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NREM sleep alpha and sigma activity in Parkinson's disease: Evidence for conflicting electrophysiological activity?

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HIGHLIGHTS

- Sleep EEG spectral patterns investigated in eight newly diagnosed, non-depressed, non-demented, drug-naïve Parkinson's disease patients compared to nine healthy aged controls.
- Concomitantly increased scalp EEG alpha and sigma activity found during non-REM sleep in Parkinson's disease.
- These sleep microstructure changes may represent evidence for altered electrophysiological mechanisms leading to sleep–wake instability in early disease stages.

ABSTRACT

Objectives: Sleep EEG spectral patterns were investigated in eight newly diagnosed, non-depressed, non-demented, drug-naïve Parkinson's disease patients compared to nine controls.
Methods: Mean relative spectral power density calculated for 0.25 Hz frequency bins and for classical EEG frequency bands.
Results: Differences between patients and controls were most prominent in non-REM sleep, specially around 8.6 Hz (slow alpha), 12.5 Hz (fast alpha/slow sigma) and 15 Hz (fast sigma). Slow alpha showed lower *p*-values over frontal and occipital electrodes, whereas fast sigma activity was more important on central and parietal sites. Significantly increased NREM sleep alpha activity was found in left and right frontal (Mann–Whitney $U = 12{,}000$, $p = .021$; $U = 14{,}000$, $p = .036$), left and right central ($U = 14{,}000$, $p = .036$), left parietal and left occipital ($U = 13{,}000$, $p = .027$; $U = 15{,}000$, $p = .046$) areas. Increased sigma activity was found in right frontal ($U = 14{,}000$, $p = .036$), left central ($U = 12{,}000$, $p = .021$), left and right parietal ($U = 12{,}000$, $p = .021$; $U = 13{,}000$, $p = .027$) and left occipital ($U = 15{,}000$, $p = .046$) areas.
Conclusions: Concomitantly increased scalp EEG alpha and sigma activity was found during NREM sleep in initial Parkinson's disease.
Significance: These non-REM sleep microstructure changes may represent evidence for altered electrophysiological mechanisms leading to sleep–wake instability in early disease stages.

1. Introduction

Most of what is known about Parkinson's disease (PD) electrophysiology pertains to wakefulness (W). Cortex–basal nuclei interactions in PD have been traditionally modeled from the waking state perspective (Jankovic, 2012). It is during W that disease-

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defining motor disability becomes readily apparent. Resting tremor diminishes as non-REM (NREM) sleep intervenes (Vendette et al., 2007). Dramatic changes in firing patterns take place in forebrain, brainstem and thalamocortical structures during the wake–sleep transition (WST) (McGinty and Szymusiak, 2011). Particularly at thalamic reticulum (RE)–thalamocortical (TC) neurons, a state of synchronized rhythmic activity is associated with NREM sleep, in contrast with desynchrony or tonic activation during W/REM states (Steriade and Llinás, 1988). The major cortical NREM sleep EEG rhythms result from intrinsic neuronal properties and synaptic organization of cortical and thalamic circuits modulated by regulatory systems (Destexhe and Sejnowski, 2003; McGinty and Szymusiak, 2011). Interestingly, basal nuclei have been proposed as key regulators of sleep stability and sleep–wake behaviors (Qiu et al., 2010).

Sleep disorders (SD) are among the most frequent non-motor manifestations of PD (Chaudhuri et al., 2006; Raggi et al., 2013). Severe global sleep disruption is often present in advanced disease stages, affecting quality of life and posing significant therapeutic challenges. Factors influencing SD in PD, however, are not straightforward. Even in initial PD stages, SD patterns are still a matter of debate (Sixel-Döring et al., 2014). Some studies indicate that few symptoms and/or NREM sleep architecture changes may be expected in the majority of drug-naïve, non-depressed, non-demented patients (Wetter et al., 2001; Brunner et al., 2002; Gagnon et al., 2004). This is intriguing as PD is characterized by nigral dopaminergic pathology, but it is also associated with extensive nondopaminergic involvement. Lewy body accumulation starts early in non-dopaminergic brainstem structures involved in arousal and sleep/wake cycle regulation (Braak et al., 2003). Dopamine itself has been associated with wake-promoting activity and significant circadian fluctuation has been implied for dopaminergic neurotransmission (Videnovic and Golombek, 2013). Mesocortical dopamine circuits have also been implicated in W promotion and may be directly involved in PD-related SD.

Surprisingly little is known about sleep EEG microstructure in initial PD stages when one considers that sleep EEG patterns might reflect changes in basal nuclei influence over thalamo-cortically expressed sleep–wake behaviors, even in the absence of major sleep symptoms and possibly in the presence of early compensatory mechanisms for dopamine insufficiency. Three studies have investigated REM sleep microstructure in early-stage PD. In one study, no differences were found between patients and controls (Gagnon et al., 2004). Of note, these were patients on levodopa therapy, expected to influence EEG spectral composition. In drug-naïve, early-stage PD, increased activity in the upper theta and alpha range was found during REM sleep episodes on the first night section (Wetter et al., 2001) and on the second half of each REM sleep episode (Mouret, 1975). It was interpreted as increased REM sleep pressure and homeostasis dysregulation (Wetter et al., 2001). However, arousal contamination was not ruled out on those studies. A single study that investigated NREM sleep microstructure found reduced delta activity and a trend towards increased sigma activity in non-treated, early-stage PD patients compared to age-matched controls (Brunner et al., 2002). As sigma activity is related to sleep spindles (Steriade, 1993), this interesting finding stands in contrast with the verification of reduced NREM sleep spindle activity in the context of advanced PD with several non-motor complications (Comella et al., 1993).

The present study evaluated sleep EEG spectral patterns in newly diagnosed, non-depressed, non-demented, drug-naïve PD patients in comparison to age- and gender-matched controls, taking special care to avoid data contamination from EEG arousals, limb movements and obstructive respiratory events.

2. Methods

2.1. Patients and control subjects

PD outpatients who underwent investigation from May 2007 to June 2008 in a University-affiliated Movement Disorders Clinic in Southern Brazil were prospectively and consecutively enrolled. All subjects provided informed written consent and the study was approved by the local ethics committee. Selected patients had to fulfill United Kingdom Parkinson's Disease Society Brain Bank PD clinical diagnostic criteria (Hughes et al., 1992), including a positive response to l-dopa treatment. However, two polysomnography (PSG) studies (adaptation and baseline) were collected before initiation of therapy. Information on demographic variables, medication regimen, sleep symptoms and disease history was obtained through semi-structured interview for patients as well as controls. For both groups, exclusion criteria were Mini-Mental State Examination score below 24 (Folstein et al., 1975; Bertolucci et al., 1994), any form of previous PD treatment and presence of other neurological or psychiatric disorders, according to a DSM-IV-based structured clinical interview. No patient or control could be taking hypnotic drugs. Depressive symptoms were additionally assessed by Beck Depression Inventory (BDI) (Beck et al., 1961; Gorenstein and Andrade, 1996). Subjective sleep quality was evaluated by Pittsburgh Sleep Quality Inventory (PSQI) (Buysse et al., 1989; Bertolazi et al., 2011). Subjective sleepiness was assessed by the Epworth Sleepiness Scale (ESS) (Johns, 1991; Bertolazi et al., 2009). PD symptoms were scored according to Hoehn and Yahr modified version (HY) and Unified Parkinson's Disease Rating (UPDRS) scales (Hoehn and Yahr, 1967; Fahn et al., 1987). PD patients with respiratory and other sleep symptoms were included, but PSG studies showing apnea/hypopnea index (AHI) above 20 were excluded.

PSG data was initially collected from 14 patients. At the time of PSG recordings, PD patients were not taking, and had never taken, any dopaminergic drugs. Six patients were excluded due to subsequent absence of consistent levodopa response or early treatment interruption (2), failure to perform the second PSG (1), technical artifacts in PSG (1) and PSG showing AHI > 20 (2). Final patient analysis therefore pertains to eight subjects, identified as PD group. Five PD group patients had stable chronic medical conditions: systemic arterial hypertension (3), gastritis (1) and diabetes mellitus (1). They were taking enalapril (3), propranolol (3), aspirin (2), diuretics (2), digoxin (1), omeprazole (1) and metformin (1). One patient was in regular use of imipramine. One other patient took herbal teas to facilitate sleep on the weeks preceding sleep studies. On the basis of UPDRS-III (motor) scores, two patients had tremor-dominant, two had non-tremor dominant and four had mixed disease types. Two patients had unilateral involvement only (HY 1), three had unilateral and axial involvement (HY 1.5) and three had bilateral disease with no balance impairment (HY 2). Six patients had motor symptoms first noted on the left side. No patient had REM sleep behavior disorder (RBD) symptoms.

The Control (C) group consisted of nine non-PD volunteers with no PD first-degree relatives and no subjective sleep complaints (insomnia, daytime sleepiness, snoring, witnessed apnea or RBD symptoms). A tenth control subject was excluded from analysis due to PSG artifacts. Three control subjects reported systemic hypertension and one reported gastritis. They were taking captopril (1), propranolol (2), diuretics (1) and omeprazole (1).

2.2. Sleep studies

Subjects slept two nights in the sleep laboratory, in a quiet and dark room. The first night was considered as adaptation and the