Abnormal Neural Reactivity to Unpredictable Sensory Events in Attention-Deficit/Hyperactivity Disorder

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Background: Cortical oscillations in the sensorimotor region in the 8–12-Hz range ("mu rhythms") are associated with basic somatosensory and motor processes as well as top-down processes such as learning, attention, expectancy, and inhibition. Recent studies suggest that reactivity of these rhythms to sensory input reflects a link between perception and action and that abnormalities in this reactivity might reflect impairment in perception-to-action mechanisms. Individuals with attention-deficit/hyperactivity disorder (ADHD) are impaired in tasks requiring sensorimotor function, attention, expectancy, and inhibition, yet their sensorimotor mu responses are unknown. Thus, we investigated mu reactivity in a group of adults with ADHD.

Methods: Sixteen adults with ADHD and 16 matched control subjects received median nerve stimulation in predictable patterns (trains of four stimuli followed by 4-sec gap) or unpredictable patterns (randomly presented trains of two, four, or six stimuli followed by 4-sec gap). With magnetoencephalography, we examined the effects of stimulus patterning (predictable, unpredictable) on mu reactivity to somatosensory stimuli.

Results: Compared with control subjects, the ADHD group showed lower mu reactivity overall and no modulation by unpredictable somatosensory input. By contrast, the control group showed robust mu reactivity to stimuli presented in unpredictable but not predictable patterns. These changes were stronger in the contralateral hemisphere compared with the ADHD group.

Conclusions: Cortical mu rhythms are modulated by stimulus predictability and might be involved in attentional alerting (awareness of when an unexpected stimulus occurs). Diminished mu modulation in adult ADHD suggests a possible underlying deficit in the perception-to-action system.

Key Words: ADHD, attention, magnetoencephalography, mu rhythm, predictability, sensorimotor

A stimulus is easier to detect and perhaps more salient when we are aware of some of its features in advance, such as where or when it will occur. This awareness, or "perceptual set" (1), enables us to bias processing of and response to future stimulus events. An accurate perceptual set requires the capacity to attend to and select incoming relevant information while blocking out irrelevant stimuli. Subsequent response preparedness relies on an accurate perceptual set. Collectively, we can define the stimulus-response dynamic as a "perception-to-action" system (2,3). It has been suggested that modulation or "reactivity" of ongoing mu rhythms (sensorimotor oscillations of 8–12 Hz) reflect the activation of this perception-to-action system (2,3).

During simple movement preparation or tactile stimulation, mu rhythms are suppressed and show a characteristic pattern of event-related desynchrony (ERD) (4–7) followed by an increase in power above baseline levels (event-related synchrony [ERS]). Typically these changes are stronger in the contralateral hemisphere (7–10). Mu ERD also occurs during higher-order demands such as movement imitation (11), movement observation (12), the mental imagery of movement (6,13), motor pattern learning (14), and expectancy of a sensorimotor event (15,16). Mu ERD is involved in attentional alerting (stronger ERD) and habituation (weaker ERD) to somatosensory input (7,17). Mu ERS assists in top-down modulation of attentional control by blocking communications from task-irrelevant brain regions (18).

Diminished mu reactivity has been found in several neuropsychiatric populations such as obsessive-compulsive disorder (19), Tourette syndrome (20), and autism (21,22). Correlations of sensorimotor mu dysfunction with behavioral symptoms in these populations suggest that mu deficits might underlie some of their behavioral traits. Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder generally characterized by impairments in sensorimotor function and attention. Moreover, individuals with ADHD show little benefit from receiving prior information about a future event (23,24). Collectively, this evidence suggests impairment in the perception-to-action system in ADHD.

Previously, we reported diminished modulation in somatosensory beta oscillations in adults with ADHD in response to sensory stimuli (25). However, our methods and analysis did not permit precise characterization of the stimulus-response dynamics of the mu rhythm. Moreover, hemispheric lateralization of sensorimotor activity was not investigated. Accordingly, in the current study we used magnetoencephalography (MEG) to examine mu reactivity in adults with ADHD and matched control subjects. Participants were presented with both predictable and unpredictable patterns of somatosensory stimuli to characterize effects on mu rhythms. Also, we examined mu rhythms in both contralateral and ipsilateral hemispheres to investigate their lateralization in ADHD. Given that mu ERD is stronger during alerting to unpredictable somatosensory stimuli than during habituation to repetitive stimuli (7,17), we hypothesize that mu ERD will be stronger in response to unpredictable than predictable somatosensory stimuli in our control subjects. In view of

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previously documented impairments in attention and alerting and lack of benefit from predictability in ADHD (24,26,27), we predicted diminished modulation of mu ERD for this clinical group.

Methods and Materials

Participants

We studied 16 right-handed adults (7 women) with a diagnosis of ADHD (mean age: 30.3 ± 3.11 years) and 16 healthy age-matched, right-handed control subjects (7 women; mean age: 29.02 ± 4.7 years), of whom 10 control subjects and 9 with ADHD had participated in our previous study (25). However, the current study incorporates a different dataset than reported previously. Adults with ADHD were recruited from an outpatient neuropsychiatry clinic in a mental health center in a large metropolitan city. All had received a confirmed clinical diagnosis of ADHD on the basis of DSM-IV criteria. Healthy adult volunteers were recruited by advertising in the same mental health center and other community organizations. All participants completed a telephone-based Intake Screening Questionnaire (screens for psychopathology and education level); adults with ADHD also completed the World Health Organization Adult ADHD self-report scale (ASRS) Screener (28). This 6-item scale has strong psychometric properties (28,29), and positive responses to at least four of these items are predictive of the disorder. In this ADHD sample, the mean number of positive responses to the first six items was 4.19 (SD = 1.05). Six of the 16 adults with ADHD were currently taking stimulant medication (4 methylphenidate, 1 dextroamphetamine, 1 combined methylphenidate and dextroamphetamine) to treat their ADHD symptoms. These individuals stopped their medication at least 48 hours before testing. Participants were excluded if they wore orthodontic braces, had any nonremovable metal, had a diagnosis of psychosis or a neurological disorder, or were left-handed.

Equipment

A 151-channel MEG system (VSM MedTech, Ltd., Vancouver, Canada) was used to measure somatosensory evoked fields. The MEG signals were filtered with an online bandpass of .3–300 Hz and recorded at a 1250-Hz sampling rate. Head position in relation to the MEG sensors was determined by measuring the magnetic field generated by three fiducial reference coils just before and after each experimental session. If head movement exceeded .5 cm during task performance, the data were not examined and the experimental condition was redone. This was required for one participant (male, ADHD) for one condition (predicted stimulus pattern). T_1-weighted structural magnetic resonance images (MRI) (axial three-dimensional spoiled gradient echo sequence) were obtained for each participant with a 1.5-Tesla Signal Advantage system (GE Medical Systems, Milwaukee, Wisconsin). During MRI data acquisition, three radiographic markers were positioned at the same anatomical landmarks as the fiduciary coils to allow coregistration of the MEG and MRI data.

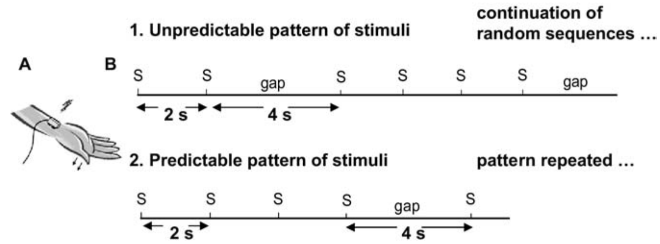

Figure 1. Median nerve stimulation: unpredictable and predictable paradigms. **(A)** A nonpainful, electrical pulse was administered cutaneously to the right median nerve evoking a passive thumb twitch. **(B)** The stimulus (**S**) was presented in two conditions: 1) unpredictable pattern: stimuli occurred in randomly presented trains of two, four, or six stimuli followed by gap; 2) predictable pattern: stimuli always occurred in trains of four stimuli followed by gap. In both experiments there were 332 stimulus events and 83 gaps.

Paradigms

Participants lay supine with head resting in the MEG helmet in the magnetically shielded room and fixated on a small visual target (yellow circle, 3 cm in diameter) on the ceiling to restrict head and eye movements. Somatosensory stimuli were nonpainful electrical pulses of .2-msec duration, applied cutaneously to the right median nerve at a rate of .5 Hz (stimulus onset asynchrony [SOA] of 2 sec), just above motor threshold (eliciting a small, passive, thumb twitch). Each participant completed two median nerve stimulation paradigms in counterbalanced order: 1) Unpredictable Pattern: stimuli were presented in random trains of 2, 4, or 6 stimuli followed by a 4-sec gap before the next train; these patterns were randomized for every individual; and 2) Predictable Pattern: stimuli were always presented in trains of four stimuli followed by a 4-sec gap before the next train. In both conditions there were a total of 332 stimuli and 83 gaps between trains over a 14-min trial (Figure 1). We presented stimuli in trains with a constant within-train SOA (2 sec) to promote stimulus expectancy. To investigate the effects of temporally unpredictable events on mu reactivity, we restricted our statistical analyses to the period after the last stimulus in a train for both experimental conditions (as described in the following). This approach allowed us to examine both early (mu ERD) and late (mu ERS) reactivities to temporally predictable and unpredictable events.

This study was approved by the institutional research ethics board and conducted in compliance with the Declaration of Helsinki. All participants provided informed written consent.

Data Analyses

Beamformer Spatial Analysis. Initial spatial analyses were performed on the basis of a beamformer method (synthetic

Table 1. Temporal Boundaries of mu Rhythms Applied in Statistical Analyses

	Contralateral		Ipsilateral	
	Unpredictable	Predictable	Unpredictable	Predictable
Mu ERD (Control)	−1.7 to −1.1	−1.7 to −1.1	−1.8 to −1.2	−1.8 to −1.2
Mu ERD (ADHD)	−1.7 to −1.1	−1.7 to −1.1	−1.7 to −1.1	−2.0 to −1.4
Mu ERS (Control)	−.4 to .2	−.4 to .2	0 to .6	−.8 to −.2
Mu ERS (ADHD)	−.4 to .2	−.4 to .2	−.6 to 0	−1.4 to −.8

All frequency boundaries were 8–12 Hz. All values in seconds.
ERD, event-related desynchrony; ERS, event-related synchrony; ADHD, attention-deficit/hyperactivity disorder.