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Cholinergic modulation of MEG resting-state oscillatory activity in Parkinson's disease related dementia

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ABSTRACT

Objective: EEG and MEG studies in Parkinson's disease (PD) related dementia (PDD) have shown a slowing of resting-state, oscillatory activity compared to non demented PD. Aim of the present MEG study was to determine whether treatment with the cholinesterase inhibitor rivastigmine would reverse this slowing of resting-state activity in PDD patients.
Methods: In eight PDD patients, whole head MEG was recorded in a resting-state condition before and after treatment with rivastigmine. Relative spectral power was calculated in the delta, theta, alpha, beta and gamma frequency bands in fronto-central, parieto-occipital and temporal regions.
Results: After treatment with rivastigmine, PDD patients demonstrated an increase in relative power in the alpha range in parieto-occipital and temporal regions together with a diffuse increase in beta power. Furthermore, a decrease of delta power in fronto-central and parieto-occipital regions was found.
Conclusions: Treatment with the cholinesterase inhibitor rivastigmine at least partly counteracts the slowing of resting-state brain activity that is known to occur in PD related dementia.
Significance: Our observations emphasize the prominent role of degeneration of the cholinergic system in the pathophysiology of dementia in PD. In the future, MEG might contribute to the selection of PD patients who may optimally benefit from cholinergic treatment.

1. Introduction

Dementia develops in up to 60% of patients suffering from Parkinson's disease (PD) (Buter et al., 2008) and contributes significantly to the impairment of the quality of life and to caregiver distress. Parkinson's disease related dementia (PDD) mainly consists of a prominent dysexecutive syndrome together with memory complaints and is often accompanied by psychotic symptoms, mainly visual hallucinations (Emre et al., 2007). The pathophysiological mechanisms of cognitive dysfunction and dementia in PDD are still poorly understood. Although the loss of nigrostriatal and corticopetal dopaminergic (and serotonergic and noradrenergic) projections systems may contribute to the development of dementia in PD, it is generally believed that additional mechanisms are probably involved, most notably degeneration of cholinergic cortical projections and/or local cortical Lewy body- and tau-pathology (For review, see (Bosboom et al., 2004)).

EEG studies have demonstrated a slowing of background oscillatory activity in PDD patients (Neufeld et al., 1988, 1994; Soikkeli et al., 1991; Tanaka et al., 2000), correlating with the degree of mental impairment. Recently, using relative power spectral analysis of resting-state magneto encephalography (MEG) data, we found a qualitatively different pattern of slowing of background activity in demented compared to non demented patients (Bosboom et al., 2006). Whereas in PD without dementia an increase in theta and a decrease of beta power were found compared to healthy controls, in PDD an additional increase of relative delta power and a decrease of alpha band power could be demonstrated relative to the non demented patients, supporting the assumption that different or at least additional pathophysiological mechanisms are involved in the development of PDD.

Animal as well as human studies have demonstrated that the cholinergic system has a modulatory influence on cortical brain rhythms. Cholinergic stimulation mainly results in a shift in the power spectrum towards faster frequencies, whereas interference with cholinergic function leads to an increase in slow wave activity (Buzsaki et al., 1988; Detari and Vanderwolf, 1987; Dringenberg et al., 2000; Ebert and Kirch, 1998; Osipova et al., 2003; Ray and Jackson, 1991; Ricceri et al., 2004; Riekkinen et al., 1991). Considering the presence of a cholinergic deficit in PD, this would suggest that a hypofunctional cholinergic system might be responsible for

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the observed slowing of background oscillatory activity in PDD. Along this line of reasoning, it seems likely that treatment aimed at restoring cholinergic function would at least partly reverse the observed slowing of background activity in PDD.

To date, treatment with cholinesterase inhibitors is the only proven, albeit symptomatic treatment for PDD. The same holds for Alzheimer's disease (AD), like PDD characterized by prominent cholinergic deterioration. The action of cholinesterase inhibitors is aimed at increasing cholinergic brain activity by interfering with the function of the enzyme acetyl (and/or butyryl) cholinesterase, responsible for the breakdown of acetylcholine in the brain. In AD, several cholinesterase inhibitors such as rivastigmine, galantamine and donepezil, were found to be (equally) effective in the treatment of mild to moderate AD (for review see (Birks, 2006)). In PDD, a number of open label studies and a randomized, placebo-controlled, multicenter study with rivastigmine have shown beneficial effects on cognitive function as well as on psychotic symptoms (Bullock and Cameron, 2002; Burn et al., 2006; Emre et al., 2004; Reading et al., 2001; Rowan et al., 2007; Wesnes et al., 2005).

In AD patients, treatment with cholinesterase inhibitors is associated with a decrease of low frequency EEG activity (Adler and Brassen, 2001; Adler et al., 2004; Brassen and Adler, 2003; Gustafson et al., 1987; Jelic et al., 1998; Kogan et al., 2001). In PDD, however, the effects of increasing cholinergic tone on changes in cortical rhythmic activity are largely unknown. In an EEG study, Fogelson et al. found a diffuse increase in relative alpha amplitude after 12 weeks of treatment with rivastigmine, but significant changes in other frequency bands could not be demonstrated (Fogelson et al., 2003). MEG studies in patients are as of yet not available. In non demented patients, we demonstrated slowing of resting-state oscillatory activity already in the earliest (Stoffers et al., 2007) as well as more advanced stages of disease (Bosboom et al., 2006), which has not been convincingly reported in previous EEG studies (Sinanovic et al., 2005; Gagnon et al., 2004; Tanaka et al., 2000; Neufeld et al., 1994, 1988; Soikkeli et al., 1991).

The aim of this study was to study the effects of treatment with the cholinesterase inhibitor rivastigmine on spectral power distribution in PDD patients using MEG. Our hypothesis was that treatment with rivastigmine would result in (partial) reversal of the slowing of background oscillatory activity that is a characteristic of PDD.

2. Materials and methods

2.1. Subjects

A group of eight demented PD patients was studied immediately before and after a mean period of 29.3 weeks (range 19–48 weeks) of ongoing treatment with the cholinesterase inhibitor rivastigmine. Seven patients participated in a large double-blind, randomized, placebo-controlled trial with rivastigmine (Emre et al., 2004), one patient was treated in an open label setting. All patients underwent a full physical and neurological examination and fulfilled the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDSBB) clinical diagnostic criteria for probable Parkinson's disease (Gibb, 1988) as well as the DSM-IV criteria (American Psychiatric Association, 1994) for dementia. Each patient had a Mini Mental State Examination (MMSE) score (Folstein et al., 1975) of 24 or lower out of a maximum of 30 points, with lower scores indicating worse cognition. Blood examination and MR-imaging were performed to exclude other potential causes of dementia. Additional cognitive assessment consisted of the cognitive section of the CAMDEX: the CAMCOG (Roth et al., 1986). A total of 107 points is the maximal score on this test with higher scores indicating better cognition.

Disease stage and severity were assessed using the (modified) Hoehn & Yahr-scale (H&Y; range 0–5 with higher scores indicating more advanced disease stage) (Jankovic et al., 1990) and the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS; range 0–108 with higher scores indicating worse motor functioning) (Fahn et al., 1987), respectively. Exclusion criteria for PD patients consisted of stereotactic surgery in the past and the use of anticholinergics, neuroleptics or cholinesterase inhibitors.

All patients were treated with a combination of levodopa and a decarboxylase inhibitor and six patients were treated with a dopamine agonist as well. The study protocol was approved by the medical ethical committee of the VU University Medical Center. After careful explanation of the procedures, all subjects gave written informed consent prior to participating.

2.2. MEG-procedures

MEG-data were acquired using a 151 channel whole head MEG system (CTF Systems Inc., Port Coquitlam, BC, Canada), with patients seated in a magnetically shielded room (Vacuum-schmelze GmbH, Hanau, Germany). Both the baseline and the follow up MEG recording were performed in a no task, eyes closed, resting-state condition, approximately one hour after patients had taken their first morning dose of antiparkinsonian medication.

The recording pass band was 0–125 Hz with a sample rate of 312.5 Hz. A third-order software gradient was applied. Two approximately 13 s long artifact-free epochs (sample rate 312.5 Hz; 4096 samples) were selected for further analysis. Epoch selection was always done by the same investigator (JLWB), who was blinded for the time of measurement (baseline or follow up). MEG-recordings were filtered offline with a band pass of 1–48 Hz.

Relative band power of every MEG channel was computed for the two 13 s epochs in the following frequency bands: 1–4 Hz (delta), 4–8 Hz (theta), 8–13 Hz (alpha), 13–30 Hz (beta) and 30–48 Hz (gamma). Results of the two epochs were averaged for each subject.

To reduce the number of comparisons before and after treatment, the MEG channels were clustered into three regions of interest: fronto-central, parieto-occipital and temporal (Fig. 1). Mean relative spectral power in these clustered groups of MEG channels was used in the statistical analysis. The midline channels (Z) were left out of this clustering. Of the original 151 channels, one channel (MLO41) was not available due to technical problems.

2.3. Statistical analysis

2.3.1. Demographics

Differences between the baseline and follow up measurement in the distribution of (modified) Hoehn and Yahr (1967) scores were analyzed by means of χ^2-tests. Analyses with regard to within-subject changes from baseline to follow up in UPDRS motor scores and CAMCOG and MMSE scores were analyzed using the Wilcoxon signed rank test.

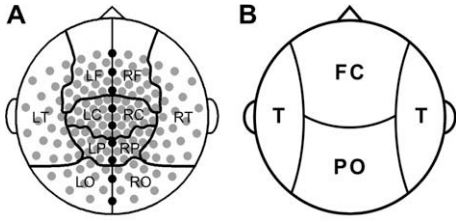

Fig. 1. (A) Schematic representation of the distribution of individual MEG sensors. (B) Schematic representation after clustering into three regions of interest, which were used in the statistical analysis.