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Journal of Psychosomatic Research 66 (2009) 51 – 57

Journal of Psychosomatic Research

Power spectral analysis of sleep EEG in twins discordant for chronic fatigue syndrome

Roseanne Armitage[a,*], Carol Landis[b], Robert Hoffmann[a], Martha Lentz[b], Nathaniel Watson[c], Jack Goldberg[d], Dedra Buchwald[e]

[a]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
[b]Department of Biobehavioral Nursing and Health Systems, School of Nursing, University of Washington, Seattle, WA, USA
[c]Department of Neurology, University of Washington, Seattle, WA, USA
[d]Department of Epidemiology, University of Washington, Seattle, WA, USA
[e]Department of Medicine, University of Washington, Seattle, WA, USA

Received 9 October 2007; received in revised form 16 July 2008; accepted 28 August 2008

Abstract

Objective: The purpose of the study was to evaluate quantitative sleep electroencephalogram (EEG) frequencies in monozygotic twins discordant for chronic fatigue syndrome. **Methods:** Thirteen pairs of female twins underwent polysomnography. During the first night, they adapted to the sleep laboratory, and during the second night, their baseline sleep was assessed. Visual stage scoring was conducted on sleep electroencephalographic records according to standard criteria, and power spectral analysis was used to quantify delta through beta frequency bands, processed in 6-s blocks. Data were averaged across sleep stage within each twin and coded for sleep stage and the presence or absence of chronic fatigue syndrome (CFS). A completely within-subjects repeated measure multivariate analysis of variance evaluated twin pairs by frequency band by sleep stage interactions and simple effects. The relationship between alpha and delta EEG was also assessed across twin pairs. **Results:** No significant differences in spectral power in any frequency band were found between those with CFS and their nonfatigued cotwins. Phasic alpha activity, coupled with delta was noted in five subjects with CFS but was also present in 4/5 healthy twins, indicating this finding likely reflects genetic influences on the sleep electroencephalogram rather than disease-specific sleep pathology. **Conclusions:** The genetic influences on sleep polysomnography and microarchitecture appear to be stronger than the disease influence of chronic fatigue syndrome, despite greater subjective sleep complaint among the CFS twins. EEG techniques that focus on short duration events or paradigms that probe sleep regulation may provide a better description of sleep abnormalities in CFS.

Keywords: Chronic fatigue syndrome; Power spectral analysis; Quantitative EEG; Sleep; Twins

Introduction

Chronic fatigue syndrome (CFS) is characterized by profound fatigue lasting at least 6 months accompanied by disturbances of sleep, cognition, mood, musculoskeletal pain, and other symptoms [1]. Insomnia and insufficient, non-restorative sleep are among the most common and disabling symptoms [2–6]. Clinic-based studies have found that patients with CFS often have poor sleep efficiency [5,7–12] and, occasionally, intrinsic sleep disorders such as obstructive sleep apnea [2,5,7,8,13]. These studies, however, have methodological differences and limitations including the absence of comparison groups [5,8,11,13], failure to include laboratory sleep data [6,14], use of in-home sleep studies [10,14], reporting of clinical sleep disorders without data on sleep architecture [2], and the inclusion of only a single laboratory night [2,5,8,10,12,13]. Small but rigorously conducted studies have not provided strong evidence for striking abnormalities in sleep architecture among most patients with CFS [15,16]. Thus, methodological differences, the lack of control for many genetic and environmental factors, and the inherent limitations

* Corresponding author.
E-mail address: rosearmi@umich.edu (R. Armitage).

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doi:10.1016/j.jpsychores.2008.08.004

of standard electroencephalogram (EEG) likely contribute to the inability to reproducibly detect differences in sleep microarchitecture between CFS and healthy control groups.

Quantitative EEG analysis procedures may be a more sensitive metric for evaluating sleep abnormalities in clinical populations than traditional manual sleep stage scoring [17,18]. One study of sleep clinic patients with chronic fatigue demonstrated increased "slow delta" power and a higher cyclic alternating pattern (CAP) rate in the CFS group [19]. Increased alpha activity during sleep also has been inconsistently observed in fibromyalgia [20–25], a disorder closely related to CFS that is characterized by chronic, unexplained, widespread pain [26]. The limited studies of quantitative sleep EEG in CFS or other related disorders provided a strong rationale for the present study.

Cotwin control studies offer a powerful alternative to traditional approaches that compare CFS patients to healthy or depressed individuals, while controlling for genetic and numerous environmental factors [27]. This research design is particularly valuable in studies of sleep where genetic factors contribute substantially to sleep architecture [28], the number of data points generated is large, and the range of values observed in normal individuals is wide. We therefore compared the power spectral analysis of sleep EEGs between twins discordant for CFS to answer these questions: does sleep architecture differ between twins with CFS and their nonaffected cotwins and is there greater prevalence of alpha-activity phase-locked with delta in the twins with CFS?

Methods

Participants

From 1997 to 1999, 22 sets of CFS discordant twins from the University of Washington CFS Twin Registry were chosen for a 7-day in-person evaluation based on registry information and telephone screening establishing the presence or absence of symptoms consistent with the Centers for Disease Control (CDC) diagnostic criteria of CFS [1,15,29,30]. Twins were required to (1) be at least 18 years of age; (2) be reared together; (3) be discordant for CFS (one twin met the CDC CFS criteria, the other did not); (4) be negative for HIV; (5) abstain from alcohol and caffeine and, based on their personal physicians' advice, discontinue all medications at least 2 weeks prior to the evaluation; and (6) travel to Seattle together [31].

To determine if a twin met CDC CFS criteria, we used responses to the CFS symptom checklist, diagnoses generated by the Diagnostic Interview Schedule (Version III-A) [32] and information from review of the subject's medical records. To meet criteria, debilitating fatigue must have been present for at least 6 months with endorsement of at least four of eight CFS symptoms. Exclusionary medical and psychiatric conditions must have been absent. The same inclusion and exclusion criteria (e.g., body mass index, specific psychiatric disorders) and review processes were applied to the fatigued and nonfatigued twins. Medical records covering the last 5 years were reviewed by a physician knowledgeable about CFS (D.B.) for exclusionary medical conditions. A psychologist and infectious disease specialist also independently reviewed the twins' medical charts to verify health status and approve twins for participation. Prior to the scheduled visit, we confirmed that the ill twin still met CFS criteria and that the control twin was devoid of CFS.

Between 2000 and 2003, the twins were contacted about participating in a follow up study. Of the 22 original pairs of twins, 14 agreed to participate in a second week-long evaluation. Written informed consent was obtained from all twins in accordance with regulations of the University of Washington Institutional Review Board. A waiver of consent was obtained from the University of Michigan Institutional Review Board to conduct the statistical analysis of the data at University of Michigan.

Depression was assessed using the Diagnostic Interview Schedule, a structured interview based on *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* [32]. Monozygosity was initially determined using previously validated self-report methods [33,34], then confirmed with analysis of restriction fragment length polymorphisms. DNA samples were extracted and digested with the restriction endonuclease *Hae*III. The restriction fragments were separated by molecular size in agarose gel, Southern-blotted onto nylon membrane, and hybridized with a variable number of tandem repeat probes. With six probes, the probability of monozygosity can be ascertained with 99.9% certainty [35].

Each pair of twins spent three consecutive nights and 1 day in the University of Washington Sleep Research Laboratory in temperature controlled, sound-attenuated rooms. All sleep recording equipment was located in a central control room separate from the individual sleeping rooms. Twins were instructed to follow a set sleep schedule for 1 week prior to coming to the laboratory based on an average of their nightly sleep schedule ascertained from a 2-week sleep diary. This schedule was adjusted for twins who traveled to Seattle from Eastern, Central and Mountain time zones.

Throughout the study, the Sleep Research Laboratory investigators and technicians were blind to the illness status of the twins. During the first night, the twins adapted to the laboratory; baseline sleep data from the second night are reported here. The third night was an experimental manipulation night reported elsewhere [36]. The twins completed a 10-item postsleep questionnaire each morning before getting out of bed.

Clinical characteristics

Body mass index was computed from measured weight and height. Both history of and current major depression were assessed using the National Institute of Mental Health Diagnostic Interview Schedule. Depression was assessed using the Diagnostic Interview Schedule (Version III-A) [35], a structured interview based on *Diagnostic and*