# Diminished modulation of preparatory sensorimotor mu rhythm predicts attention-deficit hyperactivity disorder severity

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**TITLE PAGE**

**Title:**

Diminished Modulation of Preparatory Sensorimotor Mu Rhythm Predicts Attention-deficit Hyperactivity Disorder Severity

**Short title:**

Diminished Mu Rhythm Predicts ADHD Severity

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**Conflict of Interest:**

Jan Buitelaar has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly BV, Lundbeck and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. Cornelis Kan participated in an adult-ADHD advisory and consultancy board for Eli Lilly BV and an adult-ADHD academy for Eli Lilly BV. All other authors have nothing to declare.

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**ABSTRACT**

**Background** Attention-deficit hyperactivity disorder (ADHD) is characterized by problems in regulating attention and in suppressing disruptive motor-activity, i.e. hyperactivity and impulsivity. We recently found evidence that aberrant distribution of posterior alpha band oscillations (8-12 Hz) is associated with attentional problems in ADHD. The sensorimotor cortex also produces strong 8-12 Hz band oscillations, namely the mu rhythm, and is thought to have a similar inhibitory function. Here, we now investigate whether problems in distributing alpha band oscillations in ADHD generalize to the mu rhythm in the sensorimotor domain.

**Methods** In a group of adult ADHD (n=17) and healthy control subjects (n=18; aged 21-40 years) oscillatory brain activity was recorded using magneticencephalography during a visuo-spatial attention task. Subjects had to anticipate a target with unpredictable timing and respond by pressing a button.

**Results** Preparing a motor response, the ADHD group failed to increase hemispheric mu lateralization with relatively higher mu power in sensorimotor regions not engaged in the task, as the controls did ($F_{1,33}$=8.70; $p$=.006). Moreover, the ADHD group pre-response mu lateralization not only correlated positively with accuracy ($r_s$=.64; $p$=.0052) and negatively with intra-individual reaction time variability ($r_s$=-.52; $p$=.033), but it also correlated negatively with the score on an ADHD-rating scale ($r_s$=-.53; $p$=.028).

**Conclusions** We suggest that ADHD is associated with an inability to sufficiently inhibit task-irrelevant sensorimotor areas by means of mu oscillatory activity. This could explain disruptive motor-activity in ADHD. These results provide further evidence that impaired modulation of alpha band oscillations is involved in the pathogenesis of ADHD.

21 **TEXT**

22

23 **Introduction**

24 Attention-deficit Hyperactivity Disorder (ADHD) is characterized by a pervasive pattern of
25 developmentally inappropriate inattentive, impulsive and hyperactive behaviors that typically begin
26 during the preschool years and often persist into adulthood (Polanczyk et al., 2007, Fayyad et al., 2007,
27 Association, 2000, Simon et al., 2009). Attention-deficit symptoms cover problems in directing and
28 sustaining attention, whereas hyperactivity and impulsivity symptoms cover a surplus of motor-activity
29 in general and an inability to suppress motor-activity when unwanted or socially inappropriate.

30 A longstanding hypothesis characterizes ADHD as a disorder of cognitive and behavioral inhibition [for
31 reviews see (Nigg, 2005, Sergeant et al., 2003, Barkley, 1997, Adams et al., 2008, Boonstra et al., 2010)].
32 Top-down controlled oscillations in the alpha band (8-12 Hz) are thought to play a key role in functional
33 inhibition of cortical areas [for a review see e.g. (Klimesch et al., 2007, Jensen and Mazaheri, 2010, Foxe
34 and Snyder, 2011)]. In a prior study we reported evidence that failure to regulate cortical alpha activity
35 is related to attentional problems in ADHD. Aberrant posterior hemispheric alpha lateralization was
36 shown to be associated with visuo-spatial attention problems in adults with ADHD (ter Huurne et al.,
37 2013). We now investigate whether these problems in orchestrating alpha band oscillations extend to
38 the sensorimotor domain, as problems in inhibiting motor actions is part of the pathology of ADHD .

39 As in visual areas, oscillations in the alpha band are also observed in sensorimotor cortex known as the
40 mu rhythm. The functional role of the mu rhythm seems to be similar to the visual alpha rhythm. When
41 a motor act is prepared, observed, imagined or executed robust modulations of the mu rhythm are seen
42 over sensorimotor cortex (Stancak and Pfurtscheller, 1996, Pfurtscheller et al., 2006, Babiloni et al.,

2004, Salmelin and Hari, 1994, Muthukumaraswamy et al., 2004, Pfurtscheller and Neuper, 1994, Pfurtscheller et al., 1994). A *decrease* in mu is observed in sensorimotor areas that *are* involved in performing the motor action, while at the same time an *increase* is observed in sensorimotor areas ipsilateral to the engaged body part. With this, it is thought that sensorimotor mu has a similar function as alpha in sensory cortex, to functionally inhibit cortical areas (Neuper et al., 2006, Salmelin and Hari, 1994).

Although mu modulation has been related to failing suppression of motor responses in healthy subjects (Mazaheri et al., 2009), little research has been done on the mu rhythm in ADHD patients. Yordanova et al. measured mid-line electroencephalographic mu-band activity during motor-responses in an auditory attention task in children with ADHD. Although there were no differences in mu suppression during motor response generation, the ADHD group did show mu suppression after stimuli that did not require motor responses (Yordanova et al., 2013). This could support the idea that diminished mu modulation is involved in impulsive motor responding in ADHD. Another magnetoencephalography (MEG) study investigated *somatosensory* mu modulation after median nerve stimulation in adults with ADHD, showing diminished mu reactivity in ADHD, especially with unpredictable stimulation (Dockstader et al., 2009).

Notably, in both patient studies, deviant mu modulation was related to preparation and anticipation. When anticipating and preparing a goal directed motor action task relevant motor regions should be ready to engage on demand, while at the same time activity in task-irrelevant motor areas should be suppressed. In ADHD, mu modulation could be impaired resulting in insufficient inhibition of task-irrelevant cortical areas causing unwanted and disruptive motor-output. To test this hypothesis we set out to investigate 1) whether preparatory sensorimotor mu modulation is impaired in patients with ADHD by evaluating hemispheric mu lateralization; and 2) whether the ability to modulate sensorimotor

mu relates to the ability to suppress disruptive motor actions, as expressed by ADHD symptom severity in daily life. To this end analyses were conducted on pre-existing MEG data recorded in a group of adults with and without ADHD when performing a visual spatial attention task that required (preparing for) motor responses.

## Materials and Methods

The dataset that was used for the analysis was published before elsewhere, for more details see (ter Huurne et al., 2013). The study was approved by the local medical-ethical committee (committee for protection of human subjects of the Arnhem/Nijmegen region; CMO protocol number 2009/260) and was performed according to the declaration of Helsinki. Written informed consent was obtained from all participants prior to study entry.

### *Subjects*

Forty-one adults (ages 21-40 years) were recruited from an existing database, the Dutch cohort of the International Multicenter persistent ADHD CollaboraTion (IMpACT) study (Hoogman et al., 2011). After excluding 6 participants for reasons described below, 17 ADHD patients and 18 IQ, age, handedness and gender matched healthy control subjects remained for final analysis. For demographic information see Table 1. Subjects in the patient group met the DSM-IV-TR criteria of ADHD, and none in the control group did. All participants were assessed using the Diagnostic Interview for Adult ADHD [(Kooij J, 2007), http:/www.divacenter.eu/DIVA.aspx]. In addition, a quantitative measure of clinical symptoms was obtained using the self-report of the ADHD DSM-IV Rating Scale (DuPaul G, 1998, Kooij et al., 2005). General exclusion criteria were any (co-morbid) psychiatric, as assessed using the Structured Clinical Interview for DSM-IV (SCID-I), or neurological disorder and prescription medication use (other than psychostimulant or anti-conceptive drugs). If subjects used psychostimulants they were requested to temporarily discontinue their medication (at least 18 hours) before and during the experiment. An

estimation of IQ was made using a subset of the Wechsler Adult Intelligence Scale (WAIS). Handedness was determined using the Edinburgh Handedness Inventory (Oldfield, 1971).

*Task*

We used a cued visuo-spatial covert attention task. For the current study the cuing is not of interest. The basic outline of each trial was as follows (also see Figure 1). After a baseline period of 0.6 s with no visual stimulation the trial would start. The start of the trial was marked by the central presentation of a visual cue (an arrow pointing to the left or right) or in 1/6 of the trials a question mark (neutral cue condition) flanked on both sides by a random-dot-kinematogram (RDK). The cue would disappear after 0.2 s while the RDKs stayed on. After an interval of 0.6 to 1.1 s (jittered) the dots in the RDKs would start moving coherently for 0.3 s, on one side horizontally (left- or rightwards) and on the other vertically (up- or downwards). Subjects were instructed to detect the direction of the horizontal movement. In 80 % of the trials the horizontal movement would be in the RDK on the cued side (valid cue trials) and in 20 % of the trials in the RDK on the non-cued side (invalid cue trials). Subjects were instructed to respond as quickly as possible by pressing a left (for leftward movement) or right button (for leftward movement) using the index and middle finger of their dominant hand. After each trial, feedback was given on accuracy. A total of 864 trials were presented lasting 2-2.5 s. A session lasted about 45 minutes per subject. Prior to the recordings, subjects participated in a practice session with 120 trials lasting 5 minutes. During the experiment subjects were seated in front of a projector screen, with a distance of 72 cm between eyes and screen. Subjects were instructed not to move during the experimental trials. The visual stimuli were presented using an EIKI XL 100 projector with 60 Hz refresh rate. Behavioral responses were collected with a Current Designs HH-1x4-C fiber optic response device. We used the software Matlab Psychtoolbox for presenting the stimuli.

*MEG acquisition*

A 275-sensor whole-head MEG system with axial gradiometers (CTF, Inc., Vancouver, Canada), located at the Donders Centre for Cognitive Neuroimaging, Nijmegen was used to record oscillatory brain activity. Signals were low-pass filtered at 300 Hz and sampled at 1200 Hz. Eye-movements were identified in records using the electrooculogram (EOG) from electrodes placed at the lateral canthus of each eye, eye-blinks from electrodes placed above and below the left eye. Using three head localization coils (positioned on the nasion and two ears) x-, y- and z-coordinates were recorded to calculate head positions with respect to the MEG sensor array (Stolk et al., 2013).

*Data analysis*

For each subject behavioral performance in terms of percent correct responses (accuracy) was determined. One control subject was excluded from further analyses because performance was at chance level. Offline analysis of the MEG recordings was done using Matlab 7.5.0 and the Fieldtrip software package (http:/www.ru.nl/fcdonders/fieldtrip/). Data was down-sampled to 600 Hz and low-pass filtered at 150 Hz. For each trial head-movement was calculated with respect to the head-position in the first trial and with respect to the preceding trial (inter-trial head movement). For one of the ADHD subjects data on head position was missing due to a technical error. For the rest of the subjects trials with head-movement that exceeded 1 cm with respect to the first trial and beyond 1 mm with respect to the prior trial were rejected. The MEG signals were transformed from axial gradiometers to planar gradients to facilitate the interpretation of the topographic mapping of the magnetic fields (Bastiaansen and Knosche, 2000). The planar gradient makes data interpretation easier since the strongest field is situated above the neural source. Trials were visually inspected for horizontal shifts of gaze and muscle artifacts, rejecting trials with extremely high variance, muscle artifacts and sustained horizontal EOG shifts of more than 50 µV from baseline. Three control and two ADHD subjects were excluded from further analyses because more than 2/3 of their trials had to be rejected due to horizontal eye-movement. Subsequently, independent component analyses (ICA) was used to identify eye-blink and

heartbeat artifacts in the data (Jung et al., 2000). Artifactual components were semi-automatically identified by correlations between independent components (ICs) activation time courses and the vertical EOG and electrocardiography time courses. ICs with the strongest correlation were visually inspected and rejected.

For each trial, time-frequency representations (TFRs) of power were calculated with respect to trial onset (cue-locked; -0.6 to 1.4 s; ) and with respect to the button press (response-locked; -1.4 to 0.6 s). A fast Fourier transformation (FFT) approach was used. For frequencies between 5 and 30 Hz with a resolution of 1 Hz an adaptive sliding window (shifting in 0.05 s steps) of five cycles length ($\Delta t = 5/f$) was used after multiplying a Hanning taper. To calculate event related synchronization (ERS) and event related desynchronization (ERD) TFRs of all trials were baseline corrected using a relative change baseline of -0.25 to -0.1 s with respect to trial onset. The data of all trials were averaged, using all condition types (neutral cue, valid cue and invalid cue) both correctly and incorrectly answered.

To select two regions of interest (ROIs) the cue-locked data was used, averaging the TFR data of all trials and all subjects irrespective of group or handedness (n = 35). To minimize selection bias we avoided using the response locked data and contrasts that were later used to investigate the main hypotheses [see next paragraphs; (Kilner, 2013)]. Selection criteria for the RIOs were: 2 homologue groups, one group in each hemisphere, of 3 contingent sensors with the strongest ERS in the 10-12 Hz frequency band, in the 0.4 to 0.8 s time-interval after trial onset (cue-locked data). This topographic distribution and frequency band correspond to prior reports of sensorimotor mu ERS (Pfurtscheller et al., 2000, Pfurtscheller et al., 2006, Pfurtscheller and Neuper, 1997). The time interval was chosen such that subjects were preparing for an upcoming motor action, but at the same time avoiding spill of the actual motor activity of the button-press.

Next, for each subject time resolved hemispheric mu lateralization indices (MLI) were calculated using the left and right ROI; contra- and ipsilateral refers to the ROI with respect to the hand used for responding:

$$MLI = \frac{\mu\, power_{Ipsilateral} - \mu\, power_{Contralateral}}{\mu\, power_{Ipsilateral} + \mu\, power_{Contralateral}} \qquad \textbf{Eq. 1}$$

This allows the use of the same measure of mu lateralization for all subjects, irrespective of which hand was used for button presses.

*Statistical analysis*

In order to statistically test differences in hemispheric mu lateralization two periods of interest were defined: (1) A baseline interval (-0.25 to -0.1 s with respect to trial onset), to assess whether there were differences in MLI between the groups in rest (no motor preparation); and (2) a pre-response interval, to assess whether there were differences in MLI between the groups when preparing for a motor action. The pre-response interval was defined such that it was as long as possible without overlapping with the baseline interval or the actual motor action. To do so, the length of the frequency adaptive sliding window that was used for the FFT was taken into account (see *Data analysis* section). The length is greatest at the lowest frequency, 10 Hz. With a window length of 5 cycles for 10 Hz, the window length was 0.5 s (5/10 Hz), 0.25 s on each side of the time-point. With a minimal trial-length of 0.8 s plus reaction time, we (conservatively) defined the start of the pre-response interval with respect to the button-press as -0.9 s plus the 0.25 s correction for window length (-0.65 s). The end was defined as the time of button-press (t = 0 s) minus the 0.25 s correction for window length (-0.25 s). For each subject mean MLI was calculated for these time intervals and differences were statistically tested. Repeated measures ANOVAs were used, with a between-subject factor group (control and ADHD) and a within-subject factor time interval (baseline and pre-response interval). All statistical analyses we done using SPSS 19.0 for Windows (IBM SPSS Inc., Chicago, Illinois).

## Results

There were no significant differences in demographic variables between the groups (Table 1), nor in total number of trials after rejections (control: 677±144 [mean, SD]; ADHD: 701±129; $p$ = .61), nor in mean intra-trial head movement (control: 0.052±0.023 mm; ADHD: 0.048±0.025 mm; $p$ = .66), as shown using independent samples t-tests. As expected, groups did differ in score on the ADHD self-report (control: 2.28±2.76; ADHD: 11.1±3.09; $p$ <.001; see Table 1).

*Behavioral data*

As reported in (ter Huurne et al., 2013) there were differences between the groups in task performance concerning effect of cuing. With respect to reaction times, the ADHD group did not benefit from cuing as the controls did. With respect to accuracy, the ADHD group showed a lack of cuing effect for right targets. For more details see (ter Huurne et al., 2013). For the current study the effect of cuing was not of interest, so the data of all conditions independent of cue-type were collapsed. There were no statistically significant differences between the groups in overall accuracy (control: 82.9±10.2%; ADHD: 80.7±11.7%; $p$ = .55), nor in overall mean reaction time (control: 642±93.1 ms; ADHD: 626±90.4 ms; $p$ = .59). As an additional measure of performance we regarded intra-individual variance in reaction time, as increased variability has been associated with ADHD [for a review see (Kofler et al., 2013)]. Also in our sample reaction time coefficient of variability (SD/mean) was higher in the ADHD group, but this difference was not statistically significant, although trending (control: 0.21±0.036; ADHD: 0.24±0.067; $p$ = .11, equal variances not assumed; independent samples t-tests).

*Sensorimotor Mu Lateralization*

First, the two ROIs were identified using the cue-locked TFR data as described in the method section (n = 35; f = 10-12 Hz; t = 0.4 – 0.8 s). Figure 2 A shows the two homologue groups of 3 contingent sensors with the strongest ERS in the specified time interval and frequency band that were selected. The

topography is consistent with prior reports (Pfurtscheller et al., 2000, Pfurtscheller et al., 2006, Pfurtscheller and Neuper, 1997). Figure 2B shows the TFRs and topographic plots for both the cue-locked and response-locked data of the two groups separately. The TFRs of both ROIs show an increase in the 10-12 Hz mu band in the preparation interval. Although the overall mu power increase appeared to be weaker in the ADHD group (especially in the right hemisphere, see Figure 2B right panels) the topography, time course and frequency range of mu were similar between the groups.

Using the selected ROIs, we then calculated the MLI (Eq. 1) for each subject. The MLI characterizes the hemispheric lateralization in the mu band with respect the hand used for the button press. Figure 3A shows the time course of mean MLI for both groups. A positive MLI corresponds to a relatively larger mu power in ipsilateral sensors as compared to contralateral sensors with respect to the response hand, i.e. a relatively increased mu activity in sensorimotor areas that are not engaged in the task. In the control group mu lateralization started to increase immediately after trial onset and kept increasing until the button press was made. The ADHD group showed a delayed and smaller MLI increase.

After calculating MLI for the baseline and pre-response interval, a repeated measures ANOVA was done with a between subjects factor group (control and ADHD) and a within subject factor time interval (baseline and pre-response interval). The analysis revealed a significant 2-way group × time interval interaction ($F_{1,33}$ = 8.70; $p$ = .006), see Figure 3B. Post hoc analyses showed that in the control group there was a highly significant difference between the MLI in the baseline interval compared to the pre-response interval (respectively [resp.]: 0.004±0.071; 0.216±0.067 [mean, SEM]; $p$ < .0001). In contrast, there was no significant difference between the baseline and pre-response interval in the ADHD group (resp.: 0.042±0.054; 0.055±0.046; $p$ = .81). Comparing the groups, pre-response MLI was borderline significantly weaker in the ADHD group ($p$ = .059), which is likely to explain the overall effect. There was no significant difference in baseline MLI between the groups ($p$ = .61).

We conclude that there were distinct differences between the groups in terms of mu lateralization (Figure 3). The controls strongly lateralized mu band oscillations when preparing for the button-press, with relatively higher mu power in sensors corresponding to the sensorimotor cortex ipsilateral to the responding hand. In the ADHD group, however, there was no such preparatory lateralization of mu.

*Correlations between Mu Lateralization and ADHD symptoms*

Next we investigated whether this diminished preparatory lateralization of mu oscillatory activity is associated with ADHD symptoms in daily life. The analysis revealed a statistically significant negative correlation between the individual pre-response MLI and the individual score on the ADHD self report in the ADHD group (Spearman correlation; $r_s$ = -.53; $p$ = .028; Figure 4A). This means that the less an ADHD subject was able to lateralize the mu activity in preparation of a motor action, the more ADHD symptoms were present in daily life. Additional analyses revealed that pre-response mu lateralization was also predictive of performance on the task. A strong positive correlation was found between pre-response MLI and overall accuracy ($r_s$ = .64; $p$ = .0052; Figure 4B) and a negative correlation between pre-response MLI and reaction time coefficient of variability ($r_s$ = -.52; $p$ = .033; Figure 4C). This shows that in the ADHD patient group relatively weaker preparatory mu lateralization was associated with relatively higher error rates and stronger intra-individual variability in reaction time. No significant correlation was found between pre-response MLI and mean reaction time ($r_s$ = .29; $p$ = .25).

In sum, the control group showed strong modulation of mu oscillatory activity in preparation of an upcoming goal directed motor-action, with relatively higher mu power in task irrelevant sensorimotor regions. However, the ADHD patient group failed to show this preparatory mu lateralization. Moreover, the lack of preparatory mu lateralization in the ADHD group was not only predictive of performance on the task, but also of ADHD symptoms in daily life.

**Discussion**

In the present study we investigated whether ADHD is associated with impaired modulation of the sensorimotor mu rhythm. MEG signals were recorded in a group of ADHD patients and a group of healthy controls performing a visual attention task involving preparation of a motor response.

As expected, robust mu rhythm modulation was measured in sensors corresponding to sensorimotor areas when subjects prepared for a motor response. In the healthy controls the increase in mu synchronization was strongly lateralized relative to the hand used for the button press, with relatively higher mu power in the ipsilateral compared to the contralateral hemisphere. The ADHD group however failed to show this increase in mu-laterality in preparation of the response. Moreover, the degree of preparatory mu-lateralization was shown to correlate negatively with the number of daily life symptoms of the ADHD patients. Additionally, we found that the individual degree of pre-response mu lateralization was predictive of accuracy on the task (positive correlation) and intra-individual variability in reaction time (negative correlation). Taken together, these results indicate problems in adequately modulating sensorimotor mu activity in preparation of motor actions in patients with ADHD. Not only is the individual extend of these problems predictive of behavioral task performance, it is also predictive of the amount of experienced problems in controlling disruptive motor activity and attentional processes in daily life.

Like in anticipatory attention, motor preparation is characterized by selection (Brunia 1999). In order to achieve behavioral goals relevant motor regions are selected and recruited, while others are selectively suppressed. In the current study subjects had to anticipate a target with unpredictable timing, ready to respond with a predetermined motor action. Crucial for maintaining the selected motor program is functional inhibition of task irrelevant areas to guard it from disruption. Corroborating prior studies (Babiloni et al., 2004, Pfurtscheller et al., 1994) the control group showed a relative increase in mu

rhythm over task irrelevant sensorimotor areas in preparation of the response to prevent disruption or interruption by task irrelevant movement.

Interestingly, in the ADHD group this demarcation between task relevant and task irrelevant areas as expressed by a difference in mu activity was diminished. Yordanova et al. found an abnormal drop in mu reactive to a non-target in ADHD (Yordanova et al., 2013), likely corresponding to failing *reactive* suppression of motor regions. We now show that ADHD is also characterized by failing *proactive* functional inhibition of motorcortical areas by tonically increasing mu to *prevent* unwanted movement (Aron, 2011).

The individual ability to lateralize mu proved to be predictive of behavioral performance on the current task and ADHD severity as measured by the ADHD-selfreport. This underlines the importance of functional inhibition of the sensorimotor cortex by mu, not only in an experimental setting, but also in daily life function. Furthermore, modulation of sensorimotor mu could prove a useful biological marker of ADHD, mutually enforced by other disorder specific alterations in neuronal oscillatory activity (Mazaheri et al., 2014, Mazaheri et al., 2010).

At this point, the exact neuro-anatomical origin of the reduced mu lateralization in ADHD is unknown. Likely candidates are disruptions in function of the prefrontal cortex and the basal ganglia (Rubia et al., 1999, Chambers et al., 2009, Clark et al., 2007, Rubia et al., 2001, Cubillo et al., 2010, Teicher et al., 2000, Majid et al., 2013) and also the thalamus (Saalmann et al., 2012, Hughes and Crunelli, 2005, Devos et al., 2006).

A methodological limitation to the present study is that the data was used for analyses in a prior study (ter Huurne et al., 2013). Although it is encouraged to maximize benefits from patient datasets, it is hard to statistically correct for this. Furthermore, self report measures were used to assess daily life ADHD

symptoms. Clinically rated symptom scales could be preferable as a subset of ADHD patients is recognized to be unable to reliably rate their symptoms themselves.

The present results are further evidence that impaired regulation of alpha band activity is part of the neural substrate of ADHD. After showing behavioral implications of aberrant modulation of alpha band activity in the sensory system in ADHD (ter Huurne et al., 2013) we now show aberrant modulation of same frequency band mu rhythm in the motor system, which is predictive of ADHD severity. Combined this presents evidence for a central role for aberrations in modulation and orchestration of alpha band oscillations in ADHD, affecting multiple functional domains. Future studies should focus on dynamics and interactions of alpha band oscillatory activity on a network level. In addition, the effect of pharmacological interventions on alpha modulation should be assessed.

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## Conflict of Interest

Jan Buitelaar has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly BV, Lundbeck and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. Cornelis Kan participated in an adult-ADHD advisory and consultancy board for Eli Lilly BV and an adult-ADHD academy for Eli Lilly BV. All other authors have nothing to declare.

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**Legends**

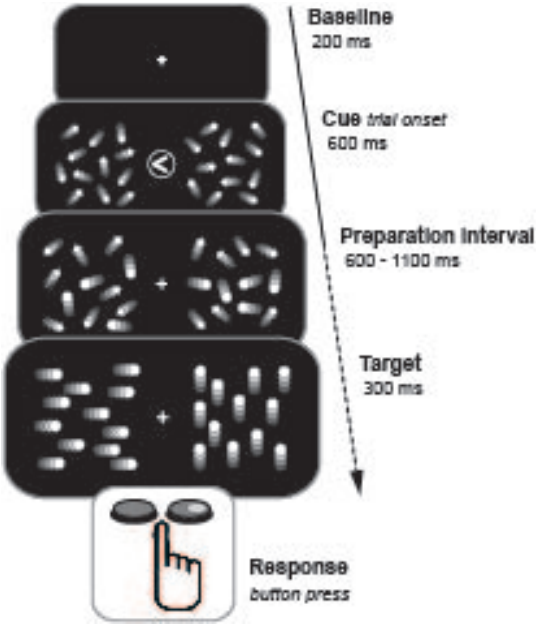


Figure 1. Schematic overview of the experimental paradigm. After a baseline period an attentional cue flanked by random-dot-kinetograms (RDK's) demarked trial onset. Cue validity was 80 %. After a jittered preparation interval, in one of the RDK's the dots would start moving coherently in horizontal direction. Subjects had to report as quickly as possible in which direction the dots had moved by pressing one of two buttons using their dominant hand.

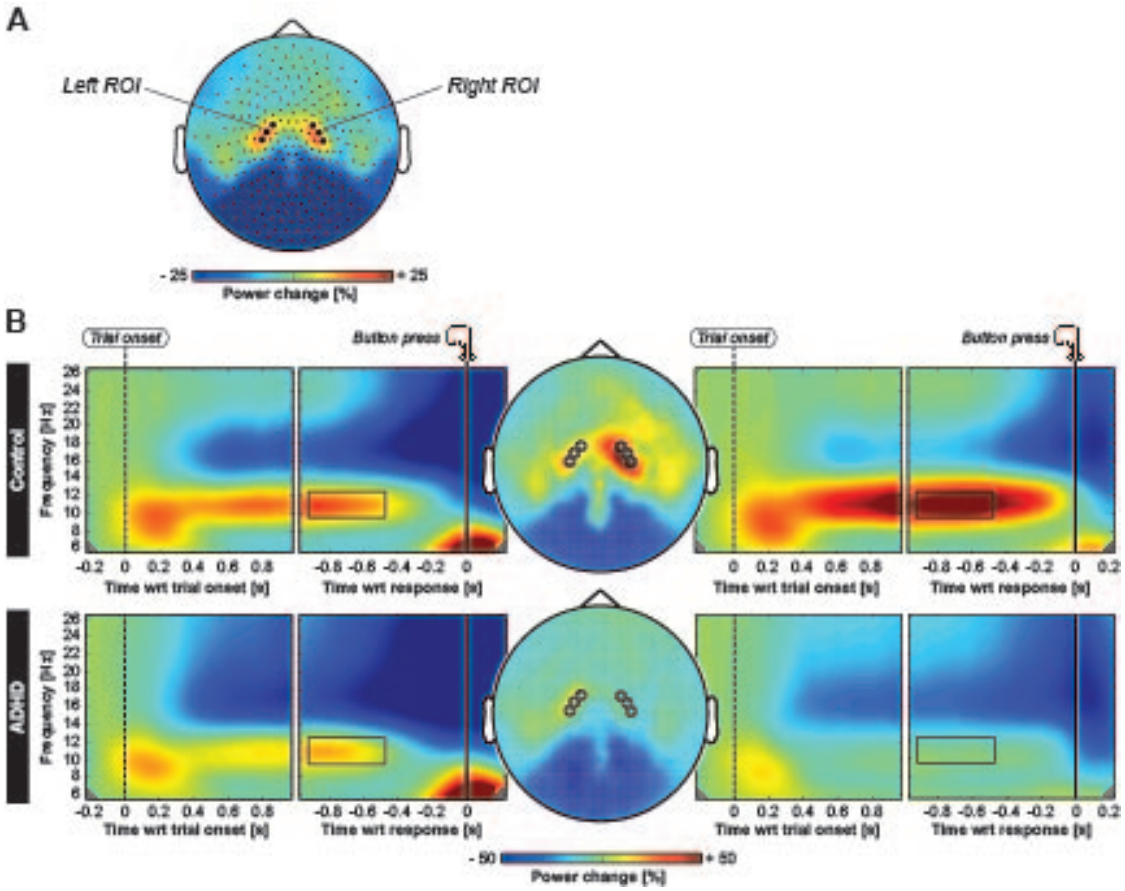


Figure 2. (A) Topographic representation of mean power of all subjects (n=35), frequency range 10 to 12 Hz, time interval 0.4 to 0.8 s with respect to trial onset (cue-locked data). Black dots denote the sensors with the strongest ERS which were selected as the left and right ROIs that were later used to calculate the mu lateralization index. (B) Topographic plots and TFRs of left and right ROIs for both groups separately (wrt: with respect to). Left panels show the TFRs of the left ROI, the right panels the TFRs of the right ROI. Dotted lines denote trial onset, solid lines denote time of response. The squares denote the corresponding time and frequency of the topographic maps shown in the middle. Black and white circles denote the left and right ROI sensors. Although mu-band ERS seems less pronounced in the ADHD group (especially for the right hemisphere), the topography, time course and frequency range of mu are quite similar between the groups.

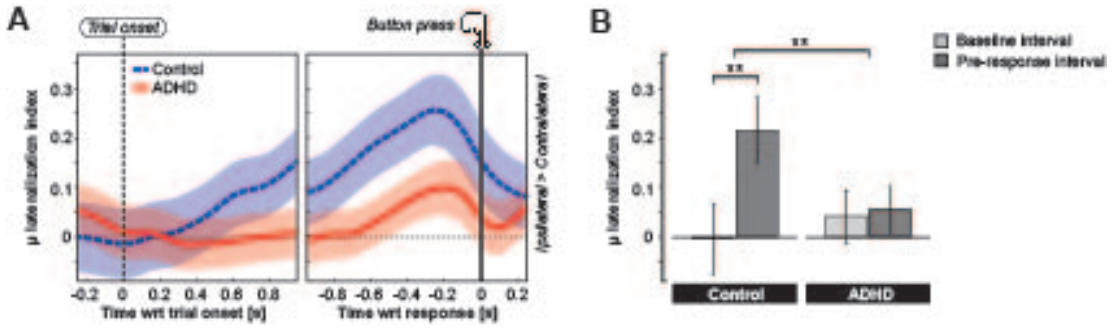


Figure 3. (A) Mean mu lateralization index (MLI) plotted against time, lighter color denotes standard error of the mean (wrt: with respect to). Left panel shows MLI with respect to trial onset, right panel shows MLI with respect to the button-press (response). A positive MLI means higher mu in sensors ipsilateral than cortralateral of the responding hand. Note that in the ADHD group (red solid line) mu lateralization starts later and is smaller than in the control group (blue dotted line). (B) Mean MLI in the baseline interval ($t$ = -0.25 to -0.1 s with respect to trial onset) and the pre-response interval ($t$ = -0.65 to -0.25 s with respect to button-press) for both groups. In contrast to the control group, the ADHD group does not show a significant increase in MLI.

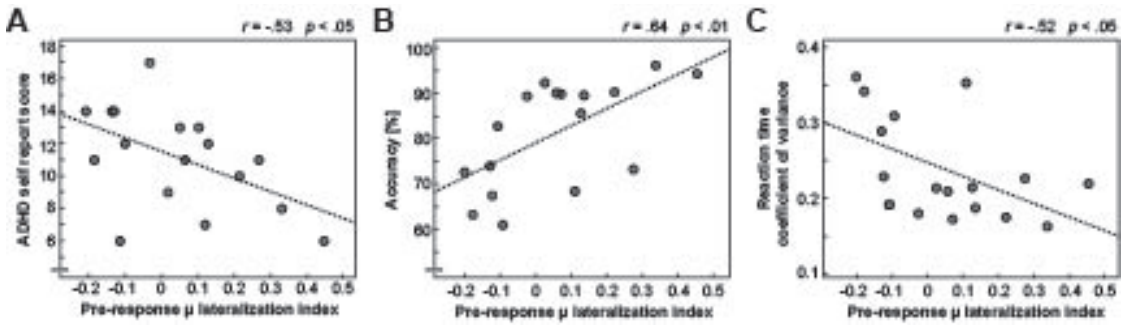


Figure 4. (A) Individual pre-response mu lateralization index (MLI) of the ADHD group plotted as a function of number of ADHD symptoms as measured by the ADHD self report. There is a negative linear relationship between mu lateralization strength and ADHD severity in daily life. (B) Pre-response

MLI of the ADHD group plotted against accuracy on the task, showing a strong positive relationship between the degree of mu lateralization and accuracy. (C) Pre-response MLI of the ADHD group plotted against reaction time coefficient of variability. Stronger mu lateralization is associated with smaller intra-individual variability in reaction time.