Methylphenidate selectively modulates one sub-component of the no-go P3 in pediatric ADHD medication responders

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ABSTRACT

Methylphenidate (MPH) has been shown to modulate the amplitude of the no-go P3 component of the event-related potential (ERP; Øgrim, Aasen, & Brunner, 2016). Using group independent component analysis, the no-go P3 from a cued go/no-go task has been separated into two sub-components (Brunner et al., 2013). This study investigated whether sub-components of the no-go P3 could be identified in children with ADHD, and how MPH modulates their amplitudes. ERPs were registered twice (on/off MPH) in 57 children with ADHD classified as medication responders in a four-week medication trial. Two no-go P3 sub-components were identified. In the MPH session, the amplitude of one sub-component, the IC P3no-go$_{early}$ (mean latency 378 ms, with a central distribution), was significantly larger than at baseline, whereas the other sub-component, the IC P3no-go$_{late}$ (mean latency 428 ms, with a centro-frontal distribution), was not significantly affected. These results add to the literature documenting that the no-go P3 consists of two overlapping phenomena with different functional correlates.

1. Introduction

The no-go P3 component of the event-related potential (ERP) has repeatedly been found to be of reduced amplitude in children with Attention Deficit Hyperactivity Disorder (ADHD; Albrecht et al., 2013; Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010; Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005; McLoughlin et al., 2010). In response to a dose of stimulant medication, this component has been found to increase dramatically in those children with ADHD who were reported by parents and teachers to benefit from medication, but not in medication non-responders (Øgrim, Aasen, & Brunner, 2016). The most common stimulant used to treat ADHD is methylphenidate (MPH), and there is general agreement that this medication reduces the core symptoms of inattention, hyperactivity and impulsivity in the majority of children and adolescents diagnosed with the disorder (Banaschewski et al., 2016; Storebo et al., 2015). There are indications, however, that the no-go P3 is not a unitary phenomenon, but rather consists of two overlapping and functionally different subcomponents (Brunner et al., 2013, 2015). This study investigates whether such sub-components can be identified in children with ADHD, and whether the effects of MPH are different for these sub-components.

ERP components are computed on the basis of a scalp-recorded electrical potential, which is a mixture of temporally overlapping activity from distinct, spatially distributed sources. This overlap causes an "impurity problem", as any peak in the ERP could be the mixture of several independent phenomena. An approach to this problem that is becoming increasingly popular is to use blind source separation methods such as independent component analysis (ICA). ICA is most commonly applied to continuous EEG or single trial ERPs from one individual. This results in a component solution fitted to each individual, but introduces a challenge in component selection when comparing individuals. Group ICA, however, results in a single component solution for the entire group on which ICA is performed, resulting in a potentially poorer fit for the individual participant, but guarantees that the same component is compared across individuals. Studies using group ICA applied to ERPs from a cued go/no-go task indicate that the no-go P3 consists of two fronto-centrally maximal sub-components with positive polarity in the no-go P3 latency range in healthy adults and children (Brunner et al., 2013; Kompatsiari, Candrian, & Mueller, 2016). One component has a shorter latency than the other and a central distribution, and the other has a slightly later latency and a fronto-central maximum. The amplitudes of the two sub-

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components are associated with different neuropsychological test parameters (Brunner et al., 2015) and are differentially modulated by speed vs. accuracy instructions (Aasen & Brunner, 2016), indicating that they reflect different functions. We have previously argued that the shorter latency no-go P3 sub-component, named the IC P3no-go$_{early}$, may reflect activation of a stimulus–(non-)response (S–R) association (Aasen & Brunner, 2016). We will refer to this as the *activation hypothesis* of no-go P3. The later latency sub-component, named the IC P3no-go$_{late}$, was suggested to reflect a monitoring function evaluating the need to down-adjust pre-potency. These functional interpretations give rise to predictions regarding MPH effects on these no-go P3 sub-components.

1.1. Effects of MPH on mental representations and behavioral adjustment

At the biochemical level, MPH seems to exert its effects by blocking catecholamine transporters, lengthening the time catecholamines remain in the synaptic gap (Swanson & Volkow, 2002). At normal therapeutic doses, MPH increases the availability of norepinephrine and dopamine in the prefrontal cortex, without having much effect in other regions of the brain (Berridge et al., 2006; Spencer, Devilbiss, & Berridge, 2015). Catecholamines do not have an unequivocal effect on cognition. Rather, both too low and too high availability of catecholamines impair cognition (Gamo & Arnsten, 2011), which could be why not all children with ADHD profit from such medications. Therefore, this study will focus on children and adolescents with ADHD reported to *profit* from MPH.

A well-established model used to test the molecular mechanisms of prefrontal cortex function, pioneered by the work of Goldman-Rakic (1995), is to study neuronal responses to stimuli in a spatial working memory task. Using this model, it has been firmly established that, at optimal levels, dopamine and norepinephrine strengthen working memory representations by decreasing the signal-to-noise ratio in neural firing patterns (see review by Gamo & Arnsten, 2011). If the IC P3no-go$_{early}$ reflects one such representation, as assumed by the activation hypothesis (Aasen & Brunner, 2016), we would expect the IC P3no-go$_{early}$ to increase in amplitude in response to a dose of MPH.

The second no-go P3 sub-component has been related to behavioral adjustments. A meta-analysis of one such type of adjustments, post-error slowing, has shown that patients with ADHD slow down responses after committing an error to a lesser degree than controls (Balogh & Czobor, 2016). Like errors, no-go or incongruent stimuli also lead to slowing in the following trial, referred to as post-conflict slowing, and there are indications that similar adjustment mechanisms are activated by errors and conflict (Verguts, Notebaert, Kunde, & Wühr, 2011). If MPH improves response-threshold adjustments after errors and no-go trials, this should result in fewer premature responses. In our previous study, however, changes in commission error rates were independent of both reports of medication response and MPH effects on the no-go P3 (Øgrim et al., 2016) suggesting that response-threshold adjustments are not central for understanding how MPH modulates ADHD symptoms or the no-go P3. Only a few studies have investigated the effects of stimulants on post-error slowing. Of these, one study found no effects on post-error slowing (Jonkman, van Melis, Kemner, & Markus, 2007), and one found no effects at lower doses, and *speeding* rather than slowing after errors at higher doses (Wardle, Yang, & de Wit, 2012). The one study that did find increased post-error slowing in response to MPH also investigated post-conflict slowing, but did not find the same MPH effect for post-conflict as for post-error slowing (Moeller et al., 2014). As we have hypothesized that the IC P3no-go$_{late}$ amplitude reflects signaling to decrease response pre-potency after (correct) no-go trials, and MPH

does not seem to improve such response-threshold modulations, we do not expect an MPH effect on the IC P3no-go$_{late}$.

1.2. Another impurity problem of ERPs – averaging

Usually, ERPs are computed as averages over many trials, leading to information about systematic trial-to-trial fluctuations or time-on-task changes being lost. Such changes could, for instance, be informative in the study of processes related to learning, sustained attention, or fatigue, which are all camouflaged in averaged ERPs. This is potentially important in the study of medications reducing the symptoms of ADHD, as two of the symptoms of this disorder concern the ability to *sustain* attention or effort (American Psychiatric Association, 2013). This means that if MPH improves how long participants are able to sustain attention, MPH effects on no-go P3 could be explained by smaller decrements in amplitude over time. To rule out this possibility, this study will also investigate the time-on-task modulation of the no-go P3 sub-component amplitudes, and its interaction with the MPH effect.

2. Methods

2.1. Procedure

All participants underwent one ERP registration without stimulant medication, and a second registration on a single dose of MPH. The first registration was conducted when participants agreed to take part in the study, and the second at the onset of the four-week medication trial. The time interval between the two ERP registrations was between 1 and 45 weeks, with a median time interval of 7 weeks. Some families wanted to postpone onset of the medication trial period, causing longer time-intervals between recordings for these participants. Of the participants included in the study, 41 (72%) received a dose of 10 mg MPH and 16 (28%) received a dose of 15 mg MPH one hour before the second ERP registration. The latter were above 14 years of age, and were not small for their age. After the medication trial, participants were either classified as medication responders or non-responders based on daily ratings of ADHD symptoms from the children's parents and teachers during the trial period. Only medication responders were included in this study. For details of the diagnostic procedures and classification as medication responder or non-responder, see Øgrim et al. (2016). Informed consent was obtained from the parents of all participants prior to ERP registration and medication trial. The Regional Committee for Medical Research Ethics approved the study.

2.2. Participants

The participants in the study were 57 children and adolescents (17 girls, 40 boys) aged between 7 and 17 years (mean age 11.9 years, SD = 2.5 years). The participants were selected from a group of 91 children and adolescents with a diagnosis of ADHD who were offered a clinical trial of MPH. These participants are the same as those participants receiving MPH in Øgrim et al. (2016). None of the participants had a history of brain injury or an IQ below 70. 11 participants were excluded because of excessive artifacts in the EEG, leaving less than 25% of no-go trials after artifact correction on one or both ERP registrations. One participant was excluded because of non-compliance during the four-week trial period. 22 of the 79 candidates for participation were classified as MPH non-responders and were excluded from this study.

2.3. Task

EEG was recorded during the performance of a cued go/no-go task (Kropotov & Ponomarev, 2009) with three categories of stimuli – animals (A), plants (P), and humans (H). These stimuli were presented in four different combinations of stimulus categories: A-A, A-P, P-P and P-H, where the first stimulus served as a cue. The participants were instructed to respond to the second stimulus in A-A pairs only by pressing a mouse button as quickly and accurately as possible, and to withhold responses to A-P pairs. No response was required on P-P or P-H trials.

During task performance, the participants sat approximately 1,5 m from a 17″ computer screen. The task contained 20 different images of each category. The images were drawings selected from children's textbooks presented against a white background. The images were of approximately equal size and luminance. The first and second stimulus in A-A and P-P pairs were identical. The task consisted of 400 trials, 100 of each of the four stimulus combinations. Each stimulus was presented for 100 ms. A new trial was presented every three seconds, with a 1100 ms cue-target interval, and 1900 ms from the onset of the imperative stimulus to the onset of the cue in the next trial. The trials were presented in a pseudo-random fashion, so that each quartile of the task contained an equal number of trials of each type.

2.4. ERP registration

EEG was recorded on a 21-channel Mitsar EEG-system (http://www.mitsar-medical.com), with a bandpass of 0.3–50 Hz, and sampling rate of 250 Hz. EEG was registered from 19 electrodes on a tin electrode cap (www.electrocap.com) containing electrodes Fz, Cz, Pz, Fp1/2, F3/4, F7/8, T7/8, P7/8, C3/4, P3/4, and O1/2, fitted in accordance with the 10/20 system. The ground electrode was placed between electrodes Fp1/2 and Fz electrodes. The electrodes were referenced to earlobe electrodes. Impedance was kept below 5 kΩ.

After registration, the data were re-referenced offline to the common average montage, before correction and rejection of artifacts. Eye-blink artifacts were corrected by zeroing the activation of ICs corresponding to eye-blinks using ICA on the raw EEG (Jung et al., 2000; Vigario, 1997). Epochs of EEG with absolute amplitude exceeding 100 μV were automatically marked and excluded from further analysis. The mean number of artifact and error-free no-go trials used to compute ERPs in the baseline registration was 76 (range 30–99) and 84 (range 29–99) in the registration on a dose of MPH.

2.5. Group ICA decomposition

Group ICA was performed on ERPs from the no-go condition rather than raw EEG, as ERPs give better signal-to noise ratio in the input data, and the chance of underfitting when we only have 19 electrodes is reduced. The ERPs from each participant in the time interval of 0–700 ms after the onset of the no-go stimulus were temporally concatenated before Infomax ICA (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997) was conducted on the 19-channel ERPs from the 2 × 57 participants (from the baseline and MPH registrations). These data gave an unmixing matrix of 19 columns (electrodes) and 19,950 rows (250 Hz × 0.7 s × 114 ERPs). To select ICs for analysis, each IC was back-projected to the grand mean ERPs collapsed across participants and sessions (baseline/MPH), and compared with the raw no-go P3 at Cz (see Fig. A1). ICs with clear positive fluctuation at Cz (where the medication effects on the no-go P3 best predicted reduction in ADHD symptoms in Øgrim et al., 2016), with onset and offset in time interval of the no-go P3 were selected for further analysis. The selected ICs were back-projected to each participant's ERPs by means of spatial filtration (Makeig & Onton, 2012) before latencies and amplitudes of the ERP components of each individual were measured.

2.6. Amplitude and latency measurement

ERP component amplitudes were measured as the local peak amplitudes (Luck, 2014) within the time interval 300–500 ms post no-go stimulus onset. This time interval was selected on the basis of the onset and offset of the no-go P3 component in the grand mean ERP waveform collapsed across participants and sessions. The amplitude of the raw no-go P3 was measured at the midline electrodes, Fz, Cz and Pz. The amplitudes of the no-go P3 ICs were measured at the electrode with the largest amplitude, which, due to the ICA decomposition, is stable across participants. All amplitudes were measured relative to a 100 ms pre-stimulus baseline.

ERP component latencies were measured in order to enable comparison of the raw ERP and ICs. Latencies were measured using a relative criterion fractional area (FA) approach using an in-house MATLAB program. This method measures the latency as the median point in time within the area surrounding the peak of the component of interest. The entire time window of the FA must lie within the pre-defined no-go P3 time interval ± 50 ms (i.e. 250–550 ms post S2). The onset of the FA is defined individually by finding the component's local peak amplitude, and going back to the point in time where the component reaches 50% of this component's peak-to-peak amplitude. The offset of the area is defined as the point in time where the amplitude returns to, or comes closest to, returning to the onset amplitude again.

2.7. Statistics

The data were analyzed using SPSS version 21.0. Differential effects of session on the amplitudes of sub-components of the no-go P3 were investigated using a sub-component by session repeated measures ANOVA. It was known a priori that the raw no-go P3 component is affected by MPH, and the aim of the study was to investigate whether the effect of session could be attributed to one or several of the no-go P3 sub-components. We expected an effect on only one sub-component, and corrections for multiple comparisons could bias our results in line with our expectancies. Therefore, no correction of multiple comparisons was made when testing the specific effect of session on each sub-component.

To investigate the relationship between intra-individual changes in commission error rates and no-go P3 sub-component amplitudes from baseline to the MPH measurement, Pearson's or Spearman's correlations were performed as appropriate for parametric or non-parametric variables.

To test whether effects of time-on-task were affected by MPH, and whether the time-on-task effects were different for no-go P3 sub-components, time-on-task (first vs. second vs. third sub-block of task performance) by session repeated measures ANOVAs were performed, using Greenhouse-Geisser corrections when assumptions of sphericity were not met. Each sub-component was investigated separately. Post hoc contrasts were investigated using Bonferroni correction for multiple comparisons. As the aim of this analysis was to investigate how long participants were able to sustain attention, all post hoc contrasts were performed relative to the sub-block where attentional resources were assumed to be the least depleted, i.e. the first sub-block.

3. Results

Behaviorally, the effect of the MPH relative to the baseline session was a mean RT reduction of 29.4 ms (SD = 51), a mean reduction in variability (standard deviation) of RT of 38.9 ms (SD = 40), a mean of 2.9 (SD = 6) fewer commission errors, and a mean of 9.9 (SD = 11) fewer omission errors. The left panel of Fig. 1 shows the effect of session on the raw no-go P3 component at the midline electrodes. This effect was significant at Cz (mean difference 4.36 μV; $CI_{95\%}$ = 3.45, 5.27) and
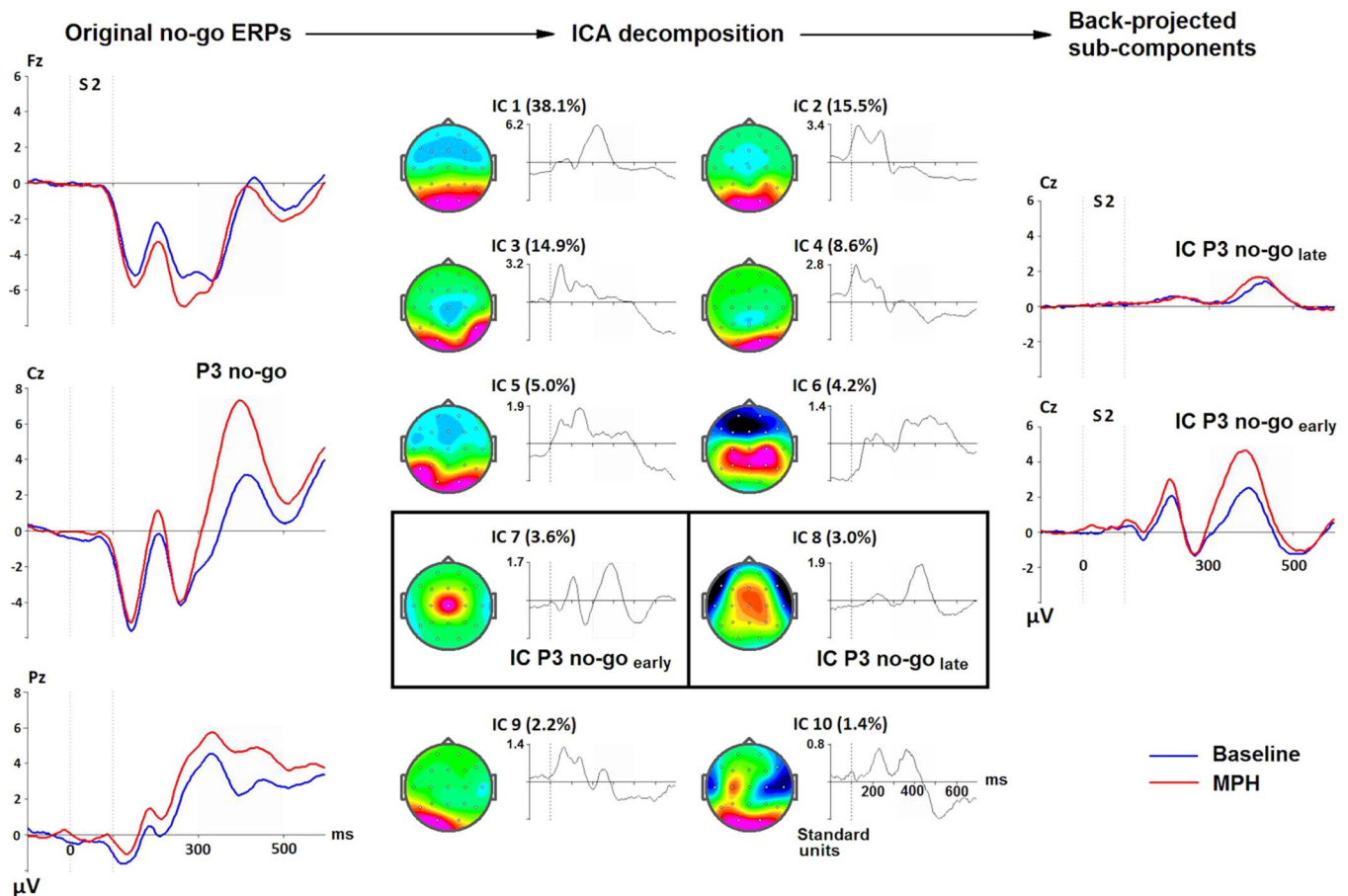
Fig. 1. Left: MPH effect on the raw no-go P3 at the midline electrodes. Center: The 10 independent components (ICs) explaining 95% of the total signal variance in the no-go condition. Black frames mark the selected no-go P3 sub-components. Right: MPH effects on the two back-projected no-go P3 sub-components. The shaded area marks the time interval of the raw no-go P3 at Cz.

Pz (mean difference 1.94 μV; $CI_{95\%}$ = 1.06, 2.82), but not at Fz (mean difference 0.26 μV; $CI_{95\%}$ = −0.78, 1.29). The effect of session on no-go P3 amplitude at Cz was not significantly related to the time between sessions (r_s = −0.09, p = .503), and was not different for those receiving a dose of 10 vs. 15 mg of MPH ($F(1,56)$ = 0.07, p = .795).

3.1. Independent components of the no-go P3

Of the 19 ICs obtained by the group ICA, two components showed clear positivity in the midline region with onset and offset in the no-go P3 time interval (300–500 ms). The middle panel of Fig. 1 shows the IC scalp topographies and time courses of the 10 ICs (of the 19 IC in total) that explained most of the signal variance, together explaining > 95% of the signal variance in the no-go condition. Fig. A1 in the Appendix A shows the contribution of each of the 10 ICs to the raw ERP at Cz (collapsed across sessions), where the effect of session was largest. Component 7 had a positive fluctuation in the time interval between 300 and 460 ms (mean latency 378 ms) after onset of the no-go stimulus that was maximal at Cz. Component 8 had a positive fluctuation in the time interval between 350 and 500 ms (mean latency 428 ms) after onset of the no-go stimulus that was also maximal at Cz, but also stretched forward towards Fz and backward to Pz. As component 7 had a somewhat shorter latency than component 8, the components are referred to as IC P3no-go$_{early}$ and IC P3no-go$_{late}$, respectively.

The relationship between the latencies and amplitudes of the raw no-go P3 component and its ICA-derived sub-components can be seen in the scatter plots in Fig. A2 in the Appendix A. As can be observed, the latency of the no-go P3 at Cz (mean latency: 407 ms at baseline session,

Table 1
Descriptive statistics.

	N	Baseline session Mean (SD)	MPH session Mean (SD)	Mean difference Mean (SD)	p
No-go P3 amplitude (μV)	57				
Fz		1.06 (3.8)	1.32 (4.9)	0.25 (3.9)	.623
Cz		4.46 (4.4)	8.83 (4.5)	4.36 (3.4)	< .001
Pz		5.69 (4.0)	7.63 (4.7)	1.94 (3.3)	< .001
IC amplitude at Cz (μV)	57				
IC P3no-go$_{early}$		4.18 (3.8)	6.53 (4.0)	2.35 (2.8)	< .001
IC P3no-go$_{late}$		1.89 (1.5)	2.34 (1.9)	0.46 (1.9)	.082

396 ms at MPH session) fell in between the latencies of the two sub-components, whereas the Cz amplitude was most related to the IC P3no-go$_{early}$ amplitude. At Fz, however, the no-go P3 latency was somewhat later (mean latency: 429 ms at baseline session, 422 ms at MPH session) than at Cz, and both the latency and amplitude of the component corresponded more to the characteristics of the IC P3no-go$_{late}$.

3.2. Effects of MPH on the no-go P3 sub-components

The effects of session on the no-go P3 sub-components are shown in the right panel of Fig. 1. Table 1 shows the descriptive statistics of the
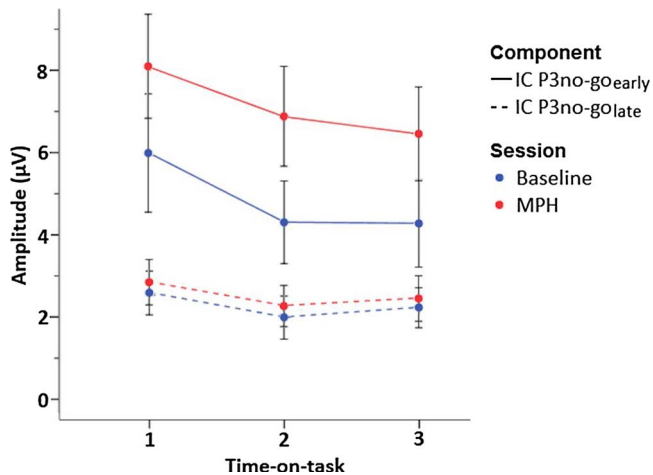
Fig. 2. Mean amplitudes with 95% confidence intervals of the IC P3no-go$_{early}$ (solid line) and IC P3no-go$_{late}$ (dashed line) in the first, second and third tercile of the task at baseline (blue) and on MPH (red).

amplitudes of the raw no-go P3 and sub-components. The 2×2 sub-component (IC P3no-go$_{early}$/IC P3no-go$_{late}$) by session (baseline/MPH) ANOVA revealed that the effect of session was significantly larger for the IC P3no-go$_{early}$ than for the IC P3no-go$_{late}$ ($F(1,56) = 15.47$, $p < .001$, $\eta_p^2 = .22$). Planned contrasts revealed that session had a significant effect on the IC P3no-go$_{early}$ (mean difference 2.35 μV; $CI_{95\%} = 1.62, 3.09$) but not the IC P3no-go$_{late}$ (mean difference 0.46 μV; $CI_{95\%} = -0.06, 0.97$).

3.3. Relationship between no-go P3 sub-components and commission errors

Neither commission error rates nor the IC P3no-go$_{late}$ amplitude changed significantly from baseline to the MPH session. The test where the participants made fewer commission errors were, however, associated with larger IC P3no-go$_{late}$ amplitudes ($r_s = -0.356$, p = .007), in line with our prediction. Changes in IC P3no-go$_{early}$ amplitude was not significantly correlated with changes in commission error rates ($r_s = 0.087$, p = .521).

3.4. Effects of time-on-task

The mean amplitudes and 95% confidence intervals of the two no-go P3 sub-components at the first, second and third sub-block of the task can be seen in Fig. 2. For the IC P3no-go$_{early}$, the time-on-task by session repeated measures ANOVA resulted in a main effect of time-on-task ($F(2,112) = 9.40$ $p < .001$, $\eta_p^2 = 0.14$), with the amplitude decreasing from the first (T1) to the second (T2), to the third (T3) sub-block of the task. Post hoc contrasts revealed that this decrease was significant both from T1–T2 ($F(1,56) = 11.24$, $p = .003$, Bonferroni corrected; $\eta_p^2 = 0.17$) and T1–T3 ($F(1,56) = 14.65$, $p < .001$, Bonferroni corrected, $\eta_p^2 = 0.21$). The time-on-task by session interaction was not significant ($F(2,112) = 0.06$ $p = .925$, $\eta_p^2 = 0.00$), however, indicating that the effect of session on the IC P3no-go$_{early}$ cannot be explained by a reduced time-on-task effect when the participants received MPH.

Time-on-task also had a significant effect on the IC P3no-go$_{late}$ ($F(2,112) = 6.08$, $p = .003$, $\eta_p^2 = 0.10$). This component, however, decreased in amplitude from T1 to T2, and then increased slightly again to T3. Post hoc contrasts revealed that whereas the T1–T2 difference was statistically significant ($F(1,56) = 10.39$, $p = .004$, Bonferroni

corrected; $\eta_p^2 = 0.16$), the T1–T3 difference was not ($F(1,56) = 4.76$, $p = .066$, Bonferroni corrected; $\eta_p^2 = 0.08$). The time-on-task by session effect was not significant ($F(2,112) = 0.03$ $p = 0.961$, $\eta_p^2 = 0.00$), indicating that the null effect of session on the IC P3no-go$_{late}$ amplitude in the main analysis was relatively stable over the three sub-blocks of task performance.

4. Discussion

As predicted, the ICA decomposition resulted in two no-go P3 sub-components with similar characteristics as those previously identified in healthy adults and children. Of these components, only the shorter latency component, the IC P3no-go$_{early}$, was significantly modulated by a dose of MPH. This effect was present from the outset of task performance, and was not significantly modulated by time-on-task. Although the IC P3no-go$_{late}$ amplitude was not significantly affected by MPH, intra-individual changes in this component's amplitude were related to corresponding changes in commission error rates, in line with the hypothesis that the component is involved in adjustments of the speed-accuracy trade-off.

4.1. Activation as an alternative to inhibition

Before turning to the details of the MPH effect on the IC P3no-go$_{early}$ and the activation hypothesis, a few comments on the concept of inhibition are needed. Due to its appearance in a condition where one must refrain from performing a pre-potent response, the no-go P3 is often assumed to reflect inhibition. Although this interpretation has immediate appeal, it faces a number of problems. First, it is necessary to define what is meant by inhibition when referring to the function of the no-go P3. Some proponents of the inhibition hypothesis of the no-go P3 assume the component to reflect *response* inhibition – i.e. the cancelling of an initiated motor output (Fallgatter & Strik, 1999; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004; Wessel & Aron, 2015). Accumulating evidence, however, indicates that participants need about 200–250 ms to stop a response (e.g. Band, Ridderinkhof, & van der Molen, 2003), and reduction in motor neuron excitability is seen as early as 150–180 ms after the presentation of a no-go stimulus (Raud & Huster, 2017; van den Wildenberg et al., 2010). These findings indicate that response inhibition is initiated far earlier than the no-go P3 latency range, and also before the P3 onset (for a counter-argument see Wessel & Aron, 2015). Rather than reflecting processes that must take place *before* executing or stopping an action, the late latency of both the target P3b and the no-go P3 indicate that these components reflect processes having more indirect effects on actions.

The activation hypothesis of the IC P3no-go$_{early}$ suggests that this component reflects activation of a mental representation linking the no-go stimulus to a non-response. This hypothesis parallels the S–R link hypothesis of the target P3b (Verleger, Baur, Metzner & Smigasiewicz, 2014). Beyond being elicited in different conditions, the P3b and IC P3no-go$_{early}$ also have different topographical distributions, and are differentially modulated by speed vs. accuracy instructions (Aasen & Brunner, 2016) and stimulant medication (Øgrim et al., 2016) indicating that there are important differences between them. There is some evidence, that in the presence of pre-potent response options, the no-go S–R link is represented as a *negation* of the dominant S–R link (Kuhn & Brass, 2010). That is, the non-action representation is dependent on, and secondary to, its contrasting action representation. Oberauer (2010) argues, that the more similar or associated S–R representations are with each other; the more they will cause interference and affect performance. The activation hypothesis of the IC P3no-go$_{early}$

assumes that the interference from the target S–R link is resolved through facilitation of the associated but incompatible S–non-R link, requiring the involvement of frontal resources. This facilitation, or energization as we have termed it in previous studies (Aasen & Brunner, 2016; Brunner et al., 2015) may be what is improved by MPH in the medication responders in this study. Note that this model merely requires that attention is shifted from the target S–R link (Animal ⇒ press button) to the S–non-R link (Plant ⇒ don't press button); it does not require an independent *cognitive* inhibition function, i.e. suppression of cognitive representations, a process which has been argued to be unnecessary (Friedman & Miyake, 2017; MacLeod, 2007), and even redundant and at conflict with the principle of Occams razor (Hommel, 2015). When attention to the S–non-R link increases, this will automatically reduce attention to the target S–R link. The next target cue will, however, shift this balance again.

The activation hypothesis of the IC P3no-go$_{early}$ implies that this component is understood as the activation of a sub-dominant working memory representation. Like the IC P3no-go$_{early}$, working memory function is highly affected by fluctuations in catecholamine activity in the prefrontal cortex (Arnsten, 2013), and the present results are therefore in accordance with literature documenting that MPH improves working memory function (Arnsten & Dudley, 2005; Coghill et al., 2014; Ilieva, Hook, & Farah, 2015; Mehta, Goodyer, & Sahakian, 2004). More specifically, optimal availability of norepinephrine in prefrontal cortex has been shown do increase neuronal responses to relevant representations, whereas dopamine reduces firing to irrelevant representations (Gamo & Arnsten, 2011). As MPH affects the availability of both of these catecholamines, studies using selective norepinephrine and dopamine agents are needed to disentangle their relative contributions to the effect on the IC P3no-go$_{early}$ observed in this study.

Importantly, however, the MPH effect in this study cannot be expected in all other tasks eliciting P3 components, as these involve different S–R characteristics and levels of pre-activation. Due to such differences, tasks inducing less (or more) pre-activation of S–R links may show different MPH effects on the P3s elicited from those tasks. For instance, Wessel (2017) has shown the level of pre-potency affects the no-go P3 amplitude, with less pre-potency being associated with smaller amplitudes. This difference may be crucial for whether one finds an MPH effect on different P3 component amplitudes.

4.2. The no-go P3 and monitoring

Most theories of the no-go P3′s function that do not interpret the component as reflecting response inhibition or cognitive inhibition regard the most probable function of the component as related to some type of monitoring. It has been suggested that monitoring in the no-go condition involves monitoring whether inhibition was successful (outcome monitoring; see review by Huster, Enriquez-Geppert, Lavallee, Falkenstein, & Herrmann, 2013). We would argue, however, that outcome monitoring in the no-go condition is redundant. A system that can identify relevant characteristics of incoming stimuli and activate their corresponding S–R links would not need an additional process to evaluate the correctness of this categorization. In both correct and error trials, however, there may be a need for adjusting response thresholds, and this adjustment may need to be larger if the pre-potency of the wrong response was high, or if the wrong response was executed.

In the introduction, we argued that a monitoring function in the no-go condition should covary with the rate of commission errors, as better response threshold adjustments should result in fewer premature responses. Like all behavioral parameters, however, commission errors

may occur for a number of reasons beyond poor monitoring of response threshold. Improvements in monitoring should, however, be related to reduced error rates. We therefore only investigated whether intra-individual *changes* in commission errors were related to corresponding changes in either of the two identified no-go P3 sub-components. These results revealed that only intra-individual variation in the IC P3no-go$_{late}$, but not the IC P3no-go$_{early}$, was significantly related to the corresponding variation in commission error rate. These results support our hypothesis that the type of monitoring activated in successful no-go trials is not affected by MPH, and that this monitoring function is probably reflected in the IC P3no-go$_{late}$ and not the IC P3no-go$_{early}$. As the effect of MPH on the IC P3no-go$_{late}$ was non-significant, we maintain the null hypothesis that MPH does not affect monitoring in the no-go condition.

4.3. Time-on-task effects

Mean scores from long-lasting tasks cannot demonstrate whether an observed group difference can be explained by differential time-on-task effects, or whether the group difference is already present at the beginning of the task. It was therefore important to investigate whether time-on-task effects could explain the MPH effect on the no-go P3 before interpreting the present results. This possibility was ruled out, as the results did not demonstrate any significant modulation of the MPH effect by time-on-task for neither the IC P3no-go$_{early}$ nor IC P3no-go$_{late}$. The few studies that have previously employed time-on-task designs to study sustained attention in ADHD populations have found mixed results regarding whether sustained attention really is impaired in ADHD populations (Dekkers et al., 2017; Johnson et al., 2007; van der Meere, Shalev, Borger, & Gross-Tsur, 1995) and whether such time-on-task effects are reduced in response to MPH (Lufi, Bassin-Savion, & Rubel, 2015; van der Meere et al., 1995). It is therefore questionable whether time-on-task effects are really central to understanding ADHD or MPH effects, although some such effects may exist in some tasks or under some task conditions. Either way, such effects do not seem to be central in explaining the MPH effect on the IC P3no-go$_{early}$ found in this study. Rather than considering sustained attention to be a continuous process of increasing inattention over time, some researchers have related this concept to *fluctuations* in attentiveness (attentional lapses) over time. This perspective has produced promising results in the study of sustained attention in ADHD (e.g. Yordanova et al., 2011). A future approach could therefore be to investigate whether trial-to-trial variability in no-go P3 amplitude is reduced in response to MPH, and whether this may underlie the observed effect of MPH on the averaged component.

4.4. ICA-decomposition validity

Temporal concatenation of the ICA input data holds the assumption that a component will have identical scalp distribution across subjects, an assumption which is violated to some degree due to such factors as differences in cortical folding and electrode placement (Huster, Plis, & Calhoun, 2015). Another factor that could violate this assumption is that maturation or MPH could lead to topographical changes in components. In the present study, such factors could reduce the accuracy of the decomposition. Despite the possible effects of development and medication on no-go P3 topography, the ICA decomposition resulted in two no-go P3 sub-components with characteristics similar to those previously identified using the same method in adults, giving some indication that the results are not coincidental. One component was centrally distributed with a shorter latency than the second component,

which had a distribution that also spread to more frontal regions.

Furthermore, as ICA is a *blind* source separation method with a predefined number of resulting components, it could, principally, end up with any kind of result – meaningful or not. Components identified by ICA should therefore be validated against external, ICA-independent, measures, such as the differential medication effects in this study. It may also be reassuring to know that the two no-go P3 sub-components, including the differential medication effects, can be discerned in the raw ERP – the input data for the ICA in this study (see left panel in Fig. 1). When plotting the individual latencies of the no-go P3 at Fz and Cz against the latencies of the ICs, one can observe high correspondence between the IC P3no-go$_{late}$ and Fz latencies, whereas the latency at Cz falls in-between that of the IC P3no-go$_{early}$ and IC P3no-go$_{late}$ (see Appendix A). The same pattern of correlations can be observed for the amplitudes. In one of our previous studies (Brunner et al., 2015) we have, however, demonstrated how meaningful relationships between behavior and ERP components may disappear when only examining raw ERPs. Therefore, when ICA-derived components have been validated against external standards and found to give meaningful results, these components may be used to uncover brain-behavior relationships that are occluded in the mixed raw signal, producing low replicability of results and null-findings where meaningful underlying relationships exist.

4.5. Study limitations

No placebo control or cross-over design was employed in the present study, implying that the observed effect on the IC P3no-go$_{early}$ could be influenced by knowing when one receives medication, as well as by training effects. The no-go P3 effect was different for children reported to be responders versus non-responders in our previous study (Øgrim et al., 2016), which is at least an indication that general training effects do not seem to be sufficient to explain the present results. Potential placebo effects cannot, however, be ruled out. The possibility

that the present results could be explained by placebo effects acting specifically on the IC P3no-go$_{early}$, leaving the IC P3no-go$_{late}$ relatively unaffected, is still quite intriguing. Also, if this is the case, the present findings still indicate that the two no-go P3 sub-components are functionally different, supporting the overarching objective of investigation in the present study.

6. Conclusions

The no-go P3 component in children diagnosed with ADHD can be dissected into two sub-components. In medication responders, MPH only affects the early and not the late sub-component. These results demonstrate that the two identified sub-components seem to not only be separable by ICA in terms of their independent time courses, but they are also modulated by different mechanisms. In contrast to interpreting the early component as an inhibition or monitoring process, as has been common in the literature on the no-go P3, we suggest that this component may reflect activation of a sub-dominant S–R representation, which is facilitated by MPH in medication responders. As the MPH effect on this component predicts reductions in ADHD symptoms as reported by parents and teachers, the present findings indicate that an ERP component measured in the laboratory, can teach us important lessons about factors affecting function in everyday life.

Conflict of interest

None. ClinicalTrials.gov. Identifier: NCT02695355.
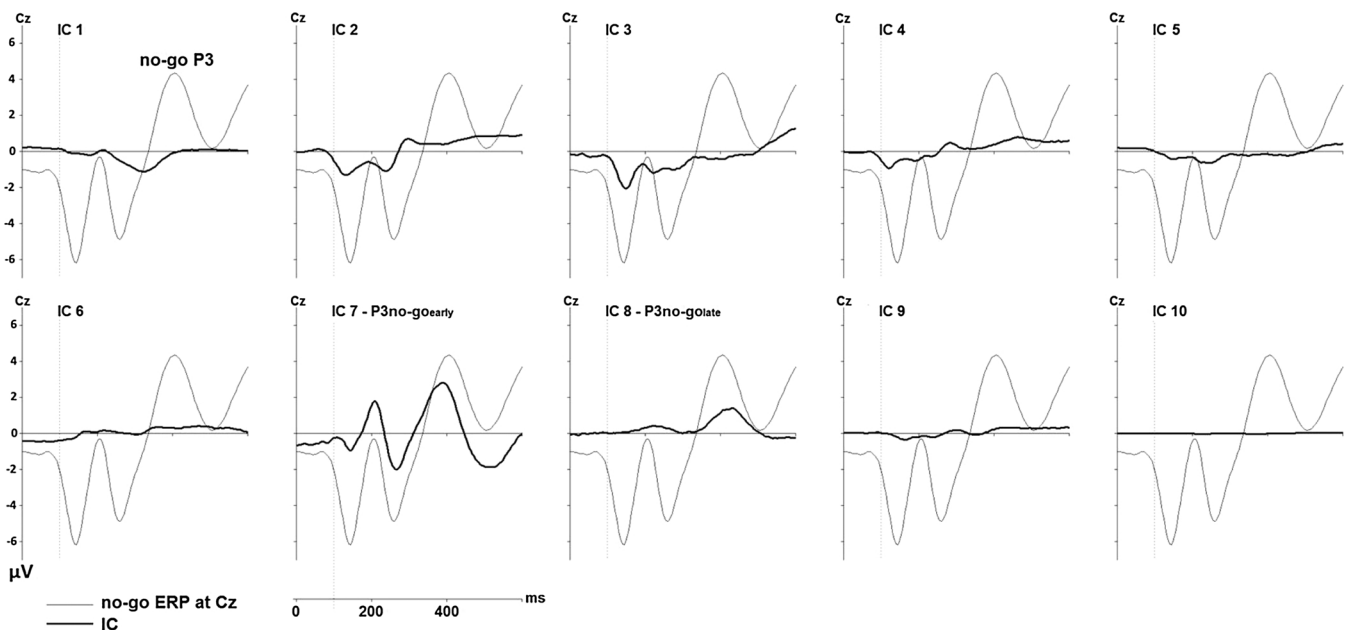
Appendix A

Fig. A1. Independent components back-projected to Cz.
The thin line shows the raw no-go P3 collapsed across participants and sessions at the Cz electrode. The thick lines show the contribution of each of the ten largest ICs to the ERP at Cz.
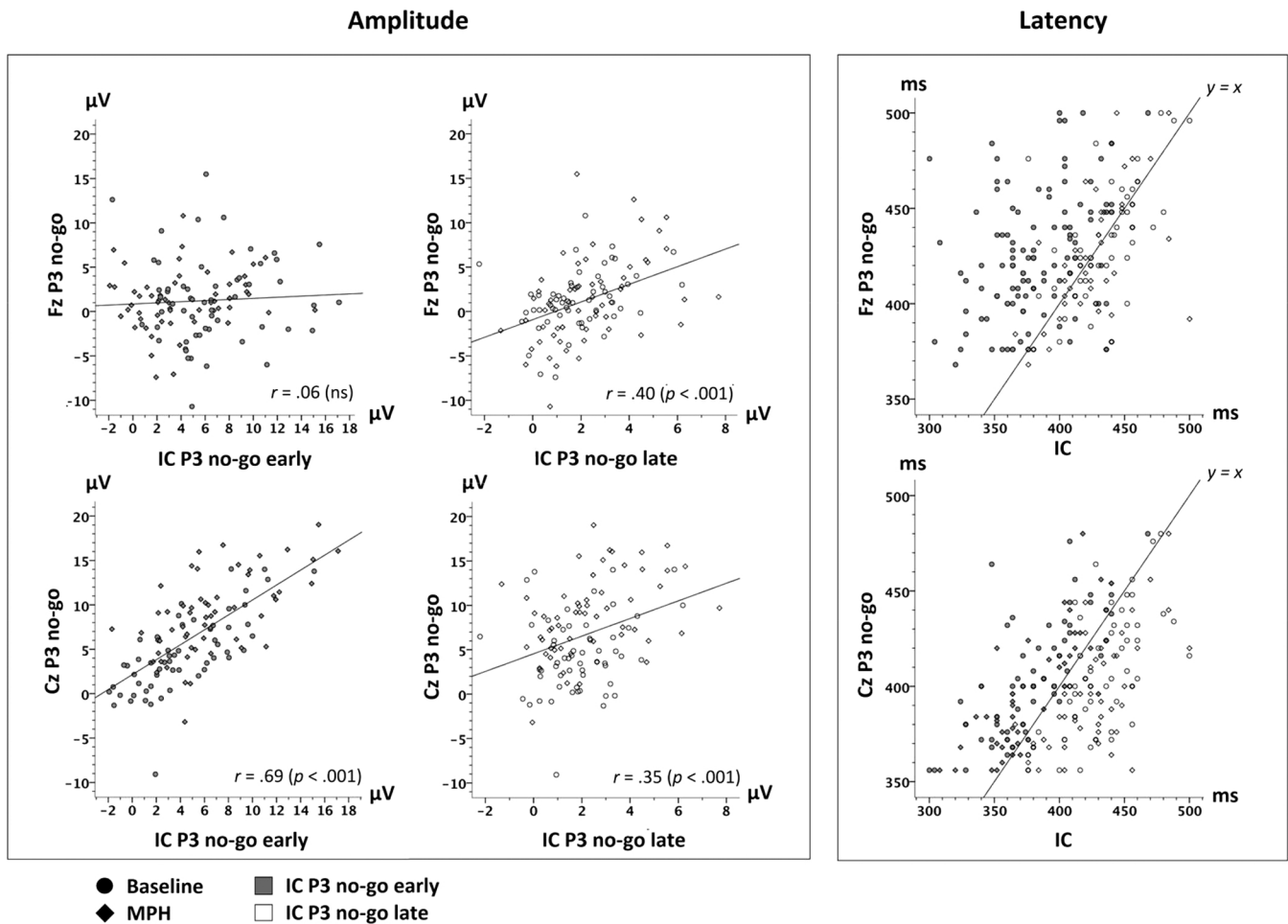
Amplitude

Latency

● **Baseline** ■ **IC P3 no-go early**
◆ **MPH** □ **IC P3 no-go late**

Fig. A2. The relationship between the raw no-go P3 (y-axis) and ICA derived sub-components (x-axis). Circles reflect values at baseline; diamonds reflect values on MPH. Lines represent regression lines for amplitudes and identity lines (y = x) for latencies. Left: Raw no-go P3 and IC P3no-goearly amplitudes at Fz (upper panel) and Cz (lower panel). Middle: Raw no-go P3 and IC P3no-golate amplitudes at Fz and Cz. Right: Raw no-go P3 and IC P3no-goearly (dark grey) and IC P3no-golate (white) latencies at Fz and Cz.

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