




# The Importance of Sleep for Successful Neurorehabilitation after Stroke

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## Abstract

Sleep has important clinical implications for neurorehabilitation after stroke. We aimed to systematically explore sleep (including naps) as an essential factor in the neurorehabilitation of patients after stroke. After titles and abstracts were screened, 49 full texts were reviewed, and 7 were included in this review. Data were extracted and assessed for quality and risk of bias. We looked at any neurorehabilitation setting, and compared sleep with no sleep and explored these factors in stroke patients versus healthy individuals. Rehabilitation is critical for many activities that may need to be learned or re-learned following stroke and for returning to everyday life. In this context, sleep is essential in neurorehabilitation and physical therapy practice as it supports neuroplasticity, memory, and learning. The available data suggest that sleep should be considered in the treatment plan for successfully targeted physiotherapy to optimize cognitive and motor learning. Physical therapists should advise about sleep hygiene and therapies to improve sleep, both quality and quantity.

## Keywords

- ▶ sleep
- ▶ sleep disorders
- ▶ stroke
- ▶ rehabilitation
- ▶ neurorehabilitation
- ▶ physical therapy
- ▶ neuroplasticity

## Introduction

Proper sleep has important clinical implications for the learning and re-learning of movements and activities of daily life for optimal stroke rehabilitation. At any age, sleep is necessary for the health of the entire organism as a complex behavioral and physiological process.<sup>1,2</sup> In many cases, there is a bidirectional relationship between sleep and other neurological conditions (e.g., stroke),<sup>3</sup> and the treatment of comorbid sleep disturbances may improve the symptoms of other diseases and facilitate neurorehabilitation.<sup>4</sup> Within this context, sleep disorders of any kind can negatively affect neuroplasticity and recovery.

Sleep changes throughout life, and changes according to our lifestyle, genetics, aging, chronic conditions, and illness.<sup>5</sup> In quantity and quality, insufficient sleep can lead to several physiological and behavioral changes, including neurological diseases.

There is a significant relationship between sleep disorders and stroke. Stroke patients often experience sleep disturbances. Up to 40% of individuals with chronic stroke and 70% of those with acute stroke have sleep-wake disorders, including insomnia, excessive daytime sleepiness, hypersomnia, fatigue,<sup>6</sup> and sleep-disordered breathing (SDB).<sup>7</sup> Objective changes in post-stroke sleep are controversial. There is a lack of literature on objective findings of

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sleep-in specific stages of stroke, related to the period of recovery that takes place after the initial stroke event. These sleep patterns change over time varies between the stages (acute, first 2 weeks after stroke onset; subacute stage, from 3-11 weeks post-stroke; and chronic stage, more than 12 weeks; subdivided into early chronic stage, from 12-24 weeks post-stroke, and chronic stage, more than 24 weeks after stroke onset). Literature on acute stages of stroke include a reduction in sleep duration and sleep efficiency, an increase in wake after sleep onset, indicating sleep fragmentation,<sup>8-10</sup> increased N1 sleep stage, decreased N3<sup>10</sup> and REM sleep stages.<sup>11</sup> When analyzed in patients after chronic stroke, reductions in N1, N3 and REM sleep stages have been found,<sup>9,11</sup> as the patients presented relatively more time in the N2 sleep stage where sleep spindles were prominent.<sup>10,12,13</sup> These changes seem to be implicated in motor skill learning and may impair neurorehabilitation.

After a stroke, one of the most common sleep disorders is sleep-disordered breathing (SDB). SDB such as obstructive sleep apnea (OSA) can improve after the acute stroke phase. However, up to 60% of the patients still show an abnormal apnea-hypopnea index (AHI) >10/h at PSG exam, and 30% show a severe AHI >30/h, approximately three months after the stroke.<sup>14</sup> OSA has been identified as an independent risk factor for stroke and is associated with a detrimental effect on stroke recovery and associated with higher mortality.<sup>15-17</sup>

There is mounting evidence that rehabilitation is a critical factor in the post-stroke outcome, which is not surprising considering the many activities that need to be learned or re-learned.<sup>18-21</sup> Additionally, new therapies that target restorative processes are under development as many existing physical therapy interventions have been shown to reduce post-stroke deficits. These include an increased variety of types of exercise for strengthening, fitness intervention, constraint-induced movement therapy, advanced task-related skills, repetitive task practice,<sup>22</sup> robotic and telehealth devices.<sup>23</sup> In this context, we propose that sleep can promote motor learning acquisition and is an essential contributory factor in the rehabilitation of stroke patients. While there is some evidence that sleep facilitates motor skill acquisition and memory (motor) consolidation, there is no guidance on whether sleep can help the damaged brain reorganize during stroke recovery. Therefore, the specific research questions for this systematic review regarding adults following stroke were:

Does sleep (including naps) matter as a contributing factor for neurorehabilitation in patients after stroke?

Should physiotherapists evaluate and care for sleep disorders in patients following stroke?

## Material and Methods

### Identification and Selection of Studies

A systematic review was performed on clinical trials investigating the influence of sleep on post-stroke neurorehabilitation. The Preferred Reporting Items for Systematic reviews

and Meta-Analyses (PRISMA) guidelines were followed.<sup>24</sup> This review was prospectively registered with PROSPERO (ID registration # 146873).

Six electronic scientific databases: MEDLINE, CINAHL/EBSCO, Cochrane Library, Embase, PEDro, and Scopus, were searched to find studies in English from inception to January 15<sup>th</sup>, 2022. Controlled vocabulary (Medical Subject Headings in PubMed) and keywords were incorporated for stroke, sleep, neuroplasticity, plasticity, motor learning, physical therapy, neurorehabilitation, and rehabilitation for inclusion and exclusion criteria (► **Figure 1**).

Two authors (CF and FMSC) independently screened the titles and abstracts for eligibility. The full-text article was read when the abstracts were unclear. If conflicts arose and agreement on full-text inclusion could not be reached, a third author (BJM) was the arbiter for final study eligibility. Following the full-text screening, a hand search was performed for additional manuscripts.

### Assessment of Characteristics of Studies

The Oxford Centre assessed the risk of bias for Evidence-Based Medicine levels of evidence (classes I-V) were used to ascertain study design.<sup>25</sup> The methodological index for the non-randomized study<sup>26</sup> (MINORS) tool was used to assess the risk of bias of the included clinical trials. MINORS has a maximum score of 24. A higher rate indicates a more precise estimate of the influence of studied determinants. The 27-item Downs and Black<sup>27</sup> checklist was used to assess the risk of bias of the randomized controlled trials. The score ranges were given corresponding to quality levels and varied from excellent (26-27), good (20-25), fair (15-19), to poor ( $\leq 14$ ) quality. Due to the heterogeneity and nonuniformity of the data in the included studies, the results are summarized descriptively.

### Data Analysis

Two authors (CF and FMSC) collected and recorded data in a customized database using Microsoft Excel, Version 2010 (Microsoft Corporation Redmond, WA). Data regarding study design, sample size, age, type of stroke, time since stroke, measures of stroke severity, intervention, the duration between the learning activity and recall, motor domain assessment, offline comparison, sleep measures, other measures, and evidence of sleep-dependent motor consolidation/learning were recorded.

## Results

### Study Selection Process

The study selection process followed PRISMA guidelines (► **Figure 2**). A total of 66 references were imported for screening. After removing duplicates ( $n = 17$ ), 49 publications underwent title and abstract screening. After full-text analyses, we excluded 42 studies. Of the remaining seven studies, 2 were randomized controlled trials, and 5 were case-control trials. From 7 investigations, 6 found evidence for sleep-dependent neuroplasticity of motor consolidation and learning (► **Table 1**).

<p><b>Inclusion Criteria</b></p> <p><b>Design</b></p> <ul style="list-style-type: none"> <li>• Observational studies including comparative studies such as case-control and cohort designs</li> </ul> <p><b>Participants</b></p> <ul style="list-style-type: none"> <li>• adult patients (<math>\geq 18</math> years) following stroke, both ischemic or hemorrhagic</li> <li>• magnetic resonance imaging or computed tomography to confirm stroke</li> </ul> <p><b>Task/Intervention</b></p> <ul style="list-style-type: none"> <li>• any physiotherapy/neurorehabilitation task except transcranial magnetic stimulation</li> </ul> <p><b>Outcome measures</b></p> <ul style="list-style-type: none"> <li>• motor learning following sleep or nap of any duration</li> </ul> <p><b>Comparisons</b></p> <ul style="list-style-type: none"> <li>• healthy participants <i>versus</i> stroke patients</li> <li>• sleep <i>versus</i> no sleep</li> </ul>
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**Fig. 1** Inclusion criteria.

### Characteristics of Studies

Two randomized control studies<sup>28,29</sup> was assessed using the 27-item Downs and Black scale and were rated as fair quality. Five non-randomized studies<sup>30-34</sup> were evaluated using the MINORS tool, rating 13-15 (► **Table 2**). Regarding the Oxford Scale for the level of evidence, two were rated as level I,<sup>29,30</sup> four rated as level III,<sup>30-32,34</sup> and one rated as level IV<sup>33</sup> (► **Table 3**).

Five studies investigated the chronic stroke phase,<sup>28,30-32,34</sup> one examined the acute stroke phase,<sup>33</sup> and one did not mention the time since the stroke.<sup>29</sup> The type of stroke (ischemic or hemorrhagic) was reported in two studies.<sup>28,33</sup> Four studies measured stroke severity using the Orpington Prognostic Scale at baseline<sup>29-31,34</sup> to assess stroke severity (minor, moderate, significant).

Six studies used a continuous motor tracking test and a retention test,<sup>28-32</sup> and one of these included spatial and temporal tracking accuracy.<sup>29</sup> One study used action observation<sup>33</sup> - none of the studies used to exercise or physical therapy to promote sleep. Regarding the duration of sleep, the studies adopted short and very short-term protocols: one investigation lasted four weeks,<sup>33</sup> all others were shorter (12 hours to two days) and included a task and a retention test after a nap or nighttime sleep.

Three studies used polysomnographic examination<sup>28,32,34</sup> to compare data and assess PSG variables combined with subjective measures of sleep, such as sleepiness, subjective sleep quality, and a sleep log. One study did not

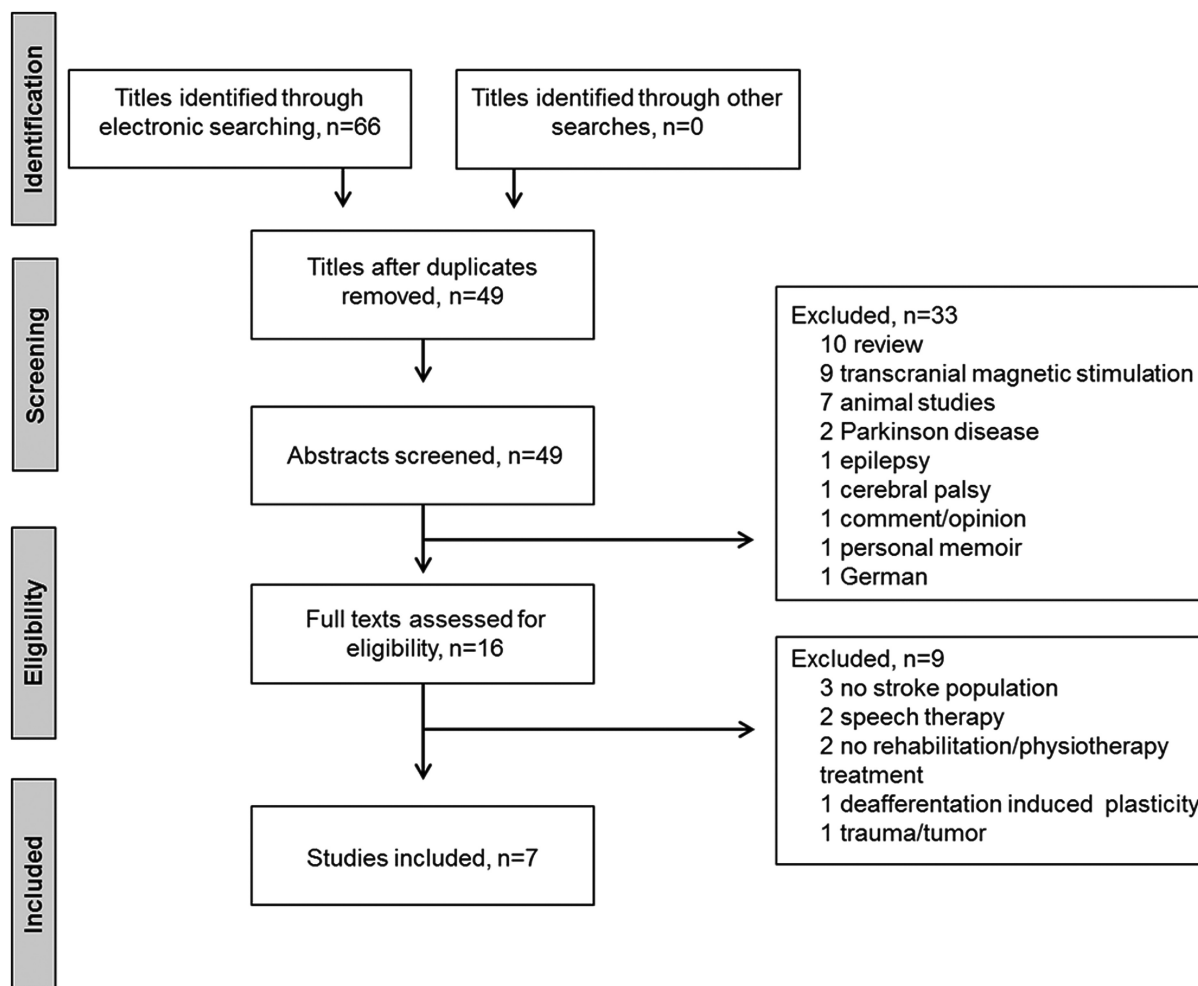
use any measure of sleep,<sup>33</sup> and six of them used subjective measures of sleepiness (i. e. Stanford Sleepiness Scale - which quantifies sleepiness and alertness levels at different times during the day), sleep quality (i.e., Pittsburgh Sleep Quality Index which assesses overall sleep quality in the past month), and a sleep log for one week (sleep diary).<sup>28-32,34</sup>

Five studies from the same research group compared patients following stroke with healthy controls<sup>29-32,34</sup> but analyzing different samples of participants, the stroke patients demonstrated offline improvements in motor learning. One study that did not use a control group suggested improving motor learning in participants who took a quick long nap (90-120 min) after the task compared to the no sleep group.<sup>33</sup>

One study did not find any evidence of sleep contributing to motor learning abilities when comparing participants following a stroke in 3 groups: no nap (wakeful rest), a short nap (10-20 min), and a long nap (50-80min).<sup>28</sup> This was the only study that measured wakefulness via PSG to rule out sleep during the protocol objectively.

### Discussion

This review aimed to assess sleep (nighttime sleep and naps) as a contributing factor for physical therapy/neurorehabilitation in patients following stroke. Across the studies, we observed a



**Fig. 2** Flow chart presenting the selection of eligible studies, according to PRISMA.

near-consensus that motor consolidation was improved by nighttime sleep and long naps ( $\geq 90$  min).

The only investigation that found no evidence of sleep-dependent motor improvement<sup>28</sup> compared the performance of patients following a stroke in a visuomotor adaptation task, with individuals divided into three groups, either having a short or longer daytime nap or no nap all. One hypothesis to explain these results may be the length of the naps in this study<sup>28</sup> which were shorter than one sleep cycle, as they found that napping seemed to make no difference. The average length of the first NREM/REM sleep cycle is about 70 to 100 minutes, and the average length of the second and later cycles is about 90 to 120 minutes.<sup>35</sup> Thus, it may be that none of the groups achieved deep sleep, considered to be restorative and essential for memory consolidation. Moreover, all the three groups had a “tendency” of performance improvements, but with no significant statistical differences, which might have different outcomes in a larger sample. The lack of confirmation of a sleep-dependent motor improvement<sup>28</sup> might also be because of assessing older adults. There is evidence that older adults have disrupted sleep with interference by medications and by age itself,<sup>35</sup> which might have decreased their sample’s brain

plasticity. Advanced age brings both sleep and memory changes.<sup>36–38</sup> Another possible explanation for the finding of no evidence of sleep-dependent consolidation in one study<sup>28</sup> may be related to stroke type. This was one of only two studies that included information on the type of stroke, identifying hemorrhagic stroke.<sup>28</sup> There is some evidence that rehabilitation is more effective after hemorrhagic stroke than after ischemic stroke,<sup>39</sup> despite hemorrhagic stroke being responsible for more deaths and disability-adjusted life-years lost than ischemic stroke.<sup>39</sup> Individuals who have had a hemorrhagic stroke may have an altered prognosis for acquiring and reacquisition of skills. Sleep could also be different between ischemic and hemorrhagic stroke.

Another point to consider about the investigations is the choice of the upper extremity (UE) to perform the tasks. This varies among studies, making comparison of the studies complex and may have influenced the overall results. Participants completed the task with the contralesional UE/stroke impaired UE in 2 studies,<sup>28,33</sup> while in the other five, it was served with ipsilesional UE/less affected UE.<sup>29–32,34</sup>

Neuroplastic cortical reorganization begins immediately after a stroke. After focal injury of the motor cortex and its

**Table 1** Summary of included studies

Article	Study design	N	Age/ Participants	Type of stroke	Time since stroke	Measures on stroke severity	Task/ Intervention	Side of upper extremity performed intervention	Duration of rehabilitation or intervention	Motor domain assessment	Comparison	Sleep measures	Other measures	Evidence of sleep dependent motor consolidation
Backhaus et al, 2018 <sup>28</sup>	RCT	30	46-82 Stroke participants vs NIC	Ischemic + Hemorrhagic	> 6 months (chronic)	none	Continuous motor tracking task	Impaired UE	3 sessions in 2 days	FMUE 9HPT	Wakeful rest vs short nap (10-20 min) vs long nap (50-80min)	PSQI SSS PSG	BDI MMSE	No
Lubart et al, 2017 <sup>33</sup>	CT	20	66-86 Stroke participants	Ischemic	1 week after stroke (acute)	none	Action observation + 1 h/week of PT session	Impaired UE	4 weeks	FMUE CAHAI	Immediate long nap (90-120 min nap) vs no sleep (control)	None	MMSE	Yes
Al-Dughmi et al, 2017 <sup>32</sup>	CT	26	40-75 Stroke participants vs NIC	NS	> 6 months (chronic)	none	Continuous motor tracking task + retention test	Non-affected UE	24 hours	TMT	Stroke vs no stroke	PSQI 3 PSG	MMSE Stroop Test D2 Task VFT	Yes
Siengsukon et al, 2015 <sup>34</sup>	CT	30	40-75	NS	> 6 months (chronic)	OPS	Continuous motor tracking task + retention test	Non-affected UE	24 hours	FMUE	Sleep vs no sleep; stroke vs no stroke	SSS PSQI Sleep log 3 PSG	GDS MMSE	Yes
Siengsukon and Boyd, 2009a <sup>9</sup>	RCT	30	47-73	NS	NS	OPS	Spatial + temporal tracking accuracy + retention test	Non-affected UE	12 hours	FMUE	Sleep vs no sleep; stroke vs no stroke	SSS PSQI Sleep log	MMSE GDS	Yes
Siengsukon and Boyd, 2009b <sup>30</sup>	CCT pseudo	80	NS Stroke participants vs NIC	NS	> 6 months (chronic)	OPS	Continuous motor tracking task + retention test	Non-affected UE	12 hours	FMUE	Sleep implicit vs no sleep implicit; sleep explicit vs no sleep explicit	SSS PSQI Sleep log	MMSE GDS EI	Yes
Siengsukon and Boyd, 2008 <sup>31</sup>	CCT pseudo	36	40-73 Stroke participants vs NIC	NS	> 6 months (chronic)	OPS	Continuous motor tracking task + retention test	Non-affected UE	12 hours	FMUE	Sleep vs no sleep	SSS PSQI Sleep log	MMSE GDS EI	Yes

9HPT: Nine-hole Peg Test; BDI: Beck Depression Inventory; CAHAI: Chedoke Arm and Hand Activity Inventory; CCT pseudo: Case-control trial pseudorandomized; CT: Controlled Trial; EI: Edinburgh Inventory; FMUE: Fugl-Meyer Upper Extremity Score; GDS: Geriatric Depression Scale; MMSE: Mini Mental State Examination; NIC: Neurologic Intact Controls; NS: Not Stated; OPS: Orpington Prognostic Score; PSG: Polysomnography Exam; PSQI: Pittsburgh Sleep Quality Index; PT: physical therapy sessions; RCT: Randomized Controlled Trial; SSS: Stanford Sleepiness Scale; TMT: Trail-Making Test from Delis-Kaplan Executive Function System; UE: upper extremity; VFT: Verbal Fluency Task.

**Table 2** Risk of bias scores of included studies

Article	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Backhaus et al, 2018 <sup>28,†</sup>	1	1	0	1	0	1	1	0	1	0	0	0	0	0	0	1	1	1	1	1	1	0	1	0	0	0	0	
Lubart et al, 2017 <sup>33*</sup>	2	2	2	1	0	0	0	0	0	2	2	2																
Al-Dughmi et al, 2017 <sup>32,*</sup>	2	1	2	1	0	0	0	0	2	2	2	2																
Siengsukon et al, 2015 <sup>34*</sup>	2	2	2	1	0	0	0	0	2	2	2	2																
Siengsukon and Boyd, 2009a <sup>29,†</sup>	1	1	1	1	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1	1	1	0	1	0	0	1	0	0
Siengsukon and Boyd, 2009b <sup>30*</sup>	2	2	2	1	0	0	0	0	1	2	2	2																
Siengsukon and Boyd, 2008 <sup>31*</sup>	2	2	2	1	0	0	0	0	1	2	2	2																

MINORS item number: 0: not reported; 1: reported but inadequate; 2: reported and adequate. Item 1: Clearly stated aim. Item 2: Inclusion of consecutive patients. Item 3: Prospective collection of data. Item 4: Endpoints appropriate to the aim of the study. Item 5: Unbiased follow up of the study endpoint. Item 6: Appropriate follow-up period. Item 7: Loss to follow up less than 5%. Item 8: Prospective calculation of the sample size. Item 9: Adequate control group. Item 10: Contemporary groups. Item 11: Baseline equivalence of groups. Item 12: Adequate statistical analyses.

Downs and Black scale item number: 0: No; 1: Yes. Items 1-10: assessed whether the information provided was sufficient to allow the reader to make an unbiased assessment of the finding of the study. Items 11-13: assessed external validity – which addressed the extent to which findings from the study could be generalized to the population from which the study participants were derived. Items 14-20: assessed potential bias – which addressed biases in the measurement of the intervention and the outcome. Items 21-26: assessed confounding – which addressed bias in the selection of the study participants. Item 27: assessed the power of the study – which attempted to assess whether the negative findings from the study could be due to chance.

<sup>†</sup>Rated using the Downs and Black scale (0-27 points, 27 item number).

<sup>\*</sup>Rated using the methodological index for nonrandomized studies for comparative studies (MINORS, 0-24 points, 12 item number).

descending pathways, the remaining portions of the brain usually undergo a considerable structural and functional reorganization that happens in peri-lesional areas and the ipsilesional and contralesional cortices.<sup>40-42</sup> Experimental investigations have shown that task-specific training in rehabilitation and repetitive exercise are critical factors in promoting synaptogenesis and are central elements in repairing motor weakness following stroke.<sup>43-45</sup> Skill acquisition and transfer of skills to other activities are more effectively achieved by incorporating context-relevant task-specific significant activities than repetition exercise or passive modalities.<sup>46</sup> Sleep also plays a role in the offline processing and consolidation of motor memory in healthy individuals. One investigation found no improvement after sleep in stroke patients or the group of healthy controls.<sup>28</sup>

Only 1 study<sup>33</sup> was done in the acute phase of stroke and showed evidence for sleep-dependent motor learning. Ideally, neurorehabilitation should start as soon as possible after the stroke because of the greater chance of positive results. However, despite the six remaining studies performing the intervention in the chronic stroke phase, improved motor function was observed in 5 of them, showing that even in the chronic phase the intervention can have beneficial effects.

Three studies did not evaluate stroke severity<sup>28,32,33</sup> despite this being a crucial factor in recovery: the more severe stroke, the lower the chance of successful rehabilitation.

All studies investigated outcomes over a relatively short period of rehabilitation. There is a need for more extended studies of more than four months to properly establish the results of neurorehabilitation, physical therapy, and functional exercises for daily living beyond any short-term placebo effect. Extended studies can help form a consensus on whether improved sleep may have a positive relationship within rehabilitation, thus improving motor learning outcomes in patients following stroke.

Rehabilitation after stroke consists of new skill acquisition, sensorimotor tasks, and forming new memories within this context. We need strategies to increase the amount of rehabilitation practice and promote its effectiveness; optimizing sleep may well be an essential part of this process.

In a rat stroke model, the detrimental effects of sleep disturbance on neuroplasticity and functional recovery impacted long-term active recovery and endogenous brain restorative processes, including axonal sprouting, synaptogenesis, neurogenesis, and angiogenesis.<sup>47</sup>

Sleep-dependent memory consolidation is influenced by features of the task, such as the involvement of specific task-related neural substrates and post-training sleep characteristics.<sup>31</sup> This is a 2-way relationship: following stroke, patients may have sleep difficulties and sleep disorders, and these sleep problems affect their neurorehabilitation.

In our review, only three studies investigated sleep patterns in stroke patients. They showed objective changes,<sup>28,32,34</sup> such as increases in superficial sleep and a decrease in sleep efficiency, sleep duration, deep sleep (N3 sleep stage), and REM sleep stage, which are consistent with the literature<sup>8,10,13,48</sup> and might hamper motor



**Table 3** Level of evidence and risk of bias of manuscripts included in the review

Article	Level of Evidence (Design)	Risk of Bias*
Backhaus et al, 2018 <sup>28</sup>	I (RCT)	13/27 <sup>†</sup>
Lubart et al, 2017 <sup>33</sup>	IV (CT)	13/24
Al-Dughmi et al, 2017 <sup>32</sup>	III (CCT)	14/24
Siengsukon et al, 2015 <sup>34</sup>	III (CCT)	15/24
Siengsukon and Boyd, 2009a <sup>29</sup>	I (RCT)	16/27 <sup>†</sup>
Siengsukon and Boyd, 2009b <sup>30</sup>	III (CCT pseudo)	15/24
Siengsukon and Boyd, 2008 <sup>31</sup>	III (CCT pseudo)	15/24

CCT pseudo: Case-Controlled Trial pseudorandomized; CCT: Case-Controlled Trial; CT: Controlled Trial; RCT: Randomized Controlled Trial.

\*Rated using the methodological index for nonrandomized studies for comparative studies (MINORS, 0-24 points), unless otherwise indicated.

<sup>†</sup>Rated using the Downs and Black scale (0-27 points).

rehabilitation. There is some evidence that sleep stages are linked to specific memory consolidation. N2 sleep stage appears to be important in improvement of simple motor tasks.<sup>49</sup> In an investigation of individuals who learned a new task compared to a control group who did not, the authors found a significantly higher density of sleep spindles (12-15Hz), a microarchitectural characteristic of sleep.<sup>44</sup> Sleep EEG spindles and slow-wave activity (SWA) are altered in stroke.<sup>9</sup> Another study showed that improved motor task performance after a sleep period was directly correlated with an increase in the percentage of N2 sleep stage.<sup>45</sup> During N2 sleep stage, special conditions for cortical restorative processes may be established, such as changes in thalamocortical circuits and temporary deafferentation of sensory influx to the cortex.<sup>50</sup> Stable N2 sleep stage is a component for prolonged sleep and metabolic restoration.<sup>50</sup>

Decreased N3 sleep stage may represent neuronal dysfunction, negatively affecting functional recovery and motor learning in patients following stroke.<sup>13</sup> Spectral EEG has shown an increase in SWA, a power band between 1 and 4.5 Hz, which is usually highest shortly after falling asleep and is one of the main features of the N3 sleep stage. Generalized SWA can reflect cortical plasticity and could be used as a predictive measure of recovery in patients with stroke.<sup>9,51,52</sup> Higher SWA during sleep has been associated with improved performance in a motor learning task in healthy individuals.<sup>51</sup> Higher focal SWA in the infarct area in wake and sleep indicates the presence of dysfunctional slow waves, which are a marker of profound neuronal suppression and cerebral damage.<sup>52</sup> In this context, decreased SWA during sleep can be linked to the absence of input from the relevant body part,<sup>53</sup> indicating that subsequent increases in cortical SWA reflect synaptic potentiation triggered by learning.

Cortical plasticity is linked to local sleep regulation, and when synaptic strength is reduced, local sleep need is also reduced.<sup>54</sup> In some aquatic mammals (cetaceans) and birds, one hemisphere can remain awake while the other is in slow-wave sleep – an adaptive response that permits them to swim, fly or monitor the environment. Local SWA induction is triggered by a learning task (such as in rehabilitation),

suggesting that local plastic changes associated with learning may be involved. SWA can be selectively induced in defined regions of the cerebral cortex.<sup>51</sup> In this context, there is evidence that SWA might help synaptic adaptation.<sup>52,54-57</sup> Since the evidence points to decreased N3 sleep stage in stroke survivors,<sup>57</sup> we assume less SWA in the damaged brain. In this review, none of the trials used spectral EEG to investigate sleep microarchitecture, which could significantly contribute to our understanding of the changes taking place in successful rehabilitation. N3 sleep stage and SWA appear to be a requirement for maintaining sustainable learning, and further investigations into “local sleep” in humans are warranted. One last point to consider is the lack of sleep disorders investigation in the sample – which may have affected the performance of the participants analyzed.

The studies in this review had good methodological quality. However, the assessment was complicated by four factors relating to the heterogeneity of the studies: i) the duration of the neurorehabilitation regimen, ii) post-stroke function, iii) UE evaluation (ipsilateral or contralateral to lesion side), and iv) comparisons between different groups. Thus, there is a need for further high-quality randomized controlled trials investigating sleep and neurorehabilitation protocols. Currently, even well-done case-control trials and other retrospective designs could add substantially to this area.

Although a methodologically rigorous review process was used for this systematic review, several methodological issues need to be discussed. Most studies had relatively small sample sizes. Many of the studies reported in this review were underpowered. In addition, it was impossible to perform a meta-analysis, which could add value to a review because it may generate new information not available in any of the original individual papers. Meta-analysis of the included studies was not performed because of the small number of studies and the vast heterogeneity of stroke severity and treatment outcomes. The findings of this review were summarized dichotomously instead of providing estimates of the effects and an indication of the uncertainty around the forecast.

## Conclusions

This systematic review found that published neurorehabilitation interventions included nighttime sleep and long naps ( $\geq 90$ mins after intervention) as the intervention improved motor consolidation in patients following stroke. Neuroplasticity in stroke patients needs to be enhanced by intensive rehabilitation and physical therapy, and this review shows that this should include the treatment of sleep disorders to maximize outcomes. After a stroke, sleep disorders of any kind (e.g., OSA, insomnia, circadian rhythm disorders) can negatively influence neuroplasticity recovery and physical rehabilitation. Future research must consider sleep-related memory consolidation within the scope of physical therapy and neurorehabilitation practice for this field to advance.

A better understanding of the role that sleep plays in regulating plasticity could eventually lead to innovative therapeutic approaches for brain disorders that address sleep disturbances and sleep loss, thereby impacting stroke rehabilitation. Factors such as alertness resulting from sleep disorders may also play an essential role in facilitating rehabilitation efforts. Connecting two fields that have thus far generally remained separate – the study of sleep and plasticity, and the study of sleep and neurorehabilitation and physical therapy – has potential to improve functional outcomes.

### Conflict of Interest

None declared.

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Responsibility for the content of the text rests with the authors alone.

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## SEARCH STRATEGY

Databases: MEDLINE, CINAHL/EBSCO, Cochrane Library, Embase, PEDro and Scopus

Topic: stroke [MeSH]

Topic: sleep [MeSH]

Topic: rehabilitation [MeSH] OR physical therapy [MeSH]

Topic: neuroplasticity [MeSH] OR plasticity [MeSH] OR motor learning [MeSH]

SEARCH #1 = sleep AND plasticity AND stroke = 32 manuscripts

SEARCH #2 = stroke AND plasticity AND sleep AND rehabilitation = 10 manuscripts

SEARCH #3 = stroke AND (plasticity OR motor learning) AND sleep AND (rehabilitation OR physical therapy) = 24 manuscripts