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Effects of rivastigmine on visual attention in subjects with amnestic mild cognitive impairment: A serial functional MRI activation pilot-study

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ABSTRACT

A pilot study to investigate the effects of rivastigmine on the brain activation pattern due to visual attention tasks in a group of amnestic Mild Cognitive Impaired patients (aMCI). The design was an initial three-month double blind period with a rivastigmine and placebo arms, followed by a nine-month open-label period. All patients underwent serial functional magnetic resonance imaging (fMRI) at baseline, and after three and six months of follow-up. Primary endpoint was the effect of rivastigmine on functional brain changes during visual attention (face and location matching) tasks. There were five in the rivastigmine arm and two in the placebo arm.

The face matching task showed higher activation of visual areas after three months of treatment but no differences compared to baseline at six months. The location matching task showed a higher activation along the dorsal visual pathway at both three and six months follow ups.

Treatment with rivastigmine demonstrates a significant effect on brain activation of the dorsal visual pathway during a location matching task in patients with aMCI. Our data support the potential use of task fMRI to map specific treatment effects of cholinergic drugs during prodromal stages of Alzheimer's disease (AD).

1. Introduction

Cholinesterase-inhibitor therapy is currently approved as a treatment for the mild to moderate stages of Alzheimer's disease (AD) dementia. The potential beneficial use in patients with mild cognitive impairment (MCI) or prodromal AD, however, is still an unresolved issue and awaits evidence-based confirmation using improved clinical trial designs. Over the last few years, the identification of potentially efficacious compounds for treatment during the earlier stages of AD and cognitive decline has been advanced. In this context, a general scientific consensus has been reached on suitable functions of magnetic resonance imaging (MRI) biomarkers for improving novel drug development and discovery (Merlo Pich et al., 2014). Several neuroimaging studies report evidence of statistically significant effects of cholinesterase inhibitors on in vivo neuroimaging markers in memory impaired individuals (Apostolova et al., 2013; Dubois et al., 2015; Goekoop et al., 2004, 2006; Jack et al., 2008; Miettinen et al., 2011; Petrella et al., 2009; Risacher et al., 2013; Saykin et al., 2004; Schuff et al., 2011).

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In addition to the memory impairments that are characteristic of MCI and AD patients, early work in AD also found impairments in attention (Baddeley et al., 1986; Greenwood et al., 1997; Parasuraman et al., 2000, 1992) and recent work has extended the findings to MCI (Alegret et al., 2009; Bublak et al., 2011; Okonkwo et al., 2008; Saunders and Summers, 2011). The characteristics of the impairment in MCI are in deficits in complex visual-perceptual perception (Alegret et al., 2009), in pre-attentive visual processing in MCI followed by attentive processing in mild AD patients (Bublak et al., 2011). Further support for attentional deficits in MCI was found by Okonkwo et al. (2008) where they tested MCI for impairments in simple, divided and selective attention, and found that greatest number of MCI patients were impaired in divided attention while impairments in simple attention were present in the fewest MCI patients. Another study that examined amnestic MCI (aMCI) and non-amnestic MCI (naMCI) patients found that over a 10 month period there was a significant decline in divided attention in the aMCI group whereas there was decline in sustained attention in both naMCI and aMCI groups (Saunders and Summers, 2011). The effects in the attentional domain have been found not only in MCI but also in healthy non-demented middle and older individuals that carry the *APOE ε4* allele, where *APOE ε4* carriers had decreased performance in redirecting visuospatial attention, retention of memory for location, and attentional modulation of memory of target location (Greenwood et al., 2005, 2000). At the same time that different attentional impairments domains are being detailed in various risk groups, the neurochemical innervation are also being investigated (Davidson and Marrocco, 2000; Witte et al., 1997). Lesions of the cholinergic system in monkeys led to impairments of attention but not memory and learning (Voytko et al., 1994).

Various studies have examined the effect of acute cholinergic enhancement using physostigmine in AD patients. They have found selective increases in activation in the perceptual areas during the encoding phase in working memory (Petrella et al., 2009); moreover, activation in the visual cortex was modulated across a range of attentional and memory tasks (Bentley et al., 2008, 2004; Furey et al., 2000c, 1997, 2008). During periods of high attentional demand, acetylcholine is diffusely released throughout the neocortex to modulate processing in the visual cortices and in parietal and frontal lobe (Sarter and Bruno, 1997). Cholinergic input to visual cortex has been shown to sharpen stimulus representations through a combination of signal amplification and noise suppression (Sato et al., 1987). The objective of this study was to perform a pilot study to investigate the effects of rivastigmine on the brain activation pattern due to visual attention tasks in a group of aMCI patients. The design was an initial three-month double blind period with rivastigmine and placebo arms, followed by a nine-month open-label period. All patients underwent serial functional magnetic resonance imaging (fMRI) at baseline, and after three and six months of follow-up. Primary endpoint was the effect of rivastigmine on functional brain changes during visual attention (face and location matching) tasks. Of interest also was the feasibility of performing such a study over a 1 year period that included multiple neuroimaging scans. To our knowledge, this is the first open-label study investigating the effect of cholinergic treatment with rivastigmine on brain activation changes during a visual perception fMRI task in MCI patients.

2. Methods

2.1. Patients

A total of 12 aMCI patients diagnosed according to Petersen criteria (Petersen et al., 2001) were enrolled in study at an academic expert memory clinic and were randomly assigned to either verum or placebo arm (2/3 probability into the verum arm). Five patients in the verum arm and two patients in the placebo arm completed the study. Of the 3 patients in the verum arm that did not complete study one discontinued during double blind phase and 2 discontinued during open label phase. There were four patients assigned into placebo arm, one discontinued during the placebo phase, the second one discontinued during the open label phase. The results from the placebo arm will not be presented due to small numbers. Any comorbidity, such as cerebrovascular disease, was excluded by medical history, EEG, ECG, psychiatric evaluation, laboratory tests, and MRI examination. The study was approved by the Ethics Review Board of the Faculty of Medicine of the Ludwig-Maximilian-University, Munich, Germany. All patients signed a consent form after the study was explained to them. The study was performed from August 2002 to June 2006. The subjects included in this study overlap with those of previous publications and the overlap is only with the baseline measurements (Bokde et al., 2008, 2006).

2.2. Design

The design of the study was one year in length with an initial three months double-blind phase where the participants received either rivastigmine or placebo. After the initial phase, all patients received rivastigmine (open label) for nine months. The titration for the Rivastigmine was 3 mg/day in the first month, 6 mg/day in the second month, and 9 mg/day in the third month, in two daily doses. All patients remained at 9 mg/day until end of the study. In the open label phase, all patients underwent the above reported titration process.

The primary outcome variables were represented by the fMRI measured brain activation changes; the secondary outcome variables were represented by the neuropsychological measures. Notably, the practicality of performing a drug-fMRI study over one-year period was also investigated.

At entry into the study, all patients underwent the fMRI tasks and psychometric assessment. The CERAD (Consortium to Establish a Registry for Alzheimer's Disease) test battery was carried out to detect the neuropsychological performance. The fMRI cognitive tasks were performed at entry, three months (end of the double blind phase), and six months after the inclusion in the study. The CERAD battery was performed on the entire sample on the same day of fMRI scans (baseline, 3 months, 6 months) and 1 year follow-up from baseline.

2.3. Stimuli and tasks

The two tasks were a face and location matching task with a common control task (Bokde et al., 2008). The face matching task consisted of two faces presented simultaneously and participants were asked to decide on each trial if a pair of faces was identical or not. If they were, the subject had to respond by pressing a button in the right hand. No response was required if the faces were dissimilar. The faces were grey scale stimuli where only the face was visible. Each trial was 2.8 s long with an interval between pairs of faces of 0.318 s. There were 8 trials per block and there were 3 blocks of the task in each run (each block was 24.944 s long). The number of matched pair of faces was 80%. The faces are from the Max Planck Institute for Biological Cybernetics database (Blanz and Vetter, 1999). All the faces were seen only once by the study subject except in trials were both faces matched.

The location matching task consisted of two abstract images located within a smaller square. The smaller square was located within a large square. The subject had to decide if the relative location of the small square relative to the larger one was the