A comparative study on the neurophysiological mechanisms underlying effects of methylphenidate and neurofeedback on inhibitory control in attention deficit hyperactivity disorder

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**A B S T R A C T**

In Attention Deficit Hyperactivity Disorder (AD(H)D), treatments using methylphenidate (MPH) and behavioral interventions like neurofeedback (NF) reflect major therapeutic options. These treatments also ameliorate executive dysfunctions in AD(H)D. However, the mechanisms underlying effects of MPH and NF on executive functions in AD(H)D (e.g. the ability to inhibit prepotent responses) are far from understood. It is particularly unclear whether these interventions affect similar or dissociable neural mechanisms and associated functional neuroanatomical structures. This, however, is important when aiming to further improve these treatments. We compared the neurophysiological mechanisms of MPH and theta/beta NF treatments on inhibitory control on the basis of EEG recordings and source localization analyses. The data show that MPH and theta/beta NF both increase the ability to inhibit pre-potent responses to a similar extent. However, the data suggest that MPH and NF target different neurophysiological mechanisms, especially when it comes to functional neuroanatomical structures associated with these effects. Both treatments seem to affect neurophysiological correlates of a ‘braking function’ in medial frontal areas. However, in case of the NF intervention, inferior parietal areas are also involved. This likely reflects the updating and stabilisation of efficient internal representations in order to initiate appropriate actions. No effects were seen in correlates of perceptual and attentional selection processes. Notably, reliable effects were only obtained after accounting for intra-individual variability in the neurophysiological data, which may also explain the diversity of findings in studies on treatment effects in AD(H)D, especially concerning neurofeedback.

1. Introduction

Attention Deficit (Hyperactivity) Disorder (AD(H)D) is one of the most prevalent neuropsychiatric conditions in childhood and is characterised by inattention, hyperactivity and impulsivity (Thomas et al., 2015). Stimulants and methylphenidate (MPH) in particular are recommended as first-line pharmacological treatment (American Academy of Pediatrics, 2011; Childress and Sallee, 2014; Mattingly et al., 2017). A large body of evidence shows very good effects of MPH in terms of AD(H)D symptom reduction (Abikoff et al., 2004; Barkley et al., 1991; Kratochvil et al., 2002; MTA, 2004; Van der Oord et al., 2008), academic achievements (Hechtman et al., 2004), quality of life (Döpfner et al., 2011) and neurocognitive functioning including inhibition and the control of impulsive responses (Boonstra et al., 2005; Broyd et al., 2005; Konrad et al., 2007; Pietrzak et al., 2006; Sevecke et al., 2006). Particularly the amelioration of inhibitory control deficits has been associated the dopaminergic actions of MPH (Cubillo et al., 2014; Nandam et al., 2011; Pauls et al., 2012; Tannock et al., 1989).

Yet, it has also been shown that > 40–60% of patients discontinue this treatment for several reasons (Duric et al., 2017; Garbe et al., 2012; Pappadopulos et al., 2009). Even though similar discontinuation rates have been observed in one non-pharmacological treatment study (Duric et al., 2017), these treatment approaches are steadily gaining popularity (Dosreis et al., 2017; Ng et al., 2017; Schatz et al., 2015). Amongst non-pharmacological approaches, neurofeedback (NF) has gained increasing acceptance and interest. In the case of frequency-based neurofeedback, cortical activity is recorded from the patient's head using simple EEG electrodes. The recorded activity (i.e. the power of neural oscillations like theta and beta in the case of frequency-band NF) is directly fed back to the patients via a simple computer.
game or animation. Even though various limitations and possible confounders have been discussed (Cortese et al., 2016; Micoulaud-Franchi et al., 2015; Sonuga-Barke et al., 2013), many studies including randomized controlled trials have shown that neurofeedback effectively ameliorates AD(H)D symptoms and associated problems (Arns et al., 2009; Arns and Strehl, 2013; Bakshayesh et al., 2011; Baumeister et al., 2016; Bluschke et al., 2016a; Gevensleben et al., 2010; Holtmann et al., 2014; Lofthouse et al., 2012; Micoulaud-Franchi et al., 2014, 2015). Neurofeedback approaches have also been shown to increase the ability to inhibit prepotent responses (Baumeister et al., 2016; Bluschke et al., 2016a). These positive effects of NF can likely be attributed to the high relevance of neuronal oscillations for complex cognitive processes (Cavanagh and Frank, 2014; Cohen, 2014; Helfrich and Knight, 2016; Hwang et al., 2016; Singer, 2017). In this regard, especially medial frontal theta oscillations have been demonstrated to reflect an important mechanism mediating cognitive control (Cavanagh and Frank, 2014). On the symptom level, MPH and NF have directly been compared in its efficacy, but results are contradictory and depend on sample size, inclusion criteria and study design (Fuchs et al., 2003; Meisel et al., 2014; Moreno-García et al., 2015; Rossiter and Vaque, 2016).

Yet, the mechanisms underlying positive effects of MPH and NF on executive functions and inhibitory control in AD(H)D are far from being understood and it is particularly unclear whether MPH and NF interventions affect similar or dissociable neural processes and functional neuroanatomical structures. This, however, is important to further improve these treatment approaches. The goal of this study is to compare the neurophysiological mechanisms underlying effects of MPH and theta/beta NF treatment on inhibitory control. We focus on inhibitory control because this ability is of high clinical relevance in AD(H)D (Bluschke et al., 2016a; Paul-Jordanov et al., 2010; Pliszka et al., 2007; Seifert et al., 2003). We compare the cognitive-neurophysiological changes on the basis of EEG recordings and source localization analyses, because event-related potential (ERP) correlates of distinct inhibitory control sub-processes have been well-described (for review: Huster et al., 2015). It has repeatedly been shown that a frontal-midline Nogo-N2 ERP-component reflects pre-motor processes like conflict monitoring or updating of the response program, while a Nogo-P3 ERP-component reflects evaluative processing of the successful outcome of the inhibition (Beste et al., 2011, 2010, 2009; Huster et al., 2013), or the motor response inhibition itself (Wessel and Aron, 2014).

Considering MPH treatment effects, several studies have reported significant Nogo-P3 amplitude increases in response inhibition tasks (Paul-Jordanov et al., 2010; Pliszka et al., 2007; Seifert et al., 2003). This suggests that neurophysiological processes related to the process of motor response inhibition itself are normalized during treatment. The few studies that have examined neurophysiological changes associated with neurofeedback focussed on mechanisms that were actually trained during the respective neurofeedback protocols (Gevensleben et al., 2009; Janssen et al., 2016a, 2016b; Wangler et al., 2011). For a broader assessment of NF effects it is important to consider neurophysiological processes that are not equal to the trained neurofeedback parameters but represent distinct and established correlates of the behaviour or function to be improved during treatment. To the best of our knowledge, only one study has so far demonstrated a reliable effect of the applied neurofeedback protocol at the behavioral level and a corresponding improvement on specific neurophysiological mechanisms (i.e. modulations of the Nogo-P3) that does not reflect a directly trained neurophysiological parameter (Bluschke et al., 2016a). Studies comparing NF and MPH effects using neurophysiological methods at the important inhibitory control dimension in AD(H)D either use no standardized neurofeedback training protocol with a consistent target frequency and electrode for all treated patients (Ogrim and Hestad, 2013), or only provide limited data on changes at the behavioral level consistent with changes at the neurophysiological level (Geladé et al., 2018; Janssen et al., 2016a).

Regarding the neurophysiological mechanisms being modulated by MPH and NF interventions, it is further important to consider that the likelihood to detect reliable treatment effects at the neurophysiological level is significantly compromised when intra-individual variability in neurophysiological processes is high (Mückschel et al., 2017; Ouyang et al., 2011, 2015a). The ERP method can only yield accurate insights into the neurophysiological processes of cognitive functions when there is little intra-individual variability (Mückschel et al., 2017; Ouyang et al., 2011, 2015a). This represents a significant problem in the context of AD(H)D, as this patient group is characterised by high intra-individual variability (Mückschel et al., 2017; Ouyang et al., 2011, 2015a). This is especially the case for ERP components with longer latencies (like the P3 ERP component) (Ouyang et al., 2015b, 2017; Verleger et al., 2014), which are important in the context of response inhibition. Therefore, we hypothesize that no reliable treatment effects will be observed using standard ERPs and expect that reliable treatment effects are only obtained after accounting for intra-individual variability in the EEG data. Since intra-individual variability in EEG data can also bias source localization results (Bodmer et al., 2018), it is even more important to account for intra-individual variability when aiming to compare the effects of MPH and NF on a system-neurophysiological level. To do so, we apply residue iteration decomposition (RIDE) (Ouyang et al., 2011, 2015a). RIDE decomposes neurophysiological data based on timing and timing variability and calculates three functionally distinct component clusters (Ouyang et al., 2011, 2015a). The S-cluster refers to stimulus-related processes (like perception and attention), the R-cluster refers to response-related processes (like motor preparation/execution) and the C-cluster refers to intermediate processes between S and R (like response selection) (Ouyang et al., 2017, 2011). It has been shown that the C-cluster is modulated during the inhibition of responses and is assumed to reflect processes similar to the (Nogo)-P3; i.e. a ‘braking function’, or a mechanism that is important for the inhibition of automated response tendencies (Bluschke et al., 2016a; Bodmer et al., 2018; Chmielewski et al., 2018; Friedrich et al., 2018; Mückschel et al., 2017; Ouyang et al., 2015b). Neuroanatomically, this braking function has specifically been attributed to the right inferior frontal cortex and its subcortical projection to the subthalamic nucleus (Aron et al., 2015, 2014; Gillies and Willshaw, 1998). This behavioral brake has been suggested to be switched on when it is necessary to stop or pause an action and can be triggered by external signals and internal goals (Aron et al., 2014; Bianco et al., 2017). The braking function has been suggested to be weakened in patients with ADHD, leading to problems in situations in which actions need to be stopped based on exogenous or endogenous stimuli (Aron et al., 2014). This represents a clear connection to the increased impulsivity and response inhibition deficits frequently observed in these patients on the behavioral level. Conversely, the C-cluster has most consistently been shown to be modulated during response inhibition processes in the P3 time window, even though some effects are also reported during stimulus-related processes reflected by the S-cluster (Chmielewski et al., 2018; Mückschel et al., 2017). Therefore, and because the C-cluster has been shown to best reflect differences in response inhibition mechanisms between AD(H)D subtypes (Bluschke et al., 2017), we hypothesize that effects of MPH or NF treatment on response inhibition should be reflected by C-cluster modulations in the P3 time window. No or much weaker effects are expected in the S-cluster. We hypothesize that activation in the C-cluster will be more pronounced and/or occur earlier after MPH/NF treatment. At the behavioral level we expect that the rate of false alarms will decrease due to MPH/NF treatment. From a functional neuroanatomical perspective, the medial frontal cortex and inferior parietal cortices have been shown to reflect modulations in the C-
cluster (Bodmer et al., 2018; Friedrich et al., 2018, 2017) and to represent neuroanatomical correlates of the braking function underlying response inhibition (Aron et al., 2015, 2014). Functions of the medial frontal cortex are strongly modulated by the meso-corticolimbic system, which is dominated by D2 receptors (Nieoullon, 2002). MPH prolongs the time during which dopamine is available in the synaptic cleft and entails a stronger dopamine D2 receptor activation (Volkow et al., 2005; Volz et al., 2008). In contrast to the medial frontal cortex, parietal areas show a much less dense dopaminergic innervation (Nieoullon, 2002). We therefore hypothesize that (inferior) parietal areas are less important for the effects of MPH treatment on response inhibition.

2. Materials and methods

2.1. A-priori sample size estimation

In a previous study on the effects of NF on response inhibition in AD (H)D it has been shown that the effect size of the treatment was partial eta squared ($\eta_p^2 = 0.1$ (Bluschke et al., 2016a)). We therefore used this estimate to calculate the required sample size in the current study to detect an effect of treatment with a power of at least 95%. The power calculation using G*Power revealed a total sample size of $N = 39$; i.e. $N = 13$ patients per group (MPH, NF and waiting list control). However, as outlined below, a total sample of $N = 61$ was enrolled in the study; i.e. $N \approx 20$ per group.

2.2. Sample description

Only patients in whom AD(H)D diagnoses had been determined according to standard clinical guidelines by a team of experienced child and adolescent psychiatrists and psychologists (incl. family and school interviews and questionnaires, IQ and attention testing, exclusion of possible somatic differential diagnoses via blood analyses, EEG, audiometry and vision testing) were included in the study. All participants fulfilled criteria for AD(H)D according to ICD-10 (F90.0, F90.1 or F98.8). Patients with additional severe or acute psychiatric comorbidities in their clinical history (e.g. autism, tics, depressive episode etc.) were excluded from the study. $N = 20$ patients (18 male, 9.7 ± 1.9 years, IQ: 98.7 ± 12.2) were included in the MPH group. T1 testing took place before the first medication intake. T2 testing took place 8 weeks after the first intake. $N = 23$ patients (all male, 10.2 ± 1.2 years, IQ: 101.3 ± 12.2) participated in an 8-week theta/beta neurofeedback training. $N = 18$ patients were included in a waiting list control (WLC) group (15 male, 11.1 ± 2.0 years, IQ: 98.8 ± 11.6). In this group, any ongoing treatment for AD(H)D remained consistent and no new interventions were initiated during Some patients from the NF and WLC group (NF: $n = 11$; WLC: $n = 8$) were taking AD(H)D medication consistently throughout the course of the study, with no changes occurring between time point T1 and T2. This could therefore not affect performance differences between T1 and T2. The administered medications were heterogeneous and included immediate or extended release methylphenidate (NF: $n = 9$; WLC: $n = 6$), atomoxetine (NF: $n = 1$; WLC: $n = 1$) and lisdexamfetamine (NF: $n = 1$; WLC: $n = 1$). Please refer to the discussion section for a further elaboration on this aspect.

The three groups differed significantly in regards to age ($F(2,58) = 4.4$, $p = .02$) with participants in the MPH group being significantly younger than the waiting list control group ($p = .016$). Based on this age difference, the factor Age was included as a covariate in all further analyses. There were no significant group differences in IQ ($F(2,58) = 0.28$, $p = .75$). In the AD(H)D Symptom Checklist (Döpfner et al., 2008) parents rated their children on a scale of 0 (no problems) to 3 (severe problems) in regards to AD(H)D core symptoms. No group differences were found concerning inattention ($F(2,56) = 0.07$, $p = .93$) (MPH group: 2.0 ± 0.74; neurofeedback group: 1.9 ± 0.65, waiting list controls: 2.0 ± 0.86 (average raw scores)). There were no differences regarding hyperactivity scores ($F(2,57) = 0.04$; $p = .96$) (MPH group: 1.15 ± 0.81, neurofeedback group: 1.1 ± 0.77, waiting list controls: 1.1 ± 0.89 (average raw scores)) and impulsivity ($F(2,56) = 0.24$; $p = .79$) (MPH group: 1.7 ± 0.89, neurofeedback group: 1.7 ± 0.69, waiting list controls: 1.5 ± 1.0 (average raw scores)). All participants were right-handed and there was no difference in the degree of handedness ($p > .6$). All subjects and their parents or legal guardians provided informed written consent according to the Declaration of Helsinki and the study was approved by the local ethics committee of the Medical Faculty of the TU Dresden.

2.3. Medication with methylphenidate

All patients included in the MPH group started the intake of methylphenidate immediately after T1 testing. Initially, all patients received a low dose of immediate release methylphenidate and switched to extended-release MPH during the course of treatment. According to clinical guidelines, this dose was increased until i) a significant and satisfactory symptom reduction was reported by parents or ii) the target dose of 1 mg/kg body weight had been reached. Final doses ranged from 10 mg to 40 mg extended-release MPH per day.

2.4. Neurofeedback protocol

Theta/beta-ratio neurofeedback training took place in two weekly sessions (1 h each) over a period of 8 weeks. During the course of the training, patients were trained to downregulate theta power (4–8 Hz) and to upregulate beta power (13–20 Hz) which were recorded at electrode Cz. Electrodes above and below the left eye were used to record eye movements and to correct for motion artifacts since these could alter the results if not accounted for. The reference electrode was placed on the left mastoid and an electrode on the forehead was used as the ground electrode. Theta and beta frequency ranges were presented to participants via a custom-made software (“Self-regulation and Attention Management” (“SAM”), University of Erlangen). Time intervals containing artifacts occurring as a result of excessive movement were discarded online and were not included in the feedback procedure. In case of excessive movements, children were shown a sad smiley face, reminding them to reduce movements. A two-minute interval was used for to record theta and beta power at rest at the beginning of each session (baseline). During the training, children were able to move a cartoon character or car on the screen by regulating the frequencies in the required direction (immediate feedback). Within the animation, frequencies were also shown to the children via moving bars on the screen. During each session 3–6 neurofeedback blocks were conducted, each lasting from 5 to 10 min. From session 4–5 onwards, transfer blocks were introduced in which children were given a task (e.g. attention games, reading, school work) and were required to perform it without directly seeing feedback on the screen. In these cases, they received delayed feedback about their ability to regulate the recorded oscillations in the desired direction. After every training block (with immediate or delayed feedback), performance was reviewed with the participant. In adherence to standard protocols (Gevensleben et al., 2010, 2009), neurofeedback training was supplemented by elements of behavioral therapy, including psychoeducation, the development of attentional strategies, homework and a token system.

2.5. Task

A standard Go/Nogo task was used to examine response inhibition performance (Beste et al., 2011; Chmielewski et al., 2015) at time points T1 and T2. Within the Go/Nogo task, either the word ‘DRÜCK’ (German for ‘PRESS’, Go stimulus) or ‘STOP’ (Nogo stimulus) was presented for 300 ms in white font on a black background. A motor response with the right index finger was required as fast as possible (i.e.
within 500 ms) when seeing the ‘DRÜCK’ stimulus. Participants had to refrain from responding when seeing the ‘STOP’ stimulus. The intertrial interval (ITI) was jittered between 1600 ms and 1800 ms. The experiment consisted of 248 Go trials and 112 Nogo trials presented in a pseudo-randomized order. The task lasted approximately 20 min.

2.6. EEG recording and analysis

The EEG was recorded with an equidistant electrode setup from 60 Ag/AgCl electrodes with a sampling rate of 500 Hz (reference at Fpz, ground electrode at \( \theta = 58, \phi = 78 \)). Electrode impedances were kept below 5 k\( \Omega \). Data processing took place analogous to the procedure described in (Bluschke et al., 2016a): During off-line data processing, the recorded data was down-sampled to 256 Hz and a band-pass filter (0.5–20 Hz, slope: 48 db/oct) was applied. Technical artifacts were removed during the manual inspection of the raw data. They were identified by their shape in the raw EEG data (e.g. gross and sharp increases in amplitudes over very short time periods; i.e. “offsets” in the time series data). An independent component analysis was subsequently used to detect and remove periodically occurring artifacts (pulse artifacts, horizontal and vertical eye movements). Data was subsequently used to detect and remove periodically occurring artifacts. Data was segmented (locked) to the onset the Go and Nogo stimuli (\( \pm 200 \) ms–1500 ms). Only trials with correct responses on Go and without responses on Nogo trials were analysed further. Remaining artifacts were removed using an automatic artefact rejection procedure with an amplitude criterion (maximal amplitude: \( +200 \) \( \mu \)V, minimal amplitude: \( -200 \) \( \mu \)V) and using a maximal value difference of \( 200 \) \( \mu \)V in a 200 ms interval as well as an activity below 0.5 \( \mu \)V in a 100 ms period as rejection criteria. A current source density transformation was used to allow a reference-free evaluation of the EEG data which helps to find the electrodes showing the strongest effects (Nunez and Pilgrien, 1991). Data were then baseline corrected to a time interval from \( -200 \) ms to 0 ms and segments were averaged for each condition. In a data-driven approach, single-subject ERP-amplitudes were quantified as the mean amplitude in a defined time interval. The choice of electrodes and time windows was validated using a statistical procedure described in Mückschel et al. (2014), which is as follows: Within each of the visually detected search intervals (see below), the peak amplitude was extracted for each electrode. Each electrode was subsequently compared against the average of all other electrodes using Bonferroni-correction for multiple comparisons. Only electrodes that showed significantly larger mean amplitudes (i.e., negative for N-potentials and positive for the P-potentials) than the remaining electrodes were selected. This validation procedure revealed the same electrodes and time windows as identified by visual inspection. The following electrodes were chosen for ERP quantification on the basis of the scalp topography: The P1 (105–125 ms) and N1 (190–210 ms) components were measured over electrode P7, P8, P9 and P10. P2 amplitudes were exported from electrodes P3 and P4 (290–310 ms). Electrodes FCz and Cz were used to measure the N2 (290–310 ms). The P3 component was quantified at Cz and Pz (500–650 ms).

2.7. Residue iteration decomposition (RIDE)

To account for intra-individual variability in the data, residue iteration decomposition (RIDE) was run using established protocols (Chmielewski et al., 2018; Mückschel et al., 2017; Ouyang et al., 2015a, 2015b). The RIDE toolbox and manual are available at http://cns.hkbu.edu.hk/RITE.htm. It is important to note that the spatial filter properties of the CSD do not violate assumptions of RIDE since the decomposition is conducted separately for each single electrode channel (Ouyang et al., 2015a).

As mentioned, RIDE decomposes the ERP single-trials data into three clusters that are either correlated to the stimulus onset (S-cluster or to the response time (R-cluster), as well as a central C-cluster with variable latency, which is estimated initially and iteratively improved. However, in a Go/Nogo task the R-cluster cannot reliably be estimated in Nogo trials due to a low frequency of responding in these trials (Ouyang et al., 2013). Therefore, the R-cluster was not computed and only the S-cluster and the C-cluster were calculated as done in previous studies by our group (Chmielewski et al., 2018; Mückschel et al., 2017). Full details on the RIDE methods can be found elsewhere (Ouyang et al., 2011, 2015a). However, briefly, RIDE uses a nested iteration scheme for latency estimation through which the latency estimation of the C-cluster is improved. The initial latency of the C-cluster is estimated using a time window function. In an iterative procedure, the S-cluster is removed, and the latency of the C-cluster is re-estimated based on a template matching approach. Information about the validity of the template matching approach used by the RIDE algorithm can be found elsewhere (Ouyang et al., 2011, 2013, 2015a). During processing, the initial time window for the estimation of the C-cluster was set to 200 to 700 ms after stimulus onset. The time window is assumed to cover the range within which each component is supposed to occur (Ouyang et al., 2015a). The time window for the S-cluster was set to \( \pm 200 \) to 400 ms around stimulus onset. The choice of electrodes and time windows to quantify the RIDE clusters were also validated using a statistical procedure described in Mückschel et al. (2014). For the RIDE-based analysis, the following electrodes were chosen on the basis of the scalp topography: In the S-cluster, the P1 RIDE (105–125 ms) and N1 RIDE (190–210 ms) were measured over electrodes P7, P8, P9 and P10. The P2 RIDE component (270–290 ms) was quantified at electrodes P3 and P4. Furthermore, the N2 RIDE component in the S-cluster (380–420 ms) was measured at electrode Cz. The C-cluster data was used to quantify activation in the P3 time window (P3 RIDE). Based on visual inspection, we exported two time windows (460–475 ms and 550–565 ms) at electrodes Cz and Pz.

2.8. Source localization analysis

To estimate the sources of neurophysiological effects induced by MPH and NF treatment we used sLORETA (standardized low resolution brain electromagnetic tomography; (Pascual-Marqui, 2002). sLORETA provides a single linear solution to the inverse problem without a localization bias (Marco-Pallarés et al., 2005; Pascual-Marqui, 2002; Sekihara et al., 2005). There is also evidence from EEG/fMRI and EEG/TMS studies underlining the validity of the sources estimated using sLORETA (Dippel and Beste, 2015; Sekihara et al., 2005). For sLORETA, the intracerebral volume is partitioned into 6239 voxels at 5 mm spatial resolution. The standardized current density at each voxel is calculated in a realistic head model using the MNI152 template. Since the standard ERP data did not reflect reliable effects of treatment and because these were only seen in the RIDE C-cluster data (please see results section), only the C-cluster was used. As this study focuses on the modulation of neurophysiological mechanisms during the inhibition of responses we (i) contrasted Nogo trials and Go trials within each group and (ii) contrasted Nogo trials between groups. Comparisons were based on statistical non-parametric mapping (SnPM) using the sLORETA-built-in voxel-wise randomization tests with 2500 permutations. The logic of a randomization test using SnPM (Nichols and Holmes, 2002) is that if there is no experimental (i.e. group) effect, the labeling of the groups is arbitrary. Given the null hypothesis that the labellings are arbitrary, the significance of a statistic expressing the group effect is then assessed by comparison with a distribution of values obtained when group-memberships are permuted (Nichols and Holmes, 2002). The randomization exchanges (permutes) the group memberships by changing the group membership at the level of the individual subjects. Because the method is non-parametric it does not require Gaussian distribution of the data. Voxels with significant differences (p < .50, corrected for multiple comparisons) between contrasted groups were located in the MNI-brain www.uinzh.ch/keyinst/NewLORETA/sLORETA/sLORETA.htm. In the Figure, regions of critical activations are given in critical t-values. For the sLORETA procedure and the estimation of the sources underlying...
significant differences in amplitudes of ERP components between groups/conditions, only the time windows used for RIDE amplitude quantification were used. It has previously been shown that RIDE does not distort source localization analyses using sLORETA, since source localization results based on ERPs and RIDE decomposed data were highly similar (Chmielewski et al., 2018).

2.9. Statistics

Within the current study design, it is the goal to examine the differential effects of the three treatment conditions (between-subjects factor Group (MPH vs. neurofeedback vs. waiting list status)) across the two time points (within-subject factor Time Point (T1 vs. T2)). Especially it is important to examine whether the effects differ with the experimental demands (i.e. to execute or withhold a response) (within-subject factors Go/Nogo (Go vs. Nogo)). Albeit complex, this design is necessary in order to capture all possible effects and any interactions between them and to test the postulated hypotheses. When necessary, the factor Electrode was used as an additional within-subject factor in the analysis of the neurophysiological data. In addition, the P3RIDE analysis based on the C-cluster also contained the factor Latency (460-475 ms vs. 550-565 ms). Based on the significant age difference between the groups (see Sample Description), the factor Age was included as a covariate in all analyses (i.e. mixed effects ANCOVAs were calculated). Greenhouse-Geisser correction was applied and post-hoc tests were Bonferroni-corrected when necessary. One-way ANOVAs and paired t-tests were used to examine any significant main effects or interactions further. All variables were normally distributed as indicated by Kolmogorov-Smirnov tests (all z < 1.05; p > .2).

To examine in how far possible lack of effects between the testing time points was reliable and to quantify the evidence in favor for this lack of effects (i.e. the null hypothesis), we calculated Bayesian statistics on the basis of the ANOVA results as proposed by Masson (2011) and Wagenmakers (2007). We present the Bayesian information criterion (BIC) as well as the probability of the null hypothesis being true (p(H0|D)). The degree of evidence for the null hypothesis for was classified according to the criteria put forward by Raferty (1995).

3. Results

3.1. Behavioral data

For the descriptive data, the mean and standard error are given. Concerning the number of false alarms in the Nogo trials (see Fig. 1), the main effects of Group (F(2,56) = 0.05, p = .95, ηp2 = 0.002) and Time Point (F(1, 56) = 2.2, p = .2, ηp2 = 0.04) were not significant. However, we found a significant interaction between Group and Time point (F(2,56) = 3.8, p = .029, ηp2 = 0.12). The obtained effect size ηp2 = 0.12 is well in line with the estimates assumed in the power analysis and is also in line with previous data on NF effects on inhibitory control in AD(H)D (Bluschke et al., 2016b). A post-hoc power calculation using G*Power revealed that the achieved power for this interaction effect was 99%. Within the waiting list control group, we found no differences between testing at T1 (47.1% ± 5.9) and T2 (48.6% ± 5.5) (F(1,17) = 0.14, p = .7, ηp2 = 0.008). Bayesian statistics provide further evidence for the null hypothesis in this case (ΔBIC = 2.74, p (H0|D) = 0.80). After initiation of treatment with MPH (time point T2), participants committed significantly fewer false alarms (42.7% ± 5.4) in Nogo trials than at time point T1 (54.4% ± 4.5) (F(1,19) = 6.8, p = .02). After neurofeedback, a similar pattern emerged. These participants committed significantly fewer errors on Nogo trials at T2 (43.4% ± 4.9) than at T1 (50.4% ± 5.3) (F(1,22) = 6.4, p = .02). Importantly, the magnitude of change between time points T1 and T2 did not differ significantly between the patients treated with MPH (−13.1% ± 5.2) and those treated with neurofeedback.
In terms of correct response to Go stimuli (see Fig. 1), no significant differences were found between time points for either the patients treated with MPH (T1: 78.1% ± 6.2, T2: 84.6% ± 6.7), those taking MPH group: There was significant main effect of GoNogo (F(1,56) = 19.1, p < .001; \( \eta_p^2 = 0.5 \)) (T1: 239 ± 96 ms; T2: 171 ± 69 ms). This difference was not significant within the patients treated with NF (F(1,22) = 1.1; p = .3; \( \eta_p^2 = 0.05 \); T1: 204 ± 75 ms; T2: 189 ± 62 ms) or in the waiting list controls (F(1,17) = 0.2; p = .65; \( \eta_p^2 = 0.01 \); T1: 168 ± 56 ms; T2: 162 ± 76 ms).

In summary, we found thus specific improvements in the ability to inhibit prepotent responses in the Nogo trials in the patients treated with MPH and in those taking part in neurofeedback. The magnitude of improvement did not differ between these groups. No such changes were observed in the waiting list controls or in regards to performance or speed in the Go trials.

3.2. Neurophysiological data

3.2.1. Standard ERP analysis

Our analyses examining the change between T1 and T2 separately for all three groups, treated with NF (F(1,22) = 1.1; p = .3; \( \eta_p^2 = 0.02 \)) or the waiting list controls (T1: 96.1% ± 3.8, T2: 95.2% ± 6.1) or the MPH group (F(1,56) = 9.7, p = .003; \( \eta_p^2 = 0.15 \)), showing that the N1RIDE component was larger in Nogo trials (−66.6 ± 3.7 μV/m^2) than in Go trials (−54.4 ± 3.8 μV/m^2). All other main effects and interactions were not significant (all F < 2.2, all p > .15, all \( \eta_p^2 < 0.04 \)).

The component in the P2-time window (P2RIDE) for the three groups, both time points and for Go and Nogo trials is shown in Fig. 3B.

There were no significant main effects or interactions concerning the P1RIDE amplitude (all F < 2.5, all p > .07, all \( \eta_p^2 < 0.12 \)). Concerning the N1RIDE amplitude, we found a main effect of GoNogo (F(1,56) = 9.7, p = .003, \( \eta_p^2 = 0.15 \)), indicating that irrespective of all other factors, N1RIDE amplitudes were always larger in Nogo (25.9 ± 2.5 μV/m^2) than in Go trials (9.3 ± 1.6 μV/m^2). Most importantly, there was a significant 5-way interaction of Group * Time Point * GoNogo * Electrode * Latency window (F(2, 56) = 3.9, p = .025, \( \eta_p^2 = 0.12 \)).

Concerning the P3RIDE amplitude in the C-Cluster, we found a significant main effect of GoNogo (F(1,56) = 71.4, p ≤ .001, \( \eta_p^2 = 0.6 \)), indicating that irrespective of all other factors, P3RIDE amplitudes were always larger in Nogo (25.9 ± 2.5 μV/m^2) in Go trials (9.3 ± 1.6 μV/m^2). Most importantly, there was a significant 5-way interaction of Group * Time Point * GoNogo * Electrode * Latency window (F(2, 56) = 2.8, p = .044, \( \eta_p^2 = 0.12 \)).

At electrode Cz, we found a significant Time Point * GoNogo interaction at the earlier (460-475 ms) (F(1,19) = 8.6, p = .008, \( \eta_p^2 = 0.31 \)) but not at the later latency window (550-565 ms) (F(1,19) = 0.02, \( \eta_p^2 = 0.001 \)). For the earlier latency window, the main effect of Time Point was only significant in the case of Nogo trials (F(1,19) = 5.2, p = .04, \( \eta_p^2 = 0.21 \)), indicating significantly higher P3RIDE amplitudes after (46.3 ± 11.4 μV/m^2) compared to before (22.3 ± 10.2 μV/m^2) MPH treatment. This was not the case when examining Go trials (F(1,19) = 0.98, p = .33, \( \eta_p^2 = 0.05 \)) (T1: 12.2 ± 5.8 μV/m^2; T2: 6.3 ± 5.6 μV/m^2). Taken together, these analyses show that activation in the C-Cluster becomes larger in Nogo trials after MPH administration at electrode Cz in the earlier time window. The sLORETA analysis (Fig. 4) revealed activation differences in the medial frontal cortex and the anterior cingulate cortex (ACC) (BA24, BA32). For the significant results in the above-mentioned consecutive ANOVAs, post-hoc power calculations showed that the power was always > 90%.

Within the group of patients treated with NF, the interaction of Time Point * GoNogo * Electrode * Latency window was not significant. However, the interaction of Time Point * Electrode * Latency window did reach statistical significance (F(1, 21) = 5.7; p = .03, \( \eta_p^2 = 0.21 \)). At
electrode Cz, we found no significant interactions or main effects involving the factor Time Point (all F < 2.5, all p > .13, \( \eta^2_p < 0.1 \)). At electrode Pz, however, the main effect of Time Point was significant (F(1,21) = 7.2, p = .014, \( \eta^2_p = 0.26 \)), indicating a more pronounced P3RIDE component after (26.1 ± 3.9 μV/m²) compared to before neurofeedback (13.7 ± 4.8 μV/m²). This effect was independent of trial type or latency (no interactions involving the factors GoNogo or Latency, all F < 3.5; all p > .08, \( \eta^2_p < 0.14 \)). The sLORETA analysis contrasting the C-cluster pooled across Go and Nogo trials between different time points (contrast: pre < post) revealed activation differences in the medial frontal cortex, but also in the inferior parietal cortex (BA40) encompassing the temporo-parietal junction (TPJ). No such interactions showing any T1-T2 differences were significant for the waiting list control group (all F < 1.5, all p > .24, \( \eta^2_p < 0.08 \)). For the significant results in the above-mentioned consecutive ANOVAs, post-hoc power calculations showed that the power was always > 90%.

4. Discussion

In the current study, we directly compared the system-neurophysiological mechanisms associated with MPH treatment and theta/beta neurofeedback training in children with AD(H)D on response inhibition processes. We focussed on response inhibition, because this ability is of high clinical relevance in AD(H)D (Bluschke et al., 2016a; Paul-Jordanov et al., 2010; Pliszka et al., 2007; Seifert et al., 2003). Response inhibition can mostly be examined in tasks investigating response inhibition like the Go/Nogo task, and neurophysiological methods like EEG/ERP pick up neurophysiological processes associated with response inhibition. As an important methodological aspect not considered in any previously published study on MPH and/or NF effects
in AD(H)D, we accounted for intra-individual variability in the EEG data since this may bias the evaluation of neurophysiological mechanisms associated with NF and MPH treatment effects.

On the behavioral level, response inhibition in the applied Go/Nogo task significantly improved in patients treated with MPH and patients treated with NF; i.e. the rate of false alarms in Nogo trials was significantly reduced at time point T2 (post treatment), compared to T1 (pre treatment). Response inhibition improved to a similar degree in both the groups and the degree of change observed for the NF intervention was comparable to other data (Bluschke et al., 2016). No changes were observed in the waiting list controls. This is also supported by a Bayesian analysis of the data showing that there was strong evidence in favor for the null hypothesis, i.e. the degree of change in false alarm rates between T1 and T2 was the same in MPH and NF intervention. This is especially important to consider because the a-priori power analysis shows that the study design was sufficiently powered. Furthermore, we found a significant reduction of Go reaction time variability in patients treated with MPH but not those treated with NF or included as waiting list controls. Thus, NF is not as effective in reducing reaction time variability as it is the case for MPH. This could be explained by the direct influence of MPH on (particularly tonic aspects of) the dopaminergic system (Badgaiyan et al., 2015). This result shows that it is important to account for intraindividual variability when examining the neurophysiological data, which was the focus of this study. Indeed, for the neurophysiological level, the data suggest that MPH and NF target different neurophysiological mechanisms:

No changes occurred in earlier components such as P1, N1, P2 and N2, when analysing standard ERPs or in regards to the waiting list controls. The same was the case for the S-cluster data in the time windows of the P1, N1, P2 and N2. The finding that no reliable effects explain the results at the behavioral level very likely reflects issues related to the intra-individual variability of the EEG data, which is known to be high in AD(H)D (Gmehlin et al., 2014; Henríquez-Henríquez et al., 2014; Lin et al., 2015; Plessen et al., 2016; Saville et al., 2015) also at the neurophysiological level (Alba et al., 2016; Bluschke et al., 2017, 2018; Gonen-Yaacovi et al., 2016; Lazzaro et al., 1997). The finding that the S-cluster data did still not reveal effects explaining the behavioral data suggests that perceptual and attentional selection processes, known to play an important role in response inhibition (Bodmer and Beste, 2017; Friedrich et al., 2018; Stock et al., 2016), are not modulated and do not underlie MPH- and NF-induced performance increases in behavioral inhibition. Notably, the C-cluster data reflected interactive effects which can explain the MPH and NF effects at the behavioral level, and post-hoc power analyses revealed that the effects are reliable because the power was above 95%:

For the MPH group it is shown that the C-cluster was larger in Nogo trials after treatment, while no effects were evident in Go trials. During Nogo-trials, the Nogo-P3 and the C-cluster have been suggested to

Fig. 3. Stimulus-locked waveforms (current source density) and topographic maps (for Nogo trials only) for activation in the RIDE S-Cluster. Figure shows A) P1RIDE/N1RIDE, B) P2RIDE and C) N2RIDE component for Go and Nogo trials, for both time points (T1 = baseline testing, T2 = testing after 8 weeks of intervention/waiting list status) and for all three experimental groups (MPH = patients treated with methylphenidate; NF = patients treated with neurofeedback; WLC = patients included as waiting list controls). Point 0 denotes Go/Nogo stimulus onset. In the topographic maps (shown only for Nogo trials), blue denotes negative deflections whereas red denotes positive ones.


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reflect a ‘braking function’, or a mechanism that is important when inhibiting automated response tendencies (Bluschke et al., 2016a; Bodmer et al., 2018; Chmielewski et al., 2018; Friedrich et al., 2018; Mückschel et al., 2017; Ouyang et al., 2015a). These mechanisms seem to become stronger as an effect of MPH treatment. Treatment with MPH thus seems to reduce the postulated weakness of the braking function in ADHD (Aron et al., 2014). From a neurobiological perspective, MPH prolongs the time during which dopamine is available in the synaptic cleft and leads to a stronger dopamine D2 receptor activation (Volkow et al., 2005; Volz et al., 2008). Yet, it needs to be noted that the noradrenaline system is also affected by MPH. Notably, it has been shown that the dopamine D2 receptors and the meso-corticolimbic dopamine system strongly modulate processes reflected by the Nogo-P3 (Beste et al., 2016, 2010). Other lines of evidence show that dopamine D2 receptor agonists improve inhibitory control in healthy subjects (Nandam et al., 2013) and that blocking D2 receptors negatively affects inhibitory control in animals (Eagle et al., 2011). The source localization results for the current study show that MPH-induced modulations in C-cluster activation during Nogo trials were associated with activation differences in the anterior cingulate cortex (ACC) (BA24, BA32) for the patients treated with MPH. For the patients treated with NF, sLORETA showed activation differences in the medial frontal cortex, but also in the inferior parietal cortex (BA40) encompassing the temporo-parietal junction (TPJ). Colours indicate the critical t-value (corrected for multiple comparison using SnPM).
performance are based on neurophysiological mechanisms different to the effects of MPH. In contrast to MPH, the effects of NF were less specific on the neurophysiological level because NF-induced modulations of the C-cluster were evident in Go and Nogo trials. However, since behavioral performance in Go trials (RT and error rate) was not modulated between T1 and T2, the induced effects in Go trials are unlikely to be important for the behavioral effects to emerge. Nevertheless, the source localization analysis also indicates that treatment with NF modulates different processes than treatment with MPH since in addition to medial frontal areas, inferior parietal areas (BA40, TPJ) were also found to be associated with NF-induced modulations of the C-cluster amplitudes. A modulation of medial frontal areas associated with the Nogo-P3 was also obtained in another study examining the effects of NF using a Go/Nogo task (Bluschke et al., 2016a). However, this study did not account for intra-individual variability in the data. When this was done, other recent studies examining response inhibition processes more generally already found that modulations in the C-cluster amplitude are associated with inferior parietal areas and the medial frontal cortex (Bodmer et al., 2018; Friedrich et al., 2018, 2017). To understand the relevance of the obtained modulations of inferior parietal areas in the current study, it is important to consider that the applied neurofeedback protocol combined a modulation in the theta frequency band and the beta frequency band. Even though the NF effects can therefore not be attributed to the action of a particular frequency band, it is important to stress that theta oscillations associated with inhibitory control are mediated via brain regions encompassing the left tempo-parietal junction (TPJ, BA40) (Dippel et al., 2016). The TPJ has been suggested to processes task-relevant stimuli to update internal representations of the environmental context to initiate appropriate actions (Geng and Vossel, 2013). Theta oscillations have also been suggested to encode a “surprise signal” (Cavanagh and Frank, 2014). This putative function of the theta oscillations fits well into the possible functional role of the TPJ (Geng and Vossel, 2013) and the Go/Nogo paradigm applied in the current study which contained more Go-than Nogo-trials which involve the processing of a “surprise signal”. Crucially, beta oscillations have also been suggested to be important for the stabilisation of processes protecting cognitive operations against interfering events (Engel and Fries, 2010). Together, it is possible that the applied NF protocol may have modulated these processes making it possible to update and stabilize mental representations in order to initiate appropriate actions or inhibitory control. This may particularly be the case when these processes are ‘surprising’. Together, it becomes apparent that MPH and NF have similar effects on behavioral inhibition performance, but the underlying mechanisms are different. In particular, the treatment with NF is likely to modulate neural processes beyond those affected by MPH. This interpretation is further evidenced by the source localization findings showing that medial frontal areas are modulated by both interventions, while parietal areas are only affected by NF.

5. Implications

While the neurophysiological mechanisms associated with treatment effects seem to be different between MPH and NF interventions, the behavioral results suggest that both interventions are equally effective to treat inhibitory deficits as examined using the Go/Nogo task in the current study. This is of high clinical relevance because it has been shown that a significant proportion of patients discontinue MPH treatment for several reasons and prefer non-pharmacological treatment approaches (Dosreis et al., 2017; Garbe et al., 2012; Ng et al., 2017; Schatz et al., 2015). The finding that both interventions seem to target complementary cognitive-neurophysiological processes and functional neuroanatomical structures may provide the basis for a combined MPH + NF intervention. Since MPH and NF target different mechanisms, this may explain why combined MPH + NF interventions have been suggested to be more effective when treating executive dysfunctions in AD(H)D than one intervention form alone (González-Castro et al., 2015). It is possible that medial frontal mechanisms, targeted by MPH, and parietal mechanisms, targeted by NF, may have additive effects in terms of efficacy. Considering that the NF effects seem to be associated with parietal areas, it may be possible to further boost the effects of a neurofeedback treatment by including brain stimulation methods during the NF intervention. Especially transcranial direct current stimulation (tDCS) could be useful in this regard as there is evidence that this technique improves AD(H)D symptoms and cognitive functions (Rubia, 2018).

6. Limitations

One limitation is that the allocation of patients to the different intervention groups y was not randomized in the current study. However, this study did not intend to examine the effectiveness of the NF and MPH treatment approaches per se since these have been demonstrated previously (refer introduction section). The goal of this study was to examine the neural mechanisms targeted by these interventions and to evaluate any differences between them. While it may also be argued that the sample size is moderate and may limit generalizability, it is important to stress that the sample size was based on power calculations using estimates of published data and that the obtained effect sizes are in line with that. Post-hoc power analysis of the actually employed statistical model further revealed that the study is sufficiently powered. This, together with the Bayesian analysis of the data, also allows reliable conclusions about aspects of the study that showed no differential effects between NF and MPH treatments; i.e. that attentional selection processes were unaffected. It may be argued that the heterogeneous medication profile in the NF group may confound the results. However, since the medication profile was not changed between T1 and T2, the effects in the NF at T2 cannot be attributed to the medication effects. Moreover, the waiting list control group also included subjects with a similar heterogeneous medication profile. The finding that no changes between T1 and T2 were observed here further underlines that the effects in the NF group are due to the NF intervention. Yet, especially considering that implication of the findings that for combined MPH and NF treatments, further validations of the results are required.

7. Summary

In summary, the study shows that MPH and theta/beta NF treatments increase the ability to inhibit prepotent responses to a similar extent in patients with AD(H)D. However, the data suggest that MPH and NF target different neurophysiological mechanisms, especially when it comes to functional neuroanatomical structures associated with these effects. Both treatments seem to affect neurophysiological correlates of a ‘braking function’ in medial frontal areas. However, in case of the NF intervention, inferior parietal areas also are involved, likely reflecting how efficient internal representations can be updated and stabilized to initiate appropriate actions. No effects were seen in correlates of perceptual and attentional selection processes. Notably, the study shows that it is important to account for intra-individual variability in the neurophysiological data when evaluating MPH/NF treatment effects in AD(H)D at the system-neurophysiological level. This aspect may also partly explain the diversity of findings in studies on treatment effects in AD(H)D, especially concerning neurofeedback treatment effects.

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Submission declaration

The authors confirm that work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and that, if accepted, it will not be published elsewhere without the written consent of the copyright-holder.

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