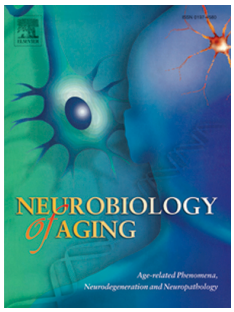

Quality of Sleep Predicts Increased Frontoparietal Network Connectivity in Mild Cognitive Impairment Patients

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Quality of Sleep Predicts Increased Frontoparietal Network Connectivity in Mild Cognitive Impairment Patients

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ABSTRACT

High quality of sleep may mitigate the impact of pathophysiological mechanisms in mild cognitive impairment (MCI) through functional connectivity reorganization of neural networks underlying higher cognitive functions. Thirty-eight MCI patients stratified into high and low quality of sleep according to a self-reported questionnaire for sleep habits, and 38 controls underwent resting-state functional MRI. Independent component analysis was used to reconstruct the default mode (DMN) and frontoparietal (FPN) networks. High quality of sleep was associated with increased FPN connectivity among MCI. Moreover, a positive coupling of connectivity between networks was found in MCI reporting high quality of sleep, congruently with the pattern observed in controls, while this coupling was disrupted in MCI with low quality of sleep. An association between FPN connectivity and language scores was observed in MCI. These findings suggest a relationship between sleep quality and FPN connectivity in MCI, that may underlie compensatory mechanisms to overcome advancing neurodegeneration.

1. Introduction

Mild cognitive impairment (MCI) refers to a potential transitional state between normal cognition and dementia (Jack et al., 2018). However, different lifestyles might reduce or increase the risk of developing dementia. Several studies have shown an association between poor sleep quality and increased risk of cognitive decline (for a review, see Shi et al., 2018). Notably, when patients with Alzheimer's disease (AD) were treated for sleep disturbances, significantly slower cognitive decline over a 3-year follow-up period was observed (Troussière et al., 2014). This association is not surprising; sleep has indeed been identified as a state that renormalizes synaptic homeostasis promoting and optimizing the consolidation of new memories (Tononi and Cirelli, 2014; de Vivo et al., 2017; Diekelmann and Born, 2010).

Moreover, the link between sleep alterations and pathophysiological mechanisms occurring in AD/MCI have been investigated in several studies. Huang et al. (2012) reported fluctuation of soluble amyloid β (Aβ), the molecular hallmark of AD, with the sleep–wake cycle, similar to the diurnal fluctuations observed in mice (Kang et al., 2009). These studies raise the possibility that poor sleep may promote Aβ deposition, increasing the risk of developing AD. Furthermore, treatment for obstructive sleep apnea, a common sleep disorder associated with risk of dementia (Yaffe et al., 2011), was found to be characterized by a significant change of Aβ level in cerebrospinal fluid (CSF) (Ju et al., 2019). These observations suggest a potential mechanism through which sleep may modify the underlying pathophysiological processes, increasing or decreasing the risk of developing AD (Musiek and Holtzman, 2016).

However, the determinants of this association are still unclear. Recently, a relationship between the molecular pathology of several neurodegenerative disorders and neural connectivity at rest has been suggested (Buckner et al., 2005; Palop and Mucke, 2016; Pini et al., 2020a; 2020b; Seeley et al., 2009; Warren et al., 2013). Data supporting this assumption come from

resting-state functional magnetic resonance imaging (rsfMRI). This technique assumes that anatomically separate brain regions exhibiting blood oxygen fluctuations correlated in time are functionally connected, and together form resting state networks. Each of these networks has been linked to specific cognitive and sensory-motor functions (Laird et al., 2011). Connectivity alterations within the default mode network (DMN) have been linked with memory deficits, the core clinical symptom of AD (Buckner et al., 2005). This network includes the angular gyrus, the ventromedial prefrontal cortex, and the posterior cingulate cortex, with the latter hub showing the greatest vulnerability to AD pathological changes (Pievani et al., 2017). Alterations of network topology in AD and MCI patients have also been assessed by electroencephalography (EEG) studies (Franciotti et al., 2019; Babiloni et al., 2013), reinforcing the assumption that network alterations in these patients are not epiphenomena but related to pathophysiological mechanisms (Babiloni et al., 2013).

DMN breakdown can occur early in the cascade of AD events and might even precede Aβ accumulation (Jones et al., 2016; Palmqvist et al., 2017). Furthermore, AD shows functional alterations beyond the DMN, involving the frontoparietal network (FPN) (Palmqvist et al., 2017; Zhao et al., 2019). This network includes the lateral prefrontal cortex and temporoparietal regions and it has been linked with executive functions, and its left component, in particular, with language abilities (Smith et al., 2009; Wylie and Regner, 2014). Palmqvist et al. (2017) reported in cognitively unimpaired adults that, although the DMN was the most prominent network showing anatomical overlap with early Aβ accumulation, involvement of FPN was also evident. Moreover, they reported decreased inter-connectivity between DMN and FPN as CSF Aβ decreased, suggesting an association between advancing AD pathology and reduced DMN-FPN coupling (Palmqvist et al., 2017).

These findings may suggest a mediatory effect of DMN and FPN functional connectivity between sleep and AD pathology, even in the prodromal stages. An association between sleep disturbance and DMN connectivity has already been reported in MCI (McKinnon et al., 2016). However, to date, no studies have investigated the effect of sleep quality on the FPN in this clinical population. The aim of this study was to clarify the relationship between sleep quality in MCI patients and functional connectivity in the FPN. Specifically, we investigated whether MCI patients with high sleep quality would exhibit different and divergent patterns of FPN connectivity mediating positive effects on cognition. Moreover, we expected to find a relationship between sleep quality and coupling of connectivity between networks in MCI.

2. Methods

2.1 Participants

We retrospectively analyzed data collected in MCI patients and healthy controls (HC) at the Fondazione Ospedale San Camillo IRCCS, Lido, Venice (Italy) as part of the European VPH-DARE project (www.vph-dare.eu). The study was approved by the joint ethics committee of the Health Authority Venice and San Camillo IRCCS (Protocol number 2014.08). All participants gave informed consent prior to participation in the study. Each participant underwent clinical assessment, neuropsychological evaluation, and MRI scan, including structural and rsfMRI sequences. Sleeping behavior was assessed as part of the clinical evaluation through the Sleep Continuity in Alzheimer's Disease Scale (SCADS), a validated Italian self-report questionnaire for the assessment of sleep disturbances in dementia (Manni et al., 2013). Administration of the SCADS is detailed elsewhere (Palmer et al., 2018).

We included patients with a clinical diagnosis of MCI according to Albert's core clinical criteria (i.e., objective evidence of cognitive decline with preservation of independence in

functional abilities) (Albert et al., 2011). The control group included age-matched HC with neuropsychological performance within the normal range who completed the same cognitive assessment, the same MRI protocol, and the SCADS questionnaire. Inclusion criteria for controls were a normal neuropsychological performance on the cognitive battery, with no personal history of neurological, psychiatric or cerebrovascular disorders. Exclusion criteria for all participants were as follows: diagnostic entities of clinical concern (brain tumor, hydrocephalous, lesions indicative of multiple sclerosis, large cysts, and excessive leukoaraiosis); chronic or acute cerebrovascular disease; history of transient ischemic attacks; presence of uncontrolled brain seizures; significant neuropsychiatric diagnoses such as major depression, anxiety or psychosis. Sleep apnea and presence of sleep disturbances were not used as exclusion criteria.

Only individuals with available MRI and SCADS data were included in the present analysis. MCI patients were stratified into higher (HSq-MCI) and lower (LSq-MCI) subjective sleep quality, based on the median SCADS score (pooled sample = 18) as a cut-off. Because there is no validated cut-off to categorize subjects into high or low sleep quality groups, we used the median of the SCADS distribution. This was equivalent to the median reported in the original paper describing the questionnaire (Manni et al., 2013). Scores under the cut-off marked MCI with a better self-reported quality of their sleep, while MCI reporting a SCADS score above the cut-off judged their sleep as of poor quality.

2.2 Clinical and Cognitive evaluation

Patients and controls performed an extensive neuropsychological assessment including evaluation of: i) global cognitive status with the Mini-Mental State Examination (MMSE) (Measso et al., 1993); ii) memory through the prose memory test (Novelli et al., 1986a), paired

associates learning test (Novelli et al., 1986a), and recall of Rey complex figure tests (Caffarra et al., 2002a); iii) language with phonemic and semantic fluency (Novelli et al., 1986b), Token (De Renzi and Faglioni, 1978), and confrontation naming tests (Novelli et al., 1986b); iv) executive functions with Stroop (Caffarra et al., 2002b), digit span backward (Monaco et al., 2013), digit cancellation tests (Orsini et al., 1987), and the similarity subtest from the Wechsler Adult Intelligence Scale (Wechsler, 1981).

2.3 MRI acquisition

Patients and controls completed an MRI scan on a Philips Achieva 1.5 T scanner using an 8-channel head coil (IRCCS Fondazione Ospedale San Camillo, Venice, Italy). Structural MRI images were acquired with turbo field echo sequence according to the following parameters: TR=7.666 ms, TE=3.59 ms, flip angle=8°, matrix size 240×240×280, voxel size 1×1×0.6 mm. RsfMRI scans consisted of two consecutive runs of 120 T2*-weighted echo planar imaging volumes each acquired in 20 axial slices (TR=2 ms; TE=50 ms; flip angle=90°; matrix size=80×80; voxel size 2.875×2.875×6 mm). Each acquisition was preceded by 20 s of preliminary dummy scans, set to allow the scanner to reach equilibrium.

2.4 MRI preprocessing

Structural data were segmented using FreeSurfer version 6.0 (http://surfer. nmr.mgh.harvard.edu/). Vertex-wise analysis was used to explore differences in cortical thickness by using a general linear model implemented in FreeSurfer.

Functional data were preprocessed using FMRIB's Software Libraries (FSL v.6.0.0; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). RsfMRI runs were temporally concatenated to obtain a whole rsfMRI scan of 240 volumes for each participant. Volumes were motion corrected,

temporally filtered (100s), and each functional dataset was registered to its corresponding structural image with a rigid-body transformation, followed by a linear registration to a MNI template. For each fMRI volume, the framewise displacement (FD) was estimated and those volumes with more than 0.5 mm FD were regressed out from the time series (i.e., spike regression). A total of 7 HC and 5 MCI patients were excluded from further analysis because less than 120 non-affected volumes (i.e., 4 min) were detected. Confounding variables also included the average signal of white matter (WM) and CSF, six motion parameters, the derivative of these eight parameters, and the square of these sixteen variables. Five principal components of WM and CSF were included as confounding variables to minimize further the effect of physiological noise (Behzadi et al., 2007). Finally, images were spatially smoothed using a 6 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

To quantify changes in rsfMRI connectivity, independent component analysis (ICA) was performed in the pooled sample of MCI and HC using the Group ICA Toolbox (GIFT version 3.0a; http://mialab.mrn.org/software/gift/). The number of independent components extracted (n=46) was chosen according to the minimum description length criteria, a method for automated dimensionality estimation (Li et al., 2007). The resulting group maps were used to compute individual components, through a back-reconstruction step. The estimated spatial maps were then converted into z-scores. Functional networks were identified through a template matching spatial correlation procedure with standard templates (Shirer et al., 2012), and visually inspected to exclude those likely representing physiologic and/or motion artefact, according to spatial topology, time-series and low frequency content in the power spectra. According to our hypothesis, we selected the DMN and FPN, with this latter split in its left (LFPN) and right (RFPN) components. The spatial maps of these networks are shown in Fig. 1.

2.5 Statistical analysis

Group differences in sociodemographic and neuropsychological features were assessed with Kruskal-Wallis or χ^2 tests, as appropriate. All the analyses were performed using the SPSS package release 23.0 (SPSS Inc., Chicago, IL) and *P* values < .05 were considered statistically significant. Differences in neuropsychological variables were corrected for multiple comparisons with Bonferroni correction (i.e., n = 12; p < .004) to control for type I error.

Cortical thickness analysis was corrected for multiple comparisons after Montecarlo simulation (p < .05) to test for differences in the following contrasts: HSq-MCI *vs.* HC; LSq-MCI *vs.* HC; HSq-MCI *vs.* LSq-MCI. Sex was included as a covariate for all comparisons.

Non-parametric inference based on permutations using FSL randomise (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise) with 5000 permutations was used to investigate FC differences across groups. Multiple comparisons were corrected across space using family-wise error (FWE) based on permutation testing at a threshold-free-cluster enhancement (TFCE). To investigate differences between controls and MCI groups the following contrasts were tested: HC > HSq-MCI; HC > LSq-MCI at a TFCE level of $p < .05$. Differences across MCI groups (i.e., HSq-MCI *vs.* LSq-MCI) were tested at a TFCE level of $p < .025$ corresponding to a two-tailed $p < .05$, given that randomise correction is only performed on one tailed tests. Each contrast was restricted to the corresponding network by computing the one-sample binary network spatial maps from the whole sample through a non-parametric analysis using the TFCE method (5000 permutations; $p < .05$ FWE corrected). Sex and gray matter at voxel-level were included as covariates (model 1). Additionally, we adjusted for cognitive status, including a "memory factor" from a principal component analysis (PCA) of cognitive test (model 2). Specifically, a PCA with Oblimin rotation was used to reduce scores (z-transformed using the mean and standard deviation from the whole sample) from a neuropsychological test battery.

PCA identified two factors accounting for more than 55% of the total variance (Supplementary Fig. S1). The first factor included all of the language and executive function tests, except for the Stroop error score, and was labelled as “language-executive factor”. The second factor, including all memory scores and Stroop error score, was labelled as “memory factor”. Only the memory factor was considered as a covariate in model 2, because memory represents the clinical core of MCI/AD patients. Moreover, Mann-Whitney test comparing cognitive factors between MCI groups showed significant differences for the “memory factor” ($U=233$; $p = .04$), while no differences were reported for the “language-executive factor” ($U=250$; $p = .126$).

The association between FPNs and DMN was investigated to assess differences in network coupling across MCI groups as follows: mean functional connectivity was computed within individual GIFT maps thresholded at connectivity z-score > 2, which roughly corresponds to level of connectivity of p=.05 for a given voxel with respect to the whole network. Then partial correlations were computed between the mean connectivity of the networks of interest (i.e., DMN-LFPN, DMN-RFPN, and LFPN-RFPN). Both covarying models (model 1 and model 2, without structural MRI) were implemented in this study, to investigate the contribution of cognition to between network connectivity. Finally, each correlation coefficient was converted into z-score using Fisher's r-to-z transformation and compared using the formula from Cohen and Cohen (1983). Between network coupling-connectivity pattern was computed also within the HC group, for comparison purposes.

Finally, we investigated voxel-wise interactions between cognition and functional connectivity only in MCI groups, accounting for sex, brain atrophy, and memory (model 2). The same non-parametric model previously described was used (5000 permutations; $p < .05$ FWE-corrected). Moreover, we implemented a more lenient threshold to correct for multiple comparisons through a cluster-forming threshold of $t=3.6$ (corresponding to $p < 0.001$

uncorrected) and a cluster-wise significance level of p<0.05 FWE corrected. To reduce the number of comparisons, a single composite score was computed for each cognitive domain, as follows: for each test we transformed the corresponding raw scores into z-scores according to the mean and standard deviation of the whole sample. For reaction time and error tests, the inversion was computed for coherence with other cognitive scores. Correlations were performed to investigate the relationship between the FPNs and language and executive functions. Memory was not considered in this analysis, because was inserted as a covariate to control for disease severity.

3. Results

Thirty-eight MCI patients and 38 age-matched HC with available SCADS score and MRI exam were retrieved from the VPH –DARE dataset. Based on median SCADS, 18 MCI patients were included in the HSq-MCI group and 20 in the LSq-MCI group. MCI patients and controls were matched for age (HC: 74 ± 5; HSq-MCI: 74 ± 7; LSq-MCI: 75 ± 7; p = .466) and years of education (HC: 12 ± 4; HSq-MCI: 10 ± 4; LSq-MCI: 11 ± 4; p = .420), consumption of cigarettes and coffee cups (HC: 10 ± 13; HSq-MCI: 5 ± 5; LSq-MCI: 7 ± 10; p = .557; HC: 9 ± 7; HSq-MCI: 11 ± 7; LSq-MCI: 10 ± 9; p = .626, respectively) and use of hypnotic medication (HC: 11%; HSq-MCI: 6%; LSq-MCI: 10%; p = .826). Although not significant, there was a tendency for a difference for sex (p = .139) (See Table 1). Therefore, sex was included as a covariate for the connectivity analysis.

Cognitive analysis showed differences in most of the neuropsychological tests between controls and MCI groups surviving for multiple comparison (p < .004), except for scores on the phonemic fluency and digit span backward tests (p > .05). *Post-hoc* analysis showed that both MCI groups had lower MMSE scores compared to controls. Overall, on memory and executive

functions, both MCI groups had lower performance compared to controls, while on language, scores on the Token and Naming test were lower only in HSq-MCI compared to controls. Semantic fluency test was lower in both MCI groups compared to control. No significant differences in scores on the cognitive tests were observed between the two MCI sub-groups.

3.1 Cortical thickness analysis

Compared to controls, neither HSq-MCI, nor LSq-MCI patients showed reduced cortical thickness after controlling for multiple comparisons with the Montecarlo simulation ($p < .05$). Similarly, no differences in cortical thickness were found between MCI groups.

3.2 Network functional connectivity differences

Model 1 showed reduced connectivity within the posterior cingulate cortex (PCC) and the right angular gyrus (rAG) of DMN in HSq-MCI compared to controls ($p < .05$ FWE-corrected) (Fig. 2, Panel A; Table 2). By contrast, no differences were reported within the DMN in the LSq-MCI group compared with HC. No significant functional connectivity differences were found between MCI groups and HC within both the LFPN and RFPN, while RFPN showed significant increased connectivity within the right inferior frontal gyrus (rIFG) in HSq-MCI compared to LSq-MCI ($p < .025$ FWE-corrected) (Fig. 2, Panel A; Table 2). When cognition was included as a covariate (model 2), DMN clusters detected in model 1 were no longer significant, while increased connectivity of the rIFG-RFPN in HSq-MCI compared to LSq-MCI remained significant ($p < .025$ FWE-corrected; Fig. 2, Panel B).

Post-hoc analysis showed significant divergent associations (assessed with Spearman's correlation) in MCI patients between functional connectivity of DMN-PCC and DMN-rAG and RFPN-rIFG clusters with SCADS scores. Within the MCI sample, functional connectivity of

DMN clusters was positively associated with SCADS scores (rho = .502; p = .003), while rIFG-RFPN connectivity was negatively correlated (rho = -0.551; p = .001) (Fig. 3, Panel C). No significant correlations were found in HC between SCADS scores and connectivity of these clusters (DMN-PCC-rAG: r = -0.016; p = .931; rIFG-RFPN: r = 0.004; p = .983) (Fig. 3, Panel C). A second *post-hoc* analysis was run for the RFPN clusters identified in model 2, confirming the finding of a positive association between SCADS score and rIFG-RFPN connectivity (MCI: r = -0.524; p = .002; HC: r = 0.010; p = .959).

3.3 Coupling connectivity

Both covarying models showed significant positive between networks associations in the HSq-MCI groups (Supplementary Fig. S2). Specifically, in model 1, the DMN and FPNs in HSq-MCI showed significant positive associations (rDMN-LFPN = 0.571; p = .03; rLFPN-RFPN = 0.727; p = .002), while DMN and RFPN showed a positive coupling trend, although it did not reach statistical significance (rDMN-RFPN = 0.480; p = .07). In contrast, no significant between network correlations were detected for LSq-MCI (rDMN-RFPN = 0.086; p = .75; rDMN-LFPN = 0.348; p = .19; rLFPN-RFPN = 0.194; p = .47). Positive associations between network connectivity in HSq-MCI and null results in LSq-MCI were confirmed by model 2 (Supplementary Fig. S2). When we compared the correlation coefficients of the MCI sub-groups, we found significant differences for the LFPN-RFPN coupling connectivity (p = .048) (Fig. 3). Notably, the between network connectivity patterns in HSq-MCI were similar to the coupling pattern observed in controls (Fig. 3, Supplementary Fig. S2).

3.4 Interaction effects between connectivity and cognition across MCI groups

A significant interaction effect between the language composite score and a cluster mapping to the right frontal gyrus within the RFPN emerged only with the lenient cluster-

forming threshold (k=42; MNI: 44, 30, 6; $p < .05$ cluster FWE-corrected) (Fig. 4, Panel A). No significant interactions across MCI groups were reported between LFPN-language and FPNs-executive function. A *post-hoc* analysis showed a divergent association between language performance and functional connectivity of the right frontal gyrus between HSq-MCI and LSq-MCI ($p < .001$). This cluster was spatially congruent with the cluster reported in the previous analysis comparing functional connectivity between HSq-MCI and LSq-MCI (Fig. 4, Panel B).

4. Discussion

In the present study, we assessed the relationship between functional connectivity of large-scale networks and sleep quality in MCI patients. To our knowledge, this is the first study reporting a link between sleep and FPN connectivity in MCI. In HSq-MCI we found increased connectivity within the right inferior frontal gyrus of the RFPN. In contrast, no connectivity changes were observed in LSq-MCI. A *post-hoc* analysis showed a significant association between SCADS with RFPN connectivity in MCI. Furthermore, HSq-MCI showed a significant positive between network connectivity coupling, which was disrupted in LSq-MCI patients. Finally, a significant divergent relationship among MCI groups was observed between the right frontal gyrus of the RFPN and language performance, suggesting divergent trajectories of FPN connectivity associated with self-reported sleep quality.

Overall, these results might suggest possible compensatory mechanisms linked with self-reported high quality of sleep and mediated by enhanced frontal RFPN connectivity in MCI. Similar mechanisms have been observed in cognitively intact individuals. Recently, Byun and colleagues (2020) reported increased network functional connectivity linked with better cognition in participants with sleep disorders. These findings are echoed by a study in a pooled sample of cognitively healthy and MCI patients with obstructive sleep apnea (Naismith et al.,

2020). Moreover, studies investigating cognitive reserve - defined as the ability to maintain cognition relatively well in the presence of brain pathology – described similar associations. Cognitively normal adults with high FPN connectivity maintained better memory performance compared to participants with lower FPN connectivity at comparable levels of entorhinal tau burden (Neitzel et al., 2019). Moreover, Franzmeier et al. (2017) reported an association between higher frontal cortex functional connectivity and higher cognitive reserve in MCI. These authors concluded that enhanced frontal connectivity might mitigate the effect of emerging AD pathology, as suggested by greater reductions of PCC metabolism observed in MCI with higher cognitive reserve (Franzmeier et al., 2017). We hypothesize that sleep may play a similar role: high quality of sleep might help to overcome advancing neurodegeneration in MCI (and progression to dementia), through plasticity compensatory mechanisms involving FPN functional connectivity. Indeed, when cognition was not considered as a covariate in the analysis (model 1), we found reduced DMN connectivity in HSq-MCI. This finding might suggest that HSq-MCI present with higher pathological burden, and increased FPN connectivity associated with sleep quality might underlie compensatory mechanisms sustaining cognitive functions not primarily involved in AD pathology (e.g., language abilities). Finally, MCI cohorts did not exhibit cortical thickness reduction, in line with the assumption that functional network shows early vulnerability, predicting future brain atrophy (Palop and Mucke 2016). Moreover, MCI patients showed a heterogeneous pattern of cortical thinning reflecting potentially different clinical phenotypes, not highlighted by conventional diagnostic criteria (Edmonds et al., 2016; Ossenkoppele et al., 2015), which might explain this null result. In contrast, functional connectivity exhibits a more homogeneous pattern, resulting in robust findings surviving multiple comparison correction, as implemented in this study.

The coupling connectivity analysis support a close relationship between sleep quality and network connectivity. In HSq-MCI we reported a positive DMN-LFPN profile and a positive trend for DMN-RFPN, that was disrupted in LSq-MCI. The DMN-FPN association might reflect between-network compensatory mechanisms in MCI reporting high sleep quality, since enhanced resting-state DMN-FPN coupling supports internally guided attention (Smallwood et al., 2012). In addition, Spreng and colleagues (2010) reported that DMN supports cognitive demand for goal-directed task when its activity is coupled with the FPN. Interestingly, coupling connectivity between FPN and DMN may be driven by dopamine (Dang et al., 2012), a neurotransmitter involved in sleep modulation (Volkow et al., 2012). These results suggest that among MCI patients, higher quality of sleep may reflect coupling connectivity between DMN and FPN mediated by biochemical mechanisms, resulting in connectivity upregulation. In contrast, low sleep quality may disrupt this association, with detrimental effects. This result is in line with previous studies reporting that cognitive decline after sleep deprivation is associated with imbalance in functional brain networks (Wirsich et al., 2018), reinforcing the assumption of an interaction between reduction of cortical connectivity and sleep (Vecchio et al., 2017; Bertini et al., 2004). This assumption is further supported by the interaction analysis, reporting a divergent association between RFPN and language abilities across MCI groups. This result is congruent with previous studies suggesting that the inferior frontal gyrus is involved in the FPN and classically activated in both fluency and categorization fluency tasks (Foulon et al., 2018).

Among the study's limitations was that we included MCI patients defined on the basis of clinical criteria. No evidence of AD molecular pathology was available for these patients, and we cannot rule out the possibility that this group included some individuals without AD pathology. Future studies should investigate whether the relationship between sleep and FPN is mediated by levels of Aβ or tau proteins. Moreover, further longitudinal studies are needed to assess the rate

of progression to dementia in MCI stratified according to sleep quality. Although these issues limit the generalizability of the present findings to the AD field, this study might be important to unravel pathological brain processes linked with potential reversible mechanisms, and associated with early clinical deficits, such as sleep disorders. Moreover, data were acquired on a 1.5 T MR scanner, which provides lower sensitivity and signal-to-noise ratio compared to a 3 T MR scanner. Finally, sleep disturbances were assessed through a self-reported measure. AD patients tend to underestimate their sleep disturbances, and objective sleep measures (e.g., actigraphy) are more strongly related to cognitive dysfunction in the prodromal stage of dementia, limiting the use of subjective sleep questionnaires (Cabanel et al., 2020; Most et al., 2012). However, it has been suggested that sleep disturbances in MCI could be determined on the basis of both subjective and objective measures (Hita-Yañez et al., 2013). Moreover, subjective assessment of sleep quality may be more sensitive to underlying behavioral symptoms with a significant impact on functional disability (Naismith et al., 2011), although some studies have reported no association between cognition and sleep disturbance (Mecca et al., 2018).

In conclusion, our results promisingly show that sleep quality in MCI modulates functional connectivity of the FPN. Future studies on larger and independent samples are needed to confirm these observations and to establish the casual relationship between sleep and FPN. These findings may help the development of new effective interventions by assisting in the identification of surrogate markers of clinical efficacy. Moreover, functional connectivity is emerging as a promising tool for non-invasive brain stimulation approaches targeting neural networks in clinical populations (Pievani et al., 2016; Pini et al., 2018). Future studies should assess the relationship between connectivity and sleep in the very earliest stages of disease. This information would pave the way for the development of new treatments aimed at slowing cognitive decline and restoring sleep quality.

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Conflict of interest The authors declare that they have no conflict of interest

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Fig. 1. Networks of interest derived from the pooled sample of MCI patients and controls.

Fig. 2. Group comparison between MCI groups and controls. Panel A (model 1): reduced functional connectivity was observed within the default mode network (DMN) in MCI patients with higher self-reported sleep quality (HSq-MCI) compared to healthy controls, while increased frontoparietal network (FPN) was observed in the latter group compared to MCI patients reporting lower sleep quality (LSq-MCI). Panel B (model 2): increased right FPN connectivity in HSq-MCI compared to LSq-MCI was confirmed including cognition as a covariate, while difference in DMN was not significant. Panel C: *post-hoc* correlations between Sleep Continuity in Alzheimer's Disease Scale (SCADS) scores and clusters showing significant functional connectivity (FC) differences within the DMN and the right FPN; model 1 (left and middle panel) show a positive correlation in MCI patients between SCADS and FC of the right FPN cluster and a negative correlation with DMN clusters. No significant associations were reported in healthy controls (HC); model 2 (right panel) confirmed the negative correlation in MCI between the cluster of the right FPN and SCADS. Red: MCI patients; blue: HC. Non-parametric Spearman's correlation ($p<0.05$) was used to assess significant relationship. Gaussian smoothing (sigma=1) was applied for better visualization. PCC: posterior cingulate cortex; A: anterior; AG: angular gyrus; I: inferior; IFG: inferior frontal gyrus; R: right; S: superior.

Fig. 3. Panel A: coupling connectivity between the default mode network (DMN) and left and right frontoparietal networks (LFPN and RFPN, respectively) in MCI patients stratified according to the Sleep Continuity in Alzheimer's Disease Scale scores. The high self-reported sleep quality MCI (HSq-MCI) group showed significant DMN-LFPN and LFPN-RFPN

correlations, while between-networks connectivity was disrupted in low self-reported sleep quality MCI patients (LSq-MCI). Moreover, HSq-MCI displayed significant higher coupling LFPN-RFPN connectivity compared to LSq-MCI. Purple: HSq-MCI; Orange: LSq-MCI. Panel B: the pattern of LFPN-RFPN coupling connectivity in HSq-MCI was similar to the between network connectivity pattern of controls.

Fig. 4. A) Voxel-wise analysis for the MCI groups × language interaction within the right frontal gyrus of the right frontoparietal network (RFPN) (cluster-forming threshold of t=3 and a cluster-wise significance level of p<0.025-FWE corrected). B) Clusters within the right frontal gyrus of the RFPN significantly associated with sleep quality in MCI. Blue: cluster showing increased conectivity within the RFPN in HSq-MCI compared to LSq-MCI; Red: cluster showing significant interaction with language performance in MCI groups. BA: Brodmann area; MNI: Montreal Neurological Institute space.

Supplementary Fig. S1. Cognitive factors identified through a principal component analysis of the neuropsychological battery tests. Factor 1: executive-language; factor 2: memory.

Supplementary Fig. S2. Network connectivity coupling between the default mode network (DMN), the left frontoparietal network (LFPN), and the right frontoparietal network (RFPN) in healthy controls and MCI stratified into high (HSq-MCI) and low quality of sleep (HSq-MCI). Similar results were reported covarying for sex (model 1) and covarying for sex and cognitive status (model 2). Symbols denote different p-value thresholds: ** $p < 0.005$; * $p < 0.05$; # $p < 0.07$.

Table 1. Sociodemographic and neuropsychological characteristics

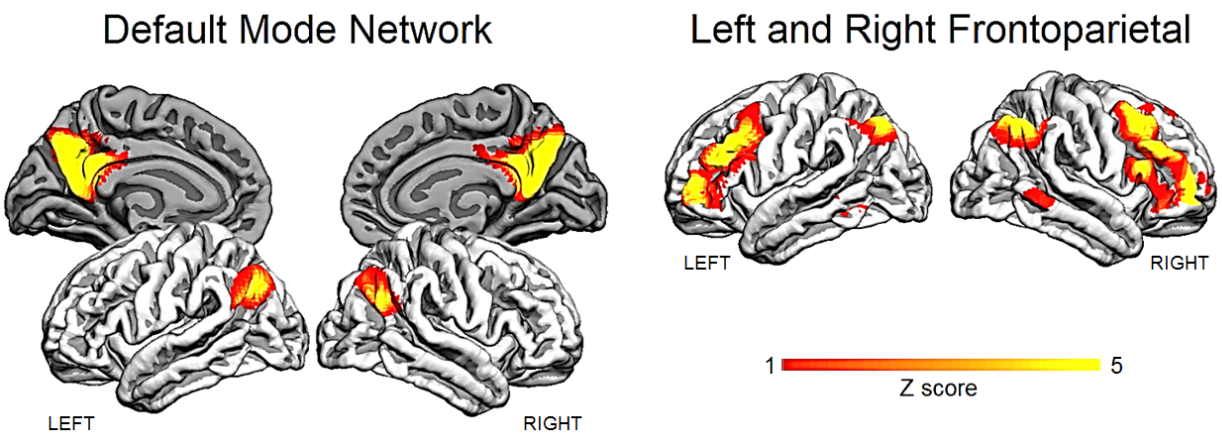
	HC (n=38)	HSq-MCI (n=18)	LSq-MCI (n=20)	p-value
Age	74 ± 5	74 ± 7	75 ± 7	.466
Education	12 ± 4	10 ± 4	11 ± 4	.420
Sex (male%)	37 %	24%	13%	.139
Cigarettes (daily)	10 ± 13	5 ± 5	7 ± 10	.557
Coffee cups (weekly)	9 ± 7	11 ± 7	10 ± 9	.626
Hypnotics (%)	11%	6%	10%	.826
SCADS	19 ± 5	15 ± 2 * #	22 ± 3	<.001
MMSE	29 ± 1	24 ± 3 *	27 ± 2 *	<.001
Memory				
Rey figure – delayed	14 ± 6	4 ± 4 *	7 ± 6 *	<.001
Prose memory	25 ± 7	13 ± 10 *	15 ± 9 *	<.001
Paired Associates Learning	11 ± 4	6 ± 3 *	9 ± 5 *	<.001
Language				
Verbal fluency phonemic	33 ± 11	28 ± 12	28 ± 13	.365
Verbal fluency semantic	39 ± 8	26 ± 16 *	29 ± 10 *	<.001
Token test	34 ± 2	31 ± 2 *	32 ± 3	<.001
Naming test	19 ± 2	16 ± 4 *	18 ± 1	.001
Executive Functions				
Digit Cancellation	52 ± 6	41 ± 10 *	46 ± 8	<.001
Similarities	22 ± 3	13 ± 4 *	17 ± 4 *	<.001
Stroop time	23 ± 9	43 ± 31 *	36 ± 19 *	.002
Stroop error	0.6 ± 1.3	7.7 ± 8.5 *	3.6 ± 6.2 *	<.001
Digit span backward	4.3 ± 0.9	3.6 ± 1.2	3.9 ± 0.7	.109

Differences across groups were assessed with the non-parametric Kruskal-Wallis and Chi square when appropriate. * marks significant differences *vs*. controls; # marks significant differences *vs*. LSq-MCI. HC: healthy controls; HSq-MCI: high quality of sleep MCI group; LSq-MCI: low quality of sleep MCI group; MMSE: Mini-mental state examination; SCADS: Sleep Continuity in Alzheimer's Disease Scale.

Table 2. Voxel-wise comparison of functional network connectivity between MCI groups and controls.

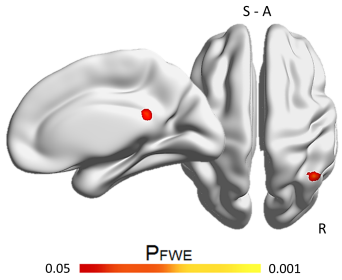
Covarying model	Network	Brain Regions	Side	Cluster size	MNI			BA	p^{FWE}
					x	y	z		
	Healthy controls > HSq-MCI								
Model 1	DMN	Angular gyrus	R	25	40	-58	40	39	.028
		PCC	M	10	6	-40	20	23	.031
	HSq-MCI > LSq-MCI								
	Right FPN	Inferior frontal gyrus	R	9	50	28	4	45	.014
Model 2	**HSq-MCI > LSq-MCI**								
	Right FPN	Inferior frontal gyrus	R	30	50	28	4	45	.003

Grey matter at voxel-level and sex were included as covariates in model 1. Grey matter at voxel-level, sex and cognitive status ("memory factor") were included as covariates in model 2. BA: Brodmann area; DMN: default mode network: FPN: frontal parietal network; HSq-MCI: high self-reported sleep quality MCI group; LSq-MCI: low self-reported sleep quality MCI group. PCC: posterior cingulate cortex.



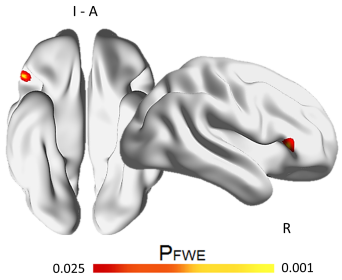
A Default Mode Network

Healthy controls > HSq-MCI



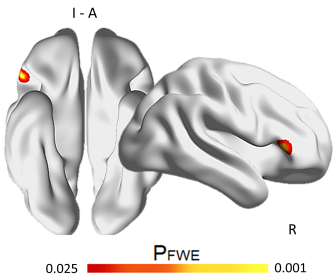
Right Frontoparietal Network

HSq-MCI > LSq-MCI

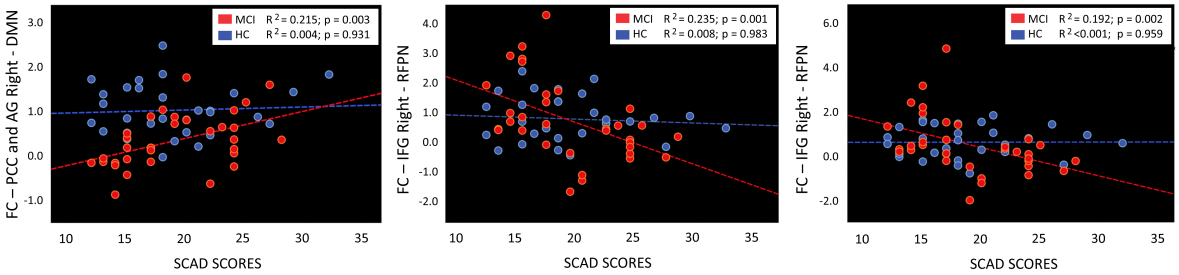


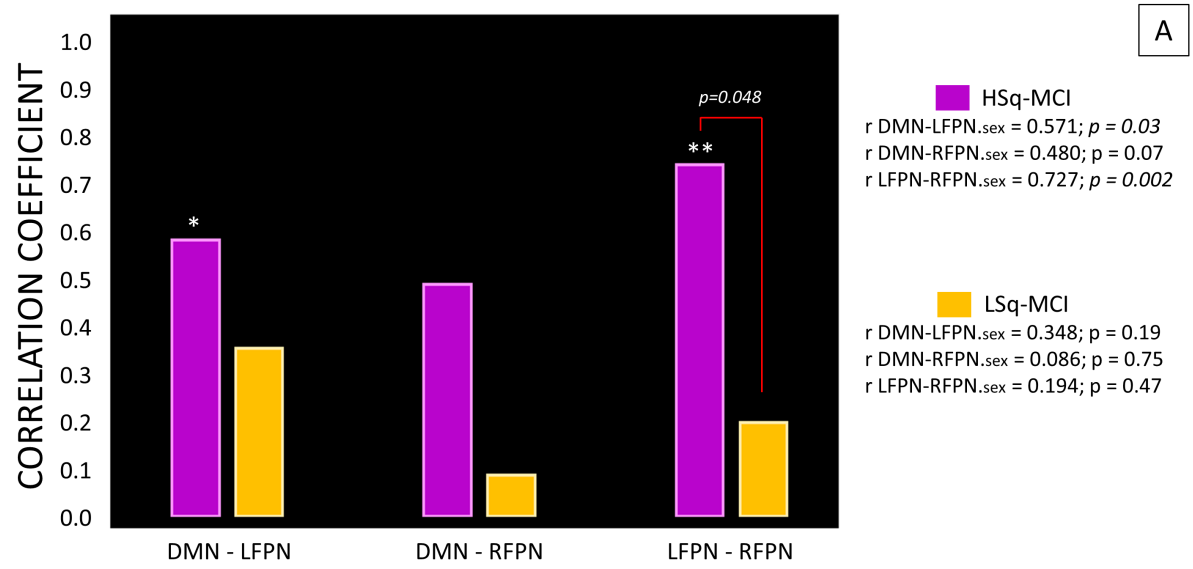
B Right Frontoparietal Network

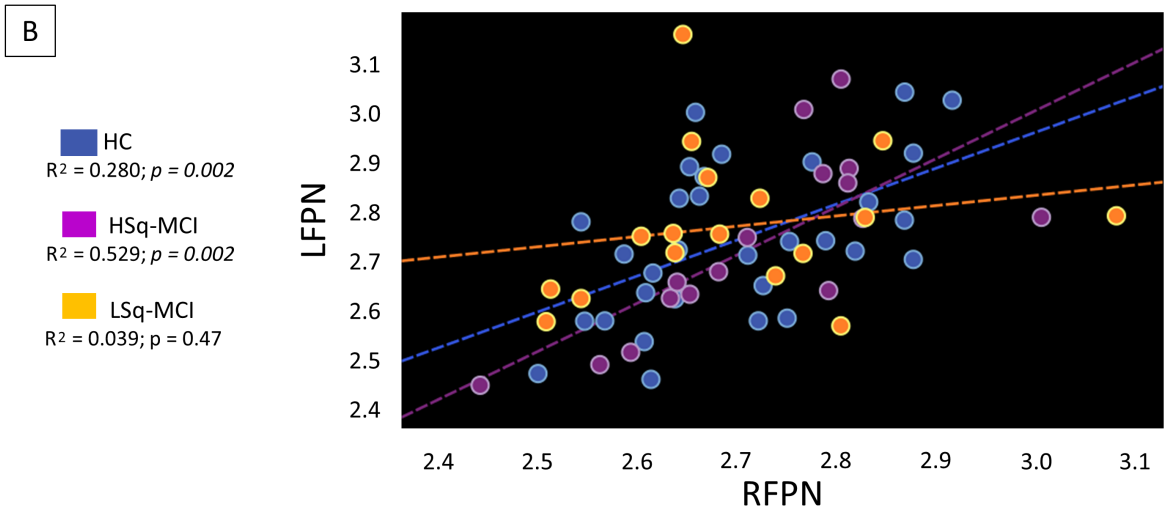
HSq-MCI > LSq-MCI



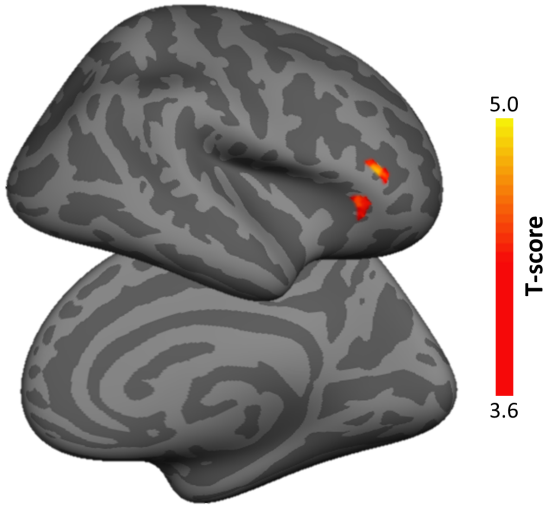
C Associations between functional connectivity and SCAD scores in MCI patients and controls



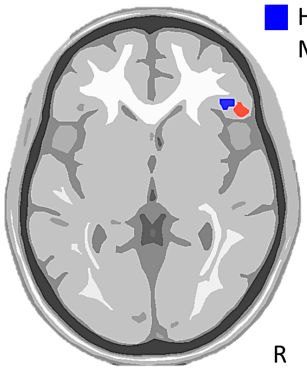

A
CORRELATION COEFFICIENT
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
*
**
p=0.048
DMN - LFPN
DMN - RFPN
LFPN - RFPN
HSq-MCI
r DMN-LFPN.sex = 0.571; p = 0.03
r DMN-RFPN.sex = 0.480; p = 0.07
r LFPN-RFPN.sex = 0.727; p = 0.002
LSq-MCI
r DMN-LFPN.sex = 0.348; p = 0.19
r DMN-RFPN.sex = 0.086; p = 0.75
r LFPN-RFPN.sex = 0.194; p = 0.47


B
HC
R² = 0.280; p = 0.002
HSq-MCI
R² = 0.529; p = 0.002
LSq-MCI
R² = 0.039; p = 0.47
LFPN
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.4
2.5
2.6
2.7
2.8
2.9
3.0
3.1
RFPN

A INTERACTION EFFECT RFPN x LANGUAGE



B INFERIOR FRONTAL GYRUS - RFPN



Sleep is associated with frontoparietal network in mild cognitive impairment

Brain network functional coupling and sleep quality are related

Sleep might underlie compensatory mechanisms through frontoparietal connectivity