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Brain perfusion during rapid-eye-movement sleep successfully identifies amnestic mild cognitive impairment

Pauline Brayet [a, b], Dominique Petit [b], Andrée-Ann Baril [b, c], Nadia Gosselin [b, d], Jean-François Gagnon [a, b], Jean-Paul Soucy [e, i], Serge Gauthier [f], Marie-Jeanne Kergoat [c, g], Julie Carrier [b, d], Isabelle Rouleau [a, h], Jacques Montplaisir [b, c, *]

[a] Department of Psychology, Université du Québec à Montréal, Montréal, Canada
[b] Center for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur de Montréal, Montréal, Canada
[c] Faculty of Medicine, Université de Montréal, Montréal, Canada
[d] Department of Psychology, Université de Montréal, Montréal, Canada
[e] Montreal Neurological Institute, McGill University, Montréal, Canada
[f] McGill University Research Centre for Studies in Aging, Douglas Hospital, Verdun, Canada
[g] Research Center, Institut universitaire de gériatrie de Montréal, Montreal, Canada
[h] Neurology Service, Hôpital Notre-Dame du CHUM, Montréal, Canada
[i] PERFORM Centre, Concordia University, Montréal, Canada

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ABSTRACT

Introduction: Prodromal markers of Alzheimer's disease (AD) have been derived from wakefulness. However, brain perfusion during rapid-eye movement (REM) sleep could be a sensitive marker of amnestic mild cognitive impairment (aMCI), as activation of REM sleep relies more on the cholinergic system.
Methods: Eight subjects with aMCI, and 16 controls, underwent two single-photon emission computed tomography (SPECT) scans with tracer injected during REM sleep then wakefulness.
Results: Perfusion in the anterior cingulate cortex was significantly decreased in aMCI cases compared to controls for both conditions. That defect was much larger and more severe in REM sleep (1795 voxels) compared to wakefulness (398 voxels), and extended to the middle cingulate cortex and the olfactory cortex. Hypoperfusion in the anterior cingulate cortex during REM sleep allowed better classification than hypoperfusion found in wakefulness (93.8 vs 81.3%).
Conclusion: REM sleep imaging is a valuable tool with which to identify individuals at risk of developing AD.

1. Introduction

Several studies have looked at markers of incipient Alzheimer's disease (AD) in mild cognitive impairment (MCI) subjects, including: quantitative electroencephalography (qEEG); and several structural and functional brain imaging techniques such as magnetic resonance imaging (MRI), beta-amyloid and fluorodeoxyglucose (FDG), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). Despite positive results, those qEEG and imaging markers have failed to reliably predict the conversion to AD in MCI subjects at an individual level [1,2].

Most of these prodromal markers of AD have been derived from studies in the awake state. There are several reasons for believing that studying individuals during a particular stage of sleep – rapid eye movement (REM) – may be more sensitive and specific for early detection of incipient AD. REM sleep is a state characterized by cortical activation, which recurs every 80–90 min throughout the night with noticeable lengthening toward the end of the night. The percentage of this sleep stage, which usually remains stable throughout aging, has been shown to decrease in tandem with cognitive decline [3]. REM sleep could be of high interest for research in AD because it is characterized by a predominance of

* Corresponding author. Center for Advanced Research in Sleep Medicine, Hôpital du Sacré-Cœur de Montréal, 5400 boul. Gouin Ouest, Montréal, Québec, H4J 1C5, Canada. Fax: +1 514 338 3893.
E-mail address: jy.montplaisir@umontreal.ca (J. Montplaisir).

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cholinergic neuronal activity accompanied by an inhibition of several other neuronal systems that are typically active during wakefulness. In fact, while cortical activation during wakefulness is assured by several systems, that of REM sleep depends mostly on cholinergic and glutamatergic neurons [4,5]. The cholinergic system is therefore "unmasked" during REM sleep compared to wakefulness. Since cholinergic systems degenerate early in AD (even in the MCI stage) [6], investigation of individuals during REM sleep may have considerable additional value in identifying cholinergic dysfunctions in amnestic MCI (aMCI) subjects or prodromal AD. Based on this rationale, it has previously been shown that qEEG during REM sleep, more than qEEG performed during wakefulness, distinguishes aMCI subjects from both non-amnestic MCI (naMCI) subjects and normal controls [7]. Electroencephalogram (EEG) slowing in REM sleep, but not in wakefulness, has been correlated with other markers of neurodegeneration in early AD, such as global cognitive impairment and the interhemispheric asymmetry of cerebral blood flow assessed by SPECT [8,9]. Despite having shown the superiority of REM sleep over wakefulness for detection of prodromal or early AD, this surface EEG technique is not sensitive enough to identify aMCI subjects on an individual basis.

In the present study, the objective was to determine whether brain perfusion (which assesses both cortical and sub-cortical regions) measured during REM sleep could be a more sensitive marker of aMCI among older individuals compared to brain perfusion performed during wakefulness. To evaluate brain perfusion, single-photon emission computed tomography (SPECT) measuring regional cerebral blood flow (rCBF), a functional nuclear imaging technique, was performed. Because rCBF is closely linked to neuronal activity, its distribution level is presumed to reflect neuronal activity intensity in different areas of the brain. To assess REM sleep brain perfusion, SPECT is a better technique than PET, since it captures the state at the time of the radiotracer injection and the images can be acquired later, allowing subjects to sleep in a normal bed instead of the scanner [10]. Because REM sleep mostly involves cholinergic activity, it was hypothesised that brain perfusion using SPECT during REM sleep would better discriminate aMCI individuals from healthy subjects.

2. Methods

2.1. Sample

Participants aged 65–85 years and with at least seven years of schooling were included in this study. Most participants were recruited as controls by advertisements in a local newspaper. Neurologists referred two aMCI subjects. The following conditions were considered exclusion criteria: presence of dementia according to the DSM-5 criteria, sleep apnea syndrome, narcolepsy, REM sleep behavior disorder, major psychiatric disorders, alcohol or drug abuse, history of stroke or brain injury, uncontrolled hypertension or diabetes, chronic obstructive pulmonary disease, brain tumor, encephalitis or EEG abnormalities suggestive of epilepsy. In all, 80 participants underwent a neuropsychological evaluation, questionnaires and polysomnography (PSG) recording. The injection during REM sleep and subsequent data acquisition was successful in 47 (59%) of the participants. Of them, 19 (40%) were found to have sleep apneas on the PSG (ie, >15 apneas-hypopneas per hour of sleep) and were excluded. Participants were divided in three groups based on their neuropsychological assessment: with memory impairments (aMCI group), with cognitive dysfunctions but without significant memory impairment (non-amnestic MCI group), and without cognitive deficits (control group). Non-amnestic MCI subjects were excluded. As a result, 24 participants were included in the final sample: eight with aMCI (four women, four men; mean age: 75.0 ± 6.2 years) and 16 healthy controls (10 women, six men; mean age: 71.3 ± 4.3 years). The hospital's ethics committee approved the research protocol and all participants gave written informed consent.

2.2. Procedures

Subjects filled out questionnaires, participated to a complete neuropsychological assessment, underwent a night of PSG, and had two high-resolution SPECT rCBF sessions: one with the radiotracer injected during REM sleep and the other during wakefulness. A blood sample was collected to assess participants' apolipoprotein E (APOE) polymorphisms.

2.2.1. Questionnaires

The Epworth Sleepiness Scale was used to document subjective daytime sleepiness [11]. Depression and anxiety symptoms were assessed using the Beck Depression Inventory-II and the Beck Anxiety Inventory [12,13].

2.2.2. Neuropsychological assessment and aMCI diagnosis

The cognitive abilities of all participants were assessed using a battery of neuropsychological tests and a structured interview. Five cognitive domains were evaluated: verbal and non-verbal learning and memory, executive functions, attention, visuospatial abilities, and language [7]. Participants were diagnosed with aMCI according to the criteria proposed by Petersen et al. [14], which include objective evidence of memory decline, compared to age-equivalent and education-equivalent individuals, that is not better explained by a medical or psychiatric condition or by substance abuse, and preserved activities of daily living (ie, housekeeping, shopping, meal preparation, medication management, finances, transportation). Raw scores were converted to z-scores according to the best available norms considering age, education and sex. A performance with a z-score ≤ -1.5 on at least two tests in the same cognitive domain was defined as cognitive decline in that domain (see Table 1 for list of diagnostic cognitive tests). To be included in the study, control subjects had to be exempt of cognitive decline in all domains and aMCI subjects had to have a predominant cognitive decline in the "verbal and non-verbal episodic learning and memory" domain, alone or with concomitant impairment in another cognitive domain. Because the study wanted to test sensitivity and specificity of REM sleep SPECT regional cerebral blood flow (rCBF: perfusion) imaging and to evaluate subjects with very early aMCI, it was decided not to consider the presence of a cognitive complaint as a necessary diagnostic criterion.

2.2.3. Polysomnographic recording

Polysomnography was performed at the Center for Advanced Research in Sleep Medicine of the Hôpital du Sacré-Coeur de Montréal, Montreal, Canada. Since REM sleep is predominantly at the end of the night, sleep recordings started between 00:00 and 01:00 to maximize the probability of REM sleep occurring after 06:30, which was the time at which the radiotracer was received at the hospital. PSG was obtained for one night with a Grass polygraph (amplifier gain 10,000; bandpass 0.3–100 Hz) and signals were digitized at a sampling rate of 256 Hz using Harmonie software (Stellate Systems, Montreal, Canada). The montage included EEG leads, bilateral electrooculography and chin electromyography for sleep staging, as well as a nasal canula, thoracic and abdominal strain gauges and pulse oxymetry to monitor respiration. Sleep stages, apneas, and hypopneas were visually scored on 30-s epochs according to standard criteria [15].

2.2.4. SPECT rCBF acquisitions and analysis

All subjects underwent two ^{99m}Technetium-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) SPECT studies with a high-