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Title: Comparison of Theta Beta Ratio in Children With Attention Deficit/Hyperactive Disorder and Specific Learning Disorder During Active EEG

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Abstract

Introduction: Theta-Beta Ratio (TBR) has been claimed as a biomarker to diagnose Attention Deficit and Hyperactivity Disorder (ADHD). However, the effectiveness of this index to differentiate between different groups of disorders is still under discussion. The primary purpose was to determine to what extent active TRB can differentiate between children with ADHD and specific Learning Disorder (sLD) as the most common comorbid disorder.

Methods: Two groups of school-aged children with sLD (N=15) and ADHD (N=15) were diagnosed through a process of clinical interview and observation. Electroencephalography (EEG) was recorded in both groups during active condition. The implemented cognitive task was the visual continuous performance task (VCPT). TBR in sites of CZ and Fz, and cognitive measures of VCPT were calculated in the aforementioned groups.

Results: There was no significant differences in cognitive measures (containing Commission, Omission, Reaction Time, and Variability of Reaction Times) shown in two matched groups of children with sLD and ADHD. According to TBR, two groups demonstrated no significant results in comparison.

Conclusion: TBR cannot be considered as a reliable biomarker to differentiate between those groups of psychological disorders that contain primary cognitive deficits and require the allocation of attention and working memory loads.

Keywords: TBR, ADHD, sLD, VCPT, EEG

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent chronic childhood mental illnesses, affecting 4-12 percent of all school-aged children and persisting in roughly 66-85 percent of cases (Getahun, et al., 2013). And affects individuals across the lifespan (Sonuga-Barke, et. al., 2013). It is characterized by age-inappropriate, chronic, and pervasive symptoms of inattention, hyperactivity, and/or impulsivity, which are linked to a high risk of scholastic failure, interpersonal difficulties, and mental illness (Sonuga-Barke, et. al., 2013).

Electroencephalography (EEG) measurements show the relationship between intracranial electrical currents and the resultant voltages on the scalp, which represent certain aspects of brain electrical activity and processing. Many pieces of research have been conducted to compare brain activity in children with ADHD to normal controls, particularly utilizing EEG, in order to shed more light on the underlying neurophysiology of ADHD and to study subtypes of ADHD with varied responses to treatment (Arns, et al, 2012).The most commonly reported EEG characteristics associated with ADHD are increased slow wave power (delta, theta) and/or decreased fast wave power (beta), which are occasionally combined and indexed as theta/ beta ratio (TBR), the ratio of theta band (4-7 Hz) power divided by beta band (13-30 Hz) power. Arns et al., 2013; Bink et al., 2014; Lenartowicz and Loo, 2014; Barry et al., 2003). Previous studies that employed TBR to distinguish an ADHD group from a control group found a sensitivity of 87% and a specificity of 94%. (Chen et al., 2019).

A significant increase in power in the theta band might be used to establish an ADHD diagnosis. In ADHD, elevated theta might be regarded as a sign of inattention and executive dysfunction (Ogrim, Kropotov, & Hestad, 2012). However, the diagnostic value of the TBR biomarker increases when it can make a differentiation between ADHD and other disorders (especially other neurodevelopmental dysfunctions). Nevertheless, very little research has been done on the discriminative power of TBR index for psychological disorders. In a study cooldige et al. (2007) investigated differential power of TBR among children with different psychological problems and found its lack of power both in terms of sensitivity and specificity to diagnose children with ADHD.

This is especially critical in the matter of children with learning disabilities (LD). Previous research have indicated high comorbidity for ADHD and LD in children. That is, attention deficit hyperactivity disorder containing the highest comorbidity rate with learning disorder, occurs

simultaneously 33 to 45% of the time with reading disability and 11% of the time with mathematical disability (Mayes, Calhoun, & Crowell, 2000; DuPaul, Gormley, & Laracy, 2013; Butterworth and Kova, 2013). The rate is so high that has lead Hendrickson et al. (2007) to consider attention impairments as one of the subgroups of learning disorder, along with verbal and non-verbal types.

In the other hand, wide range of EEG studies have shown greater theta and less beta power in frontal areas in children with LD in comparison to control group (ex. Jäncke, Saka, Badawood, & Alhamadi, 2019). In their research on LD children, Jäncke and Alahamadi (2016) found that theta/beta and theta/alpha ratios were much higher in learning disabilities children than in healthy children, indicating a significant slowdown of EEG oscillations, particularly for frontal scalp positions (involved in the control of executive functions, attention, planning, and language).. Moreover, in a review of the studies both considered or disregarded ADHD comorbidity, Chabot et al. (2001) indicated that in addition to alpha and theta deviations, elevated ratio of theta to beta has been shown in children with learning disabilities. Chabot concluded that due to the overlap of behavioral symptoms and common neural infrastructure, attention deficit might be considered as one of the subgroups of learning disability.

In the present study the power of to TBR biomarker to differentiate between ADHD and LD will be investigated during the cognitive task condition.

Material and Methods

Subjects

In this descriptive causal-comparative study, we examined 2 different groups of children: 15 children who reached the criteria for Specific Learning Disorder (SLD) according to DSM 5 (4 girls and 11 boys, mean age: 8.8 and SD: 1.14) and 15 children who reached the criteria for ADHD according to DSM-5 (3 girls and 12 boys, mean age: 8.9 and SD: 1.12). The sample was collected from students with complaints of difficulty in academic achievements who were referred to the Atieh Clinical Neuroscience Center (Tehran, Iran) from July to November 2020.

A clinical psychologist, an educational psychologist, and a psychiatrist checked the criteria with parents during psychological interview and observed the child in separate sessions. Subjects who received a joint diagnosis from all three specialists were included in the study. The subjects were matched in two groups based on age. Normal intelligence ability was tested earlier in children with SLD diagnosis by revised version of Tehran-Stanford-Binet intelligence scale. Exclusion criteria were history of neurological and/or psychiatric problems, severe sociocultural disadvantages, abnormal psychomotor development, and visual and auditory deficits. Excluded children with the anxiety, mood, or other psychiatric disorders, received the diagnosis through the interview process. Furthermore, all three presentations of ADHD were included in the study.

Visual Continuous Performance Task (VCPT)

In this study we used Visual Continuous Performance Task (VCPT). This test was a cued go/no-go task and primarily served to assess the executive function of suppressing an action. The 400 trials were divided into four categories, each of which consisted of a pair of sequentially presented visual stimuli. In go trials, a picture of an animal is followed by a picture of an animal and the participant is asked to press a button as fast as possible. In no-go trials the participant is asked to refrain from clicking the button, since a picture of an animal is followed by a picture of a plant. No action is needed in ignore trials. In this condition a picture of plant is followed by a picture of a plant or a human (in the novelty condition a picture of a plant is followed by a picture of a human being, the latter being presented along with a novel sound), (Mueller et al., 2010). VCPT was presented via open-source Python software synchronized with EEG Studio software recording electroencephalograph data.

Electroencephalographic Recording

Electroencephalograms were recorded using the 19-channel Mitsar-EEG system (Mitsar, Russia) in active (VCPT task) state. We used 19 silver-chloride electrodes that were fixed to the scalp according to the international 10-20 system using Electro-Cap (ElectroCap, Inc, OH) with its electrodes placed on Fp1/Fp2, F3/F4, C3/C4, P3/P4, O1/O2, F7/F8, T3/T4, T5, T6, Fz, Cz, and Pz. The EEG input signals were referenced to linked ears, filtered between 0.5 to 40 Hz, and digitized at a rate of 500 Hz. The ground electrode was placed on the forehead. All electrode

impedances were kept below 5 kΩ. EEG was recorded for at least 22 minutes during VCPT task. The participants were sat in a comfortable chair in a dimly lit, acoustically isolated room. The participants were instructed to sit still and not blink or move their eyes. For artifact correction and preprocessing, WinEEG software was used. Artifact-contaminated epochs (eye blinks, rapid eye movements, slow head, or body movements, and myographic artifacts) were automatically marked and excluded from further analysis. The exclusion thresholds were set as follows: (a) 100 μV for nonfiltered EEG; (b) 50 μV for slow waves in the 0–1Hz band; and (c) 20 μV for fast waves filtered in the 20–35 Hz band. For EEG data analysis, not less than 30 artifact-free EEG epochs were used (around 60 s).

Data Analysis

WinEEG software was used for artifact correction and preprocessing. Artifact-contaminated epochs (eye blinks, rapid eye movements, slow head, or body movements, and myographic artifacts) were automatically marked and excluded from further analysis. The exclusion thresholds were set as follows: (a) 100 μV for nonfiltered EEG; (b) 50 μV for slow waves in the 0–1Hz band; and (c) 20 μV for fast waves filtered in the 20–35 Hz band. For EEG data analysis, not less than 30 artifact-free EEG epochs were used (around 60 s).

After applying the quick Fourier transform, the absolute power was computed for the theta (4–8Hz) and beta1 (13–20 Hz) frequency bands in Fz & Cz. The Theta Beta Ratio (TBR) computed in these regions and the T test wase used for comparing the groups' mean. It should be mentioned that for getting close to the normal distribution, we applied independent T-test after calculating the logarithms for the amplitude numbers.

Results

Table 1 presents the demographic characteristics of the participants. The participants' age ranged 7-10 years. To compare age and gender groupings, the Chi-square test was performed. The Chi-square test revealed no significant differences ($P<0.05$) between the groups in terms of age and gender variables, as shown in Table 1. Therefore, it can be argued that both groups of SLD and ADHD were almost similar in age and gender characteristics.

Table 1. Demographic characteristics

Variables		No. (%)		Chi-Square	P
		ADHD (N=15)	SLD (N=15)		
Age (years)	7	2(40)	3(60)	1.45	0.69
	8	4(66.7)	2(33.3)		
	9	3(37.5)	5(62.5)		
	10	6(54.5)	5(45.5)		
Gender	Girl	3(42.9)	4(57.1)	0.18	0.67
	Boy	12(52.2)	11(47.8)		

We compared the group's performance in VCPT task based on Omission (t= 0.021), Commission (t= 0.292), Reaction Time (t= -1.281) and Variance in Responses (t= 1.091). Table 2 declares that there is no significant difference between two groups regarding behavioral variables ($P<0.05$).

Table 2. Comparison of behavioral parameters during VCPT task.

	Mean±SD		t	df	p
	ADHD	**SLD**			
Omission	13.66±12.151	13.53±20.982	0.021	28	0.98
Commission	2.20±2.833	1.93±2.120	0.292	28	0.77
RT (ms)	426.89±240.585	520.000±146.257	-1.281	28	0.21
VR	21.50±6.310	18.74±7.460	1.091	28	0.28

Based on Table 3, the results of the independent t-test indicated no significant difference between the groups regarding TBR in Fz (t= -0.492, Pvalue= 0.62) and Cz (t=0.406, Pvalue=0.68) during VCPT condition (P<0.05). Therefore, no significant difference was found between SLD and ADHD children in terms of Theta Beta Ratio in Cz and Fz sites during VCPT task.

Table 3. Theta Beta Ratio (TBR) comparison between groups during VCPT task in Cz and Fz.

	Mean±SD		t	df	p
	ADHD	SLD			
FZ	5.45±2.247	5.99±3.680	-0.492	28	0.62
CZ	7.29±3.086	6.58±2.784	0.406	28	0.68

Discussion

In this study theta/beta ratio during a visual CPT was investigated in children with ADHD as compared to children with sLD. EEG data was recoded on frontal and central sites. In addition, differences in performance of these groups in VCPT were also calculated. Our analysis revealed significant distinction neither in TBR nor in cognitive measures of CPT.

The ADHD group as compared to sLD presented no difference in central and frontal TBR during attention task. There is an almost total lack of literature comparing TBR of these groups while doing a cognitive performance task. However, the controversial issues of TBR differentiation power for people with LD and especially ADHD is still ongoing. Many studies have shown increased TBR or simply elevated slow waves in individuals with ADHD (e.g Markovska-Simoska & Pop-Jordanova, 2017; Fonseca et al., 2008; Ogrim et al., 2012; Boutros et al., 2005; Chabot et al. 2001; Monastra et al., 2001) and learning disabilities (e.g Jäncke et al., 2018; Jäncke & Alhamadi, 2015; Fernandez et al., 2003; Chabot et al. 2001). For example, Markovska-Simoska and her colleague reported 81% accuracy in differentiation unmedicated ADHD individuals from healthy controls using TBR power. Although TBR abnormalities have typically been found in ADHD populations, several studies failed to replicate the differences (e.g Saad et al., 2015; Poil et al., 2014; Arns & Gordon, 2014; Arns et al., 2013; Barry et al., 2009; Murias et. Al, 2007).

Even if the TBR power to differentiate between ADHD and HC is assumed reliable, it might not be an effective biomarker unless it also differentiates ADHD from other mental conditions (especially neurodevelopmental disorders). In a leading investigation by Coolidge et al., in a group of children with different emotional and behavioral problems QEEG was utilized as

diagnostic tool. Using TBR to diagnose ADHD among children with vast range of psychological issues, Coolidge et al. found a sensitivity of 50% and a specificity of 36% differentiating ADHD (as estimated by parents) from other psychological disorders (Coolidge et al., 2007). In the current study differentiation and sensitivity/specificity measures were not calculated, but the results are consistent with foresaid study showing TBR inefficiency to be counted for differentiating ADHD from other mental health issues.

In most of the studies on this matter, the conventional most regular approach of QEEG research (i.e eyes-open or eyes-closed resting condition) (Klimesch, 1999) has been used. In this approach we can examine baseline (tonic) features of the brain in resting state. By comparison, only scarce literature exists on QEEG under active conditions that are mostly focused on brain dynamics while doing a task on an even-related (phasic) paradigm. P300 amplitude and latency in attention tasks (such as oddball, CPT and GoNogo) are reported as a common component to study aspects of processing in ADHD literature (e.g Barry et al., 2003; Fallagater et al., 2004; Clarke et al., 2019) and to compare information processing and inhibition in individuals with ADHD and LD (e.g Lubar et atl., 1990; Buchman et al, 2011). Jonkman et al. (2000) came with reduced P300 amplitude to target stimuli in children with ADHD, while in new stimuli P300 was normal. They claimed it shows deficit in attention allocation, but not poorer cerebral processing capacity. On the other side, tonic arousal as presented by frontal TBR, is shown to be increased rather than phasic arousal (i.e P300 component) in various attention tasks in healthy subjects (Howell, Stein, & Russell, 2010). Our current research hereby has been an attempt to investigate TBR in ADHD and LD as tonic arousal index in frontocentral areas during a task which requires both inhibition and attention allocation. Accordingly, though there was no difference in TBR in children with ADHD and LD during the task, there might still be distinctive TBR in ADHD group in default mode resting state. As shown by several aforementioned research latency and amplitude in P300 might be a more effective biomarker index to investigate hypothetical differences between these disorders while doing cognitive tasks.

On the other hand, main executive functions have long been associated with the frontal cortex (Fiske & Holmboe, 2019). Many studies have acknowledged midfrontal TBR as a marker for span of cognitive functions rather than brain arousal index. According to the findings, theta oscillation might be related both to inhibitory control (Angelidis et al., 2018; Cavanagh and

Frank, 2014; Putamen et al., 2014), attention (Guo et al, 2020; Onton et al., 2005), and processing speed (Zhang et al., 2017).

In a series of studies, Barry et al. (2004, 2005, 2009) found no link between TBR and skin conductance level as a widely acceptable measure of arousal. Clarke and his colleges (2019) investigated association between TBR and amplitude and latency of P300 ERP component during an attentional task, showing TBR as linked with cognitive capacity in normal group. Accumulating evidence on individuals ADHD (Gou et al., 2020; Picken et al., 2020; Halawa et al., 2017; Markovska-Simoska & Pop-Jordanova, 2017; van Dongen-Boomsma et al., 2010) also confirms that frontal TBR is related to executive, most notably attentional, control. Given the nearly consistent results in the role of TBR in cognitive control, it is reasonably expected to find elevated TBR index during cognitive performance tasks in the groups with cognitive impairments. And training cognitive abilities might decrease the index during the rehabilitation, as Sari et al. (2015) has found about anxious people with executive dysfunctions.

In our findings in line with QEEG results, no differences in attention, inhibitory control, and processing speed were found between the groups with LD and ADHD. Complying with our findings, there are many studies showing executive dysfunctions in individuals with ADHD and sLD. As Barkley (1997) suggested ADHD is claimed to emerge from a primary deficit in executive functions with specific core of dysfunctional response inhibition, which has been investigated in several diagnostic and therapeutic studies (e.g., Baumeister et al, 2018; Azami et al, 2016; Buchmann, 2011; Martinussen et al, 2005; Cornoldi et al, 2001; Mariani & Barkley, 1997). While there are other investigations showing the importance of inhibition and attention impairments associated with mathematics and reading underachievement (Cartwright et al, 2012; Merrell & Tymms, 2001; Gaub & Carlson, 1997). Executive functions in people with pure ADHD, pured LD, and combined LD+ADHD have been compared in several research, mostly seen similar difficulties in inhibitory control (Abou El Wafa et al., 2020; Ghamarigivi, Narimani, & rabeei, 2010; Passolunghi et al., 2005) and regulation of attention resources (Martinussen & Tannock, 2006, Wu et al., 2002), while more severe impairment was observed in children with comorbidity (Purvis & Tannock, 2000; Huang et al., 2016).

Considering the findings, observing similar cerebral activations in frontocentral areas in these groups during a cognitive task may confirm the role of Theta/Beta oscillations in attention and inhibition.

Limitations of this study

This study has a number of restrictions. The medication usage in subjects was not controlled and we have no data that would determine if there were a difference between unmedicated vs. medicated children. Resting state EEG in addition to different cognitive tasks in active condition, may demonstrate greater accuracy to differentiate between ADHD and LD. Also including larger sample size will result in more convincing results, especially with age considerations to contemplate maturational delay. These are challenges for future research.

Ethical Considerations

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration revised in 2008. Informed consent was obtained from legally authorized representative (parents) of all subjects to be included in the study.

Authors Contributions

Fatemeh Gholamali Nezhad: Data collection, Data analysis, writing (the methodology, results, and abstract), and reviewing.

Mahdieh Sadat Mirmohammad: Writing the discussion and reviewing.

Reza Rostami: Supervision.

Hanieh Ahmadi: Writing the introduction draft.

Conflict of Interest

All authors confirm that they have no conflicts of interest.

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