

ELECTROENCEPHALOGRAPHIC COHERENCE IN SEMILOBAR HOLOPROSENCEPHALY

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ABSTRACT

Objective: To evaluate the interhemispheric electroencephalographic coherence in patients with semilobar holoprosencephaly (HPE).

Methods: We analyzed the interhemispheric coherence values in the frontal and parietal regions in a group of 6 semilobar HPE patients and 15 controls from age 12 months to 6 years. The coherence values were obtained for frequency bands of delta, theta, alpha, and beta.

Results: In semilobar HPE patients the frontal interhemispheric coherence values in delta and theta bands were significantly higher than controls. Both groups showed age dependent increase in the frontal coherence values. No group differences were seen in alpha and beta bands. In the parietal regions the coherence values was slightly higher in the delta range for the semilobar HPE group, but similar for both groups in other frequency bands.

Conclusions: The higher interhemispheric coherence values seen in the frontal regions in semilobar HPE patients may reflect the lack of interhemispheric separation in the anterior hemispheres and frequently associated thalamic nonseparation in this condition. The lack of group differences in the posterior hemispheres may reflect relative sparing of these regions in the semilobar subtype of HPE.

INTRODUCTION

Holoprosencephaly (HPE) is a complex developmental brain malformation in which the primary defect is the failure of the rostral neural tube to bifurcate into the two cerebral hemispheres. Based on the degree of hemispheric nonseparation, HPE has traditionally been classified into three “classic” types: alobar, semilobar, and lobar (Figure 1) (DeMyer et al., 1964). Classic HPE results from a primary defect in patterning of the basal forebrain during the first four weeks of embryogenesis (Golden, 1999). In semilobar HPE, there is a failure of separation of the anterior hemispheres, while some portion of the posterior hemispheres show separation. The frontal horns of the lateral ventricle are absent, but posterior horns are present. The corpus callosum is absent anteriorly, but the splenium of the corpus callosum is present.

Recent studies of the electroencephalogram (EEG) in patients with HPE have demonstrated frequent hypersynchronous slow (theta) and fast (beta) activity (Clegg et al., 2002; Hahn et al., 2003; Yang et al., 2004). In the present study, we further investigate the hypersynchrony by examining the interhemispheric coherence of EEG patterns at various frequency bands in patients with semilobar HPE.

METHODS

PATIENT SELECTION

Six children diagnosed with semilobar HPE between the ages of 12 months and 6 years were selected for the study. These patients were prospectively enrolled between 1998 and 2002 as a part a larger study at the Carter Centers (a national consortium funded by not-for-profit private foundations) investigating the clinical characteristics of HPE. Inclusion criteria of the study were the diagnosis of semilobar HPE confirmed by review of imaging studies, neurological evaluation at one of the Centers, and an EEG. At the time of the EEG, the patients did not have a prior history of seizures. Each Institutional Review Board approved the study prior to initiation. Informed consent was obtained from each subject’s parents.

For the control group we examined normal EEGs of 15 patients in the same age range who were referred to the EEG lab for syncope or staring spells. Patients referred

for history of seizures or any prior neurologic problems were excluded.

ELECTROENCEPHALOGRAPHIC RECORDINGS

All recordings were made in the Departments of Neurology at Lucile Packard Children’s Hospital (Palo Alto, CA) or Texas Scottish Rite Hospital (Dallas, TX). EEGs were performed using a 24-channel digital recording technique using the same instruments (Neuroconcepts, Inc). The International 10-20 System was used for electrode placements. The sampling frequency was 250 Hz. The time constant for low frequency filtering was 0.1 s and high frequency filter was set at 70 Hz.

COHERENCE ANALYSIS

The following EEG derivations were recorded: F3-A1, F4-A2, P3-A1, and P4-A2. We used ipsilateral-ear reference rather than linked-ears reference, as the latter appeared to inflate interhemispheric coherence (Nunez et al., 1997). Occipital leads were not evaluated as some of the patients had a dorsal cyst over the occipital regions. For each subject, two segments of artifact-free EEG (duration 120 seconds) were chosen for coherence analysis during stage 1 and 2 sleep states. Coherence analyses of these EEG epochs were performed using Persyst Insight II EEG analysis software (Prescott, AZ). Interhemispheric coherence analyses were based on bipolar derivations, i.e., {(F3-A1) – (F4-A2)} for frontal and {(P3-A1) – (P4-A2)} for parietal regions. The frequency bands used in the coherence summaries were: delta, 0.5 – 4 Hz; theta, 4 – 8 Hz; alpha 8 – 13 Hz; and beta 13 – 32 Hz.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 11. To assess for age-specific trends in coherence values regression analysis was performed. Simple linear regression was found to give a good fit of the data when a significant age-dependent correlation was present. Nonlinear regression analysis using log-linear regression did not yield significantly improved fit of the data. Group comparison of the coherence regression analyses was performed using ANCOVA when the test for homogeneity-of-slopes indicated that this was a valid method. When the test of homogeneity of the slopes indicated that the regression slopes were significantly different, t-test was used for means

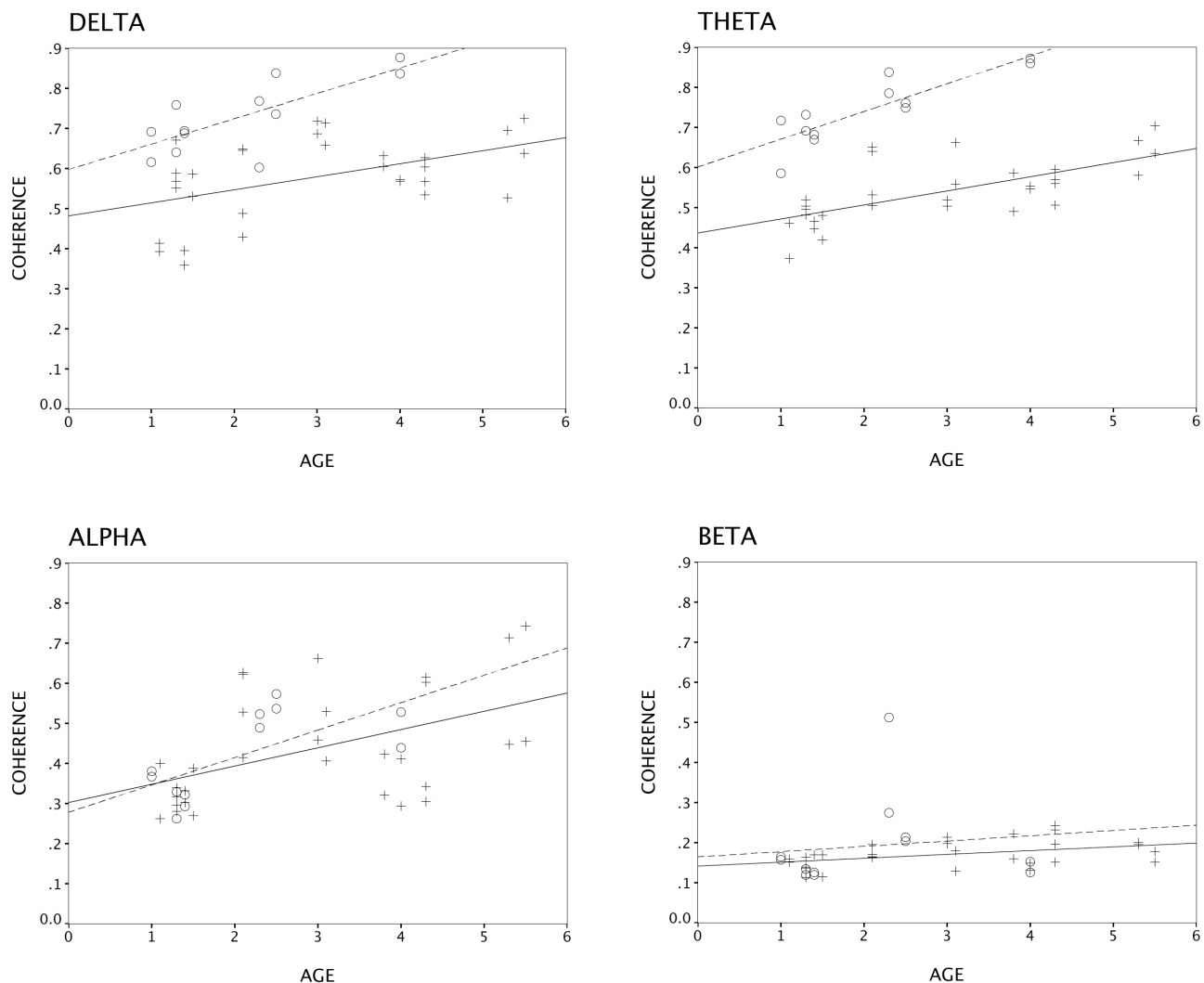


Figure 1. Frontal interhemispheric coherence versus age in stage 1 and 2 sleep states. The four graphs correspond to the frequency bands from delta to theta. Ordinate: coherence values for the frequency band for semilobar HPE patients (○) and controls (+). Abscissa: age in years. The regression lines were determined by linear least-squared method for semilobar HPE patients (dotted line) and controls (solid line).

comparisons of coherence values between the two groups.

RESULTS

Frontal interhemispheric coherence. In Figure 1 the frontal coherence values of semilobar HPE and the control groups are plotted according to age. In the delta and theta ranges the interhemispheric coherence in both groups rises continuously with increasing age. This age-specific trend is highly significant for both groups (see Table 1 for significance values). In the delta and theta ranges, the interhemispheric coherence values are significantly higher in the semilobar HPE group compared to controls (Table 2).

In the alpha range, the coherence values for both groups show a gradual trend of increasing with age, but are lower than those of delta and theta frequency bands (Figure 1). No significant differences were noted between the two groups (Table 2).

In the beta range, the coherence values for both groups are lowest of all frequency bands. For the control group there was a small but significant increase in coherence with age ($p = 0.18$), but no significant increase was noted for the semilobar HPE group.

Parietal interhemispheric coherence. In the control group the coherence values showed an increase with age that was significant for each of the frequency bands (Table 1). The highest coherence values were in the delta range,

TABLE 1.

Result of linear regression related to interhemispheric coherence by frequency range versus age. Values represent correlation coefficient R. Values in parentheses represent the significance (p-value) of the slope.

	Delta	Theta	Alpha	Beta
Frontal interhemispheric coherence				
Control	.478 (.008)	.673 (<.001)	.476 (.008)	.429 (.018)
Semilobar HPE	.746 (.005)	.865 (<.001)	.673 (.017)	.126 (N.S.)
Parietal interhemispheric coherence				
Control	.638 (<.001)	.676 (<.001)	.583 (.001)	.432 (.017)
Semilobar HPE	.073 (N.S.)	.255 (N.S.)	.410 (N.S.)	.167 (N.S.)

N.S. = no significant correlation

TABLE 2

Coherence comparisons between semilobar HPE and control groups using ANCOVA by frequency ranges. Coherence values was used as the dependent variable, condition (semilobar HPE or control) as the factor, and age as the covariate.

	Delta	Theta	Alpha	Beta
Frontal interhemispheric coherence				
Significance	<.001	<.001	N.S.	N.S.
Parietal interhemispheric coherence				
Significance	.008	N.S.*	N.S.*	N.S.

N.S. = no significant correlation

* ANCOVA analysis was not utilized because of failure of homogeneity-of-slopes test. T-test was used instead

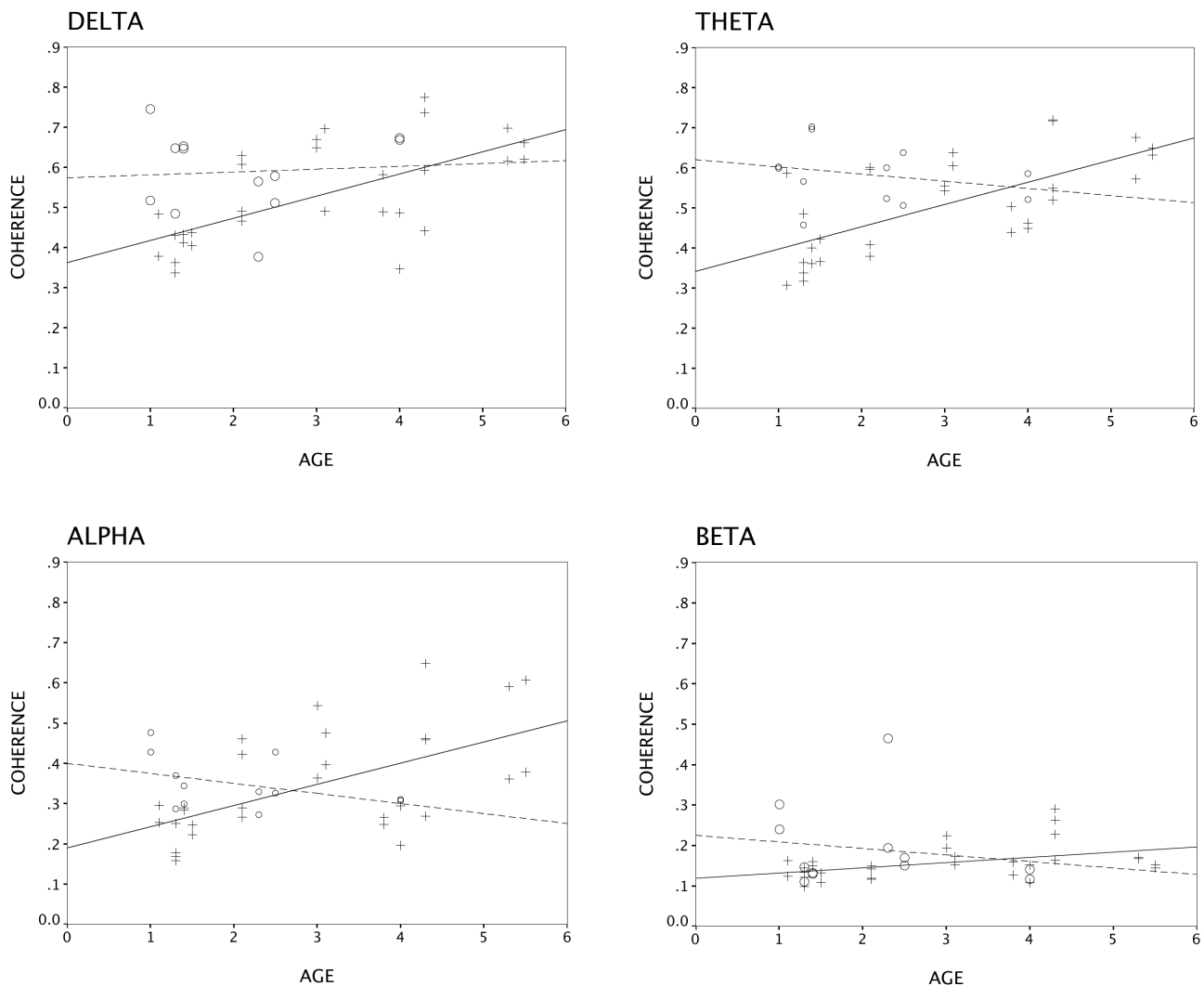


Figure 2. Parietal interhemispheric coherence versus age in stage 1 and 2 sleep states by frequency bands. The arrangement of the figures is same as that in Figure 1. Semilobar HPE patients (○) and controls (+). The regression lines were determined by linear least-squared method for semilobar HPE patients (dotted line) and controls (solid line).

followed in order by theta, alpha, and beta (Figure 2). For the semilobar HPE group none of the regression lines for the frequency bands showed a significant trend (neither increasing nor decreasing) with age. The coherence values for delta band in semilobar HPE group was slightly higher than controls when analyzed using ANCOVA (Table 2). This group difference was not as large as compared to that in the frontal region. The coherence values in theta, alpha, and beta frequency ranges were similar to those of the control group.

DISCUSSION

Holoprosencephaly is a congenital malformation of the central nervous system in which there is a failure of the

rostral neural tube to bifurcate into the two hemispheres. This results in incomplete cleavage of the cerebral hemispheres and deep brain structures. There is a spectrum in the severity of these malformations with semilobar HPE being a moderately severe subtype. There have been several previous reports of EEGs in HPE patients (DeMyer and White, 1964; Habedank and Thomas, 1970; Watanabe et al., 1976; Clegg et al., 2002; Hahn et al., 2003; Yang et al., 2004). Hypersynchronous slow rhythmic activity has also been reported in patients with HPE (Habedank and Thomas, 1970; Watanabe et al., 1976; Veneselli et al., 1999). In a recent study we found that the most common abnormal pattern was the presence of hypersynchronous theta activity during wakefulness and drowsiness/sleep (Hahn et al., 2003). The EEGs displaying hypersynchronous theta activity

were correlated with a higher degree of hemispheric and thalamic nonseparation.

To examine this phenomenon further, we performed coherence analysis in patients with semilobar HPE. In the study of functional relationships, coherence analysis provides important information on cerebral activity. Coherence measures the correlation between two EEG signals as a function of frequency. Hence it provides a method for identifying frequency bands that contain inter-channel synchronization (Ruchkin, 2005). The coherence between EEG signals from different brain areas depends on the structural connection and functional coupling between these regions (Schmid et al., 1992). Coherence analysis has been used to study the perturbations of normal EEG development in various conditions including Down's Syndrome (Schmid et al., 1992), prematurity (Als et al., 2004), and hemispheric strokes (Gottselig et al., 2002; Kulak and Sobaniec, 2005). We, therefore, chose coherence analysis to further study the interhemispheric connectivity in this midline brain malformation.

The coherence analysis shows that in the frontal regions the interhemispheric coherence (i.e., the coherence between the right and left sides of the frontal regions) was significantly higher in the delta and theta frequency bands for semilobar HPE patients compared to controls. In semilobar HPE brains the frontal regions are the most affected area, i.e., the part of the brain where there is the most severe nonseparation of the hemispheres. For alpha and beta frequency bands we were not able to demonstrate significant group differences. However, the coherence values were generally lower than those for the slower frequency bands. Interestingly in the parietal regions the coherence values for all of the bands did not significantly differ between the two groups except for a modest difference in the delta range. This may be because in semilobar HPE the posterior hemispheres (including the parietal lobes) are better separated. We hypothesized previously that hypersynchronous slow activities seen in HPE are due to the nonseparations of the thalamic nuclei and cerebral hemispheres in HPE. The finding of higher coherence values for delta and theta bands in the frontal but not parietal regions in semilobar HPE patients support our hypothesis.

In general, the coherence was greater for slow waves than fast activity ($\delta > \theta > \alpha > \beta$). This is in agreement with previous studies in normal children (Schmid et al., 1992; Barry et al., 2005). In our previous study we also noted *hypersynchronous beta* activity during sleep in many EEGs (Hahn et al., 2003). However, we did not find significantly higher coherence values for semilobar HPE patients for alpha or beta frequencies compared to controls. The lower coherence values in

alpha and beta bands indicate that the EEG signal is less well synchronized in these bands, and hence, less susceptible to perturbations of interhemispheric connections seen in HPE.

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