

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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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

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

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

11 **Results** Preparing a motor response, the ADHD group failed to increase hemispheric mu lateralization
12 with relatively higher mu power in sensorimotor regions not engaged in the task, as the controls did
13 ($F_{1,33}=8.70$; $p=.006$). Moreover, the ADHD group pre-response mu lateralization not only correlated
14 positively with accuracy ($r_s=.64$; $p=.0052$) and negatively with intra-individual reaction time variability
15 ($r_s=-.52$; $p=.033$), but it also correlated negatively with the score on an ADHD-rating scale ($r_s=-.53$;
16 $p=.028$).

17 **Conclusions** We suggest that ADHD is associated with an inability to sufficiently inhibit task-irrelevant
18 sensorimotor areas by means of mu oscillatory activity. This could explain disruptive motor-activity in
19 ADHD. These results provide further evidence that impaired modulation of alpha band oscillations is
20 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.,

43 2004, Salmelin and Hari, 1994, Muthukumaraswamy et al., 2004, Pfurtscheller and Neuper, 1994,
44 Pfurtscheller et al., 1994). A *decrease* in mu is observed in sensorimotor areas that *are* involved in
45 performing the motor action, while at the same time an *increase* is observed in sensorimotor areas
46 ipsilateral to the engaged body part. With this, it is thought that sensorimotor mu has a similar function
47 as alpha in sensory cortex, to functionally inhibit cortical areas (Neuper et al., 2006, Salmelin and Hari,
48 1994).

49 Although mu modulation has been related to failing suppression of motor responses in healthy subjects
50 (Mazaheri et al., 2009), little research has been done on the mu rhythm in ADHD patients. Yordanova et
51 al. measured mid-line electroencephalographic mu-band activity during motor-responses in an auditory
52 attention task in children with ADHD. Although there were no differences in mu suppression during
53 motor response generation, the ADHD group did show mu suppression after stimuli that did not require
54 motor responses (Yordanova et al., 2013). **This could support the idea that diminished mu modulation is
55 involved in impulsive motor responding in ADHD. Another magnetoencephalography (MEG) study
56 investigated somatosensory mu modulation after median nerve stimulation in adults with ADHD,
57 showing diminished mu reactivity in ADHD, especially with unpredictable stimulation (Dockstader et al.,
58 2009).**

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

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

70 **Materials and Methods**

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

76 *Subjects*

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

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

91 *Task*

92 We used a cued visuo-spatial covert attention task. For the current study the cuing is not of interest.
93 The basic outline of each trial was as follows (also see Figure 1). After a baseline period of 0.6 s with no
94 visual stimulation the trial would start. The start of the trial was marked by the central presentation of a
95 visual cue (an arrow pointing to the left or right) or in 1/6 of the trials a question mark (neutral cue
96 condition) flanked on both sides by a random-dot-kinematogram (RDK). The cue would disappear after
97 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
98 moving coherently for 0.3 s, on one side horizontally (left- or rightwards) and on the other vertically (up-
99 or downwards). Subjects were instructed to detect the direction of the horizontal movement. In 80 % of
100 the trials the horizontal movement would be in the RDK on the cued side (valid cue trials) and in 20 % of
101 the trials in the RDK on the non-cued side (invalid cue trials). Subjects were instructed to respond as
102 quickly as possible by pressing a left (for leftward movement) or right button (for leftward movement)
103 using the index and middle finger of their dominant hand. After each trial, feedback was given on
104 accuracy. A total of 864 trials were presented lasting 2-2.5 s. A session lasted about 45 minutes per
105 subject. Prior to the recordings, subjects participated in a practice session with 120 trials lasting 5
106 minutes. During the experiment subjects were seated in front of a projector screen, with a distance of
107 72 cm between eyes and screen. Subjects were instructed not to move during the experimental trials.
108 The visual stimuli were presented using an EIKI XL 100 projector with 60 Hz refresh rate. Behavioral
109 responses were collected with a Current Designs HH-1x4-C fiber optic response device. We used the
110 software Matlab Psychtoolbox for presenting the stimuli.

111 *MEG acquisition*

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

119 *Data analysis*

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

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

140 For each trial, time-frequency representations (TFRs) of power were calculated with respect to trial
141 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
142 fast Fourier transformation (FFT) approach was used. For frequencies between 5 and 30 Hz with a
143 resolution of 1 Hz an adaptive sliding window (shifting in 0.05 s steps) of five cycles length ($\Delta t = 5/f$) was
144 used after multiplying a Hanning taper. To calculate event related synchronization (ERS) and event
145 related desynchronization (ERD) TFRs of all trials were baseline corrected using a relative change
146 baseline of -0.25 to -0.1 s with respect to trial onset. The data of all trials were averaged, using all
147 condition types (neutral cue, valid cue and invalid cue) both correctly and incorrectly answered.

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

158

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

$$162 \quad MLI = \frac{\mu power_{Ipsilateral} - \mu power_{Contralateral}}{\mu power_{Ipsilateral} + \mu power_{Contralateral}} \quad \text{Eq. 1}$$

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

165 *Statistical analysis*

166 In order to statistically test differences in hemispheric mu lateralization two periods of interest were
 167 defined: (1) A baseline interval (-0.25 to -0.1 s with respect to trial onset), to assess whether there were
 168 differences in MLI between the groups in rest (no motor preparation); and (2) a pre-response interval, to
 169 assess whether there were differences in MLI between the groups when preparing for a motor action.

170 The pre-response interval was defined such that it was as long as possible without overlapping with the
 171 baseline interval or the actual motor action. To do so, the length of the frequency adaptive sliding
 172 window that was used for the FFT was taken into account (see *Data analysis* section). The length is
 173 greatest at the lowest frequency, 10 Hz. With a window length of 5 cycles for 10 Hz, the window length
 174 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
 175 reaction time, we (conservatively) defined the start of the pre-response interval with respect to the
 176 button-press as -0.9 s plus the 0.25 s correction for window length (-0.65 s). The end was defined as the
 177 time of button-press ($t = 0$ s) minus the 0.25 s correction for window length (-0.25 s). For each subject
 178 mean MLI was calculated for these time intervals and differences were statistically tested. Repeated
 179 measures ANOVAs were used, with a between-subject factor group (control and ADHD) and a within-
 180 subject factor time interval (baseline and pre-response interval). All statistical analyses we done using
 181 SPSS 19.0 for Windows (IBM SPSS Inc., Chicago, Illinois).

182 **Results**

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

188 *Behavioral data*

189 As reported in (ter Huurne et al., 2013) there were differences between the groups in task performance
190 concerning effect of cuing. With respect to reaction times, the ADHD group did not benefit from cuing as
191 the controls did. With respect to accuracy, the ADHD group showed a lack of cuing effect for right
192 targets. For more details see (ter Huurne et al., 2013). For the current study the effect of cuing was not
193 of interest, so the data of all conditions independent of cue-type were collapsed. There were no
194 statistically significant differences between the groups in overall accuracy (control: $82.9 \pm 10.2\%$; ADHD:
195 $80.7 \pm 11.7\%$; $p = .55$), nor in overall mean reaction time (control: 642 ± 93.1 ms; ADHD: 626 ± 90.4 ms; $p =$
196 $.59$). As an additional measure of performance we regarded intra-individual variance in reaction time, as
197 increased variability has been associated with ADHD [for a review see (Kofler et al., 2013)]. Also in our
198 sample reaction time coefficient of variability (SD/mean) was higher in the ADHD group, but this
199 difference was not statistically significant, although trending (control: 0.21 ± 0.036 ; ADHD: 0.24 ± 0.067 ; p
200 $= .11$, equal variances not assumed; independent samples t-tests).

201 *Sensorimotor Mu Lateralization*

202 First, the two ROIs were identified using the cue-locked TFR data as described in the method section ($n =$
203 35 ; $f = 10\text{-}12$ Hz; $t = 0.4 - 0.8$ s). Figure 2 A shows the two homologue groups of 3 contingent sensors
204 with the strongest ERS in the specified time interval and frequency band that were selected. The

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

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

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

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

232 *Correlations between Mu Lateralization and ADHD symptoms*

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

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

250 **Discussion**

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

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

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

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

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

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

287 **At this point, the exact neuro-anatomical origin of the reduced mu lateralization in ADHD is unknown.**
288 **Likely candidates are disruptions in function of the prefrontal cortex and the basal ganglia (Rubia et al.,**
289 **1999, Chambers et al., 2009, Clark et al., 2007, Rubia et al., 2001, Cubillo et al., 2010, Teicher et al.,**
290 **2000, Majid et al., 2013) and also the thalamus (Saalman et al., 2012, Hughes and Crunelli, 2005, Devos**
291 **et al., 2006).**

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

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

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

305

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319

320 **Conflict of Interest**

321 Jan Buitelaar has been in the past 3 years a consultant to/member of advisory board of/and/or speaker
 322 for Janssen Cilag BV, Eli Lilly BV, Lundbeck and Servier. He is not an employee of any of these companies,
 323 and not a stock shareholder of any of these companies. He has no other financial or material support,
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 325 and consultancy board for Eli Lilly BV and an adult-ADHD academy for Eli Lilly BV. All other authors have
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328 **References**

- 329 ADAMS, Z. W., DEREFINKO, K. J., MILICH, R. & FILLMORE, M. T. 2008. Inhibitory functioning across ADHD
 330 subtypes: recent findings, clinical implications, and future directions. *Dev Disabil Res Rev*, 14,
 331 268-75.
- 332 ARON, A. R. 2011. From reactive to proactive and selective control: developing a richer model for
 333 stopping inappropriate responses. *Biol Psychiatry*, 69, e55-68.
- 334 ASSOCIATION, A. P. 2000. *Diagnostic and statistical manual of mental disorders (4th ed., text rev.)*,
 335 Washington, DC, American Psychiatric Press.
- 336 BABILONI, C., BRANCUCCI, A., ARENDT-NIELSEN, L., BABILONI, F., CAPOTOSTO, P., CARDUCCI, F.,
 337 CINCOTTI, F., ROMANO, L., CHEN, A. C. & ROSSINI, P. M. 2004. Alpha event-related
 338 desynchronization preceding a go/no-go task: a high-resolution EEG study. *Neuropsychology*, 18,
 339 719-28.
- 340 BARKLEY, R. A. 1997. Behavioral inhibition, sustained attention, and executive functions: constructing a
 341 unifying theory of ADHD. *Psychol Bull*, 121, 65-94.
- 342 BASTIAANSEN, M. C. & KNOSCHE, T. R. 2000. Tangential derivative mapping of axial MEG applied to
 343 event-related desynchronization research. *Clin Neurophysiol*, 111, 1300-5.
- 344 BOONSTRA, A. M., KOIJ, J. J., OOSTERLAAN, J., SERGEANT, J. A. & BUITELAAR, J. K. 2010. To act or not
 345 to act, that's the problem: primarily inhibition difficulties in adult ADHD. *Neuropsychology*, 24,
 346 209-21.
- 347 CHAMBERS, C. D., GARAVAN, H. & BELLGROVE, M. A. 2009. Insights into the neural basis of response
 348 inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev*, 33, 631-46.
- 349 CLARK, L., BLACKWELL, A. D., ARON, A. R., TURNER, D. C., DOWSON, J., ROBBINS, T. W. & SAHAKIAN, B. J.
 350 2007. Association between response inhibition and working memory in adult ADHD: a link to
 351 right frontal cortex pathology? *Biol Psychiatry*, 61, 1395-401.
- 352 CUBILLO, A., HALARI, R., ECKER, C., GIAMPIETRO, V., TAYLOR, E. & RUBIA, K. 2010. Reduced activation
 353 and inter-regional functional connectivity of fronto-striatal networks in adults with childhood
 354 Attention-Deficit Hyperactivity Disorder (ADHD) and persisting symptoms during tasks of motor
 355 inhibition and cognitive switching. *J Psychiatr Res*, 44, 629-39.

- 356 DEVOS, D., SZURHAJ, W., REYNS, N., LABYT, E., HOUDAYER, E., BOURRIEZ, J. L., CASSIM, F.,
 357 KRYSTKOWIAK, P., BLOND, S., DESTEE, A., DERAMBURE, P. & DEFEBVRE, L. 2006. Predominance
 358 of the contralateral movement-related activity in the subthalamo-cortical loop. *Clin*
 359 *Neurophysiol*, 117, 2315-27.
- 360 DOCKSTADER, C., GAETZ, W., CHEYNE, D. & TANNOCK, R. 2009. Abnormal neural reactivity to
 361 unpredictable sensory events in attention-deficit/hyperactivity disorder. *Biol Psychiatry*, 66, 376-
 362 83.
- 363 DUPAUL G, P. T., ANASTOPOULOS A 1998. *ADHD Rating Scale–IV: Checklists, Norms and Clinical*
 364 *Interpretation*, New York, Guilford Press.
- 365 FAYYAD, J., DE GRAAF, R., KESSLER, R., ALONSO, J., ANGERMEYER, M., DEMYTTENAERE, K., DE
 366 GIROLAMO, G., HARO, J. M., KARAM, E. G., LARA, C., LEPINE, J. P., ORMEL, J., POSADA-VILLA, J.,
 367 ZASLAVSKY, A. M. & JIN, R. 2007. Cross-national prevalence and correlates of adult attention-
 368 deficit hyperactivity disorder. *Br J Psychiatry*, 190, 402-9.
- 369 FOXE, J. J. & SNYDER, A. C. 2011. The Role of Alpha-Band Brain Oscillations as a Sensory Suppression
 370 Mechanism during Selective Attention. *Front Psychol*, 2, 154.
- 371 HOOGMAN, M., AARTS, E., ZWIERS, M., SLAATS-WILLEMSE, D., NABER, M., ONNINK, M., COOLS, R., KAN,
 372 C., BUITELAAR, J. & FRANKE, B. 2011. Nitric oxide synthase genotype modulation of impulsivity
 373 and ventral striatal activity in adult ADHD patients and healthy comparison subjects. *Am J*
 374 *Psychiatry*, 168, 1099-106.
- 375 HUGHES, S. W. & CRUNELLI, V. 2005. Thalamic mechanisms of EEG alpha rhythms and their pathological
 376 implications. *Neuroscientist*, 11, 357-72.
- 377 JENSEN, O. & MAZAHERI, A. 2010. Shaping functional architecture by oscillatory alpha activity: gating by
 378 inhibition. *Front Hum Neurosci*, 4, 186.
- 379 JUNG, T. P., MAKEIG, S., HUMPHRIES, C., LEE, T. W., MCKEOWN, M. J., IRAGUI, V. & SEJNOWSKI, T. J.
 380 2000. Removing electroencephalographic artifacts by blind source separation. *Psychophysiology*,
 381 37, 163-78.
- 382 KILNER, J. M. 2013. Bias in a common EEG and MEG statistical analysis and how to avoid it. *Clin*
 383 *Neurophysiol*, 124, 2062-3.
- 384 KLIMESCH, W., SAUSENG, P. & HANSLMAYR, S. 2007. EEG alpha oscillations: the inhibition-timing
 385 hypothesis. *Brain Res Rev*, 53, 63-88.
- 386 KOFLER, M. J., RAPPORT, M. D., SARVER, D. E., RAIKER, J. S., ORBAN, S. A., FRIEDMAN, L. M. &
 387 KOLOMEYER, E. G. 2013. Reaction time variability in ADHD: a meta-analytic review of 319
 388 studies. *Clin Psychol Rev*, 33, 795-811.
- 389 KOOIJ J, F. M. 2007. *Diagnostisch Interview voor ADHD (DIVA) bij volwassenen*, the Hague, the
 390 Netherlands, DIVA Foundation.
- 391 KOOIJ, J. J., BUITELAAR, J. K., VAN DEN OORD, E. J., FURER, J. W., RIJNDERS, C. A. & HODIAMONT, P. P.
 392 2005. Internal and external validity of attention-deficit hyperactivity disorder in a population-
 393 based sample of adults. *Psychol Med*, 35, 817-27.
- 394 MAJID, D. S., CAI, W., COREY-BLOOM, J. & ARON, A. R. 2013. Proactive selective response suppression is
 395 implemented via the basal ganglia. *J Neurosci*, 33, 13259-69.
- 396 MAZAHERI, A., COFFEY-CORINA, S., MANGUN, G. R., BEKKER, E. M., BERRY, A. S. & CORBETT, B. A. 2010.
 397 Functional disconnection of frontal cortex and visual cortex in attention-deficit/hyperactivity
 398 disorder. *Biol Psychiatry*, 67, 617-23.
- 399 MAZAHERI, A., FASSBENDER, C., COFFEY-CORINA, S., HARTANTO, T. A., SCHWEITZER, J. B. & MANGUN,
 400 G. R. 2014. Differential oscillatory electroencephalogram between attention-
 401 deficit/hyperactivity disorder subtypes and typically developing adolescents. *Biol Psychiatry*, 76,
 402 422-9.

- 403 MAZAHERI, A., NIEUWENHUIS, I. L., VAN DIJK, H. & JENSEN, O. 2009. Prestimulus alpha and mu activity
 404 predicts failure to inhibit motor responses. *Hum Brain Mapp*, 30, 1791-800.
- 405 MUTHUKUMARASWAMY, S. D., JOHNSON, B. W. & MCNAIR, N. A. 2004. Mu rhythm modulation during
 406 observation of an object-directed grasp. *Brain Res Cogn Brain Res*, 19, 195-201.
- 407 NEUPER, C., WORTZ, M. & PFURTSCHELLER, G. 2006. ERD/ERS patterns reflecting sensorimotor
 408 activation and deactivation. *Prog Brain Res*, 159, 211-22.
- 409 NIGG, J. T. 2005. Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: the
 410 state of the field and salient challenges for the coming decade. *Biol Psychiatry*, 57, 1424-35.
- 411 OLDFIELD, R. C. 1971. The assessment and analysis of handedness: the Edinburgh inventory.
 412 *Neuropsychologia*, 9, 97-113.
- 413 PFURTSCHELLER, G., BRUNNER, C., SCHLOGL, A. & LOPES DA SILVA, F. H. 2006. Mu rhythm
 414 (de)synchronization and EEG single-trial classification of different motor imagery tasks.
 415 *Neuroimage*, 31, 153-9.
- 416 PFURTSCHELLER, G. & NEUPER, C. 1994. Event-related synchronization of mu rhythm in the EEG over the
 417 cortical hand area in man. *Neurosci Lett*, 174, 93-6.
- 418 PFURTSCHELLER, G. & NEUPER, C. 1997. Motor imagery activates primary sensorimotor area in humans.
 419 *Neurosci Lett*, 239, 65-8.
- 420 PFURTSCHELLER, G., NEUPER, C. & KRAUSZ, G. 2000. Functional dissociation of lower and upper
 421 frequency mu rhythms in relation to voluntary limb movement. *Clin Neurophysiol*, 111, 1873-9.
- 422 PFURTSCHELLER, G., PREGENZER, M. & NEUPER, C. 1994. Visualization of sensorimotor areas involved in
 423 preparation for hand movement based on classification of mu and central beta rhythms in single
 424 EEG trials in man. *Neurosci Lett*, 181, 43-6.
- 425 POLANCZYK, G., DE LIMA, M. S., HORTA, B. L., BIEDERMAN, J. & ROHDE, L. A. 2007. The worldwide
 426 prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry*, 164,
 427 942-8.
- 428 RUBIA, K., OVERMEYER, S., TAYLOR, E., BRAMMER, M., WILLIAMS, S. C., SIMMONS, A. & BULLMORE, E.
 429 T. 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor
 430 control: a study with functional MRI. *Am J Psychiatry*, 156, 891-6.
- 431 RUBIA, K., TAYLOR, E., SMITH, A. B., OKSANEN, H., OVERMEYER, S. & NEWMAN, S. 2001.
 432 Neuropsychological analyses of impulsiveness in childhood hyperactivity. *Br J Psychiatry*, 179,
 433 138-43.
- 434 SAALMANN, Y. B., PINSK, M. A., WANG, L., LI, X. & KASTNER, S. 2012. The pulvinar regulates information
 435 transmission between cortical areas based on attention demands. *Science*, 337, 753-6.
- 436 SALMELIN, R. & HARI, R. 1994. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms
 437 related to thumb movement. *Neuroscience*, 60, 537-50.
- 438 SERGEANT, J. A., GEURTS, H., HUIJBREGTS, S., SCHERES, A. & OOSTERLAAN, J. 2003. The top and the
 439 bottom of ADHD: a neuropsychological perspective. *Neurosci Biobehav Rev*, 27, 583-92.
- 440 SIMON, V., CZOBOR, P., BALINT, S., MESZAROS, A. & BITTER, I. 2009. Prevalence and correlates of adult
 441 attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry*, 194, 204-11.
- 442 STANCAK, A., JR. & PFURTSCHELLER, G. 1996. Mu-rhythm changes in brisk and slow self-paced finger
 443 movements. *Neuroreport*, 7, 1161-4.
- 444 STOLK, A., TODOROVIC, A., SCHOFFELEN, J. M. & OOSTENVELD, R. 2013. Online and offline tools for head
 445 movement compensation in MEG. *Neuroimage*, 68, 39-48.
- 446 TEICHER, M. H., ANDERSON, C. M., POLCARI, A., GLOD, C. A., MAAS, L. C. & RENSHAW, P. F. 2000.
 447 Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder
 448 shown with functional magnetic resonance imaging relaxometry. *Nat Med*, 6, 470-3.

- 449 TER HUURNE, N., ONNINK, M., KAN, C., FRANKE, B., BUITELAAR, J. & JENSEN, O. 2013. Behavioral
 450 consequences of aberrant alpha lateralization in attention-deficit/hyperactivity disorder. *Biol*
 451 *Psychiatry*, 74, 227-33.
 452 YORDANOVA, J., KOLEV, V. & ROTHENBERGER, A. 2013. Event-related oscillations reflect functional
 453 asymmetry in children with attention deficit/hyperactivity disorder. *Suppl Clin Neurophysiol*, 62,
 454 289-301.
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Legends

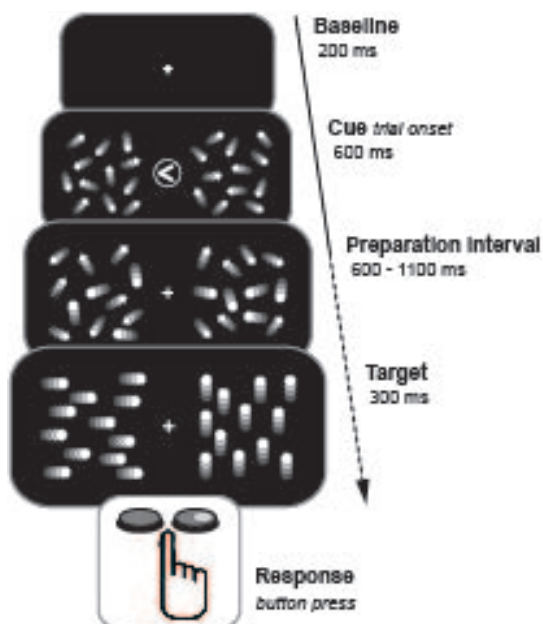


Figure 1. Schematic overview of the experimental paradigm. After a baseline period an attentional cue flanked by random-dot-kinetograms (RDK's) demarked trial onset. Cue validity was 80 %. After a jittered preparation interval, in one of the RDK's the dots would start moving coherently in horizontal 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.

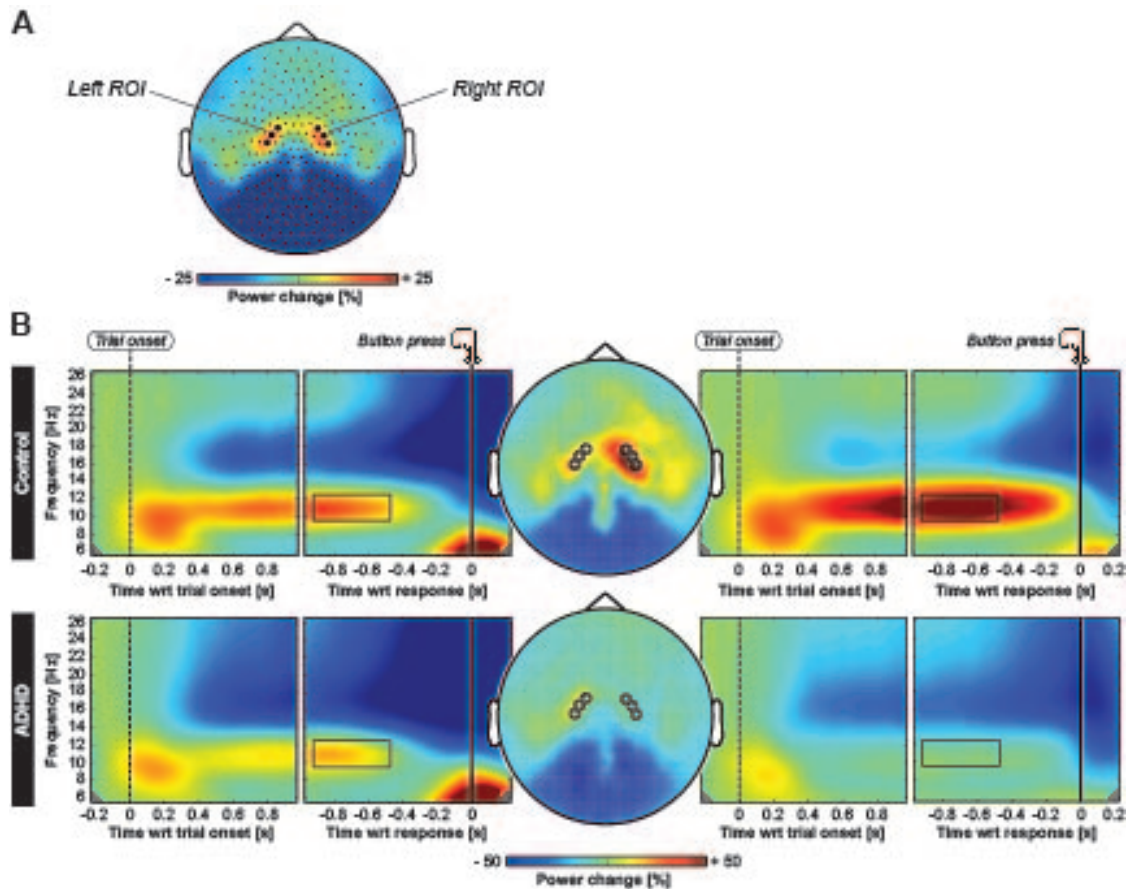


Figure 2. (A) Topographic representation of mean power of all subjects ($n=35$), frequency range 10 to 12 Hz, time interval 0.4 to 0.8 s with respect to trial onset (cue-locked data). Black dots denote the sensors with the strongest ERS which were selected as the left and right ROIs that were later used 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.

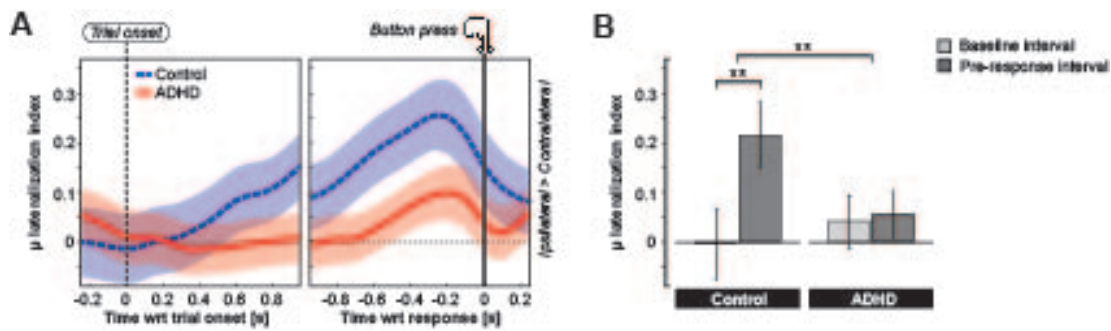


Figure 3. (A) Mean mu lateralization index (MLI) plotted against time, lighter color denotes standard error of the mean (wrt: with respect to). Left panel shows MLI with respect to trial onset, right panel shows MLI with respect to the button-press (response). A positive MLI means higher mu in sensors ipsilateral than contralateral 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.

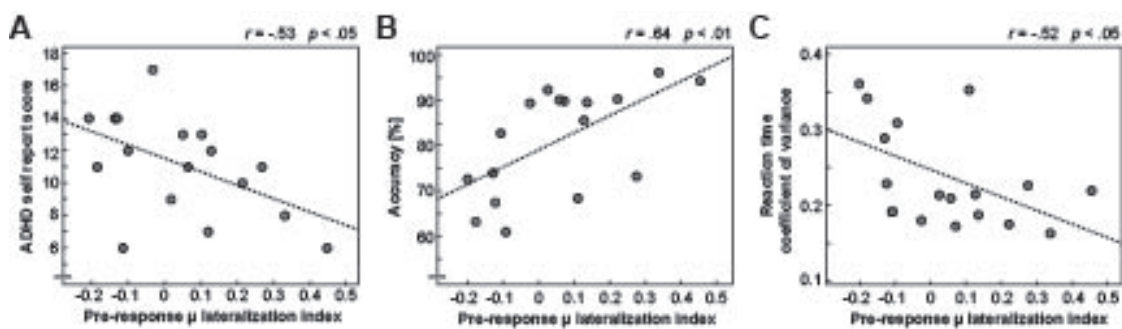


Figure 4. (A) Individual pre-response mu lateralization index (MLI) of the ADHD group plotted as a function of number of ADHD symptoms as measured by the ADHD self report. There is a negative linear relationship between mu lateralization strength and ADHD severity in daily life. (B) Pre-response

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.



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