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Low-resolution brain electromagnetic tomography (LORETA) identifies brain regions linked to psychometric performance under modafinil in narcolepsy

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Abstract

Low-resolution brain electromagnetic tomography (LORETA) showed a functional deterioration of the fronto-temporo-parietal network of the right hemispheric vigilance system in narcolepsy and a therapeutic effect of modafinil. The aim of this study was to determine the effects of modafinil on cognitive and thymopsychic variables in patients with narcolepsy and investigate whether neurophysiological vigilance changes correlate with cognitive and subjective vigilance alterations at the behavioral level. In a double-blind, placebo-controlled crossover design, EEG-LORETA and psychometric data were obtained during midmorning hours in 15 narcoleptics before and after 3 weeks of placebo or 400 mg modafinil. Cognitive investigations included the Pauli Test and complex reaction time. Thymopsychic/psychophysiological evaluation comprised drive, mood, affectivity, wakefulness, depression, anxiety, the Symptom Checklist 90 and critical flicker frequency. The Multiple Sleep Latency Test (MSLT) and the Epworth Sleepiness Scale (ESS) were performed too. Cognitive performance (Pauli Test) was significantly better after modafinil than after placebo. Concerning reaction time and thymopsychic variables, no significant differences were observed. Correlation analyses revealed that a decrease in prefrontal delta, theta and alpha-1 power correlated with an improvement in cognitive performance. Moreover, drowsiness was positively correlated with theta power in parietal and medial prefrontal regions and beta-1 and beta-2 power in occipital regions. A less significant correlation was observed between midmorning EEG LORETA and the MSLT; between EEG LORETA and the ESS, the correlation was even weaker. In conclusion, modafinil did not influence thymopsychic variables in narcolepsy, but it significantly improved cognitive performance, which may be related to medial prefrontal activity processes identified by LORETA.

Keywords: Sleepiness; Psychostimulant; Electroencephalography; Cognition; Prefrontal activity

1. Introduction

Neuroimaging studies, including positron emission tomography (PET) (Wu et al., 1991; Thomas et al., 2000) and functional magnetic resonance imaging (FMRI) (Portas et al., 1998), suggest that activity levels

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in brain systems involved in arousal and attention may influence cognitive performance following total sleep deprivation (TSD). The serial addition/subtraction task used by Thomas et al. (2000) required both arithmetic working memory and attentional resources, and it showed decreased activation in related regions such as the prefrontal cortex, the inferior parietal lobe and the anterior cingulate gyrus. This suggests that brain regions involved in working memory and arithmetic might be vulnerable to vigilance alterations.

In narcolepsy, excessive daytime sleepiness (EDS) is the most disabling feature at the behavioral level and responsible for an overall disruption of normal daytime functioning (Overeem et al., 2001). At the neurophysiological level, it is based on a deterioration of vigilance. Vigilance has been defined as the availability and grade of organization of man's adaptive behavior, which is in turn dependent upon the dynamic state of the neuronal network (Head, 1923). Since the early 1980s, several studies have attempted to demonstrate the relationship between sleepiness and cognitive performance in narcoleptic subjects (Broughton et al., 1982; Aguirre et al., 1985; Levander and Sachs, 1985; Godbout and Montplaisir, 1986; Ollo et al., 1987; Rogers and Rosenberg, 1990; Pollack et al., 1992; Smith et al., 1992; Henry et al., 1993). The findings obtained generally failed to demonstrate significant performance differences to controls and remained inconclusive in the question of whether performance decrements in narcolepsy are explained by attentional or organic cognitive mechanisms.

Investigations using functional neuroimaging techniques, including PET (Cohen et al., 1988; Buchsbaum et al., 1990; Pardo et al., 1991), single photon emission computed tomography (SPECT) (Rezai et al., 1993) and regional cerebral blood flow (rCBF) (Roland and Friberg, 1985; Deutsch et al., 1987; Posner and Petersen, 1990; Pardo et al., 1991), concluded that the right hemisphere (and in particular the right parietal, temporal and prefrontal regions) plays a prominent role in the maintenance of a vigilance state (Posner and Petersen, 1990). In the last decade, electrophysiological neuroimaging techniques such as EEG low-resolution brain electromagnetic tomography (LORETA) were developed to identify brain regions that are involved in neuropsychiatric disorders and are the targets of therapeutic drug action (Pascual-Marqui et al., 1999; Saletu et al., 2002; Weber et al., 2005).

Modafinil is a central wake-promoting psychostimulant with a lower risk of CNS, cardiovascular or gastrointestinal adverse events, abuse and dependence (Mitler et al., 2000). As early as in 1986, the first human pharmaco-EEG studies in normal elderly subjects demonstrated a vigilance-promoting effect of modafinil (CRL 40476), characterized by an increase in alpha and slow beta activity and a decrease in delta, theta and very fast beta activity as compared with placebo, which was also demonstrated behaviorally by psychometry (Saletu et al., 1986) and confirmed later by clinical trials in alcoholic organic brain syndrome (Saletu et al., 1993). The efficacy, safety and tolerability of modafinil in narcolepsy patients have been demonstrated in controlled trials (US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). In a recent study, LORETA objectified a functional deterioration of the fronto-temporo-parietal network of the right hemispheric vigilance system in narcolepsy and a therapeutic effect of modafinil on the left hemisphere, which is less affected by the disease (Saletu et al., 2004).

The aim of the present study was (1) to examine the effects of modafinil compared with placebo on cognitive performance and thymopsychic variables in narcoleptic patients, (2) to correlate significant and clinically relevant psychometric changes in midmorning hours with neurophysiological alterations measured by EEG LORETA at the same time, and (3) to explore the relation between these EEG-LORETA findings and MSLT results reflecting objective sleepiness over 1 day as well as ESS data indicating subjective sleepiness over a period of 1 week.

2. Methods

2.1. Study design, patients, and inclusion and exclusion criteria

In the double-blind, placebo-controlled crossover study, 16 drug-free patients (10 males, 6 females; aged 21–59 years; mean age 39.1±13.3 years; all right-handed) with the ICD-10 diagnosis of narcolepsy (G 47.4) were included. Fifteen completed the study; one patient had to be excluded because of noncompliance with the protocol requirements (did not appear for scheduled visits).

Screened patients complaining of excessive daytime sleepiness first underwent neuropsychiatric, physical and laboratory examinations (including HLA typing for DQB1*0602 or dopamine receptor 2 positivity) and then spent 2 recording nights in the sleep laboratory (adaptation and baseline night).

Inclusion criteria called for patients of either sex, satisfying the criteria of the International Classification of Sleep Disorders (ICSD) (American Sleep Disorders Association, 1997) for narcolepsy. In addition, the