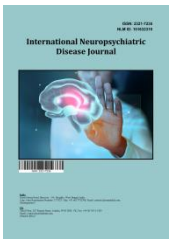

International Neuropsychiatric Disease Journal

Volume 20, Issue 3, Page 93-100, 2023; Article no.INDJ.106385
ISSN: 2321-7235, NLM ID: 101632319

The Potential Role of Sleep in Post-stroke Motor Learning

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/INDJ/2023/v20i3403

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/106385

Short Communication

Received: 21/07/2023
Accepted: 26/09/2023
Published: 03/10/2023

ABSTRACT

Stroke is the primary contributor to the commencement of adult disability in the United Kingdom, and individuals who survive a stroke frequently encounter challenges in reacquiring motor abilities, which has a substantial influence on their overall well-being. Sleep disturbance is a prevalent issue affecting approximately 50% of those who have experienced a stroke. The established literature demonstrates the advantageous impacts of sleep on motor learning in individuals without health complications. However, the precise contribution of sleep to motor learning in individuals recovering from stroke remains inadequately comprehended. The objective of this review was to analyze and consolidate the available research pertaining to motor learning after stroke, with the intention of ascertaining the presence and mechanisms of this association. Sleep-induced motor learning has two distinct phases, namely sleep preceding learning (SBL) and sleep after learning (SAL). These stages facilitate the consolidation of memory and reinforce the connections between different regions of the cerebral cortex, thereby decreasing the need for the medial temporal lobe (MTL) to bind information. There is a limited yet promising body of evidence suggesting that sleep has a role in modulating motor learning and rehabilitation outcomes following a stroke. There is evidence suggesting that sleep has a positive impact on motor learning following a stroke. Several studies have shown that stroke patients exhibit increased tracking accuracy after a night of sleep compared to those who do not sleep. Sleep disruptions have an adverse effect on the functional recovery of those who have experienced a stroke, with a special emphasis on those who have suffered from moderate strokes. There exists a correlation between suboptimal sleep patterns and impaired

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motor recovery following a stroke, however the use of sedative medications does not yield substantial enhancements in sleep quality or rehabilitation outcomes. Moreover, the utilization of sedatives may potentially have adverse effects on memory function and neural connectivity. Although the current research shows promise, it is important to acknowledge its limitations, which include the use of subjective sleep assessments and cross-sectional study designs. In order to demonstrate a more conclusive relationship between sleep and post-stroke motor recovery, future research endeavors should incorporate objective sleep assessment techniques, longitudinal methodologies, and randomized crossover designs. In summary, the current body of research suggests a potentially beneficial impact of sleep on motor learning following a stroke. However, it is important to exercise caution when interpreting these findings due to limitations in the methodologies employed. In order to comprehensively comprehend the influence of sleep on post-stroke motor recovery, it is imperative to conduct further research employing robust study designs and objective sleep assessment techniques. Such investigations have the potential to enhance rehabilitation efforts and mitigate healthcare expenses.

Keywords: Stroke; post stroke; Parkinsonism; neuronal lesion; dystonia; motor recovery.

1. INTRODUCTION

Most humans complete surprisingly complex motor behaviours every day (e.g. walking, running, eating). We execute them efficiently and the perceptual and behavioural aspects of the tasks blend together seamlessly. For the 4% of individuals suffering from a functional disability in the UK, (equates to approximately 2.65 million individuals; GOVUK., 2014) however, performing even the most simple motor behaviours can be an arduous task. Stroke is most common cause of adult onset disability. There are an estimated 1.2 million stroke survivors in the UK with approximately 110,000 new strokes each year (Stroke Association, 2018). Of these survivors, two-thirds are expected suffer from long term movement disability (NICE, 2019). Currently, NHS costs for stroke care is £26 billion a year (NICE, 2019) with £5.2 billion spent on social care (Stroke Association, 2017) and £3.4 billion spent on early-supported discharge and rehabilitation [1-4].

Depending on size and location of consequent neuronal lesion(s), stroke survivors may suffer from a variety of movement problems including: weakness, spasticity, dystonia, tremor, chorea and parkinsonism. Falls (average of 6.55 falls suffered per person, per year; equates to circa 720,500 annual falls; Weerdesteyn et al., 2008) and fall related injuries (e.g. disabilities, fractures) are common complications among stroke survivors with 5% (36025) of overall falls expected to result in a fracture. Thus, patients may undertake motor rehabilitation therapy to assist with recovery from the initial deficit, or, to assist with recovery from a secondary disability suffered as a consequence of stroke [5-8].

In the pursuit of safe and efficacious motor recovery, scientific research has attempted to identify key variables that influence movement rehabilitation. In recent years, promising (albeit limited) evidence suggests that sleep is one key modulator of motor learning and therefore, post-stroke rehabilitation outcomes [9]. Interestingly, it is estimated that 50% of stroke patients suffer from insomnia (with N3 sleep particularly curtailed; Jirakittayakorn and Wongsawat., 2018) and that 5.66% (40,780) of stroke-related falls can be attributed to daytime sleepiness and inattention [10]. Therefore, it is not unreasonable to suggest that sleep-enhancement therapy could be used to assist stroke patients suffering from a primary or secondary post-stroke movement disorder [11].

2. EMPIRICAL REVIEW

The rationale underpinning this review, therefore, was to examine and synthesize most recent and relevant literature concerning sleep and post-stroke rehabilitation outcomes. Before reviewing pertinent literature, however, it is first important to consider mechanism(s) by which sleep deprivation (SD) and sleep enhancement may influence post-stroke motor learning [12-14].

Many researchers hypothesize that post-stroke SD originates from hypothalamic-pituitary-adrenal (HPA) axis hyperactivity. Hyperactivity can be caused by either deficit itself or by secondary consequences such as stress or anxiety. In any case, parvocellular neurosecretory neurons within the paraventricular nucleus (PVN) of the hypothalamus are signalled to accelerate production and secretion of corticotrophin-

releasing factor (CRF; a neurohormone). This triggers a chemical cascade resulting in uncontrolled glucocorticoid binding activity (see Fig. 1).

High glucocorticoid binding activity then induces excessive cAMP signalling (Arnsten, 2009) which enables extensive, coordinated shunting of cAMP network inputs (Delmas and Brown, 2005). This promotes amygdala functions (brain area which stimulates fear conditioning and consolidation of emotionally relevant information i.e. 'bottom-up' reflexive regulation) but impairs PFC functions (brain area which protects representational knowledge from interference of external or internal distractions, inhibits inappropriate actions and promotes task-relevant operations i.e. 'top-down' thoughtful regulation; Arnsten, 2009) [15,16]. The dorsolateral PFC (DLPFC) interacts with sensory and motor cortices to regulate attention, working memory and action. Thus, a reduction in both persistent firing and tuning of DLPFC neurons causes an individual to attend to irrelevant stimuli in place of relevant stimuli which (further) impairs sleep-onset (cycle of decline), working memory, concentration, alertness and consequently performance [17]. Ergo, motor learning is not as efficacious whilst deprived of sleep [18].

3. SLEEP-INDUCED MOTOR LEARNING

Sleep-induced motor learning can be divided into 2 key phases [19]: sleep before learning (SBL) and sleep after learning (SAL). Sleep (primarily stage-2 SWS) before learning primes the cerebral cortex (short-term memory store) and hippocampus (consolidates novel memories) for receiving new information by transferring and consolidating newly acquired, relevant memories into neocortical structures (long-term memory store) to restore hippocampal encoding capacity for next day of practice [20,21]. SAL then

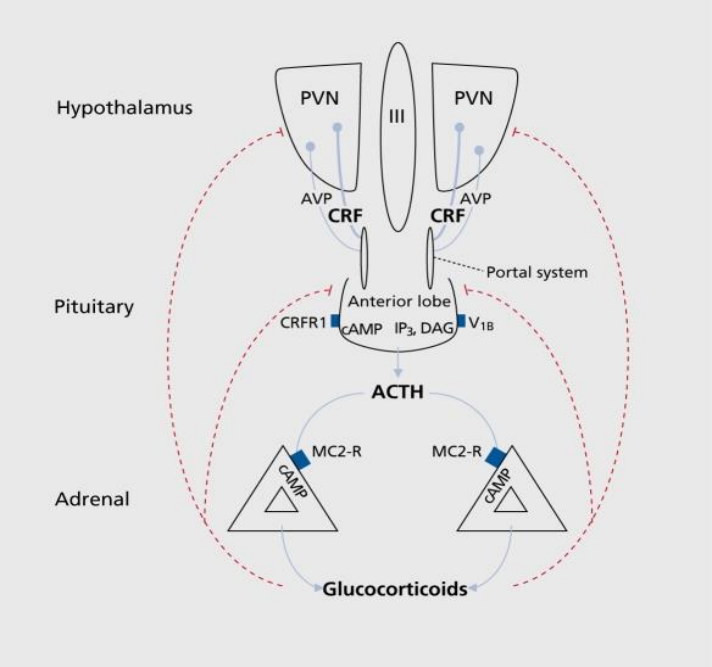

Fig. 1. Schematic Depiction of the biomolecular processes underpinning HPA-axis hyperactivity. Parvocellular neurosecretory neurons within the paraventricular nucleus (PVN) of the hypothalamus are signalled to accelerate the production and secretion of corticotrophin-releasing factor (CRF; a neurohormone) into the hypophyseal portal system (Smith, 2006). CRF is then transported into the anterior pituitary gland, where it binds to its type-1 receptor (CRFR-1) to activate adenylate cyclase. This stimulates adrenocorticotropic hormone (ACTH) release from the pituitary corticotropes. ACTH then binds melanocortin type 2-receptor in parenchymal cells of the adrenocortical zona fasciculata. This initiates the cAMP pathway which facilitates glucocorticoid (e.g. noradrenaline and dopamine) secretion from the adrenal cortex (see figure 1; Smith, 2006). Substantially elevated levels of noradrenaline and dopamine inhibit NREM sleep and trigger uncontrolled stimulation of lower-affinity α1-receptors and D1-receptors respectively

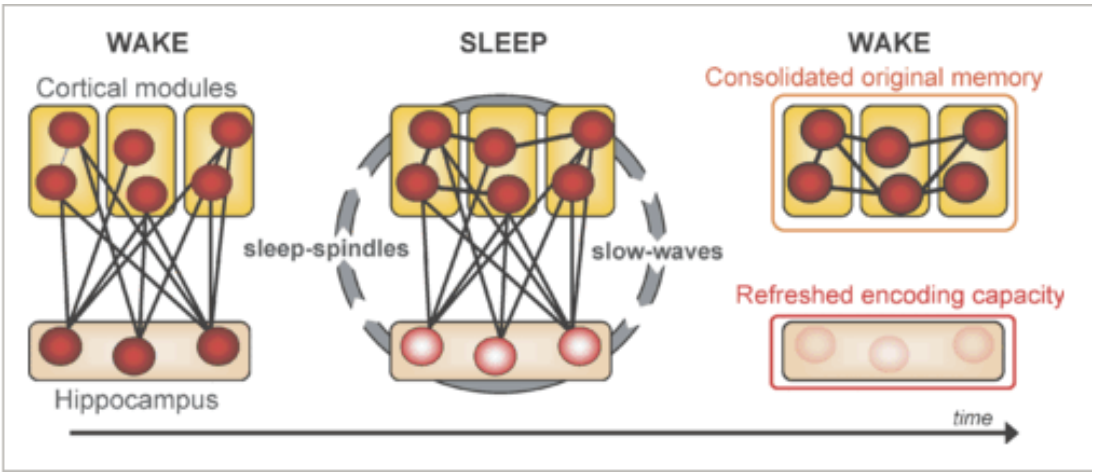

Fig. 2. Schematic representation of offline learning (Walker, 2009) –

enables newly encoded memories to be consolidated and stored as engrams within the CNS (akin to that of a computer 'file transfer') to facilitate future performance [22].

According to the classical model of sleep dependent ML, structures contained within medial temporal lobe (MTL; most notably the hippocampal complex) are central to both SBL and SAL [23]. More specifically, these structures link together patterns of cortical activation that were present during initial encoding to facilitate formation and retrieval of novel motor memories. Alongside binding patterns of cortical activation, hippocampus has been suggested to play a key role in offline reactivation of such networks. It is hypothesized that repetition of these reactivation processes through multiple bouts of nightly sleep cycles strengthen and thereby, reinforce initially weak neocortical connections [24,25]. Thus, initial dependence on MTL binding subsides as newly acquired information is progressively integrated into neocortical circuits (LTM; see Fig. 2). Over time, therefore, offline reinforcement enables newly acquired information to be activated within the cortex, independently of the hippocampus.

An advanced version of this classical hypothesis has since been proposed by Buzsaki [26]. Buzsaki [27] suggests a model of consolidation that is dependent upon two key states of hippocampal activity. The first pertains to a state of wakeful 'recording' which shifts to a second state of offline 'playback'. Playback lasts for up to 3-hours and is characterised by bursts of neural activity that occur during SWS and are termed 'sharp-waves' or 'sleep spindles' (conducted within hippocampal place cells and cortical structures respectively). Interestingly, these bursts of activity are replayed at a speed that is approximately 20 times faster than prior online experience and may represent a specific spatial location that occurred during 'recording' [28,29]. Thus, neuronal activity experienced whilst awake may be replayed nocturnally during SWS, potentially representing motor memory processing.

Together, therefore, both versions of classical hypothesis suggest two key predictions regarding offline motor learning [30]. First, is that offline-consolidation promotes and strengthens formation of cortico-cortical connections to produce motor memories that are more resistant to interference (SAL). Second, is that offline strengthening of these cortico-cortical connections reduces dependence on MTL binding by increasing hippocampal encoding capacity (SBL).

In support of sleep-induced learning, Siengsukon and Boyd [31] observed that sleep may enhance post-stroke movement learning. Researchers split stroke patients and healthy controls into either a sleep (baseline test in evening and post-test in morning following sleep) or no-sleep group (baseline test in morning and post-test that evening). Each group were instructed to complete a continuous tracking task (CTT; use of a hand-driven joystick to track a target moving horizontally across a computer screen). Interestingly, sleep-induced improvements in spatial tracking accuracy (more negative score denotes less error; -1.4 vs -0.3 = 21.4% improvement; p=0.014 vs p=0.556 respectively) and temporal tracking accuracy (positive scores indicate improved time lag of tracking at

retention; 60ms vs -2ms = 31% improvement; p=0.036 vs p=0.962) were only evident in the sleep-stroke group. This indicates that sleep enhances ML in stroke patients but not healthy individuals.

In agreement with Siengsukon and Boyd [32], Joa et al., 2017 conducted a multi-centre observational study on mild-moderate stroke patients (n=280) and reported that Berg Balance Scale (Korean version) score improvements were significantly lower in a disturbed-sleep group (assessed by a health professional using Diagnostic Statistical Manual of Mental Disorders criteria to define patients with any sleep disturbance) compared to a normal sleep group. This effect was even maintained after adjusting for confounders such as age, sex and hypnotics usage. Interestingly, when results were analysed according to stroke-severity, significant improvements in balance were only maintained by moderate-stroke sufferers and not by mild-stroke sufferers. This suggests that sleep disturbance has a negative influence on functional recovery following moderate, but not mild stroke.

Similarly, Iddagoda et al. [33] reported an inverse association between poor sleep quality (assessed through PSQI; completed at baseline (pre-stroke) and prior to discharge (post-stroke)) and rehabilitation outcomes as assessed by Functional Independence Measure (assesses degree of disability depending on patients score in 18 motor and cognitive function categories; Rs. −0.317, P = 0.005) in a prospective cohort study of 104 Adult, Australian stroke patients from two major stroke units in Western Australia. This suggests that poor sleep quality impedes post-stroke motor recovery.

Interestingly, it was also reported by Iddagoda et al. [34] that sedatives were used by 18.2% of patients with no impact on either sleep quality or rehabilitation being identified. Similar findings have also been reported by Kim et al. [35], who identified no significant effect of hypnotics-use on sleep-patterns in a sample of subacute stroke patients (n=30) with insomnia (experimental group; hypnotics consumed) vs those without insomnia (control; placebo) at 3-weeks follow-up. It should be noted, however, that hypnotics administration did temporarily enhance sleep among the experimental condition, which may have contributed toward insomnia patients obtaining functional and cognitive outcomes that were (statistically) comparable to those achieved by non-insomnia patients. Given that improvements in sleep were not maintained at 3-weeks follow-up, however, it is doubtful that optimal sleep-induced motor benefits were attained by the insomnia group.

This is concerning given that hypnotics are the mainstay prescription for post-stroke insomnia. More worrying still is that hypnotics use has been linked with a 2-fold increase in depression, over 3-times as many in-hospital falls, a 4-fold increase in overall mortality [36] and a consequential overall cost (of hypnotics) to the NHS of approximately £72 million per annum [37]. Moreover, recent research has also identified sleep induced by some hypnotics (e.g. zolpidem) may actually damage neuronal connections and impair memory rather than enhance learning [38]. This suggests that stroke patients will actually experience detriments and not benefits to their motor performance after using hypnotics to enhance sleep.

There are noteworthy limitations within discussed research that may limit reliability of results. First, is recurrent utilisation of subjective self-report tools when assessing sleep (e.g. PSQI). Falck et al. [39] identified that stroke survivors sleep for 0.25-hours less than they subjectively report. Therefore, true sleep-post stroke movement learning effects may not have been accurately depicted within research conducted until present. In future, experimenters should utilise objective tools (e.g. polysomnography) to minimise measurement errors whilst assessing sleep.

Second, is cross-sectional design of multiple studies. Cross-sectional research utilises a ‘snapshot’ measurement of both exposure (sleep) and outcome (post-stroke movement learning). Therefore, it is not possible to infer causal relationships from such research because reverse-causality cannot be denied (i.e. cannot refute that alterations in movement learning influenced sleep), and because other confounding variables (e.g. diet) may have influenced result outcomes. Forthcoming research should utilise longitudinal designs to ease issues related to reverse-causality, and also, so that effects of sleep on post-stroke movement learning effects can be more accurately assessed [40-42].

A final issue is that none of the studies were crossover or single subject design. Because there are multiple variables (e.g. age, diet) that may confound the sleep-movement learning

relationship, it cannot be ascertained that individuals from distinct groups would have reacted to different conditions (e.g. sleep vs no-sleep) in same way. Future research studies should utilise randomized cross-over designs so that confounding variables have less influence on result outcomes.

4. CONCLUSION

In conclusion, discussed research suggests a promising role of sleep for post-stroke motor learning. However, current evidence is derived primarily from cross-sectional studies which utilised self-reported sleep assessments. Due to such methodological limitations, a beneficial role of sleep for movement learning after stroke cannot be established. In future, research studies should utilise either prospective, longitudinal or randomized crossover designs and objective sleep assessments so that true effects of sleep on post-stroke motor learning can be more accurately portrayed.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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The peer review history for this paper can be accessed here:
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