Published in final edited form as:

J Psychiatr Res. 2010 July ; 44(9): 605–615. doi:10.1016/j.jpsychires.2009.11.012.

ADHD Familial Loading and Abnormal EEG Alpha Asymmetry in Children with ADHD¹

T. Sigi Hale, Susan L. Smalley, Jeff Dang, Grant Hanada, James Macion, and Sandra K. Loo
Division of Child and Adolescent Psychiatry and Center for Neurobehavioral Genetics at the UCLA Semel Institute

Abstract

Objective—Abnormal brain laterality (ABL) is indicated in ADHD. ADHD and brain laterality are heritable. Genetic factors contributing to lateralization of brain function may contribute to ADHD. If so, increased ADHD family loading should be associated with greater ABL. Previous studies have shown increased rightward alpha asymmetry in ADHD. We tested whether this was more pronounced in ADHD children with increased ADHD family loading.

Methods—We compared EEG alpha asymmetry at rest and during the Conner's Continuous Performance Test (CPT) in ADHD children with and without ADHD affected parents, and replicated our findings in a second larger sample. The replication study additionally stratified the parent-affected sample by parental persistent versus non-persistent ADHD status, increased spatial resolution of EEG measures, and assessed low versus high alpha.

Results—*Study-1:* The parent-affected group showed increased rightward asymmetry across frontal and central regions and reduced rightward parietal asymmetry during an eyes closed (EC) condition, as well as increasing rightward parietal asymmetry with advancing age during the CPT. *Study-2* replicated these findings and further delineated influences of low versus high alpha, recording site, and effects of parental persistent versus non-persistent ADHD status.

Conclusion—Increased ADHD familial loading was associated with increased rightward frontal asymmetry. In contrast, increased rightward parietal asymmetry was associated with *reduced* ADHD family loading. Frontal results are consistent with an ADHD endophenotype. Parietal results suggest an ADHD adaptive trait prevalent with less ADHD family loading. Age effects indicate a unique developmental course among ADHD children whose parents have non-persistent ADHD.

Keywords

laterality; asymmetry; attention; hemisphere; alpha; development

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is thought 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 possibility is highlighted by a growing body of research demonstrating atypical brain laterality (ABL) in ADHD (Fassbender & Schweitzer, 2006;

¹This work was funded in part by National Institute of Mental Health Grant MH058277 (Smalley), National Institute of Child Health and Human Development Grant HD40275 (Loo), National Institute of Neurological Disease and Stroke NS054124 (Loo), and by National Institute of Mental Health Grant MH082104 (Hale).

Correspondence and Reprint Requests: T. Sigi Hale., UCLA Semel Institute, 760 Westwood Plaza, Room 47-448, Los Angeles, CA 90095, Phone: 310-206-7489, FAX: 310-206-4446, sig@ucla.edu.

Hale, Bookheimer, McGough, Phillips, & McCracken, 2007; Hale et al., 2005; Hale et al., 2009; Hale, Zaidel, McGough, Phillips, & McCracken, 2006; Smalley, Loo, Yang, & Cantor, 2005; Stefanatos & Wasserstein, 2001). Observations of ADHD-like symptoms following right-sided brain damage (Heilman, Voeller, & Nadeau, 1991), and indications that brain systems important for attention and arousal regulation seem to be right lateralized (Aston-Jones, Foote, & Bloom, 1984; Corbetta, Miezin, Shulman, & Petersen, 1993; Pardo & Raichle, 1991), have led some researchers to suggest a 'right hemisphere deficit' model of ADHD (for review see: Stefanatos et al., 2001). However, brain imaging research has not supported a strictly right lateralized deficit, as abnormal brain structure and function are indicated in both hemispheres across several studies (Durstun, 2003; Valera, Faraone, Murray, & Seidman, 2006). Nonetheless, some consistent patterns of ABL in ADHD have emerged.

Functional imaging studies of brain activity at rest or during simple (i.e., non-executive function) tasks have shown reduced left hemisphere (LH) (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998; Seig, Gaffney, Preston, & Jellings, 1995; Zametkin et al., 1993; Zametkin et al., 1990) and/or increased RH (Baving, Laucht, & Schmidt, 1999; Chabot & Serfontein, 1996; Hale et al., 2007; Hale et al., 2009; Swartwood, Swartwood, Lubar, & Timmermann, 2003) activation. Brain imaging studies testing the association between brain structure and task performance have shown increased association with right hemisphere (RH) grey and white matter, suggesting increased RH mediation of task performance (Casey et al., 1997; Casey et al., 2007; Hill et al., 2003; Matero, Garcia-Sanchez, Junque, & et al., 1997; Yeo et al., 2003). Functional imaging studies testing the association between brain activation and concomitant task performance have shown increased RH cortical activation to be associated with both better task performance and increased ADHD symptoms (Ernst et al., 2003; Vaidya et al., 2005). Multiple behavioral laterality studies have demonstrated increased RH contribution and LH deficits during early-stage or basic forms of lateralized information processing (Campbell et al., 1996; Hale et al., 2005; Hale et al., 2006; Malone, Kershner, & Siegel, 1988) with one study demonstrating this profile could be modulated by top-down attentional resource suggesting it is a brain-state associated phenomenon (Hale et al., 2006). Consistent with this, a growing body of work shows that ADHD with or without comorbid reading disorders involves linguistic processing speed deficits, implicating poor LH function (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). Finally, findings of reduced corpus callosum size (Seidman, Valera, & Makris, 2005) and abnormal left-right EEG coherence (Barry, Clarke, McCarthy, Selikowitz, & Johnstone, 2005; Chabot et al., 1996; Clarke et al., 2007) indicate abnormal interhemispheric interaction in ADHD.

Together, these findings indicate a possible model of ABL in ADHD that involves increased RH contributions during early-stages of information processing, associated poor LH function, and abnormal interhemispheric interaction. This notion is consistent with the 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. Moreover, this model is consistent with observed executive function deficits in ADHD, inasmuch as such operations depend on efficient LH encoding of stimuli and associated LH processing in support of higher-order cognitive operations (Hale et al., 2008).

Finally, we point out that in key domains of lateralized brain function (language, motor, sex-differences) ADHD exhibits characteristics consistent with increased R>L asymmetry of function. For example, ADHD has been associated with: increased RH contribution and impaired LH function during lateralized language tasks (cited above), increased leftward motor

asymmetry (Niederhofer, 2005; Reid & Norvilitis, 2000), and increased prevalence among males (Berry, Shaywitz, & Shaywitz, 1985), who on average show increased RH and reduced LH cognitive ability compared to females (Jones, Braithwaite, & Healy, 2003; Joseph, 2000). Given this pattern of results, and the well-supported understanding that ADHD (Biederman, 1998; Smalley, 1997) and brain laterality (Geschwind, Miller, DeCarli, & Carmelli, 2002; Thompson et al., 2001) have heritable components, it seems reasonable to consider that genetic factors contributing to the development of lateralization of brain function may also contribute to liability for ADHD. If true, increased familial loading for ADHD should also be associated with more pronounced ABL. To test this, we compared groups of ADHD children with and without ADHD affected parents (i.e., more or less ADHD family loading) on measures of EEG alpha asymmetry during two resting states and one cognitive activation condition.

Alpha asymmetry (i.e., the relative proportion of alpha power (8–12Hz) in each hemisphere) is a common means of assessing lateralized brain function in clinical populations (Bruder et al., 1997; Harmon-Jones et al., 2008) (Strelets, Garakh, Novototskii-Vlasov, & Magomedov, 2006; Stroganova et al., 2007). It reflects a relatively stable trait with good internal consistency and test–retest reliability (Tomarken, Davidson, Wheeler, & Kinney, 1992). Approximately 60% of its variance is estimated to reflect a trait component, and 40% a state component (Hagemann, Naumann, Thayer, & Bartussek, 2002). EEG studies of ADHD strongly suggest anomalous alpha activity in this population (for review see Barry, Clarke, & Johnstone, 2003), while medication studies have shown that increased alpha may be an important feature of ADHD methylphenidate response (Loo, Hopfer, Teale, & Reite, 2004; Song, Shin, Jon, & Ha, 2005). Moreover, two studies in children (Baving et al., 1999; Chabot et al., 1996) and one in adults (Hale et al., 2009) have demonstrated increased rightward alpha asymmetry in ADHD, which is consistent with studies showing that this characteristic is generally associated with traits such as: reduced reward responsiveness, a lack of inhibition toward aversive experience, and increased approach behaviors (Davidson, 1992).

According to the traditional view of EEG alpha, which indicates an inverse relationship between alpha activity and brain activation (for review see: Shaw, 1996), these alpha asymmetry findings conflict with the above cited literature suggesting greater reliance on RH processing strategies in ADHD. However, a growing body of research indicates that the traditional view of EEG alpha is not complete. Several studies have now documented increasing alpha activity during active cognitive challenges- albeit under circumstances that do not require active sensory processing (Cooper, Burgess, Croft, & Gruzelier, 2006; Cooper, Croft, Dominey, Burgess, & Gruzelier, 2003; and for review see: Klimesch, Sauseng, & Hanslmayr, 2007; Palva & Palva, 2007; Shaw, 1996). Novel theories addressing this issue have essentially converged on the notion that EEG alpha activity may reflect the relative proportion of top-down (i.e., self-directed) versus bottom-up (i.e., sensory-directed) processing (Klimesch et al., 2007; Palva et al., 2007; Shaw, 1996). In other words, alpha activity may increase with endogenous self-directed operations and decreases with exogenous sensory-directory operations. According to this novel understanding, the associations between ADHD and increased rightward alpha asymmetry and increased reliance on RH strategies are not inconsistent. Both can be taken to reflect greater RH top-down control over processing in ADHD.

Based on the above-cited literature and this more recent conceptualization of EEG alpha, we hypothesized that ADHD children with ADHD affected parents would show increased rightward alpha asymmetry relative to ADHD children with unaffected parents. Subsequent to this study, we performed an additional replication study using an independent, larger sample and expanded protocol to further substantiate and delineate our initial findings. Both studies are reported here.

STUDY-1

METHODS

Subjects—The sample consisted of 50 children with ADHD from 23 multiplex families, each family having at least two ADHD affected children aged 7–18 years old. After receiving verbal and written explanations of study requirements participants provided written informed consent/assent approved by the UCLA Institutional Review Board. The UCLA ADHD Genetics study (Smalley et al., 2000a) was on hiatus and families were re-contacted for participation in a pilot EEG study. During their initial participation in the ADHD Genetics Study, parents had been diagnosed using Schedule for Affective Disorders and Schizophrenia – Lifetime Version (SADS-LAR; (Fyer, Endicott, Mannuzza, & Klein, 1995) for parents- supplemented by the Behavioral Disorders section from the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997) to query childhood ADHD status. During the present study, parents and children were interviewed directly using the KSADS-PL to assess for ADHD and other psychiatric disorders. 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. 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. For complete diagnostic procedures and inter-rater reliabilities, see (Smalley et al., 2000b). Subjects were excluded for: neurological disorder or significant head injury resulting in concussion, low birth weight, or Full Scale IQ < 70. Subjects on stimulant medication were asked to discontinue use for 24 hours prior to their visit.

Procedures—EEG recording used 40 silver chloride electrodes in the International 10/20 locations referenced to linked ears. EEG recording consisted of 2 baseline conditions (each lasting 5 minutes) [eyes open (EO) and eyes closed (EC)], and the Conners’ Continuous Performance Test (CPT) (lasting 14 minutes) (Conners, 1994). The CPT test requires subjects to monitor a computer screen while single letters are sequentially and centrally presented with varying inter stimulus intervals. Subjects must press the space bar with every letter presentation except for the letter X.

Continuous EEG data was reviewed off-line and segments containing movement, muscle, or recording artifact were removed. EEG power (μV^2) was averaged for each condition and exported in the Alpha band (8–12Hz). Electrodes were grouped by region into three asymmetry measures: frontal, central, and parietal. Power in left and right sided electrodes for each region were averaged: front right: AF2, F4, F8, FC2, FC6; front left: AF1, F3, F7, FC1, FC5; central right: C4, T4; central left: C3, T3; posterior right: CP2, CP6, P4, PO2, PO8, T6; posterior left: CP1, CP5, P3, PO1, PO7, T5. Then the following calculation was performed ($R-L/R+L*1000$) -producing frontal, central, and parietal laterality indices (FLI, CLI, PLI) for each condition (ex. EC-FLI, EO-FLI, CPT-FLI).

Data Analysis—All analyses were performed in SPSS version 15. To investigate the association of EEG alpha asymmetry with familial loading for ADHD, parental ADHD status was used as a proxy for higher genetic loading of ADHD risk genes. Subjects with at least one parent diagnosed with ADHD were assigned to the parent-affected group (PA+) (n=24). A lifetime diagnosis of ADHD was utilized, meaning the parent met diagnostic criteria for ADHD in the past, regardless of their current ADHD status. Remaining subjects were assigned to the parent-unaffected group (PA-) (n=26). Age and sex, which are important factors in brain laterality research (Geschwind et al., 2002; Zaidel, Aboitiz, Clarke, Kaiser, & Matteson, 1995), were included as covariates in all analyses. Significant findings were retested with anxiety and mood disorder status entered as covariates in separate analyses.

To examine the effect of genetic loading for ADHD on EEG alpha asymmetry three repeated measure ANOVAs were run, one for each recording condition (EC, EO, CPT), with alpha asymmetry as the dependent variable, group as the between subject factor, brain-region (FLI, CLI, PLI) as a within subject factor, and age and sex entered as covariates. Univariate analyses were used to test simple effects.

Results

Clinical: Groups did not differ in IQ, age, sex, or comorbidity (table 1).

Alpha Asymmetry: A significant brain-region x group interaction for the EC condition [$F(1, 48) = 3.64, p = .03$] (see Figure 1), indicated a pattern of increased rightward alpha asymmetry in the frontal and central regions and reduced rightward alpha asymmetry in the parietal region among PA+ subjects. Simple effects univariate analyses showed that group differences for frontal regions were trending toward significance: FLI [$F(1, 48) = 3.2, p = .08$]; CLI [$F(1, 48) = 2.6, p = .11$]; while no group difference was suggested in the parietal region: PLI [$F(1, 48) = .59, p = .44$]. There were no significant results for the EO condition. Under the CPT condition, no group differences were observed. However, there was a significant age x brain-region interaction [$F(1, 48) = 4.08, p = .02$]. Simple effects univariate analyses indicated the age effect was present in the parietal region only: PLI [$F(1, 48) = 4.7, p = .036$], FLI [$F(1, 48) = 1.83, p = .18$], CLI [$F(1, 48) = .15, p = .69$]. Results were not appreciably altered by co-varying for anxiety and mood disorder in separate analyses (see table 2)

Post-hoc Analyses: To further explore the observed age effect on parietal alpha asymmetry measured during the CPT, we sought to test whether this age effect was differentially expressed in PA+ versus PA- children. We thought it critical to evaluate this possibility as such differences, if present, would bear on planned future case-control analyses, and moreover, given that PA+ families are more heavily loaded for persistent ADHD, such differences could potentially help to elucidate mechanisms underlying persistent versus non-persistent forms of the disorder. Thus, to test for group differences in the observed age-effect for the CPT-PLI measure, we examined partial correlations between age and CPT-PLI for each group separately while adjusting for sex. PA+ subjects showed a strong correlation ($r = .70, p = .0004$) while PA- showed no correlation ($r = -.04, p = .85$) (see figure 2). Adjusting for comorbid anxiety and mood did not alter these results: PA+ group: anxiety adjusted ($p = .0003$), mood adjusted ($p = .0003$); and PA- group: anxiety adjusted ($p = .80$), mood adjusted ($p = .52$).

STUDY 2

INTRODUCTION

This study sought to replicate the findings of study-1, which were: (a) *PA+ subjects showed a pattern of increased rightward alpha asymmetry in frontal and central regions along with reduced rightward alpha asymmetry in the parietal region during the EC condition, and (b) PA+ subjects demonstrated increasing rightward parietal alpha asymmetry with advancing age during the CPT.* This replication study uses a larger completely independent sample and adds several important design elements that help to substantiate and further delineate the nature of the observed study-1 effects. Additional measures associated with brain laterality are added and adjusted for in all significant findings (in addition to adjustments for co-morbid anxiety and mood disorder). These included a quantitative measure of handedness and four different measures of linguistic ability (described below). Furthermore, asymmetry in low (8–10hz) and high (10–12hz) alpha bands is assessed. Low-alpha has been postulated to reflect diffuse attentional and brain-state phenomenon, while high-alpha is postulated to reflect more localized and task-specific processing (for review see: Klimesch, 1999; Pfurtscheller, Neuper, & Krausz, 2000). Also, rather than averaging signal across frontal, central, and parietal

electrodes (i.e., FLI, CLI and PLI measures), electrode specific laterality indices are utilized (ex. F4-F3) thereby increasing the spatial resolution of these analyses.

Furthermore, larger sample sizes allowed us to make two key study changes. First, we stratified the parent-affected sample (PA+) into two groups: 1) those with at least one parent currently diagnosed with ADHD [i.e., persistent parental ADHD, (PA+p)], and those with at least one parent who had childhood ADHD only [i.e., remitted parental ADHD, (PA+r)]. This allowed us to directly assess whether persistent versus non-persistent ADHD family loading was associated with differential effects in ADHD offspring. Next, the current larger study sample also allowed us to re-test all significant findings with only the oldest sibling from each family included (i.e., no sib-pairs). This directly examined whether non-independent data structure from sib-pairs influenced our results.

METHODS

Subjects—This sample consisted of 218 children with ADHD from 135 multiplex families, each family having at least two ADHD affected children aged 5–18 years old. There were multiple cases where data from only a single sibling was available due to attrition, non-compliance, and/or technical problems with EEG recording. The PA+p group was composed of 27 singletons, 29 sib pairs, 3 groups of 3 siblings, and 2 groups of 4 four siblings (total $n=102$) with a mean age of 11.3 and range of 5–18 years. The PA+r group was composed of 16 singletons, 11 sib pairs, and 4 groups of 3 siblings (total $n=50$) with a mean age of 10.2 and range of 5–17 years. The PA– group was composed of 21 singletons, 21 sib pairs, and 1 group of 3 siblings (total $n=66$) with a mean age of 11.4 and range of 5–18 years. For secondary sib-pair adjusted analyses (i.e., with only the oldest child from each family included) n -sizes for each group adjusted to: PA+p ($n=61$), PA+r ($n=31$), and PA– ($n=43$).

Clinical assessment procedures were identical to study 1 (see above), except for the addition of a shortened version of the Edinburgh Handedness Inventory (Oldfield, 1971) and four measures of linguistic ability. The handedness inventory uses seven questions regarding hand preference and produces scores ranging from negative 14 (indicating maximum left-handedness), to positive 14 (indicating maximum right-handedness). This measures was dichotomized with scores ranging from 8–14 indicating ‘definite right-handedness’, and scores less than 8 indicating ‘not definite right-handedness’. The four measures of linguistic ability included: the WAIS-R vocabulary sub-test (uses age-scaled scores to assess ability to generate definitions for words), the 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).

Procedures—Testing procedures were identical to study-1 except for the following. The Conner’s CPT was reprogrammed with one alteration. The original Conner’s CPT counter balances the order of inter-stimulus intervals (ISIs: 1, 2, 4 seconds) across 6 blocks. The reprogrammed CPT variant used in study-2 randomized the order of ISIs within each block.

EEG recording and processing were identical to study-1 except for the following. Different recording location, technicians, and recording equipment were utilized [study-1 used Neuroscan system (Compumedics Neuroscan- <http://www.neuroscan.com/landing.cfm>): study-2 used Manscan system (SAM Technology- <http://www.manscaneeg.com>)]. With the new EEG equipment an automatic artifact detection procedure was added. Here, continuous EEG data was subjected to automatic artifact detection via MANSCAN software designed to identify dead and bad channels, vertical and horizontal eye movements, saturation, muscle and movement artifact, and line frequency interference. Subsequent to this, data were visually inspected and any residual contaminants were removed. Furthermore, for each electrode, EEG

power (μV^2) was exported in 1hz bins from 1–20 Hz and then averaged from 8–10 Hz composing a ‘low-alpha’ measure (LA), and from 10–12 Hz composing a ‘high-alpha’ (HA) measure. Finally, for EC and CPT conditions only, laterality indices (LIs) were generated for nine homologous left-right electrode pairs (AF4-AF3, F4-F3, F8-F7, C4-C3, FT8-FT7, T8-T7, TP8-TP7, P4-P3, P8-P7) using the same calculation as study-1 ($R-L/R+L * 1000$).

Data Analysis—Two planned analyses (described below) were performed to replicate and further delineate study-1 findings. All significant results were re-examined in separate analyses adjusting for handedness, anxiety and mood disorder, the four measures of linguistic ability, and with only the oldest sibling per family included (i.e., no sib-pairs).

Replication 1: *Study-1 finding: PA+ subjects showed a pattern of increased rightward alpha asymmetry in frontal and central regions along with reduced rightward alpha asymmetry in the parietal region during the EC condition.* Linear regression analysis was utilized to re-test this effect. Grouping variables for PA+p and PA+r subjects were entered as predictors (with PA– group serving as the reference) along with predictors age and sex. The nine laterality indices for the EC condition were entered as outcome variables in separate analyses for both low and high alpha.

Replication 2: *Study-1 finding: PA+ subjects demonstrated increasing rightward parietal alpha asymmetry during the CPT task with advancing age.* To re-examine this effect partial correlations between age and the three parietal CPT LIs (TP8-TP7, P4-P3, P8-P7) were assessed for both low and high alpha in each group separately while controlling for sex.

Results

Clinical: Groups did not significantly differ in IQ, age, sex, ADHD type, or co-morbid anxiety and mood disorder. There were no group differences for linguistic ability barring one instance showing that the PA+p group had better reading ability than the PA+r group. There were trends suggesting that the PA+r group was younger than the other groups. Furthermore, one significant finding indicated that the PA+r group had fewer non-right handed subjects than the PA– group, and a trend suggested the same in comparison to the PA+p group. (see table 3).

Replication 1: Regression analysis replicated study-1 frontal and parietal asymmetry results. Findings are detailed in table 4. Both PA+p and PA+r groups showed significantly increased rightward low-alpha asymmetry at F4-F3 compared to the PA– group. Additionally, both groups showed the same pattern of reduced rightward high-alpha asymmetry at P4-P3 compared to PA– subjects, however, this effect only reached trend-level significance among PA+r subjects. In short, both PA+p and PA+r groups demonstrated the same pattern of findings—increased rightward frontal asymmetry and reduced rightward posterior asymmetry relative to PA– subjects, with the difference being the strength of effects (see figure 3). Adjusting for handedness, anxiety and mood disorder, or linguistic abilities did not appreciably alter the results. Results at F4-F3 for PA+r group were no longer significant with only a single sibling per family included, which may reflect the small sample size ($n=31$) following removal of 19 of 50 subjects from this group.

Replication 2: Correlation analysis replicated the study-1 age effect of increasing rightward parietal alpha asymmetry among PA+ children during the CPT, but in this case, the effect was found to be specific to ADHD children from families heavily loaded for non-persistent ADHD (i.e., PA+r children) (see figure 4). The effect was robust in this group and occurred for both low and high alpha and across multiple parietal LIs. PA+p and PA– groups showed no age effect. Adjusting for handedness, anxiety and mood disorder, or linguistic abilities, as well as

retesting with only the oldest sibling per family included did not appreciably alter the results (see table 5).

DISCUSSION

Abnormal brain laterality (ABL) is well established in ADHD. It is also well established that both ADHD (Biederman, 1998; Smalley, 1997) and brain laterality (Geschwind et al., 2002; Thompson et al., 2001) have heritable components. This work investigated whether genes contributing to ABL might also contribute to liability for ADHD reasoning that if this were true, ABL should be more pronounced in families more heavily loaded for ADHD. Increased rightward EEG alpha asymmetry in ADHD was established in two previous child studies (Baving et al., 1999; Chabot et al., 1996) and in one adult study (Hale et al., 2009). We therefore examined this measure in ADHD children with and without ADHD affected parents, predicting that children with ADHD affected parents (i.e., more ADHD family loading) would show greater rightward alpha asymmetry. This prediction was born out for frontal but not parietal regions across two independent samples. Moreover, we discovered an unexpected finding in study-1, which we replicated in study-2, indicating that ADHD children from families heavily loaded for non-persistent ADHD exhibited a unique developmental trajectory with respect to alpha asymmetry, which brings to bear the possibility of unique etiologic mechanisms (possibly gene actions) in this group.

In study-1 we found that PA+ children had a pattern of rightward frontal and central alpha asymmetry along with leftward parietal asymmetry during the EC condition. However, simple effects analyses indicated that region specific group differences only trended toward significance for frontal and central regions, while no group difference was apparent in the parietal region. Study-2 elucidated why this was so. Here, during the EC condition, we found a significant group difference in the frontal region that was specific to the F4-F3 electrode pair and the low-alpha frequency band (8–10Hz). Furthermore, we saw a robust group differences in the parietal region that was specific to the P4-P3 electrode pair, high-alpha (10–12Hz), and driven mainly by ADHD children who had a parent diagnosed with persistent (PA+p) versus remitted (PA+r) ADHD. Thus, our failure to observe region specific effects in study-1, aside from a small sample size, was likely due to a lack of anatomical and frequency-band specificity used in that study.

Increased rightward alpha asymmetry in frontal brain regions has been previously demonstrated in ADHD. Baving et al., (1999) found increased rightward alpha asymmetry at F4-F3 during an EO condition in ADHD children. Chabot et al., (1996) found rightward frontal alpha asymmetry in ADHD children during an EC condition. Hale et al., (2009) found rightward low-alpha asymmetry in ADHD adults in the fronto-temporal region (FT8-FT7) during an EC condition, and in this same region for both low and high alpha during the CPT. The current study adds that this ADHD characteristic is more pronounced with increased ADHD family loading. Consistent with this, previous studies have reported an association between parental ADHD affection status and frontal lobe function in ADHD children. Loo et al., (2008b) found increased ADHD familial loading was associated with reduced frontal alpha power, and in another study, that adhd children who had ADHD affected mothers performed more poorly on cognitive tasks understood to depend on frontal lobe function (i.e., stroop color-word conflict, trails-b, and working memory) (Loo et al., 2008a). Indeed, it is interesting to consider that these effects may have been associated with increased rightward alpha asymmetry in the superior frontal brain region. Regardless, the current study suggests that ABL in the superior frontal brain region is a familial and possibly genetic component of ADHD that may prove useful as an ADHD endophenotype.

Increased rightward alpha asymmetry in parietal regions has also been demonstrated in ADHD. The findings of Chabot et al., (1996) of increased rightward alpha asymmetry in ADHD children were, in fact, most pronounced in the parietal region, and Hale et al, (2009) also found that adults with ADHD exhibited increased rightward parietal alpha asymmetry at P4-P3 in both low and high alpha during an EC condition, and in low alpha during the CPT. The current study demonstrates that this feature of ADHD *does not* increase with increased ADHD family loading. Instead, it decreases. Study-2 showed that ADHD children with currently affected parents showed the least parietal rightward asymmetry, those with ADHD remitted parents had slightly more, and those with unaffected parents had, by a significant margin relative to PA+p subjects, the most.

Having a lower ADHD family loading (through parents) has been previously associated with better clinical outcome (Hurtig et al., 2007; Loo et al., 2008a; Loo et al., 2008b), and here we see it is also associated with increased rightward parietal alpha asymmetry. It seems reasonable to consider that rightward parietal alpha asymmetry might reflect some form of ADHD-adaptive or compensatory phenomenon. For instance, a compensatory processing strategy and/or a protective gene action that is most available to those ADHD children with less ADHD family loading. Regardless, the observed parietal alpha asymmetry results are not consistent with this being a straightforward ADHD endophenotype. Instead, it may prove useful as biological marker that indexes an ADHD adaptive or compensatory phenomenon that is perhaps associated with a better clinical outcome.

In the current study, we observed that increased ADHD family loading was associated with both *increased* rightward frontal asymmetry and *decreased* rightward parietal asymmetry among ADHD children. Interpretation of this pattern of results with respect to underlying brain function is suggested based on novel understandings of EEG alpha. As noted previously, EEG alpha has been traditionally viewed as being inversely related to brain activation. This notion stemmed from consistent observations of increased alpha activity with closed versus opened eyes, and multiple subsequent studies have shown decreasing alpha activity with active cognition (for review see: Shaw, 1996). However, the completeness of this model has been recently challenged (Cooper et al., 2003; Klimesch et al., 2007; Palva et al., 2007; Shaw, 1996). Simultaneous EEG alpha recording with either fMRI (Goldman, Stern, Engel, & Cohen, 2002; Martinez-Montes, Valdes-Sosa, Miwakeichi, Goldman, & Cohen, 2004) or PET imaging (Sadato et al., 1998; Schreckenberger et al., 2004) have demonstrated both negative and *positive* associations between alpha activity and brain activation. Moreover, increased alpha activity during active and/or cognitively demanding challenges has been reported across multiple studies (the so called paradoxical alpha response) (Cooper et al., 2006; Cooper et al., 2003; and for review see: Klimesch et al., 2007; Palva et al., 2007; Shaw, 1996). To account for this, novel theories of EEG alpha have been proposed that essentially converge on the idea that alpha activity indexes the proportion of self-directed/intentional (top-down) versus sensory-directed (bottom-up) processing (Klimesch et al., 2007; Palva et al., 2007; Shaw, 1996). According to this, alpha asymmetry may reflect hemispheric disparities (or complementary processes) with respect to the proportion of 'sensory' (bottom-up) versus 'self' (top-down) directed brain function. Consistent with this, some brain laterality research has suggested that the hemispheres can adopt complimentary roles with respect to sensory and control processes, such as error monitoring, depending on which hemisphere is best suited for, or more actively mobilized toward, task-associated sensory processing (Hochman & Eviatar, 2006).

Within this framework our findings can be taken to reflect increased right-frontal top-down control over processing with increased ADHD family loading. This is consistent with studies demonstrating increased RH strategy use in ADHD (Campbell et al., 1996; Hale et al., 2007; Hale et al., 2005; Hale et al., 2006; Malone et al., 1988), imaging studies showing increased

RH activation (Baving et al., 1999; Chabot et al., 1996; Hale et al., 2007; Hale et al., 2009; Swartwood et al., 2003), reduced LH activation (Ernst et al., 1998; Seig et al., 1995; Zametkin et al., 1993; Zametkin et al., 1990), and increased association between right-sided brain structure and function and task performance in ADHD (Casey et al., 1997; Casey et al., 2007; Ernst et al., 2003; Hill et al., 2003; Matero et al., 1997; Vaidya et al., 2005; Yeo et al., 2003). Indeed, the current study suggests that these reported laterality differences might be more pronounced with increased ADHD family loading. Moreover, given the importance of LH frontal-lobe functioning in goal-directed behavior (Collette & Van der Linden, 2002; Matsubara, Yamaguchi, Xu, & Kobayashi, 2004), it is conceivable that ADHD impairments in this domain might reflect insufficient LH frontal control over processing. Conversely, greater RH frontal control may align with increased novelty seeking reported in ADHD (Cho et al., 2008; Goldberg, Podell, & Lovell, 1994).

Interpretation of parietal finding is less straightforward. In this framework, our findings suggest that *having less ADHD family loading* is associated with *having greater RH control* over processing in posterior brain regions. However, and perhaps particularly relevant for posterior brain regions, this also suggests relatively increased orientation toward LH specialized bottom-up processing. ADHD has been consistently associated with linguistic processing deficits, particularly with regard to naming speed (Brock et al., 2003; Nigg et al., 2002; Rucklidge et al., 2002; Semrud-Clikeman et al., 2000; Stevens et al., 2002; Tannock et al., 2000; Weiler et al., 2000; Willcutt et al., 2005). Thus, habitually increased orientation toward LH specialized bottom-up processing may be consistent with a compensatory or adaptive process that is perhaps most accessible to those with less ADHD genetic loading.

Lastly, in study-1 we discovered an unexpected age effect such that ADHD children with an ADHD affected parent exhibited increasing rightward alpha asymmetry with advancing age. This effect was specific to the parietal brain region during the CPT. We replicated this effect in study-2 but found it was specific to subjects from families heavily loaded for non-persistent ADHD. Based on the association of reduced ADHD family loading and better clinical outcome (described above), and the association of reduced ADHD family loading and increased rightward parietal asymmetry, we suggested above that this characteristic may reflect some form ADHD adaptive or compensatory mechanism. The observed age effect indicates that this hypothesized ADHD compensatory mechanism likely undergoes a unique developmental course among PA+r children, highlighting the possibility of unique etiologic mechanisms in this group (possibly gene actions). Moreover, given these children are from families heavily loaded for non-persistent ADHD, it is interesting to consider that such mechanisms might be specific to non-persistent forms of the disorder. Consistent with this, Shaw et al., (2006) reported that ADHD children who exhibited better clinical outcomes (i.e., remediating or non-persisting ADHD) exhibited normalization of cortical thickness specifically in the right parietal lobe with advancing age. It is possible that this, and our observed age effect on parietal alpha asymmetry, might reflect overlapping mechanisms associated with non-persistent ADHD. Regardless, the observed age effect on parietal alpha asymmetry strongly suggests that ADHD children who have a parent with non-persistent ADHD undergo a unique developmental course, highlighting the possibility of unique etiologic mechanism (possibly gene actions) in this group.

In summary, the current study demonstrated that increased rightward *frontal* alpha asymmetry, previously observed in ADHD children and adults, is especially pronounced in ADHD children who have an ADHD affected parent (i.e., with increased ADHD family loading). This suggests that *frontal* alpha asymmetry may prove useful as an ADHD endophenotype. In addition, we found that increased rightward *parietal* alpha asymmetry was associated with *having less* ADHD family loading, and that this trait increased with advancing age among children who had a parent with non-persistent ADHD. Given the association of reduced ADHD family

loading and better clinical outcome (discussed above), both parietal asymmetry findings seem generally consistent with them reflecting an ADHD-adaptive or compensatory phenomenon that, in ADHD children, is more available with lower ADHD family loading. Moreover, the finding that this trait increases with advancing age among ADHD children from families heavily loaded for non-persistent ADHD suggests a unique developmental trajectory and etiologic mechanisms (possibly gene actions) in this group, which may prove to be specific to non-persistent forms of the disorder.

Limitations

Our study groups contained sibling-pairs, which raises the important issue of data independence. To address this, we tested all significant results in study-2 with only the oldest sibling from each family included and found the findings to be largely unchanged, barring two instances. Group differences between PA⁻ and PA^{+r} subjects at F4-F3 during the EC condition adjusted to a p-value of .127, which could reflect the 38% reduction of sample size for the PA^{+r} group in this analysis. Additionally, trend level group differences between PA⁻ and PA^{+r} subjects at P4-P3 during the EC condition adjusted to a p-value of .51. Here, it is less likely that the reduction in sample size underlies this substantial loss of significance. To explore the possibility of non-independent data in this case, sibling correlations for this measure were examined for PA⁻ and PA^{+r} groups and found to not approach significance (nor were sibling correlations significant for any other reported measure in this study in any group). Nonetheless, the trend level result of PA^{+r} subjects showing less rightward alpha asymmetry than PA⁻ subjects is taken as preliminary pending independent replication. Importantly, this does not in any way affect the interpretation of our parietal finding during the EC condition, which is upheld by the observed robust group differences between PA⁻ and PA^{+p} subjects, with the added component that PA^{+r} subjects were middling between these extremes.

Planned future investigations with larger sample sizes will allow us to utilize more sophisticated approaches (multilevel modeling, hierarchical linear modeling, mixed models, complex survey analysis, etc.) to directly characterize the effects of the dependent data structure. Moreover, given evidence of familiarity effects that are specific to maternal affection status (Loo et al., 2008a), future studies with larger samples sizes should examine the effects of ADHD family loading stratified by maternal versus paternal affection status. Lastly, we did not look separately at ADHD subtypes and it is possible that the familiarity of EEG measures differs in patients with various ADHD subtypes. There were no group differences in the proportion of ADHD subtypes in either study 1 or 2. The average percentage of subtypes across both studies and study groups was: combined= 54%, inattentive= 45%, and hyperactive 4%. It is important to note that our samples did not contain appreciable numbers of hyperactive subtypes and so our findings may not generalize to this group. Future studies should more carefully consider differences across ADHD subtypes.

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Figure 1. Study-1 Group Differences in Alpha Asymmetry During EC Condition (adjusted for age and sex)

Group difference for EC EEG alpha asymmetry across frontal (FLI), central (CLI), and parietal (PLI) laterality indices; asymmetry scores > 0 = rightward asymmetry; asymmetry scores < 0 = leftward asymmetry; PA- = ADHD children with no ADHD affected parents; PA+ = ADHD children with at least 1 ADHD affected parent.

Figure 2. Study-1 Scatter Plots of Age Effects on CPT-PLI Alpha Asymmetry in PA- and PA+ groups

Scatter plots of age effects on parietal alpha asymmetry (PLI= parietal laterality index) during the CPT; PA- = ADHD children with no ADHD affected parents; PA+ = ADHD children with at least 1 ADHD affected parent; Pearson correlation analysis of age and the CPT-PLI measure for PA- and PA+ groups are shown.

Figure 3. Study-2 Mean Group differences in Alpha Asymmetry During EC Condition

PA- = ADHD children with no ADHD affected parents; PA+r = ADHD children with at least 1 remitted ADHD parent; PA+p = ADHD children with at least 1 currently affected ADHD parent; error bars show standard error

Figure 4. Study-2 Scatter Plots of Age Effect on Parietal Alpha Asymmetry During the CPT
 Age effects on parietal laterality indices; LA = low alpha; HA = high alpha; PA- = ADHD children with no ADHD affected parents; PA+r = ADHD children with at least 1 remitted ADHD parent; PA+p = ADHD children with at least 1 currently affected ADHD parent; pearson correlations between age and parietal laterality indices are shown.

Table 1

Study-1 Subject Demographics

Clinical Variables	PA+ (n=24)	PA- (n=26)	Statistic
Estimated Full IQ	$\bar{X}$ = 110.2, std= 12.5	$\bar{X}$ = 111.9, std=12.6	$t = .44, p = .66$
Age	$\bar{X}$ = 12.8, std=3.4	$\bar{X}$ = 13.3, std=2.8	$t = .49, p = .62$
Sex	6F, 18M	9F, 17M	$\chi^2 = .55, p = .46$
ADHD Type	14C, 10I	12C, 14I	$fe = .41$
Anxiety	6 affected	5 affected	$fe = .74$
Mood	2 affected	4 affected	$fe = .67$

Estimated Full IQ: estimated from block-design and vocabulary subtest of WAIS-R; ADHD Type: C= combined, I=inattentive, H=hyperactive; χ^2 = chi-square test; fe = Fisher's Exact Test; Anxiety/ Mood reflect definite diagnosis of any anxiety or mood disorder as assessed by direct interview using KSADS-PL (see text for reference).

Table 2

Study-1 Summary of Adjusted p-values for EC & CPT findings

results of interest	primary analyses	adjusted for anxiety	adjusted for mood
EC			
brain region X group	.03	.032	.037
FLI group effect	.08	.078	.088
CLI group effect	.11	.10	.11
PLI group effect	.44	.46	.45
CPT			
brain region X age	.02	.017	.011
FLI age effect	.18	.19	.18
CLI age effect	.69	.68	.98
PLI age effect	.036	.038	.005

primary= original analyses; adjusted for anxiety and mood = separate analyses with these factors added as covariates along with age, sex

Study-2 Subject Demographics

Table 3

Clinical Measures	PA+p (n=102)	PA+r (n=50)	PA- (n=66)	statistics		
				PA+p: PA-	PA+r: PA-	PA+p: PA+r
IQ	$\bar{X}=111, s=14.2$	$\bar{X}=106, s=24.8$	$\bar{X}=111, s=16.2$	$t=-.06, p=.95$	$t=1.2, p=.22$	$t=-1.5, p=.13$
Age	$\bar{X}=11.3, s=3.44$	$\bar{X}=10.2, s=3.39$	$\bar{X}=11.4, s=3.36$	$t=.10, p=.92$	$t=1.9, p=.065$	$t=1.9, p=.06$
Sex	41F, 61M	21F, 29M	25F, 41M	$\chi^2=.09, p=.76$	$\chi^2=.20, p=.65$	$\chi^2=.04, p=.83$
Handedness	12NR, 90R	1NR, 49R	9NR, 56R	$\chi^2=.14, p=.71$	$fe: p=.04^*$	$fe: p=.06$
ADHD Type	65C, 44I, 2H	28C, 19I, 2H	30C, 31I, 4H	$fe: p=.25$	$fe: p=.57$	$fe: p=.67$
Anxiety	44%	46%	33%	$\chi^2=1.9, p=.16$	$\chi^2=1.9, p=.17$	$\chi^2=.05, p=.83$
Mood	11.7%	8%	12%	$\chi^2=.005, p=.9$	$fe: p=.55$	$fe: p=.58$
Vocabulary	$\bar{X}=11.7, s=2.9$	$\bar{X}=11.2, s=4.2$	$\bar{X}=11, s=3.5$	$t=-1.5, p=.14$	$t=.25, p=.8$	$t=-.96, p=.34$
Reading	$\bar{X}=106, s=14.5$	$\bar{X}=101, s=15$	$\bar{X}=104, s=13$	$t=-1.2, p=.22$	$t=1.1, p=.23$	$t=-2.2, p=.03^*$
Spelling	$\bar{X}=104, s=14.6$	$\bar{X}=100, s=15$	$\bar{X}=102, s=15.5$	$t=-.55, p=.58$	$t=.56, p=.58$	$t=-1.1, p=.25$
Phonologic	$\bar{X}=114, s=15.6$	$\bar{X}=111, s=16$	$\bar{X}=110, s=16$	$t=-1.5, p=.14$	$t=-.12, p=.9$	$t=-1.2, p=.22$

IQ: estimated full-IQ from block-design and vocabulary subtest of WAIS-R; Handedness: R=definite right handedness, NR=non-definite right handedness (see methods); ADHD Type: C= combined, I=inattentive, H=hyperactive; t= t-test; χ^2 = chi-square test; fe = Fisher's Exact Test; Anxiety & Mood reflect definite diagnosis of any anxiety or mood disorder as assessed by direct interview using KSADS-PL (see text for reference); vocabulary = WAIS-R vocabulary sub-test; reading & spelling = Wide Range Achievement Test Revised (WRAT-R) reading and spelling subtest; phonologic = Woodcock-Johnson Word-attack Revised (WJ-R);

* = p-value < .05; bold = trend results;

Table 4

Study-2 Linear Regression Analysis of Group differences in Alpha Asymmetry During EC condition (adjusted for age and sex)

model variables	SB	t	p	hand	anx	mood	voc	read	spell	phon	1-sib
adjusted p-values											
<u>EC low alpha F4-F3</u>											
PA+r	.18	2.27	.024	.04 [^]	.033	.021	.023	.021	.023	.016	.127
PA+p	.20	2.56	.011	.009 [^]	.015	.011	.01	.016	.013	.011	.049
<u>EC high alpha P4-P3</u>											
PA+r	-.14	-1.79	.075	.12	.09	.08	.073	.052	.055	.12	.51
PA+p	-.23	-2.9	.004	.009	.005	.004	.003	.004	.003	.009	.002

PA+r = ADHD children with at least 1 remitted ADHD parent (i.e., only childhood diagnosis); PA+p = ADHD children with at least 1 currently affected ADHD parent; results show PA+r and PA+p groups compared against PA- group (PA- group has no ADHD affected parents); SB= standardized beta; adjusted p-values = PA+r and PA+p group effects adjusted for possible confounding factors; Anx & Mood reflect definite diagnosis of any anxiety or mood disorder as assessed by direct interview using KSADS-PL (see text for reference); hand = handedness;

[^] = effect of handedness was significant in model; voc = WAIS-R vocabulary sub-test; read & spell = Wide Range Achievement Test Revised (WRAT-R) reading and spelling subtest; phon = Woodcock-Johnson Word-attack Revised (WJ-R); 1-sib = retested effects with only a single sibling from each family included;

* = p-value < .05; bold = trend results.

Study-2 PA+r Group Adjusted p-values for Significant Correlations Between Age and Parietal Asymmetry During the CPT

Table 5

results of interest	adjusted p-values							
	hand	anx	mood	voc	read	spell	phon	1-sib
TP8-TP7 (LA)	.005	.006	.003	.005	.004	.003	.002	.01
P8-P7 (LA)	.035	.056	.048	.03	.035	.027	.07	.07
TP8-TP7 (HA)	.007	.009	.004	.006	.005	.005	.009	.02
P4-P3 (HA)	.009	.013	.015	.009	.009	.01	.014	.01

HA= high alpha; LA= low alpha; adjusted p-values = partial correlations adjusted for possible confounding factors (in addition to the adjustment for sex); Anx & Mood reflect definite diagnosis of any anxiety or mood disorder as assessed by direct interview using KSADS-PL (see text for reference); hand = handedness; voc = WAIS-R vocabulary sub-test; read & spell = Wide Range Achievement Test Revised (WRAT-R) reading and spelling subtest; phon = Woodcock-Johnson Word-attack Revised (WJ-R); 1-sib = retested correlations with only a single sibling from each family included.