Short communication

The Potential Role of Sleep in Post-Stroke Motor Learning

Comment [U1]: Mention briefly about method if any, Discussion is missing, add acknowledgement

Abstract

In the pursuit of safe and efficacious motor recovery, scientific research has attempted to identify key variables that influence movement rehabilitation.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. 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.

Comment [U2]: Elaborate the abstract in comprehensive way

Keywords: parkinsonism, neuronal lesion, dystonia, motor recovery

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 UKwith 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 (e.g. movement).

Comment [U3]: reference?

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 (Bansil et al., 2012). 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(Weerdesteyn et al., 2008). 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.

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 (Walker et al., 2014). 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 (Schmid et al., 2013).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.

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.

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, parvocellularneurosecretory 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 figure 1).

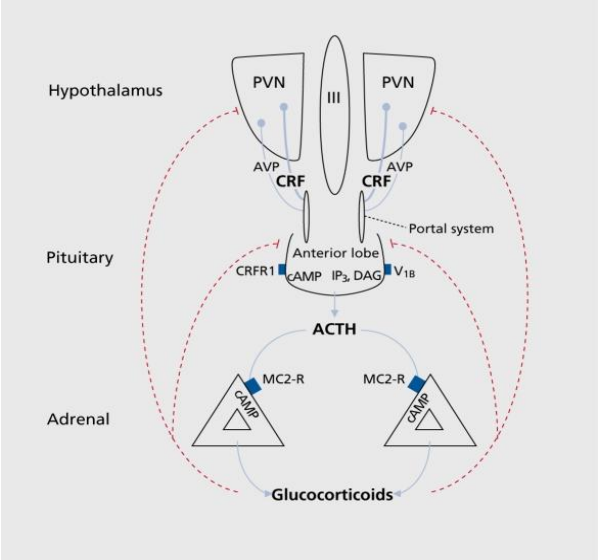

Figure 1: Schematic Depiction of the biomolecular processes underpinning HPA-axis hyperactivity. Parvocellular neurosecretory neurons within the paraventricular nucleus (PVN) of the hypothalamus are signalled to accelerate the production and secretion of corticotrophin-releasing factor (CRF; a neurohormone) 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. – MayNeed Permission or to redraw

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). The dorsolateral PFC (DLPFC) interacts with sensory and motor cortices to regulate attention, working memory and action. Thus, a reduction in both persistent

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Comment [U6]:

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 (Chee et al., 2008). Ergo, motorlearning is not as efficacious whilst deprived of sleep.

Sleep-induced motor learning

Sleep-induced motorlearningcan be divided into 2 key phases (Walker et al., 2008): 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 restorehippocampal encoding capacity for next day of practice (Walker, 2009). SAL then 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 (Walker 2009).

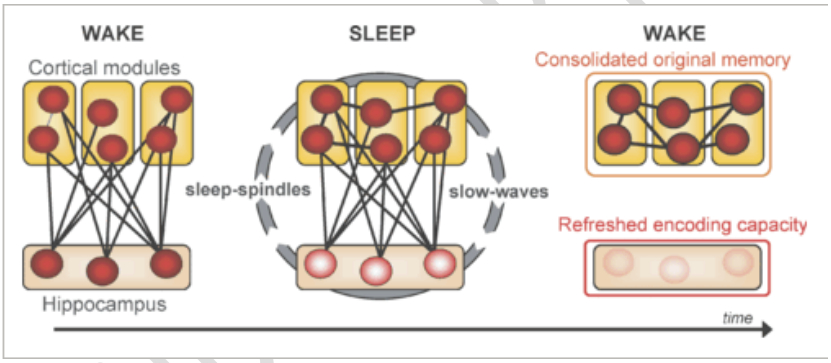
According to the classical model of sleep dependent ML, structures contained within medial temporal lobe (MTL; most notably the hippocampal complex) are central to both SBL and SAL (Squire et al, 1992). More specifically, these structures link together patterns of cortical activation that were present 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 (McClelland et al., 1992). Thus, initial dependence on MTL binding subsidesas newly acquiredinformation is progressively integrated into neocortical circuits (LTM; see figure 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 (1996). Buzsaki (1996) 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 andis characterised by bursts of neural activity that occur during SWS and are termed 'sharp-waves' or 'sleep spindles' (conductedwithin hippocampal place cellsand cortical structures respectively).Interestingly, these bursts of activity are replayedat a speed that is approximately 20 times faster than prior online experience and may represent a specific spatial location that occurred during 'recording' (Mednick et al., 2013). Thus, neuronal activity experienced whilst awake may be replayed nocturnally during SWS, potentially representing motor memory processing.

Comment [U7]: How?

Together,therefore, both versions of classical hypothesis suggest two key predictions regarding offline motor learning(Walker, 2009). First, is that offline-consolidation promotes and strengthens formation of cortico-cortical connections to producemotor 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).

Figure 2: Schematic Representation of Offline Learning (Walker, 2009) – Permission may be Needed



In support of sleep-induced learning, Siengsukon and Boyd (2009) observed that sleep mayenhance 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.

Comment [U8]: Reason why not in healthy individual ?

In agreement with Siengsukon and Boyd (2009), 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., (2019) 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., (2019) 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., (2010), 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 (Kripke et al., 2017) and a consequential overall cost (of hypnotics) to the NHS of approximately £72 million per annum (Hafner et al., 2017). Moreover, recent research has also identified sleep induced bysome hypnotics (e.g. zolpidem) may actually damageneuronal connections and impair memory rather thanenhance learning (Berdyyva et al., 2014). This suggests thatstroke patients will actually experience detriments and not benefits totheir motor performance after using hypnotics to enhancesleep.

There are noteworthylimitations within discussedresearch that may limit reliability of results. First, is recurrent utilisation of subjective self-report tools when assessing sleep(e.g. PSQI).Falck et al., (2019) identified that stroke survivors sleep for 0.25-hours less than theysubjectively 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 notpossible 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 haveinfluenced result outcomes. Forthcoming research should utilise longitudinal designs to ease issuesrelated to reverse-causality, and also, so that effects of sleep on post-stroke movement learning effects can be more accurately assessed.

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.

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-reportedsleepassessments. 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.

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References:

Comment [U9]: Reference should be in proper format as per journal guidelines

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