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Recurrence analysis of the EEG during sleep accurately identifies subjects with mental health symptoms

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ABSTRACT

Analysis of brain recurrence (ABR) is a novel computational method that uses two variables for sleep depth and two for sleep fragmentation to quantify temporal changes in non-random brain electrical activity. We postulated that ABR of the sleep-staged EEG could identify an EEG signature specific for the presence of mental health symptoms. Using the Mental Health Inventory Questionnaire (MHI-5) as ground truth, psychological distress was assessed in a study cohort obtained from the Sleep Heart Health Study. Subjects with MHI-5 <50 ($N=34$) were matched for sex, BMI, age, and race with 34 subjects who had MHI-5 scores >50. Sixteen ABR markers derived from the EEG were analyzed using linear discriminant analysis to identify marker combinations that reliably classified individual subjects. A biomarker function computed from 12 of the markers accurately classified the subjects based on their MHI-5 scores (AUROC=82%). Use of additional markers did not improve classification accuracy. Subgroup analysis (20 highest and 20 lowest MHI-5 scores) improved classification accuracy (AUROC=89%). Biomarker values for individual subjects were significantly correlated with MHI-5 score ($r=0.36$, 0.54 for $N=68$, 40, respectively). ABR of EEGs obtained during sleep successfully classified subjects with regard to the severity of mental health symptoms, indicating that mood systems were reflected in brain electrical activity.

1. Introduction

The relation between psychological distress and the pattern of the electroencephalogram (EEG) recorded from distressed subjects has been studied since the discovery of the EEG (Lemere, 1936). In major depressive disorder (MDD), for example, many attempts were made to identify visual features, spectral characteristics, or other linear properties of the signal that would allow identification of risk, confirm diagnosis, permit monitoring of the effect of treatment, and/or predict treatment response (Olbrich and Arns, 2013). Changes in absolute or relative alpha power were probably the most frequently identified variables associated with MDD, but not with sufficient consistency to warrant clinical application (Knott and Lapierre, 1987; Pozzi et al., 1995; Grin-Yatsenko et al., 2009; Jaworska et al., 2012).

Various methods based on analysis of the nonlinear dynamical complexity in the EEG were proposed for studying mental disorders (Bystritsky et al., 2012). Within the limitations of this perspective (Rapp, 1994), various approaches were developed to distinguish between the presence and absence of MDD (Olbrich and Arns, 2013) and to predict treatment efficacy (Arns et al., 2014). Similar observations were reported for other mental disorders including schizophrenia (Paulus and Braff, 2003) and autism (Bosl et al., 2011).

Analysis of brain recurrence (ABR) is a computational method designed to detect and quantify deterministic temporal patterns in the EEG (non-random brain activity) not detectable by conventional EEG methods such as pattern-recognition or spectral analysis (Carrubba et al., 2012a). ABR was used to study a range of problems in basic and clinical neuroscience (Frilot et al., 2014). Patients with multiple sclerosis were identified using ABR (Carrubba et al., 2010; Carrubba et al., 2012b), and it was used to create a novel paradigm in which the concepts of sleep depth and variability could be quantified (Carrubba et al., 2012a; Wang et al., 2013). Employing markers based on these variables, patients with mild or moderate obstructive sleep apnea were distinguished using the sleep-staged EEG from a single derivation (Wang et al., 2013), illustrating the concept that a complex physiologic disorder leaves an objectively discernible and specific footprint on brain electrical activity.

We became interested in whether the sleep-acquired EEG could similarly be used to classify subjects with psychological distress. Our ultimate goal was to develop objective analytical methods to help in the diagnosis and classification of subjects with neurocognitive

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disorders. In the present study we tested the hypothesis that sleep depth and fragmentation markers extracted from the staged, sleep-acquired EEG could be employed to accurately assign subjects into classes with higher or lower levels of distress, using scores from the Mental Health Inventory questionnaire (MHI-5) as ground truth. If the subjects could be correctly classified, we planned to interpret the result as an indication that psychological distress was objectively associated with a specific type of algorithmically-determinable change in the sleep EEG.

2. Methods

2.1. Patients

Fig. 1 shows the basic stages of the analysis. The study cohort was chosen from the 6441 participants in the Sleep Heart Health Study (SHHS), a multi-center study sponsored by the National Heart, Lung and Blood Institute and conducted in ten U.S. communities to determine the cardiovascular and other consequences of sleep-disordered breathing (Quan et al., 1997). All SHHS participants underwent overnight polysomnography (PSG) between 1995 and 1998. The present investigation took advantage of the EEG data in the PSG, the scores from the MHI-5, and relevant covariate information collected during the baseline SHHS examinations.

The cohort studied was chosen from SHHS participants for whom mental health status, age, gender, body mass index (BMI), and race were ascertained within 1 year of polysomnography. Participants with sleep apnea, type 2 diabetes, stroke, myocardial infarction, angina, heart failure, coronary angioplasty, or coronary artery bypass graft surgery were excluded. We arbitrarily regarded a scaled MHI-5 score less than 50 as indicating impaired mental health. The cohort was formed by randomly choosing subjects with scores less than 50, and matching them for gender, age (± 2 years), BMI (± 2 kg/m^2), and race with subjects who had MHI-5 scores greater than 50. When there was more than one possible choice, the subject was chosen randomly. The two sub-cohorts were well matched on all pertinent characteristics except for MHI-5 score (the variable used to define the sub-cohorts) (Table 1). The low RDI scores indicated that the subjects did not have sleep apnea. We arbitrarily chose sub-cohorts of 34 subjects, which was about half of the subjects available in the less-than-50 group. All research-related procedures were approved by the institutional review boards for human research at the institutions where the data was collected.

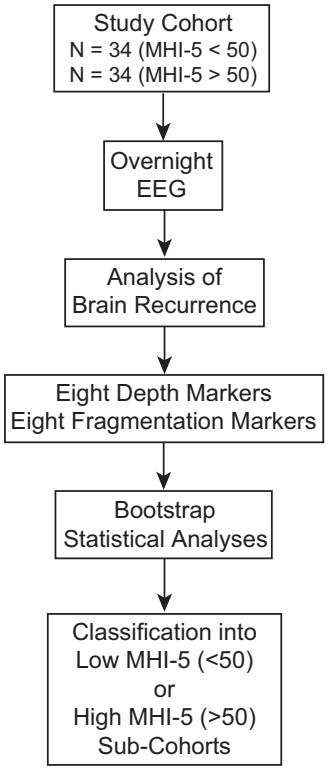

Fig. 1. Experimental design.

Table 1
Characteristics of the study cohort. BMI, body mass index. MHI-5, Mental Health Inventory-5. Mean $\pm$ SE. C, Caucasian. RDI, Respiratory Disturbance Index.

	MHI-5 < 50	**MHI-5 > 50**
N	34	34
Race (C/non-C)	29/5	29/5
Age (years)	58.6 ± 2.3	58.7 ± 2.3
Male/Female	12/22	12/22
BMI (kg/m^2)	25.6 ± 0.6	25.9 ± 0.6
RDI	1.6 ± 0.2	1.3 ± 0.2
MHI-5	40.5 ± 1.4	78.4 ± 2.1

2.2. Measure of mental health

The MHI-5 screening instrument asked "How much of the time during the last month have you: (1) been a very nervous person; (2) felt calm and peaceful; (3) felt downhearted and blue; (4) been a happy person; and (5) felt so down in the dumps that nothing could cheer you up?" Each answer was scored 1–6 (subject range 5–30), with higher scores indicating better mental health. For analysis, the total score was linearly transformed into a variable with a range from 0 to 100. In a population-based sample, the overall accuracy of the MHI-5 in identifying mood disorders is 88%, using a cut-off of 60 points or less (Rumph et al., 2001). In a population of patients with HIV, the best cut-off score for major depression (84%) was 52 (Holmes, 1998).

2.3. Polysomnograms

PSGs were recorded using the Compumedics P Series system (Abbots Ford, Victoria, Australia) (Quan et al., 1997) and were obtained from the SHHS database (National Heart Lung & Blood Institute, 2012). Details regarding the recording procedures were described elsewhere (Redline et al., 1998). Each PSG was about eight hours in duration and had been divided by the original SHHS investigators into 30-second epochs and classified into one of five mutually exclusive stages, four stages of sleep (REM, N1, N2, N3) or the stage of wake after sleep onset (WASO). The PSGs contained EEGs recorded from C3–M2 and C4–M1, sampled at 125 Hz, and were provided as MAT files. For analysis, the EEGs were interpolated to 500 Hz (our laboratory standard sampling frequency for the EEG) using a standard algorithm (Matlab, Mathworks, Natick, MA, USA), filtered using an FFT digital filter to pass 0.5–35 Hz, and evaluated by means of custom codes in a standard numerical computing environment (Matlab). We chose 35 Hz as the cut-off because we had previously determined that it produced the best balance between capturing essentially all the energy in the EEG while providing good protection against common artifacts that appear in the sleep EEG above 35 Hz. The EEGs from both derivations were analyzed, but only the results from C3–M2 are presented here because the C4–M1 results were essentially identical.

2.4. Analysis of brain recurrence

Analysis of brain recurrence (ABR) is a nonlinear technique for extracting information from the EEG. The basic idea is that although brain electrical activity appears irregular, it actually exhibits recurrent patterns that can be detected and quantified, thereby permitting evaluation of the relation between the recurrences and behavioral or clinical observations. ABR is based on the conjecture that brain function is mediated by electrical activity in localized neuronal networks and their inter-network electrical synchronization (Carrubba et al., 2012a). In this perspective, an EEG from any derivation is regarded as a delocalized measure of the instantaneous electrical state of the brain, and the extent of the law-governed (as opposed to random) behavior contained in the EEG resulting from the network activity is quantified using ABR. The basic signal-processing techniques and their applicability to model-independent analyses of nonstationary signals like EEGs were previously described (Zbilut and Webber, 2006). Briefly, 5-component vectors (points in a five-dimensional mathematical hyperspace) were formed that consisted of the EEG amplitude at t and four earlier times identified by four successive lags of five points (10 ms). The sequence in hyperspace of all such vectors obtainable from one second of the EEG (480 vectors, given our choices of sampling rate, vector dimension, and delay time) was interpreted as a path that was determined by law-governed (non-random) activity in the brain. The amount of such activity was quantified using the variables *percent recurrence* (r), defined as the percent of the 480 vectors in the path that were near other vectors (and hence were recurrent), and *percent determinism* (d), defined as the percent of the recurrent points that were adjacent to at least one other recurrent point. Detailed analysis of these variables provides a theoretical rationale for why they quantify the amount of law-governed activity in the EEG (Zbilut and Webber, 2006; Frilot