EEG Alpha Asymmetry in Schizophrenia, Depression, PTSD, Panic Disorder, ADHD and Conduct Disorder

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Key Words

Alpha Rhythm Laterality
Attention-Deficit/Hyperactivity Disorder
Conduct Disorder
Depression
Panic Disorder
Post-Traumatic Stress Disorder
Schizophrenia

ABSTRACT

Models of laterality infer distinct aspects of EEG alpha asymmetry in clinical disorders, which has been replicated for over three decades. This biomarker now requires a more fine-grained assessment of its clinical utility as a diagnostic and treatment predictive marker. Here, within the same study we assessed resting brain laterality across six clinical disorders, for which deviant laterality has been implicated as core dysfunction. These disorders were evaluated in comparison to a large normative dataset (~1,900) from the Brain Resource International Database. EEG alpha asymmetry was assessed in the frontocentral region, for resting Eyes Closed and Eyes Open conditions. Schizophrenia was characterized by significantly greater left lateralized alpha power than controls, indicating a deficit in left frontal activity at rest, which may relate to "disconnections" across wider fronto-temporal networks. The depression group showed a trend-level tendency towards the opposite pattern of greater right-lateralized activity than controls. The remaining anxiety and behavioral disorders did not show any significant deviance in alpha asymmetry from the normative control group. However, at a non-significant level laterality for these groups was generally consistent with expected directions, suggesting a propensity towards a particular lateralization but still remaining within the normative range. Overall, the results of the current study indicate that EEG alpha asymmetry may show the most clinical utility as a biomarker for schizophrenia and depression in comparison to other clinical disorders.

INTRODUCTION

For more than three decades, lateralization of neural activity has been implicated in the neurobiology of a range of clinical disorders involving a core dysfunction in emotion-related processes, as well as aspects of emotional functioning within the healthy population. These laterality patterns have been observed in baseline neural activity at rest, as well as during task performance designed to engage specific hemispheric regions. One of the most commonly used indices of resting state laterality is EEG alpha power asymmetry, with suppression of alpha power suppression being indicative of higher levels of cognitive activity.[1]

The brain "at rest" actually consists of highly active neural networks, and this baseline activity reflects an underlying neural environment within which all incoming information is processed and specific tasks are performed.[2] Consequently, these baseline conditions can provide an important context for the functioning of more specific neural networks for stimulus processing and task performance, particularly in clinical disorders.

Schizophrenia has been classically associated with abnormalities of the left hemisphere, as well as deficits in interhemispheric communication, across studies spanning brain lesions, epileptic foci, and neuropsychological profiles.[3,4] Functional EEG evidence also supports this left hemisphere deficit in schizophrenia, including reports of left lateralized resting EEG alpha (indicating reduced left hemisphere activity).[4-6]

Depressive disorders have also been commonly associated with specific lateralized dysfunction, although in depression an additional shift along an anterior-posterior axis has been implied. Right lateralized resting alpha (indicating reduced right hemisphere activity) has been reported in parietal and temporal regions in depression,[4,5,7] while the opposite frontal asymmetry of left lateralized alpha has been reported, similar to that found in schizophrenia.[8-10] However, a number of studies have also failed to find this effect of deviant frontal alpha asymmetry for depression.[11-14]

It has been postulated that these differing laterality findings in depression may relate to subtypes of anxiety symptoms, and associated differences in laterality between frontal and parieto-temporal regions.[15] Reports of resting EEG alpha asymmetry in anxiety disorders include left lateralized parietal alpha in post-traumatic stress disorder (PTSD),[12] and left lateralized global and frontal alpha in panic disorder.[16,17]

Deviant functional laterality has also been implicated in attention-deficit/hyperactivity disorder (ADHD) and associated externalizing behavior disorders. Abnormalities of the right hemisphere in ADHD have been implicated from a range of sources,[18] including greater right lateralization of EEG alpha in adult ADHD.[19] By contrast, externalizing behavioral problems that are often comorbid with ADHD,[20] have been associated with greater left lateralized frontal alpha power,[21,22] similar to findings reported for schizophrenia.

Emotional functioning in healthy individuals has also been associated with functional brain laterality in the frontal region. Greater left frontal activity (reduced left alpha) has been linked to positive emotion or approach-related behavior, and greater right frontal activity to negative emotion or avoidance-related behavior.[8,23]

In addition, healthy males and females have been reported to differ in functional brain laterality. However, two different patterns of sex differences have been reported: 1) males showing more right

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lateralized and females more left lateralized neural activity,[24,25] and 2) males tending to be more lateralized in general (regardless of direction), with females showing a more symmetrical pattern of neural activity.[26-28] Additionally, several studies have failed to find either of these sex differences in functional laterality.[29-31]

In the current study, we assessed resting frontal alpha asymmetry across several clinical disorders for which deviant laterality has been implicated, encompassing schizophrenia (first episode), major depressive disorder, PTSD, panic disorder, and childhood and adolescent ADHD and conduct disorder. These clinical groups were assessed in comparison to a very large sample of healthy individuals (~ 1,900) from the Brain Resource International Database. This large healthy sample was also used to determine the normative distribution of resting frontal alpha asymmetry, and to assess the influence of age and sex across the lifespan (6 to 87 years).

METHOD

Participants

This study comprises data from 1,908 healthy control participants and 567 participants across 6 clinical groups, from the Brain Resource International Database (BRID).[32,33] Participants ranged from 6 to 87 years of age. Clinical group numbers are provided in Table 1.

Exclusion criteria for healthy control participants included a personal or first degree family history of DSM-IV Axis 1 disorders,[34] or a personal history of physical brain injury, neurological disorder or other serious medical condition, or drug or alcohol addiction (using the AUDIT (Alcohol Use Disorders Identification Test) of WHO)[35] and the Fagerstrom Tobacco Dependency Questionnaire.[36] Individuals with a potential anxiety or depressive disorder were also excluded from the control group, with screening based on the Patient Health Questionnaire (PHQ).[37] Participants were additionally required to refrain from smoking and caffeine for 2 hours prior testing, and to refrain from alcohol for 12 hours prior to testing. All participants voluntarily signed a written informed consent form to participate in the database, in accord with local ethical guidelines.

All clinical diagnoses were made according to DSM-IV diagnostic criteria.

All schizophrenia patients were experiencing their first episode of psychosis, and were recruited within 3 months of first presentation to mental health services with psychotic symptoms. Diagnosis was made through clinical interviews with three senior psychiatrists and the Positive and Negative Syndrome Scale (PANSS).[38] Diagnosis of major depressive disorder was made by trained research officers according to DSM-IV criteria using the Mini-International Neuropsychiatric Interview (MINI),[39] and were either medication naïve or washed out at the time of testing. Diagnosis of PTSD was made by clinical psychologists using the Clinician-Administered PTSD scale (CAPS)[40] and the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID).[41] Diagnosis of panic disorder was made according to the panic disorder module of the MINI[39] and the Composite International Diagnostic Interview (CIDI-Auto 2.1).[42] Participants with ADHD were diagnosed by pediatricians using a semistructured clinical interview, and were either medication naïve or washed out at the time of testing. ADHD and conduct disorder were both diagnosed in accordance with DSM-IV diagnostic criteria.

Data acquisition and reduction

Resting EEG data was recorded during Eyes Open and Eyes Closed conditions. For the Eyes Open condition, participants rested quietly for 2 minutes while focusing on a red dot on a computer screen in front of them. For the Eyes Closed condition, participants rested quietly with their eyes closed for 2 minutes.

Table 1

Participant group numbers

Group	Males	Females	Total
Healthy Controls	971	937	1908
Schizophrenia (First Episode)	33	17	50
Major Depressive Disorder	38	54	92
Post-traumatic Stress Disorder	25	23	48
Panic Disorder	13	35	48
ADHD (6-11 years)	112	28	140
ADHD (12-17 years)	129	40	169
Conduct Disorder	20	0	20

Participants were seated in a sound and light attenuated room, set at an ambient temperature of 24°C. Data was acquired from 32 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 electrode sites, 4 EOG channels, orbicularis oculus and masseter (Quikcap; NuAmps; 10-10 electrode international system). Data was recorded relative to the virtual ground, but referenced offline to linked mastoids (although see below for further average referencing performed for the present study). Horizontal eye movements were recorded with electrodes placed 1.5cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3mm above the middle of the left eyebrow and 1.5cm below the middle of the left bottom eye-lid. Skin resistance was < 5 kOhms. A continuous acquisition system was employed and data was EOG corrected offline.[43] The sampling rate was 500 Hz. A low pass filter with attenuation of 40dB per decade above 100 Hz was employed prior to digitization. For the purpose of calculating alpha power asymmetry, all recording channels were re-referenced using an average referencing technique, such that the average of all channels was calculated and subtracted from each individual channel.

Average power spectra were computed for 28 epochs for both the Eyes Open and Eyes Closed conditions, by dividing the 2 minutes of recorded EEG into adjacent 4 second intervals. Spectral power analysis was performed on each 4 second interval by first applying a Welch window to the data, and then performing a Fast Fourier Transform (FFT). The power spectrum for the alpha band was calculated between 8 and 13 Hz.

For the purpose of this study, alpha asymmetry was calculated for the electrode pair FC3 and FC4. Alpha asymmetry was calculated by performing a natural log transformation of alpha power at each of these sites, and then subtracting the values for FC3 from FC4 (Alpha asymmetry = ln (FC4 + 1) – ln (FC3 + 1)). For alpha asymmetry scores, outliers beyond 3 standard deviations were removed (but not replaced) prior to analysis, separately for each clinical group and the control group.

Data analysis

Alpha asymmetry values for clinical groups were assessed using z scores, calculated separately for children (6-11 years), adolescents (12-19 years) and adults (20-87 years). For each clinical group, one-sample t-tests were used to determine whether alpha asymmetry z scores significantly differed from controls (a z-score of zero). All analyses were tested against a significance level of p=.05.

The normative distribution of alpha asymmetry within the healthy control group was assessed using a one-sample t-test, tested against a

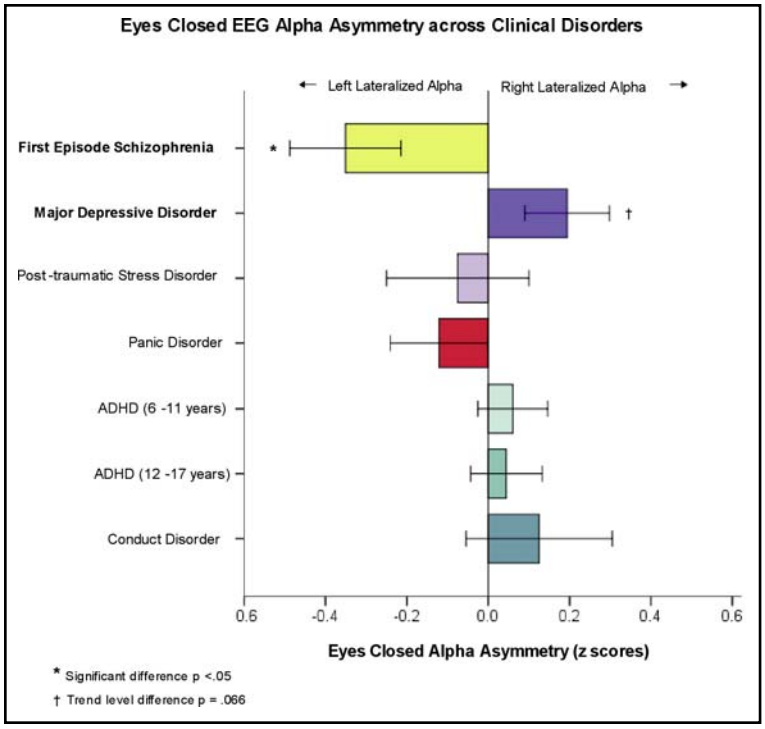

Figure 1.
Eyes Closed EEG Alpha Asymmetry across Clinical Disorders
Using z scores to compare clinical groups with age-appropriate healthy controls, the First Episode Schizophrenia group shows greater left lateralized EEG alpha asymmetry, while the Depression group shows a trend towards greater right lateralized alpha asymmetry. This was found for the Eyes Closed but not the Eyes Open condition. No other clinical groups showed significant effects for EEG alpha asymmetry.

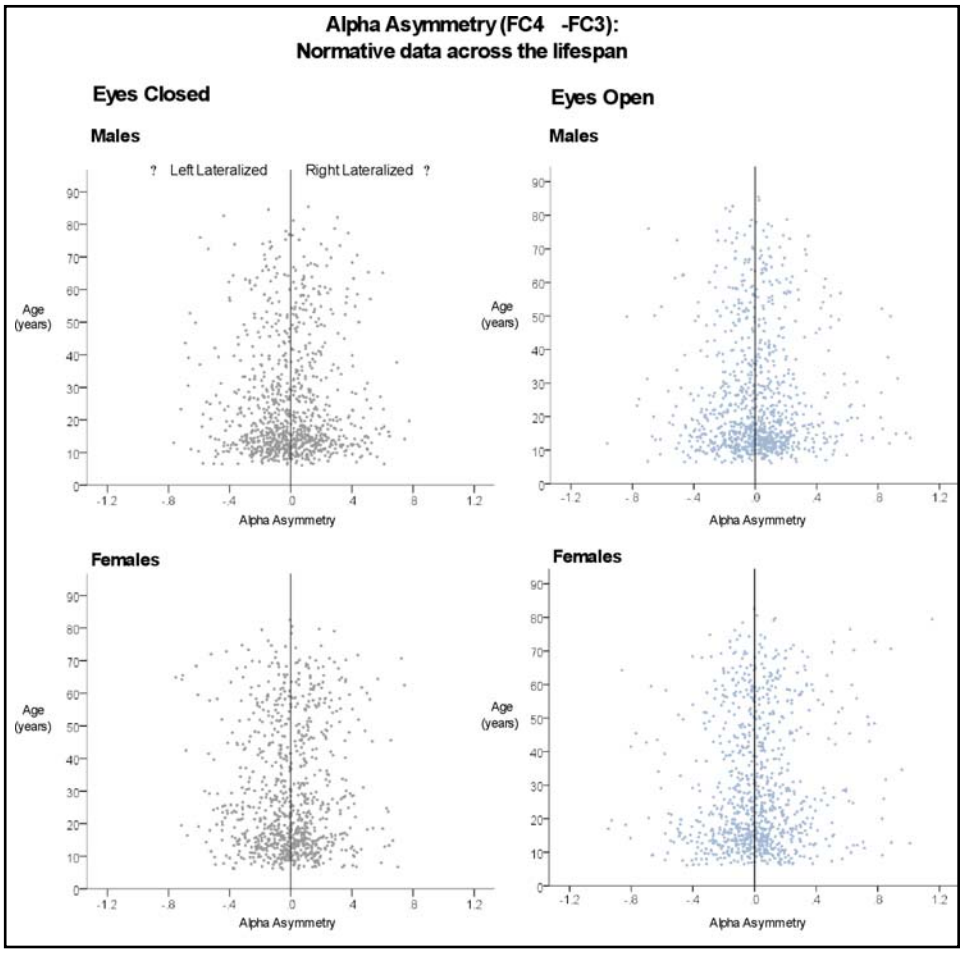

Figure 2.
Normative lifespan data for alpha asymmetry
In 1,908 healthy participants spanning 6 to 87 years of age, EEG alpha asymmetry over the group is found to statistically have an equal distribution of left and right laterality across individuals. Alpha asymmetry largely does not show any effects of age across the lifespan, or any differences between males and females. The one exception to this is 70-87 year old females, who show relatively greater right lateralized alpha power in the eyes open condition, indicating relatively greater activation of the left frontocentral region in older females.

value of zero (reflecting symmetry) against a significance level of p=.01, separately for eyes open and eyes closed conditions. The influence of age and sex on this distribution was assessed using univariate analyses of variance (ANOVAs), with age and sex as between subjects variables. Separate analyses were conducted for eyes closed and eyes open conditions, for both asymmetry scores and the absolute value of asymmetry scores (to assess any effects of the degree of asymmetry, regardless of direction). For the purpose of these analyses, healthy participants were divided into 8 age groups: 6-11 years (N = 357; 201 males, 156 females), 12-19 years (N = 599; 335 males, 264 females), 20-29 years (N = 327; 159 males, 168 females), 30-39 years (N = 160; 83 males, 77 females), 40-49 years (N = 142; 58 males, 84 females), 50-59 years (N = 150; 58 males, 92 females), 60-69 years (N = 118; 48 males, 70 females), 70-87 years (N = 55; 29 males, 26 females). All analyses were tested against a stringent significance level of p=.01, due to the power of the large sample size used. Any subsequent follow-up analyses for significant effects were tested against a significance level of p=.05, using a bonferroni correction for multiple comparisons across each set of analyses (consequently, age comparisons across 8 groups are tested against a significance level of p=.006, and sex comparisons across 2 groups are tested against a significance level of p=.025).

RESULTS

For the eyes closed condition, the schizophrenia group showed significantly greater left lateralization of alpha power ($t = 2.62$, $p<.05$), while the depression group showed a trend towards greater right lateralization of alpha power ($t = 1.86$, $p = .066$) (see Figure 1). Neither of these groups showed any significant difference in alpha power asymmetry for the eyes open condition, however there was also no significant difference between the eyes closed and eyes open conditions for these groups, suggesting that the additional suppression of alpha in the eyes open condition may slightly reduce but not remove these effects.

No significant differences were found for the remaining clinical groups in EEG alpha power asymmetry for either the eyes open or eyes closed conditions.

Healthy controls showed an equal distribution of left and right asymmetry of alpha power for both the eyes open and eyes closed conditions (average asymmetry not different from zero), assessed for the full control group and also separately for males and females. For alpha asymmetry values in the eyes closed condition, and for absolute alpha asymmetry values for both eyes closed and eyes open conditions, MANOVAs indicated no influence of age or sex on this normative distribution across the lifespan. For the eyes open condition there was a significant age by sex interaction effect ($F_{7,1837} = 3.37$, $p < .01$), reflecting an age effect in females only ($F_{7,1837} = 3.37$, $p < .01$) of a linear trend towards relatively more right than left alpha power with increasing age ($t_{918} = 3.43$, $p < .001$). This appeared to be primarily driven by the oldest age group, as this was the only age group to show a significant sex difference in alpha asymmetry ($F_{1,53} = 9.03$, $p < .01$), due to right lateralized alpha power in 70-87 year old females ($t_{25} = 3.37$, $p < .025$) and a symmetrical alpha power distribution in 70-87 year old males. All other age groups showed a symmetrical alpha distribution and no sex differences (See Figure 2).

DISCUSSION

We investigated resting brain laterality across six clinical disorders, for which deviant laterality has been implicated as a core dysfunction. This extends previous studies by assessing all of these disorders within the same study, and evaluating asymmetry in comparison to a single, very large normative group (using z scores), rather than smaller and different control groups.

Schizophrenia was characterized by significantly more left lateralized frontal alpha than controls, and the major depressive disorder group showed a trend towards the opposite pattern of more right lateralized frontal alpha than controls (see Figure 1). This is in accordance with previous reports of a left frontal deficit in schizophrenia, and a possible right hemisphere deficit in depressive disorders. Lateralized effects were, however, restricted to these two clinical disorders. None of the remaining anxiety or behavioral disorders showed a significant deviance from the normative group in resting frontal alpha asymmetry.

Schizophrenia has been conceptualized as a disorder of neural "disconnection," particularly within fronto-temporal networks and with greater prominence in the left than the right hemisphere.[44-47] The current finding of a left frontal deficit in the resting state implies that this "disconnection" may not only occur during specific tasks of stimulus processing. Rather, it may affect the function of the underlying baseline neural environment, within which all additional and more specific processes take place. However, given that the left frontal region forms only one part of wider fronto-temporal networks that have been implicated in schizophrenia, further investigation is warranted to evaluate the function of other aspects of these networks at rest. Additionally, the presence of this left frontal deficit in a first episode schizophrenia group provides support for alpha asymmetry as a biomarker for the causal neurobiology underlying schizophrenia, rather than long-term effects of illness duration.

The opposite pattern of a trend towards right hemisphere dysfunction in depression is somewhat consistent with previous reports of a right parieto-temporal deficit in depressive disorders. Given that previous studies have reported either no laterality or left-lateralized alpha in the frontal region, with right lateralized parieto-temporal alpha, it is possible that the reported right partieto-temporal laterality pattern extends anteriorly into the frontocentral region, with left-lateralized activity being restricted to more prefrontal regions. Alternately, it is also possible that the current trend-level results at the frontocentral location may be influenced by laterality localized to the parieto-temporal region, particularly if there is an absence of distinct lateralized activity in more anterior frontal regions. Further investigation with source localization analysis across different regions is required to more precisely determine the sources and distribution of lateralized activity in depression.

The absence of significantly lateralized activity in the remaining anxiety and behavioral disorders suggests that previous reports of deviant laterality in these conditions may reflect a propensity to be either left or right lateralized, while remaining within the range of normal individual variability. This pattern is supported in the current results, for although not significant, anxiety disorders (PTSD, panic disorder) appear more left lateralized, while behavioral disorders (ADHD, conduct disorder) appear more right lateralized (see Figure 1).

The secondary aim of this study was to assess the normative distribution of frontal alpha asymmetry, and the influence of age and sex on this distribution. In 1,908 healthy individuals spanning 6 to 87 years of age, EEG alpha asymmetry was found to have an equal distribution of left and right laterality across individuals during both the eyes closed and eyes open conditions. This normative distribution was found to be largely unaffected by age-related change across the lifespan or by sex differences. The single exception to this was the oldest female age group (70-87 years), which showed a pattern of right

lateralized alpha in the eyes open condition, indicating relatively greater left than right frontal activation. The remaining age groups did not show any sex differences and all had an equal distribution of left and right laterality across individuals. This absence of sex differences prior to 70 years of age suggests that previously reported sex differences in functional brain laterality may not be clearly evident at rest, but rather become more apparent during tasks that preferentially recruit specific hemispheric regions.

This finding of left lateralized activation (right lateralized alpha power) in the oldest female group may reflect higher levels of positive affect among this group, given that greater left frontal activation has been associated with positive affect in healthy individuals.[8,23] We have previously reported an age-related shift in medial prefrontal systems involved emotion processing,[48] such that in older age the early automatic processing of positive emotion cues proceeds with less top-down regulation than at younger ages – a shift that is also associated with improved emotional wellbeing. The current findings of left lateralized frontal activation in the oldest female group may similarly reflect an age-related shift towards positive emotion in frontal networks, evident for females in baseline resting state laterality. However, it should be noted that in the current study the sample size for 70-87 year old females was relatively small, with only 26 individuals. As such, these results require replication in a larger sample size, and in relation to more specific aspects of emotional functioning.

Although alpha asymmetry was found to have an equal distribution of left and right laterality across individuals, there may well be differences within this normal distribution between those individuals who are left compared to right lateralized, particularly in regard to emotion-related functioning, and future research into these potential differences is warranted. This large normative distribution may also serve as a useful reference point in the future selection of control groups for clinical disorders, to ensure a representative distribution of left and right lateralization of resting baseline activity in healthy controls

Alpha asymmetry has been explored for over three decades as a biomarker for clinical disorders. It has stood the test of time, but now requires a more fine-grained analysis of the extent of its clinical utility as diagnostic and treatment predictive marker. The results of the current study indicate that this measure may be most useful as a biomarker for schizophrenia and depression than for other clinical disorders, although further fine-grained analysis and consideration of factors such as symptom subtypes and treatment response are required to further explore this clinical utility. This kind of analysis requires a database of this size to assess its true predictive validity.

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DISCLOSURE AND CONFLICT OF INTEREST

We also acknowledge that E. Gordon holds significant equity and stock options in Brain Resource Ltd.

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