



Atypical EEG beta asymmetry in adults with ADHD[☆]

T. Sigi Hale^{*}, Susan L. Smalley, Patricia D. Walshaw, Grant Hanada, James Macion, James T. McCracken, James J. McGough, Sandra K. Loo

Department of Psychiatry and Biobehavioral Sciences, UCLA Semel Institute for Neuroscience and Human Behavior, United States

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ABSTRACT

Background: Abnormal brain laterality (ABL) is well established in ADHD. However, its clinical specificity and association to cognitive and clinical symptoms is not yet understood. Previous studies indicate increased right hemisphere (RH) contribution in both ADHD and reading impaired samples. The current study investigates whether this ABL characteristic occurs in adults with ADHD absent comorbid language impairment.

Methods: EEG beta asymmetry was compared in 35 adult ADHD subjects and 104 controls during rest and active cognition. Group differences in beta asymmetry were then further evaluated for association to linguistic and attentional abilities, as well as association to beta asymmetry measures across different brain regions.

Results: Adults with ADHD showed pronounced rightward beta asymmetry ($p = .00001$) in inferior parietal regions (P8–P7) during a continuous performance task (CPT) that could not be attributed to linguistic ability. Among ADHD subjects only, greater rightward beta asymmetry at this measure was correlated with better CPT performance. Furthermore, this measure showed a lack of normal association (i.e., observed in controls) to left-biased processing in temporal-parietal (TP8–TP7) brain regions important for higher order language functions.

Conclusion: Adult ADHD involves abnormally increased right-biased contribution to CPT processing that could not be attributed to poor language ability. This appears to also involve abnormal recruitment of LH linguistic processing regions and represents an alternative, albeit less effective, CPT processing strategy. These findings suggest different pathophysiologic mechanisms likely underlie RH biased processing in ADHD and reading impaired samples.

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1. Introduction

To date, psychiatric research has been largely oriented toward trying to characterize disorder-specific impairment. However, mounting evidence of heterogeneity, comorbidity, and overlapping clinical and cognitive deficits suggests an additional approach is warranted whereby we also seek to characterize ‘what is common’ (i.e., shared neurobiological, affective, and cognitive features), and then in turn, try to understand how such general dysfunction gets uniquely expressed across disorders.

To this end, abnormal brain laterality (ABL) appears to be a highly convergent feature of psychiatric illness. It has been

implicated in some form with most major disorders (e.g., ADHD, Dyslexia, autism, schizophrenia, bi-polar, anxiety, depression, etc.) (Annett, 1996; Asai, Sugimori, & Tanno, 2009; Baloch, Brambilla, & Soares, 2009; Blumberg et al., 2003; Brambilla & Tansella, 2007; Downhill et al., 2000; Escalante-Mead, Minshew, & Sweeney, 2003; Hori, Ozeki, Terada, & Kunugi, 2008; Kieseppa et al., 2010; Kleinhans, Miller, Cohen, & Courchesne, 2008; Monaghan & Shillcock, 2008; Morinaga et al., 2007; Robichon, Bouchard, Demonet, & Habib, 2000; Rotenberg, 2004; Schweiger, Zaidel, Field, & Dobkin, 1989; Stanfield et al., 2008; White, Nelson, & Lim, 2008), and may partly underlie noted overlap of affective and cognitive impairments among such disorders (e.g., impaired: linguistic processing, emotion/arousal regulation, working memory, attention, etc.) (Amir, Beard, Burns, & Bomyea, 2009; Burdick et al., 2009; Calhoun & Mayes, 2005; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lonnqvist, 2008; Escalante-Mead et al., 2003; Hari & Renvall, 2001; Leung, Lee, Yip, Li, & Wong, 2009; Micco et al., 2009; Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2007; Simonsen et al., 2009; Uekermann, Abdel-Hamid, Lehmkamper, Vollmoeller, & Daum, 2008; Vaessen, Gerretsen, & Blomert, 2009; Vasic, Lohr, Steinbrink, Martin, & Wolf, 2008). In short, normal

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^{*} Corresponding author at: UCLA Semel Institute, 760 Westwood Plaza, Room 47-448, Los Angeles, CA 90024, United States. Tel.: +1 310 206 7489; fax: +1 310 206 4446.

E-mail address: sig@ucla.edu (T.S. Hale).

integration of hemispherically specialized processing likely represents a key feature of the brain's basic operating system,¹ and as such, ABL may be an inherent feature of psychiatric illness and contribute to similarly expressed clinical and cognitive impairments.

Given this generality, a key challenge of psychiatric brain laterality research is to try to elucidate shared versus unique aspects of ABL that might reflect general versus disorder-specific impairment (Crow, Crow, Done, & Leask, 1998; Smalley, Loo, Yang, & Cantor, 2005). We have addressed one small component of this challenge by first trying to characterize the nature of ABL in ADHD using behavioral laterality, EEG, and fMRI methodologies. This and other work has suggested a model that involves RH biased processing during early stages of information processing and/or simple forms of cognition, associated LH impairments, and abnormal interhemispheric interaction (Hale, Bookheimer, McGough, Phillips, & McCracken, 2007; Hale, Loo, et al., 2009; Hale et al., 2005; Hale, Smalley, Dang, et al., 2009; Hale, Smalley, Hanada, et al., 2009; Hale, Zaidel, McGough, Phillips, & McCracken, 2006). This pattern of ABL appears to contribute to ADHD deficits for more complex executive function (EF) operations dependent on normal LH functioning (Hale et al., 2007) and can be remediated via top-down attentional control (Hale et al., 2006). Moreover, it seems consistent with several ADHD characteristics such as: slow naming speed (Bedard, Ickowicz, & Tannock, 2002; Brock & Christo, 2003; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002; Rucklidge & Tannock, 2002; Semrud-Clikeman, Guy, Griffin, & Hynd, 2000; Tannock, Martinussen, & Frijters, 2000; van Mourik, Oosterlaan, & Sergeant, 2005; Weiler, Bernstein, Bellinger, & Waber, 2000; Willcutt, Pennington, Olsen, Chhabildas, & Hulslander, 2005b), increased left-handedness (Reid & Norvilitis, 2000), increased prevalence among males (Berry, Shaywitz, & Shaywitz, 1985; Jones, Braithwaite, & Healy, 2003; Joseph, 2000), and increased novelty seeking (Cho et al., 2008; Goldberg, Podell, & Lovell, 1994; Lynn et al., 2005). Additionally, suspected low-dopamine and dysregulated noradrenergic function in ADHD (Pliszka, 2005) may also align with abnormal $R > L$ contribution as these systems appear to exhibit some degree of left and right hemisphere specialization respectively (Tucker & Williamson, 1984).

An important outcome of this developing model is that ABL in ADHD appears to be highly similar to ABL reported in Dyslexia, which is a frequently comorbid disorder. ADHD–Dyslexia comorbidity has been estimated to range between 25% and 40% (Semrud-Clikeman, Biederman, & Sprich-Buchminster, 1992), and like ADHD, Dyslexia has been associated with RH biased processing during early stages of information processing (for review see: Pugh et al., 2000; Shaywitz & Shaywitz, 2008) and abnormal interhemispheric interaction (Dhar, Been, Minderaa, & Althaus, 2010; Monaghan & Shillcock, 2008; Robichon et al., 2000). This pattern of ABL in Dyslexia also appears to be associated with abnormal brain-state orientation as it seems to be conditionally expressed (Ortiz, Exposito, Miguel, Martin-Loeches, & Rubia, 1992; Pugh et al., 2000; and for review: Shaywitz & Shaywitz, 2008) and can be partly remediated through intensive training of LH encoding strategies (Penolazzi, Spironelli, Vio, & Angrilli, 2010). However, multiple factors indicate that there may be different pathophysiologic mechanisms underlying this shared pattern of ABL in ADHD and Dyslexic populations.

The posterior callosal region is abnormally small in ADHD (Seidman, Valera, & Makris, 2005), but appears to be abnormally large in Dyslexia (Monaghan & Shillcock, 2008). Moreover, event related potential (ERP) studies indicate opposite patterns of abnormal callosal transfer times. ADHD is associated with atypically fast left-to-right transfer in combined type, or atypically slow right-to-left transfer in inattentive type (Rolfe, Kirk, & Waldie, 2007), while Dyslexia shows the opposite pattern of abnormally fast right-to-left and slow left-to-right transfer (Davidson & Saron, 1992). Furthermore, Dyslexia shows abnormal structural asymmetries of the planum temporale that have not been identified in ADHD (Heim & Keil, 2004). Finally, our own behavioral laterality (Hale, Loo, et al., 2009; Hale et al., 2005, 2006) and imaging studies (Hale et al., 2007; Hale, Smalley, Dang, et al., 2009; Hale, Smalley, Hanada, et al., 2009) have demonstrated that greater RH contribution in ADHD adults is not likely attributable to comorbid reading impairment. Still, additional research is needed to further substantiate whether increased RH contribution is an independent feature of ADHD, or reflects comorbid language impairment. The current study utilizes EEG beta spectral power (12–25 Hz) to address this matter.

There is ongoing debate about the nature of EEG beta, however, multiple studies have shown it to be associated with attention-directed early stage information processing (Bekisz & Wrobel, 2003; Deiber et al., 2007; Liang, Bressler, Ding, Truccolo, & Nakamura, 2002; Ray & Cole, 1985; Wrobel, 2000), and particularly so in the parietal regions (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Ray & Cole, 1985; Schutter, Putman, Hermans, & van Honk, 2001; Senkowski, Molholm, Gomez-Ramirez, & Foxe, 2006; Wrobel, 2000). More specifically, it is thought to be associated with mechanisms that potentiate early stage encoding of attentionally selected sensory information (for review see: Bekisz & Wrobel, 2003; Deiber et al., 2007; Wrobel, 2000). Consistent with this, EEG beta activation has been shown to track hemispherically specialized operations with leftward biased expression during verbal tasks and rightward biased expression for non-verbal tasks (Ray & Cole, 1985; Schutter et al., 2001). If ADHD and Dyslexia involve abnormal increased orientation toward RH biased processing, right-lateralized EEG beta activity should be evident in both groups. Moreover, if this is an independent feature of both disorders, it should be present in Dyslexia absent comorbid attention difficulties, and in ADHD absent comorbid reading difficulties.

To this end, multiple previous studies have shown increased RH parietal beta activity to be an independent feature of Dyslexia (i.e., without comorbid attention difficulties) (for review see: Rippon & Brunswick, 2000). Two studies have directly examined lateralized EEG beta activation in ADHD— one study of ADHD children with and without reading disorders (Clarke, Barry, McCarthy, & Selikowitz, 2002), and one in a reading impaired adult ADHD sample (Clarke et al., 2008). Both studies reported increased RH parietal beta activity in ADHD. The child study demonstrated this effect in ADHD children both *with* and *without* reading impairment. The adult ADHD study did not parse the effect of comorbid language impairment.

The current study extends this line of research by further examining whether increased RH EEG beta activity is evident among linguistically normal adults with ADHD (i.e., without comorbid language impairment). We do this during three conditions that place varying demands on attention-directed information processing (eyes closed, eyes open, Conner's Continuous Performance Test – CPT), and additionally examine the effects of language ability on all significant findings. Based on our own and others' previous work indicating greater RH contribution in ADHD, and the previous report of increased RH beta activation in normal reading ADHD children, we hypothesized that increased RH EEG beta activity would be present in normal reading adults with ADHD.

¹ The brain's basic operating system is conceptualized here as the broad neural network comprised of major cognitive subsystems (e.g., linguistic, visual/spatial, working memory, attention, arousal, emotion, etc.) and the executive mechanism by which processing is integrated across these sub-domains.

2. Methods and materials

2.1. Participants

The sample consisted of 139 adults (104 controls and 35 ADHD) recruited from an ongoing UCLA ADHD family genetics study (Smalley et al., 2000). Participation in this study required that families had at least 2 ADHD affected offspring. Thus, all subjects in the current study (cases and controls) were the biological parents of children with ADHD. After receiving verbal and written explanations of study requirements participants provided written informed consent approved by the UCLA Institutional Review Board. Through the UCLA ADHD Genetics Study all subjects were screened for ADHD and other psychiatric disorders via direct interviews using the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (SADS-LAR; Fyer, Endicott, Mannuzza, & Klein, 1995) supplemented with the Behavioral Disorders supplement from the Schedule for Affective Disorders and Schizophrenia for school aged children – Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997). All interviews were conducted by clinical psychologists or highly trained interviewers with extensive experience in psychiatric diagnoses. ‘Best estimate’ diagnoses were determined after individual review of diagnoses, symptoms, and impairment level by senior clinicians (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982). Inter-rater reliabilities were computed with a mean weighted kappa of 0.84 across all diagnoses with a greater than 5% occurrence in the sample. Handedness was assessed with a shortened version of the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects were excluded based on the following criteria: currently taking psychoactive medication, past or current documented neurological disorder, a significant head injury resulting in concussion, a diagnosis of schizophrenia or autism, or an estimated Full Scale IQ < 80. Inclusion criteria for the present study required a current diagnosis of ADHD and for non-ADHD controls, no evidence of past or current ADHD (i.e., reporting 4 or fewer ADHD symptoms in childhood and as adults). Subject demographics, including comorbidity, are presented in Table 1.

2.2. Electrophysiologic measures

EEG recording was carried out using 40 silver chloride electrodes using the International 10/20 locations and was referenced to linked ears. Eye movements were monitored by electrodes placed on the outer canthus of each eye for horizontal movements and by electrodes above the eye for vertical eye movements. EEG recording consisted of two baseline conditions lasting 5 min each [eyes open (EO) and eyes closed (EC)] and a cognitive activation condition lasting 15 min (Conners’ Continuous Performance Test – CPT) (Conners, 1994).

Continuous EEG data were subjected to automatic artifact detection via MANSCAN software (SAM Technology, Inc., San Francisco, CA, <http://www.manscaneeg.com>) designed to identify dead and bad channels, vertical and horizontal eye movements, saturation, muscle and movement artifact, and line frequency noise. Subsequent to this automated procedure an experienced EEG technician then visually inspected all data and identified any residual contaminants. Next, continuous EEG was broken into 1-second epochs and artifact-containing epochs were removed on a channel specific basis. Remaining artifact free epochs were then Fast Fourier Transformed (FFT) using MANSCAN EEG software, which uses a Welch’s Periodogram approach (Welch, 1967). We specified 1-second data segments, with 50% overlap, and a Hanning Windowing function to generate spectral content at a 1 Hz resolution. Spectral data were then averaged for each condition (EC, EO, and CPT), and EEG power (μV^2) from 1 to 21 Hz was exported in 1 Hz bins (e.g., 0–1, 1–2, ... 20–21). Technicians involved in the EEG recording and processing were blind to ADHD diagnostic status.

A very broad conceptualization of ‘beta’ includes frequencies ranging from 12 to 30 Hz. However, an important recent study used a complete neuromuscular blockade to directly assess electromyogenic (EMG) artifact in scalp recorded EEG and concluded that while frequencies 21 Hz and up were highly susceptible to EMG artifact, the lower aspect of beta was not (Whitham et al., 2007). We therefore restricted our analyses to the lower aspect of beta (i.e., up to the 20–21 1-Hz bin) to try to reduce exposure to possible EMG artifact. Additionally, beta activity between 12 and 16 Hz frequencies, often referred to as the sensory-motor rhythm, may index unique aspects of brain function (for review: Egner & Gruzelier, 2001; Serman,

2000). Thus, for the current study, absolute power between 12–16 Hz and 16–21 Hz frequencies were averaged for each electrode composing ‘low’ (beta1) and ‘high’ (beta2) measures. These bands are non-overlapping, as Beta1 extends to the 15–16 1-Hz signal, while Beta2 begins at the 16–17 1-Hz signal.

In the current study, our interest was specifically to evaluate the model of $R > L$ biased processing in ADHD. We therefore utilized measures of power asymmetry rather than examining group differences separately in each hemisphere. Laterality indices (LIs) were generated for nine homologous right-left electrode pairs (AF4-AF3, F4-F3, F8-F7, F18-F17, T8-T7, TP8-TP7, P4-P3, P8-P7, O2-O1) using the following standard calculation: $[(R - L)/(R + L) \times 1000]$.

2.3. Behavioral measures

The CPT requires subjects to monitor a central fixation on a computer screen while single capital letters are sequentially and centrally presented during six continuous blocks of 20 trials with either 1, 2, or 4 second inter-stimulus intervals (ISIs) (2 blocks for each ISI). The order of ISI-block presentation is randomized within subjects. The task requires subjects to press the space bar using their dominant hand with every letter presentation except for the letter ‘X’. The ‘X’ occurs on 10% of the trials within a given ISI-block. Behavioral performance was assessed using the following standard CPT measures (Conners, Epstein, Angold, & Klaric, 2003): (1) commission errors: a failure to inhibit response when an ‘x’ is presented, (2) omission errors: a failure to respond when any letter other than ‘x’ is presented, (3) hit reaction time: response time for all letters other than ‘x’, (4) hit reaction time standard error: reaction time variability, (5) response bias: signal detection measure (beta) indicating impulsive versus conservative response styles, and (6) sensitivity: signal detection measure (d-prime) indicating accuracy adjusted for false alarms.

To assess language function in our sample we used: WAIS-R vocabulary subtest (uses age-scaled scores to assess ability to generate definitions for words), Woodcock-Johnson Word-attack Revised (WJ-R) (uses age-scaled scores to assesses phonological ability), and the Wide Range Achievement Test Revised (WRAT-R) spelling and reading subtest (uses age-scaled scores to assess spelling and reading abilities).

2.4. Statistical analyses overview

Our data analytic approach comprised primary and secondary analyses. Primary analyses sought to establish group differences in EEG beta asymmetry and examine whether such differences were impacted by measured language and/or attention abilities. Three analyses were performed: (1) assessment of group differences in EEG beta asymmetry, (2) assessment of group differences in language ability and the impact of language ability on beta asymmetry findings, and (3) assessment of group differences in attention ability and the impact of attention ability on beta asymmetry findings.

Secondary analyses were performed to further characterize the nature of ABL in ADHD. Specifically, we examined whether detected beta asymmetry abnormalities in ADHD, occurring at discrete laterality indices, were also associated with abnormal integration of lateralized processing across the scalp. To do this, for each group we evaluated correlations between beta asymmetry measures showing case/control differences and the remaining beta asymmetry measures spanning the scalp.

Initial testing of EEG beta asymmetry in adults with ADHD and controls is the main focus of the current study and is therefore held to a very conservative Bonferroni corrected significance threshold. Additional analyses aimed at further characterizing the nature of uncovered EEG group differences are reported at $p = .05$. Due to EEG artifact and/or technical challenges associated with EEG recording, n -sizes vary across analyses. Thus, analysis specific n -sizes are reported. Moreover, secondary analyses to further characterize the nature of uncovered EEG group differences only included subjects whose data contributed to the primary result.

2.4.1. Primary statistical analyses

2.4.1.1. Step 1: beta asymmetry. For each condition (EC, EO, and CPT), SPSS 15.0 general linear model univariate procedure was used to assess for group differences in high and low beta for the 9 LIs, producing 54 analyses. A Bonferroni corrected significance threshold of $p < .0009$ was utilized to assess significance. Age, sex, handedness,

Table 1
Study demographics.

Clinical variables	Controls ($n = 104$)	ADHD ($n = 35$)	Statistic
Estimated full IQ	$\bar{X} = 112$, std = 14.3	$\bar{X} = 110$, std = 14.9	$t = .7$, $p = .48$
Age	$\bar{X} = 44.7$, std = 5.9	$\bar{X} = 44.6$, std = 5.9	$t = .06$, $p = .95$
ADHD type	n/a	5 C, 27 I, 3 H	n/a
Sex	51 F, 53 M	22 F, 13 M	$\chi^2 = 2$, $p = .16$
Non-right handed	9 NR, 95 R	3 NR, 32 R	fe , $p = 1$
Anxiety	21 affected	17 affected	$\chi^2 = 10.6$, $p = .001$
Mood	6 affected	7 affected	$\chi^2 = 6.2$, $p = .01$

Estimated full IQ: estimated from block-design and vocabulary subtest of WAIS-R; ADHD type: C, combined; I, inattentive; H, hyperactive; NR, non-right handed; R, right-handed; χ^2 , chi-square test; fe , Fisher’s exact test; Anxiety/mood reflect definite diagnosis of at least 1 current anxiety and/or mood disorder as assessed by direct interview using SADS-LAR (see text for reference).

and the presence of an anxiety and/or mood disorder were entered as covariates in all analyses to control for their possible influence on lateralized brain function (Bruder et al., 1997; Toga & Thompson, 2003; Zaidel, Aboitiz, Clarke, Kaiser, & Matteson, 1995). Subjects responded during the CPT with their dominant hand. Thus, under the CPT condition, co-varying for handedness also adjusts for response hand.

2.4.1.2. Step 2: language ability. To evaluate language ability and its potential impact on beta asymmetry findings we performed three analyses. First, ADHD and control groups' mean performance for language tests were compared using *t*-test. Next, Pearson's correlations between EEG measures showing significant case/control differences and language measures were examined for the whole group (i.e., groups combined) and for each group separately. Finally, univariate analyses showing significant case/control differences in EEG beta asymmetry were reexamined while co-varying for language measures in separate analyses.

2.4.1.3. Step 3: attention ability. To examine the effects of attention ability on significant beta asymmetry findings we performed the same three analyses described above, but substituted CPT for linguistic behavioral measures.

2.4.2. Secondary statistical analyses

Interaction of brain regions. Pearson's correlations between beta asymmetry measures showing significant case/control differences and remaining beta asymmetry measures in the same frequency band (i.e., beta 1 or 2) were examined for each group separately. Group differences in the patterns of correlations are reported, and we used Fisher's *r* to *z* transformations to evaluate group differences in the strength of correlations where at least one group showed a significant effect.

3. Results

3.1. Primary results

3.1.1. Step 1: beta asymmetry

One significant finding and one trend emerged. Both indicated increased rightward beta2 (16–21 Hz) asymmetry in adults with ADHD at the P8–P7 laterality index. The significant finding occurred during the CPT condition with controls ($n=84$) showing leftward asymmetry (mean = -78.6 , SE = 11.4) and ADHD subjects ($n=31$) showing rightward asymmetry (mean = 26.8 , SE = 19.3); [$F(1,114)=21.2$, $p=.00001$]. The trend occurred during the eyes open condition with the same pattern [controls ($n=81$): mean = -40 , SE = 13.2 ; ADHD ($n=30$): mean = 16.8 , SE = 21.9]; [$F(1,111)=4.7$, $p=.033$].

To help contextualize these findings and examine whether group differences in P8–P7 asymmetry were specific to the beta2 frequency band, we performed additional post hoc analysis of P8–P7 asymmetry in delta (1–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), and alpha2 (10–12 Hz) frequencies, as well as total power (1–21 Hz) for the EO and CPT conditions. No additional result approached significance ($p>.21$). These post hoc analyses were performed using the same univariate approach described above for the primary beta asymmetry analyses.

Note: The goal of subsequent analysis is to further characterize the reported group difference in beta2 asymmetry at P8–P7 during the CPT. Hence, only subjects whose data contributed to this effect (84 controls, 31 ADHD) are included in the following analyses.

3.1.2. Step 2: association with language

t-test indicated groups did not differ on any measure of language function (see Table 2). Correlation analysis between CPT P8–P7 beta2 asymmetry and language measures with both groups

combined, or for each group separately, showed no significant associations (data not shown). Re-testing group differences for CPT P8–P7 beta2 asymmetry with language measures added as covariates in separate analyses did not alter the findings. *p*-values for the group difference remained significant (*p*-values < .0003). **Note:** The WRAT-R reading score was significant as a covariate ($p=.024$), while other language measures entered as covariates did not approach significance.

3.1.3. Step 3: association with attention

t-test indicated a group difference for CPT performance with ADHD impairments for commission errors [(ADHD: mean = 12.8 , SD = 6.85 ; controls: mean = 9.7 , SD = 6.07); $t(111)=-2.27$, $p=.025$]; and reduced sensitivity [(ADHD: mean = $.61$, SD = $.19$; controls: mean = $.70$, SD = $.18$); $t(111)=2.32$, $p=.02$]. Correlation analysis between CPT P8–P7 beta2 asymmetry and CPT behavioral measures with both groups combined showed no significant associations. Analysis of correlations for each group separately showed that for ADHD subjects only greater rightward beta2 asymmetry was associated with fewer commission errors ($r=-.36$, $p=.048$), and there was a non-significant trend suggesting that it may also be associated with increased sensitivity ($r=.31$, $p=.09$). Controls showed no correlations between the EEG measure of interest and any CPT behavioral measures. Re-testing group differences for CPT P8–P7 beta2 asymmetry with CPT behavioral measures added as covariates in separate analyses did not alter the findings. *p*-values for the group effect remained significant (*p*-values < .00001).

3.2. Secondary results

Interaction of brain regions. Analysis of correlations between CPT P8–P7 beta2 asymmetry and the additional CPT beta2 laterality indices (LIs), showed a different pattern of associations in our two groups. Among controls, P8–P7 was positively correlated with LIs that were immediately anterior and superior to its location (TP8–TP7, P4–P3), while among ADHD subjects, P8–P7 was positively correlated only with the visual-cortical region (O2–O1). A Fisher *r* to *z* transformation was used to test for group differences in the strength of these correlation effects. These analyses indicated: (1) group differences in the correlations between P8–P7 and TP8–TP7 were pronounced ($z=3.35$, $p=.0004$), (2) group differences in correlations between P8–P7 and O2–O1 marginally trended toward significance ($p=.13$), and (3) there were no group differences in the correlations between P8–P7 and P4–P3 (see Table 3).

An additional post hoc analysis was performed to determine whether this pattern of abnormal brain-region association was 'asymmetry specific'. We assessed the correlations between individual electrode P8 and surrounding electrodes TP8, P4, O2, and between the individual electrode P7 and surrounding electrodes TP7, P3, O1 in each group, and found strong positive correlations in all cases for both groups (*r*-values > .63, *p*-values < .0001). Thus, the pattern of group differences in brain-region associations was specific to the associations among beta asymmetry measures across different anatomical sites.

Table 2

Group comparison of language ability- non-significant differences.

Language measure	Controls	ADHD	Statistic
Vocabulary	$\bar{X} = 12.5$, std = 3.03	$\bar{X} = 11.8$, std = 3.23	$t=.11$, $p=.28$
Phonology	$\bar{X} = 111.3$, std = 15.9	$\bar{X} = 110.5$, std = 15.02	$t=.22$, $p=.82$
Spelling	$\bar{X} = 102.8$, std = 12.2	$\bar{X} = 103.2$, std = 12.3	$t=-.14$, $p=.89$
Reading	$\bar{X} = 104.7$, std = 9.06	$\bar{X} = 104.9$, std = 10.6	$t=-.06$, $p=.95$

See text Section 2.3 for description of task measures; table shows *t*-test mean comparison of ADHD and control subjects performance for language measures.

Table 3

Pearson's correlations between P8-P7 Beta2 asymmetry and additional parietal laterality indices measured during the CPT in adults with ADHD and controls.

	T8-T7	TP8-TP7*	P4-P3	O2-O1
Controls	$r = .22, p = .07$	$r = .56, p < .00001$	$r = .30, p = .008$	$r = .12, p = .30$
ADHD	$r = .05, p = .79$	$r = -.13, p = .49$	$r = .31, p = .09$	$r = .36, p = .05$

Pearson's correlation analysis of P8-P7 beta2 asymmetry measured during the CPT and other parietal beta2 CPT asymmetry measures.

* Significant group difference in the magnitude of correlation effects based on Fisher's r to z transformation ($p = .0004$); Additional anterior measures with non-significant or trending results are not shown.

4. Discussion

The current study uncovered a robust finding that showed adults with ADHD had abnormally increased rightward beta2 (16–21 Hz) asymmetry at P8-P7 electrodes (inferior parietal region) during the Conner's Continuous Performance Task (CPT). This could not be attributed to language ability as there were: (1) no group differences in vocabulary, phonologic, spelling, or reading abilities, (2) no significant correlations between the beta asymmetry measure of interest and any linguistic measure (with both groups combined or separately in each group), and (3) group differences in beta asymmetry remained highly significant after adjusting for linguistic abilities.

This clearly demonstrates atypical right lateralization of brain function in adults with ADHD during the CPT – a task that consistently shows ADHD impairments (Riccio & Reynolds, 2001). It also suggests that this ABL phenotype does not depend on comorbid language impairment in adult ADHD subjects. This is consistent with the previous study by Clarke et al. (2002) that showed increased RH beta activation in ADHD children both *with and without* comorbid reading impairment, and aligns with previous research demonstrating RH biased processing in ADHD (Campbell et al., 1996; Casey et al., 1997; Fassbender & Schweitzer, 2006; Hale et al., 2007; Hale Loo, et al., 2009; Hale et al., 2005; Hale, Smalley, Dang, et al., 2009; Hale, Smalley, Hanada, et al., 2009; Hale et al., 2006; Malone, Kershner, & Siegel, 1988).

This finding, in conjunction with previous Dyslexia research, supports the view that RH biased processing is an independent feature of both ADHD and Dyslexia – meaning, it is not strictly associated with comorbid language impairment in ADHD, or comorbid attention impairment in Dyslexia. If true, this brings to bear two key possibilities: (1) RH biased processing may be associated with different pathophysiologic mechanisms in these groups or (2) RH biased processing might reflect a shared mechanism (or mechanisms) that does not necessarily cause language impairment in ADHD, or attention impairment in Dyslexia. In either case, this putative shared ABL characteristic highlights that understanding ABL in ADHD will likely require reconciling how right-biased processing in this population differs from, and/or convergences with, right-biased processing in Dyslexia. Differences in posterior callosal structure and function (for review see: Monaghan & Shillcock, 2008; Seidman et al., 2005), and planum temporale asymmetry (Heim & Keil, 2004), suggest there are unique ABL mechanisms in these groups, however, we do not yet know whether, or how, these contribute to RH biased processing.

Given the conceptual importance of this topic and its relevance to our main study finding, our secondary results are discussed along with relevant Dyslexia research and theoretical considerations, to try to elucidate a preliminary model of RH biased processing in ADHD versus Dyslexia. This discussion is speculative and presented only to help facilitate the development of a working conceptual framework for future research on this topic. All subsequent reference to beta asymmetry refers only to the CPT P8-P7 beta2 measure showing the current study's robust group difference.

4.1. Secondary results and theoretical implications

Adults with ADHD showed reduced sensitivity (d-prime) and increased commission errors during the CPT. These deficits are common in ADHD and indicate impaired ability to discriminate between 'respond' and 'inhibit' trials, and to inhibit responses (Riccio & Reynolds, 2001). Dyslexia (i.e., without comorbid attention difficulties) has not been consistently associated with CPT deficits (Taroyan, Nicolson, & Fawcett, 2007). Furthermore, beta asymmetry in ADHD subjects correlated with CPT measures showing deficits, but not with unimpaired language abilities. In contrast to this, RH biased beta activity in Dyslexia has been shown to correlate with poor language ability (Penolazzi et al., 2010). Finally, rightward beta asymmetry in ADHD subjects was associated with better CPT performance; whereas increased RH beta activity (and RH biased processing in general) in Dyslexia has been largely associated with worse cognitive ability and interpreted to reflect RH compensation for LH language impairment (Penolazzi et al., 2010; Rippon & Brunswick, 2000; Shaywitz & Shaywitz, 2008).

These ADHD-Dyslexia differences, in conjunction with noted callosal and planum temporale differences, seem consistent with there being different pathophysiologic mechanisms underlying ABL in these groups. One possibility is that ABL in ADHD reflects a default RH biased processing strategy (i.e., a top-down mechanism), but RH compensation for LH language impairment in Dyslexia (i.e., a bottom-up mechanism). Although speculative, this view aligns with our previous adult ADHD studies showing: (1) right-biased processing and associated linguistic impairments could be normalized via top-down reallocation of attentional resources (Hale et al., 2006), and (2) ABL-associated linguistic impairments could be directly attributed to RH biased processing versus impaired LH ability (Hale et al., 2005, 2006). To our knowledge, no similar examples of dynamic top-down mediation of ABL and associated language impairment exist in Dyslexia.

Furthermore, the notion of top-down or attention-mediated ABL effects in ADHD seems to be generally consistent with the variable and general expression of cognitive deficits in this population. Cognitive variability has been increasingly recognized as a core feature of ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006), with recent studies indicating it might involve abnormal shifting from resting to task-oriented brain states (Uddin et al., 2008). Moreover, given the strong association of goal directed actions to LH function (Baddeley, Chincotta, & Adlam, 2001; Barkley, 1997), this abnormal brain-state regulation might be directly associated with RH biased processing. Regarding the generality of impairments, core deficits in ADHD (e.g., working memory, behavioral inhibition, processing speed, etc.) do not appear to show substantial ADHD-specificity (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005a), while deficits for processing linguistic surface features, particularly phonologic, more clearly distinguish Dyslexia-specific pathology (Shaywitz & Shaywitz, 2008). In short, multiple factors highlighted above suggest different pathophysiologic mechanisms likely underlie ABL in these groups. We speculate that this involves a default attention-mediated RH biased processing strategy in ADHD (i.e., a top-down mechanism), versus LH impairment and RH compensation in Dyslexia (i.e., a bottom-up mechanism).

The current study uncovered an additional important finding indicating a link between RH biased processing and abnormal LH function in ADHD. Among controls, leftward beta asymmetry at P8-P7 (inferior-parietal/temporal-occipital regions) showed a strong positive correlation to leftward beta asymmetry at TP8-TP7 (temporal-parietal regions). This brain-region association is expected to occur with normal linguistic encoding operations (in the current study subjects processed letter stimuli during the CPT) (Shaywitz & Shaywitz, 2008). However, rightward beta asymmetry at P8-P7 in ADHD subjects showed no such association.

A similar pattern of abnormal network function has been described in Dyslexia (Shaywitz & Shaywitz, 2008), and perhaps relevant to this, recent studies have identified naming speed deficits to be independent features of both groups (Willcutt, Pennington et al., 2005b). Accordingly, ADHD and Dyslexia appear to share the ABL-associated characteristics of RH biased processing, abnormal LH network function, and slower naming speeds. This highlights that differentiating ABL in these disorders will likely require elucidating both the nature of RH biased processing and associated abnormal LH function.

Our speculative model above suggests that shared abnormal LH function stems from RH biased processing in ADHD, but a primary LH impairment with RH compensatory processing in Dyslexia. However, a primary shared ABL mechanism cannot be ruled out. For example, LH dysfunction in both groups at the level of naming speed operations could account for both convergent abnormal LH function and, in theory, also produce RH biased compensatory processing in each disorder. Still, it seems difficult to reconcile this possibility with the multiple ABL-associated ADHD-Dyslexia differences noted above. Future studies should directly examine the relationship between RH biased processing and slower naming speeds in these populations to try to further resolve this matter.

In summary, the current study demonstrated rightward beta2 (16–21 Hz) asymmetry in the inferior parietal brain region (P8–P7) of adults with ADHD during the Conner's CPT that could not be attributed to comorbid language impairment. Secondary results further suggested this was associated with: (1) better CPT performance for measures that showed ADHD impairment (i.e., commission errors and d-prime), and (2) a lack of normal association to left-biased processing in temporal-parietal regions (TP8–TP7) important for higher order language functions. These findings, in conjunction with previous Dyslexia research, suggest RH biased processing may be an independent feature of both ADHD and Dyslexia, and we speculate that RH biased processing may reflect a top-down or attention-mediated bias toward RH encoding strategies in ADHD, but RH compensation for LH impairment in Dyslexia. However, a common subclinical ABL generating mechanism, perhaps associated with slower naming speeds in both populations, cannot be ruled out. Lastly, we would like to point out that, regardless of etiology, ABL-associated abnormal LH function in both ADHD and Dyslexia might contribute to additional shared deficits for EF operations dependent on intact LH ability (e.g., verbal working memory and set-shifting) (Barkley, 1997; Seidman, 2006; Shaywitz & Shaywitz, 2008; Willcutt, Pennington, et al., 2005b).

If our speculative model of ABL in ADHD versus Dyslexia proves correct, it may inform future ADHD treatment. Recent work has shown long-term training to facilitate greater LH contribution can transition Dyslexic subjects from atypical RH biased processing strategies to a more normal LH based encoding strategy (Simos et al., 2002). This demonstrates ABL can be normalized in Dyslexia. If abnormal cognition in ADHD involves increased orientation toward RH biased processing, with no fixed LH impairment, training to normalize hemispheric contribution in this population should be particularly effective at ameliorating cognitive deficits.

4.2. Limitations

An important limitation of the current study is the focus on EEG beta activity, as some have indicated that this measure is frequently contaminated by electromyogenic (EMG) signal. As noted previously, an important recent study used a complete neuromuscular blockade to directly assess EMG artifact in scalp recorded EEG and concluded that while frequencies above 20 Hz (i.e., 21 Hz and up) were highly susceptible, the lower aspect of beta was not (Whitham et al., 2007). Our analyses were restricted to this lower aspect of beta (i.e., up to the 20–21 1-Hz bin). Nonetheless, this remains

a highly debated topic, and as such, we have taken several additional measures to evaluate the possibility that EMG contamination underlies our results.

In order for EMG to have produced abnormal rightward beta2 asymmetry in adults with ADHD it would have needed to show opposite patterns of lateralization in our two groups during the CPT (i.e., right-biased expression in ADHD, left-biased expression in controls, or both). The most obvious means to produce such an effect would be if groups differed in response hand. However, all subjects responded with their dominant hand and roughly 90% of each group was right-handed (i.e., there were no group differences in handedness or response hand). Furthermore, co-varying the handedness/response hand variable had no effect on our findings. It is also noteworthy that we also observed (trend-level: $p = .03$) rightward beta asymmetry in ADHD subjects during an eyes-opened condition that has no response component, and a previous study in ADHD children has reported a similar effect during an eyes closed condition (Clarke et al., 2002).

The next biggest concern is that right-handed responding (and/or associated right-sided muscle tension) was particularly problematic in producing right-lateralized EMG among ADHD subjects—owing to their hyperactive temperaments and associated increased motor arousal. We reexamined our main finding with hyperactive and combined subtypes removed (8 of 31 ADHD subjects), and found it to be unchanged ($p = .00007$). Moreover, hyperactive and combined subtypes did not differ from inattentive subtypes in the magnitude of the P8–P7 beta2 asymmetry effect ($p = .86$). Barring this hyperactivity source of signal contamination, it is difficult to conceive of another reason why right-lateralized EMG should be particularly problematic in ADHD adults. Nevertheless, four additional post hoc analyses further examine this possibility.

First, susceptibility to EMG signal increases with more lateral and inferior electrode placement (Goncharova, McFarland, Vaughan, & Wolpaw, 2003; Whitham et al., 2007). If beta activity at P8 reflects EMG artifact among ADHD subjects, then activity at the adjacent inferior electrode (P10) should be stronger. In contrast to this, Beta2 mean power was higher at P8 than at P10 (P8: mean = $154 \mu\text{V}^2$; P10: mean = $148 \mu\text{V}^2$). Next, muscle contamination is expected to be more prevalent in higher beta and gamma ranges (Goncharova et al., 2003; Whitham et al., 2007). If our finding was due to muscle contamination the effect should be stronger in the adjacent higher frequency band (i.e., 21–26 Hz). However, the effect was weaker in this range (about half as strong) and would not have reached significance via our Bonferroni corrected threshold. Thirdly, if the beta laterality effect in ADHD reflects EMG artifact at the P8 electrode, this should be less well correlated (compared to controls) with ostensibly real brain activity at the homologous and contralateral P7 electrode. In contrast to this, P8–P7 correlations were equally high for both groups (controls: $r = .93$, ADHD: $r = .91$). Finally, EMG artifact is understood to have a relatively diffuse spatial distribution (Goncharova et al., 2003; Whitham et al., 2007). However, beta2 asymmetry at anterior (TP8–TP7, T8–T7, FT8–FT7, F8–F7) or posterior (O2–O1) locations to our robust effect at P8–P7 showed no group differences. It seems unlikely that EMG across 31 ADHD subjects would produce such a robust and highly site-specific laterality effect. In short, we cannot definitively rule out EMG contamination in our data. However, given the above arguments and additional post hoc analyses, we feel this possibility is remote. Additional study limitations are presented below.

All subjects in the current study (i.e., both cases and controls) were the biological parents of children with ADHD. Thus, our control sample may possess a higher loading of ADHD susceptibility factors (both genetic and non-genetic) than a more typically obtained control sample. This may have reduced our ability to detect case/control differences. Furthermore, because of a possi-

ble increase in ADHD susceptibility genes in our control group, the interpretation of rightward EEG beta asymmetry in ADHD as a possible endophenotype is not straightforward and is therefore not addressed in the current study (i.e., this would require an additional control sample absent ADHD offspring).

An additional limitation of the current study is the relatively small sample size of the ADHD group. Replication with a larger ADHD sample is needed to assure the validity of the current findings. Also, it is important to note that the current EEG beta asymmetry findings and their association to CPT attentional measures may not generalize to ADHD children, and that they may be specific to the inattentive subtype as few hyperactive or combined subtypes were included in the current study. Finally, adult ADHD subjects in the current study were not directly identified in childhood, and as such, may not be equivalent to adult ADHD subjects that were.

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