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Slow wave sleep in the chronically fatigued: Power spectra distribution patterns in chronic fatigue syndrome and primary insomnia

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HIGHLIGHTS

- Evidence for similarly lower central ultra slow (US) delta power (0.3–0.79 Hz) proportions during slow wave sleep (SWS) in both primary insomnia and chronic fatigue syndrome in comparison to controls.
- Lower US power proportions relate mainly to perceived sleep quality impairment and daytime fatigue intensity.
- Clinical distinction between both conditions relates to a different frontal EEG power distribution during SWS in primary insomnia.

ABSTRACT

Objectives: To investigate slow wave sleep (SWS) spectral power proportions in distinct clinical conditions sharing non-restorative sleep and fatigue complaints without excessive daytime sleepiness (EDS), namely the chronic fatigue syndrome (CFS) and primary insomnia (PI). Impaired sleep homeostasis has been suspected in both CFS and PI.
Methods: We compared perceived sleep quality, fatigue and sleepiness symptom-intensities, polysomnography (PSG) and SWS spectral power distributions of drug-free CFS and PI patients without comorbid sleep or mental disorders, with a good sleeper control group.
Results: Higher fatigue without EDS and impaired perceived sleep quality were confirmed in both patient groups. PSG mainly differed in sleep fragmentation and SWS durations. Spectral analysis revealed a similar decrease in central ultra slow power (0.3–0.79 Hz) proportion during SWS for both CFS and PI and an increase in frontal power proportions of faster frequencies during SWS in PI only. The latter was correlated to affective symptoms whereas lower central ultra slow power proportions were related to fatigue severity and sleep quality impairment.
Conclusions: In combination with normal (PI) or even increased SWS durations (CFS), we found consistent evidence for lower proportions of slow oscillations during SWS in PI and CFS.
Significance: Observing normal or increased SWS durations but lower proportions of ultra slow power, our findings suggest a possible quantitative compensation of altered homeostatic regulation.

1. Introduction

Sleepiness and excessive daytime sleepiness (EDS) in particular have been related to non-restorative sleep (NRS) complaints and to impaired sleep homeostasis in primary sleep disorders (PSD) (Stone et al., 2008). However, even in the absence of EDS and of

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a comorbid PSD, chronic fatigue syndrome (CFS) and primary insomnia (PI) patients also systematically complain of NRS (Wilkinson and Shapiro, 2012). In addition, given that chronic daytime fatigue and EDS are different phenomena both related to NRS complaints, it seems in turn unlikely for their respective relations to sleep being of the same nature (Neu et al., 2014).

Chronic fatigue is known to be different from EDS. In contrast to sleepiness or EDS, its relationships to sleep remain disputed. Chronic fatigue has been described as being associated to systemic disorders and being independent from primary sleep disorders (Hossain et al., 2005; Neu et al., 2010a). The chronic fatigue syndrome (CFS) is a nosographically described exclusionary syndrome without known etiology. Its main symptoms feature chronic fatigue, without EDS and not alleviated by rest, effort intolerance or post-exertion malaise and complaints of non-restorative sleep (NRS) or un-refreshing morning arousals. NRS is systematically reported in CFS despite adequate and stable timing of sleep periods and even despite the absence of sleep maintenance difficulties or other identifiable PSD based on polysomnographic (PSG) recordings. The latter is sometimes referred to 'pure' CFS patients (i.e. without PSD and without EDS) (Neu et al., 2007, 2008; Mariman et al., 2013). Additional symptoms comprise flu-like symptoms, diffuse muscle or joint pain and cognitive complaints. Previous study results about sleep in CFS reported similar (Majer et al., 2007) or increased SWS (Kishi et al., 2011; Neu et al., 2009), higher NREM alpha power (Moldofsky et al., 1975), lower delta power (Decker et al., 2009) or increased relative delta power during SWS (Guilleminault et al., 2006) and idiopathic micro-arousals (Neu et al., 2008; Le Bon et al., 2012). Most discrepancies among these studies can be attributed to methodological issues, mainly concerning exclusion criteria for comorbid PSDs or to different approaches in assessing spectral power (Mariman et al., 2013; Le Bon et al., 2012). At last, a possible dysfunction of sleep homeostasis in CFS has previously been suggested in a report about CFS-discordant twins. The latter showed a failure of adequate homeostatic response after sleep deprivation in the CFS-diagnosed twins only (Armitage et al., 2007). Moreover, a central decrease of slow oscillation (<1 Hz) spectral power (referred to as ultra slow delta or US) in comparison to healthy controls (Le Bon et al., 2012) and to a PSD (Neu et al., 2014) extended the hypothesis about a potential homeostatic dysfunction in two independent samples of CFS without EDS and without PSD. However, it remains unclear whether lower US power during SWS is a common phenomenon associated to chronic fatigue in general or is solely related to etiopathogenesis of CFS.

PI is also essentially a syndrome, based on complaints of sleep initiation or maintenance difficulties, possible early morning awakenings and complaints of NRS (Moul et al., 2002) and daytime fatigue (Yang et al., 2009; Valko et al., 2008). Conceptual description of PI has mainly focused on hyperarousal following a neurocognitive model comprising physiological arousal and cognitive arousal. Consecutively, previous PSG studies mainly reported increased power in higher sleep-EEG frequency bands (i.e. sigma, beta) in PI (Feige et al., 2013; Spiegelhalder et al., 2012; Cervena et al., 2013). Nevertheless, there is currently also sufficient evidence suggesting dysfunction of sleep homeostasis in PI (Pigeon and Perlis, 2006). Pigeon and Perlis (2006) described several lines of evidence for homeostatic dysfunction in a recent review about PI: lower increase or rebound of SWS than controls after sleep deprivation, reduced SWS pressure, reduced delta power without reduced SWS duration, longer SWS-latencies, normal or even decreased objective daytime sleepiness as measured by multiple sleep latency tests (MSLTs), less sleepiness than controls after sleep deprivation and differences of sleep stage proportion increases during recovery after total sleep deprivation. Hence, PI is therefore also a valid model of daytime fatigue which is not EDS (lower sleep pressure, difficulties of sleep initiation despite complaints of insufficient sleep or NRS). Disregarding a prior report mentioning decreased low-frequency and increased higher frequency NREM EEG in subjective insomnia (Krystal et al., 2002), a specific reduction of NREM sleep slow oscillations has however currently only been described in a case report of fatal familial insomnia (Gemignani et al., 2012).

In contrast to currently prevailing assumptions of chronic daytime fatigue being rather independent from sleep or presenting at least with more indirect relations to sleep than daytime sleepiness, it might therefore well be that chronic fatigue which is not sleepiness presents with associated impaired sleep homeostasis, at least in certain clinical conditions.

Thus, based upon these insights about sleep complaints' related chronic daytime fatigue without sleepiness in CFS and in PI and potential homeostatic dysfunction, we hypothesize that different chronic daytime fatigue associated conditions present with potentially similar dysfunction in sleep homeostasis with respect to slow wave activity (SWA). As such, lower US power during SWS might be associated to chronic fatigue in different conditions irrespective of syndromic definition, nosography or even etiology. In contrast to sleep-resolving sleepiness, the latter might therefore indicate a possible common underlying pathophysiology of sleep related maintenance of chronic daytime fatigue that does not resolve with sleep.

2. Methods

2.1. Setting

The present study was carried out in a population assigned to a general university hospital's sleep laboratory. Inclusion of subjects was based on clinical and technical selection criteria (see below) and the results of a full night polysomnographic recording (PSG).

2.2. Participants

CFS patients and control subjects were in large parts similar to a previous study sample described in detail elsewhere (Neu et al., 2014). Based on PSG recordings, medical files and demographical data, PI patients were carefully selected on a retrospective basis, in order to correspond as close as possible with the two other groups. CFS patients were recruited according to CDC diagnostic criteria (Fukuda et al., 1994) without co-morbid mental disorders or PI according to DSM IV criteria (APA, 2000) and after exclusion of a primary sleep disorder (PSD). Further inclusion criteria for all subjects were a minimum time in bed (TIB) of 300 min and a minimum total sleep time (TST) of 240 min during a full night PSG. All included subjects were free from hypnotics or other relevant neuropsychopharmacological treatment (including antidepressants) for at least 3 weeks prior to recording. Further exclusion criteria were significant co-morbid or overlapping medical conditions (including major depression, bipolar or psychotic disorders) potentially interfering with the above-mentioned daytime conditions and inclusion diagnoses, and treatment essays under PSG recording or any co-morbid sleep disorders. All patients in our lab completed questionnaires about life style and drinking habits. Patients with a consumption of more than two units of alcohol per day were excluded.

Both patient groups were compared to a good sleeper control (GSC) group without NRS, from locally recruited healthy volunteers. They were paid between 100 and 150 Euros by private funding for their participation. Regular sleep-wake schedules were required and shift work was not allowed. No significant somatic condition and no current or past mental disorder were allowed

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