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Rethinking a Right Hemisphere Deficit in ADHD ¹

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Abstract

Introduction—Early observations from lesion studies suggested right hemisphere (RH) dysfunction in ADHD. However, a strictly right-lateralized deficit has not been well supported. An alternatively view suggests increased R>L asymmetry of brain function and abnormal interhemispheric interaction. If true, RH pathology in ADHD should reflect interhemispherically networked and over-activated functioning. We evaluated these assertions.

Methods—Four elements of lateralized brain function were measured: LH specialized, RH specialized, LH with interhemispheric processing (LH/IH), and RH with interhemispheric processing (RH/IH). Next, we tested their association with cognitive ability, psychiatric comorbidity, and sibling correlations in 79 children with ADHD.

Results—RH/IH processing was uniquely associated with other outcome measures. There were no associations for independent RH or LH function alone.

Conclusions—Interhemispherically networked RH processing is critical in ADHD. Additionally, lack of association between LH specialized processing and cognitive ability (especially for verbal cognitive tasks) supports increased RH mediation of task processing.

ADHD is often considered to represent an extreme on a normal continuum of liability (Lubke et al., 2007). However, no specific biological continuum of liability has yet been identified. One interesting possibility is highlighted by a growing body of research showing that atypical brain laterality (ABL) may be a core component (Fassbender & Schweitzer, 2006; Hale, Bookheimer, McGough, Phillips, & McCracken, 2007; Hale et al., 2005; Hale, Zaidel, McGough, Phillips, & McCracken, 2006; Smalley, Loo, Yang, & Cantor, 2005; Stefanatos & Wasserstein, 2001). The first indications of ABL in ADHD stemmed from observations that unilateral right-sided brain damage produced symptoms reminiscent of ADHD (Heilman, Bowers, Valenstein, & Watson, 1986), and by attention research showing that the right hemisphere (RH) plays a critical role in shifting attention (Corbetta, Miezin, Shulman, & Petersen, 1993), sustaining attention (Pardo & Raichle, 1991), and regulating arousal (Aston-Jones, Foote, & Bloom, 1984). Subsequently, some behavioral studies have supported a RH deficit (for review see Stefanatos & Wasserstein, 2001). However, lesion and ‘brain-system’ associational evidence is inconclusive as to what it can tell us about the nature of lateralized brain function. Localized lesions likely impact system-wide distributed neural networks and to the extent that arousal and attention regulation mechanisms implicated in ADHD are strictly

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right-lateralized, they are still expected to impact, and be impacted by, left hemisphere (LH) contributions (Mesulam, 1988). Thus, from these associations we cannot determine what aspects of putatively altered brain function might underlie ADHD symptoms. Furthermore, behavioral studies using tasks conceptualized to tap RH function cannot by themselves rule out LH contribution to poor task performance.

Indeed, the complex interactive nature of neural-networks highlights that lateralized pathology cannot be well understood in isolation from whole-brain function. Moreover, imbalanced left/right brain contributions to processing and/or poor interhemispheric interaction could result in impaired ‘utilization’ of otherwise intact lateralized resources. In short, apparent abnormalities of RH function in ADHD may arise from complex interactive whole-brain operations and do not necessarily reflect strictly right-lateralized damaged processing. Consistent with this view, ADHD brain imaging studies to date do not support a strictly right-lateralized deficit, but instead suggest a complex pattern of ABL that has not yet been adequately described.

Structural imaging studies of ADHD indicate widespread reductions in both grey and white matter volumes across all four cerebral lobes (in both hemispheres) and including brain regions that sub serve basic sensory processing, limbic functions, and higher cognitive operations (Ashtari et al., 2005; Seidman, Valera, & Makris, 2005). Such differences suggest system-wide rather than site-specific or strictly lateralized abnormalities. Moreover, ADHD functional imaging studies of complex mental operations have shown mixed results with regard to brain laterality. Such studies have demonstrated both reduced and increased left and right hemisphere activation (Durstun et al., 2003; Ernst et al., 2003; Hale et al., 2007; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Pliszka, Liotti, & Woldorff, 2000; Rubia et al., 1999; Schulz et al., 2004; Schweitzer et al., 2004; Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004; Vance et al., 2007), as well as both reduced and increased bilateral activations (Durstun et al., 2003; Hale et al., 2007; Rubia et al., 1999; Schulz et al., 2004; Schweitzer et al., 2004; Tamm, Menon, & Reiss, 2006).

Perhaps more informative with regards to brain laterality are studies that directly examine the relationship between brain structure or function and ADHD behavior and/or clinical impairment. For instance, several structural imaging studies have reported increased association between task performance and RH grey and white matter in ADHD subjects compared to controls (B.J. Casey et al., 1997; B. J. Casey et al., 2007; Hill et al., 2003; Matero, Garcia-Sanchez, Junque, & et al., 1997; Yeo et al., 2003). Furthermore, functional imaging studies have shown abnormally increased RH cortical activation in ADHD subjects to be associated with both better task performance and increased ADHD symptoms (Ernst et al., 2003; Vaidya et al., 2005). These studies suggest that ADHD may involve an increased orientation toward RH processing.

Interestingly, functional imaging studies of brain activity at rest or during simple (i.e., non-executive function) tasks have also demonstrated increased RH activation in ADHD (Baving, Laucht, & Schmidt, 1999; Chabot & Serfontein, 1996; Hale et al., 2007; Swartwood, Swartwood, Lubar, & Timmermann, 2003). However, other resting-state studies have shown reduced LH activation (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998; Seig, Gaffney, Preston, & Jellings, 1995; A. J. Zametkin et al., 1993; A.J. Zametkin et al., 1990), perhaps, also indicating abnormal LH function. Indeed, a growing body of work has shown that ADHD with or without comorbid reading disorders involves linguistic processing speed deficits (Brock & Christo, 2003; Nigg, Butler, Huang-Pollock, & Henderson, 2002; Rucklidge & Tannock, 2002; Semrud-Clikeman, Guy, Griffin, & Hynd, 2000; Stevens, Quittner, Zuckerman, & Moore, 2002; Tannock, Martinussen, & Frijters, 2000; Weiler, Bernstein, Bellinger, & Waber, 2000; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005)- implicating poor LH function.

Behavioral laterality testing that directly measures left and right hemisphere contributions to early-stage or basic forms of information processing demonstrates both increased RH contributions and poor LH function in ADHD. Malone et al.,(1988) reported that ADHD individuals failed to demonstrate a normal LH advantage (suggesting relatively greater RH contribution) for a lateralized naming task that normalized with Methylphenidate, while Campbell et al.,(1996) reported that methylphenidate selectively slowed responses only to the stimuli expected to produce a RH advantage. Both studies concluded that there was a baseline over-reactivity of right fronto-striatal circuitry in ADHD. Additionally, Hale et al., (2005; 2006) used two well-studied behavioral laterality paradigms to investigate lateralized linguistic and emotion processing in adults with ADHD. These studies indicated abnormally increased reliance on RH processing strategies, LH linguistic impairments, and reduced left/right interaction among ADHD subjects. Furthermore, ADHD subjects were shown to have an advantage compared to controls for emotion processing specialized to the RH and their task performance completely normalized under certain attentional conditions indicating that ABL in ADHD, and the associated impairments, was modulated by top-down attentional resources (Hale et al., 2006).

Lastly, an additional important clue as to the nature of ABL in ADHD stems from several reports of reduced corpus callosum size (for review see: Seidman et al., 2005) and abnormal left/right EEG coherence (Barry, Clarke, McCarthy, Selikowitz, & Johnstone, 2005; Chabot & Serfontein, 1996; Clarke et al., 2007). These findings strongly suggest abnormal interhemispheric interaction in ADHD.

In sum, research to date does not support a strictly right-lateralized deficit in ADHD, nor does it clearly support the view that RH specialized function in ADHD is fundamentally impoverished (i.e., a RH lesion model). Instead, we suggest a model of ABL in ADHD that involves increased RH contribution, poor LH function (R>L), and abnormal interhemispheric interaction. Although this notion requires further substantiation, it is more consistent with the current body of literature than a strictly right-lateralized deficit. Moreover, this model is consistent with a view expressed by Fassbender and Schweitzer (2006) who argued, based on a review of ADHD brain imaging literature, that ADHD involved a general increased tendency to rely on neuroanatomy associated with visual/spatial and motoric processing (rather than linguistic processing) during active cognition.

The current study performs preliminary analyses to evaluate key tenets of this theory: 1) that RH pathology in ADHD reflects abnormal RH *with abnormal interhemispheric interaction* versus abnormal RH function alone, and 2) that abnormal RH function in ADHD is better characterized as being overly-activated or overly-contributing to task processing rather than being fundamentally impoverished.

We use several well-studied behavioral laterality measures that tap four key domains of lateralized brain function: LH specialized, RH specialized, LH with a requirement for interhemispheric interaction (LH/IH), and RH with a requirement for interhemispheric interaction (RH/IH) (see methods). With these measures, we perform three levels of analysis. First, we test the association between behavioral laterality measures and performance on a battery of standard cognitive (SC) tasks (i.e., tasks that do not assess lateralized information processing). This examines which aspects of lateralized brain function are associated with general cognitive ability in ADHD. Next, we examine the relationship between behavioral laterality measures and psychiatric comorbidity. This examines which aspects of lateralized brain function are associated with ADHD clinical impairment. Lastly, in a subset of our sample for which sibling data is available, we examine sibling correlations for behavioral laterality measures. This evaluates which aspects of lateralized brain function demonstrate familiarity-indicating a possible genetic contribution to ABL.

To evaluate whether RH/IH versus RH specialized processing is more critical in ADHD we compare the extent to which these measures show association with cognition, comorbidity, and/or familiarity. Additionally, if RH contribution to task processing is abnormally elevated in ADHD there should be a loss of association between LH specialized function and SC tasks performance (especially for verbal SC tasks). In short, findings of robust associations between independent LH or RH specialized function and clinical and cognitive measures will counter the main tenets of our model. Alternatively, findings of predominant association with RH/IH processing and limited or no associations with independent LH function (signaling abnormally increased RH mediation of task processing) will align with the above cited literature in supporting a model of increased R>L asymmetry of brain function and abnormal interhemispheric interaction in ADHD, and justify further testing of this theory.

Methods

Subjects

The current sample consists of 79 children with ADHD from 79 multiplex families. These children represent the oldest sibling qualifying for the study from each family. An additional sample of 33 ADHD affected siblings who qualified for the study was utilized for sibling correlation analysis. Sample demographics are presented in table 1. After receiving verbal and written explanations of study requirements, all participants provided written informed consent/assent approved by the UCLA Institutional Review Board. Families were identified through an ongoing ADHD Genetics study (for study methods see Smalley et al., 2000) during which each member of the family was administered a semi-structured diagnostic interview (KSADS or SADS-LAR), and a best estimate procedure was used to determine ADHD diagnostic status. Additional specific inclusion criteria for participation in the current study included: 1) definite diagnosis of ADHD, and 2) performance to criterion level on the Emotion/Word (EW) laterality task. Specifically, subjects had to perform significantly above chance in at least 1 of the 4 EW measures. Subjects were excluded from participation if they were positive for any of the following: neurological disorder, significant head injury resulting in concussion, or full scale IQ <80. Subjects on stimulant medication were asked to discontinue use for 24 hr prior to their visit.

Procedures

Testing for standard and lateralized behavioral measures occurred on the same day as part of the ongoing UCLA ADHD Genetics Studies program. In this study subjects undergo two cognitive testing sessions. The first session occurs in the morning and involves a battery of standard cognitive (SC) measures including: WISC-III: Information, Coding, Similarities, Arithmetic, Block Design, Vocabulary, Digit Span, Spatial Span; PIAT-R: Spelling, Reading Recognition, Word Attack; The Halstead-Reitan Neuropsychological Test Battery: Trail Making B; Stroop Task. The second session occurred in the afternoon during which time participants underwent EEG recording while performing additional cognitive tasks. Two laterality tasks, the consonant-vowel (CV) dichotic listening task and the box-checking (BC) tasks were administered during the 1st session, and one laterality task, the emotion/word (EW) dichotic listening task were administered during the 2nd session while undergoing EEG recording (Note: no EEG data are reported in the current study). Laterality tasks are described below.

Dichotic Listening Tasks—Dichotic listening used simultaneous binaural presentations of phonetically similar stimuli. Because dichotic presentations suppress ipsilateral auditory channels, the stimuli presented in each ear project initially to the opposite hemisphere via fibers that cross at the superior olive and inferior colliculus (Ivry R.B. & Robertson L.C., 1998; Zaidel, 1976). Thus, detecting targets in the left ear, for instance, indexes RH processing ability

and visa versa. For both dichotic listening tasks, stimuli were presented with flat frequency response headphones (Sony Pro MDR7506). To control for variability in auditory sensitivity, subjects were allowed to adjust their own volume setting during a stimulus introduction period.

1) The Emotion-Word (EW) dichotic listening task (M.P. Bryden & MacRae, 1989): This task assesses lateralized processing of emotional prosody and word stimuli and consistently yields a LH advantage for 'word' and a RH advantage for 'emotion' processing (M.P. Bryden & MacRae, 1989). Subjects listen to dichotic presentations of four words (bower, dower, tower, power) spoken in four different emotional tones of voice (happy, sad, angry, neutral), and are required to detect either the word 'bower' or the emotion tone of voice 'sad' in separate blocked conditions. After each stimulus pair presentation subjects signaled with a forced choice button press whether the target was present or not. Note: each condition uses the same stimuli and only instructions to the subject change between conditions.

This paradigm provides four distinct measures of lateralized brain function: two that are conceived to tap independent left and right hemisphere processing (LH word processing & RH emotion processing), and two that are more likely to require interhemispheric interaction (RH word processing & LH emotion processing) (Borod, Bloom, Brickman, Nakhutina, & Curko, 2002; M.P. Bryden & MacRae, 1989; Grimshaw, Kwasny, Covell, & Johnson, 2003; Iacoboni & Zaidel, 1996; Zaidel, 1976, 1983). The requirement for interhemispheric interaction occurs in the circumstance where a given hemisphere is challenged to do something it is not good at (i.e., RH word processing, or LH processing of negative emotional prosody). Under such circumstances, interhemispheric interaction is more likely to take place as the task-dominant hemisphere makes contributions to processing- either by taking over task processing completely, or by interacting in some manner with the non task-dominant hemisphere (Iacoboni & Zaidel, 1996; Zaidel, Clarke, & Suyenobu, 1990).

The order of presentation of task (emotion; word) was counterbalanced across all subjects. Response hand was alternated between subjects with half the participants using either their left or right hand to respond. Responses were recorded with vertically oriented microswitches to avoid confounds associated with left/right orientation of response choices (Iacoboni, Woods, & Mazziotta, 1996). Each task (emotion, word) consisted of 96 trials, half of which contained the target. Target presentations were divided equally between both ears, for a total of 24 target presentations per ear/per task, and were counter-balanced such that all possible permutations of the target occurred an equal number of times in each ear. The remaining 48 trials that did not contain the target were divided equally among the remaining stimuli. The same emotional prosody or word never occurred simultaneously in each ear. This experiment took approximately 15 minutes. Stimulus introduction and practice sessions were provided for each task.

2) The Consonant-Vowel (CV) dichotic listening task (Kimura, 1967): This task assesses hemispheric competence for phonetic processing and consistently yields a LH advantage in normal subjects. Subjects listen to dichotic presentations of pairs of six consonant vowel sounds (ba, da, ga, pa, ta, ka) and must "say which sound they hear best" after each presentation of a stimulus pair. Work in split-brain patients indicates that the LH is able to perform this task independently, while the RH is not, and must transfer information to the LH for processing (S. P. Springer & Gazzaniga, 1975; Sally P. Springer, Sidtis, Wilson, & Gazzaniga, 1978). Thus, the CV task is conceptualized as providing one direct measure of LH processing, and one that depends on interhemispheric interaction (i.e., right-to-left transfer of phonetic stimuli).

During testing, subjects were first visually acquainted with the stimulus (ba, da, ga, pa, ta, ka). Next, subjects listened to monaural presentations of these stimuli and were required to

accurately identify each stimulus once in each ear. Inability to do this excluded that subject from the study.

Testing comprised 30 trials containing all possible dichotic pairings of the 6 stimuli used. This results in 10 presentations of each stimulus with 5 occurring in each ear. The stimulus set was randomized and then presented in this order for each subject. Subjects were scored for each trial on whether they reported the left ear stimulus, the right ear stimulus, or were incorrect.

The Box Checking (BC) Task (Tapley & Bryden, 1985)—This paper and pencil task assesses lateralized motor function and provides a laterality measure that emphasizes motor function rather than information processing. Subjects are presented with a matrix of small boxes (22 rows and 27 columns) and are asked to make check-marks in as many boxes as they can in one minute (this is done once with each hand). Subjects are instructed to start at the top row of boxes and go left-to-right and then continue to the next row while checking boxes as quickly and as accurately as possible.

Although predominant control over uni-manual motor function occurs via the contralateral hemisphere, abundant research demonstrates that interhemispheric processing is critical during uni-manual responses (Carson, 2005). Indeed, mirror movements of the ‘non-responding’ limb are common in children until about the age of 9 when callosal fibers become fully myelinated (Dennis, 1976). Thus, both left and right hand BC measures are conceptualized to involve lateralized control over contralateral responses, however, an interhemispheric component is also assumed. The BC task taps a potentially important domain of lateralized brain function in ADHD given the reported increase of leftward motor asymmetry in this population implicating abnormal lateralization of motor function (Niederhofer, 2005; Reid & Norvilitis, 2000).

Data Analysis

For each laterality task (EW, CV, BC) a separate set of regression analyses were performed to test the association between laterality measures and dependent variables of interest which includes: fifteen SC tasks (continuous variables), and three psychiatric comorbidity measures (binary variables). Linear regression was used for analysis of SC tasks, logistic regression was used for analyses of psychiatric comorbidity. Independent predictors included laterality measures and 4 additional variables relevant to lateralized brain function (age, gender, handedness, and ‘rested’).

The importance of age, gender, and handedness on brain laterality is well established (Geschwind, Miller, DeCarli, & Carmelli, 2002; Habib et al., 1991; Zaidel, Aboitiz, Clarke, Kaiser, & Matteson, 1995), while several reports show that ‘level-of-fatigue’ is also important (Chee et al., 2006; Drummond, Meloy, Yanagi, Orff, & Brown, 2005; Johnsen, Laberg, Eid, & Hugdahl, 2002; Manly, Dobler, Dodds, & George, 2005). Thus, we included these variables to account for their possible impact on laterality results. The ‘rested’ variable reflects a self-report rating from 1 to 5 that assesses whether subjects felt ‘tired’ versus ‘awake’ on the day of testing. This variable was dichotomized with scores of 4 or 5 labeled ‘tired’, and scores of 1, 2, or 3 labeled ‘awake’. The handedness variable was assessed by seven questions regarding hand preference taken from the Edinburgh Handedness Inventory (Oldfield, 1971). This measure produces scores ranging from negative 14 (indicating maximum left-handedness), to positive 14 (indicating maximum right-handedness). This measure was dichotomized with scores ranging from 8-14 indicating ‘definite right-handedness’, and scores less than 8 indicating ‘not definite right-handedness’.

For each laterality task, we test association with 15 SC tasks. The large number of analyses performed makes this study vulnerable to false positive errors. To address this, we used a

conservative significance threshold of $p \leq .01$, with findings of p -values between .011 and .05 listed as statistical trends.

Data entry for the cognitive measures and CV and BC task were performed using a double-entry verification procedure in SAS version 9.1 (SAS, 1999). The EW task is computerized with all responses recorded and coded automatically. All analyses were performed in SPSS version 15.0. Outliers and univariate normality were examined for each variable. Outlier analysis using a criterion of 3 standard deviations resulted in the removal of 6 data points (4 from the Stroop Conflict task, 2 from the dichotic listening emotion task). Skewness and kurtosis were less than 1.5 for all variables. Total sample size is listed for each regression analysis as this number varied for individual tasks.

Results

Analysis 1: Association of EW laterality with SC tasks and psychiatric co-morbidity

Results of regression analyses of the effects of EW laterality on SC task performance are detailed in table 2. Five SC tasks showed significant positive association with EW laterality. In all of these results, SC task showed exclusive association with the left ear (LE) word measure- with no other EW laterality measure approaching significance. The LE word measure taxes RH word processing ability and involves interhemispheric interaction to access superior LH specialized linguistic processing. Thus, an increased ability for RH with interhemispheric processing (RH/IH) predicted better SC tasks performance. In addition, five trend level findings also indicated an exclusive and positive association between SC tasks and LE word processing (i.e., RH/IH).

Two of three psychiatric comorbidity measures showed trend level positive association with the right ear (RE) emotion measure, with no other EW laterality measures approaching significance. The RE emotion measure taxes LH 'sad-tone' emotion processing and likely requires interhemispheric interaction to access superior RH specialized 'sad-tone' emotion processing. Thus, increased LH/IH processing ability predicted positive diagnosis for Mood disorder and Oppositional Defiant Disorder (ODD).

Analysis 2: Association of CV laterality with SC tasks and psychiatric co-morbidity

Results of regression analyses of the effect of CV laterality on SC task performance are detailed in table 3. Seven SC tasks showed significant positive association with CV laterality ($p < .01$). In five of these, SC tasks showed association predominantly and/or exclusively with LE CV trials, while two results indicated approximately equal association with both left and right ear CV scores. The LE CV measure taxes RH phoneme processing, which is known to require right-to-left transfer of information, while RE trials tax LH phoneme processing. Thus, results indicate that increased ability mainly for RH/IH processing predicted better performance on SC tasks. Three additional SC tasks showed trend level positive association with CV laterality. Two of these indicated exclusive association with LE CV scores (i.e., RH/IH processing), and one showed approximately equal association with both LE and RE CV scores. No co-morbidity outcome variable showed association with CV laterality.

Analysis 3: Association of BC laterality with SC tasks and psychiatric co-morbidity

Results of regression analyses of the effect of BC laterality on SC task performance are detailed in table 4. Five SC tasks showed significant positive association with BC laterality. Three of these results indicated exclusive or predominate association with left hand box checking scores. Two of these results indicated association with both left and right handed box checking (with stronger association for the right hand). Left handed box checking is conceptualized to tap RH/IH processing, while right handed box checking is conceptualized to tap LH/IH processing.

Thus, results indicate that increased ability mainly for RH/IH processing predicted better performance on SC tasks. No co-morbidity outcome variable showed association with BC laterality.

Analysis 4: Sibling Correlations for Laterality Measures

Pearson's correlation analyses showed significant sibling correlations for the EW task right ear emotion measures ($r = .55$, $p = .001$), and a trend suggested sibling correlations for the BC task left hand measure ($r = .42$, $p = .02$). No other laterality measure showed sibling correlations.

Summary of Results

The primary focus of this study is to assess the 'pattern' of association between laterality measures and performance on SC tasks. Thus, we provide below a summary table of all results. Results are organized according to conceptually different aspects of lateralized brain function to help highlight the observed pattern of association (see table 5).

Post-Hoc Analyses: Potential contribution of language impairment

Some studies suggest that dyslexia may be associated with a compensatory rightward shift of language function (Bloch & Zaidel, 1996; Schweiger, Zaidel, Field, & Dobkin, 1989). To assess the effects of poor language function on our results we re-ran analyses with subjects scoring 1.5 or more standard deviations below the mean for the reading recognition task removed. This resulted in 9 subjects being removed. The reading recognition task is highly sensitive to language impairment (Astrom, Wadsworth, & DeFries, 2007). Removing these subjects did not appreciably change the overall pattern of results. Three of 33 results become non-significant, with 2 of 33 showing very weak trends. Twenty-eight of 33 results were not appreciably altered.

Discussion

The general aim of the current study was to try and better characterize putative RH pathology in ADHD. Our review of relevant ADHD research indicated that a strictly right-lateralized deficit was not well supported. Instead, we suggested an alternative model of increased R>L asymmetry of brain function and abnormal interhemispheric interaction in ADHD. We then performed preliminary analyses to evaluate key tenets stemming from this model: 1) that RH pathology in ADHD reflects abnormal RH function *with abnormal interhemispheric interaction* versus RH function alone, and 2) that RH pathology in ADHD reflects abnormally increased RH mediation of task processing versus impoverished RH function. Our preliminary findings are consistent with these ideas.

We did not find any associations with independent RH specialized function and SC task performance. This suggests that independent RH function alone is not predicative of ADHD cognitive abilities and contradicts the notion of a strictly right-lateralized deficit. Instead, across three different laterality tasks, we observed a clear pattern of predominant association between SC task performance and laterality measures tapping RH/IH processing. For the EW task, *all* results involved RH word processing, which is conceptualized to depend upon right/left integration of processing (M.P. Bryden & MacRae, 1989; Grimshaw et al., 2003; Iacoboni & Zaidel, 1996; Zaidel et al., 1990). For the CV task, the clear majority of results involved RH phonetic processing, which is conceptualized to require right-to-left transfer of stimuli (S. P. Springer & Gazzaniga, 1975; Sally P. Springer et al., 1978). For the BC task, left-handed box checking was more strongly associated with SC task than right-handed box checking, and left-handed box checking is conceptualized to involve both RH and interhemispheric processing (Carson, 2005; Dennis, 1976). In short, the clear majority of our results involved a type of lateralized processing where the RH is challenged to do something it is not very good at (i.e.,

linguistic processing and coordinating writing like movements), and therefore likely requires interhemispheric interaction. The better ADHD subjects were at this type of processing, the better they were at performing SC tasks. This generally indicates that, rather than isolated RH processing, it is *interhemispherically networked* RH processing that is critical in ADHD.

Next, we had reasoned that increased RH mediation of task processing should be reflected in a reduction or loss of associations between LH specialized processing and SC task performance (especially for verbal SC tasks such as reading recognition, spelling, word attack, vocabulary, color-naming, color-word naming). For the EW laterality task there were no associations between cognition and LH specialized processing with all results reflecting association with RH/IH processing. The other two laterality tasks (CV and BC tasks) did show some association between LH specialized function and cognition, but in these cases, the associations were actually bilateral indicating equally strong or stronger association with RH/IH processing. Moreover, there were several results with these tasks that showed exclusive association with RH/IH processing. This pattern of findings is generally consistent with the notion of increased RH mediation of SC task processing and supports the view that RH pathology in ADHD may reflect over-activated versus impoverished RH function.

Previous research demonstrates that the observed pattern of association between laterality measures and SC task performance highlighting RH/IH forms of processing and decreased association for LH specialized function is unusual. For example, a recent study using the CV tasks with a population of 10-13 year old normal and reading disabled subjects *did* report association between the LH measure and a test of language comprehension- *with no association for the RH/IH measure* (Asbjørnsen & Helland, 2006). Likewise, a recent study using the CV task with a population of dyslexic children showed association between the LH measure and tests of reading, sentence dictation, rapid naming, and language comprehension- *with no associations for the RH/IH measure* (Helland, Asbjørnsen, Hushovd, & Hugdahl, 2007). Additionally, stronger relative LH ability during the CV task in normal and reading impaired subjects has been associated with better reading ability (M. P. Bryden, 1970; Hugdahl, Helland, Faerevaag, Lyssand, & Asbjørnsen, 1995). Based on these results, and several reports of linguistic deficits in ADHD (Brock & Christo, 2003; Nigg et al., 2002; Rucklidge & Tannock, 2002; Semrud-Clikeman et al., 2000; Stevens et al., 2002; Tannock et al., 2000; Weiler et al., 2000; Willcutt et al., 2005), it is somewhat surprising that we did not observe any associations with independent LH function alone and SC tasks- especially those tasks that directly measure linguistic abilities.

One explanation for this might be that linguistic impairments in ADHD could be ancillary to more primary abnormalities of RH/IH processing. In other words, language impairments in ADHD might be a secondary consequence of an increased utilization of RH processing- rather than LH impaired processing per se. This notion is consistent with our previous work showing that linguistic impairments in adults with ADHD were not absolute and could be modified with attentional changes (i.e., top-down control) over lateralized processing (Hale et al., 2006). Indeed, it is interesting to consider that language impairment in ADHD may result from abnormal *utilization* of neural resources (i.e., abnormal R>L asymmetry of brain function) rather than inherently damaged processing. If true, this would suggest that dyslexic and ADHD associated linguistic impairments may be etiologically distinct and perhaps distinguishable by the extent to which top-down attentional control can mediate the impairment. This notion should be tested in future studies.

Another conceptual point is that the proposed increase of RH contribution to processing in ADHD may, by default, bring to bear abnormal interhemispheric interaction. Males on average exhibit better visual-spatial and poorer linguistic abilities compared to females (implicating greater RH versus LH ability) (Jones, Braithwaite, & Healy, 2003; Joseph, 2000), and males

also appear to demonstrate reduced left/right integration of processing (Schmithorst & Holland, 2007). Thus, it is interesting to consider that LH mediated goal-directed or executive action (Collette & Van der Linden, 2002; Matsubara, Yamaguchi, Xu, & Kobayashi, 2004) may require greater left/right integration of processing than do RH specialized operations. If true, abnormal interhemispheric interaction in ADHD may evolve from an increase of RH biased processing. In support of this, normal subjects have been shown to exhibit faster right-to-left than left-to-right callosal transfer (Moes, Brown, & Minnema, 2007), which may reflect greater LH control over processing; while ADHD subjects have been shown to exhibit faster left-to-right transfer in combined type, or markedly slower right-to-left transfer in inattentive type—perhaps signaling reduced LH control over processing (Rolfe, Kirk, & Waldie, 2007).

Regardless of the exact mechanism, the current study provides preliminary support for the notion that RH/IH processing, rather than independent RH processing, plays a predominant role in mediating cognitive abilities in ADHD; and that RH pathology in ADHD reflects abnormally increased rather than impoverished RH contribution to task processing. These results are consistent with the proposed model of increased R>L asymmetry of brain function and abnormal interhemispheric interaction in ADHD. As stated above, this model is consistent with the suggestion that ADHD involves an increased tendency to rely on neuroanatomy associated with visual/spatial and motoric processing (rather than linguistic processing) during active cognition (Fassbender & Schweitzer, 2006). It is also consistent with several key attributes of ADHD.

For instance, ADHD with or without comorbid reading disorders involves linguistic processing speed deficits (Brock & Christo, 2003; Nigg et al., 2002; Rucklidge & Tannock, 2002; Semrud-Clikeman et al., 2000; Stevens et al., 2002; Tannock et al., 2000; Weiler et al., 2000; Willcutt et al., 2005), which implicates poor LH function. Also, ADHD is associated with increased left-sided motor preference (Niederhofer, 2005; Reid & Norvilitis, 2000). Left-sided motor preference is associated with reduced LH and increased RH contributions to language function (Geschwind et al., 2002; Toga & Thompson, 2003) and reduced callosal volumes (Hoffman & Polich, 1999). Furthermore, ADHD is more common in males (Berry, Shaywitz, & Shaywitz, 1985). Males on average exhibit better visuo-spatial and poorer linguistic abilities compared to females (Jones et al., 2003; Joseph, 2000), and may also exhibit greater lateralization of brain function (Schmithorst & Holland, 2007). Thus, it is interesting to consider that increased RH relative to LH function along with reduced left/right integrative processing might represent a risk factor ADHD, and may partly explain increased incidence among males.

Lastly, suspected abnormalities of dopamine and norepinephrine systems in ADHD might also be consistent with a model of R>L asymmetries of brain function. Tucker and Williamson (1984) proposed that the LH is predominately organized around dopamine functions associated with complex motor programming and speech; while the RH is predominantly organized around noradrenergic functions important for regulating arousal, orienting individuals to new stimuli and integrating bilateral perceptual information. A resting-state PET study has shown specific decreases of left sided dopamine metabolism in ADHD (Ernst et al., 1998); and a model by McCracken (1991) has suggested that ADHD involves dysregulation of the brain-stem nucleus locus ceruleus that produces approximately 80% of the brains largely *right lateralized* norepinephrine projections. Thus, it is interesting to speculate that dis-regulated hyper-noradrenergic along with hypo-dopaminergic function may correspond to R>L asymmetry of brain function in ADHD.

The final result of interest in the current study is that, of eight laterality measures tested, *only* the right ear emotion measure from the EW task showed significant sibling correlations and association with psychiatric comorbidity. In this measure subjects must detect a ‘sad’ emotional tone-of-voice presented in the right ear projecting initially to the LH. The RH is

specialized for processing this stimulus (M.P. Bryden & MacRae, 1989), and work by Grimshaw et al (2003) has suggested that the LH cannot process this stimulus at all and must therefore relay the signal to the RH for processing. According to this, the only measure showing robust sibling correlations and association with comorbidity is one that likely requires left-to-right transfer and then RH processing. This result is noteworthy given the recent report that ADHD may involve faster left-to-right transfer times than normal controls. It is interesting to consider that LH/IH processing may index a more familial trait-like component of ABL in ADHD; whereas RH/IH processing, which did not show appreciable sibling correlations or association with comorbidity, may reflect a more developmental compensatory cognitive strategy that is variably expressed across individuals (especially during cognitively demanding task)- but shares the common feature of increased RH contributions.

In summary, several laterality measures from three behavioral laterality tasks were utilized to test the association of lateralized brain function and cognition in children with ADHD. Across each of these paradigms a clear pattern emerged indicating that RH/IH processing is particularly associated with cognition across a wide variety of standard cognitive measures used to assess cognitive function in children with ADHD. Additionally, no measure of specialized left or right hemisphere function alone showed exclusive association with cognitive function indicating that system-wide left/right interactive dynamics, rather than independent left or right hemisphere function, is likely of issue in ADHD. The finding of reduced associations for LH specialized processing and SC tasks (especially for verbal SC tasks) supports the notion of increased RH mediation of task processing in ADHD. Together, these results are consistent with our previous work in adult subjects, and other's findings, suggesting increased R>L asymmetries of brain function and abnormal interhemispheric interaction in ADHD.

We speculate that genetic and/or environmental factors supporting trait or state increases of R>L asymmetry of brain function might be associated with risk for ADHD. Furthermore, it is important to note that abnormal increased orientation toward R>L asymmetries of brain function may contribute to both impaired working memory and behavioral inhibition often observed in ADHD (Stevens et al., 2002). Also, it is important to note that the proposed increased R>L asymmetry of brain function in ADHD may reflect a pathological increased orientation toward what is otherwise a normal brain-state that serves to enhance RH contributions during non-language dependent and/or non-goal directed types of processing. Given the importance of intact LH language abilities for goal-directed executive functions, this view seems plausible (Barkley, 1997).

Lastly, a single measure that taxes LH/IH processing was the only to show robust sibling correlations, and trends suggested that better performance on this measure predicted positive diagnosis for Mood Disorder and ODD. We speculated this may reflect a more familial component of abnormal brain laterality in ADHD, and that it may underlie the development of alternative processing strategies that emphasize RH/IH form of processing.

Limitations

Several analyses were performed for this study making it vulnerable to type 1 errors, however, the clear pattern of results implicating RH/IH processing across three laterality tasks provides some assurance that associations between laterality measures and cognition do not reflect a chance distribution of false positive errors. Moreover, the result that *we did not* find any association between independent LH or RH processing is noteworthy.

Although sibling correlation analyses show a single robust result, these were done with a small sample and require replication in a larger data set. Moreover, it will be important in future studies to repeat these analyses with a well-matched control group to better identify the exact

nature of alternate processing in childhood ADHD. Still, the current analysis importantly demonstrates that laterality results in childhood ADHD are consistent with our previous findings in ADHD adults and align with our theory of abnormal R>L asymmetry and interhemispheric interaction.

The utility of trying to distinguish pure ADHD from ADHD with comorbid language impairment assumes that ADHD with language impairment represents a qualitatively different group (i.e., those with comorbid Dyslexia). However, sub-clinical or state-dependent language impairment may exist as a durable feature of ADHD. Indeed, there is growing evidence indicating that ADHD with or without reading impairment involves some form of impaired linguistic processing (Brock & Christo, 2003; Nigg et al., 2002; Rucklidge & Tannock, 2002; Semrud-Clikeman et al., 2000; Stevens et al., 2002; Tannock et al., 2000; Weiler et al., 2000; Willcutt et al., 2005). Importantly, our previous work in adults showed linguistic impairments during a dichotic listening task *that were entirely eliminated under conditions of focused attention (i.e., the language impairment was mediated by top-down attention)* (Hale et al., 2006).

As mentioned above, excessive orientation toward a RH dominant brain-state may limit or diminish LH functions in ADHD. If true, ADHD populations are expected to, on average, indicate some language impairment. However, ADHD language impairment may be categorically different from that observed in Dyslexia. In ADHD, language impairment may show variable strengths of expression associated with variability in state and trait driven orientation toward a RH dominant mode of processing. To our knowledge, there are no examples of dyslexia language impairment being alleviated by top-down processing control. Thus, ADHD subjects with the lowest reading recognition scores in our sample may represent the most extreme cases of RH biased processing at the time of testing rather than being representative of a dyslexic component in our sample. Thus, controlling for language impairment in our sample potentially eliminates the effect of interest in this research (i.e., abnormal R>L asymmetries of brain function). Nonetheless, removing these subjects did not appreciably change the overall pattern of results. Only 3 of 33 results dropped out completely, with 2 of 33 showing very weak trends. 28 of 33 results were not appreciably altered.

Lastly, future studies to evaluate our developing theory should include a control group and directly test the effects of ADHD subgroup and gender on the association of lateralized brain function and cognition, comorbidity, and sibling correlations.

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Table 1
Sample Demographics

Clinical Variables	Main Study Sample: n=79	Additional Siblings: n=33
Age	$\bar{x}$ =12.6, s=3.18	$\bar{x}$ =11.21, s=2.6
Estimated Full IQ	$\bar{x}$ =113.6, s=16.2	$\bar{x}$ =115, s=13.4
ADHD Subtype	39I, 39C, 1H	19I, 14C, 0H
Handedness	68R, 11NR	29R, 4NR
Sex	49M, 30F	21M, 12F
Anxiety	11 affected	2 affected
Mood	10 affected	2 affected
ODD	30 affected	11 affected

I= inattentive subtype; C=combined subtype; H=hyperactive subtype; R= right-handed; NR= non right-handed; M= male; F=female; Anxiety= at least 2 positive anxiety symptoms obtained with KSAD; Mood= any mood symptom from KSAD; ODD= positive diagnosis of oppositional defiant disorder obtained with KSAD.

Table 2
Regression Results for EW task, adjusted for age, gender, handedness, and 'rested'

EW task Measures	S. C. Beta	t score	p value	EW task measures	S. C. Beta	t score	p value
Similarities (n=77)				Vocabulary (n=77)			
LE emot	.080	0.692	.491	LE emot	.041	0.332	.741
RE emot	.011	0.100	.921	RE emot	.029	0.244	.808
LE word	.402	3.528	.001**	LE word	.292	2.418	.018*
RE word	-.018	-0.151	.880	RE word	.054	0.434	.666
Reading Recognition (n=76)				Arithmetic (n=76)			
LE emot	.069	0.584	.561	LE emot	.116	0.975	.333
RE emot	.018	0.156	.876	RE emot	.099	0.859	.393
LE word	.352	2.987	.004**	LE word	.269	2.28	.026*
RE word	.07	0.574	.568	RE word	.147	1.212	.23
Spelling (n=76)				Word attack (n=77)			
LE emot	.06	0.517	.607	LE emot	-.031	-0.277	.783
RE emot	.014	0.129	.898	RE emot	-.053	-0.499	.619
LE word	.329	2.854	.006**	LE word	.243	2.204	.031*
RE word	.102	0.858	.394	RE word	-.015	-0.13	.897
Trails b (n=77)				B			
LE emot	.029	0.232	.817	LE emot	.025	0.073	.727
RE emot	-.063	-0.528	.599	RE emot	.193	0.077	.012*
LE word	-.344	-2.806	.007**	LE word	-.114	0.086	.184
RE word	.056	0.448	.655	RE word	-.085	0.079	.279
Information (n=76)				Mood (n=78)			
LE emot	.014	0.122	.903	LE emot	.112	0.119	.348
RE emot	.072	0.646	.521	RE emot	.321	0.137	.019*
LE word	.321	2.798	.007**	LE word	-.081	0.142	.569
RE word	-.049	-0.416	.679	RE word	.042	0.119	.726

** indicates a significant association with the dependent variable ($p \leq .01$);
 * indicates a trend suggesting association with the dependent variable ($p \leq .05$);
LE emot= left ear score for emotion condition; **RE emot**= right ear score for emotion condition; **LE word**= left ear score for word condition; **RE word**= right ear score for word condition; **n**= total sample used for analysis; **S.C. beta**= standardized beta coefficients;
 ^ =Logistic regression was used for these analyses (all other analyses used linear regression);
Note: for trails b task lower scores equal better performance.

Table 3
Regression Results for CV tasks, adjusted for age, gender, handedness, and 'rested'

CV Task Measures	S. C. Beta	t score	p val.	CV Task Measures	S. C. Beta	t score	p val.
Similarities (n=70)				Vocabulary (n=70)			
LE	.395	2.405	.019*	LE	.46	2.745	.008**
RE	.415	2.497	.015*	RE	.362	2.14	.036*
Reading Recognition (n=69)				Word attack (n=69)			
LE	.365	2.156	.035*	LE	.513	3.852	.000**
RE	.33	1.935	.058	RE	.533	3.968	.000**
Spelling (n=69)				Arithmetic (n=69)			
LE	.466	2.738	.008**	LE	.525	3.135	.003**
RE	.302	1.758	.084	RE	.305	1.802	.076
Trails_b (n=70)				Digit span (n=70)			
LE	-.447	-2.606	.01**	LE	.451	2.666	.01**
RE	-.306	-1.767	.082	RE	.365	2.133	.037*
Information (n=69)				Block Design (n=70)			
LE	.544	3.316	.002**	LE	.352	2.101	.04*
RE	.577	3.483	.001**	RE	.228	1.348	.182

** indicates a significant association with the dependent variable ($p \leq .01$);

* indicates a trend suggesting association with the dependent variable ($p \leq .05$);

LE= left ear score; **RE**= right ear score; **n**= total sample used for analysis; **S.C. beta**= standardized beta coefficients; **Note:** for trails b task lower scores equal better performance.

Table 4
Regression Results for BC task, adjusted for age, sex, handedness, and ‘rested’

BC task Measures	S. C. Beta	t score	p value	BC task Measure	S. C. Beta	t score	p value
Similarities (n=73)				Stroop Color Naming (n=71)			
left hand	.418	2.716	.008**	left hand	.303	3.382	.001**
right hand	.11	0.618	.539	right hand	.49	4.746	.000**
Coding (n= 73)				Stroop Word Naming (n=71)			
left hand	.534	3.876	.000**	left hand	.237	2.559	.013*
right hand	.209	1.312	.194	right hand	.343	3.204	.002**
Stroop Conflict (n=71)							
left hand	.324	3.425	.001**				
right hand	.225	2.056	.044*				

** indicates a significant association with the dependent variable ($p \leq .01$);
* indicates a trend suggesting association with the dependent variable ($p \leq .05$);
left hand= left hand score; **right hand**= right hand score; **n**= total sample used in analysis; **S.C. beta**= standardized beta coefficients

Table 5

Summary of Results (P values)

Measures	Independent			With Interhemispheric			
	LH	RH	LH/IH	LE EW emot	RE EW emot	R-hnd BC	RH/IH
	RE EW word	LE EW emot	RE CV	RE EW emot	RE EW emot	R-hnd BC	LE CV
Reading rec.							.035
Spelling							.008
Word attack			.000				.000
Vocabulary			.036				.008
Color naming						.000	.001
Col-word naming						.002	.013
Similarities			.015				.019
4Coding							.008
Arithmetic							.000
Information			.001			.026	.003
Trails B						.007	.002
Block Design							.011
Stroop Conflict							.040
Digit Span			.037			.044	.001
Spatial Span							.010
Psychiatric Comorbidity							
ODD				.012			
Mood				.019			
Anxiety							
Sibling Correlations							
sib 1 : sib 2				.001 +			.021 +

RE EW word= right ear trials during the word condition of the EW task; **RE CV**= right ear trials of the CV task; **LE EW emot**= left ear trials during the emotion condition of the EW task; **RE EW emot**= right ear trials during the emotion condition of the EW task; **R-hnd BC**= right hand condition of the BC task; **LE EW word**= left ear trials during the word condition of the CV task; **LE CV**= left ear trials of the CV task; **L-hnd BC**= left hand condition of the BC task; **reading rec.**= reading recognition task.