Biological Psychology 87 (2011) 334–339

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Changes in sleep theta rhythm are related to episodic memory impairment in early Alzheimer's disease

Pascal Hot[a,*], Géraldine Rauchs[b], Françoise Bertran[b], Pierre Denise[c], Béatrice Desgranges[b], Patrice Clochon[b], Francis Eustache[b]

[a] LPNC-UMR CNRS 5105, Université de Savoie, Chambéry, France
[b] Inserm – EPHE – Université de Caen/Basse-Normandie, Unité U923, GIP Cyceron, CHU de Côte de nacre, Caen, France
[c] Inserm ERI27, Caen, France

ARTICLE INFO

Article history:
Received 28 July 2010
Accepted 7 April 2011
Available online 21 April 2011

Keywords:
Alzheimer's disease
Episodic memory
Slow wave sleep
Theta rhythm

ABSTRACT

Impairments have been reported both in sleep structure and episodic memory in Alzheimer's disease [AD]. Our objective was to investigate the relationships between episodic memory deficits and electroencephalography [EEG] abnormalities occurring during sleep in patients with early AD. Postlearning sleep was recorded in 14 patients with mild to moderate AD, and 14 healthy elderly controls after they performed an episodic memory task derived from the Grober and Buschke's procedure. For each sleep stage, the relative power and mean frequency in each band were analyzed. Relative to agematched controls, AD patients presented faster mean theta frequency in both REM sleep and slow wave sleep [SWS]. In AD patients, a correlative analysis revealed that faster theta frequency during SWS was associated with better delayed episodic recall. We assume that increased theta activity reflects changes in neuronal activity to maintain memory performance, indicating that compensatory mechanisms already described at the waking state could also be engaged during SWS.

1. Introduction

Alzheimer's disease [AD] is characterized by neuronal loss, neurofibrillary tangles, and senile plaques, which first develop in the entorhinal cortex and the hippocampus (Braak and Braak, 1991; Delacourte et al., 1999). At the cognitive level, memory impairments come first and affect both the anterograde and retrograde components of episodic memory (Desgranges et al., 2002; Piolino et al., 2003; Eustache et al., 2004). Such impairments are classically explained by changes in the medial temporal lobe (including the hippocampus), a critical brain area for memory processing (Squire and Alvarez, 1995; Morris, 1996; Nadel and Moscovitch, 1997).

Recently, it has been suggested that memory decline in AD could also be the consequence of impairment in sleep-dependent memory consolidation (Rauchs et al., 2010). Indeed, cumulative evidence supports the existence of off-line reprocessing of recently acquired memories within hippocampal networks during sleep (for reviews, see Rauchs et al., 2005; Diekelmann and Born, 2010). Sleep deprivation and neuroimaging studies have mainly demonstrated the crucial role of slow wave sleep ([SWS] = stage 3 + 4) for consolidation of declarative, episodic memories (e.g., Plihal and Born, 1997; Peigneux et al., 2004). These works are in agreement with the "hippocampo-neocortical dialogue" hypothesis proposed by Buzsaki (1996). According to this model, recently acquired memories are reactivated, during SWS, within hippocampal networks. These reactivations occur in a coordinated manner with slow oscillations and sleep spindles, and will favor a transfer of memory traces towards neocortical areas where memories will be stored for the long term. Recent functional magnetic resonance imaging studies have provided evidence of such a transfer of memory traces during post-learning sleep (Gais et al., 2007; Rauchs et al., 2011). Moreover, electroencephalographic [EEG] recordings have shown that the theta rhythm (brain activity between 4 Hz and 7.5 Hz) seems to be sensitive to the elicitation of memory consolidation processes that depend on hippocampus activity (Fogel et al., 2009; Klimesch, 1996; Cantero et al., 2003). In AD, sleep disturbances have been investigated in several studies (see Petit et al., 2004 for review), mainly for diagnostic purposes or clinical viewpoints. They reported both an accentuation of sleep changes occurring during normal ageing (Bombois et al., 2010) and a reduction of the amount of REM sleep specific to AD patients (Petit et al., 2005; Christos, 1993; Dykierek et al., 1998) but at a late stage of the disease (Gagnon et al., 2006). Cellular studies report disorders of the cortical cholinergic activity, involved in the regulation of sleep (Coyle et al., 1983; Montplaisir et al., 1998). The cholinergic system has been identified as one of the major neurotransmitter systems involved in memory (Blokland, 1996; Everitt and Robbins, 1997). This finding is particularly relevant, considering data from animal

* Corresponding author.
E-mail address: pascal.hot@univ-savoie.fr (P. Hot).

0301-0511/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.biopsycho.2011.04.002

and human studies supporting the suggestion that AD is related to cholinergic system dysfunction (see White and Ruske, 2002, for a review). To date, the contribution of sleep disturbances to memory impairments in AD remains largely unknown (Rauchs et al., 2010). Mizuno et al. (2004) reported that increasing the amount of REM sleep by administration of the cholinesterase inhibitor donepezil in moderate AD patients improves cognitive functioning. However, this study did not clearly establish the link between declarative memory impairment and changes in sleep architecture, particularly because patients were relatively advanced in the disease and presented a global decline of sleep architecture.

Considering that unique compensatory brain processes have been reported in AD patients at the first stage of the disease (Dickerson et al., 2005), it can be assumed that (i) early changes could occur in post-learning EEG sleep before the alteration of sleep organization reported in mild to moderate AD patients, and (ii) these changes should be related to episodic memory decline. A recent sleep study with amnestic mild cognitive impairment [aMCI] patients, a prodromal stage of AD, confirms that inadequate memory consolidation is related to declines in subjective sleep indices (Westerberg et al., 2010). In our group, we also found that early AD patients with the faster spindles had the better performance in the episodic memory task (Rauchs et al., 2008). Converging studies point out that spindles are related to memory performance, but the involvement of brain structures sustaining the elicitation of the spindles has to be unraveled. These well-designed studies did not yet define what kind of brain processes are modulated in AD during sleep.

The aim of the present study is to further investigate the relationships between episodic memory deficits and sleep changes by focusing on changes during sleep stages in theta activity, a brain index of declarative memory processes. As reported in our previous study on spindles, we predict that changes in theta activity occur before the massive sleep disorganization occurring during the spread of AD. To examine subtle changes in brain activity during sleep, we focus on early AD patients with no clear sleep architecture disorganization.

2. Materials and methods

2.1. Subjects

Fourteen unmedicated AD patients (seven men and seven women; mean age (±SD): 76.7 ± 3.8 years) participated in this study (mean Mini-Mental State Examination [MMSE] score (±SD) [Folstein et al., 1975, French version: Hugonot-Diener et al., 2008]: 24.8 ± 2.4, range: 21–28). All were prospectively selected on the basis of a neurological examination and a neuropsychological assessment, using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable AD (McKhann et al., 1984). Structural magnetic resonance imaging showed no focal abnormality. All patients were reexamined over a 12-month period to confirm the AD diagnosis. At the time of the study, none of the patients were being or had been treated with specific medication such as anti-acetylcholinesterase agents. Fourteen elderly healthy subjects (6 men and 8 women) also participated (mean age (±SD): 76.7 ± 4.1 years; mean MMSE score (±SD): 29.4 ± 1), who were paired according to their age and level of education. All controls had no history of neurological or sleep disorder, and none were being treated with medications at the time of the study. All subjects were right-handed and native French speakers. They gave their written consent to participate in the study after detailed information was given to them, and the study was done in accordance with the Declaration of Helsinki following approval by the Regional Ethics Committee. All participants (both AD and control groups) got all the information including benefit and risk of the study.

2.2. Sleep recordings and analysis

For all subjects, sleep was recorded in the sleep laboratory for two consecutive nights. The first night was used to accustom the subjects to the experimental conditions, including the placement of the electrodes; data were analyzed for the second night only. Polysomnographic sleep acquisition was performed with the Nicolet Acquisition System and included continuous recordings of EEG, electrooculogram, electromyogram recorded at the chin, and electrocardiogram [ECG]. EEG activity was recorded with derivations at the left (T3/O1) and right (T4/O2) temporo-occipital areas of the extended 10–20 international system (Nuwer et al., 1999), using Ag/AgCl electrodes with a vertex ground and a right ear reference. The impedance for all electrode sites was kept below 10 kΩ. The EEG filter band pass was 0.03–35 Hz and was digitized at 125 Hz. As recommended by Claus et al. (2000), we used bipolar rather monopolar EEG recordings because they allowed us to restrict the uptake area of recorded brain activity.

Three additional electrodes were placed at the outer canthus and supraorbitally to the right eye with a bipolar recording for electrooculogram activity. Two of us (FB, PH) scored sleep data (i) to monitor the quality of recordings throughout the night; (ii) to classify sleep stages following the criteria defined by Rechtschaffen and Kales (1968); and (iii) to screen artifacts. Individual EEG recordings were manually inspected for any remaining eye movement, ECG, electromyogram, or movement-related artifacts. In addition, the potential ECG contribution to the EEG was eliminated off-line by submitting the data to an ECG correction algorithm with source separation (fast ICA algorithm [Hyvarinen and Oja, 2000]). Lastly, four EEG epochs (16 s) before and after each change of sleep stage were also rejected to limit the uncertainties at the level of transition of sleep stage.

Computerized spectral analysis was performed with fast Fourier transformation [FFT] on the all-night filtered EEG after elimination of epochs with artifacts. Spectral analysis was performed on both T3/O1 and T4/O2 derivations. Before computing the FFT, the data were tapered with the Hamming window. The FFT was computed on artifact-free epochs of 512 points corresponding to a duration of 4 s. The FFT was realized for each sleep stage on the total number of epochs corresponding to the maximal number of artifact-free epochs observed in all subjects. Consequently, the total sample size was different for each stage, but similar for all subjects. We obtained the following data: SWS: 225 epochs; REM: 119 epochs. Frequency bands were defined as follows: delta (1.5–4 Hz); theta (4–7.5 Hz); alpha (7.5–12.5 Hz); beta (12.5–30 Hz). Two parameters were measured from the spectral analysis for each frequency band. The relative power ([RP], percentage) was calculated by dividing the absolute power in each frequency band by the total power of the whole spectrum. The use of RP has been recommended in previous EEG studies of dementia (Nuwer, 1988; Rodriguez et al., 1999). In particular, we preferred using RP rather than absolute power because the former is not affected by the electric properties of the head volume conductor. Moreover, RP recorded in a particular area is more strongly associated with local EEG than is absolute power (Claus et al., 2000). The second parameter recorded for each frequency band was the mean frequency [MF], which is the weighted sum of spectral estimates divided by absolute power in the frequency band.

2.3. Neuropsychological assessment

Episodic memory was assessed with an original task derived from Grober and Buschke's procedure (1987). Our procedure is designed to limit the interference from semantic memory impairment by using only those verbal items whose semantic integrity has been strictly verified individually (for the detailed procedure, see Giffard et al., 2001; Eustache et al., 2001). After this procedure, the episodic memory task was proposed after a 4–6-h delay. This task consisted in learning 15 words, presented by series of three on separate cards. The subject was asked to point out and to read aloud each item (e.g., salad) in response to the name of its category, which was verbally given by the examiner as a cue (e.g., vegetable). After all three words were correctly named, the three cards were removed and an immediate verbal cued recall was proposed, in the same order as in the previous identification task, again in response to the category cue (e.g., What was the vegetable?). If the subject was unable to recall an item in response to its cue, the pointing and reading aloud procedure was repeated for this item until a correct response was obtained. After the immediate cued recall for a group of three items was correctly performed, the next set of items was presented. Immediately following the processing of the 15 items, retrieval was assessed with cued recall with the same cues as in the learning phase. A delayed cued recall and a recognition task were proposed after a night of sleep. The originality of this task, compared with that used in other studies by our group, lies in the fact that we proposed five consecutive trials of cued recall to favor the encoding of most of the words and to avoid, as much as possible, floor effects when retesting AD patients the next day. In summary, we measured a score of delayed cued recall, a forgetting rate (defined as [((immediate cued recall − delayed cued recall)/immediate cued recall) × 100]), and the proportion of correct recognitions. The procedure has been specifically designed for AD patients to detect lapse of episodic memory, but also to reduce the dramatic decrease in performance classically observed with delayed recall tasks.

2.4. Statistical analyses

Statistical analyses of qEEG parameters and neuropsychological data were performed with SAS software (SAS Institute Inc., version 9.1).

Neuropsychological scores were compared by using unpaired Student's *t* tests. Differences in qEEG indices were analyzed by the means of a General Linear Model (GLM). The Levene test was used to verify the homogeneity of the variances and the degree of freedom of the Student's *t* test was adjusted when it was required.

qEEG changes were performed on T3/4. AD modulated EEG activity on the whole scalp, but to a greater extent at the temporal sites, which were first affected by senile plaques and neurofibrillary tangles at this early stage. For this reason, we focused