Application of linear and non-linear time series analysis to neonatal EEG activity.

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Introduction

The human EEG has been a steady source of clinical information for many decades. EEG research has recently accelerated - in part fueled by an interest in the use of technologies such as MEG, source localization and the most recent renewal of interest in seizure prediction. In particular, substantial attention has recently been given to the application of non-linear time series methods to the analysis of EEG epochs containing seizures and the time periods just preceding the seizures. Early reports were optimistic that deterministic chaos measures could be used to detect and/or predict seizures. Following a wave of initial enthusiasm for the application of the deterministic chaos non-linear time series analysis there arose a series of criticisms regarding the potential pitfalls in the application of these metrics. These criticisms have served the field well in that they have spawned increasingly sophisticated metrics and an increased awareness of the pitfalls of interpreting such measures. Armed with improved methods and an increased appreciation of the limitations of these measures a number of investigators have continued to report the successful application of dynamical systems measures to the detection and prediction of seizures.

One of the most challenging areas of EEG analysis is in the interpretation of neonatal EEGs. Seizures in this age group are not uncommon, yet conventional interpretative rules of EEG analysis are not easily applied to this age group. The sensitivity and specificity of the EEG for the detection of seizures is significantly compromised in neonates. Hence, there is a clear need for improved methods of EEG analysis in this age group. It is therefore surprising that there has been so little attention given to the application of these "newer" non-linear measures to the infant population. Normal adult human EEG studies offer only modest support for the presence of low dimensional chaos in EEG recordings, although there are clear and reproducible changes in chaos measures and other non-linear systems measures during seizures. We report herein on the application of linear and non-linear time series analyses to the characterization of the human neonatal EEG and perform a preliminary comparison to older infants.

Hypotheses

1) Neonates like older subjects will demonstrate reliable linear and non-linear components to the underlying structure of the EEG.
2) Complexity measures of population behavior will be lower in neonates than adults
3) The differences in non-linear measures associated with state changes will be lower in infants than adults.
4) The phylogentically more recent frontal lobe structures will show greater immaturity, that is lower complexity, than the phylogenetically older lobes.

Methods

Patient selection – All patients were obtained from the University of Chicago neonatal intensive care unit, and were born from 29 to 38 week gestation. Patients were selected among those who had undergone an EEG as part of a clinical evaluation. None of the patients were receiving CNS active medications, none had seizures, none had intra-ventricular hemorrhage, all had clear evidence of both sleep and wake states and none (retrospectively) had significant neurological problems. The clinical interpretation of all of the EEGs was that they were normal. The majority of the infants were being screened as part of an apnea evaluation. Similar criteria were applied to the older infants, who were obtained from the records of the routine ambulatory EEG laboratory.

Segment Selection - EEG segments were selected by scrolling through the record and selecting the first 30 sec. epoch in which the patient's state was clear and free of artifacts. Three replications of awake and sleep segments were selected. The segments were each 30 seconds in duration, sampled at 400 Hz, filtered from 1 to 70 Hz and then transferred into MatLab before subsequent processing.

EEG Analysis – Typical measures included Lyapunov exponents, correlation dimension, maximum likelihood measure of dimension, two forms of Kolmogorov entropy, eigenstructure and a normalized measure of non-linearity (z). Time delays and embedding dimension were data adaptive and the entropy measures are noise corrected.

Results

The most striking differences, as a function of age, were in the Kolmogorov entropy with mean values for the infants of 18 compared to 49 for the older infants. However, correlation dimension (4.6 vs. 3.7) was also lower in the infants and the eigenstructure marginally higher. The age dependent entropy difference was true for multiple brain regions. In the awake older infants there was a clear and dramatic decline of more than 70% in entropy as the subjects fell asleep, in contrast to the neonates where the drop in entropy was nearly 25%. The state dependency of the entropy drop was true for all scalp locations. The eigenstructure did not change with state. The state dependency of correlation dimension did not reach significance either.

Discussion

There is a clear age dependency to the EEG measures of non-linearity – both deterministic chaos and non chaotic. There were also changes as a function of state (declining entropy with the onset of sleep), which were modest in the neonates and dramatic in the older children. Finally, while the chaos measures suggest that the frontal region is the most immature all brain regions showed the developmental and state dependencies. We optimistically conclude that the deterministic chaos measures are promising in their application to the human neonate but that use of these measures will require age dependent norms and careful attention to patient state.