# RELATIONSHIP BETWEEN SLEEP DISORDERS AND COGNITIVE FUNCTIONS IN PATIENTS WITH MULTIPLE SCLEROSIS

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**Abstract**

**Background:** Currently, 47- 62% of multiple sclerosis (MS) patients complain of intermixed sleep disturbances that have profound impacts on their quality of life. Despite robust evidence for sleep disturbance as a modifiable risk factor in development of cognitive dysfunction, as well evidence that modifying sleep-related behaviours improves insomnia, fatigue and depression in MS, relationship between sleep disturbance and cognitive dysfunction in MS remains understudied.

**Purpose:** This study aimed to investigate the relationship between sleep disorders and cognitive functions in patients with multiple sclerosis.

**Subjects and Methods:** Seventy patients with RRMS with sleep disorders from both sexes were recruited. Their age ranged from 20 to 50 years old and their Expanded Disability Status Scale (EDSS) score ≤ 5. Twenty age and sex matched RRMS without sleep disorders were included as a control group. All participants were submitted to the Arabic version of Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) to evaluate sleep disorders. Computer Based Cognitive Assessment (RehaCom system) was also used to evaluate cognitive functions.

**Results:** A highly significant difference was detected between the study and control groups as regard mean scores of PSQI and ESS ($P < 0.001$) being higher in the study group. The mean score of Figural memory was significantly lower in the study group compared to controls (P= 0.031), also, the mean score of reaction behavior tends to be significantly lower in the study group (P= 0.06). A significant negative correlation was found between scores of PSQI scale and Reaction behavior domain (P= 0.049). No significant correlation was found between scores of PSQI scale and attention and concentration domain (p= 0.841), Figural memory domain (P= 0.150), or Logical reasoning domain (P= 0.721). No significant correlation was detected between scores of ESS and attention and concentration domain, Figural memory domain, Reaction behavior domain, or Logical reasoning domain (P> 0.05).

**Conclusion:** there is a relation between sleep disorders measured by PSQI, figural memory and reaction behavior in patients with remission relapsing MS (RRMS).

**Keywords:** Noradrenaline, terlipressin, and hepatorenal syndrome

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## 1. INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating heterogeneous, multifactorial, immune-mediated disease, **(Pérez-Martín et al., 2016).** MS disability is not only due to motor disorders or associated neurological deficits, but also because of accompanied cognitive impairment (CI) and/or depression and sleep disorders, **(Platas and Martin, 2018).**

Sleep disorders (SD) were recorded in MS involving poor sleep that has negative impacts, plus immunotherapy and symptomatic medications as well other MS-associated symptoms, **(Veauthier et al., 2015).** Obstructive sleep apnea, insomnia and restless legs syndrome (RLS) are among usually reported sleep disorders in general population, unless it is further increased among MS patients, **(Braley et al., 2016).**

Almost, cognitive dysfunction is consequential symptoms of MS, involving impairments in attention, processing speed, working memory, learning, executive function, visuospatial processing and language function affect 42% to70% of MS populations and constitute a major cause of loss of employment and reduced quality of life, **(Braley et al., 2016).**

Since attention, processing speed, working memory, executive functions and verbal episodic memory are disrupted in whom with primary progressive MS. In secondary progressive MS (SPMS) patients, disrupted working memory, information processing speed, verbal fluency and verbal episodic memory are higher than relapsing remitting MS (RRMS) patients, **(Brochet & Ruet, 2019).**

To available data, numerous studies suggest that obstructive sleep apnea and other sleep disturbances are modifiable risk factors for cognitive dysfunction in the general population, **(Sumowski et al., 2021).** Unless, relationship between gold-standard measures of cognitive function, sleep apnea and other objective measures of sleep disturbance remain virtually unstudied in patients with MS and the potential role for sleep-based interventions to improve cognitive functioning in MS has yet to be fully explored, **(Odintsova & Kopchak, 2021).** Consequently, this study was conducted to investigate the relationship between sleep disorders and cognitive functions in patients with multiple sclerosis.

## 2. METHODOLOGY

This is a cross-sectional observational study carried at out Outpatient clinic of Faculty of Physical Therapy and Kasr Alaini Multiple Sclerosis Unit (KAMSU) at Faculty of Medicine, Cairo University, in the period between July 2022 and February 2023. The study was approved by the ethics committee of a college of physical therapy Cairo university (No: P.T.REC /012/004193), the study was performed in accordance with relevant guidelines and regulations. An informed consent was contained from all patients.

Seventy patients with RRMS with sleep disorders diagnosed and referred by a neurologist were included. They were from both sexes with EDSS $\leq 5$ based on **Riccitelli et al., (2022).** Their age ranged from 20 to 50 years old and no relapses for the previous three months, plus having normal vision and hearing. Twenty age and sex matched RRMS without sleep disorders served as controls. Exclusion Criteria were: patients with mechanical or neuromuscular lesions, cardiovascular disorders such as unstable angina, recent myocardial infarction within last three months, cognitive heart failure, significant heart valve dysfunction or unstable hypertension or pulmonary disorders, auditory lesions, sensory impairments due to other causes than MS i.e., diabetes mellitus, current or history of psychiatric diseases such as depression or anxiety, basal ganglia affections associated with sleep disorders, heavy smokers or excessive caffeine intake, specially before sleeping.

- **PROCEDURES:**

**Sleep disorder evaluation**

**1) The Arabic version of Pittsburgh Sleep Quality Index (PSQI):**

Pittsburgh Sleep Quality Index is a valid and reliable self-rated questionnaire that gives impression on sleep quality, sleep latency, sleep duration, usual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over one month, The sum of scores for these seven components yields one global score. Scoring of the answers is based on a 0 to 3 scale and a global sum equal or larger than 5 indicates a "poor" sleeper, **(Dietch et al., 2016 Furtado et al., 2016).** The Arabic version of PSQI was translated and had been used in number of studies and it was found to be valid and reliable, **(Shokry et al., 2016).**

**2) The Arabic version of Epworth Sleepiness Scale (ESS):**

ESS is s self-reporting questionnaire that measures the general level of daytime sleepiness it is composed of 8 items to rate on a 4 –point scale (0–3). A higher score indicates higher level of daytime sleepiness. Using a cut-off score > 10, it is possible to identify individuals with excessive daytime sleepiness. Scores >16 indicates ever sleepiness **(Furtado et al., 2016).** Subjects were asked to rate their likelihood of dozing off or falling asleep in the eight scenarios on a scale of 0 to 3, based on their regular way of life in recent times. The Arabic version of ESS was translated and had been used in number of studies and it was found to be valid and Reliable **(Ahmed et al., 2014).**

**3) Cognitive functions evaluation**

RehaCom is a comprehensive system of procedures for computer-based cognitive assessment and rehabilitation. It includes activation and stimulation of several cognitive domains such as (attention, memory, visual-spatial processes and executive functions) **(Łojek & Bolewska, 2013).** RehaCom assesses attention, memory, visual spatial processes, executive functioning, word memory, verbal memory (i.e., whole text, not just individual words) and figural memory. The program contains several modules with different levels of difficulty, automatically increasing task difficulty level as the subject successfully executes simpler procedures. Recording of number of errors and test completion time for all patients and a results file enables continuity over several sessions and database storage of results. The computer gives patients appropriate instruction and feedback on performance in their own language**, (Fernández et al., 2012).**

## STATISTICAL ANALYSIS:

All statistical tests were performed through the statistical package for social studies (SPSS) version

20 for windows. (IBM SPSS, Chicago, IL, USA). Descriptive statistics in form of mean, standard deviation and frequency was conducted for the subject's demographics. Pearson Correlation Coefficient was conducted to determine the correlation between cognitive measures and sleep. The significance level was set at P < 0.005.

## 3. RESULTS

The study group included seventy patients with RRMS; their mean age, weight, height and BMI were 32.81 ± 10.84 years, 74.81 ± 16.26 kg, 162.91 ± 7.28 cm and 28.16 ± 5.82 Kg/m2 respectively. While, the control group involved twenty RRMS patients without sleep disorders; their mean age, weight, height and BMI were 31 ± 11.12 years, 68.08 ± 14.47 kg, 164.6 ± 6.18 cm and 25.07 ± 4.21 Kg/m2 respectively. There was no significant difference between both groups regarding mean age, weight or height (P>0.05), while there was a significant difference between both groups regarding mean BMI being higher in the study group (P<0.05). Also, there was no significant difference between both groups (P<0.05), as regards gender distribution. **(Tables 1,2).**

**Table (1):** Demographic characteristics of participants

| | **Study group x̄ ± SD** | **Control group x̄ ± SD** | **MD** | **t-value** | **p-value** | **Sig.** |
|---|---|---|---|---|---|---|
| **Age (years)** | 32.81 ± 10.84 | 31 ± 11.12 | 1.81 | 0.647 | 0.522 | NS |
| **Weight (kg)** | 74.81 ± 16.26 | 68.08 ± 14.47 | 6.73 | 1.784 | 0.083 | NS |
| **Height (cm)** | 162.91 ± 7.28 | 164.6 ± 6.18 | -1.69 | -1.033 | 0.309 | NS |
| **BMI (Kg/m$^2$)** | 28.16 ± 5.82 | 25.07 ± 4.21 | 3.09 | 2.636 | 0.012 | S |

NS: non significant S: significant

**Table (2):** Sex Distribution in participants

| | **Males No (%)** | **Females No (%)** | **x2** | **p-value** | **Sig.** |
|---|---|---|---|---|---|
| **Study Group (N:70)** | 21 (30%) | 49 (70%) | 1.575 | 0.209 | NS |
| **Control (N: 20)** | 9 (45%) | 11 (55%) | | | |
| **Total** | 30 (33.3%) | 60 (66.7%) | | | |

NS: non significant

There was a highly significant difference in the mean scores of PSQI and ESS between the study and control groups (P <0.001), being higher in the study group. **Table (3)**

**Table (3):** Comparison of mean scores of PSQI and ESS between both groups.

| | Study group x̄ ± SD | Control group x̄ ± SD | MD | p-value | Sig. |
|---|---|---|---|---|---|
| PSQI scale | 10.66 ± 4.5 | 4.5 ± 1.36 | 6.16 | <0.001 | HS |
| Epworth scale | 7.81 ± 4.43 | 5 ± 2.2 | 2.81 | <0.001 | HS |
| SD: standard deviation, P value: Probability value, MD: Mean difference, HS: highly significant | | | | | |

There mean score of Figural memory was significantly lower in the study group compared to controls (P= 0.031), also, the mean score of reaction behavior tends to be significantly lower in the study group (P= 0.06). However, there was no significant difference between both groups regarding mean scores of attention and concentration (P= 0.706) or logical reasoning (P= 0.081). **Table (4)**

**Table (4):** Comparison of mean scores of RehaCom domains between both groups

| | **Study group x̄ ± SD** | **Control group x̄ ± SD** | **MD** | **p-value** | **Sig.** |
|---|---|---|---|---|---|
| **Attention & Concentration** | 5.43 ± 1.48 | 5.55 ± 1.19 | -0.12 | 0.706 | NS |
| **Figure memory** | 4.33 ± 1.73 | 5.2 ± 1.47 | -0.87 | 0.031 | S |
| **Reaction behavior** | 3.59 ± 1.67 | 4.4 ± 1.64 | -0.81 | 0.06 | ≈ |
| **Logical reasoning** | 4.11 ± 1.61 | 4.8 ± 1.47 | -0.69 | 0.081 | NS |
| SD: standard deviation, P value: Probability value, MD: Mean difference, HS: highly significant, ≈ trendwise significant | | | | | |

A significant negative correlation was detected between scores of PSQI scale and Reaction behavior domain (P= 0.049), otherwise, no significant correlation was detected between scores of PSQI scale and attention and concentration domain (P= 0.841), Figural memory domain (P=0.150), or Logical reasoning domain (P= 0.721). **Table (5)**

**Table (5):** Correlation between scores of PSQI scale and RehaCom domains

| | **Mean ± SD** | **R - value** | **P- value** |
|---|---|---|---|
| **PSQI scale score** | 9.29 ± 4.77 | | |
| **Attention & Concentration score** | 5.46 ± 1.42 | -0.021 | 0.841 |
| **Figure memory score** | 4.52 ± 1.7 | -0.153 | 0.150 |
| **Reaction behavior score** | 3.77 ± 1.69 | -0.208 | 0.049* |
| **Logical reasoning score** | 4.27 ± 1.6 | -0.038 | 0.721 |
| R value: Pearson`s correlation coefficient, * significant | | | |

No significant correlation was found between scores of Epworth scale and attention and concentration domain, Figural memory domain, Reaction behavior domain or Logical reasoning domain (P > 0.05). **Table (6)**

**Table (6):** Correlation between scores of Epworth scale and RehaCom domains

| | **Mean ± SD** | **R - value** | **P- value** |
|---|---|---|---|
| **Epworth scale score** | 7.19 ± 4.2 | | |
| **Attention & Concentration score** | 5.46 ± 1.42 | 0.057 | 0.593 |
| **Figure memory score** | 4.52 ± 1.7 | -0.059 | 0.578 |
| **Reaction behavior score** | 3.77 ± 1.69 | -0.082 | 0.440 |
| **Logical reasoning score** | 4.27 ± 1.6 | 0.012 | 0.907 |
| R value: Pearson`s correlation coefficient, P<0.05: Significant | | | |

## 4. DISCUSSION

MS disrupts physical, cognitive, emotional and social functioning, thus contributing substantially to disability and reduced quality of life **(Burke et al., 2016),** thereby exacerbating attentional and processing speed deficits, also promoting additional deficits in domains of memory, verbal fluency and executive function **(Krupp et al., 2011).**

This study revealed a highly significant decrease in scores of PSQI and EES in study group compared to controls. Figural memory and reaction behaviour scores were significantly decreased in the study group compared to controls. The mean scores of scores of attention and logical reasoning were less in the study group though the difference was not significant. Our findings were in the same line with **Hughes et al. (2018)** who stated that self-reported measures of sleep only moderately correlated with perceived cognitive function, also **van Geest et al. (2017)** found that perceived sleep disturbances were more strongly correlated with perceived than objective cognitive dysfunctions in MS populations.

In line with our findings, many studies have shown significant associations between cognitive impairment and sleep disturbances in MS, however obvious correlations detected depending on subjective and objective measures of sleep and cognitive impairment yield discrepant patterns of associations **(Hughes et al., 2018). Hughes et al., (2016)** had reported that 58% of self-reported subjective cognitive measures of global cognitive dysfunction showed significant associations, even after controlling for depression and fatigue and were consistent for cross-sectional and longitudinal designs.

Our results also came in agreement with earlier clinical trials had been conducted by **Clancy et al., (2015)** who had stated that non-pharmacological interventions for improving sleep, which most commonly feature psychoeducation, cognitive and behavioral techniques have shown modest to large effects on insomnia, fatigue and depression according to **Majendie et al., (2016).** Unless, the downstream benefits of such interventions on cognitive dysfunction are unknown. Moreover, **Gonzalez-Platas et al., (2016)** ensured that obstructive sleep apnea represents 2-21% with MS have increased fatigue and diminished quality life compared with undiagnosed or low-risk patients **(Braley & Chervin, 2015),** might correlate with impaired cognition in MS, **(Veauthier et al., 2016).**

**van Geest et al., (2017)** had stated that multi-factorial fatigue due to immunologic abnormalities, endocrine influences, axonal loss, altered patterns of cerebral activation, sleep disorders, depression and medications used to treat MS symptoms or immunomodulatory and immunosuppressive treatments. Also, **Sahraian et al., (2017),** stated that fatigue deteriorates cognitive domains in MS populations involving processing, memory and attention with significant socioeconomic consequences, **(Abbasi et al., 2016).** As well, **Schellaert et al., (2018)** had 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

Our results also agreed with **Braley et al., (2016)** who concluded that the association between obstructive sleep apnea and cognitive functioning in MS, might contribute to cognitive dysfunction in MS. **Gunes et al., (2021)** also recorded that sleep disorders were highly interrelated in MS. On the other hand, MS duration and gender appears to influence relationship between sleep quality and cognitive dysfunction, **(Vitkova et al., 2016).** Moreover, **Sumowski et al., (2021),** stated that sleep disturbances increase the risk of co-morbidities and could contribute to depression, cognitive impairment and fatigue symptoms, plus memory dysfunction which worsen the prognosis of multiple sclerosis.

Another conflicting opinion of **Hughes et al., (2018)** who ensured that sleep physiology is linked to memory in animals, healthy adults, and sleep-disordered populations; however, links between sleep disturbance and memory deficits in MS patients remain unclear. On the other hand, a conflicting explanation has been offered by **Ferri et al., (2007)** who stated that sleep deprivation appears to reduce hippocampal dendritic spine density and synaptic efficiency in animals and humans, thereby leading to worse memory.

In disagreement with current study results, previous studies conducted by **Loerbroks et al., (2010),** who had ensured that a move from 7–8 hours' sleep per night to ≥ 9 hours over a period of 8.5 years was associated with a doubling of the prevalence of cognitive impairment. Prior clinical trial of **Veauthier et al., (2011)** also reported a conflicting result regarding MS often associated with memory dysfunction and with mood disorders that poorly understood.

## 5. CONCLUSION

In conclusion, patients with MS had shown obvious sleep disorders that might exacerbate cognitive dysfunction especially in the domains of figural memory and reaction behavior.

## CONFLICT OF INTEREST

The authors declared no conflict of interest.

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