Neuropsychologia 102 (2017) 45–51

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Frontal alpha asymmetry predicts inhibitory processing in youth with attention deficit/hyperactivity disorder

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ARTICLE INFO

Keywords:
ADHD
Frontal Asymmetry
Disinhibition
EEG
Source Localization

ABSTRACT

Introduction: Atypical asymmetry in brain activity has been implicated in the behavioral and attentional dysregulation observed in ADHD. Specifically, asymmetry in neural activity in the right versus left frontal regions has been linked to ADHD, as well as to symptoms often associated with ADHD such as heightened approach behaviors, impulsivity and difficulties with inhibition. Clarifying the role of frontal asymmetry in ADHD-like traits, such as disinhibition, may provide information on the neurophysiological processes underlying these behaviors.

Method: ADHD youth (ADHD: n = 25) and healthy, typically developing controls (TD: n = 25) underwent an electroencephalography (EEG) recording while completing a go/no-go task—a commonly used test measuring behavioral inhibition. In addition, advanced signal processing for source localization estimated the location of signal generators underlying frontal alpha asymmetry (FA) during correct and incorrect trials.

Results: This is the first study in ADHD to demonstrate that the dorsal-lateral prefrontal cortex (DLPFC) may be responsible for generating frontal alpha. During failed inhibition trials, ADHD youth displayed greater FA than TD youth. In addition, within the ADHD group, frontal asymmetry during later processing stages (i.e., 400–800 ms after stimulus) predicted a higher number of commission errors throughout the task.

Conclusions: These results suggest that frontal alpha asymmetry may be a specific biomarker of cognitive disinhibition among youth with ADHD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder associated with cognitive and behavioral dysregulation. This dysregulation has been ascribed to brain abnormalities in ADHD individuals. In particular, structural and functional hemispheric asymmetries and atypical brain laterality have been purported as potential biomarkers of ADHD-like traits (Bradshaw and Sheppard, 2000; Hale et al., 2009a, 2009b; Hale et al., 2007; Stefanatos and Wasserstein, 2001; van Ewijk et al., 2012). One trait often observed among individuals with ADHD is behavioral disinhibition—the inability to stop distractions, control behaviors, and self-regulate (Barkley, 1997). However, whether there is a relationship between hemispheric asymmetry and disinhibited behaviors in ADHD is less clear. With compromised inhibitory functioning purported as a foundational deficit in ADHD (Barkley, 1997), increased understanding of the neurobiological mechanisms contributing to such behaviors is warranted.

Behavioral disinhibition and impulsivity have recently been linked to abnormalities in the approach system (Neal and Gable, 2016). Similarly, ADHD has been conceptualized as a disorder of excessive approach-related tendencies (Keune et al., 2011, 2015; Mitchell, 2010). Consistent with this idea, approach-related tendencies, as assessed with self-report measures, have been shown to predict hyperactive—impulsive symptoms in a sample of young adults (Mitchell, 2010). Adults with an ADHD diagnosis have demonstrated greater behavioral approach in experimental and self-report measures as compared with unaffected adults (Mitchell et al., 2011). Using this theoretical framework to understand ADHD behaviors, frontal alpha asymmetry (FA), a neurophysiological (EEG) index of approach-related sensitivity (Coan and Allen, 2003; Harmon-Jones and Allen, 1997), must be considered as a viable biomarker for examining disinhibition in individuals with ADHD. Frontal alpha EEG asymmetry is the difference in alpha-band (8–12 Hz [Hz]) activity over right vs. left frontal hemispheres of the brain. Because alpha power is thought to be inversely related to cortical activation, higher left cortical activity is associated with elevated right frontal alpha power (Allen et al., 2004; Davidson, 1988; Laufs et al., 2003). For the sake of clarity in this manuscript, all FA findings will represent *greater right alpha power* (i.e., greater left

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http://dx.doi.org/10.1016/j.neuropsychologia.2017.06.003
Received 19 January 2017; Received in revised form 30 May 2017; Accepted 2 June 2017
Available online 03 June 2017
0028-3932/

frontal activation). Increased FA has been linked to self-reported approach motivation, whereas decreased FA has been linked with withdrawal or avoidance (Davidson, 1998; Depue and Iacono, 1989). In addition to approach-related behaviors, FA has also been linked to traits common to ADHD such as reduced reward responsiveness, aggression, and difficulties with inhibition (Davidson, 1998; Rybak et al., 2006), providing additional support for the potential role of FA in ADHD.

Only a few studies have directly examined FA in ADHD, particularly in children. In a study of 4–8 year-old males, those with ADHD during an eyes-open resting condition showed higher right alpha power, consistent with greater FA, than those without ADHD (Baving et al., 1999). Similar findings of higher alpha power in the right hemisphere were reported in a broader (i.e., 6–17 years old), co-ed sample of ADHD youth. These findings showed high specificity in distinguishing ADHD youth from healthy, unaffected controls (Chabot and Serfontein, 1996). Additionally, ADHD youth with a parent who also has ADHD (i.e., greater familial loading for ADHD), versus those with an unaffected parent, showed greater frontal alpha asymmetry during an eyes closed condition (Hale et al., 2010), indicating that there may be a genetic component of FA.

Adult studies have also shown similar findings where greater frontotemporal asymmetry (FT8-FT7), in the 8–10 Hz range of alpha (low-alpha), during an eyes-closed condition was associated with ADHD group status, versus healthy controls (Hale et al., 2009a, b). In a replication study that used a composite measure of frontal alpha asymmetry during eyes open and closed, ADHD adults also displayed higher right frontal alpha power, and those with greater FA had more ADHD symptoms (Keune et al., 2011). Taken together with the youth samples, these results suggest that FA may be a heritable, trait-like feature of ADHD that persists throughout the lifetime of the disorder.

While FA, measured during resting states, appears to be a robust correlate of ADHD, these studies provide no information on how, or whether, frontal alpha asymmetry affects inhibitory behavior. One study of adults with and without ADHD, collected EEG data during a continuous performance task (i.e., go/no-go task) and showed that the ADHD group displayed higher FA during the task than non-ADHD controls, specifically in the lower alpha band (8–10 Hz) and in the FT8-FT7 region (Hale et al., 2009a, b). Importantly, however, the EEG data was averaged across the 14-min task, providing no differential information on the relationship between FA and specific events such as commission errors, which indicate disinhibited behaviors. While there seems to be strong support for a relationship between ADHD and FA, there is no research linking FA in ADHD youth with *in the moment* behaviors such as inhibition.

Not only is there a paucity of work examining FA response to stimuli, many studies average FA across a long time-interval providing limited information on whether FA is a dynamic process or where in the inhibitory processing stream it may have effects. The first second following a stimulus has been highlighted as the critical time window for when the majority of inhibitory processes are thought to unfold (Pires et al., 2014), where early stages (0–200 ms) are considered to reflect automatic processes of inhibition and later stages (400–800 ms) reflect top down, controlled processes of inhibition. Using this standard convention, examining FA at different time points during an inhibitory trial could clarify its role in the information processing stream.

Additionally, to our knowledge, all of the work examining frontal asymmetry in ADHD has used channel-based indices such as the lateral frontal sites (F7/F8) and mid-frontal sites (F3/F4) to calculate asymmetry that has revealed little consistency in which channels are related to ADHD. Frontal asymmetry in lateral-frontal regions (Hale et al., 2009a, b; Keune et al., 2015), mid-frontal regions (Keune et al., 2011), and in averages from the frontal regions of each hemisphere (Hale et al., 2010) have all been reportedly associated with ADHD. The use of differing methods for data analysis and processing likely contributes to the inconsistencies in the literature and further complicates the interpretations gleaned from the data.

Rather than selecting electrode sites that have demonstrated equivocal results in the literature, source-resolved analyses may provide more robust findings. Because of volume conduction and smearing of brain signals by the scalp, more commonly used channel signals contain mixtures of both relevant and irrelevant brain and non-brain sources. These "mixing" limits the effective signal to noise ratio and reduces the statistical value within the data. To improve the quality of the data, source localization uses independent components analysis (ICA) to "unmix" brain from non-brain (artifacts such as muscle, eye movements, line noise) signals and localizes the cortical sources from which the scalp signal emanates. Using ICA and source analyses for identification of relevant information (e.g., the source generator of frontal alpha) reduces the likelihood that the resulting measures contain an admixture of information—thus increasing the effective signal-to-noise ratio of the information gleaned from the data. In fact, recent work has suggested that alternative methods that reduce the contributions of non-frontal sources in FA may provide a better index of FA and increase the quality of results. Suggested methods include current source density (CSD), source localization and ICA (Smith et al., 2017).

While scalp/channel-based analyses of EEG are commonly used in psychiatric research, the use of source-resolved time-frequency analysis allows one to capture neural processes with greater spatial resolution and specificity to specific anatomic regions. Indeed, a recent review demonstrated that using unmixed signals from source-resolved analyses can be more powerful in unmasking clinical group differences (Loo et al., 2015; Stewart et al., 2010). Importantly, recent research in psychopathology and behavior has begun to move in the direction of source-localization to clarify the functional role of these brain processes (e.g., Auerbach et al., 2015; Schiller et al., 2014).

Using ICA and source localization methods, the current study aimed to identify the location of the cortical generators of frontal asymmetry—a purported neurophysiological correlate of psychopathology, and examine the role of FA in inhibitory processing across youth with ADHD as compared to those who are typically developing (TD). Specifically, we were interested in two questions. First, we examined whether FA could distinguish ADHD from TD youth. Given the lack of work examining *evoked* (i.e., stimulus-locked) FA in youth with ADHD, we initially examined whether ADHD and TD youth differed in brain activity across trials. We anticipated that youth with ADHD would exhibit greater FA than TD, but it was unclear whether group differences would be present during *both* correct and incorrect trials, suggesting a trait-like difference between the groups, or if ADHD and TD youth would only differ during failed inhibition trials, suggesting state-like differences in brain activity during disinhibition. To further characterize the role of FA in the inhibitory process, we segmented trials into 3 time windows to capture both the “automatic” (0–200 ms, 200–400 ms) and “controlled” (400–800 ms) phases of inhibitory processes (Pires et al., 2014).

Second, we examined whether FA could be a biomarker of disinhibited behavior. That is, we examined the effects of FA at each time point, as well as the potential moderating effects of clinical group status (i.e., the interaction of FA x group) on behavior (i.e., commission errors). If FA is associated with greater approach-related behaviors, we would expect that, regardless of group status, higher FA would predict more disinhibition, as demonstrated by higher number of commission errors. To examine the specificity of this relationship we tested FA during correct trials and FA during failed inhibition trials as predictors of the number of commission errors throughout the task. With the research in event-related FA in ADHD versus TD youth so limited, it remained unclear whether the individual effects of FA and ADHD would interact (i.e., be potentiated).