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Brain and cognitive correlates of sleep fragmentation in elderly subjects with and without cognitive deficits

Claire André, Clémence Tomadesso, Robin de Flores, Pierre Branger, Stéphane Reheul, Florence Mézenge, Brigitte Landeau, Vincent de la Sayette, Francis Eustache, Gaël Chételat, Géraldine Rauchs

Abstract

Introduction: Sleep disturbances are increasingly recognized as a risk factor for Alzheimer’s disease. However, no study has assessed the relationships between objective sleep fragmentation (SF) and brain and cognitive integrity across different cognitive stages, from cognitively unimpaired elderly subjects to patients with subjective cognitive decline and/or mild cognitive impairment.

Methods: 30 cognitively unimpaired elderly participants and 36 patients with subjective cognitive decline and/or mild cognitive impairment underwent a neuropsychological evaluation, structural MRI, 18F-fluorodeoxyglucose, and 18F-florbetapir-PET scans, and an actigraphy recording over a minimum of six consecutive nights. Multiple regression and mediation analyses were performed between SF parameters, neuroimaging data, and cognitive scores.

Results: In cognitively unimpaired elderly participants, SF intensity mediated the association between frontohippocampal hypometabolism and lower executive functioning. Moreover, to a lower extent, increased SF variability was related to thalamic atrophy and ventromedial prefrontal amyloid burden. However, in patients with subjective cognitive decline and/or mild cognitive impairment, SF no longer contributed to the expression of cognitive deficits.

Discussion: These findings suggest that SF may directly contribute to lower cognitive performance in cognitively unimpaired elderly subjects. Therefore, treating sleep disturbances before the onset of cognitive deficits may help to cope with brain alterations and maintain cognitive functioning.

Keywords: Sleep; Aging; Subjective cognitive decline; Mild cognitive impairment; MRI; Amyloid; Glucose metabolism; Actigraphy; Sleep fragmentation

1. Introduction

As no curative treatment for Alzheimer’s disease (AD) is currently available, it is particularly important to identify modifiable lifestyle factors that might help prevent, delay the onset, or slow down the progression of the disease. In this context, there is a growing interest in better characterizing age-related sleep changes and their associations with AD. Indeed, aging is characterized by a progressive decline in sleep quality, including a decrease in non-rapid eye movement (NREM) sleep, paralleled by greater sleep fragmentation (SF) [1]. Moreover, age-related changes in sleep quality have been related to cognitive decline and increased risk of developing dementia [2–4]. Sleep disturbances are also a core symptom of AD [1]. They worsen with dementia severity and are related to patients’ cognitive deficits,
especially memory impairments [5]. Accumulating evidence indicates that the disruption of slow-wave sleep, the deepest NREM sleep stage predominating during the first part of the night, is associated with increased beta-amyloid (Aβ) deposition in the brain [6–8], a hallmark of AD known to start decades before the apparition of the first cognitive symptoms [9]. Moreover, several self-reported sleep parameters, including longer sleep latency [10,11] and shorter sleep duration [12], have been associated with increased amyloid deposition in frontal areas and/or in the precuneus. In addition to amyloid deposition, sleep disruption may also be associated with neuronal injury, as measured with gray matter atrophy or hypometabolism, both known to be closely related to cognitive decline [13,14]. Previous studies reported that, in cognitively unimpaired elderly subjects, poor self-reported sleep quality is related to reduced gray matter volume in frontal regions and the insula [10,15], and that increased actigraphy-measured sleep fragmentation is associated with atrophy in the orbitofrontal cortex [16].

However, we lack a comprehensive overview of the relationships between objective measures of sleep quality and amyloid deposition, atrophy, and brain glucose metabolism in cognitively unimpaired elderly participants. Furthermore, we have no information about these links in patients with subjective and/or objective cognitive deficits. Clarifying these associations using complementary neuroimaging modalities that reflect different aspects of brain integrity, and across different cognitive stages, would help determining to what extent and at which stage of the disease the treatment of sleep disturbances would be beneficial to prevent cognitive decline.

Thus, the present study aims at investigating and comparing the relationships between objectively measured SF and cognitive, structural, functional, and molecular brain changes in cognitively unimpaired elderly subjects versus in patients with subjective and/or objective cognitive deficits, including patients with subjective cognitive decline (SCD) and mild cognitive impairment (MCI).

2. Materials and methods

2.1. Participants

Sixty-six participants from the IMAP+ study (“Imagerie Multimodale de la Maladie d’Alzheimer à un stade Précoces”, Caen, France) were included in the present study. They were all right-handed, native French speakers, with at least 7 years of education, living at home, without history or clinical evidence of neurological or psychiatric disorders, alcohol use disorder or drug abuse, and with a normal somatic examination. The inclusion and group classification of the participants were based on a clinical interview and a standardized neuropsychological assessment, according to internationally agreed criteria, but did not rely on neuroimaging biomarkers, as they were the main outcome measures in our analyses.

Thirty cognitively unimpaired elderly subjects were recruited from the community. They were aged over 60 years, had no memory complaint and never referred to a memory clinic, and performed in the normal range (i.e., within 1.65 standard deviation [SD] of the mean) for their age and education level in all screening tests. In addition, thirty-six patients aged over 50 years were recruited from local memory clinics, to which they attended for self-reported cognitive concerns. During the clinical interview, the physician ensured i) that the complaint was not related to current medication, psychiatric or neurological diseases (including anxiety or depression), or other medical conditions, ii) that independence in daily life was preserved, and iii) that they did not fulfill NINCDS-ADRDA criteria for probable AD [17]. Among the 36 patients, 22 had objective cognitive deficits and met clinical criteria for single or multiple domain amnestic mild cognitive impairment [18], with predominant episodic memory deficits (1.5 SD from the normal mean for age and education). Fourteen patients did not show significant objective cognitive impairment and met criteria for SCD [19]. Clinical diagnosis for patients was assigned by consensus under the supervision of senior neurologists and neuropsychologists.

Once included in the study, all participants performed a detailed neuropsychological assessment, an actigraphy recording, and three neuroimaging scans within a mean interval of 1.9 ± 3.1 months. The IMAP+ study was approved by the local ethics committee (CPP Nord-Ouest III) and registered at http://clinicaltrials.gov (nb. NCT01638949). All participants gave their written informed consent to the study before the examinations.

2.2. Cognitive assessment

Participants underwent a detailed neuropsychological assessment, encompassing multiple domains of cognition (verbal and visual episodic memory, semantic memory, working memory, executive functioning, processing speed, visuospatial abilities, language skills, and praxis), fully described in previous publications [20,21]. In the present study, analyses focused on episodic memory and executive functioning, as they are particularly sensitive to aging and AD [22], and closely related to sleep quality [23]. We used composite scores to reflect cognitive abilities with robust proxies and to minimize the issue of multiple statistical testing (see [24] and Supplementary Material for further details). Higher values always indicated better performance. Furthermore, symptoms of depression and anxiety were assessed using the Montgomery-Asberg Depression Rating Scale [25] and the trait version of the State-Trait Anxiety Inventory [26], respectively.

2.3. Actigraphy recording

2.3.1. Actigraphy data collection

The sleep-wake cycle was recorded in all participants using the MotionWatch 8 wrist-worn triaxial actigraph
(CamNTech Ltd, Cambridge, UK), for at least six consecutive nights (range: 6-8 nights; mean ± SD: 7.05 ± 0.51 nights). Participants were instructed to wear continuously the device on their nondominant wrist until the end of the recording. They had to press the event marker button at lights off and lights on, and to fill in a sleep diary on awakening each morning [27] to facilitate data analysis.

2.3.2. Actigraphy data analysis

Data were analyzed using the MotionWare software (version 1.1.25, CamNTech Ltd, Cambridge, UK) and sampled using a 5-second epoch. A sensitivity threshold of 20 counts was applied to distinguish activity from rest. For each night, the “Lights Off” and “Got Up” markers were placed by the same experimenter in the appropriate position following the event marker put by the participant and cross-validated with the light sensor data and sleep diary information. Then, “Fell Asleep” and “Woke up” markers were automatically adjusted from the combination of the activity data and the “Lights Off” and “Got Up” markers, respectively, allowing the collection of the assumed sleep time. Then, a fragmentation index was calculated as the sum of the percentages of mobile time and immobile bouts below or equal to 1 minute in the assumed sleep period. Two distinct parameters of SF were considered: SF intensity (corresponding to the mean level of fragmentation over the whole recording) and intra-individual SF variability (computed as SF standard deviation across nights) (Fig. 1). These parameters were computed over the first half of the assumed sleep duration for each subject.

2.4. Neuroimaging procedure

Participants underwent a structural T1 MRI, as well as 18F-fluorodeoxyglucose (FDG)- and florbetapir-PET scans, to measure gray matter volume, brain glucose metabolism, and amyloid burden, respectively. All examinations were performed at the Cyceron Center (Caen, France). Details on MRI and PET images acquisition and preprocessing are available in previous publications [28,29] and are fully described in the Supplementary Material. Briefly, T1-weighted images were preprocessed in SPM12. FDG-PET and florbetapir-PET images were preprocessed using MRI data for partial volume effect correction and spatial normalization. Partial volume effects-corrected normalized and scaled florbetapir-PET images were also used to extract the individual global cortical amyloid standard uptake value ratio using a predetermined neocortical mask including the entire gray matter, except the cerebellum, occipital and sensory motor cortices, hippocampi, amygdala, and basal nuclei [30].

2.5. Statistical analyses

2.5.1. Group comparisons

Between-group comparisons for demographics, cognitive scores, and sleep parameters were assessed using Student’s t-tests for continuous variables and chi-square tests for categorical variables, with statistical significance set to \( P < .05 \).

Patients’ patterns of atrophy, hypometabolism, and amyloid burden were explored using two-sample t-tests in SPM12, adjusted for age, gender, and body mass index.

2.5.2. Voxelwise regression analyses

Within each group, voxelwise multiple regression analyses were performed between SF parameters and each neuroimaging modality independently in SPM12, controlling
for age, gender, body mass index, and the complementary SF parameter (i.e., we controlled for SF variability when SF intensity was the predictive variable, and conversely). Afterward, complementary analyses were performed with the addition of several covariates to the main model. Only results obtained with the initial 4-covariates model are presented, as the main results remained essentially unchanged when adding the Mini-Mental State Examination score, depression score, or sleep medication use as covariates. We report the slight changes observed on these secondary analyses in the Supplementary Material. For all neuroimaging analyses, results were evaluated for significance at \( P < .001 \) (uncorrected) combined with a minimum cluster size determined by Monte-Carlo simulation using the AlphaSim program to achieve a corrected statistical significance of \( P < .05 \) (Supplementary Table 1). Results obtained at the same statistical threshold but with a lower cluster size were considered as trends.

2.5.3. Multiple regression analyses

Multiple regression analyses were performed between SF parameters and cognitive scores (i.e., composite scores for executive functioning and episodic memory) within each group. Age and gender were included as covariates in the regression models, and results were considered significant after applying a Bonferroni correction for multiple comparisons: the statistical threshold for significance was set to \( P = (.05/\text{number of comparisons} \right) \).

### Results

#### 3.1. Between-group differences

Demographic data, neuropsychological performance, and sleep parameters for each subgroup, as well as between-group differences, are reported in Table 1. The two groups did not differ for age, gender, years of education, body mass index, state-trait anxiety, and sleep parameters. As expected, patients with SCD/MCI presented lower global cognitive functioning (Mini-Mental State Examination

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### Table 1

Participants characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cognitively unimpaired elderly subjects (n = 30)</th>
<th>SCD/MCI patients (n = 36)</th>
<th>Group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years ± SD)</td>
<td>73.3 ± 7</td>
<td>71.5 ± 8.2</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>56.7%</td>
<td>38.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Education (years ± SD)</td>
<td>12.1 ± 3.5</td>
<td>11.8 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (mean ± SD)</td>
<td>24.5 ± 3</td>
<td>24.6 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Florbetapir SUVr (% positive)</td>
<td>1 ± 0.2 (30.8%)</td>
<td>1.2 ± 0.3 (50%)</td>
<td>( P = .011 )</td>
</tr>
<tr>
<td>MADRS (mean ± SD)</td>
<td>1 ± 1.9</td>
<td>3.4 ± 3.7</td>
<td>( P = .002 )</td>
</tr>
<tr>
<td>STAI-B (mean ± SD)</td>
<td>37.4 ± 10</td>
<td>38.8 ± 8.2</td>
<td>NS</td>
</tr>
<tr>
<td>Participants on sleep medication (number, (%))</td>
<td>1 (3.3%)</td>
<td>3 (8.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE (mean ± SD)</td>
<td>28.6 ± 1.2</td>
<td>27.6 ± 2.4</td>
<td>( P = .046 )</td>
</tr>
<tr>
<td>Mattis total score (mean ± SD)</td>
<td>140.2 ± 3.3</td>
<td>136.2 ± 6.9</td>
<td>( P = .005 )</td>
</tr>
<tr>
<td>Episodic memory composite score (mean ± SD)</td>
<td>0.0 ± 0.7</td>
<td>−0.8 ± 1.3</td>
<td>( P = .005 )</td>
</tr>
<tr>
<td>Executive functioning composite score (mean ± SD)</td>
<td>0.0 ± 0.7</td>
<td>−0.8 ± 1.7</td>
<td>( P = .020 )</td>
</tr>
<tr>
<td>Sleep parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF intensity (mean ± SD)</td>
<td>30.3 ± 14.7</td>
<td>28 ± 11.1</td>
<td>NS</td>
</tr>
<tr>
<td>SF variability (mean ± SD)</td>
<td>10.9 ± 4.7</td>
<td>11.5 ± 5.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abbreviations:** MADRS, Montgomery and Asberg Depression Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NS, nonsignificant; SCD, subjective cognitive decline; SD, standard deviation; SF, sleep fragmentation; STAI-B, State-Trait Anxiety Inventory form B; SUVr, standard uptake value ratio.

*Owing to missing data in some patients, n = 30 for episodic memory, n = 33 for the MADRS, n = 34 for executive functioning.

**Between-groups differences were assessed using Student’s t-tests for all variables, except for gender for which chi-square statistics were used. Statistical significance was set to \( P < .05 \).**

**n = 26 healthy elderly and 34 patients with valid florbetapir-PET scan. Amyloid positivity was defined as >0.985, based on mean SUVr + 2 SDs in a group of 41 healthy young individuals (aged <40 years).**

**Use of sleep medication on a regular basis (>1/week), excluding phytotherapy and homeopathy.**
score: \(t = 2.03, P = .046\); Mattis Dementia Rating Scale: \(t = 2.88, P = .005\), episodic memory \((t = 2.92, P = .005)\), and executive performance \((t = 2.39, P = .020)\). They also presented higher depressive symptoms (Montgomery and Asberg depression rating scale: \(t = -3.27, P = .002\)). Moreover, patients with SCD/MCI presented significant brain changes compared with cognitively unimpaired elderly subjects including (i) atrophy within the parahippocampal and hippocampal region, (ii) hypometabolism in the precuneus and posterior cingulate cortex, and (iii) widespread amyloid deposition mainly in frontal regions (Supplementary Fig. 1). Consistently, the global cortical amyloid standard uptake value ratio was significantly higher in patients with SCD/MCI compared with cognitively unimpaired elderly subjects \((t = -2.61, P = .011)\).

3.2. Relationships between SF and neuroimaging

Results of significant voxelwise regression analyses are presented in Fig. 2, and detailed peak statistics and coordinates of significant clusters are reported in Supplementary Table 2.

3.2.1. Cognitively unimpaired elderly subjects

SF intensity negatively correlated to brain glucose metabolism in the ventromedial prefrontal cortex, hippocampus and parahippocampus, bilaterally. No significant association was found with gray matter volume or amyloid burden.

SF variability negatively correlated to gray matter volume within the thalamus. Moreover, we observed a trend toward a positive correlation with amyloid burden in the left rectus gyrus. When sleep medication was added as a covariate in the model, both associations became trends (Supplementary Table 3). No association was found between SF variability and brain glucose metabolism.

3.2.2. Patients with SCD/MCI

SF intensity negatively correlated with brain glucose metabolism in the left insula, whereas no significant association was found with gray matter volume or amyloid burden. SF variability was not associated with any neuroimaging modality.

3.3. Relationships between SF and cognition

In cognitively unimpaired elderly subjects, SF intensity was significantly associated to worse performance in executive functioning (Fig. 3A; \(r = -0.47, P = .01\)) and episodic memory (Fig. 3B; \(r = -0.40, P = .03\)), although this latter did not survive the Bonferroni correction for multiple comparisons. By contrast, SF variability was not related to any cognitive score in this group.

We did not find any significant association between SF parameters and cognitive performance in patients with SCD/MCI (see Supplementary Table 4 for detailed results).

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**Fig. 2.** Neuroimaging correlates of SF. Results of the voxelwise regression analyses between SF parameters and neuroimaging data in cognitively unimpaired elderly participants (left part) and patients with SCD/MCI (right part). Results are presented at \(P < .001\) (uncorrected) and adjusted for age, gender, BMI, and the complementary SF parameter (i.e., SF variability when SF intensity was considered, and conversely). Abbreviations: BMI, body mass index; FDG: \(^{18}\)F-fluorodeoxyglucose; MCI, mild cognitive impairment; SCD, subjective cognitive decline; SF, sleep fragmentation.
3.4. Mediation analyses in cognitively unimpaired elderly subjects

As SF intensity was significantly associated to both executive performance and hippocampal and prefrontal glucose metabolism, these three variables were entered in causal mediation analyses. The results of the two models tested in cognitively unimpaired elderly subjects are summarized in Fig. 4. They showed that SF significantly mediated the relationship between total brain glucose metabolism and executive performance ($P = .02$; Table 2). No other mediation analysis was conducted, as no other sleep variable was significantly associated to both a brain and a cognitive variable.

4. Discussion

The present study aimed at investigating and comparing the brain and cognitive correlates of SF in healthy aging versus in a group of patients with SCD/MCI. In cognitively unimpaired elderly participants, SF intensity was related to frontal and medial temporal metabolism, and to cognitive performance, especially executive functioning. Moreover, SF variability was related to thalamic atrophy and, to a lesser extent, to frontal amyloid deposition. By contrast, in patients with SCD/MCI, we only report a significant association between SF intensity and glucose metabolism in the left insula, whereas no relationship between sleep and cognition was found.

The brain regions found to be associated with the fragmentation of the first hours of sleep include frontal and medial temporal areas, as well as the thalamus in cognitively unimpaired elderly participants, and the insula in patients. These regions are known to be closely involved in sleep physiology. They are largely involved in the generation of NREM-sleep oscillations, such as sleep spindles [32] and slow waves [33,34], that are notably critical for sleep-dependent memory processes [35,36]. Besides, these regions are also known to be particularly sensitive to aging and affected in the early stages of AD. Indeed, on the one hand, the medial prefrontal cortex is one of the first brain regions exhibiting amyloid deposition [37], and is also sensitive to glucose metabolism changes in aging and AD [38–40]. On the other hand, the medial temporal lobe is early affected by tau pathology [41], with atrophy already detectable in the preclinical and prodromal stages [42,43]. The involvement of this common set of brain regions in both sleep physiology and AD pathophysiology might at least partly underlie the (possibly bidirectional) links between sleep problems and AD.

As a first step toward characterizing the directionality of these associations, we performed causal mediation analyses. We showed that the intensity of the fragmentation of the first hours of sleep mediated the relationship between frontohippocampal hypometabolism and lower executive performance. This suggests that sleep disruption resulting from frontohippocampal hypometabolism may directly contribute to cognitive deficits in cognitively unimpaired elderly subjects. Therefore,
treatments that could improve their ability to cope with brain changes and potentially reduce their risk of cognitive decline. Nevertheless, owing to a limited statistical power, mediation analyses were restricted to a single set of variables (i.e., sleep fragmentation, brain glucose metabolism in frontohippocampal areas, and executive functioning), as they were the only ones for which the same sleep parameter was related to both a brain and a cognitive variable. Thus, these analyses are likely to picture only part of the potential associations existing between sleep, brain, and cognitive integrity. They do not preclude that some sleep changes could induce brain alterations that may, in turn, underlie cognitive deficits. Moreover, it is also likely that some brain changes are directly underlying cognitive deficits, independently from sleep disturbances.

Besides the associations between metabolic changes and SF intensity, our results reveal that a higher night-to-night variability in sleep quality over time might be associated with brain changes that might be less reversible, that is, more durable. Even if their variability is preserved sleep quality in cognitively unimpaired elderly subjects may help to cope with brain changes and maintain cognitive performance in the normal range, but such interventions may be less efficient once patients experience measurable cognitive deficits.

The present study has some strengths, including an objective sleep assessment over several consecutive nights combined to multimodal neuroimaging data, allowing us to assess the first time the relationships between sleep fragmentation intensity versus variability on structural, metabolic, and molecular brain alterations in the same sample. Moreover, these associations were evaluated both in cognitively impaired and unimpaired elderly subjects, thus helping to give a more comprehensive picture of their role at different cognitive stages. However, some limitations must be mentioned. First, our study is limited by the small sample size and the cross-sectional nature of the analyses. Further analyses should be conducted using a longitudinal design, together with larger sample sizes to complement our mediation analyses and assess the nature and directionality of the relationships between sleep and brain and cognitive integrity more exhaustively. Second, we were not able to characterize the origin of sleep disturbance (e.g., obstructive sleep apnea, periodic limb movements, or restless legs syndrome), as participants did not undergo polysomnography recordings. Further studies should aim at determining the relative contribution of the multiple factors that can cause sleep fragmentation, such as sleep disorders or lifestyle risk factors. In addition, polysomnography will also be necessary to specifically assess changes in NREM sleep oscillations, and to test the potential impact of other sleep alterations such as REM sleep disruption.

Our interpretation of the data is that the fragmentation of the first hours of sleep is associated with an alteration of brain regions typically affected in aging and AD, and may directly contribute to lower cognitive performance. However, in patients with SCD/MCI, sleep disruption may no longer contribute to the expression of cognitive deficits. Therefore, preserving sleep quality in cognitively unimpaired elderly subjects may help to cope with brain changes and maintain cognitive functioning.
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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dadm.2018.12.009.

RESEARCH IN CONTEXT

1. Systematic Review: In the existing literature, sleep disturbances are increasingly recognized as a risk factor for Alzheimer’s disease. However, no previous study has assessed the associations between sleep disruption, brain and cognitive integrity across different cognitive stages.

2. Interpretation: We showed that the disruption of the first hours of sleep is related to the alteration of brain regions typically affected in aging and Alzheimer’s disease, and may directly contribute to lower cognitive performance in cognitively unimpaired elderly participants. However, this is no longer the case in patients with subjective cognitive decline and/or mild cognitive impairment.

3. Future Direction: These findings have important clinical implications, as they suggest that treating sleep disturbances before the onset of cognitive deficits may help to cope with brain changes and maintain cognitive performance. Further studies need to be conducted on larger samples and using polysomnography to assess changes in sleep architecture and microstructure more specifically.

References
