1-1-2017

Atypical interference control in children with AD/HD with elevated theta/ beta ratio

Dawei Zhang
University of Wollongong, dwz847@uowmail.edu.au

Steven J. Roodenrys
University of Wollongong, steven@uow.edu.au

Hui Li
University Of Wollongong, hl338@uowmail.edu.au

Robert J. Barry
University of Wollongong, rbarry@uow.edu.au

Adam R. Clarke
University of Wollongong, aclarke@uow.edu.au

See next page for additional authors

Atypical interference control in children with AD/HD with elevated theta/beta ratio

Abstract

The theta/beta ratio (TBR) is a major area of interest within electroencephalogram (EEG) research in AD/HD. While researchers suggest a prognostic role for TBR in AD/HD, its relationship to behavior remains uncertain. Recent evidence suggests that elevated TBR in AD/HD may be related to atypical inhibition, particularly at an attentional level. This study aimed to examine the performance on three inhibitory tasks of children with AD/HD. Fifty-eight children with AD/HD participated, divided into an elevated TBR (ET) group and a control group (CT). A behavioral disassociation was found – compared to CT, ET showed more difficulty in inhibiting surrounding stimuli but had less day-to-day inhibitory issues measured by BRIEF. There was no significant group difference on response inhibition. The results support the prognostic value of TBR in AD/HD. Elevated TBR may be an inhibitory biomarker; further studies are needed to explore the behavioral implications in patients without elevated TBR.

Disciplines

Education | Social and Behavioral Sciences

Publication Details

Zhang, D., Roodenrys, S., Li, H., Barry, R., Clarke, A., Wu, Z., Zhao, Q., Song, Y., Liu, L., Qian, Q., Wang, Y., Johnstone, S. & Sun, L. (2017). Atypical interference control in children with AD/HD with elevated theta/beta ratio. Biological Psychology, 128 82-88.

Authors

Dawei Zhang, Steven J. Roodenrys, Hui Li, Robert J. Barry, Adam R. Clarke, Zhanliang Wu, Qihua Zhao, Yanlin Song, Lu Liu, Qiujin Qian, Yufeng Wang, Stuart J. Johnstone, and Li-Chao Sun

Atypical interference control in children with AD/HD with elevated theta/beta ratio

Da-Wei Zhang[1,2], Steven Roodenrys[1], Hui Li[3,4,], Robert J. Barry[1,2], Adam R. Clarke[1,2], Zhanliang Wu[3,4], Qihua Zhao[3,4], Yan Song[5], Lu Liu[3,4], Qiujin Qian[3,4], Yufeng Wang[3,4], Stuart J. Johnstone[1,2 #], Li Sun[3,4 #]

[1]School of Psychology, University of Wollongong, Wollongong, NSW, Australia

[2]Brain & Behaviour Research Institute, University of Wollongong, Wollongong, NSW, Australia

[3]Peking University Sixth Hospital / Institute of Mental Health, Beijing, China

[4]National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), Beijing, China

[5]State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, China

 # Correspondence should be addressed to

Li Sun

Peking University Sixth Hospital

Beijing 100191, China

Email: sunlioh@bjmu.edu.cn

Stuart J. Johnstone

School of Psychology, University of Wollongong,

Wollongong, NSW 2522, Australia

E-mail: sjohnsto@uow.edu.au

Abstract

The theta/beta ratio (TBR) is a major area of interest within electroencephalogram (EEG) research in AD/HD. While researchers suggest a prognostic role for TBR in AD/HD, its relationship to behavior remains uncertain. Recent evidence suggests that elevated TBR in AD/HD may be related to atypical inhibition, particularly at an attentional level. This study aimed to examine the performance on three inhibitory tasks of children with AD/HD. Fifty-eight children with AD/HD participated, divided into an elevated TBR (ET) group and a control group (CT). A behavioral disassociation was found – compared to CT, ET showed more difficulty in inhibiting surrounding stimuli but had less day-to-day inhibitory issues measured by BRIEF. There was no significant group difference on response inhibition. The results support the prognostic value of TBR in AD/HD. Elevated TBR may be an inhibitory biomarker; further studies are needed to explore the behavioral implications in patients without elevated TBR.

Keywords

AD/HD; EEG; Theta/beta ratio; Biomarker; Interference control; Inhibition

1. Introduction

Attention-deficit/hyperactivity disorder (AD/HD) is a common neurodevelopmental disorder with a worldwide prevalence around 5.3% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). The electroencephalogram (EEG), as a non-invasive tool to measure brain electrical activity, has been used frequently in research to objectively reflect the abnormalities of AD/HD (Barry, Clarke, & Johnstone, 2003). Past studies have reported that patients with AD/HD showed increased slow-wave activity and reduced fast-wave activity compared to healthy controls, which results in a higher slow/fast wave ratio - commonly measured as an elevated theta/beta ratio (TBR) (Barry & Clarke, 2009). An early meta-analysis demonstrated a large effect size for the AD/HD-control group difference on TBR (Snyder & Hall, 2006). In 2013, the U.S. Food and Drug Administration (2013) approved the use of TBR to assist in the identification and diagnosis of AD/HD.

However, the diagnostic value of TBR in AD/HD is controversial as recent studies have failed to replicate the group difference reported in earlier studies (Ogrim, Kropotov, & Hestad, 2012; Loo et al., 2013; Arns, Conners, & Kraemer, 2013; Zhang et al., in press). Instead, researchers are proposing the use of TBR in AD/HD for a prognostic purpose (Arns et al., 2013; Lenartowicz & Loo, 2014; Zhang et al., in press). The prognostic proposition focusses on using EEG to predict individual differences in AD/HD rather than identifying the characteristics of AD/HD. From this perspective, while TBR does not reliably differentiate the patients from healthy controls, patients with elevated TBR show features differing from those without elevated TBR. The argument is supported by the heterogeneous nature of TBR in AD/HD – about 35% of patients are estimated to have elevated TBR (Clarke et al., 2011). In addition, the prognostic value is also supported by EEG-based medication studies in which patients with higher TBR

responded better to stimulant treatment (Clarke, Barry, McCarthy, & Selikowitz, 2002; Arns, 2012).

One obstacle to using TBR for its prognostic value is to understand its behavioral meaning. The aberrant EEG activity in AD/HD was attributed to an arousal disorder in a prevailing EEG model of AD/HD, the hypo-arousal model (Satterfield & Cantwell, 1974; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992). In this model, the higher TBR in AD/HD was thought to reflect lower arousal compared to healthy controls. However, the assumption was not supported in a study that did not find the relationship between TBR and arousal in children with AD/HD (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009). Instead, it was suggested that TBR in AD/HD may provide information about cognitive processing (Barry et al., 2009). However, it is uncertain which specific tasks/processes are related to TBR. In subsequent studies, it was reported that inattentive symptoms correlated with fronto-central TBR in children with AD/HD (Loo et al., 2013; Zhang et al., in press). Patients with higher TBR showed more severe inattentive issues (Loo et al., 2013; Zhang et al., in press). These results suggest that TBR may be a marker of attentional processing, which is consistent with studies of TBR in the normal population (Putman, van Peer, Maimari, & van der Werff, 2010; Putman, Verkuil, Arias-Garcia, Pantazi, & van Schie 2014; Angelidis, van der Does, Schakel, & Putman, 2016).

In the normal population, Putman et al. (2010) explored the relationship between frontal TBR and inhibitory functions. Inhibition was conceptualized at an attentional level (attention control, also known as interference control) and at a response level (response inhibition). The study revealed negative correlations between TBR and inhibition at two levels, relationships that were further replicated in subsequent studies (e.g. Putman et al., 2014; Angelidis et al., 2016). In these studies, the participants with higher TBR performed worse on inhibitions involving attentional and response control.

As a result, TBR was considered a biomarker for inhibition (Putman et al., 2014; Angelidis et al., 2016). These results suggest that children with AD/HD who have elevated frontal TBR may be in risk of inhibitory deficits both at attentional and at response level. Following this explanation, the correlation between TBR and the inattention found in AD/HD research (Loo et al., 2013; Zhang et al., in press) may essentially reflect a weakness of attentional/interference and response control. However, these assumptions have not been empirically addressed.

Therefore, the current study aimed to explore whether elevated TBR is related to deficient inhibition in children with AD/HD. As inhibition is a broad concept (Nigg, 2000; Diamond, 2013), three types of inhibition found to be deficient in AD/HD were examined; interference control (IC), response inhibition (RI), and daily inhibition (DI). The first two terms are similar to those used in Putman et al. (2010). IC is a higher-order function of attention and plays an important role in top-down regulation, allowing individuals to preferentially process relevant stimuli and ignore irrelevant stimuli (Peterson & Posner, 2012). In comparison to healthy controls, patients with AD/HD show poor performance in IC tasks (Mullane, Corkum, Klein, & McLaughlin, 2009) and differ from controls on electrophysiological measures taken during task performance (Johnstone, Barry, Markovska, Dimoska, & Clarke, 2009; Johnstone, Barry, & Clarke 2013). In the laboratory, IC is frequently measured via a Flanker task.

RI refers to the ability to stop an inappropriate prepotent or ongoing movement (Aron, Robbins, & Poldrack, 2004). A substantial proportion of the AD/HD population show deficits in RI (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), and concurrent abnormal neural activity has been shown in electrophysiological (Dimoska, Johnstone, Barry, & Clarke, 2003; Johnstone et al., 2013) and neuroimaging studies (Aron & Poldrack, 2005). The Stop-signal task is frequently used to measure RI.

DI also measures the ability to control/stop inappropriate behaviors but the measurement is based on performance in daily life (Gioia, Isquith, Guy, & Kenworthy, 2000). While RI is usually measured by experimental computerized tasks, performance indices may only reflect pure inhibitory processes without the involvement of emotion and motivation, which is dissimilar to daily behaviors (Barkley & Fischer, 2011; Barkley, 2013). Thus, the outcomes may lack ecological validity (Barkley, 2013). Here, DI is introduced to measure inhibition in a social context, and measurement is typically via observation/questionnaires. Past studies have reported that, compared to controls, children with AD/HD show poor inhibitory control as measured by DI (McAuley, Chen, Goos, Schachar, & Crosbie, 2010; Barkley & Fischer, 2011).

As variables such as TBR are quantitative in nature, proportion/median-based split is widely used to dichotomize continuous variables into categorical variables (MacCallum, Zhang, Preacher, & Rucker, 2002; DeCoster, Iselin, & Gallucci, 2009); for example see Barry et al. (2009). The transformation allows researchers to better examine experimental hypotheses (Decoster et al., 2009; Iacobucci, Posavac, Kardes, Schneider, & Popovich, 2015). However, a common concern is that the dichotomization may bias the results, and certain justifications should be given when using the method (MacCallum et al., 2002; Decoster et al., 2009; Iacbucci et al., 2015). One consideration is whether there is a theoretical justification for the cut point (Decoster et al., 2009). In an AD/HD population, not all patients show elevated TBR (Arns et al., 2013); 35% of the patients are estimated to have elevated TBR compared to healthy controls (Clarke et al., 2011). Therefore 35% will be the cut point to categorize an elevated TBR group or a control group here.

The current study will explore whether AD/HD patients with or without high frontal TBR are differentiated on three inhibitory measures – IC, RI, and DI. We predict that patients with elevated TBR will perform worse on these inhibitory assessments.

2. Methods

2.1 Participants

The participants were recruited at child psychiatric clinics of Peking University Sixth Hospital. Clinical Diagnostic Interview Scale (CDIS), a structured clinical interview based on the DSM-IV, was conducted by psychiatrists with the participants and their parents. Diagnosis was made by a senior psychiatrist based on clinical observation and the results of the CDIS. The mandarin version of CDIS was used and it shows good sensitivity and specificity (Yang, Wang, Qian, Biederman, & Faraone, 2004). Fifty-eight children (49 males, age range 8-13 years, M = 10.2, SD = 1.5 years) participated in this study. Thirty four children were diagnosed with the predominantly inattentive type (ADHD-I) and 1 of these was comorbid with Oppositional Defiant Disorder (ODD). Twenty four children were diagnosed with the combined type (ADHD-C); four of them were comorbid with ODD and 1 was comorbid with Tic disorder. All participants had: 1) screening by the Clinical Diagnostic Interviewing Scales (Barkley, 1998); 2) no history of head trauma with loss of consciousness; 3) no history of other severe disease; 4) no history of pharmacological treatment; and 5) an IQ higher than 80 on the Wechsler Intelligence Scale III for children.

2.2 Procedure

Ethics approval was obtained from the University of Wollongong Human Research Ethics Committee (HE 15/085). Informed consent was obtained from the parent or guardian of each participant prior to accessing any records or testing.

Participants were required to complete the testing protocol in one day. In the morning, participants were in a patient room accompanied by a psychiatrist. They completed psychometric assessments and the Cambridge Neuropsychological Test Automated Battery (CANTAB) over about 2 hours. In the afternoon, resting EEG was

recorded in a room which was free from distraction, with participants seated on a comfortable chair with dimmed lighting. After EEG recording, participants were required to complete a Flanker task. The afternoon tasks lasted about 55 minutes.

2.3 Inhibitory measures

IC was measured by the Flanker task (Eriksen & Eriksen, 1974) programmed using E-prime (Psychological Software Tools, Pittsburgh, PA). The task stimuli and parameters followed Johnstone et al. (2009). There were three trial types: congruent (e.g. <<<<< or >>>>>), incongruent (e.g. <<><< or >><>>), and neutral (e.g. = = < = = or = = > = =); with 40 presentations of each trial type. Each trial began with a 500 ms central fixation cross (+) immediately followed by a stimulus which remained on-screen until a response was made or for 1500 ms if no response was made. A blank followed, of random duration between 250 – 750 ms. Children were instructed to focus on the fixation, ignore the flanking stimuli surrounding the central arrow, and respond with a left or right button press according to the direction of the central arrow. Only the first response was recorded. Correct reaction time on incongruent stimuli ($RT_{incongruent}$) minus correct reaction time on neutral stimuli ($RT_{neutral}$) was calculated to measure the interference response cost (IRC).

RI was measured by the Stop-signal task embedded in CANTAB. CANTAB is a commercial computerized battery consisting of a range of neuropsychological tasks (Chamberlain et al., 2011). Only the results of the Stop-signal task are reported in this study. In this task, children were instructed to respond as quickly as possible to bidirectional arrows. The task consisted of 320 trials with a 1000 ms inter-trial interval. In a minority of trials (25 %) when an arrow was followed by an auditory signal, they were instructed to withhold their response. The Stop-signal task used a staircase design with the stop-signal delay (SSD) varied with a 50 ms step based on task performance,

typically resulted in a 50% success on stop-signal trials. The outcome was stop-signal reaction time (SSRT), an estimate of the time taken to inhibit the response. SSRT was calculated by subtracting the $SSD_{50\%}$ (at which the participant has 50% success in stopping) from the median RT of correct Go trials (Go RT).

DI was measured by the Behavior Rating Inventory of Executive Function (BRIEF). The BRIEF is an 86-item questionnaire for assessing executive functions by observing daily behaviors, consisting of non-overlapping clinical subscales (Gioia et al., 2000). The BRIEF-Parent edition was used, and only the score of the inhibitory subscale is reported, given the stated research purpose.

2.4 EEG recording and pre-processing

Five minutes of EEG were recorded in an eyes-closed resting condition, followed by 5-minutes of recording with eyes open. The eyes-closed data were used in this study. The recording was paused if children showed signs of fatigue or restlessness. The EEG was acquired via a 128-channel system (HydroCel Geodesic Sensor Net, Electrical Geodesics, Inc., Eugene, OR). The impedance of all electrodes was less than 50 kΩ. All electrodes were physically referenced to Cz (fixed by the EGI system). The EEG was amplified with a band pass of 0.01 to 200 Hz, which was digitized on-line at a sampling rate of 1000 Hz. The EGI data were converted to allow analysis using EEGLAB and Neuroscan software version 4.3.

The EEG pre-processing followed previous studies in AD/HD (Barry et al., 2009; Clarke et al., 2011). Nineteen channels were selected based on the international 10-20 system. All channels were offline re-referenced to linked ears, and re-sampled at 256 Hz, filtered by a band-pass filter from 1 Hz to 70 Hz and a 50 Hz notch filter. Visual inspection was used to identify and exclude sections of EEG trace containing gross artefacts. The Independent Component Analysis function in EEGLAB (Delorme &

Makeig, 2004) was applied on the 19 channels to identify and exclude components related to eye and muscle movements; this is a semi-automatic process aided by a tool box in EEGLAB, ADJUST (Mognon, Jovicich, Bruzzone, & Buiatti, 2011). Then, a 3-min period was extracted from the artefact-free EEG data, and was segmented into 4 s epochs. These epochs were Fourier transformed using a Hamming window. Then EEG band power was obtained for two frequency bands: theta (3.5-7.5 Hz) and beta (12.5-25 Hz). TBR was subsequently calculated.

2.5 Statistical analysis

Frontal TBR was calculated by averaging the TBR values of frontal electrodes (Fp1, Fp2, F3, F4, F7, F8, Fz). Then, participants were divided into an elevated TBR group (ET, the value of TBR ranked top 35%) and a control TBR group (CT).

A common feature of the patients who have elevated TBR is the globally increased ratio (Clarke et al., 2011). To examine whether the ET group had this feature, a topographic analysis was conducted. The electrodes were divided into nine regions: left frontal (Fp1, F3, F7), midline frontal (Fz), right frontal (Fp2, F4, F8), left central (T3, C3), midline central (Cz), right central (T4, C4), left posterior (T5, P3, O1), midline posterior (Pz) and right posterior (T6, P4, O2). The EEG data for each region were calculated by averaging the electrodes in the region. Then, an ANOVA with between-subjects factors of Group (ET, CT) and within-subjects topographic factors of Lateral (left, midline, right) and Sagittal (frontal, central, posterior) was conducted for the theta/beta ratio. Planned contrasts were examined within the Sagittal and Lateral factors. Within the Sagittal factor, planned contrasts compared the frontal (F) and posterior regions (P), and the central region (C) with the mean of the frontal and posterior regions (F/P). Within the Lateral factor, the contrasts compared the left hemisphere (L) with the right (R), and the midline region (M) with the mean of the hemispheres (L/R). The contrasts were planned, and

there were no more of them than the degrees of freedom for the effect, so no Bonferroni-type adjustment to α was required (Tabachnick & Fidell, 2007).

ANOVA was separately used to examine the primary measures derived from the Stop-signal task and the Flanker task between groups. To examine the effect of Group on inhibitory measures, a MANOVA was conducted. Pillai's Trace tests were conducted. The behavioral data were inspected before entering the analysis. For RT-based measures, data were considered an outlier if it exceeded ±2.5 standard deviations from the mean. One case was screened out in the Flanker task. For DL, 3 cases were screened out as the scores exceed the criterion of the questionnaire. As these values were missing at random, an expectation–maximization method was used to estimate the missing values.

3. Results

3.1 Demographic and diagnostic information

Demographic and diagnostic information were compared between groups (See table 1). No significant differences were found between the ET group and the CT group for age, IQ, and scores on the AD/HD Rating Scales.

- INSERT Table 1 HERE -

3.2 TBR topographic analysis

The topographic maps for TBR for each Group are displayed in Fig. 1. TBR was larger in the midline (11.9) than the mean of the left/right hemispheres (8.6) (M > L/R: $F(1,56) = 49.58$, $p < 0.001$, $\eta_p^2 = 0.470$), larger in the frontal (10.3) than posterior (8.2) region (F > P: $F(1,56) = 43.03$, $p < 0.001$, $\eta_p^2 = 0.434$), and larger in the central (10.5) than frontal/posterior (9.3) region (C > F/P: $F(1,56) = 6.52$, $p = 0.013$, $\eta_p^2 = 0.104$), and thus showed a midline fronto-central distribution.

A Group × Lateral interaction (ET > CT × M > L/R: $F(1,56) = 10.34$, $p = 0.002$, $\eta_p^2 = 0.156$) indicated that the midline enhancement was larger in the ET (4.9) than CT

(1.8) group. A Group × Sagittal interaction (ET > CT × F > P: $F(1,56) = 4.07$, $p = 0.049$, $\eta_p^2 = 0.068$) indicated that the frontal enhancement was larger in the ET (2.7) than CT (1.4) group. Also, a main effect of Group (ET > CT: $F(1,56) = 38.49$, $p < 0.001$, $\eta_p^2 = 0.407$) indicated that the ET (12.9) had a globally elevated TBR compared to the CT (6.4).

- INSERT Figure 1 HERE -

3.3 Task performance

For the stop-signal task, the mean proportion of successful stop trials was 48.7% across participants, indicating the varied method in SST was valid. Separate ANOVAs examined Go RT and mean $SSD_{50\%}$ between the groups (Table 2). There were no significant differences.

For the Flanker task, $RT_{incongruent}$ was greater than $RT_{neutral}$ ($F(1,57) = 182.59$, $p < 0.001$, $\eta_p^2 = 0.762$), indicating that the flanker setting was valid. Separate ANOVAs examined the mean RTs on neutral and incongruent trials between the groups (Table 2). The ET group showed a larger $RT_{incongruent}$ compared with the CT group ($F(1,56) = 5.31$, $p = 0.025$, $\eta_p^2 = 0.087$).

3.4 Inhibitory functions

The results of inhibitory tasks are displayed in Table 2. There was a significant effect of Group on IRC, SSRT, and DI in Pillai's Trace ($F(3,54) = 4.29$, $p = 0.009$, $\eta_p^2 = 0.192$). Separate univariate ANOVAs were then conducted on each measure. IRC was larger in the ET than CT group (ET > CT: $F(1,56) = 5.42$, $p = 0.024$, $\eta_p^2 = 0.088$. By contrast, DI was smaller in the ET than CT group (EC < CT: $F(1,56) = 5.69$, $p = 0.020$, $\eta_p^2 = 0.092$). There was no significant difference on SSRT ($F(1,56) = 0.29$, $p = 0.590$, $\eta_p^2 = 0.005$).

As the ET group showed larger IRC and smaller DI, one-way Pearson correlations were conducted to examine if the relationships between TBR and each of these types of

inhibition were continuous. The correlations with TBR were significant (IRC: r = 0.219, N = 58, p = 0.049; DI: r = -0.227, N = 58, p = 0.043).

In summary, the results revealed that compared to the CT group, the ET group was more influenced by the interference but had less inhibitory issues in a social context. Also, the relationships between TBR and the inhibition types were continuous.

- INSERT Table 2 HERE –

3.5 Relationships among inhibitory functions in each group

As differences between groups were evident for inhibitory functions, relationships between the inhibitory tasks were further explored in the ET and CT groups separately. No significant correlations were found between the DI and other inhibitory functions in the ET (DI with IRC, r = 0.130, N = 20, p = 0.655; DI with SSRT, r = -0.291, N = 20, p = 0.213) and CT group (DI with IRC, r = 0.286, N = 38, p = 0.082; DI with SSRT, r = 0.170, N = 38, p = 0.307). However, different relationships between IRC and SSRT were found between groups. IRC was significantly correlated to SSRT (r = 0.322, N = 38, p = 0.048) in the CT group, whereas this correlation was not significant in the ET group (r = 0.135, N = 20, p = 0.570). By using a Fisher transformation, the correlations between SSRT and IRC were compared between the ET (r = 0.135, N = 20) and the CT group (r = 0.322, N = 38). The difference was not significant (p = 0.503).

4. Discussion

TBR is increasingly important as a prognostic biomarker in AD/HD research (Arns et al., 2013), although the behavioral meaning of TBR is currently uncertain. It has been suggested that TBR is related to cognitive processes rather than hypo-arousal in the AD/HD population (Barry et al., 2009). In addition, recent studies in healthy populations show that TBR is negatively correlated with inhibitory functions (Putman et al., 2010; 2014; Angelidis et al., 2016). Hence, the current study classified an elevated TBR group,

based on the proportion of the population estimated to include this feature, as indicated by cluster analysis (Clarke et al., 2011), and explored whether the patients with elevated TBR displayed weakness in three types of inhibitory tasks.

Across the groups TBR had a fronto-central distribution, which is consistent with previous studies (Clarke, Barry, McCarthy, & Selikowitz, 2001; Barry & Clarke, 2009). Compared to the CT group, the ET group showed a globally increased TBR. The result is in line with a feature in children with AD/HD who have excessive TBR (Clarke et al., 2011).

With regard to the inhibitory functions, the current study found that participants in the ET group were more influenced by interference compared to the CT group; the ET group took longer to make an accurate response when interference stimuli were present. This result supports the hypothesis and is consistent with findings in the normal population. Using a self-report scale to measure IC, Putman et al. (2010) reported that the value of TBR is negatively correlated with performance. This finding was also repeated in subsequent studies and has shown good test-retest reliability (Putman et al., 2014; Angelidis et al., 2016).

The findings of the relationships on RI and DI are in contrast to the hypotheses. In the Putman et al. (2010) study, TBR was also negatively correlated to RI; however, there was a non-significant difference of RI between groups in this study. The differing results may be due to differences in the stimuli and task paradigms. In their study, emotional stimuli were selected to investigate the relationship between TBR and emotional processing encouraged by previous findings (Knyazev, 2007). Thus, the outcome reflects an interaction between emotional processing and RI. Here, without engaging emotional processes, the outcomes reflect more pure RI processing. Furthermore, with different paradigms adopted, different aspects of RI were involved. A Go/Nogo task was used in

their study while a Stop-signal task was used here. Although both tasks measure RI, the Go/Nogo task emphasizes the ability to inhibit a response tendency whereas the Stop-signal task emphasizes the ability to inhibit an ongoing response (Verbruggen & Logan, 2008; Aron, 2011). The two paradigms are thought to elicit different types of response inhibition (Verbruggen & Logan, 2008) and different brain regions are involved in the tasks (Aron, 2011). Hence, the non-significant result here indicates that there is no difference in inhibiting an ongoing response between groups.

Also, the direction of the difference between groups on DI – patients with elevated TBR had better performance on an inhibitory score measured by BRIEF – is contradictory to expectations. The contradiction is relevant to a debate on the relationship between executive functions (EF) outcomes, including inhibition, measured by computer tasks, and the outcomes measured by reports based on daily performance (Barkley, 2013). Although EFs are operationally defined in similar ways in these two approaches, low or no correlations have been reported between the outcomes from EF tasks and those from EF questionnaires in both normal (McAuley et al., 2010) and AD/HD populations (Toplak, Bucciarelli, Jain, & Tannock, 2009; Barkley & Fischer, 2011). Two reasons may account for the disassociation. First, the outcome measured by computerized tasks reflects the pure EF without a motivational or emotional influence; so-called "cold EF" (Diamond, 2013; Barkley, 2013). On the other hand, EF questionnaires measure day-to-day activities in which motivational and/or emotional factors play an important role; so-called "hot EF" (Diamond, 2013; Barkley, 2013). Thus, the difference may result from the involvement of motivational and/or emotional factors.

The second explanation for the dissociation between task-based and questionnaire measures of EF, and the one that seems more plausible for the data reported here, is that the questionnaire-based approach may actually measure abilities other than EFs

(McAuley et al., 2010). Fast and slow brain rhythms are resourced from different brain systems and play cooperative roles in regulating behavior (for a historical review, see Knyazev, 2007). In detail, the fast wave/slow wave ratio such as TBR is suggested to reflect emotional and (or) motivational processing. For example, the TBR is related to more motivational imbalances and punishment-driven behaviors (Schutter & van Honk, 2005). Also, healthy individuals with higher TBR show weakness in inhibiting a response under the effect of emotion (Putman et al., 2010). In this way, patients with higher TBR should have performed worse on BRIEF in this study. Moreover, scores on BRIEF are widely related to math performance, reading proficiency, and other behaviors but not related to classic EF tasks including inhibitory tasks in children (McAuley et al., 2010), which suggests BRIEF may actually measure other abilities. Hence, the comparison of the inhibitory subscale between groups may in fact tap abilities other than inhibition. Our results suggest that children with AD/HD who do not show elevated TBR may have atypical functions in other domains rather than inhibition.

Furthermore, different relationships between IC and RI were found between groups – IC was correlated with RI in the CT but not ET group. The difference may reflect the smaller group size of the ET group, as the comparison of the correlations was not significant. Otherwise, this may indicate that IC and RI are separate functions in the ET group. In the normal population, behavioral studies find that IC and RI share some variance (Friedman & Miyake, 2004; Huizinga, Dolan, & van der Molen, 2006), and imaging studies reveal some pre-frontal areas that play an important role in both inhibitory functions (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Wager et al., 2005; Nee, Wager, & Jonides, 2007). Moreover, compared to adults, children tend to show less activation of these common areas (Bunge et al., 2002). Together, the

disassociation may indicate that children in the ET group may have the immature pre-frontal regions which are common neural underpinnings for inhibitory functions.

The current results have implications for the use of TBR as a prognostic biomarker in children with AD/HD. Elevated TBR was thought of as a reliable marker for classifying AD/HD from healthy controls (Snyder & Hall, 2006). However, recent evidence shows that the difference between the groups is reducing (Arns et al., 2013) and not all children with AD/HD can be characterized by increased TBR (Clarke et al., 2011). In this case, the prognostic value of TBR was proposed in AD/HD (Arns et al., 2013; Lenartowicz & Loo, 2014). A hot topic related to the TBR research is its behavioral meaning (Barry et al., 2009). An inference from current limited studies is that TBR in AD/HD may be indicative of issues in attentional processing (Loo et al., 2013; Zhang et al., in press) without further specifying which exact types of attentional functions are involved. Our results extend the findings to inhibition at the attentional level – IC, and children with elevated TBR were more influenced by task irrelevant stimuli. In other words, the elevated TBR could be a marker of a weakness in IC in AD/HD. For patients without the elevated ratio, on the other hand, a weakness was demonstrated on DI. Given past research on BRIEF, however, it may be that other abilities rather than inhibition itself may be compromised in AD/HD children without the elevated TBR.

Future studies may explore the mechanism underlying the relationship between TBR and each type of inhibition. One possible explanation comes from recent findings in cognitive neuroscience. Imaging studies report that brain resting networks interact with task-related networks and impact on behavioral output (Raichle, 2009; Northoff, Duncan, & Hayes, 2010). As EEG can detect the activity of the resting networks (Raichle, 2009), TBR may be an electrophysiological manifestation of specific resting networks, which in turn implies the inhibitory abilities. Alternatively, the relationship may be the

consequence of TBR-related problems. Arns et al. (2013) proposed that TBR may be associated with sleep duration, which can affect the neuropsychological functions (e.g. Fernandez-Mendoza et al., 2010). Thus, the relationship between TBR and inhibition may in fact result from individual differences in sleep duration.

One issue related to this study is the methodology to obtain TBR. Recently, obtaining TBR through individual frequency band rather than the fixed bands is suggested as EEG frequency bands may vary due to the effects of age (Saad, Kohn, Clarke, Lagopoulos, & Hermens, 2015). Here, the fixed band method was adopted to follow previous studies (Barry & Clarke, 2009). Further studies may extend the findings based on the individual frequency band method.

5. Conclusions

The purpose of the current study was to explore whether elevated TBR indicated an inhibitory problem in children with AD/HD in light of relevant findings in the healthy population. The results indicated a functional disassociation – children with AD/HD who have elevated TBR perform worse on interference control but perform better on day-to-day inhibition, compared to children with AD/HD who do not have elevated TBR. This suggests that TBR may be a biomarker for inhibitory functions, which further supports the prognostic value of resting EEG measures in AD/HD. Future studies might further explore the behavioral implications of the disassociation indicated by TBR in children with AD/HD.

Acknowledgements

Funding: This work was funded by the National Basic Research Program of China (2014CB846104), the National Key Technology R&D Program (2015BAI13B01), and the National Natural Science Foundation of China (81371496). The Chinese Scholarship Council provided a scholarship for D-W Zhang.

References

Angelidis, A., van der Does, W., Schakel, L., & Putman, P. (2016). Frontal EEG theta/beta ratio as an electrophysiological marker for attentional control and its test-retest reliability. *Biol Psychol, 121*(Pt A), 49-52.

Arns, M. (2012). EEG-based personalized medicine in ADHD: individual alpha peak frequency as an endophenotype associated with nonresponse. *Journal of Neurotherapy, 16*(2), 123-141.

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis. *Journal of Attention Disorders, 17*(5), 374-383.

Aron, A. R. (2011). From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biol Psychiatry, 69*(12), e55-68.

Aron, A. R., & Poldrack, R. A. (2005). The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. *Biol Psychiatry, 57*(11), 1285-1292.

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends Cogn Sci, 8*(4), 170-177.

Barkley, R. A. (1998). *Attention-deficit hyperactivity disorder : a handbook for diagnosis and treatment* (2nd ed.). New York: Guilford Press.

Barkley, R. A. (2013). *Executive functions: what they are, how they work, and why they evolved* (1st ed.): The Guilford Press.

Barkley, R. A., & Fischer, M. (2011). Predicting impairment in major life activities and occupational functioning in hyperactive children as adults: self-reported executive function (EF) deficits versus EF tests. *Dev Neuropsychol, 36*(2), 137-161.

Barry, R. J., & Clarke, A. R. (2009). Spontaneous EEG oscillations in children, adolescents, and adults. *J Psychophysiol, 23*(4), 157-173.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology, 114*(2), 171-183.

Barry, R. J., Clarke, A. R., Johnstone, S. J., McCarthy, R., & Selikowitz, M. (2009). Electroencephalogram theta/beta ratio and arousal in attention-deficit/hyperactivity disorder: evidence of independent processes. *Biol Psychiatry, 66*(4), 398-401.

Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. (2002). Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. *Neuron, 33*(2), 301-311.

Chamberlain, S. R., Robbins, T. W., Winder-Rhodes, S., Muller, U., Sahakian, B. J., Blackwell, A. D., & Barnett, J. H. (2011). Translational Approaches to Frontostriatal Dysfunction in Attention-Deficit/Hyperactivity Disorder Using a Computerized Neuropsychological Battery. *Biological Psychiatry, 69*(12), 1192-1203.

Clarke, A. R., Barry, R. J., Dupuy, F. E., Heckel, L. D., McCarthy, R., Selikowitz, M., & Johnstone, S. J. (2011). Behavioural differences between EEG-defined subgroups of children with Attention-Deficit/Hyperactivity Disorder. *Clinical Neurophysiology, 122*(7), 1333-1341.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001). Age and sex effects in the EEG: differences in two subtypes of attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 112*(5), 815-826.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2002). EEG differences between good and poor responders to methylphenidate and dexamphetamine in children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 113*(2), 194-205.

DeCoster, J., Iselin, A. M., & Gallucci, M. (2009). A conceptual and empirical examination of justifications for dichotomization. *Psychol Methods, 14*(4), 349-366.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods, 134*(1), 9-21.

Diamond, A. (2013). Executive Functions. *Annual Review of Psychology, Vol 64, 64*, 135-168.

Dimoska, A., Johnstone, S. J., Barry, R. J., & Clarke, A. R. (2003). Inhibitory motor control in children with attention-deficit/hyperactivity disorder: event-related potentials in the stop-signal paradigm. *Biol Psychiatry, 54*(12), 1345-1354.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Percept Psychophy, 16*(143-149).

Fernandez-Mendoza, J., Calhoun, S., Bixler, E. O., Pejovic, S., Karataraki, M., Liao, D., Vela-Bueno, A., Ramos-Platon, M. J., Sauder, K. A., & Vgontzas, A. N. (2010). Insomnia with objective short sleep

duration is associated with deficits in neuropsychological performance: a general population study. *Sleep, 33*(4), 459-465.
Food and Drug Administration. (2013). De novo classification request for Neuropsychiatric EEG-Based Assessment Aid for ADHD (NEBA) System. Retrieved from http://www.accessdata.fda.gov/cdrh_docs/reviews/K112711.pdf
Friedman, N. P., & Miyake, A. (2004). The relations among inhibition and interference control functions: a latent-variable analysis. *J Exp Psychol Gen, 133*(1), 101-135.
Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). Behavior rating inventory of executive function. *Child Neuropsychol, 6*(3), 235-238.
Huizinga, M., Dolan, C. V., & van der Molen, M. W. (2006). Age-related change in executive function: developmental trends and a latent variable analysis. Neuropsychologia, 44(11), 2017-2036. doi:10.1016/j.neuropsychologia.2006.01.010
Iacobucci, D., Posavac, S. S., Kardes, F. R., Schneider, M. J., & Popovich, D. L. (2015). Toward a more nuanced understanding of the statistical properties of a median split. *J Consum Psychol, 25*(4), 652-665.
Johnstone, S. J., Barry, R. J., & Clarke, A. R. (2013). Ten years on: a follow-up review of ERP research in attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 124*(4), 644-657.
Johnstone, S. J., Barry, R. J., Markovska, V., Dimoska, A., & Clarke, A. R. (2009). Response inhibition and interference control in children with AD/HD: a visual ERP investigation. *Int J Psychophysiol, 72*(2), 145-153.
Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neurosci Biobehav Rev, 31*(3), 377-395.
Lenartowicz, A., & Loo, S. K. (2014). Use of EEG to diagnose ADHD. *Curr Psychiatry Rep, 16*(11), 498.
Loo, S. K., Cho, A., Hale, T. S., McGough, J., McCracken, J., & Smalley, S. L. (2013). Characterization of the theta to beta ratio in ADHD: identifying potential sources of heterogeneity. *Journal of Attention Disorders, 17*(5), 384-392.
MacCallum, R. C., Zhang, S., Preacher, K. J., & Rucker, D. D. (2002). On the practice of dichotomization of quantitative variables. *Psychol Methods, 7*(1), 19-40.
Mann, C. A., Lubar, J. F., Zimmerman, A. W., Miller, C. A., & Muenchen, R. A. (1992). Quantitative analysis of EEG in boys with attention-deficit-hyperactivity disorder: controlled study with clinical implications. *Pediatr Neurol, 8*(1), 30-36.
McAuley, T., Chen, S., Goos, L., Schachar, R., & Crosbie, J. (2010). Is the behavior rating inventory of executive function more strongly associated with measures of impairment or executive function? *J Int Neuropsychol Soc, 16*(3), 495-505.
Mognon, A., Jovicich, J., Bruzzone, L., & Buiatti, M. (2011). ADJUST: An automatic EEG artifact detector based on the joint use of spatial and temporal features. *Psychophysiology, 48*(2), 229-240.
Mullane, J. C., Corkum, P. V., Klein, R. M., & McLaughlin, E. (2009). Interference control in children with and without ADHD: a systematic review of Flanker and Simon task performance. *Child Neuropsychol, 15*(4), 321-342.
Nee, D. E., Wager, T. D., & Jonides, J. (2007). Interference resolution: insights from a meta-analysis of neuroimaging tasks. *Cogn Affect Behav Neurosci, 7*(1), 1-17.
Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin, 126*(2), 220-246.
Northoff, G., Duncan, N. W., & Hayes, D. J. (2010). The brain and its resting state activity--experimental and methodological implications. *Prog Neurobiol, 92*(4), 593-600.
Ogrim, G., Kropotov, J., & Hestad, K. (2012). The quantitative EEG theta/beta ratio in attention deficit/hyperactivity disorder and normal controls: sensitivity, specificity, and behavioral correlates. *Psychiatry Res, 198*(3), 482-488.
Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annu Rev Neurosci, 35*, 73-89.
Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *American Journal of Psychiatry, 164*(6), 942-948.
Putman, P., van Peer, J., Maimari, I., & van der Werff, S. (2010). EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. *Biol Psychol, 83*(2), 73-78.
Putman, P., Verkuil, B., Arias-Garcia, E., Pantazi, I., & van Schie, C. (2014). EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention. *Cogn Affect Behav Neurosci, 14*(2), 782-791.
Raichle, M. E. (2009). A paradigm shift in functional brain imaging. *J Neurosci, 29*(41), 12729-12734.
Saad, J. F., Kohn, M. R., Clarke, S., Lagopoulos, J., & Hermens, D. F. (2015). Is the Theta/Beta EEG Marker for ADHD Inherently Flawed? *Journal of Attention Disorders*.

Satterfield, J. H., & Cantwell, D. P. (1974). Proceedings: CNS function and response to methylphenidate in hyperactive children. *Psychopharmacol Bull, 10*(4), 36-37.

Schutter, D. J., & Van Honk, J. (2005). Electrophysiological ratio markers for the balance between reward and punishment. *Brain Res Cogn Brain Res, 24*(3), 685-690.

Snyder, S. M., & Hall, J. R. (2006). A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. *J Clin Neurophysiol, 23*(5), 440-455.

Tabachnick, B. G., & Fidell, L. S. (2007). *Using multivariate statistics* (5th ed.). Boston: Pearson/Allyn & Bacon.

Toplak, M. E., Bucciarelli, S. M., Jain, U., & Tannock, R. (2009). Executive functions: performance-based measures and the behavior rating inventory of executive function (BRIEF) in adolescents with attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychol, 15*(1), 53-72.

Verbruggen, F., & Logan, G. D. (2008). Automatic and controlled response inhibition: associative learning in the go/no-go and stop-signal paradigms. *J Exp Psychol Gen, 137*(4), 649-672.

Wager, T. D., Sylvester, C. Y., Lacey, S. C., Nee, D. E., Franklin, M., & Jonides, J. (2005). Common and unique components of response inhibition revealed by fMRI. *Neuroimage, 27*(2), 323-340.

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biological Psychiatry, 57*(11), 1336-1346.

Yang, L., Wang, Y. F., Qian, Q. J., Biederman, J., & Faraone, S. V. (2004). DSM-IV subtypes of ADHD in a Chinese outpatient sample. *J Am Acad Child Adolesc Psychiatry, 43*(3), 248-250.

Zhang, D. W., Li H., Wu Z., Zhao, Q., Song, Y., Liu, L., Qian, Q., Wang, Y., Roodenrys, S., Johnstone, S. J., De Blasio, F. M., & Sun, Li. (in press). EEG theta/beta ratio and spectral power correlates of executive functions in children and adolescents with AD/HD. *Journal of Attention Disorders*, *2017*.