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RESEARCH ARTICLE

# Sleep disturbance and memory dysfunction in early multiple sclerosis

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## Abstract

**Objective**: Sleep-dependent memory processing occurs in animals including humans, and disturbed sleep negatively affects memory. Sleep disturbance and memory dysfunction are common in multiple sclerosis (MS), but little is known about the contributions of sleep disturbance to memory in MS. We investigated whether subjective sleep disturbance is linked to worse memory in early MS independently of potential confounders. **Methods**: Persons with early MS ($n$ = 185; ≤5.0 years diagnosed) and demographically matched healthy controls ($n$ = 50) completed four memory tests to derive a memory composite, and four speeded tests to derive a cognitive efficiency composite. Z-scores were calculated relative to healthy controls. Sleep disturbance was defined by the Insomnia Severity Index score ≥ 10. ANCOVAs examined differences in memory and cognitive efficiency between patients with and without sleep disturbance controlling for potential confounds (e.g., mood, fatigue, disability, T2 lesion volume, gray matter volume). Comparisons were made to healthy controls. **Results**: Seventy-four (40%) patients reported sleep disturbance. Controlling for all covariates, patients with sleep disturbance had worse memory ($z$ = −0.617; 95% CI: −0.886, −0.348) than patients without disturbance (z = −0.171, −0.425, 0.082, $P$ = .003). Cognitive efficiency did not differ between groups. Relative to healthy controls, memory was worse among patients with sleep disturbance, but not among patients without sleep disturbance. **Interpretation**: Sleep disturbance contributes to MS memory dysfunction, which may help explain differential risk for memory dysfunction in persons with MS, especially since sleep disturbance is common in MS. Potential mechanisms linking sleep disturbance and memory are discussed, as well as recommendations for further mechanistic and interventional research.

## Introduction

Memory dysfunction is common in multiple sclerosis (MS);[1-3] however, the risk for memory difficulty remains poorly understood.[3] Neuroimaging studies have linked memory in MS to various neuroanatomical changes (e.g., hippocampal and thalamic atrophy),[4-6] but the modest strength of such relationships suggests that other unknown influences also impact memory in MS patients. That is, disease-related changes that negatively affect the neurophysiology of learning and memory may impair memory in ways not appreciated by gray matter volumes alone.

Sleep disturbance is common in MS,[7-10] although mechanisms underlying MS-related sleep difficulty remain uncertain (for reviews[11-13]). Sleep physiology is linked to memory in animals, healthy adults, and sleep-disordered populations;[14-19] however, links between sleep disturbance

and memory deficits in MS patients remain unclear. A 2018 review identifying 12 studies on sleep and cognition in MS showed little evidence for links between sleep and objective cognition,[20] but only three studies objectively assessed memory.[21-23] One study reported a link between patient-reported sleep disturbance and visual memory in 40 persons with MS,[21] whereas another study failed to show a relationship between patient-reported sleep disturbance and objective cognition in 121 patients, but visual memory was not evaluated.[22]

Sleep deprivation appears to reduce hippocampal dendritic spine density and synaptic efficiency in animals and humans, thereby leading to worse memory (for review[24]). Homeostatic synaptic downscaling during sleep supports the encoding of new information after waking,[17,18] Sleep-dependent memory processing also involves discriminate selection of prior wake experiences which are assimilated into existing knowledge (traditionally termed "consolidation").[15] Given that sleep disturbance is common in MS, synaptic alternations due to deprivation and disruption of sleep-related memory processing may contribute to memory deficits in MS. If so, sleep treatments may represent biologically plausible interventions to improve memory, which would be valuable given the absence of validated memory treatments in MS.[25,26] Here we investigated links between sleep disturbance and memory (while controlling for important confounds such as mood, fatigue, disability, and MRI markers of disease burden) in the RADIEMS cohort of 185 early relapsing-remitting MS patients. Cognitive inefficiency (i.e., slow processing speed) is also common in MS and was examined to assess the specificity of sleep contributions to memory.

## Methods

### Patients

The Reserve against Disability in Early MS (RADIEMS) cohort consists of 185 patients aged 20 to 50 years and diagnosed with relapsing-remitting MS or clinically isolated syndrome[27] for $\leq 5.0$ years (Table 1). Key exclusions: pregnancy, clinical relapse within six weeks, history of other neurologic or neurodevelopmental condition, or serious mental illness. The current work utilized baseline data from this ongoing longitudinal cohort study. To provide an appropriate normative comparison for cognitive tasks (described below), we also enrolled 50 healthy controls who were demographically matched to RADIEMS patients (32 women, aged 32.9 $\pm$ 7.5 years) and who met the same inclusion criteria (other than MS diagnosis).

### Sleep disturbance

Patient-reported sleep disturbance was assessed by the Insomnia Severity Index (ISI):[28] an established seven-item survey on which respondents rate difficulties (a) falling

**Table 1.** Sample characteristics.

| | MS | MS (ISI < 10) | MS (ISI ≥ 10) |
|---|---|---|---|
| Sample Size[1] | 184 | 110 | 74 |
| Age (mean ± sd) | 34.3 ± 7.4 | 34.2 ± 7.1 | 34.5 ± 7.9 |
| Sex (Female:Male) | 123:61 | 74:36 | 49:25 |
| Disease Course (RRMS/ CIS) | 164/ 20 | 96/ 14 | 68/ 6 |
| Years since Diagnosis: (median, IQR) | 2.0 (0.9–3.3) | 2.0 (0.9–3.3) | 2.0 (0.8–3.5) |
| EDSS (median, IQR) | 1.0, 0.0–1.5 | 1.0 (0.0–1.5) | 1.0 (0.0–2.0) |
| MHI-5 (mean ± sd) | 71.0 ± 17.6 | 75.2 ± 14.6*** | 64.6 ± 19.7*** |
| FSS (mean ± sd) | 3.5 ± 1.5 | 3.1 ± 1.4*** | 4.2 ± 1.5*** |
| BMI (mean ± sd) | 26.8 ± 6.2 | 26.0 ± 5.5* | 28.0 ± 6.9* |
| Rx with Negative Effects on Sleep (n, %) | 27 (14.7) | 13 (11.8) | 14 (18.9) |
| Alcohol (gm; median, IQR) | 4.4 (1.1–10.0) | 5.6 (2.0–10.3)* | 2.8 (0.0–8.8)* |
| Caffeine (mg; median, IQR) | 116 (48.5–243.5) | 116.1 (50.9–243.2) | 116.8 (44.9–245.0) |
| T2LV ml (median, IQR) | 1.3, 0.5–4.3 | 1.2, 0.4–2.7** | 2.1, 0.6–5.8** |
| nThalamus ml (mean ± sd) | 21.1 ± 1.7 | 21.4 ± 1.5* | 20.8 ± 2.0* |

sd, standard deviation; RRMS, relapsing-remitting multiple sclerosis; CIS, clinically isolated syndrome; IQR, interquartile range; EDSS, Expanded Disability Status Scale; MHI-5, Mental Health Inventory; FSS, Fatigue Severity Scale; BMI, body mass index; T2LV, T2 lesion volume; ml, milliliter; gm, gram, mg; milligram.

[1]One enrolled patient with obstructive sleep apnea was excluded from the total RADIEMS sample of 185. Two enrolled patients were not permitted to undergo research MRIs due to metal in their bodies. Sample size was therefore 184 for non-neuroimaging analyses and 182 for neuroimaging analyses.

*$P < .05$.

**$P < .01$.

***$P < .001$.

 

asleep, (b) staying asleep, and (c) waking too early (0 = none, 4 = very severe), and the degree to which (d) they are dissatisfied with their sleep, (e) others notice their sleep problem, (f) they are worried/distressed about their sleep, and (g) sleep problems interfere with everyday function (0 = least, 4 = worst). We used the validated cutoff of ISI $\geq$ 10 as a marker of sleep disturbance, which showed the optimal balance of sensitivity (86.1%) and specificity (87.7%) for identifying insomnia in a large community sample.[29] Note that the ISI constitutes a measure of patient-reported sleep disturbance. Patients were not formally assessed for sleep disorders beyond a medical history review conducted with patients; however, the risk for undiagnosed obstructive sleep apnea (OSA) is low within a relatively young sample (age $\leq$ 50, mean age = 34.3 $\pm$ 7.4) consisting mostly of women. There was one patient (49-year-old man) with premorbid obstructive sleep apnea (OSA) who was excluded from analyses.

## Cognitive assessment

We utilized previously validated composite scores of memory and cognitive efficiency derived from eight tasks (four tasks each; all tasks were administered in traditional paper-and-pencil formats except where noted).[30] ***Memory*** was assessed by (1) *CANTAB Paired Associate Learning* (Cambridge Cognition, Cambridge, UK; www.cambridgecognition.com) tablet-based task wherein subjects learn and recall object-location associations;[31] (2) *Brief Visuospatial Memory Test, Revised*[32], and (3) *Selective Reminding Test*[33,34] are nonverbal (geometric shapes and locations) and verbal (word list learning) memory tests frequently used in MS;[2,33] (4) *Verbal Paired Associate Learning*[30] wherein subjects learn 12 unrelated word pairs across four trials. ***Cognitive Efficiency*** was assessed by (1) *Symbol Digit Modalities Test*[35] wherein subjects quickly state digits corresponding to symbols based on a key; (2) *Stroop Color-Word Test*[36] wherein subjects rapidly named the ink color of nonmatching printed words (e.g., "blue" written in red ink); (3) *NIH Toolbox Pattern Comparison*[37] tablet-based task wherein subjects rapidly decide whether two pictures are the same or different; (4) *Decision Speed*[30] wherein subjects quickly decide which of four common objects (e.g., dress, car, book, paper clip) is largest in real life (e.g., car). These latter four tasks each have unique cognitive requirements (e.g., inhibition, semantic decision making), but they share the requirement of quick and efficient performance, and contribute to the same latent variable.[30] We therefore refer to the composite of these tasks as "cognitive efficiency." Raw scores on all eight tasks were adjusted for age, sex, and estimated premorbid intelligence (Wechsler Test of Adult Reading[38]) using general linear models and saving residuals. Z-scores were derived for each task based on means and SDs of the aforementioned demographically matched healthy control group, which were then averaged into composite memory and cognitive efficiency scores (four tasks each; as described previously[30]). These two composite measures were normally distributed.

## Covariates

In addition to age and sex the following variables with possible links to both sleep and cognition were controlled in analyses. That is, the goal was to statistically control for potentially confounding variables that may be related to both sleep and cognition (i.e., memory), thereby isolating the independent relationship between sleep disturbance and cognition. ***Mood*** was assessed with the Mental Health Inventory (MHI-5;[39,40] continuous; persons use a six-point scale to indicate how often they have experienced symptoms of depression [three items] and anxiety [two items] over the past month; links among anxiety, depression, and sleep disturbance are well-established,[41] and worse mood is related to worse cognition in MS[42]). ***Fatigue*** was assessed with the Fatigue Severity Scale (FSS;[43] continuous; persons use a seven-point scale across nine items to indicate the severity of fatigue within the last week; given that fatigue is related to poor sleep[44] and may be related to cognition, we controlled for this potential confound). ***Body mass index*** (BMI; continuous) was calculated from height and weight; given that obesity has been linked to disturbed sleep[45] and worse cognition,[46] we included BMI as a covariate. ***Medications for which disturbed sleep is a common side effect*** (e.g., anti-depressants, beta-blockers, stimulants) were recorded (dichotomous: yes [$n$ = 27], no [$n$ = 157]). Only four patients were taking medications to improve sleep (zolpidem $n$ = 2, amitriptyline $n$ = 1, trazodone $n$ = 1). To be thorough, supplemental analyses were performed excluding these patients. ***Alcohol and Caffeine consumption*** was surveyed using a Food Frequency Questionnaire (FFQ; Harvard University 2015 Grid, analysis similar to[47]) on which patients reported their typical intake of specific beverages over the past year (e.g., beer, caffeinated tea, etc.); daily consumption of alcohol (grams) and caffeine (milligrams) was derived (quartiles due to skewness). Sample medians were used for three patients missing FFQ data. Alcohol and caffeine have potential effects on sleep and cognition and were therefore included as covariates. ***Neurologic disability*** was assessed with the Expanded Disability Status Scale (EDSS),[48] a neurologic examination evaluating visual, pyramidal, sensory, brainstem, cerebellar, and bowel and bladder function. Disability was very low in this early cohort (median EDSS = 1.0, IQR: 0.0–1.5); analyses controlled for neurologic disability (EDSS:

 

no disability 0.0–1.5, minimal disability 2.0–2.5, moderate disability ≥ 3.0). EDSS was included as a covariate because physical disability could potentially be related to both disturbed sleep and overall disease burden. Consistent with this notion, there is an a priori possibility that MS disease burden mediates links between sleep disturbance and cognition, although this remains unknown because previous studies on sleep and cognition in MS had not reported neuroimaging data. We therefore also included MRI markers of disease-related change as covariates. Patients underwent a standardized 3.0 Tesla MRI of the brain (Siemens Skyra). As described,[49] ***T2 lesion volumes*** (T2LV, log-transformed) were measured from 3D T2-weighted brain MRIs using a local thresholding segmentation technique (Jim 6.0, Xinapse System), and ***normalized gray matter volumes*** of total gray matter, thalamus, and hippocampus were measured with SIENAX[50] and FIRST[51] using lesion-filled 3D T1-weighted images and applying the volume-scaling factor to adjust for intracranial volume. Thalamus and hippocampus were chosen because atrophy of these structures is prevalent and correlated with memory in MS.[4-6,52-54]

### Statistical analysis

MANCOVAs investigated differences in memory and cognitive efficiency between patients with and without sleep disturbance controlling for age and sex (Model 1), age, sex, mood, fatigue, BMI, alcohol and caffeine consumption, medications, and disability (Model 2), and age, sex, mood, fatigue, BMI, alcohol and caffeine consumption, medications, disability, T2LV, and normalized thalamic gray matter (Model 3). Controlling for age and sex, normalized thalamic volume was more related to both memory ($r_p$ = .161, $P$ = 0.031) and cognitive efficiency ($r_p$ = 0.415, $P$ < 0.001) than were normalized volumes of total gray matter ($r_p$ = 0.072 & .342, respectively) or hippocampus ($r_p$ = 0.158 & .217, respectively). As such, normalized thalamic volume was used in MANCOVAs. Three models were used to present results that are essentially unadjusted (Model 1), adjusted for potential confounds related to sleep in the literature (Model 2), and additionally adjusted for neuroimaging markers of MS disease burden to ensure that links between sleep disturbance and poor memory are not mediated through the "third variable" of worse disease (Model 3). Composite memory and cognitive efficiency scores were used in analyses. Any significant relationships between sleep disturbance and composites were followed up with an exploratory MANCOVA to identify which of the four tasks from that composite was most related to sleep.

## Results

### Preliminary analyses

Self-reported sleep disturbance (ISI ≥ 10) was present in 40.2% (74/184) of our early MS cohort. Within our MS sample, there were no significant differences in age, sex, disease course, years since diagnosis, medications with possible negative effects on sleep, caffeine consumption, or physical disability between patients with versus without sleep disturbance (Table 1); however, patients with sleep disturbance reported worse mood (t[182] = 4.18, $P$ < 0.001) and worse fatigue (t[182] = 5.61, $P$ < 0.001), had slightly higher BMI (t[182] = 2.11, $P$ = 0.035), and lower alcohol consumption (Mann–Whitney U = 3213, $P$ = 0.038). Patients reporting sleep disturbance also had higher T2LV (Mann–Whitney U = 3034, $P$ = 0.007) and lower normalized thalamic volume (t[180] = 2.20, $P$ = 0.029). These variables were statistically controlled in subsequent analyses.

### Primary analyses

MANCOVA results (Table 2) show that patients reporting sleep disturbance had worse memory (F[1, 180] = 12.636, $P$ < 0.001, $\eta_p^2$ = .066) and worse cognitive efficiency (F[1, 180] = 8.199, $P$ = 0.005, $\eta_p^2$ = .044) than patients without sleep disturbance when controlling for age and sex (Model 1); however, in models controlling for other potential confounds (e.g., mood, fatigue, neuroimaging markers of disease; Models 2 and 3) sleep disturbance was only associated with worse memory (Model 2: F[1, 168] = 9.694, $P$ = 0.002, $\eta_p^2$=.055; Model 3: F[1, 164] = 7.410, $P$ = 0.007, $\eta_p^2$ = .043) but not cognitive efficiency (Model 2: F[1, 168] = 2.663, $P$ = .105, $\eta_p^2$ = .016; Model 3: F[1, 164] = 0.789, $P$ = 0.376, $\eta_p^2$ = .005). The relationship between sleep disturbance and memory had a medium effect size in fully adjusted models ($\eta_p^2$ = .043 to .055). Taking a medication with possible negative effects on sleep was the only other variable with a significant albeit smaller relationship to worse memory (Table 2). Also, as shown in Table 2, mood was the only independent predictor of cognitive efficiency in Model 2, and the only non-neuroimaging predictor in Model 3. Worse mood was associated with sleep disturbance (Table 1), and mediation analysis suggests that the simple association between sleep disturbance and cognitive efficiency (Model 1) was mediated through (explained by) worse mood (Sobel z = −2.07, $P$ = 0.039), which is consistent with previous work.[55] In contrast, the relationship between sleep disturbance and memory was robust against control for several potential behavioral and neuroimaging confounds in Models 2 and 3.

 

**Table 2.** MANCOVA results: Differences in memory (top panel) and cognitive efficiency (bottom panel) between multiple sclerosis (MS) patients with versus without sleep disturbance.

ANCOVA: Memory

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| Predictor | *F* | *P* | $\eta_p^2$ | *F* | *P* | $\eta_p^2$ | *F* | *P* | $\eta_p^2$ |
| Sleep Disturbance (ISI) | **12.636** | **<0.001** | **.066** | **9.694** | **.002** | **.055** | **7.410** | **.007** | **.043** |
| Age | 0.082 | .775 | .000 | 0.098 | .754 | .001 | 0.018 | .892 | .000 |
| Sex | 0.074 | .786 | .000 | 0.098 | .755 | .001 | 0.001 | .977 | .000 |
| Mood (MHI-5) | 0.309 | .579 | .002 | 0.309 | .579 | .002 | 0.309 | .579 | .002 |
| Fatigue (FSS) | | | | 2.030 | .156 | .012 | 2.058 | .153 | .012 |
| BMI | | | | 1.009 | .317 | .006 | 1.468 | .227 | .009 |
| Alcohol | | | | 0.232 | .874 | .004 | 0.202 | .895 | .004 |
| Caffeine | | | | 0.427 | .734 | .008 | 0.477 | .699 | .009 |
| Medications | | | | **3.979** | **.048** | **.023** | **4.578** | **.034** | **.027** |
| EDSS | | | | 1.209 | .301 | .014 | 1.073 | .344 | .013 |
| T2LV | | | | | | | 2.826 | .095 | .017 |
| nThal Vol | | | | | | | 0.670 | .414 | .004 |
| Sleep Disturbance: mean (95% CI) | | | | | | | | | |
| No | −0.024 (−0.193, 0.144) | | | −0.068 (−0.233, 0.097) | | | −0.087 (−0.256, 0.082) | | |
| Yes | −0.505 (−0.711, −0.300) | | | −0.441 (−0.642, −0.240) | | | −0.413 (−0.620, −0.207) | | |

ANCOVA: Cognitive Efficiency

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| Predictor | *F* | *P* | $\eta_p^2$ | *F* | *P* | $\eta_p^2$ | *F* | *P* | $\eta_p^2$ |
| Sleep Disturbance (ISI) | **8.199** | **.005** | **.044** | 2.663 | .105 | .016 | 0.789 | .376 | .005 |
| Age | 0.448 | .504 | .002 | 0.123 | .726 | .001 | 0.030 | .862 | .000 |
| Sex | 0.116 | .734 | .001 | 0.181 | .671 | .001 | 0.168 | .683 | .001 |
| Mood (MHI-5) | | | | **6.219** | **.014** | **.036** | **7.180** | **.008** | **.042** |
| Fatigue (FSS) | | | | 1.381 | .242 | .008 | 1.915 | .168 | .012 |
| BMI | | | | 0.866 | .353 | .005 | 0.612 | .435 | .004 |
| Alcohol | | | | 0.597 | .618 | .011 | 0.921 | .432 | .017 |
| Caffeine | | | | 1.682 | .173 | .029 | 1.245 | .295 | .022 |
| Medications | | | | 1.934 | .166 | .011 | 2.943 | .088 | .018 |
| EDSS | | | | 0.463 | .630 | .005 | 0.210 | .811 | .003 |
| T2LV | | | | | | | **8.643** | **.004** | **.050** |
| nThal Vol | | | | | | | **15.102** | **<0.001** | **.084** |
| Sleep Disturbance: mean (95% CI) | | | | | | | | | |
| No | −0.352 (−0.561, −0.142) | | | −0.449 (−0.649, −0.250) | | | −0.499 (−0.680, −0.318) | | |
| Yes | −0.833 (−1.088, −0.578) | | | −0.687 (−0.931, −0.444) | | | −0.614 (−0.835, −0.392) | | |

ISI, Insomnia Severity Index; MHI-5, Mental Health Inventory; FSS, Fatigue Severity Scale; BMI, body mass index; EDSS, Expanded Disability Status Scale; T2LV, T2 lesion volume; nThal Vol, normalized thalamic volume; CI, confidence interval.
Note: Bold font signifies results that are statistically significant ($P < 0.050$).

To provide context for the current findings linking sleep disturbance and memory, ANCOVA compared memory composite scores of patients with and without sleep disturbance versus the aforementioned 50 healthy controls (who completed the same memory assessments), controlling for age, sex, mood (MHI), fatigue (FSS), BMI, and medications (disability and neuroimaging were not applicable or available for controls). As shown (Fig. 1), memory was significantly worse among patients with disturbed sleep (mean; 95% CI: −0.573; −0.801, −0.345) compared with healthy controls (0.050; −0.214, 0.315, $P < 0.001$) and patients without sleep disturbance (−0.002, −0.179, 0.175, $P < 0.001$). There was no difference in memory between healthy controls and patients without sleep disturbance ($P = 0.742$).

## Additional analyses

### Measurement of mood

We used the MHI-5 as our measure of mood because it includes symptoms of depression and anxiety; however,

 

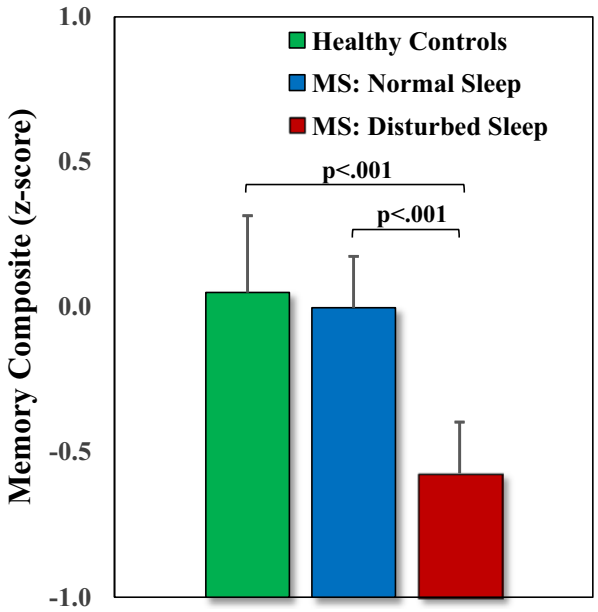


**Figure 1.** Memory across Healthy Controls and Patients with versus without Sleep Disturbance. Means and 95% confidence intervals (error bars) are plotted for differences in memory across groups, controlling for age, sex, mood (MHI), fatigue (FSS), BMI, and medications that may affect sleep. As shown, patients with sleep disturbance had worse memory than both healthy controls and patients without sleep disturbance, which did not differ from each other.

patients also completed the Beck Depression Inventory-Fast Screen (BDI-FS)[56,57] as a measure of depression. When MANCOVAs were repeated using BDI-FS results were nearly identical to those for MHI-5 in MANCOVAs examining memory and cognitive efficiency, with no changes in the results for sleep disturbance (e.g., Model 3: memory $F[1, 164] = 8.011$, $P = 0.005$, $\eta_p^2 = 0.047$; cognitive efficiency $F[1, 164] = 1.181$, $P = 0.279$, $\eta_p^2 = 0.007$]. As noted, four patients were taking medications to improve sleep. All aforementioned results linking sleep and memory remained unchanged when these four patients were removed from analyses.

## Neuroimaging

We sought to select and control for neuroimaging markers of disease burden related to cognition. Preliminary analyses identified thalamic volume as more related to memory and cognitive efficiency than total gray and hippocampal volumes. Supplemental analyses showed that thalamic volume was also more related to memory than other normalized deep gray matter volumes (caudate, putamen, pallidum, amygdala) and microstructural integrity of normal appearing white matter (NAWM) estimated as means of fractional anisotropy and mean diffusivity across NAWM after masking out T2 lesions (methods described previously[58]).

## Individual memory and cognitive efficiency tasks

MANCOVA investigated relationships between sleep disturbance and performance on the four individual memory tests composing the memory composite, controlling for age and sex (Model 1), age, sex, mood, fatigue, medications, and BMI (Model 2), and age, sex, mood, fatigue, medications, BMI, T2LV, and normalized thalamic volume (Model 3). As shown (Table 3), disturbed sleep was specifically related to paired-associate learning (PAL, V-PAL) in all models. Total learning and delayed recall scores of the SRT and BVMT-R may represent different mnemonic processes, so we also performed analyses with these scores separated out. Neither total learning nor delayed recall for either SRT or BVMT-R were related to sleep disturbance in any of the three models (Ps > .05), and relationships between sleep disturbance and memory did not differ between total learning and delayed recall (i.e., Model 3: mean $\eta_p^2$s of 0.001 vs 0.001).

To be thorough, the same MANCOVA analyses were performed to assess differences across patients with and without sleep disturbance on the four cognitive efficiency tasks. As shown (Table 3), Stroop performance was worse among patients with sleep disturbance in Model 2, but there were no differences between groups on any cognitive efficiency measure in Model 3.

 

**Table 3.** MANCOVA: Differences in individual memory and cognitive efficiency test performance in patients with vs without sleep disturbance.

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | *F* | *P* | $\eta_p^2$ | *F* | *P* | $\eta_p^2$ | *F* | *P* | $\eta_p^2$ |
| Memory | | | | | | | | | |
| CANTAB PAL | **20.710** | **<0.001** | **.103** | **18.675** | **<0.001** | **.097** | **16.833** | **<0.001** | **.090** |
| BVMT-R | 3.049 | .083 | .017 | **3.976** | **.048** | **.022** | 2.832 | .094 | .016 |
| SRT | 3.199 | .075 | .017 | 1.820 | .179 | .010 | 0.967 | .327 | .006 |
| V-PAL | **5.877** | **.016** | **.032** | **5.494** | **.020** | **.031** | **4.195** | **.042** | **.024** |
| Cognitive Efficiency | | | | | | | | | |
| SDMT | **5.430** | **.021** | **.029** | 1.991 | .160 | .011 | 0.590 | .444 | .003 |
| Stroop | **7.006** | **.009** | **.037** | **4.072** | **.045** | **.023** | 2.247 | .136 | .013 |
| Pattern Comparison | 3.072 | .081 | .017 | 1.060 | .305 | .006 | 0.385 | .536 | .002 |
| Decision Speed | 1.519 | .219 | .008 | 0.116 | .734 | .001 | 0.065 | .799 | .000 |

CANTAB PAL, CANTAB Paired Associate Learning; BVMT-R, Brief Visuospatial Memory Test, Revised; SRT, Selective Reminding Test; V-PAL, Verbal Paired Associate Learning; SDMT, Symbol Digit Modalities Test.
Note: Bold font signifies results that are statistically significant ($P < 0.050$).

### MS phenotypes and disease-modifying therapies

Sleep disturbance did not differ across MS phenotypes (CIS vs RRMS; Table 1; Fisher Exact Test p = .469), and aforementioned results did not change when phenotype was added as a covariate. Likewise, sleep disturbance did not differ across patients on different types of disease-modifying therapy (DMT; $X^2[3] = 3.419$, $P = 0.331$) defined as untreated ($N = 12$), injectable ($N = 31$; interferon β-1a, peginterferon β-1a, glatiramer acetate), oral ($N = 102$; teriflunomide, fingolimod, dimethyl fumarate), and infusion ($N = 39$; natalizumab, rituximab). Results did not change when type of DMT was added as a covariate. As mentioned in the Methods, four patients were taking medications to improve sleep (zolpidem $n = 2$, amitriptyline $n = 1$, trazodone $n = 1$). All results remained nearly exactly the same when analyses were run excluding these four patients.

## Discussion

Self-reported sleep disturbance was associated with memory dysfunction in our early MS cohort, even when controlling for important potential confounds including mood, fatigue, and neuroimaging markers of MS disease burden (T2LV, thalamic volume). The impact of sleep on memory has been well-established in studies of animals, healthy adults, and sleep-disordered populations.[14-19] Although MS patients have higher risks for both sleep disturbance[7-10] and memory impairment,[1-3] few previous studies have investigated whether disrupted sleep may contribute to poor memory in MS patients. Consistent with our finding, one prior study reported a link between patient-reported sleep disturbance and visual memory in 40 persons with MS.[21] (Likewise, sleep was most related to object-location memory on CANTAB PAL, Table 3). As reviewed,[20] the few other studies conducted on sleep and cognition in MS have not shown relationships between sleep disturbance and objective memory, but samples were typically small and/or did not measure visual memory. Our larger and more homogeneous sample (i.e., ≤5.0 years diagnosed) may have yielded more power to detect a relationship.

Current findings may hold future clinical significance, as no treatments have been well-validated to improve memory in MS.[25,26] Work should also evaluate whether effective treatment of sleep disturbance improves memory in MS patients. One recent pilot trial demonstrated the feasibility of cognitive-behavioral therapy for insomnia (CBT-I) for persons with MS,[59] although cognition was not evaluated. Future clinical trial work is therefore necessary to evaluate whether treatments to improve sleep also improve memory in MS.

Future research is needed to replicate our current findings with objective measures of sleep disturbance (i.e., polysomnography, actigraphy), which will help identify basic mechanisms of this relationship in MS. Importantly, subjective reports of sleep quality permit investigations of memory differences between patients with and without reported sleep disturbance, but finer-grained analyses of sleep quality including sleep architecture require polysomnography. In general, cross-sectional work suggests that subjective reports of sleep quality correlate well with objective sleep efficiency (percent of time in bed spent sleeping), but not with objective measurements of sleep architecture;[60,61] however, subjective and objective measures were more highly correlated when investigated longitudinally within subjects who underwent experimental manipulations of sleep quality.[62] Within-subject measurement of changes in sleep architecture and memory

 

elicited by experimentally manipulating sleep with treatment would provide a higher level of causal evidence in persons with MS, as has been demonstrated in OSA.[63]

Several potential mechanisms may underlie relationships between sleep and memory in MS. First, sleep disturbance may contribute to (or be the consequence of) disease-related changes such as new inflammatory lesion formation or cerebral atrophy, which may mediate links to memory. Indeed, animal studies demonstrate blood–brain barrier breakdown and CNS autoimmune disease exacerbation after sleep deprivation.[64,65] This does not explain our current findings because sleep disturbance remained strongly related to memory even when controlling for T2LV and cerebral atrophy. It is possible, however, that ongoing inflammatory processes not visualized by MRI may mediate these relationships, but such an explanation does not account for the specificity of our findings to memory versus cognitive efficiency. This specificity to memory is consistent with the established role of sleep physiology in both memory encoding and consolidation; however, differential sleep-related consolidation cannot fully explain our current findings because all memory assessments occurred during one session not separated by sleep. Sleep disturbance may also impair memory consolidation in MS patients, but this must be evaluated by future research investigating the relationship between sleep physiology and stability of memories beyond a single day (i.e., with intervening sleep).

The synaptic homeostasis hypothesis[18] posits that synaptic downscaling during sleep (particularly slow wave sleep) prepares synapses for encoding of new information after waking. This hypothesis may be consistent with our finding of poor encoding of newly presented information by patients reporting sleep disturbance, as basic animal and human research links sleep deprivation to reduced hippocampal dendritic spine density and synaptic efficiency, thereby leading to worse memory (for review[24]). This also appears broadly consistent with our observation specifically linking sleep disturbance to poor paired associate learning (PAL), especially for object-location pairings. The hippocampus is particularly important for associative memory across species (for review[66], especially object-location pairings[67]), which requires the type of functional interactions between the hippocampi and the cortex[68] that is impaired after sleep deprivation.[69] The CANTAB PAL task requires that persons encode object-location pairings in a single exposure using a paradigm that does not allow for rehearsal. During the V-PAL patients were presented with word-pairs that were immediately followed by other word-pairs. In addition to the associative learning aspects of these tasks, it may also be that PAL tasks are more reliant on efficient hippocampal function because information cannot be maintained within a rehearsal loop, which supports word-list learning (e.g., SRT). Although previous work has linked poorer object-location and verbal PAL to disease-related hippocampal changes in MS patients,[70,71] most clinical and research memory assessments rely on memory of word-lists or geometric shapes across learning trials.[2,33] Note that some early work suggested that memory deficits in MS patients may be due to a specific deficit in binding of contextual information at encoding.[72] Consideration of associative learning as both a sleep-related and MS-related memory deficit requires further investigation in the MS literature.

The initial observations of this study connect patient-reported sleep disturbance specifically to poor memory in early MS, even when controlling for key covariates including mood, fatigue, and disability. Disease-related sleep disturbance may be one mechanism underlying memory dysfunction in MS. Although links between sleep and memory have been reported in conditions other than MS,[14-19,73] such relationships have not been adequately addressed in MS. Our study is limited by the use of a single measure of patient-reported sleep disturbance, and reliance on traditional memory assessments conducted at one time point. Further work is needed to examine relationships between memory and objective measurements of sleep behavior and sleep architecture (i.e., polysomnography),[12] and to disentangle specific mnemonic processes that are impacted by sleep (e.g., encoding versus consolidation). Our focus on memory was informed by animal and human research outside of MS, and we included cognitive efficiency as a comparative function; however, future work on sleep in MS may also explore other functions such as attention and executive function. Biologically plausible theoretical models of MS memory dysfunction are needed, which should include careful characterizations of discrete mnemonic processes. This study provides initial evidence to inform and encourage subsequent mechanistic investigations of sleep and memory dysfunction in MS.

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## Conflicts of Interest

The authors have no potential conflicts of interest related to the work presented herein.

 

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