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Alpha desynchronization and fronto-parietal connectivity during spatial working memory encoding deficits in ADHD: A simultaneous EEG-fMRI study

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ABSTRACT

The underlying mechanisms of alpha band (8–12 Hz) neural oscillations are of importance to the functioning of attention control systems as well as to neuropsychiatric conditions that are characterized by deficits of that system, such as attention deficit hyperactivity disorder (ADHD). The objectives of the present study were to test if visual encoding-related alpha event-related desynchronization (ERD) correlates with fronto-parieto-occipital connectivity, and whether this is disrupted in ADHD during spatial working memory (SWM) performance. We acquired EEG concurrently with fMRI in thirty boys (12–16 yrs. old, 15 with ADHD), during SWM encoding. Psychophysiological connectivity analyses indicated that alpha ERD during SWM encoding was associated with *both* occipital activation and fronto-parieto-occipital functional connectivity, a finding that expands on prior associations between alpha ERD and occipital activation. This finding provides novel support for the interpretation of alpha ERD (and the associated changes in occipital activation) as a phenomenon that involves, and perhaps arises as a result of, top-down network interactions. Alpha ERD was associated less strongly with occipital activity, but associated more strongly with fronto-parieto-occipital connectivity in ADHD, consistent with a compensatory attentional response. Additionally, we illustrate that degradation of EEG data quality by MRI-amplified motion artifacts is robust to existing cleaning algorithms and is significantly correlated with hyperactivity symptoms and the ADHD Combined Type diagnosis. We conclude that persistent motion-related MR artifacts in EEG data can increase variance and introduce bias in interpretation of group differences in populations characterized by hypermobility — a clear limitation of current-state EEG-fMRI methodology.

1. Introduction

Working memory (WM), the ability to store and manipulate information transiently in memory (Baddeley, 1986, 2002), is one of core functions affected in attention deficit hyperactivity disorder (ADHD) (Castellanos and Tannock, 2002; Nigg, 2005); it is also one of the most perplexing. In support of WM system dysfunction in ADHD, group differences in behavioral performance on WM tasks consistently show medium to large effect sizes (Alderson et al., 2013; Boonstra et al., 2005; Kofler et al., 2013; Loo et al., 2007; Martinussen et al., 2005; Westerberg et al., 2004; Willcutt et al., 2005), and neuroimaging evidence indicates that patients with ADHD differ in fronto-parietal, or so called "top-down", circuitry associated with WM (Arnsten and Rubia, 2012; Bush, 2010; Castellanos and Tannock, 2002; Rubia et al., 2014). Yet stimulant medications, which target such circuitry and offer relief from related symptoms such as sustained attention or response inhibition, are inconsistent in alleviating WM symptoms (Rubia et al., 2013; Rubia et al., 2014). Moreover, spatial orienting and effects of load in WM, both of which also rely on fronto-parietal network integrity, have demonstrated a lack of group differences (Bedard et al., 2014; Huang-Pollock and Nigg, 2003; Huang-Pollock et al., 2005; Wolf et al., 2009). Such findings prompt further study of the mechanism by which dysfunction of fronto-parietal circuitry contributes to SWM deficits in ADHD.

We have demonstrated recently (Lenartowicz et al., 2014) that within a spatial working memory (SWM) delayed match-to-sample task distinct group differences may be observed during different stages of the task: preparing for WM storage, encoding content into WM, and maintaining that content in WM. The most pronounced group differences in neural responses were present during the encoding phase of the task, before WM was engaged by the maintenance delay and before

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items were to be retrieved from WM. We found that in children with ADHD event-related desynchronization (ERD) of alpha-frequency (8–12 Hz) neural oscillations during encoding was attenuated and predictive of ADHD symptoms and WM task performance. The involvement of alpha during encoding is notable, as it points to atypical fronto-parietal interactions with occipital cortex during the encoding process.

Alpha modulation during visual perception and attention has been hypothesized to be a functional mechanism by which information is selected or gated in visual cortex (Foxe and Snyder, 2011; Klimesch, 2012; Klimesch et al., 2011; Mathewson et al., 2011). Alpha ERD magnitude varies with task variables such as degree of semantic content (Klimesch, 1997; Klimesch et al., 2011), memory load and retrieval accuracy (Jensen et al., 2002; Klimesch, 1999; Klimesch et al., 1997), and visuospatial attention (Foxe and Snyder, 2011; Thut et al., 2006). Unlike other spectral phenomena (e.g., theta), ERD can reverse in sign (becoming an event-related synchronization, ERS) for stimulus inputs that are to be ignored (Foxe and Snyder, 2011; Rihs et al., 2007). Moreover, alpha ERD is thought to arise independent of perceptual processing (Klimesch et al., 2011), as it can occur before (Ergenoglu et al., 2004; Hanslmayr et al., 2007; Romei et al., 2010) or after (Freunberger et al., 2008) the stimulus, and can be absent during a stimulus when no post-perceptual processing is required (Hanslmayr et al., 2005).

Thus weakened alpha ERD in ADHD is a likely indicator of weakened top-down control during SWM encoding and, given prior association of fronto-parietal circuitry with both SWM (Awh and Jonides, 2001; Constantinidis et al., 2001; Smith and Jonides, 1997) and with alpha power (de Munck et al., 2007; Laufs et al., 2003; Liu et al., 2014; Scheeringa et al., 2009), it predicts weakened interactions between the fronto-parietal network and occipital cortex during encoding. In the context of ADHD, a confirmation of this hypothesis would imply that SWM deficits may hinge on relatively early attention control processes, and the success of these processes may directly influence the success of WM and, consequently, the presence or absence of group differences on WM tasks.

The objective of our study was therefore to test if encoding-related alpha ERD reflects fronto-parieto-occipital connectivity, whether this is disrupted in ADHD, and whether it predicts ADHD symptoms or SWM performance. While numerous studies have documented the relationship between alpha and activation in occipital, frontal and parietal cortices (de Munck et al., 2007; Goldman et al., 2002; Laufs et al., 2003; Liu et al., 2014; Moosmann et al., 2003; Scheeringa et al., 2009), the relationship between alpha and *connectivity* among these regions has not been established firmly. Multiple studies have reported fronto-parietal synchronization in the alpha range during WM tasks based on neurophysiological signals (Doesburg et al., 2009; Hummel and Gerloff, 2005; Palva and Palva, 2011; Sauseng et al., 2005; von Stein et al., 2000). However the experiment of combining EEG and fMRI in concurrent recordings to test directly if alpha modulation predicts inter-regional connectivity has been reported only by Scheeringa et al. (2012), who described decreased within-occipital connectivity during alpha ERS, but this manuscript did not include findings on alpha ERD. Moreover, a handful of studies have examined alpha related *activation* during SWM focusing on the maintenance interval and theta, using either concurrent EEG-fMRI (Michels et al., 2010; Michels et al., 2012; Scheeringa et al., 2009) or cross-subject EEG-fMRI correlations (Meltzer et al., 2007). Scheeringa et al. (2009) additionally examined alpha ERS during maintenance and reported an increase in frontal cortex, and a decrease in occipital cortex activity, which would be expected subsequent to encoding.

Finally, within ADHD, we are aware of four studies that have examined BOLD correlates of EEG signals, namely of event-related potential markers of reward (Boecker et al., 2014; Hauser et al., 2014), and of voluntary response selection (Karch et al., 2010; Karch et al., 2014), but not of encoding processes. It is notable that even within studies that employed EEG without fMRI we are aware of only two, other than our own, that have examined alpha ERD during encoding in WM (Gomarus et al., 2009; Missonnier et al., 2013). Thus whether alpha ERD reflects fronto-parieto-occipital functional connectivity, and if this relationship accounts for ADHD deficits in SWM, are both questions that warrant further study.

In the present experiment we used concurrent EEG-fMRI methodology to record both alpha ERD during encoding and associated changes in BOLD activity, and connectivity signals during SWM tasks in children with and without ADHD. The results confirm prior associations between alpha and occipital activation, expand this association to include fronto-parietal-connectivity, and demonstrate differences between children with and without ADHD in both relationships. Additionally, our findings suggest caution in EEG-fMRI assessment of populations characterized by hypermobility, such as children with ADHD Combined Type diagnosis, due to severe degradation of EEG data by MRI-amplified motion related artifacts.

2. Methods

2.1. Participants and diagnoses

A total of 30 boys (15 with ADHD, 12–16 years old) were recruited from the Los Angeles community through flyers, community organizations (CHADD; www.chadd.org), and the UCLA ADHD clinic. Exclusion criteria included: IQ < 80, history of learning disabilities, co-morbid Axis I diagnoses other than oppositional defiant disorder, and current use of psychotropic medications other than psychostimulants. Parents/participants received verbal and written explanations of study requirements and, prior to any study procedures, provided written informed permission/assent as approved by the UCLA Institutional Review Board. No participants, including those diagnosed with ADHD, were on medication during clinical assessment or testing, withholding use 24–48 h prior to session, consistent with medication half-life.

We evaluated children for ADHD and other psychiatric disorders through a semi-structured diagnostic interview with the primary caretaker (usually the mother) and a direct interview with the child using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS-PL) (Kaufman et al., 1997). Psychiatric disorders were considered present if the participant currently met full DSM-IV diagnostic criteria for any ADHD subtype. Two clinical psychologist trainees conducted all interviews. Senior clinicians (SKL, PDW) confirmed psychiatric diagnoses after individual review of symptoms, developmental course, and impairment level. We assessed full scale intelligence (FSIQ) using the Wechsler Abbreviated Scale of Intelligence (WASI), learning disability using the reading comprehension and word reading scales of the Wide Range Achievement Test 4 (WRAT), and severity of ADHD symptoms using the Strengths and Weaknesses of ADHD symptoms and Normal (SWAN) Behavior Scale (Swanson et al., 2006). Positive scores on the SWAN scale indicate more symptoms, whereas negative scores indicate fewer symptoms.

2.2. Task

We used a computerized version of the spatial working memory (SWM) task (Glahn et al., 2002; Sternberg, 1966) to assess alpha ERD during WM encoding (Fig. 1), the timing of which was adapted for fMRI. Each trial consisted of a fixation cross for 500-msec, followed by an encoding display containing 3 or 5 yellow dots (load), presented on a black background. After 2 s, the screen turned blank and remained blank for a maintenance interval of 7, 8 or 9 s, selected randomly on each trial. Next a single dot (probe) was presented for 3 s in either a location previously shown (match) or not (non-match). Participants were instructed to indicate using a left/right button press if the probe was a match or non-match to the encoding stimulus. Trials were separated by an inter-stimulus-interval (7, 8, or 9 s duration, randomized) during which the screen was blank. Of primary interest in this study were alpha ERD and neural activity/connectivity during the encoding period. We