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Bereitschaftspotential and lateralized readiness potential in children with attention deficit hyperactivity disorder: altered motor system activation and effects of methylphenidate

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Abstract
Attention deficit hyperactivity disorder (ADHD) has been linked to abnormal functioning of cortical motor areas such as the supplementary motor area, the premotor cortex and primary motor cortex (MI). The Bereitschaftspotential (BP) and lateralized readiness potential (LRP) are movement-related potentials generated by cortical motor areas. We hypothesized that the BP and LRP would be altered in children with ADHD. A group of 17 children with ADHD (mean age: 11.5 ± 1.9 years) and a control group of 16 typically developing children (mean age: 12.2 ± 2.0 years) performed movements at self-chosen irregular intervals while a 64-channel DC-EEG was registered. BP and LRP were calculated from the EEG. The ADHD group had significantly lower and on average positive BP amplitudes at Cz. In agreement with age-dependent maturation effects the LRP had a positive polarity in both groups, but lower amplitudes were found in

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the ADHD group without medication. The control group showed a mid-central negativity and a positivity over motor areas contra-lateral to the side of movement, whereas no negativity over Cz and a more diffuse positivity was found in the ADHD group. LRP group differences diminished after MPH administration as indicated by an interaction between group and time of measurement/medication. The cortical motor system shows altered functioning during movement preparation and initiation in children affected by ADHD. Positive Bereitschaftspotential polarities may represent delayed cortical maturation. Group differences of LRP were pharmacologically modulated by the catecholaminergic agent MPH.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder occurring in childhood with a prevalence of approx. 5% (Polanczyk et al., 2007). ADHD is characterized by inattentiveness, impulsive behavior and motor hyperactivity (American Psychiatric Association, 2013).

Several widespread neural networks including, among others, structures such as the pre-frontal cortex, basal ganglia and cerebellum have been implicated in the pathology of ADHD (Castellanos and Proal, 2012; Makris et al., 2009). While there is also evidence for altered functioning of cortical motor areas in ADHD, this system remains relatively understudied (Castellanos and Proal, 2012). The cortical motor system, which includes the primary motor cortex (MI), premotor cortex and the supplementary motor area (SMA) is not only involved in basic execution of movements but also plays an important role in higher-order processes like the linking of perception and stimuli to goal-directed behaviors and decision making regarding action execution (Rizzolatti and Luppino, 2001). Also, behavioral inhibition and therefore regulation of impulsive behavior crucially involves the supplementary motor area (SMA) and the premotor cortex (Bari and Robbins, 2013). Thus, dysfunctions in the motor system may potentially explain disturbances in basic motor functions but also contribute to more complex behavioral phenomena like impulsive actions in ADHD.

The Bereitschaftspotential (BP) is an event-related potential reflecting cortical activity associated with the initiation and preparation of voluntary motor actions. BP is characterized by a slow negative EEG-deflection in frontal and central leads preceeding self-initiated movements (Kornhuber and Deecke, 1965; Shibasaki and Hallett, 2006). The initial slowly ascending segment of the BP called early BP is localized at midline centro-parietal electrodes irrespective of movement side. EEG (Cui et al., 1999; Praamstra et al., 1996; Toma et al., 2002) and MEG (Deecke et al., 1982; Erdler et al., 2000) based source localization, functional MRI data (Toma et al., 2002), intracranial recordings in humans (Ikeda et al., 1992; Yazawa et al., 2000) and single cell recordings in primates (Okano and Tanji, 1987) identified the bilateral SMA, including pre-SMA the SMA-proper as the generator of early BP. The steeper second part of the BP is named late BP and shows a more lateralized scalp distribution (Shibasaki and Hallett, 2006). It is generated unilaterally in premotor cortex and primary motor cortex areas contralateral to the side of movement (Ikeda et al., 1992; Yazawa et al., 2000). In order to study asymmetrical aspects of BP associated with unilateral movements the lateralized readiness potential (LRP) has been developed. This measure reflects mostly activity in motor areas contralateral to the movement side and is closely tied to the execution of the movement (Coles, 1989; Eimer, 1998). BP and LRP together with related measures are subsumed under the term movement-related potentials (Jahanshahi and Hallett, 2003).

Few studies have examined BP in children. Developmental studies comparing different age groups found that BP is absent or shows opposite (i.e. positive) polarity in young children. With increasing age continuously more negative BP amplitudes develop into the wave forms known in adults (Chiarenza et al., 1995; Warren and Karrer, 1984). To our knowledge, the only study of self-initiated movements in children with ADHD found a trend towards reduced BP amplitudes in children with ADHD (Rothenberger et al., 1986). Reduced BP amplitudes have also been found in adults with ADHD performing self-initiated movements (Seo et al., 2013). Further support for altered functioning of cortical motor areas can be found in contingent negative variation (CNV) studies, which investigate externally cued and triggered movements. The CNV reflects motor preparation closely related to BP but also other cognitive processes like an orienting response and anticipatory attention to an expected stimulus (Bender et al., 2004; Brunia and Van Boxtel, 2001). Reduced CNV amplitudes have repeatedly been found in ADHD with varying methodologies in children (Albrecht et al., 2014; Banaschewski et al., 2008; Bluschke et al., 2018; Khoshnoud et al., 2018) and adults (Ehlis et al., 2018; Mayer et al., 2016; Michelini et al., 2018), but there have also been conflicting results (Dhar et al., 2010; Spronk et al., 2008).

Considering the role of motor functions in ADHD and the neural structures involved in generating BP and LRP the study of these movement-related cortical potentials can further the understanding of ADHD pathology. We therefore investigated BP and LRP in a group of children with ADHD and a matched unaffected control group. We hypothesized that BP and LRP would differ between ADHD and controls. We further hypothesized that methylphenidate would influence BP and LRP in the ADHD group.

2. Experimental procedures

2.1. Subjects

We recruited 20 children with ADHD and 20 healthy control children. Out of originally 20 data sets in each group, 3 in the ADHD group and 4 in the control group had to be excluded due to recording errors or excessively artifact contaminated data. Therefore,

data of 17 children with ADHD and 16 control children were analysed. The control group was matched to the ADHD group for age (controls: 12.2 ± 2.0 years; ADHD: 11.5 ± 1.9 years, $p = 0.35$.) gender (controls: 11 male, 5 female; ADHD: 12 male, 5 female) and IQ (controls: 114.5 ± 11.8; ADHD: 110.1 ± 20.0; $p = 0.44$). All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The sample of subjects in this study was previously published in an article reporting post-imperative negative variation (PINV) in a CNV paradigm (Werner et al., 2011).

The ADHD group was recruited at the Department of Child and Adolescent Psychiatry of the University of Heidelberg and a local child psychiatrist's practice. Children in the ADHD group met the DSM-IV criteria of ADHD of hyperactive or combined subtype. Diagnoses were made by experienced physicians and were confirmed using a standardized semi-structured diagnostic interview (K-SADS, (Delmo et al., 2000)). Children who suffered from other major psychiatric disorders (e.g. psychosis, major depression, bipolar disorder, autism spectrum disorder) or neurological disorders (e.g. epilepsy, migraine, history of severe head trauma, tic disorder) were excluded from this study. Common comorbidities of ADHD, which were considered unlikely to influence motor system results (specific learning disabilities, conduct disorder and oppositional defiant disorder), were not excluded. Therefore, we cannot discard the possibility that our results may have been confounded by these comorbidities. Children in the control group were recruited through newspaper advertisements. Participants in the control group had no history of psychiatric or neurological disorders and were not taking any psychotropic medication. Children in both groups had an IQ over 80 as measured by a short form of the German version of WISC-III (HAWIK-III (Schallberger, 2005)).

The study was approved by the local ethics committee. All participating children and their parents provided written informed consent according to the Declaration of Helsinki.

2.2. Procedures

Subjects were instructed to make voluntary self-paced opposition movements with their thumb at irregular time intervals. Movements were performed in two separate blocks for right sided and left sided movements, respectively. Movements had to be clearly separated from each other and any temporal rhythm was to be avoided so that each movement required a new decision to move. Participants fixated a cross on a computer screen in order to minimize eye movement artifacts. Children were observed by an EEG assistant (blind to the study hypotheses) who counted movements. The procedure was stopped after approx. 50 movements had been completed with each hand. This procedure was performed twice (T1 and T2): In the control group both T1 and T2 were performed with subjects drug-free. In the ADHD group, T1 was drug-free (at least 24 h after the last intake of MPH), while T2 was recorded 70 min after the intake of the individually prescribed dose of MPH. 11 subjects received extended release preparations with a mean dosage of 32.5 mg (0.8 mg/kg body weight) and 6 subjects received immediate release preparations with a mean dosage of 15.0 mg (0.4 mg/kg body weight).

2.3. EEG and EMG recording

A 64-channel DC-EEG was recorded during the procedure. The EEG was recorded with an elastic EEG-cap (Easycap GmbH, Germany) with an equidistant 64-electrode montage in which Cz, C3 and C4 corresponded to the international 10–20 system. The vertical and horizontal electrooculogram (EOG) was recorded with electrodes 1 cm next to the outer canthi and below the left eye. The recording system consisted of Neuroscan Synamp Amplifiers (Neuroscan Inc., USA) and Brain Vision Recorder software (Brain Products, Germany). The sampling rate was 500 Hz. An anti-aliasing filter (low-pass) was set at 70 Hz. Electrode impedances were kept below 5 kΩ. Data were recorded against a reference located halfway between Cz and FCz and transformed offline to average reference.

In addition to the EEG, we recorded electromyograms (EMG) on both hands as a trigger for movement onset. The active electrode was placed on the thenar eminence and a reference electrode was placed on the basal phalanx of the middle finger.

2.4. Data pre-processing

Trials were segmented according to movement onset (time point 0 ms) in the EMG. Trials were segmented to create time windows from 4000 ms before (−4000 ms) to 4000 ms after movement onset for further analysis. The time segment of −2000 to −1500 ms served as the baseline. We assured by visual inspection of individual and group grand averages that this baseline was before the onset of the BP in all subjects, i.e. the negative deflection always started later. In order to exclude contamination of the baseline with potentials related to the previous movement only trials without movement within the time window from −2000 to 0 ms were included in the averages.

The EEG signal was corrected automatically for DC-drifts by linear regression (Brain Vision Analyzer, Brain Products GmbH, Germany), and for eye movements and blinks by the algorithm described by Gratton et al. (1983). Artifacts were rejected automatically if the difference of two values in the segment exceeded 150 mV. This procedure was confirmed by visual inspection by an EEG-technician blind to the study hypotheses and only artifact-free trials entered further analysis.

2.5. Analysis of electrophysiological parameters

The BP amplitude was calculated as the mean amplitude from −1000 ms to 0 ms at electrode Cz.

The lateralized components of the BP can be studied by calculating the LRP, which reflects only lateralized activation contralateral to the movement and eliminates all symmetrical processes. LRP was calculated using the formula *LRP = (C4(left) - C3(left) + C3(right) - C4(right)) / 2* (Coles, 1989) with left and right referring to the respective movement side. As both hemispheres are taken into account in this calculation, the result is only one channel. LRP was also measured as the mean amplitude in the time window −1000 ms to 0 ms. In addition to electrode pairs C3/C4 LRP was also calculated in an analogous manner for C5/C6 and Cp3/Cp4. The results of each of the three electrode pairs were then averaged so that LRP reflects mainly activity in primary motor areas as the electrical dipoles generated at the top and the posterior wall of the precentral gyrus project to these surface electrodes. However, because of the relatively low spatial resolution of the EEG premotor cortex activation also influences LRP amplitudes.

EMG amplitudes were measured in order to control for movement intensity and lateralization. For the EMG analysis mean amplitudes of the rectified EMG were measured in the time window of −5 ms to 10 ms, as this window covered the ascent and decline of the EMG signal associated with the thumb movement. In order to assess whether LRP effects were based on differences in the laterality of movement intensity as measured by EMG, we calculated a measure analogous to the LRP for the EMG (lateralized EMG = (EMG right hand in right side movement -EMG left hand in right side movement) + (EMG left hand in left hand movement -EMG right hand in left side movement) / 2)).

2.6. Statistical analysis

The dependent variables BP and LRP were normally distributed according to Kolmogorov-Smirnov-Test (all $p > 0.20$).

To test for differences between groups and effects of medication we used repeated-measures ANCOVAs. The repeated-measures ANCOVA for BP included the between-subject factor GROUP (ADHD vs. controls) and the within-subject factors MOVEMENT SIDE (left vs. right hand) as well as TIME/MEDICATION (T1 vs. T2) and the covariates AGE and GENDER.

For the LRP a repeated-measures ANCOVA was calculated with the between-subject factor GROUP (ADHD vs. healthy controls) and the within-subject factors TIME/MEDICATION (T1 vs. T2) and the covariates AGE and GENDER. Significant interactions in the ANCOVA were subsequently further examined by post-hoc tests (Duncan's test). Group differences in movement intensity were assessed with a repeated-measures ANOVA with the between-subject factor GROUP and the within-subject factor MOVEMENT SIDE for the dependent variable EMG amplitude.

Regression coefficients were calculated to assess the impact of AGE on BP and LRP.

As lateralized EMG was not normally distributed, group differences for lateralized EMG were assessed by Mann-Whitney-U test and correlations by Spearmanś correlation.

3. Results

3.1. EMG activity

No significant group differences regarding EMG amplitude were detected (main effect group ($F(1; 31) = 0.34$, $p = 0.57$)).

3.2. Bereitschaftspotential

Visual inspection of data showed a slowly ascending ERP starting approximately 1000 ms before movement onset located in central leads in the control group, which we identified as BP. The grand average of the ADHD group showed a markedly less negative and mostly positive potential. Topographic maps showed a negativity located around Cz in the control group. In the ADHD group there was no negativity around Cz, and a more anteriorly located negativity was observed. In both groups a positivity over lateral motor areas contra-lateral to the side of movement was observed. Grand averages and topographies of brain electrical activity in both groups are shown in Fig. 1.

An ANCOVA for BP amplitude at Cz with the between-subject factors GROUP and within subject factors TIME/MEDICATION and MOVEMENT SIDE and covariates AGE and GENDER yielded a significant main effect for GROUP (F (1; 29) = 13.7; $p = 0.001$) and a nearly significant trend for the covariate AGE ($F(1; 29) = 1.4$; $p = 0.06$). When one outlier (see Fig. 2) in the control group with a BP amplitude of -8.75 μV (more than 2 SD above the mean) was removed, the effect of the covariate AGE turned significant (F (1; 28) = 5.8; $p = 0.02$), while the main effect for GROUP remained unaffected (F (1; 28) = 11.0; $p = 0.003$). In detail, regression coefficients for the prediction of BP by AGE (calculated without the above mentioned outlier) were (mean $\pm$ standard error): BP movement left T1 b = -0.27 ± 0.25 μV/year, BP movement right T1 b = -0.40 ± 0.21 μV/year, BP movement left T2 b = -0.14 ± 0.16 μV/year, BP movement right T2 b = -0.55 ± 0.28 μV/year. The gradients were to small for the age difference of 0.7 years to sufficiently explain group differences for BP.

The main effect for GROUP was explained by smaller (less negative) BP amplitudes in the ADHD group compared to controls. The main effect remained significant, when the covariates AGE and GENDER were removed, it thus did not depend on any of the covariates. Absolute mean values of BP were positive in the ADHD group (Table 1).

There were neither main effects for TIME/MEDICATION ($F(1;29) = 0.02$; $p = 0.88$) nor a significant GROUP X TIME/MEDICATION interaction ($F(1; 31) = 1.4$; $p = 0.25$).

3.3. Lateralized readiness potential

An ANCOVA for the dependent variable LRP with the between-subject factors GROUP and the within-subject factor TIME/MEDICATION with covariates AGE and GENDER showed no significant main effect for GROUP ($F(1; 29) = 1.04$; $p = 0.31$). However, there was a significant GROUP X TIME/MEDICATION interaction ($F(1; 29) = 5.3$; $p = 0.03$). Post-hoc Duncan's tests showed a significant difference between groups at T1 ($p = 0.0498$) but not at T2 ($p = 0.32$). There was a trend towards a difference between T1 and T2 for the ADHD group ($p = 0.08$) with the LRP increasing from T1 to T2. In the control group LRP amplitudes decreased nominally from T1 to T2 but the difference was not statistically significant ($p = 0.11$). The interaction effect remained significant when the covariates were removed, so the effect did not depend on any of the covariates. Mean LRP values were positive in both groups. Topographic maps displayed a positivity over motor cortices contra-lateral to the movement side in the control group, whereas a more diffuse and less lateralized positivity was observed in ADHD (Fig. 1). Means and standard deviations of the LRP amplitudes are shown in Table 1.

There was no significant effect of the covariate AGE (Fig. 3). Regression coefficients for the prediction of LRP by AGE were (mean $\pm$ standard error) $b = -0.05 \pm 0.17$ μV/year at T1 and $b = -0.31 \pm 0.15$ μV/year at T2.

There was no group difference for lateralized EMG ($U = 132.0$; $p = 0.90$) and no correlation between lateralized EMG and LRP (rho = 0.10; $p = 0.58$). Thus, the LRP effects do not depend on the lateralization of movement intensity.

4. Discussion

In this study we examined neural correlates of motor control in a sample of children with ADHD and an age matched control sample of unaffected children by measuring the BP and LRP.

4.1. Altered BP and ADHD

A primary result of this study is altered neural activity related to the planning and initiation of voluntary self-paced

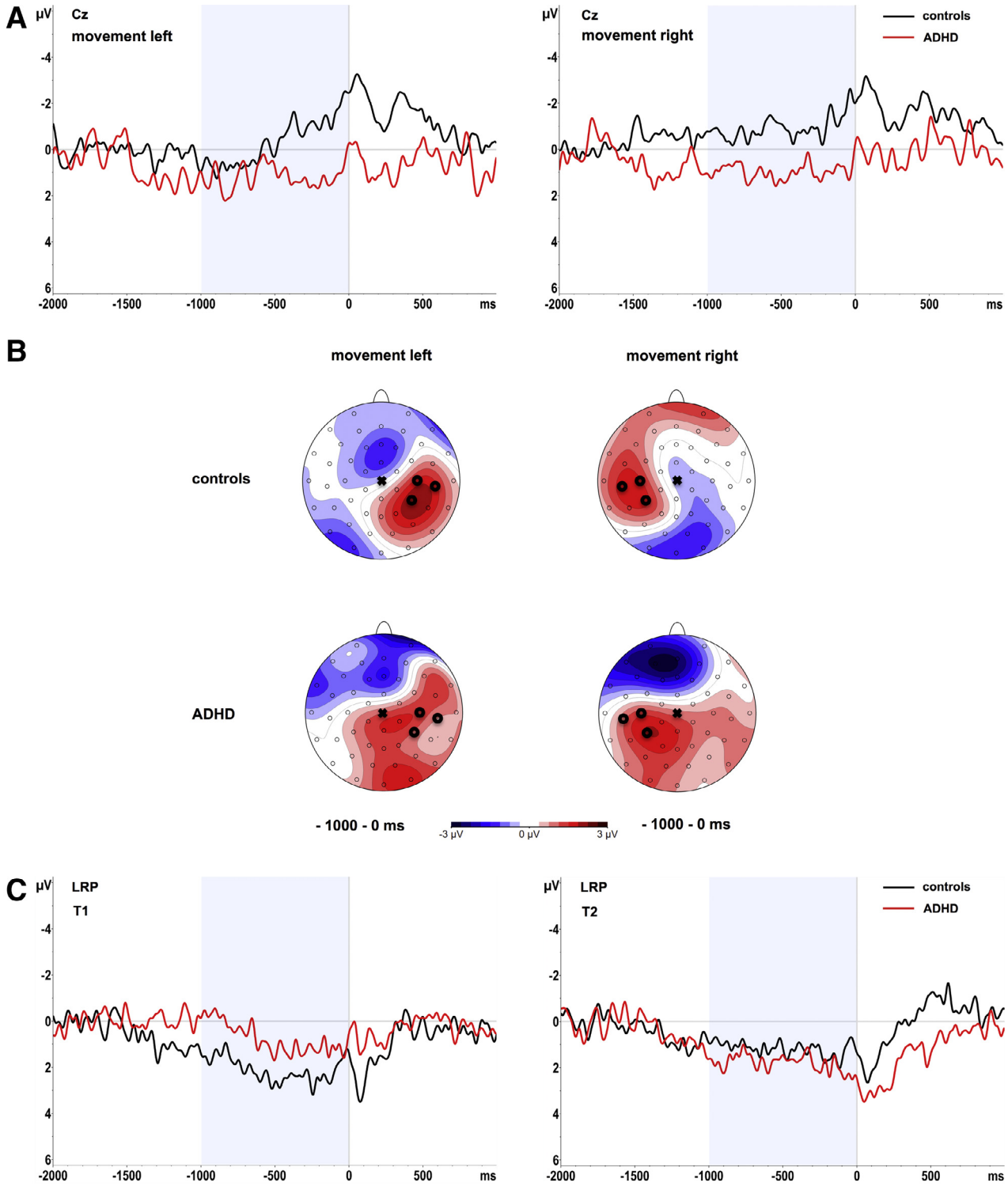

Fig. 1 (A) Grand averages of BP at electrode Cz at T1 in the control group (black) and the ADHD group (red) for left and right hand movements. BP is measured as the mean amplitude in the time window from −1000 to 0 ms. A 20 Hz low-pass filter was applied for better visualization. (B) Topographic maps for the time window −1000 ms to 0 ms for both groups and both movement sides. Crosses mark the location of electrode Cz used to calculate BP. Circles mark the location of electrodes C3, C5 and Cp3 for right hand movements and C4, C6 and Cp4 for left hand movements. These electrodes were used to calculate the LRP. (C) Grand averages of the LRP in the control group (black) and the ADHD group (red) at T1 and T2. LRP channels are calculated from the mean of the LRPs of electrode pairs C3-C4, C5-C6 and Cp3-Cp4. A 20 Hz low-pass filter was applied for better visualisation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

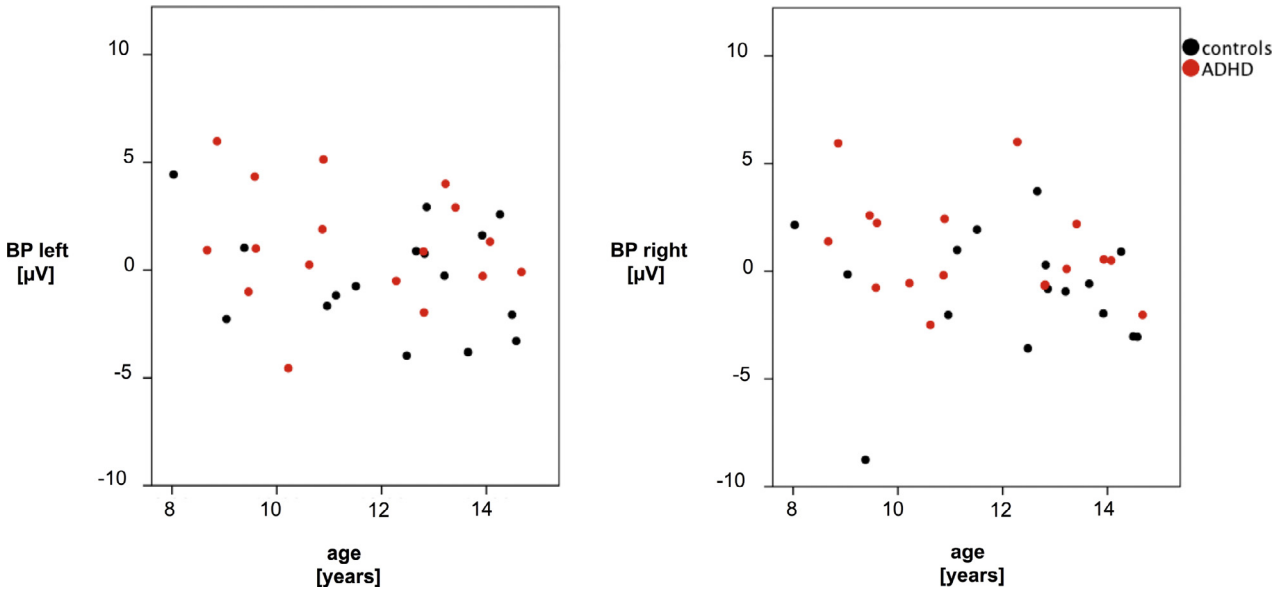

Fig. 2 Scatter plots of age and BP amplitudes in both groups for left and right hand movements.

Table 1 Means ± standard deviations of BP amplitudes for left and right sided movements and LRP amplitudes for the control group and the ADHD group at both measurement time points (T1 and T2).

	Movement	T1		T2	
		Controls	ADHD	Controls	ADHD
BP (µV)	Left	−0.3 ± 2.5	1.2 ± 2.7	−1.3 ± 2.1	0.9 ± 1.3
	Right	−0.9 ± 2.9	1.0 ± 2.4	−1.4 ± 1.9	1.8 ± 3.8
LRP (µV)		2.3 ± 1.7	0.8 ± 2.1	1.4 ± 1.3	1.8 ± 2.2

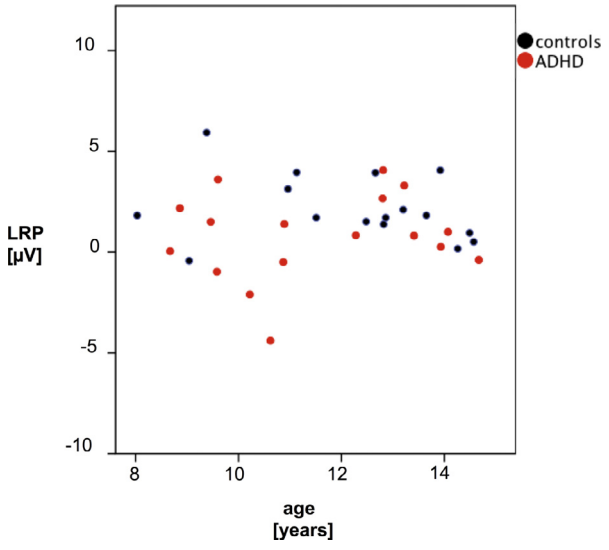

Fig. 3 Scatterplot of age and LRP amplitudes in both groups. There was no significant effect for the covariate AGE. A tendency is visible towards mean negative LRP amplitudes for subjects above twelve years, while younger subjects showed mean positive LRP with higher variability.

movements in ADHD. We found that amplitudes of BP at Cz were markedly lower in the ADHD group compared to unaffected controls. Topographic maps showed a mid-central negativity in the control group. In the ADHD group there was no negativity at Cz. ADHD subjects displayed a frontal/fronto-polar negativity, which was localized too anteriorly to reflect SMA activity. We did not analyse this negativity any further, as there was no hypothesis with regard to this area.

As BP assessed at central sites primarily reflects activity in the bilateral SMA (Ikeda et al., 1992; Shibasaki and Hallett, 2006; Yazawa et al., 2000), our findings of reduced BP suggest altered functioning of cortical areas, which constitute part of the cortical motor system. This neural system is not only implicated in basic motor functions but also in more complex behavioral processes such as volitional processes (Damasio, 1985; Goldberg, 1985), inhibition of behavior (Bari and Robbins, 2013; Simmonds et al., 2008) and motivation to act based on reward dependent reinforcement learning (Scangos and Stuphorn, 2010), which are relevant to ADHD.

While many neurobiological theories of ADHD focus on altered structure and function of prefrontal cortical areas, fronto-striatal circuits and the cerebellum (Dickstein et al., 2006; Krain and Castellanos, 2006) there is also compelling evidence linking dysfunction of cortical motor areas to ADHD. In conformity with our results a study of BP in adults also found reduced amplitudes in adult ADHD subjects (Seo et al., 2013). While the adults in this study showed reduced BP under stimulant medication, our results at T1 were obtained in medication-free children, showing that reduced BP is not a medication artifact. To our knowl-

edge, the only previous study of BP in a small group of children with ADHD also reported a trend towards decreased BP amplitudes (Rothenberger et al., 1986). Studies investigating motor preparation using CNV paradigms also reported reduced amplitudes in children (Albrecht et al., 2014; Banaschewski et al., 2008; Bluschke et al., 2018; Khoshnoud et al., 2018; Sartory et al., 2002) and in adults with ADHD (Ehlis et al., 2018; Mayer et al., 2016), although some studies found no group differences (Dhar et al., 2010; Spronk et al., 2008). Interpretation with respect to motor activity is complicated by the fact that CNV is confounded by non-motor cognitive processes (Brunia, 2003; Brunia and Van Boxtel, 2001), which may vary across the paradigms used in different studies. As BP in self-initiated movements excludes influences of processes related to stimulus processing and attention our results of BP in self-initiated movements provide more unequivocal evidence of an involvement of motor functions in ADHD.

In line with our findings MRI studies have found structural alterations of higher-order motor areas including the SMA (Duerden et al., 2012; Mostofsky et al., 2002) and functional hypoactivity in the SMA in ADHD (Cortese et al., 2012). Thus, our results add evidence to data showing altered structural and functional abnormalities in supplementary motor areas.

4.2. Positive BP as a correlate of altered brain maturation

While BP is a very robust phenomenon with a usually negative polarity in adult populations (Shibasaki and Hallett, 2006), the ADHD group in our study had an average positive BP polarity. Similar results have previously been found in young children with and without neurodevelopmental disorders. In typically developing children of approx. 7 years of age the negative deflection representing BP at frontal and central electrodes is absent, while a positive rather than negative potential is observed in children below that age (Chiarenza et al., 1995; Warren and Karrer, 1984). Comparable findings were reported for externally triggered movements (Perchet and Garcia-Larrea, 2005). Therefore, reduced or even positive BP amplitudes may be interpreted as correlates of a maturational delay in frontal cortical areas. In accordance with this concept BP amplitudes tended to become more negative in both groups of our sample as would be expected based on findings in unaffected children (Warren and Karrer, 1984).

ADHD is associated with atypical brain development (reviews in Friedman and Rapoport, 2015; Rubia, 2007). Trajectories of structural maturation run at a lower level but in parallel between ADHD and control subjects for the majority of brain regions (Castellanos et al., 2002). A prominent maturational delay was reported in the frontal cortex including higher-order motor areas in a large longitudinal structural MRI study (Shaw et al., 2007).

Longitudinal investigations of CNV show that alterations in ADHD persist through development into adulthood (Doehnert et al., 2013) arguing against a mere developmental delay. In this context, our findings of altered BP in children with ADHD together with findings in adults with ADHD (Seo et al., 2013) may reflect delayed developmental trajectories potentially leading to persisting functional alterations in adults.

An alternative explanation for lower BP amplitudes may be lower levels of intentionality (Lang, 2003), i.e. more involuntary or unplanned movements in children with ADHD. However, it seems unlikely that low intentionality alone would account for the opposite polarity of BP in the ADHD group.

4.3. Altered LRP at baseline

We found lower LRP amplitudes in the ADHD group compared to controls at baseline when both groups were not medicated. A more diffuse and less clearly lateralized positivity could be seen in the ADHD group. More diffuse topographies have previously been described in other ERP measures in ADHD (e.g. Kröger et al., 2014) possibly related to diffuse compensatory brain activity (Ma et al., 2012). Also, findings of altered lateralized activity in the premotor cortex and the primary motor cortex were reported in medication-free ADHD children performing externally triggered movements (Banaschewski et al., 2008; Bender et al., 2012; Steger et al., 2000; Yordanova et al., 1996) and in young adults with ADHD (Bozorgpour et al., 2013). Congruent findings of reduced activation of the primary motor cortex were found in fMRI investigations during self-initiated motor actions in children (Mostofsky et al., 2006) and also in adults with ADHD (Valera et al., 2010). In summary, our group effects for the LRP point to alterations in the functioning of lateral motor cortical areas in ADHD in self-initiated movements in addition to the existing literature on externally triggered actions.

4.4. Positive LRP and brain maturation

Measurement of LRP as performed in this study using the formula according to Coles (1989) usually yields negative LRP amplitudes in adults (Eimer, 1998; Gratton et al., 1988). Unexpectedly we found a lateralized positivity in electrodes over the pre-central area contralateral to the movement side manifesting as a positive LRP in both ADHD and the control group. Interpretation of these results is complicated by the fact that there is little data on LRP - especially in self-initiated movements - in children. Previous studies of BP in children performing self-initiated movements did not specifically assess LRP (Warren and Karrer, 1984). Some studies reported positive late CNV components contralateral to movement (Bender et al., 2005) and positive LRP polarities in children (Szűcs et al., 2007). However, results are mixed with some studies reporting negative potentials contralateral to movement (Steger et al., 2000; Szűcs et al., 2009). Szűcs et al. (2009) argue that LRP may be particularly sensitive to slight anatomic variation resulting in opposing polarities in different groups of children. Another possible explanation may be that inhibition of involuntary movements could be active before movement initiation. It has been suggested that gradual replacement of inhibition through axodentritic synapses resulting in positive surface potentials in children by axosomatic inhibiton producing negative surface potential in older individuals may

account for changing polarities (Otto and Reiter, 1984). In this case lower LRP amplitudes in ADHD in our study may represent lower inhibition in MI. Our data adds further evidence that children with and without ADHD may display LRPs of positive polarity but further studies assessing additional neurobiological measures of brain maturation will be necessary to assess whether LRP polarity depends on brain maturation.

4.5. Effects of MPH

While there was a significant difference in LRP amplitudes between groups at baseline, this difference was no longer detectable at T2 when the ADHD group was medicated with MPH. There was a trend towards an increase of LRP amplitudes in the ADHD group from the baseline measurement to the second measurement on medication. As there was no placebo control for the medication group it cannot be excluded that other factors contributed to the effect. In the control group (which was not medicated at T2), a decrease of LRP amplitudes from T1 to T2 was observed that was not statistically significant but may have contributed to the GROUP X TIME/MEDICATION effect. This could potentially be the result of regression to the mean. Also, decreasing amplitudes from T1 to T2 in the control group may be a result of the repetition of the task. However, as it seems unlikely that ADHD subjects would show a repetition effect in the opposite direction it is likely that the change of LPR from T1 to T2 in the ADHD group reflects the pharmacological effects of MPH. The medication effect may possibly be diminished by the relatively short drug-free interval (MPH had to be paused for at least 24 h). It is possible that larger effects would have been observed with a longer interval or drug-naïve subjects.

The medication effect is in line with studies showing improvement of motor abnormalities in ADHD by MPH on a behavioral level (Hrtanek et al., 2015; Stray et al., 2009). In addition, functional imaging studies have also reported normalization of brain function under stimulant medication in various brain areas associated with ADHD pathology including motor areas (reviewed in Rubia et al., 2014).

Movement-related potentials are generated in interaction with activity in the basal ganglia (Cunnington et al., 2002; Rektor et al., 2001) and BP is influenced by L-dopa (Dick et al., 1987). CNV has been proposed a dopaminergic marker based on dose dependent effects of MPH on late CNV amplitudes (Linssen et al., 2011). Thus, our findings on MPH and LRP may represent effects of dopaminergic neurotransmission on movement-related cortical potentials reflecting interactions of basal ganglia and cortical motor areas. However, there have also been reports disputing the dopamine hypothesis of the CNV and linking it to noradrenergic neurotransmission (Rothenberger et al., 1993). Therefore, it cannot be excluded that the noradrenergic properties of MPH may also underlie the medication effects.

We can only speculate as to why LRP is influenced by MPH while BP at Cz is not. Potential explanations may be differential structural developmental trajectories in the SMA and the primary motor cortex in ADHD (Shaw et al., 2007). Also, differential interactions of basal ganglia with different cortical areas may underlie the differential MPH effects. To our knowledge no studies have been performed previously assessing the differential effects of MPH on BP and LRP.

4.6. Limitations

The study has several limitations. First, there is a relatively small sample size. However, the effects seem to be large enough for a group effect to be detected despite the small sample. Secondly, as this study is cross-sectional, no firm conclusions can be drawn regarding the longitudinal developmental trajectories of BP in ADHD. Furthermore, the interpretation of the effects of MPH on the LRP has limitations. The control group was not medicated at T2 and there was no placebo control. Therefore, the contribution of non-pharmacological factors to the GROUP X TIME/MEDICATION interaction cannot be excluded. We suggest that future studies should include a placebo condition in the ADHD group.

4.7. Summary

In summary, we found reduced BP amplitudes with positive polarity over the SMA preceding self-initiated movements in ADHD children. This suggests altered functioning in higher-order motor areas involved in the preparation and initiation of voluntary movements. BP abnormalities may be a correlate of delayed maturation of cortical structures including the SMA. Furthermore, we found decreased (less positive) LRP amplitudes reflecting altered pre-movement activity over the premotor cortex and primary motor cortex in medication-free ADHD subjects. Reduced BP amplitudes in ADHD were not affected by MPH. LRP differences between children with ADHD and the control group were modulated by dopaminergic and/ or noradrenergic effects of MPH .

CRediT authorship contribution statement

Tomasz A. Jarczok: Formal analysis, Visualization, Writing - original draft. **Robert Haase:** Formal analysis, Writing - review & editing. **Annett Bluschke:** Formal analysis, Writing - review & editing. **Ulf Thiemann:** Writing - review & editing. **Stephan Bender:** Conceptualization, Supervision, Writing - review & editing.

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References

Albrecht, B., Brandeis, D., von Sandersleben, H.U.-, Valko, L., Heinrich, H., Xu, X., Drechsler, R., Heise, A., Kuntsi, J., Müller, U.C., 2014. Genetics of preparation and response control in ADHD: the role of DRD 4 and DAT 1. J. Child Psychol. Psychiatry 55, 914–923.

American Psychiatric Association, 2013. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition American Psychiatric Publishing, Inc., Washington, DC, London, England.

Banaschewski, T., Yordanova, J., Kolev, V., Heinrich, H., Albrecht, B., Rothenberger, A., 2008. Stimulus context and motor preparation in attention-deficit/hyperactivity disorder. Biol. Psychol. 77, 53–62.

Bari, A., Robbins, T.W., 2013. Inhibition and impulsivity: Behavioral and neural basis of response control. Prog. Neurobiol. 108, 44–79.

Bender, S., Resch, F., Klein, C., Renner, T., Fallgatter, A.J., Weisbrod, M., Romanos, M., 2012. Influence of stimulant medication and response speed on lateralization of movement-related potentials in attention-deficit/hyperactivity disorder. PLoS ONE 7, e39012.

Bender, S., Weisbrod, M., Bornfleth, H., Resch, F., Oelkers-Ax, R., 2005. How do children prepare to react? Imaging maturation of motor preparation and stimulus anticipation by late contingent negative variation. NeuroImage 27, 737–752.

Bender, S., Resch, F., Weisbrod, M., Oelkers-Ax, R., 2004. Specific task anticipation versus unspecific orienting reaction during early contingent negative variation. Clin. Neurophysiol. 115, 1836–1845.

Bluschke, A., Schuster, J., Roessner, V., Beste, C., 2018. Neurophysiological mechanisms of interval timing dissociate inattentive and combined ADHD subtypes. Sci. Rep. 8, 2033.

Bozorgpour, G., Erin, B., Klorman, R., Gift, T.E., 2013. Effects of subtype of attention-deficit/hyperactivity disorder in adults on lateralized readiness potentials during a go/no-go choice reaction time task. J. Abnorm. Psychol. 122, 868.

Brunia, C.H.M., 2003. CNV and SPN: Indices of anticipatory behavior. In: Jahanshahi, M., Hallett, M. (Eds.), The Bereitschaftspotential: Movement-Related Cortical Potentials. Springer US, Boston, MA, pp. 207–227.

Brunia, C.H.M., Van Boxtel, G.J.M., 2001. Wait and see. Int. J. Psychophysiol. 43, 59–75.

Castellanos, F.X., Lee, P.P., Sharp, W., Jeffries, N.O., Greenstein, D.K., Clasen, L.S., Blumenthal, J.D., James, R.S., Ebens, C.L., Walter, J.M., Zijdenbos, A., Evans, A.C., Giedd, J.N., Rapoport, J.L., 2002. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 288, 1740–1748.

Castellanos, F.X., Proal, E., 2012. Large-scale brain systems in ADHD: beyond the prefrontal-striatal model. Trends Cogn. Sci. 16, 17–26.

Chiarenza, G.A., Villa, M., Vasile, G., 1995. Developmental aspects of bereitschaftspotential in children during goal-directed behaviour. Int. J. Psychophysiol. 19, 149–176.

Coles, M.G.H., 1989. Modern mind-brain reading: psychophysiology, physiology, and cognition. Psychophysiology 26, 251–269.

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M.P., Castellanos, F.X., 2012. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am. J. Psychiatry 169, 1038–1055.

Cui, R.Q., Huter, D., Lang, W., Deecke, L., 1999. Neuroimage of voluntary movement: topography of the bereitschaftspotential, a 64-channel DC current source density study. NeuroImage 9, 124–134.

Cunnington, R., Windischberger, C., Deecke, L., Moser, E., 2002. The preparation and execution of self-initiated and externally-triggered movement: a study of event-related fMRI. NeuroImage 15, 373–385.

Damasio, A.R., 1985. Understanding the mind's will. Behav. Brain Sci. 8, 589 –589.

Deecke, L., Weinberg, H., Brickett, P., 1982. Magnetic fields of the human brain accompanying voluntary movement: Bereitschaftsmagnetfeld. Exp. Brain Res. 48, 144–148.

Delmo, C., Weiffenbach, O., Gabriel, M., Poustka, F., 2000. Kiddie-SADS present and lifetime version (K-SADS-PL). Fifth Edition of the German research version, Klinik für Psychiatrie und Psychotherapie des Kindes- Jugendalters der Universität Frankfurt, Frankfurt am Main.

Dhar, M., Been, P.H., Minderaa, R.B., Althaus, M., 2010. Information processing differences and similarities in adults with dyslexia and adults with Attention Deficit Hyperactivity Disorder during a Continuous Performance Test: A study of cortical potentials. Neuropsychologia 48, 3045–3056.

Dick, J.P.R., Cantello, R., Buruma, O., Gioux, M., Benecke, R., Day, B.L., Rothwell, J.C., Thompson, P.D., Marsden, C.D., 1987. The Bereitschaftspotential, l-DOPA and parkinson's disease. Electroencephalogr. Clin. Neurophysiol. 66, 263–274.

Dickstein, S.G., Bannon, K., Xavier Castellanos, F., Milham, M.P., 2006. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J. Child Psychol. Psychiatry 47, 1051–1062.

Doehnert, M., Brandeis, D., Schneider, G., Drechsler, R., Steinhausen, H.-C., 2013. A neurophysiological marker of impaired preparation in an 11-year follow-up study of attention-deficit/hyperactivity disorder (ADHD). J. Child Psychol. Psychiatry 54, 260–270.

Duerden, E.G., Tannock, R., Dockstader, C., 2012. Altered cortical morphology in sensorimotor processing regions in adolescents and adults with attention-deficit/hyperactivity disorder. Brain Res. 1445, 82–91.

Ehlis, A.-C., Deppermann, S., Fallgatter, A.J., 2018. Performance monitoring and post-error adjustments in adults with attention-deficit/hyperactivity disorder: an EEG analysis. J. Psychiatry Neurosci. 43, 396–406.

Eimer, M., 1998. The lateralized readiness potential as an on-line measure of central response activation processes. Behav. Res. Methods Instrum. Comput. 30, 146–156.

Erdler, M., Beisteiner, R., Mayer, D., Kaindl, T., Edward, V., Windischberger, C., Lindinger, G., Deecke, L., 2000. Supplementary motor area activation preceding voluntary movement is detectable with a whole-scalp magnetoencephalography system. NeuroImage 11, 697–707.

Friedman, L.A., Rapoport, J.L., 2015. Brain development in ADHD. Curr. Opin. Neurobiol. 30, 106–111.

Goldberg, G., 1985. Supplementary motor area structure and function: Review and hypotheses. Behav. Brain Sci. 8, 567–616.

Gratton, G., Coles, M.G., Donchin, E., 1983. A new method for off-line removal of ocular artifact. Electroencephalogr. Clin. Neurophysiol. 55, 468–484.

Gratton, G., Coles, M.G., Sirevaag, E.J., Eriksen, C.W., Donchin, E., 1988. Pre-and poststimulus activation of response channels: a psychophysiological analysis. J. Exp. Psychol. Hum. Percept. Perform. 14, 331.

Hrtanek, I., Ondrejka, I., Tonhajzerova, I., Snircova, E., Kulhan, T., Farsky, I., Nosalova, G., 2015. The effect of methylphenidate on neurological soft signs in ADHD. Psychiatry Investig. 12, 545–550.

Ikeda, A., Lüders, H.O., Burgess, R.C., Shibasaki, H., 1992. Movement-related potentials recorded from supplementary motor area and primary motor area. Role of supplementary motor area in voluntary movements. Brain 115, 1017–1043.

Jahanshahi, M., Hallett, M., 2003. The bereitschaftspotential: what does it measure and where does it come from? In: Jahanshahi, M., Hallett, M. (Eds.), The Bereitschaftspotential: Movement-Related Cortical Potentials. Springer US, Boston, MA, pp. 1–17.

Khoshnoud, S., Shamsi, M., Nazari, M.A., Makeig, S., 2018. Different cortical source activation patterns in children with attention deficit hyperactivity disorder during a time reproduction task. J. Clin. Exp. Neuropsychol. 40, 633–649.

Kornhuber, H.H., Deecke, L., 1965. Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. Pflüg. Arch. Für Gesamte Physiol. Menschen Tiere 284, 1–17.

Krain, A.L., Castellanos, F.X., 2006. Brain development and ADHD. Clin. Psychol. Rev. 26, 433–444.

Kröger, A., Hof, K., Krick, C., Siniatchkin, M., Jarczok, T., Freitag, C.M., Bender, S., 2014. Visual processing of biological motion in children and adolescents with attention-deficit/hyperactivity disorder: an event related potential-study. PloS One 9, e88585.

Lang, W., 2003. Surface recordings of the bereitschaftspotential in normals. In: Jahanshahi, M., Hallett, M. (Eds.), The Bereitschaftspotential: Movement-Related Cortical Potentials. Springer US, Boston, MA, pp. 19–34.

Linssen, A.M.W., Vuurman, E.F.P.M., Sambeth, A., Nave, S., Spooren, W., Vargas, G., Santarelli, L., Riedel, W.J., 2011. Contingent negative variation as a dopaminergic biomarker: evidence from dose-related effects of methylphenidate. Psychopharmacology (Berl.) 218, 533–542.

Ma, J., Lei, D., Jin, X., Du, X., Jiang, F., Li, F., Zhang, Y., Shen, X., 2012. Compensatory brain activation in children with attention deficit/hyperactivity disorder during a simplified Go/No-go task. J. Neural Transm. 119, 613–619.

Makris, N., Biederman, J., Monuteaux, M.C., Seidman, L.J., 2009. Towards conceptualizing a neural systems-based anatomy of attention-deficit/hyperactivity disorder. Dev. Neurosci. 31, 36–49.

Mayer, K., Wyckoff, S.N., Strehl, U., 2016. Underarousal in adult ADHD: how are peripheral and cortical arousal related? Clin. EEG Neurosci. 47, 171–179.

Michelini, G., Kitsune, V., Vainieri, I., Hosang, G.M., Brandeis, D., Asherson, P., Kuntsi, J., 2018. Shared and disorder-specific event-related brain oscillatory markers of attentional dysfunction in ADHD and bipolar disorder. Brain Topogr. 31, 672–689.

Mostofsky, S.H., Cooper, K.L., Kates, W.R., Denckla, M.B., Kaufmann, W.E., 2002. Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. Biol. Psychiatry 52, 785–794.

Mostofsky, S.H., Rimrodt, S.L., Schafer, J.G.B., Boyce, A., Goldberg, M.C., Pekar, J.J., Denckla, M.B., 2006. Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study of simple sequential finger tapping. Biol. Psychiatry 59, 48–56.

Okano, K., Tanji, J., 1987. Neuronal activities in the primate motor fields of the agranular frontal cortex preceding visually triggered and self-paced movement. Exp. Brain Res. 66, 155–166.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Otto, D., Reiter, L., 1984. Developmental changes in slow cortical potentials of young children with elevated body lead burden.: neurophysiological considerations. Ann. N. Y. Acad. Sci. 425, 377–383.

Perchet, C., Garcia-Larrea, L., 2005. Learning to react: anticipatory mechanisms in children and adults during a visuospatial attention task. Clin. Neurophysiol. 116, 1906–1917.

Polanczyk, G., de Lima, M.S., Horta, B.L., Biederman, J., Rohde, L.A., 2007. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am. J. Psychiatry 164, 942–948.

Praamstra, P., Stegeman, D.F., Horstink, M., Cools, A.R., 1996. Dipole source analysis suggests selective modulation of the supplementary motor area contribution to the readiness potential. Electroencephalogr. Clin. Neurophysiol. 98, 468–477.

Rektor, I., Bareš, M., Kubová, D., 2001. Movement-related potentials in the basal ganglia: a SEEG readiness potential study. Clin. Neurophysiol. 112, 2146–2153.

Rizzolatti, G., Luppino, G., 2001. The cortical motor system. Neuron 31, 889–901.

Rothenberger, A., Dumai-Huber, C., Müller, H., Müller, W., 1993. Challenging the neurochemical model of the contingent negative variation. In: Heinze, H., Münte, T., Mangu, G. (Eds.), New Developments in Event-Related Potentials. Birkenhäuser, Boston, MA.

Rothenberger, A., Kemmerling, S., Schenk, G.K., Zerbin, D., Voss, M., 1986. Movement-related potentials in children with hypermotoric behavior. Cereb. Psychophysiol. EEG Suppl. 38, 496–498.

Rubia, K., 2007. Neuro-anatomic evidence for the maturational delay hypothesis of ADHD. Proc. Natl. Acad. Sci. 104, 19663–19664.

Rubia, K., Alegria, A.A., Cubillo, A.I., Smith, A.B., Brammer, M.J., Radua, J., 2014. Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Biol. Psychiatry 76, 616–628.

Sartory, G., Heine, A., Müller, B.W., Elvermann-Hallner, A., 2002. Event- and motor-related potentials during the continuous performance task in attention-deficit/hyperactivity disorder. J. Psychophysiol. 16, 97–106.

Scangos, K.W., Stuphorn, V., 2010. Medial frontal cortex motivates but does not control movement initiation in the countermanding task. J. Neurosci. Off. J. Soc. Neurosci. 30, 1968–1982.

Schallberger, U., 2005. Welches sind die nach statistischen Kriterien besten Kurzformen des HAWIK-III? Berichte Aus Der Abteilung Angewandte Psychologie, Nr. 32. Psychologisches Institut der Universität, Zürich.

Seo, B.-K., Sartory, G., Kis, B., Scherbaum, N., Müller, B.W., 2013. Attenuated readiness potential in the absence of executive dysfunction in adults with ADHD. J. Atten. Disord. 21, 331–342.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J.P., Greenstein, D., Clasen, L., Evans, A., Giedd, J., Rapoport, J.L., 2007. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc. Natl. Acad. Sci. 104, 19649–19654.

Shibasaki, H., Hallett, M., 2006. What is the bereitschaftspotential? Clin. Neurophysiol. 117, 2341–2356.

Simmonds, D.J., Pekar, J.J., Mostofsky, S.H., 2008. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. Neuropsychologia 46, 224–232.

Spronk, M., Jonkman, L.M., Kemner, C., 2008. Response inhibition and attention processing in 5- to 7-year-old children with and without symptoms of ADHD: An ERP study. Clin. Neurophysiol. 119, 2738–2752.

Steger, J., Imhof, K., Steinhausen, H.-C., Brandeis, D., 2000. Brain mapping of bilateral interactions in attention deficit hyperactivity disorder and control boys. Clin. Neurophysiol. 111, 1141–1156.

Stray, L.L., Stray, T., Iversen, S., Ruud, A., Ellertsen, B., 2009. Methylphenidate improves motor functions in children diagnosed with Hyperkinetic Disorder. Behav. Brain Funct. 5, 21.

Szűcs, D., Soltész, F., Bryce, D., Whitebread, D., 2009. Real-time tracking of motor response activation and response competition in a stroop task in young children: a lateralized readiness potential study. J. Cogn. Neurosci. 21, 2195–2206.

Szűcs, D., Soltész, F., Jármi, É., Csépe, V., 2007. The speed of magnitude processing and executive functions in controlled and automatic number comparison in children: an electro-encephalography study. Behav. Brain Funct. 3, 23.

Toma, K., Matsuoka, T., Immisch, I., Mima, T., Waldvogel, D., Koshy, B., Hanakawa, T., Shill, H., Hallett, M., 2002. Generators of movement-related cortical potentials: fMRI-constrained EEG dipole source analysis. NeuroImage 17, 161–173.

Valera, E.M., Spencer, R.M.C., Zeffiro, T.A., Makris, N., Spencer, T.J., Faraone, S.V., Biederman, J., Seidman, L.J., 2010. Neural substrates of impaired sensorimotor timing in adult attention-deficit/hyperactivity disorder. Biol. Psychiatry 68, 359–367.

Warren, C., Karrer, R., 1984. Movement-related potentials in children. Ann. N. Y. Acad. Sci. 425, 489–495.

Werner, J., Weisbrod, M., Resch, F., Roessner, V., Bender, S., 2011. Increased performance uncertainty in children with ADHD? - Elevated post-imperative negative variation (PINV) over the ventrolateral prefrontal cortex. Behav. Brain Funct. 7, 38.

Yazawa, S., Ikeda, A., Kunieda, T., Ohara, S., Mima, T., Nagamine, T., Taki, W., Kimura, J., Hori, T., Shibasaki, H., 2000. Human presupplementary motor area is active before voluntary movement: subdural recording of Bereitschaftspotential from medial frontal cortex. Exp. Brain Res. 131, 165–177.

Yordanova, J., Dumais-Huber, C., Rothenberger, A., 1996. Coexistence of tics and hyperactivity in children: No additive effect at the psychophysiological level. Int. J. Psychophysiol. 21, 121–133.