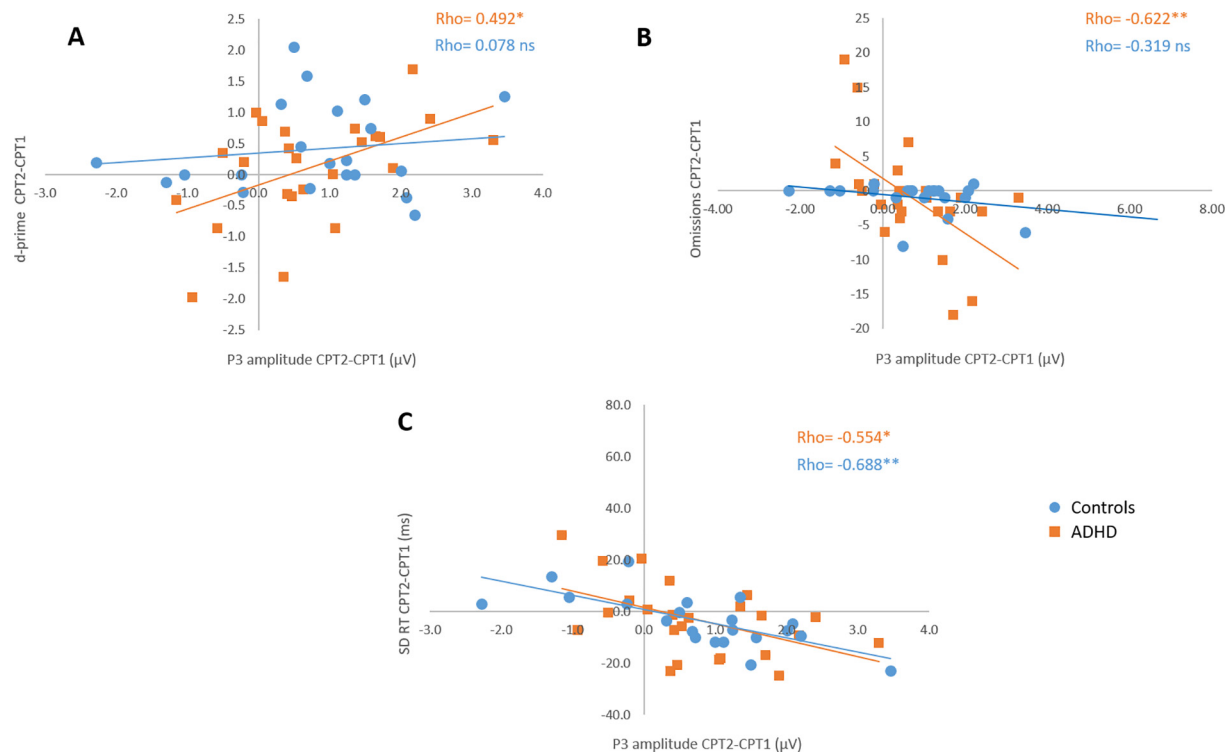
pared to the control group and independently of time (pre- or post-NFB), the ADHD group committed more omission and commission errors, showed inferior stimulus detectability (d-prime), and demonstrated more variability in RT (both SD RT and CV RT). Importantly, there was a significant time (i.e., NFB) effect on performance: stimulus detectability significantly increased and RT variability significantly decreased post-NFB, independently of diagnosis (d-prime,  $F_{(1,45)} = 5.46$ ,  $p < 0.05$ ; CV RT,  $F_{(1,45)} = 6.46$ ,  $p < 0.05$ ).

### 3.5. Relationship between modulation of ERPs and behavioral performance post- vs. pre-NFB (CPT2 – CPT1).

Significant brain-behavior relationships were observed for the amplitude of the P3 component only. As illustrated in Fig. 5, in the ADHD group, the amplitude gain of Go-P3 post- to pre-NFB was associated with an increase in stimulus detectability (d-prime: Spearman's Rho =  $0.492$ ;  $p < 0.05$ ), and a reduction of omis-



**Fig. 4.** Grand averaged ERP waveforms over central and parieto-occipital electrodes for the ADHD and healthy controls, superimposed for CPT1 and CPT2 in (A) Go condition and (B) NoGo condition. ADHD: attention deficit hyperactivity disorder; CPT: continuous performance task; ERP: event-related potential; CPT1: CPT task recorded before the 30-minute session of NFB; CPT2: CPT task recorded after the 30-minute session of NFB; NFB: neurofeedback.



**Fig. 5.** Significant associations in the ADHD group between Go-P3 amplitude and (A) d-prime, (B) omissions, (C) RT standard deviation (SD RT), superimposed with the Control group. For d-prime and omissions, the Spearman's Rho values are significant only in the ADHD group (\*  $p < 0.05$ , \*\*  $p < 0.01$ , corrected). ADHD: attention deficit hyperactivity disorder; RT: reaction time.

sion errors (Spearman's  $Rho = -0.622$ ;  $p < 0.01$ ) and RT variability (SD RT: Spearman's  $Rho = -0.554$ ;  $p < 0.05$ ). In the Control group, the amplitude gain of Go-P3 post- to pre-NFB was correlated with a reduction of RT (Spearman's  $Rho = -0.621$ ;  $p < 0.01$ ) and RT variability (SD RT: Spearman's  $Rho = -0.688$ ;  $p < 0.01$  and CV RT: Spearman's  $Rho = -0.543$ ;  $p < 0.05$ ). In this group, the amplitude gain of NoGo-P3 post- to pre-NFB was also correlated with a reduction of RT (Spearman's  $Rho = -0.580$ ;  $p < 0.05$ ) and RT variability (SD RT: Spearman's  $Rho = -0.431$ ;  $p < 0.05$ ), although the latter did not survive correction for multiple comparisons.

#### 4. Discussion

We investigated the behavioral and electrophysiological correlates of attentional and inhibitory processes during a visual continuous performance task (CPT) in adult patients with attention-deficit hyperactivity disorder (ADHD) compared to age-matched neurotypical controls, in a pre-to-post neurofeedback (NFB) intervention design. Baseline behavioral performance was significantly poorer (i.e. significantly more omission and commission errors) in ADHD as compared to controls, although we did not observe a significant delay or an amplitude reduction of the Go and/or NoGo ERP components. Interestingly however, following the 30-minute NFB training session, there was a significant increase in stimulus detectability as well as a decrease in RT variability, in both ADHD and control groups. In tandem, pre-to-post NFB comparisons of ERPs revealed an enhancement effect of NFB on the main P3 component amplitude, which correlated with measures of improved CPT performance in ADHD patients (i.e., increased d-prime and reduced omission errors and reaction time variability). This suggests that NFB had a normalizing effect on neurocognitive processes underlying the Go/NoGo task, specifically in patients with ADHD. In parallel, and consistent with previous work (Liu et al., 2020), the baseline Go-P3 amplitude correlated with the self-evaluated ADHD child-

hood score, suggesting that ERPs may be valuable electrophysiological markers of adult ADHD symptoms.

##### 4.1. Neurofeedback effect: CPT1 vs. CPT2 (pre- vs. post-NFB)

Among the main ERP components, the N1 and P3 revealed to be sensitive to NFB, as indicated by significantly larger amplitudes after the 30-minute NFB training session. Both components are known to be enhanced by selective attention processes (Hillyard and Anllo-Vento, 1998, Polich, 2007). Specifically, combined with the observed inverse correlation of the P3 amplitude with omission errors, P3 enhancement post-NFB suggests an increased recruitment of attentional resources. Additionally, d-prime positively correlated with increased P3 amplitude post-NFB, and the latter may therefore be also indicative of improved stimulus discrimination, working memory as well as enhanced inhibitory control (Polich, 2007), consistent with several studies using different EEG-NFB paradigms (Arns et al., 2012, Bluschke et al., 2016, Graczyk et al., 2014, Kropotov et al., 2005, Zioga et al., 2019).

In parallel, NFB positively affected performance independently of diagnosis, with an improvement of stimulus detectability and a reduction of RT variability. The voluntary control of ongoing activity in a primary visual region by fMRI-NFB training has been shown to improve visual sensitivity (Scharnowski et al., 2012, Shibata et al., 2011). Our results suggest that a similar effect can be obtained using EEG-NFB training of posterior alpha rhythm, closely linked to visual activation. We also observed reduced RT variability after NFB, a result previously described after multi-session SCP-NFB training in adult ADHD patients (Mayer et al., 2016).

##### 4.2. Correlations between ERP and performance changes induced by NFB

Most interestingly, the increased recruitment of neurophysiological resources (P3 enhancement) coincided with behavioral

improvements following NFB in both groups. In the control group, the correlations concerned reaction time and its variability indices, while in the ADHD group they were additionally related to stimulus perceptual processes (d-prime) and response accuracy (omissions). These observations suggest that a single session of alpha down-regulation can induce some improvement in task performance objectively assessed by the enhancement of a neural activity marker, i.e. the P3 component. Studies using down-regulation of alpha power as NFB protocol remain scarce, especially in single sessions. Using a similar methodological design in healthy adults, Ros and colleagues (Ros et al., 2013) observed an increase of salience network connectivity correlating with a reduction of mind wandering and reaction times. Our recent results obtained with the same paradigm suggested a beneficial post-effect of the 30-minute NFB session on alpha power, correlating with a reduction in impulsivity errors (Deiber et al., 2020). The present results provide additional support to the positive effect of a single-session alpha down-regulation NFB on task performance and further suggest a link with neurocognitive processes of stimulus discrimination and inhibition control in ADHD patients, as indexed by the significant association between P3 amplitude and d-prime. Previous studies have generally examined the effects of multi-session NFB on behavioral performance, and few of them have explored the ERP correlates of these effects. Using a Go NoGo task in a pre-post theta/beta NFB design of 8 weeks (16 sessions), Bluschke et al. (2016) reported no effect of NFB on P1, N1, P2 and N2 components in children ADHD. Only P3 amplitude in the NoGo trials was larger post-NFB, in parallel with an improvement of impulsive behavioral scores, suggesting that the NFB protocol primarily affects response inhibition. Similar results extending to Go P3 were obtained in ADHD children after 15–20 sessions of low beta and SMR training, and distribution of pre-to-post ERP differences suggested the activation of frontal areas (Kropotov et al., 2005). An increase of both N2 and P3 amplitudes after repetitive SMR training was also observed together with an improvement of attention, hyperactivity/impulsivity in ADHD children and adults (Arns et al., 2012), a clinical effectiveness recently replicated using individually-based qEEG training (Krepel et al., 2020). In cued-CPT tasks, multi-session training of the SCP type was consistently reported to induce an increase of the cue-related CNV amplitude, indicative of improved availability of attention resources for preparing motor response (Gevensleben et al., 2014, Heinrich et al., 2004, Mayer et al., 2016). Additionally, performance improvements were observed, such as reduction of omission errors at the CPT (Heinrich et al., 2004), RT and RT variability reduction (Gevensleben et al., 2014, Mayer et al., 2016), as well as significant attenuation of ADHD symptoms (Heinrich et al., 2004, Mayer et al., 2016). We hereby show that in adult ADHD, a single session of alpha-down-NFB positively impacted the neurocognitive processes involved in motor response (P3 correlation with RT variability), but also those related to perceptual and attentional discrimination (P3 correlation with d-prime and correct hits), which were all impaired compared to controls. This suggests that in these patients, NFB played a normalization role of the main cognitive-motor functions involved in the Go/NoGo tasks that are affected by the disorder. In the control group, NFB effect was limited to the processes involved in motor response, mainly shortening and regulating reaction time (P3 correlation with RT and RT variability).

The possibility that a learning effect due to repetition is present in the post-NFB CPT session must be acknowledged, as well as a fatigue effect due to the elapsed time-on-task. However, according to the repetition suppression effect (Grill-Spector et al., 2006), both learning and fatigue effects would result in neural response reduction rather than enhancement. Thus, the observation of increased ERP amplitudes following NFB is more compatible with a neuro-

modulatory effect on cortical activity, according to brain plasticity mechanisms (Ros et al., 2014a).

#### 4.3. Correlations between ERPs and ADHD severity

Our findings revealed a significant negative association between the Go-P3 amplitude and ADHD symptom severity under the form of various self-rated scores: evaluation of ADHD in childhood (WURS) and impulsiveness (BIS motor and total). While only the correlation with the WURS was deemed significant after statistical correction, the finding of reduced Go-P3 amplitude with increased severity of ADHD symptoms is of particular interest. While motor response variability has been reproducibly linked to ADHD severity (Adams et al., 2011, Kofler et al., 2013, Levy et al., 2018, Robinson et al., 2019), the relationship between electrophysiological measures and ADHD severity has rarely been examined. The few existing studies consistently report P3 amplitude as the most sensitive electrophysiological marker of ADHD deficit level (Liu et al., 2020, Marquardt et al., 2018, Wiersma and Roeyers, 2009), at least in idiopathic ADHD (Moavero et al., 2020). Despite trend significance, an attenuation of the P3 amplitude in motor impulsivity should be highlighted, given its previously established role in inhibitory processes (Hong et al., 2017, Nguyen et al., 2016, Shen et al., 2014). Our finding of a robust negative association between P3 amplitude and the WURS is compatible with the results of Liu and colleagues in young ADHD patients, who reported a negative correlation between this component and ADHD Problems Scale scores completed by the parents (Liu et al., 2020). Hence, combining electrophysiological markers such as ERPs with self-reported symptoms by adults with ADHD, or those of childhood ADHD by parents, could ultimately improve the clinical diagnosis and/or prognosis of this psychiatric disorder.

#### 4.4. Condition effect: Go vs. NoGo trials

We observed a significant effect of condition on N1 latency (shorter in NoGo trials) as well as on N1 and P3 amplitudes (larger in NoGo trials), in accordance with previous observations (Bluschke et al., 2018, Gajewski and Falkenstein, 2013, Nguyen et al., 2016). Response suppression to infrequent target stimuli is assumed to involve bottom-up (stimulus-driven) factors and top-down attentional modulation, both mechanisms influencing the latency (shortening) and amplitude (enhancement) of the N1 component (Chikazoe, 2010, Corbetta and Shulman, 2002, Hillyard and Anllo-Vento, 1998, Mangun and Hillyard, 1991). Attention-dependent stimulus discrimination and inhibitory processing, at their maximum expression in the NoGo trials, are the main determinants of P3 amplitude (Albert et al., 2013, Hong et al., 2017, Polich, 2007). The observation that the N2 component was not significantly affected by the condition is compatible with accounts that this component is potentially more related to conflict monitoring rather than inhibition (Donkers and van Boxtel, 2004, Hong et al., 2017, Nguyen et al., 2016, Nieuwenhuis et al., 2003).

#### 4.5. Limitations and absence of ERP group effect: ADHD vs. Control subjects

Despite significant differences in behavioral performance, our cohort of adult ADHD patients displayed ERP components of similar latency and amplitude as healthy controls. An abundant literature has addressed the electrophysiological correlates of cognitive control in ADHD children and adolescents, but fewer reports exist in adults. The observed absence of ADHD diagnosis effect on early perceptual P1 and N1 components is generally compatible with previous paradigms using relatively low perceptual processing

demands (Bluschke et al., 2018, Woltering et al., 2013), indicating the integrity of elementary visual processing in these patients. While the NoGo N2 component does not display consistent group differences, the NoGo P3 is generally reported to be of reduced amplitude in adult ADHD compared to healthy controls (Dhar et al., 2010, Fallgatter et al., 2005, Grane et al., 2016, Marquardt et al., 2018, McLoughlin et al., 2010, Rodriguez and Baylis, 2007, Wiersema et al., 2006, Woltering et al., 2013). In a meta-analysis of 6 papers in adults, Szuromi et al. (2011) highlighted a decrease of P3 amplitude in response to target detection, although the effect size was in the medium range (Cohen's  $d = -0.55$ ). A recent review analyzing the literature on ERP component differences between ADHD and non-ADHD individuals across the lifespan has shown that the P3 component was the most sensitive ADHD biomarker, while group differences were not reliable for the N2 component (Kaiser et al., 2020). However, substantial heterogeneity characterized the results, with moderate average effect sizes ( $-0.32 < d < -0.57$ ). In light of this review examining the various moderators influencing the ERPs, several factors may play a role in the absence of a significant group effect in our study. The relatively small sample size is first, as well as methodological choices such as the ratio of response inhibition trials (25% NoGo trials) and the relatively fast stimulus presentation rate, which are not favorable to inhibition in contrast to most studies (Szuromi et al., 2011, Wiersema et al., 2006). While we selected patients without comorbidities and off medication at the time of the EEG, the age of our participants in the mid-adulthood may also be a reduction factor of P3 difference across groups, as recently demonstrated (Kaiser et al., 2020, Kakuszi et al., 2020).

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2021.05.017>.

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