doi:10.1093/brain/awu029 Brain 2014: 137; 1156–1166 | 1156

BRAIN
A JOURNAL OF NEUROLOGY

A bimodal neurophysiological study of motor control in attention-deficit hyperactivity disorder: a step towards core mechanisms?

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Knowledge about the core neural mechanisms of attention-deficit hyperactivity disorder, a pathophysiologically heterogeneous psychiatric disorder starting in childhood, is still limited. Progress may be achieved by combining different methods and levels of investigation. In the present study, we investigated neural mechanisms of motor control in 19 children with attention-deficit hyperactivity disorder (aged 9–14 years) and 21 age-matched typically developing children by relating neural markers of attention and response control (using event-related potentials) and measures of motor excitability/inhibition (evoked by transcranial magnetic stimulation). Thus, an interplay of processes at a subsecond scale could be studied. Using a monetary incentives-based cued Go/No-Go task, parameters that are well-known to be reduced in attention-deficit hyperactivity disorder were analysed: event-related potential components P3 (following cue stimuli; in Go and No-Go trials) and contingent negative variation as well as the transcranial magnetic stimulation-based short-interval intracortical inhibition measured at different latencies in Go and No-Go trials. For patient and control groups, different associations were obtained between performance, event-related potential and transcranial magnetic stimulation measures. In children with attention-deficit hyperactivity disorder, the P3 amplitude in Go trials was not correlated with reaction time measures but with short-interval intracortical inhibition at rest ($r = 0.56$, $P = 0.01$). In No-Go trials, P3 and short-interval intracortical inhibition after inhibiting the response (at 500 ms post-stimulus) were correlated in these children only ($r = 0.62$; $P = 0.008$). A classification rate of 90% was achieved when using short-interval intracortical inhibition (measured shortly before the occurrence of a Go or No-Go stimulus) and the amplitude of the P3 in cue trials as input features in a linear discriminant analysis. Findings indicate deviant neural implementation of motor control in children with attention-deficit hyperactivity disorder reflecting compensatory cognitive mechanisms as a result of a basal motor cortical inhibitory deficit (reduced activation of inhibitory intracortical interneurons). Both deviant inhibitory and attentional processes, which are not related to each other, seem to be characteristic for attention-deficit hyperactivity disorder at the neural level in motor control tasks. The underlying neural mechanisms, which are probably not restricted to the motor cortex and the posterior attention network, may play a key role in the pathophysiology of this child psychiatric disorder. The high classification rate can further be interpreted as a step towards the development of neural markers. In summary, the bimodal neurophysiological concept may contribute to developing an integrative framework for attention-deficit hyperactivity disorder.

Keywords: attention deficit hyperactivity disorder; motor control; event-related potentials; transcranial magnetic stimulation; correlational analysis

Received May 20, 2013. Revised November 21, 2013. Accepted December 19, 2013. Advance Access publication February 25, 2014

Abbreviations: ADHD = attention-deficit hyperactivity disorder; SICI = short-interval intracortical inhibition; TMS = transcranial magnetic stimulation

Introduction

There is general agreement that attention-deficit hyperactivity disorder (ADHD) is a pathophysiologically heterogeneous disorder, i.e. it cannot be explained by a single core neural mechanism and different neurodevelopmental pathways exist for this child psychiatric disorder (Castellanos and Tannock, 2002; Sonuga-Barke, *et al*., 2003; Banaschewski *et al*., 2005). Besides dopaminergic and noradrenergic dysfunctions, which have been in focus for quite a long time, GABAergic and the serotonergic deviations have been reported (Brookes *et al*., 2006; Del Campo *et al*., 2011; Edden *et al*., 2012). Smaller brain volumes for the whole cortex, the cerebellum and the caudate nucleus accompanied by partly differing developmental trajectories were found (Castellanos *et al*. 2002; Shaw *et al*., 2006). Fronto-striatal, fronto-cerebellar and parietal networks, the default mode network as well as the motor system are thought to be involved (Durston *et al*., 2011; Cortese *et al*., 2012; Hart *et al*., 2012, 2013). Deficits and dysfunctional patterns have been reported related to executive functioning, response control and motor inhibition, self-regulation, working memory, delay aversion, attentional orienting, temporal processing, multi-second periodic performance fluctuations and error processing (Moll *et al*., 2000; Castellanos and Tannock, 2002; Banaschewski *et al*., 2005; Banaschewski and Brandeis, 2007; Sonuga-Barke *et al*., 2010; Yordanova *et al*., 2011). On one hand, this list, which could be continued, indicates the wide-ranging implications of ADHD. On the other hand, findings are 'getting out of hand'.

In the same line, there are a growing number of theoretical models focusing on certain aspects and linking different levels and processes. Reflecting two prominent ADHD models, the dual-pathway model suggests two distinct subtypes of the disorder characterized by either executive/inhibitory dysfunctions or delay-related deficits underpinned by different cortico-striatal circuits and modulated by different branches of the dopamine system (Sonuga-Barke 2003). According to the cognitive-energetic model, children with ADHD may show deficits at three levels (attention, state factors, and management/executive function) but an energetic dysfunction is thought to be most relevant (Sergeant, 2005).

In our opinion, empirical studies should be undertaken relating the various findings obtained at the neuropsychological and different neurobiological levels to unravel the core neural mechanisms of ADHD: Do different findings reflect the same or different mechanism(s)? Does a finding rather reflect a primary deficit or a compensatory mechanism? And related to cognitive tasks, is a deviant pattern observed at a specific processing stage the sequel to deficits at an earlier processing stage or at a higher level?

By combining different methodologies, a more detailed analysis of brain–behaviour relationships may be achieved. Finally, a combination of measures reflecting the core mechanisms of ADHD and different pathways, should allow us to clearly differentiate between typically developing children and children with ADHD. Thus, neural (biological) markers for ADHD may be identified that are expected to support diagnostic and prognostic procedures in clinical practice (Thome *et al*., 2012). For example, Solanto *et al*. (2001) obtained a classification rate of 90% in a case control study based on neuropsychological measures related to response inhibition and delay aversion documenting that it is possible to achieve high classification rates. However, neuropsychological studies allow only indirect clues about the underlying neural dysfunctions since tasks tap more than one dimension of functioning.

Moving a step in the direction described above, we investigated neural mechanisms of response inhibition/motor control in ADHD, which may reflect one of the key aspects in ADHD (Barkley, 1997; Sonuga-Barke, 2003), by combining two neurophysiological approaches: event-related potentials and transcranial magnetic stimulation (TMS).

Event-related potentials are an appropriate tool to study cognitive aspects of response control and attentional processes (Banaschewski and Brandeis, 2007). TMS allows one to measure excitability in the motor system (cortex) and is particularly prone to analyse inhibitory processes (Reis *et al*., 2008), which are less metabolically demanding than excitatory processes (Waldvogel *et al*., 2000). Both modalities provide a high temporal resolution so that an interplay of cognitive and motor-related processes at a subsecond scale can be analysed (Hoegl *et al*., 2011).

In a series of studies, event-related potential components related to response preparation (contingent negative variation), execution (Go-P3) and inhibition (No-Go-N2, No-Go-P3) have been investigated in ADHD. In Go/No-Go tasks, the contingent negative variation, the Go-P3 and the No-Go-P3 have repeatedly been reported to be reduced in children with ADHD whereas the N2 in No-Go trials seems to be comparable to typically developing children (for review see Banaschewski and Brandeis, 2007).

Response control deficits in ADHD may at least partly be preceded by (more general) state regulation deficits *inter alia* because of motivational factors (Sergeant, 2005; Banaschewski and Brandeis, 2007). In this respect, some studies reported larger influences of motivation in children with ADHD at the performance and neural level (Uebel *et al*., 2010; Liddle *et al*., 2011) though, in an event-related potential study, motivational incentives increased the No-Go-N2 and No-Go-P3 in children with ADHD and typically developing children to a comparable amount (Groom *et al*., 2010). Deviant processing of cue stimuli as reflected, for example by a reduced cue-P3 (indicating deficient attentional orienting; Brandeis *et al*., 2002; Banaschewski *et al*., 2003; Kratz *et al*., 2011*b*; Albrecht *et al*., 2013) is in line with the hypothesis of deficient state regulation in ADHD.

The TMS-based short-interval intracortical inhibition (SICI), which is thought to reflect the activity of inhibitory GABAergic interneurons in the motor cortex and to be modulated by

dopamine (Kujirai, *et al*., 1993; Ziemann *et al*., 1997*b*; Moll *et al*., 2002), can be elicited by applying a paired-pulse paradigm with interstimulus intervals <5 ms. SICI has repeatedly been reported to be reduced in children with ADHD (Moll *et al*., 2000, 2001; Gilbert *et al*., 2005, 2011; Buchmann *et al*., 2007; Hoegl *et al*., 2012) and is correlated with clinical ADHD scores (Gilbert *et al*., 2011; Hoegl *et al*., 2012). In motor tasks, SICI is interpreted as a cortical 'braking' mechanism suppressing unwanted motor cortical output in the premotor time, which needs to be released before the arrival of the excitatory drive to the motor cortex (Reis *et al*., 2008; Soto *et al*., 2010) (comparing it with a car, the brakes have to be released before pressing the accelerator; Floeter and Rothwell, 1999). SICI is also involved in actively suppressing execution of a prepared movement (Sohn *et al*., 2002; Kratz *et al*., 2009; Stinear *et al*., 2009). In children with ADHD showing a high level of hyperactivity and impulsivity, SICI at rest was found to be comparable to SICI just before starting a movement (relating this finding to the metaphor of a car, the brakes seem to be more or less released at rest in hyperactive/impulsive children).

Using a combined event-related potential/TMS approach, we aimed at a more refined analysis of motor control in ADHD. Specifically, we were interested in the following questions: (i) which neural markers of attention, response control and motor excitability/inhibition measures primarily characterize children with ADHD? And (ii) does the bimodal approach provide evidence for a deviant neural implementation of motor control in children with ADHD?

To address the first question, we conducted classification experiments (discriminant analysis) using event-related potential measures and TMS parameters as input features. For the second issue, we investigated brain–behaviour relationships by developing regression models, which were based on neurophysiological measures to predict performance measures. To study an interplay of control processes and motor excitability/inhibition, we considered associations between event-related potentials and TMS measures.

Materials and methods

Participants

Nineteen children with ADHD and 21 typically developing control subjects aged 9–14 years were included in the study. Both groups did not differ with respect to age, IQ and the distribution of hand preference (assessed with the Edinburgh Handedness Inventory; Oldfield, 1971). The sample is a subsample of our recent study (Hoegl *et al*., 2012); patients and control subjects had to fulfil more strict criteria. Table 1 summarizes the main characteristics of the sample.

Patients were recruited through the outpatient department of our clinic as well as local professionals. Based on clinical interviews with parents and patients, a medical assistant or a clinical psychologist assigned diagnoses that were supervised by a board-certified child and adolescent psychiatrist. All children of the ADHD group fit the criteria for the DSM-IV combined subtype. In the German ADHD rating scale (FBB-HKS; Döpfner and Lehmkuhl, 2000), they had to have scores of at least 1 in the subscales 'inattention' and 'hyperactivity/impulsivity'.

Children with other comorbid diagnoses than dyslexia or oppositional defiant disorder were not included in the study. Neurological impairments and learning disability (IQ <80), which was assessed with the Hamburg-Wechsler Intelligence Test for Children (third edition), were considered as exclusionary criteria. Medications other than methylphenidate (washout period of at least 48 h before testing) were not allowed.

The subjects of the control group, who were recruited from non-clinical settings, were subjected to identical screening procedures as the children with ADHD. They were included in the study if the scores in both subscales of the German ADHD rating scale were <0.5 and if they did not have any neurological or child psychiatric disorder.

Concerning TMS, low seizure thresholds, cardiovascular diseases and predisposition for syncope were exclusionary criteria (Kratz *et al*., 2011*a*). Only those children who had sufficient EEG and TMS data quality were included.

Assent was obtained from the children and written informed consent from their parents. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital of Erlangen.

Go/No-Go task and transcranial magnetic stimulation conditions

The Go/No-Go task including triggering of the magnetic stimulators (see Fig. 1 for a schematic illustration) was implemented with Presentation (Version 11.0; Neurobehavioral Systems).

The task consisted of four experimental blocks with 48 trials per block. Each trial started with the presentation of a warning stimulus (a danger traffic sign; 250 ms duration), which was followed by a test (imperative) stimulus (250 ms duration). The test stimulus was either a red stop sign (No-Go condition, 50%) or the green figure of a pedestrian traffic light (Go condition, 50%). The interval between cue and test stimulus was 1500 ms, the intertrial interval was 5000 ± 1000 ms.

To increase participants' motivation, a monetary reward (6 cents per trial) was given for correct responses in a certain time window after the Go stimulus. This time window was based on a tracking algorithm and dynamically adjusted to the 75th percentile of reaction times (Go trials) of every previous block and the practice block, respectively. In the case of a wrong reaction (no reaction to a Go stimulus within 1500 ms or reaction to a No-Go trial), the same amount of money was subtracted. The participants received acoustic feedback for fast, correct responses and for incorrect responses, respectively.

Regarding TMS, either a single-pulse or a double-pulse (interstimulus interval 3 ms) was delivered at various latencies after the test stimulus (150 ms, 300 ms or 500 ms) or 50 ms before the test stimulus. Catch trials were interspersed in the intertrial period, which served as a control condition. In summary, there were 16 different pulse $\times$ latency $\times$ Go versus No-Go conditions and two conditions (single and double pulse) for catch trials. Each condition appeared three times and varied randomly within each block (48 trials and six catch trials per block).

Procedure

Children sat on a comfortable chair with armrests to minimize movements. Task stimuli were presented on a 17-inch monitor (viewing distance: 90 cm). Subjects were instructed to react to Go stimuli by spreading the fingers of the right hand. Responses were recorded through a flexible device (switch and plastic loop) that was attached to the hand. The task was introduced to the participants and two short practice blocks (one with TMS and the other without) were run so that

Table 1 Sample characteristics

	Controls ($n = 21$)	ADHD ($n = 19$)	Statistics
Demographical data			
Age (years)	12.1 ± 1.6	12.2 ± 1.4	$t(38) = -0.25$, n.s.
IQ (HAWIK-III)	108.8 ± 13.5	107.5 ± 13.6	$t(38) = 0.30$, n.s.
Sex (male/female)	16 / 5	16 / 3	$\chi^2 = 0.40$; n.s.
Handedness (right/left)	19 / 2	18 / 1	$\chi^2 = 0.26$; n.s.
Clinical data			
Associated disorders			
Oppositional defiant disorder	-	9	
Dyslexia	-	5	
German ADHD rating scale (FBB-HKS)			
Total score	0.26 ± 0.14	1.80 ± 0.40	$t(38) = -16.5$; $P < 0.001$
Inattention	0.37 ± 0.29	1.87 ± 0.50	$t(38) = -11.7$; $P < 0.001$
Hyperactivity/impulsivity	0.16 ± 0.17	1.74 ± 0.48	$t(38) = -14.0$; $P < 0.001$

n.s. = not significant.

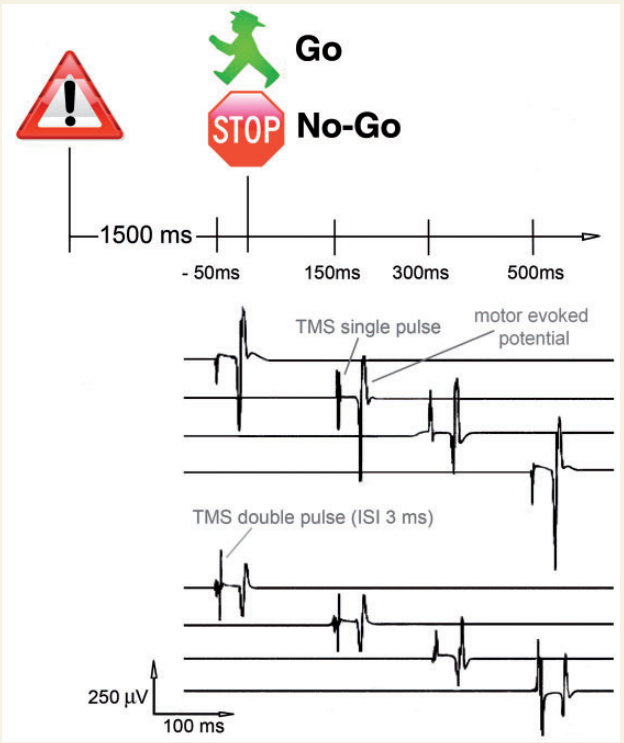

Figure 1 Illustration of the cued Go/No-Go task. TMS stimuli (single-pulses or double-pulses with an interstimulus interval (ISI) of 3 ms) were presented 50 ms before or 150, 300 or 500 ms after the onset of the test stimulus (reprinted from Hoegl *et al.*, 2012).

they could get familiar with the testing situation. For each participant, one of four experimental blocks was randomly applied without TMS.

Transcranial magnetic stimulation

Single- and paired-pulse TMS was delivered through a figure-of-eight coil (diameter of one wing = 70 mm) connected to a Magstim BiStim unit with two Magstim 200^2 stimulators (Magstim).

After finding the optimal site over the left motor cortex to elicit motor evoked potentials in the m. abductor digiti minimi of the right hand, the resting motor threshold (defined as the minimum stimulus intensity that produced a motor evoked potential >50 µV in 5 of 10 trials in the relaxed target muscle) was determined.

In the Go/No-Go task, the intensity of the conditioning stimulus was set to 75% of resting motor threshold, and the supra-theshold test stimulus was adapted (with a maximum of 20% above resting motor threshold) to evoke a single-pulse motor evoked potential with a mean peak-to-peak amplitude of 1 mV.

Data recording and preprocessing

A BrainAmp recording system (standard BrainAmp amplifier; Brain Products) was used for data acquisition. Analyses was done using the Vision Analyzer 2.0.

Brain electrical activity was recorded with sintered silver/silver chloride electrodes and Abralyt 2000 electrolyte from 23 sites according to an extended 10-20 system (recording reference: FCz, ground electrode: CPz). A standard EEG cap (Easycap) was worn but without electrode C3 (i.e. the electrode under the TMS coil). Electrooculogram electrodes were placed above and below the right eye and at the outer canthi. Filter bandwidth at recording was set to 0.016–1000 Hz (sampling frequency: 5000 Hz). Impedances were kept <20 kΩ.

Offline, the EEG was re-referenced to linked mastoids. After downsampling to 256 Hz, the EEG data were filtered with a notch filter and with a 0.1 to 30 Hz (0.01 to 20 Hz for analysis of cue trials) 12 dB/octave Butterworth bandpass filter. An ocular correction procedure (Gratton *et al.*, 1983) was used to remove the influence of blinks and other eye movements.

For the analysis of event-related responses after the cue stimulus, segments from −100 ms to 1750 ms around cue onset were built. For the analysis of Go and No-Go conditions, segments lasting from −100 ms to 500 ms around the test stimulus were considered. Only segments in which no TMS pulse occurred were used for further analyses.

For cue trials, baseline subtractions were performed because of the different high pass filter settings. The 100 ms before cue onset served as baseline. No baseline subtractions were applied for Go and No-Go trials. Trials with amplitudes greater than ±100 µV (greater than ±125 µV for analysis of cue trials) were excluded before averaging as were trials with performance errors and Go trials with participants not responding between 100 and 1000 ms post-stimulus.

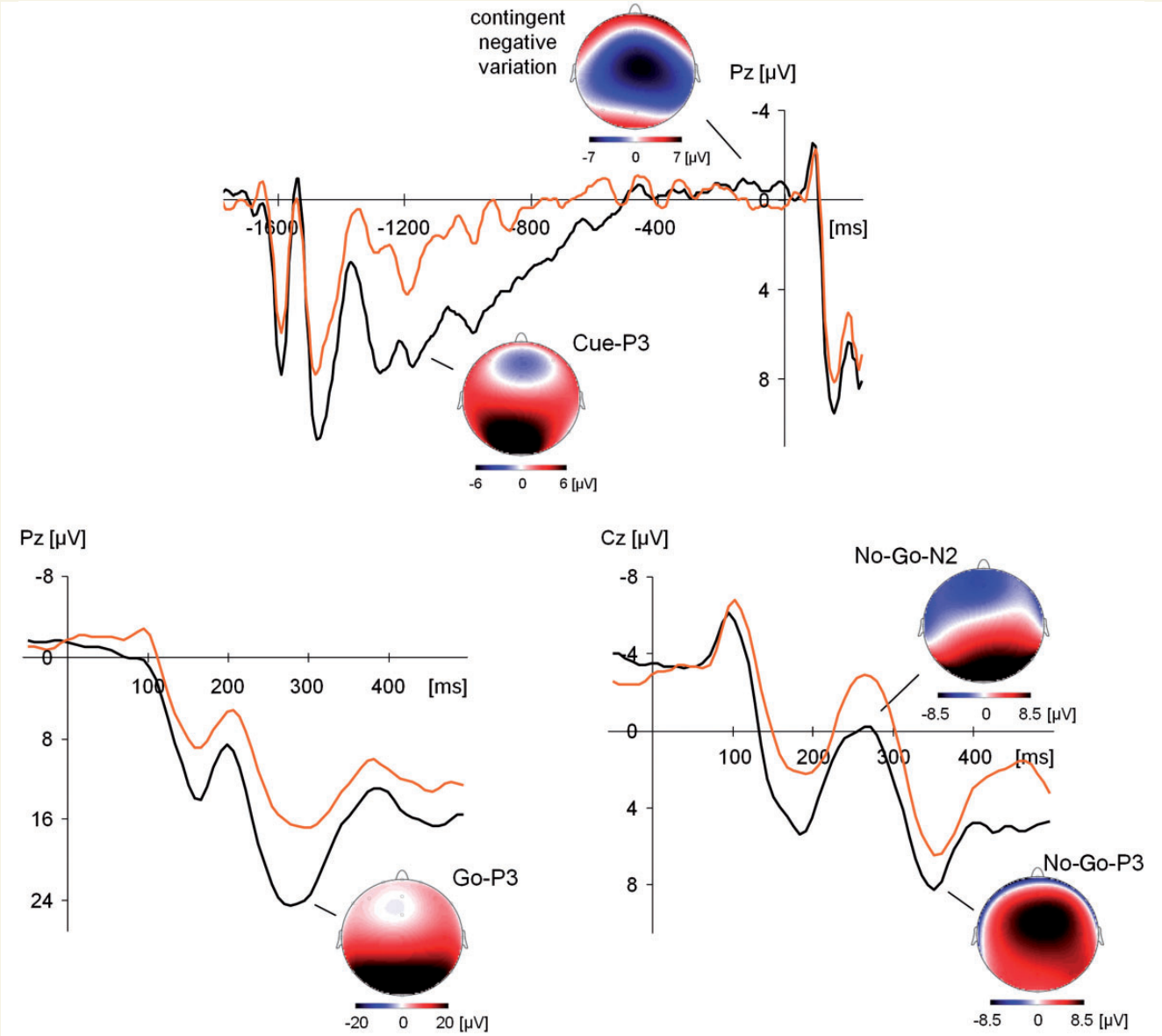

Figure 2 Grand average event-related potentials during the cued Go/No-Go task for cue trials at electrode Pz (*top*), Go trials at Pz (*bottom left*) and No-Go trials at Cz (*bottom right*) in children with ADHD (orange lines) and typically developing children (black lines). Spline-interpolated maps illustrating the topography of the event-related potential components under consideration are also depicted. Blue and red colours indicate negative and positive amplitude values, respectively.

EMG was recorded from the abductor digiti minimi muscle of the right hand (filter bandwidth: 8–1000 Hz).

Data processing and analysis

The Go-P3 was scored at Pz and the mean amplitude for the interval from 250 to 350 ms after test stimulus onset was computed. Correspondingly, a time range from 310 to 400 ms was considered for the No-Go-P3 at Cz and FCz (Fig. 2). N2 was determined as the most negative peak at Fz within the range from 170 to 280 ms post-stimulus in Go and No-Go trials. For further analyses, the difference between No-Go and Go condition (No-Go-N2 enlargement) was used. The contingent negative variation was measured at Cz as the mean amplitude in a time range from 300 to 0 ms before the test stimulus. The cue-P3 was analysed at Pz as the mean amplitude in a time range from 410 to 750 ms after cue onset.

The recorded EMG data were subdivided into segments with lengths of 300 ms (from 150 ms before until 150 ms after the TMS pulse). For TMS data analysis, we adopted the procedure used in Kratz *et al.* (2009). All segments with preactivation of the target muscle (EMG activity $>50\,\mu V$ in a time window from 110 to 25 ms before the TMS pulse) were excluded. A further peak detection was done to calculate the peak-to-peak motor-evoked potential amplitude of every segment in a time range from 20 to 50 ms after magnetic stimulation. Only trials with amplitudes between 70 μV and 4000 μV were included, which eliminated outlier values as a result of artefacts, background EMG or technical problems.

We calculated relative motor evoked potential amplitudes (mean amplitude for each pulse × latency × Go/No-Go task condition;

related to the mean of the single-pulse motor evoked potential amplitudes of the control condition) for a better comparison of the groups.

SICI was computed as 100% × (1 − ratio of conditioned to unconditioned motor evoked potential response) so that a large (respectively low) value corresponds to strong (respectively weak) inhibition.

As EMG activity was present in the major part of the Go trials starting between 250–300 ms, only Go trials with a TMS latency of 150 ms were analysed further.

Statistical analysis

Performance data [impulsivity errors (= responding during No-Go trials), mean reaction time, reaction time variability] as well as event-related potential parameters and TMS measures of the two groups were compared using unpaired *t*-tests.

SICI and relative motor evoked potential amplitudes obtained at the different latencies (within-subject factor) for the two groups (between-subject factor) were subjected to repeated measures ANOVAs. The degrees of freedom were adjusted with the Greenhouse-Geisser correction when appropriate.

To differentiate between the control and ADHD group, linear discriminant analysis was applied. Input variables were performance, event-related potential and TMS measures that were found to be significantly different between the two groups. Combinations of two variables were also considered.

Partial correlation coefficients (controlled for age) were calculated to assess the strength of the linear relationship between performance measures and neurophysiological measures as well as between event-related potential and TMS measures. Additionally, we computed linear regression models with the performance parameters as dependent variables (stepwise backwards elimination process; variables with probability values of $P > 0.1$ being removed) for the complete sample and for the two groups separately. Age and those neurophysiological variables for which at least a correlation coefficient of $P < 0.1$ was obtained were fed into the regression models. In order to avoid bias in the regression models outliers were eliminated.

$P < 0.05$ was considered to indicate significance. IBM SPSS Statistics 19.0 was used for statistical analyses.

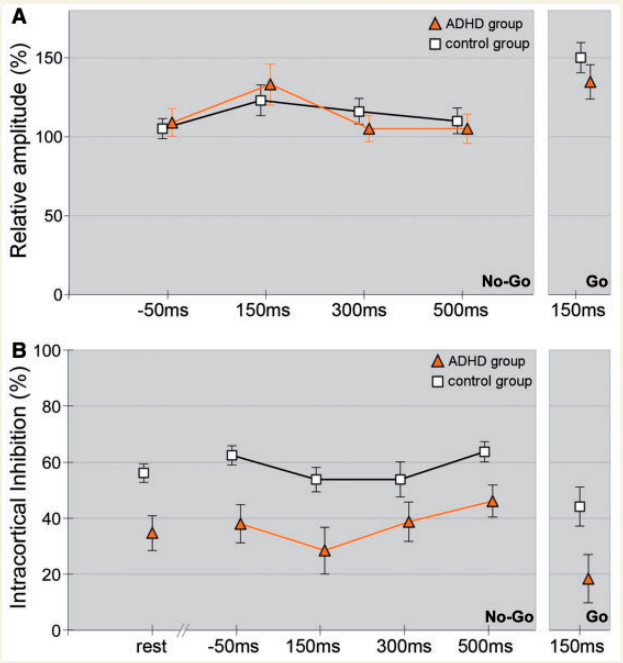

Figure 3 (**A**) Relative motor evoked potential amplitudes over the course of the No-Go trials and for the 150 ms post-stimulus condition in Go trials. (**B**) Short-interval intracortical inhibition for the passive control condition, over the course of the No-Go trials and for the 150 ms post-stimulus condition in Go trials. For each group (control, ADHD), mean ± standard error is depicted.

Results

Group differences

Statistical results are summarized in Supplementary Table 1. At the performance level, no significant group differences were found. The control group had significantly higher cue-P3 and Go-P3 amplitudes (effect sizes of ~1). For the contingent negative variation, a trend for larger (more negative) amplitudes in the control group was obtained. The No-Go-P3 and the No-Go-N2 enlargement did not differ significantly between the groups.

The ANOVA for SICI in No-Go trials revealed a significant group effect [$F(1,38) = 13.9$, $P = 0.001$] indicating reduced SICI for children with ADHD. SICI was significantly smaller in all conditions except at a latency of 300 ms post-stimulus (Fig. 3 and Supplementary Table 2), also when applying Bonferroni-Holm corrections. For SICI

Table 2 Discriminant analyses

Parameters	Specificity (%)	Sensitivity (%)	Classification rate (%)
Cue-P3 (Pz)	71.4	73.7	72.5
Go-P3 (Pz)	66.7	63.2	65.0
SICI – resting condition	76.2	63.2	70.0
SICI – pre-stimulus	76.2	57.9	67.5
Cue-P3 (Pz) and SICI – pre-stimulus	**90.5**	**89.5**	**90.0**
Cue-P3 (Pz) and SICI – resting condition	90.5	73.7	82.5
Go-P3 (Pz) and SICI – resting condition	76.2	78.9	77.5
Go-P3 (Pz) and SICI – pre-stimulus	85.7	68.4	77.5
Cue-P3 (Pz) and Go-P3 (Pz)	61.9	84.2	72.5

Measures that were found to be significantly different between the control group and the ADHD group were used as input variables for the classifier. Single measures and combinations of two measures were considered. The line for the feature combination providing the highest classification rate is printed in bold.

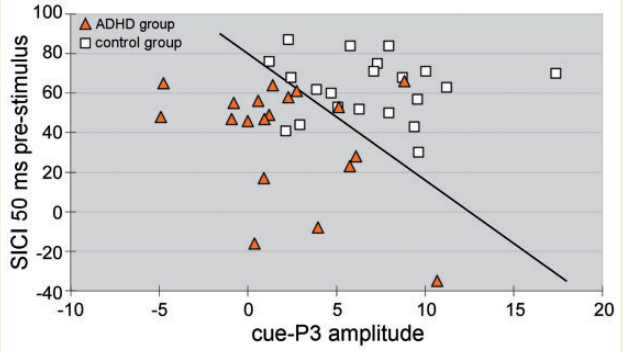

Figure 4 Scatter diagram showing the distribution of the cue-P3 amplitudes at Pz versus the SICI in the 50 ms prestimulus condition. A linear discriminant analysis (the separation line is also shown) allows us to classify 19 (of 21) children of the control group and 17 (of 19) children of the ADHD group correctly.

in the resting condition and at 50 ms prestimulus an effect size of ~1 was obtained. A trend for a linear group × latency effect was found [T-lin(1,38) = 3.57, $P = 0.07$] because of an increase of SICI from 50 ms prestimulus to 500 ms post-stimulus in the ADHD group.

Concerning motor evoked potential amplitudes to single pulses in No-Go-trials (Fig. 3), both groups did not differ significantly [factor group: $F(1,38) = 0.002$, n.s.; Group × Latency interaction: $F(3,114) = 0.78$, n.s.].

The results of the discriminant analysis are summarized in Table 2. Considering a single measure, the highest classification rate was 72.5% for the cue-P3. A combination of cue-P3 and the SICI at 50 ms prestimulus allowed us to classify 90% of the subjects correctly (Fig. 4).

Prediction of performance measures

The regression models for reaction time variability (Table 3) contained the contingent negative variation and the SICI at 50 ms pre-stimulus as significant predictor variables, accounting for ~40% of the variance for the complete samples and ~50% for the ADHD group. A larger contingent negative variation was associated with a reduced reaction time variability. A larger SICI at 50 ms prestimulus was related to a smaller variability of reaction times. The model for the control group also contained the Go-P3 as a significant predictor.

Concerning the mean reaction time, the contingent negative variation remained in all the models. The Go-P3 was a significant predictor variable in the models for the complete sample and the control group. For the control group, contingent negative variation and Go-P3 explained ~70% of the variance of the mean reaction time.

Age and mean reaction time accounted for ~30% of the variance of the commission errors. Younger children made more commission errors. Faster reaction times were associated with a larger number of commission errors though this speed-accuracy trade-off was not significant in the ADHD group. It is interesting to note that the forward model for the control group contained

Table 3 Regression models

	All	Controls	ADHD
Reaction time variability			
	R = 0.657; $F(2,38) = 13.7$, $P < 0.001$	R = 0.787; $F(3,19) = 8.66$, $P = 0.001$	R = 0.687; $F(2,18) = 7.17$, $P = 0.006$
Contingent negative variation:	β = 0.522, T = 4.14; $P < 0.001$	β = 0.449, T = 2.81; $P = 0.01$	β = 0.570, T = 3.12; $P = 0.007$
SICI – prestimulus	β = −0.350, T = −2.77; $P = 0.009$	β = −0.575, T = −3.54; $P = 0.003$	β = −0.331, T = −1.82; $P = 0.09$
Go-P3	–	β = −0.462, T = −2.78; $P = 0.01$	–
Mean reaction time			
	R = 0.699; $F(2,38) = 17.2$, $P < 0.001$	R = 0.844; $F(2,19) = 21.0$, $P < 0.001$	R = 0.617; $F(1,18) = 10.4$, $P = 0.005$
Contingent negative variation:	β = 0.610, T = 4.91; $P < 0.001$	β = 0.631, T = 4.71; $P < 0.001$	β = 0.617, T = 3.23; $P = 0.005$
Go-P3:	β = −0.212, T = −1.70; $P = 0.09$	β = −0.427, T = −3.18; $P = 0.005$	–
Commission errors, log(x + 1)-transformed			
	R = 0.534; $F(2,39) = 7.37$, $P = 0.002$	R = 0.567; $F(2,20) = 4.26$, $P = 0.03$	R = 0.553; $F(1,18) = 7.51$, $P = 0.01$
Age:	β = −0.536, T = −3.72; $P = 0.001$	β = −0.479, T = −2.42; $P = 0.03$	β = −0.553, T = −2.74; $P = 0.01$
Mean reaction time:	β = −0.268, T = −1.86; $P = 0.07$	β = −0.409, T = −2.07; $P v = 0.05$	–

Prediction of performance measures (reaction time variability, mean reaction time, impulsivity errors) based on event-related potential and TMS measures. Models were computed for the complete sample and for the two groups (control, ADHD) separately.

the SICI in the resting condition as the only significant predictor [R = 0.450; $F(1,20) = 4.83$, $P = 0.04$].

Associations between neurophysiological parameters

The regression models for the performance measures above partly differed between the control and ADHD groups. Looking at the correlations between event-related potential and TMS measures (Supplementary Table 2), significant correlations for the complete sample were found but significant correlations that were either present in the control group or in the ADHD group.

In the control group, we obtained significant correlations between the contingent negative variation and SICI at rest and SICI in No-Go trials at 150 ms post-stimulus. In the ADHD group, the strongest association was between the No-Go-P3 and SICI in No-Go trials at 500 ms post-stimulus ($r = 0.62$; $P = 0.008$).

A significant negative correlation between Go-P3 amplitude and SICI at rest was obtained for the ADHD group ($r = -0.56$; $P = 0.01$) but not for the control group ($r = -0.31$; n.s.).

Discussion

Neural mechanisms underlying motor control were studied in children with ADHD during a cued Go/No-Go task with monetary incentives. Applying a bimodal neurophysiological approach event-related potential measures representing neural markers of attention and response control and TMS-evoked measures reflecting motor excitability were considered and related to learn more about the core neural mechanisms of ADHD.

Task performance

We attempted to boost performance to the highest possible level by offering monetary incentives for correct and fast responses. Because all groups showed a comparable task performance (even concerning reaction time variability), it can be assumed that the results obtained at the neural level were not because of group differences in motivation or simply reflect poor task performance. On the other hand, missing group differences at the performance level and the lack of a no-incentive condition may be seen as a limitation in our study.

Functional significance of short-interval intracortical inhibition

In this study, new findings concerning the functional significance of SICI, which does not only play a role in response inhibition but is also related to response execution (Reis *et al*., 2008), was obtained. SICI at 50 ms prestimulus (i.e. when expecting/preparing for the Go stimulus) and the CNV, which has repeatedly been reported to be correlated with reaction time variability (Doehnert *et al*., 2012; Albrecht *et al*., 2013) allowed us to predict ~40% of the variance of reaction time variability (it must be remembered that regression models or any other kind of correlation analysis do not provide direct evidence for a causal relationship but only describe mathematical relations). A stronger SICI in the premotor time might be related to an increased focusing and a higher signal-to-noise ratio (Winterer and Weinberger, 2004), which in turn may result in more stable reaction times.

Deviant neural implementation of motor control in attention-deficit hyperactivity disorder

Different associations between performance and neurophysiological measures as well as between event-related potential and TMS measures were obtained for the control and ADHD groups indicating a deviant neural implementation of response inhibition and execution in ADHD. For example, a strong correlation between the No-Go-P3 and the SICI at 500 ms post-stimulus was found in the ADHD group only. As shown in our previous study (Hoegl *et al*., 2012), children with ADHD are able to increase SICI after inhibiting a response (compared with the resting condition, for example), probably because of a compensatory neural mechanism to allocate inhibitory resources. In this respect, the correlation between the No-Go-P3 and SICI at 500 ms post-stimulus may suggest that the No-Go-P3, representing an evaluation process of inhibition with sources in the prefrontal cortex and anterior cingulate (Beste *et al*., 2009; Hoegl *et al*., 2011), reflects this compensatory mechanism.

In contrast to the control group, the amplitude of the Go-P3 was not correlated with reaction time measures in the ADHD group but with SICI at rest. Thus, the findings related to the Go-P3 indicate that deficient SICI in ADHD does not only affect response inhibition but also motor control in general including stimulus-response associations (Yordanova *et al*., 2001).

Do the P3 in cue trials and SICI reflect core mechanisms of attention-deficit hyperactivity disorder?

In a discriminant analysis, the amplitude of the P3 in cue trials and SICI measured 50 ms before the test stimulus allowed us to classify 90% of the children correctly. A mean classification rate of 90% is superior to the results reported in event-related potential studies in children with ADHD [e.g. Heinrich *et al*., 1999 (single-trial measures): 84%; Smith *et al*., 2003: 73% in 8–12 year old children) and is comparable to a recent MRI study (Bansal *et al*., 2012) but with a fairly smaller number of features.

The cue-P3, which has consistently been found to be reduced in ADHD, does not reflect motor control in a closer sense but is rather related to attention (attentional orienting). It is thought to represent a noradrenaline-induced phasic enhancement of neural responsivity (gain) and to be generated by posterior sources. So, a reduced P3 amplitude in cue trials probably reflects an underactivation of the posterior attention system in ADHD (Brandeis *et al*., 2002; Nieuwenhuis *et al*., 2005; Banaschewski and Brandeis, 2007). As analysis was based on averaged event-related potentials, it will have to be checked whether the reduced P3 in cue trials is a general pattern or a result of multi-second fluctuations in attention so that

reduced amplitudes in only a few single trials account for the smaller cue-P3 in the averaged signal.

A reduced SICI (at rest) has also consistently been reported for ADHD and SICI is associated with clinical scores, particularly hyperactivity/impulsivity (for example, Gilbert *et al.*, 2011; Hoegl *et al.*, 2012). The present study extends this picture by demonstrating the functional significance of a reduced SICI in motor control.

SICI is mediated by inhibitory GABAergic interneurons in the motor cortex (Reis *et al.*, 2008). Dopamine-containing fibres target pyramidal cells and interneurons modulating their excitability, spatial tuning and temporal dynamics (Gao *et al.*, 2003; Markram *et al.*, 2004; Bacci *et al.*, 2005) and dopaminergic agonists have been found to increase SICI. As methylphenidate induces an increase of SICI in children with ADHD (Moll *et al.*, 2000), a reduced SICI in ADHD probably reflects an inadequate modulation of the mesocortical dopamine system playing a key role in modulating cognitive, motivational, and motor functions (Bacci *et al.*, 2005).

Both deviant inhibitory and attentional processes, which are not related to each other, seem to be characteristic for ADHD at the neural level in motor control tasks. The high classification rate—though achieved in a small sample—suggests that cue-P3 and SICI reflect core mechanisms of ADHD. Moreover, these two parameters may turn out as neural markers for ADHD indicating a potential clinical relevance of the findings.

Relation to other dysfunctional patterns in attention deficit hyperactivity disorder

SICI (measured via motor evoked potentials) reflects interneurons in the motor cortex. In our opinion, it seems rather likely that intracortical interneurons are also affected in other frontal areas (particularly the prefrontal cortex) in ADHD. Non-human primate studies (Constantinidis *et al.*, 2002; Gao *et al.*, 2003) suggested a major role of intracortical interneurons of the prefrontal cortex in working memory processes and in shaping the temporal flow of information, domains in which children with ADHD are assumed to have pronounced deficits. Correspondingly, deficiencies in noradrenergic pathways (as reflected in the smaller P3 in cue trials) are probably not restricted to the parietal cortex as noradrenaline arising from the locus coeruleus is also released in the frontal cortex mediating cognition through arousal (Sara and Bouret, 2012). So, we may argue that the same neural mechanisms underlying motor control deviations may account for dysfunctional patterns in other domains in ADHD.

Are findings specific for attention-deficit hyperactivity disorder?

The question may be raised to what extent the results of the combined event-related potential/TMS analysis concerning the neural implementation of motor control can be considered to be specific for ADHD or whether a comparable pattern is expected for other disorders characterized by hypermotoric behaviour and impulsive behaviour, respectively.

In children with tic disorders, we did not find a reduced SICI at rest, but a shortened cortical silent period in earlier studies (Moll *et al.*, 1999, 2001) with effects being additive in children comorbid for ADHD and tic disorders (Moll *et al.*, 2001). In contrast, reduced SICI (at rest) was reported for adults with tic disorders (Ziemann *et al.*, 1997*a*; Heise *et al.*, 2010). Associated disorders and/or adaptation processes may account for this discrepancy. Before the execution of a movement, SICI was reported to increase in adult patients with Tourette's syndrome and not to be statistically different from healthy controls (Heise *et al.*, 2010). Therefore, this pattern clearly differs from the TMS results in the Go condition in the present study where SICI rather tended to decrease in children with ADHD in the pre-movement period.

For ADHD, conduct disorder and the comorbidity of ADHD and conduct disorder, differential patterns regarding attentional and response control processes were obtained in an event-related potential study indicating that the comorbidity of ADHD and conduct disorder represents a separate entity (Banaschewski *et al.*, 2003).

Therefore, based on the findings from single-modality studies, we argue that the findings observed in the present study may be specific for ADHD. Future studies applying the bimodal approach in larger samples may also help to disentangle neural implementation of motor control in the presence of different comorbidities.

Conclusion

Results of the bimodal event-related potential/TMS approach provide strong evidence for deviant neural implementation of motor control in ADHD probably reflecting compensatory mechanisms due to a basal motor cortical inhibitory deficit. In this respect, interpretations from other neurophysiological studies, not taking this inhibitory deficit into account, may have to be adjusted.

Because of the high classification rate of 90% and the nature of the findings, we argue that the neural mechanisms underlying a reduced SICI and a reduced P3 amplitude in cue trials (i.e. intracortical inhibitory interneurons, which are inadequately modulated by mesocortical dopamine as well as a deficient noradrenergic system) may play a key role in the pathophysiology of ADHD. Of course, this does not exclude other core mechanisms for this heterogeneous psychiatric disorder. Moreover, different disturbances at the molecular level (e.g. transporter versus receptor; receptor subtypes) at different loci (cortical versus subcortical) may account for the described result pattern. Nevertheless, the present study may contribute to providing an integrative framework for ADHD and, perspectively, to developing neural markers for ADHD and defining ADHD subtypes based on neural dysfunctions.

Acknowledgements

The authors thank Martin Deinzer and Wolfgang Barth for their valuable support. We are very grateful to the families and particularly the children who participated in our study.
The authors declare no conflicts of interest.

Supplementary material

Supplementary material is available at *Brain* online.

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