

Therapeutic Potential of Sleep in Enhancing Post-Stroke Motor Recovery

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Abstract

Stroke is one of the most common causes of long-term disability in the elderly but also in younger subpopulations with predisposing factors. Recovery of function after stroke is often a lifelong endeavor. Poor nighttime sleep quality and daytime somnolence are commonly reported by stroke patients in the rehabilitation setting and may influence responses to rehabilitative interventions after stroke. Given that memory consolidation relies on precise sequencing of sleep events, it is conceivable that impaired sleep architecture after stroke may negatively influence motor skill learning after stroke. However, there is paucity of knowledge about sleep patterns after stroke. In this scoping review, mechanisms of sleep modulation on learning after stroke are reviewed. Stroke units and rehabilitation centers should make efforts to screen for sleep disorders and facilitate therapeutic environments that may incorporate sleep breaks into therapy regimens. Further study is needed to increase our knowledge on sleep patterns after stroke which may then pave the way for therapeutic interventions targeting sleep to enhance motor recovery after stroke.

Keywords: Stroke rehabilitation; Motor function; Sleep; Memory consolidation

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Introduction

Every year, 15 million people worldwide suffer a stroke. To date, tissue plasminogen activator remains the only FDA-approved treatment for ischemic stroke; to get this treatment, one must present inside an hour and a half of onset of side effects. Past this point, interventions are limited to prevention of future recurrence and reducing deficit.

Factors underlying recovery of stroke are still not precisely understood and rehabilitation interventions, for the most part, are empiric. Sleep-wake disturbances are among the foremost indicators that are predictive of poor prognosis of functional recovery. Furthermore, the mechanisms of neural re-organization may be susceptible to modulation by behavioral states during sleep and wakefulness which may, in part, account for inter-individual difference in stroke recovery. In this review, the link between recovery and sleep is explored with a concept report of current literature.

Mechanisms of Motor Skill Acquisition

We are constantly faced with opportunities to learn and perform motor skills, the ability of which is influenced by neural plasticity and cortical reorganization. Use and repetition through motor

practice is the conventional method utilized to develop a functional motor skill. This method is associated with increased corticomotor excitability within the primary motor cortex in conjunction with disinhibition through downregulation of extrasynaptic GABA-A mediated receptor activation, a mechanism initially suggested by animal models and strengthened by magnetic resonance spectroscopy studies [1-4]. Task-related movement representations in the primary motor cortex precede development of a stable functional motor skill [5-9].

In the hours (to days) following practice, neuronal cell machinery are activated to strengthen and stabilize the newly acquired skill via memory consolidation [10,11]. In animal models, motor learning leads to long-term potentiation (LTP) in the primary motor cortex; LTP refers to a persistent strengthening of synapses based on recent patterns of activity that produce a long-lasting increase in signal transmission between two neurons – now considered a neural correlate of memory [12]. LTD, the converse of LTP results in a long-lasting decrease of synaptic efficacy. Though the vast majority of work on LTP/LTD has focused on excitatory synapses, potentiation and depression of inhibitory transmission mediated by activation or modulation of NMDA, dopamine, GABA and serotonin receptors can also be observed in the brain [13,14]. These in turn can influence dopaminergic and/

or glutamatergic neurons to decrease cortical inhibition, thus increasing excitability. Studies in humans using noninvasive brain stimulation show that there may be similar “LTP-like” mechanisms in place that are active during motor skill learning.

Increased corticomotor excitability with practice is likely associated with or mediated by a heterosynaptic system in the primary motor cortex and prefrontal cortex. Serotonergic neurons from the Raphe nuclei project to the dopaminergic neurons in the ventral tegmental area as well as to their targets in the prefrontal cortex. Serotonin’s influence on dopaminergic tone appears to be differential resulting in increased dopamine levels the striatum and decreased in the prefrontal cortex suggesting an inhibitory effect on the prefrontal cortex [14]. Animal models demonstrate dopaminergic modulation of pyramidal cell excitability directly and indirectly through its actions on local GABAergic interneurons [15]. D1 and D2 have opposing effects in the neocortex where D1 increases interneuron excitability while D2 reduces excitability in the pyramidal neurons which has been demonstrated by actions of the receptor-D1 activates adenylyl cyclase whereas D2 receptors inhibit adenylyl cyclase [16,17].

While practice produces gains in motor performance within a session, time is also important. 24 hours after learning with no further training, significant additional gains in motor performance are evident [18]. Off-line consolidation, i.e. neural processing occurring 4 to 6 hours after the practice session [19,20]; and resistance to interference, i.e. disruption of the processing of the recently acquired motor memory trace by other new information have been shown to be time-dependent with influence from behavioral states that follow the initial period of learning [21-28]. Newly formed representations are shifted from the prefrontal cortex to more dorsal areas during the passage of time which may underlie its increased functional stability [29]. Depending on the type of information learned, the offline consolidation period may offer additional performance gains, specifically after a period of sleep.

Sleep and motor learning: Although the exact mechanisms of sleep’s role in memory consolidation remain unclear, evidence suggests that sleep supports a process whereby motor memory traces are reprocessed and transferred across distributed networks. In literature, sleep stages reported to be associated with memory consolidation are not in full agreement with one another. Most commonly, the components of sleep that are reported to have a role in offline memory consolidation are slow wave activity is characterized by electroencephalographic slow activity (0.5-4.5 Hz) that appears synchronized and oscillatory seen in stages 2 and 3 and sleep spindles (12-15 Hz) during stage 2 are correlates of cortico-thalamic interactions whose function is still not clearly understood [30-37]. Mechanisms of synaptic potentiation during wakefulness have been directly linked to the enhancement of slow wave activity as well as increased sleep spindles during the subsequent sleep following a learning period, parallel with increased expression of long-term potentiation markers during preceding wakefulness [30,31,38]. A declarative learning task induced an increase of slow wave and spindle activity in the left frontal area during sleep after a training session, which was parallel with improvement in memory performance

[39] Local changes in synaptic density due to learning may be associated with site-specific increases in slow wave activity [32]. Specific deprivation of slow wave sleep prevented visuomotor learning which supports the direct role of slow wave activity in sleep-dependent performance enhancements rather than it being considered merely a correlate of learning [40]. Intermittent transcranial direct current stimulation during early NREM sleep resulting in temporarily increased slow wave activity for 3 minutes was followed by enhanced retention in a paired-associated memory task [41]. Suppression of cortical activation, such as with immobilization, was followed by a local reduction in slow wave activity during the successive sleep episode [42]. The length of Stage 2 NREM during sleep is correlated with improved motor task performance [43] Other data shows a combination of both NREM and REM appear to be involved in consolidation of experience-dependent traces that led to improved task performance [44-48]. Transcutaneous direct current stimulation applied to the premotor area during REM sleep also enhanced learning of a finger movement sequence [49]. Reactivation of newly formed motor memory trace during sleep using a cue initially associated with skill acquisition improved performance [50,51]. Proper sequencing of sleep events involving slow wave activity during sleep appears to be central to stabilizing newly learned motor skills.

Though sleep appears to have an important role in offline consolidation, its influence over all types of learning is not equal and may change with aging. Sleep-dependent motor consolidation appears to have the most benefit on explicit motor sequence learning while other forms of procedural and implicit sequence motor learning may not be sleep-dependent [5]. Sleep also appears to facilitate the extraction of the explicit knowledge of a task and insights into skill gain [52-55]. Sleep’s role in motor skill acquisition has been consistently demonstrated in healthy adults [56].

In older adults, while the encoding of new motor memory traces is preserved, offline consolidation appears to be less robust [57]. Elderly individuals may be able to make up for the difference with a post-training nap to improve offline gains [58,59]; however current status of literature on the matter of sleep and offline consolidation in older adults is conflicting [60]. Conversely, children stabilize motor memory traces at a much faster rate compared to that of adults and shorter intervals [52,61]. Therefore the role of sleep in offline consolidation may become more important as we age.

Sleep in Motor Recovery Post-stroke

Relearning of motor skills after stroke likely involves similar mechanisms to that in adults without stroke. Alterations in sleep quality and architecture are common after stroke, particularly in the acute to subacute period where re-learning mechanisms are most operant. Sleep quality impairment and related behavioral deficits such as excessive daytime sleepiness, persistent fatigue, mood disorder such as depression and anxiety, and abulia (lack of motivation) may affect motor learning after stroke to a greater extent than that in healthy adults [62-66]. The generation of normal NREM-REM cycles and NREM sleep stages appear to be less dependent from the integrity of cortical and subcortical

structures than the production of a coherent spindle frequency activity [67]. In an age-matched controlled study of 18 stroke survivors, only the stroke survivors that slept, not the healthy controls, between practice and testing demonstrated implicit motor learning while those who did not sleep did not show learning on retention testing [65]. Whole body coordination tasks and fine motor tasks involving the hand appear to show the greatest potential for benefit from sleep [64]. Furthermore, age-matched controlled studies of 40 and 26 chronic stroke survivors showed sleep-dependent implicit and explicit motor learning [66,62].

Sleep architectural impairment that occurs post-stroke may interrupt the sequence of sleep events. The most-common significant finding compared with control subjects was increased fragmentation of sleep with frequent awakening after onset of sleep and sleep latency on actigraphy and polysomnography. This was correlated with poor sleep quality in two studies using related data sets [68,69]. Slow wave and spindle activity have not been routinely discussed in conjunction with polysomnography findings were reported in medical literature. Interestingly, both slow wave activity and spindle size post-stroke showed a positive correlation with higher functional outcome on Barthel Index [70,71]. Spindle size and activity was reported to be significantly reduced in three studies compared with healthy controls, in one study compared with the unaffected hemisphere, in two studies without controls compared with accepted normal values, non-significantly in one and no change in one [70-76]. In many of the studies mentioned above, there was a polarized focus on survivors of paramedian thalamic stroke due to interest in examining the effects of ischemic damage on the reticular activating system, the nuclei of which are primarily situated within the thalamus. Spindle activity is one of the isolated sleep events that appear to depend on the integrity of cortical and subcortical structures [67]. Evidence of restructuring rehabilitation interventions to incorporate sleep is mounting and supports an important role for screening for sleep disturbance and sleep scheduling to enhance stroke recovery [63].

Modulation of Sleep after Stroke

Behavioral Interventions: There is limited yet strong evidence suggesting that sleep sessions scheduled following movement therapy or motor learning sessions can promote offline learning and enhance gains from practice. A controlled study of 18 chronic stroke survivors showed that implicit motor learning is preferentially enhanced by sleep [65]. Chronic stroke survivors (n=8) who slept between practice and retention testing demonstrated off-line improvements in both spatial and temporal memory while those who did not sleep (n=7) and control subjects (n=7) did not demonstrate improvements [60]. Another controlled cohort of 20 chronic stroke survivors demonstrated less error on a tracking task after a night of sleep, an effect that was not seen in control subjects [62]. In a controlled study of 14 subjects with prefrontal lesions (cause of lesion not specified) demonstrated benefit on the performance of a serial reaction time task whereas those with parietal lesions and healthy controls did not [77]. While there is not enough data to suggest a specific protocol and should be prioritized as a research endeavor

by the community of neuroscience, some changes to structure of rehabilitation interventions may be undertaken to maximize effect of post-stroke therapies. An environment conducive to sleep while in the rehabilitation center needs to be ensured to limit sleep disturbance. Closer monitoring of sleep will give way to identification of such sleep disturbances.

Pharmacologic interventions: Possible role of medication for sleep modulation post-stroke comes mostly from animal studies. In humans, there are only a small number of studies using hypnotics that are not rigorous and fail to show convincing results. A randomized double blind crossover study of lorazepam and zopiclone given for post-stroke insomnia in 18 stroke survivors did not show a significant difference, though there was no comparison from baseline to post-treatment; the only functional measure, mini mental status exam, was unchanged [78]. In a controlled study of 19 stroke survivors, 9 underwent fluvoxamine treatment for depression in post-stroke patients led to progressive improvements in PSQI scores that correlated with increased serum melatonin levels during and after 4 weeks of treatment, not seen in the control group [79]. An interventional controlled study of 30 stroke survivors with trazodone, zolpidem, and triazolam showed sleep quality and architecture improvement (total sleep time, sleep latency, depth of sleep, number of nocturnal awakening, sleep quality, daytime alertness, sleep satisfaction and difficulty in falling asleep) from baseline; however, there was no difference between control and study groups [80]. Gamma-hydroxybutyrate, a GABA_B agonist used to treat narcolepsy, was shown to accelerate recovery of grip strength in animals compared with controls [81].

Most convincing evidence for pharmacologic modulation comes from animal studies using baclofen, another GABA_B agonist, consolidated sleep fragmentation and increased duration of NREM and REM as well EEG delta; post-mortem baclofen use was correlated with increased axonal sprouting in post-stroke rats [82,83]. Though baclofen has been traditionally used to treat post-stroke spasticity, search of medical literature did not yield any rigorous studies or clinical trials of baclofen for enhancing stroke recovery. Other pharmaceutical agents that enhance slow wave activity during sleep listed in medical compendia include tiagabine, gaboxadol, gabapentin, pregabalin, ritanserin, eplivanserin, mirtazapine, olanzapine, and trazodone which need greater consideration for the post-stroke population for possible therapeutic use to improve offline consolidation [84].

Noninvasive brain stimulation: Anodal transcranial direct current stimulation (tDCS), a modality-relatively inexpensive, portable and easy to use-that has been used to augment motor recovery in the upper extremity after stroke via synaptic excitation [85,86]. Typically, anodal tDCS is applied for 20-60 minutes over the skull directly over the primary motor cortex with effects (performance gain of the paretic hand) that outlast the stimulation period-up to weeks or even months following repeated stimulation in combination with motor training. However, there is significant variability in the extent of response to anodal tDCS which remains unexplained. Incidentally, tDCS applied during sleep has also been shown to reduce decay of and enhance slow wave activity during sleep with effects on performance, though there

is no clear agreement of a beneficial effect. To date, there have not been any studies that have assessed sleep in conjunction with anodal tDCS in stroke survivors.

Repetitive transcranial magnetic stimulation (rTMS) is another noninvasive modality used to improve motor recovery after stroke with a focus on the upper extremity-high frequency for excitation of primary motor cortex and low frequency for inhibition of contralesional motor areas [87]. rTMS uses more elaborate equipment in comparison with tDCS and is more expensive. There is some data on sleep changes with tDCS suggesting increased slow wave activity [88,89]. Assessment of sleep in the setting of rTMS for post-stroke recovery is lacking.

Rationale for Future Directions

With the aging population, stroke is one of the leading causes of functional impairment; recovery is more a priority than ever before that requires immediate attention and novel therapeutic avenues. Though most of medical community's clinical and scientific efforts have been aimed towards limiting acute cascades involving neurotoxicity, inflammation, and cell death, there needs to be more coordinated and focused intervention to understand neuro-recovery after stroke in order to understand the factors

associated with worsened outcome. Sleep disturbance and architectural impairment needs further study and understanding in relation with functional recovery to develop appropriate intervention. Behavioral deficits that frequently accompany sleep impairment post-stroke (excessive daytime sleepiness, persistent fatigue, depression, anxiety, and abulia) co-morbidly promote adverse health behaviors such as a sedentary lifestyle which, in turn, may exacerbate the aforementioned behavioral deficits. Additionally, sleep events are closely tied to chronic medical illness via mechanisms of autonomic regulation and related metabolic changes which may increase the recurrence of stroke resulting in worsened functional impairment. Sleep modulation after stroke remains an untapped, potential therapeutic target for enhancing stroke recovery, which may be approached through three possible avenues – behavioral (i.e. restructuring rehabilitation intervention to include sleep intervals), pharmaceutical (i.e. medications that target sleep events), and noninvasive brain stimulation (transcutaneous direct current stimulation and transcranial magnetic stimulation). As a precursor to considering these interventions, gathering sufficient evidence to unravel the mechanisms by which sleep influences CNS activity, motor re-learning and post-stroke functional recovery should be aggressively pursued.

References

- 1 Bütetfisch CM, Davis BC, Wise SP, et al. Mechanisms of use-dependent plasticity in the human motor cortex. *Proceedings of the national academy of sciences*. 2000, 9:7.
- 2 Floyer-Lea A, Wylezinska M, Kincses T, et al. Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning. *Journal of neurophysiology*. 2006, 95:3.
- 3 Liepert J, Classen J, Cohen L, et al. Task-dependent changes of intracortical inhibition. *Experimental Brain Research*. 1998, 118:3.
- 4 Stagg CJ, Bachtiar V, Johansen-Berg H. The role of GABA in human motor learning. *Current Biology*. 2011, 21:6.
- 5 Dayan E, Cohen LG. Neuroplasticity subserving motor skill learning. *Neuron*. 2011, 72:3..
- 6 Prevalence and most common causes of disability among adults-United States, 2005. *MMWR Morb Mortal Wkly Rep*. 2009, 58:16.
- 7 Classen J, Liepert J, Wise SP, et al. Rapid plasticity of human cortical movement representation induced by practice. *Journal of neurophysiology*. 1998, 79:2.
- 8 Muellbacher W, Ziemann U, Boroojerdi B, et al. Role of the human motor cortex in rapid motor learning. *Experimental Brain Research*. 2001, 136:4.
- 9 Perez MA, Lungholt BK, Nyborg K, et al. Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. *Experimental Brain Research*. 2004, 159:2.
- 10 McGaugh JL. Memory--a century of consolidation, *Science*. 2000, 287:5451.
- 11 Robertson EM, Pascual-Leone A, Miall RC. Current concepts in procedural consolidation, *Nat Rev Neurosci*. 2004, 5:7.
- 12 Cooke SF, Bliss TV. Plasticity in the human central nervous system. *Brain*. 2006, 129:7.
- 13 Lüscher C, Malenka RC. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD), *Cold Spring Harbor perspectives in biology*. 2012, 4:6.
- 14 Meunier CNJ, Callebert J, Cancela J-M, et al. Effect of Dopaminergic D1 Receptors on Plasticity Is Dependent of Serotonergic 5-HT1A Receptors in L5-Pyramidal Neurons of the Prefrontal Cortex, *PLoS One*. 2015, 10:3.
- 15 Trantham-Davidson H, Neely LC, Lavin A, et al. Mechanisms underlying differential D1 versus D2 dopamine receptor regulation of inhibition in prefrontal cortex. *The Journal of neuroscience*. 2004, 24:47.
- 16 Surmeier DJ, Ding J, Day M, e al. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. *Trends in neurosciences*. 2007, 30:5.
- 17 Seamans JK, Gorelova N, Durstewitz D, et al. Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. *The Journal of neuroscience*. 2001, 21:10.
- 18 Karni A, Meyer G, Rey-Hipolito C, et al. The acquisition of skilled motor performance: Fast and slow experience- driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences of the United States of America*. 1998, 95:3.
- 19 Brashers-Krug T, Shadmehr R, Bizzi E. Consolidation in human motor memory. *Nature*. 1996, 382:6588.
- 20 Shadmehr R, Brashers-Krug T. Functional stages in the formation of human long-term motor memory. *Journal of Neuroscience*. 1997, 17:1.
- 21 Censor N, Sagi D, Cohen LG. Common mechanisms of human perceptual and motor learning. *Nat Rev Neurosci*. 2012, 13:9.
- 22 Robertson EM. New insights in human memory interference and consolidation. *Curr Biol*. 2012, 22:2.
- 23 Cirelli C, Gutierrez CM, Tononi G. Extensive and divergent effects of sleep and wakefulness on brain gene expression. *Neuron*. 2004, 41:1.
- 24 Walker MP, Stickgold R. Sleep, memory, and plasticity. *Annu Rev Psychol*. 2006, 57.
- 25 Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. *Neuron*. 2004, 44:1.
- 26 Korman M, Doyon J, Doljansky J, et al. Daytime sleep condenses the time course of motor memory consolidation. *Nat Neurosci*. 2007, 10:9.
- 27 Hernandez PJ, Abel T. A molecular basis for interactions between sleep and memory. *Sleep Med Clin*. 2011, 6:1.
- 28 Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci*. 2010, 11:2.
- 29 Shadmehr R, Holcomb HH. Neural correlates of motor memory consolidation. *Science*. 1997, 277:5327.
- 30 Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain research bulletin*. 2003, 62:2.
- 31 Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep medicine reviews*. 2006, 10:1.
- 32 Huber R, Ghilardi MF, Massimini M, et al. Local sleep and learning. *Nature*. 2004, 430:6995.
- 33 Robertson EM, Cohen DA. Understanding consolidation through the architecture of memories. *The Neuroscientist*. 2006, 12:3.
- 34 Ellenbogen JM, Payne JD, Stickgold R. The role of sleep in declarative memory consolidation: passive, permissive, active or none? *Current opinion in neurobiology*. 2006, 16:6.
- 35 Norman KA. Declarative memory: sleep protects new memories from interference. *Current Biology*. 2006, 16:15.
- 36 Casement MD, Broussard JL, Mullington JM, et al. The contribution of sleep to improvements in working memory scanning speed: a study of prolonged sleep restriction. *Biological psychology*. 2006. 72:2.
- 37 Nader R, Smith C. A role for stage 2 sleep in memory processing. *Sleep and brain plasticity*. 2003, 87-98.
- 38 Cirelli C, Tononi G. Gene expression in the brain across the sleep-waking cycle. *Brain research*. 2000, 885:2.
- 39 Schmidt C, Peigneux P, Muto V, et al. Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. *The Journal of neuroscience*. 2006, 26:35.
- 40 Landsness EC, Crupi D, Hulse BK, et al. Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. *Sleep*. 2009, 32:10.
- 41 Marshall L, Helgadottir H, Molle M, et al. Boosting slow oscillations during sleep potentiates memory. *Nature*. 2006, 444:7119.
- 42 Huber R, Ghilardi MF, Massimini M, et al. Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat Neurosci*. 2006, 9:9.

- 43 Walker MP, Brakefield T, Morgan A, et al. Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron*. 2002, 35:1.
- 44 Ficca G, Salzarulo P. What in sleep is for memory. *Sleep Medicine*. 2004, 5:3.
- 45 Kami A, Tanne D, Rubenstein BS, et al. Dependence on REM sleep of overnight improvement of a perceptual skill. *Science*. 1994, 265:5172.
- 46 Rauchs G, Desgranges B, Foret J, et al. The relationships between memory systems and sleep stages. *J Sleep Res*. 2005, 14:2.
- 47 Stickgold R, Whidbee D, Schirmer B, et al. Visual discrimination task improvement: A multi-step process occurring during sleep. *Journal of cognitive neuroscience*. 2000, 12:2.
- 48 Fischer S, Hallschmid M, Elsner AL, et al. Sleep forms memory for finger skills. *Proceedings of the national academy of sciences*. 2002, 99:18.
- 49 Nitsche MA, Jakoubkova M, Thirugnanasambandam N, et al. Contribution of the premotor cortex to consolidation of motor sequence learning in humans during sleep. *Journal of neurophysiology*. 2010, 104:5.
- 50 Cousins JN, El-Deredy W, Parkes LM, et al. Cued memory reactivation during slow-wave sleep promotes explicit knowledge of a motor sequence. *The Journal of neuroscience*. 2014, 34:48.
- 51 Rasch B, Büchel C, Gais S, et al. Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science*. 2007, 315:5817.
- 52 Fischer S, Wilhelm I, Born J. Developmental differences in sleep's role for implicit off-line learning: comparing children with adults. *Journal of cognitive neuroscience*. 2007, 19:2.
- 53 Robertson EM, Pascual-Leone A, Press DZ. Awareness modifies the skill-learning benefits of sleep. *Current Biology*. 2004, 14:3.
- 54 Fischer S, Drosopoulos S, Tsen J, et al. Implicit learning—explicit knowing: a role for sleep in memory system interaction. *Journal of cognitive neuroscience*. 2006, 18:3.
- 55 Wagner U, Gais S, Haider H, et al. Sleep inspires insight. *Nature*. 2004, 427:6972.
- 56 Siengsukon CF, Boyd LA. Does sleep promote motor learning? Implications for physical rehabilitation. *Phys Ther*. 2009, 89:4.
- 57 King BR, Fogel SM, Albouy G, et al. Neural correlates of the age-related changes in motor sequence learning and motor adaptation in older adults. *Front Hum Neurosci*. 2013, 7:142.
- 58 Korman M, Dagan Y, Karni A. Nap it or leave it in the elderly: a nap after practice relaxes age-related limitations in procedural memory consolidation. *Neurosci Lett*. 2015, 606.
- 59 King BR, Saucier P, Albouy G, et al. Cerebral Activation During Initial Motor Learning Forecasts Subsequent Sleep-Facilitated Memory Consolidation in Older Adults. *Cerebral Cortex*. 2016, 47.
- 60 Siengsukon C, Boyd LA. Sleep enhances off-line spatial and temporal motor learning after stroke. *Neurorehabil Neural Repair*. 2009, 23:4.
- 61 Adi-Japha E, Badir R, Dorfberger S, et al. A matter of time: rapid motor memory stabilization in childhood. *Developmental science*. 2014, 17:3.
- 62 Siengsukon C, Al-Dughmi M, Al-Sharman A, Stevens S. Sleep Parameters, Functional Status, and Time Post-Stroke are Associated with Offline Motor Skill Learning in People with Chronic Stroke. *Front Neurol*. 2015, 6:225.
- 63 Gudberg C, Johansen-Berg H. Sleep and Motor Learning: Implications for Physical Rehabilitation After Stroke. *Front Neurol*. 2015, 6:241.
- 64 Backhaus W, Kempe S, Hummel FC. The effect of sleep on motor learning in the aging and stroke population - a systematic review. *Restor Neurol Neurosci*. 2015, 34:1.
- 65 Siengsukon CF, Boyd LA. Sleep enhances implicit motor skill learning in individuals poststroke. *Top Stroke Rehabil*. Jan-Feb 2008, 15:1.
- 66 Siengsukon CF, Boyd LA. Sleep to learn after stroke: implicit and explicit off-line motor learning. *Neurosci Lett*. Feb 13 2009, 451:1.
- 67 Bassetti C, Marhis J, Gugger M, et al. Hypersomnia following paramedian thalamic stroke: A report of 12 patients. *Ann Neurol*. 1996, 39:4.
- 68 Bakken LN, Kim HS, Finset A, et al. Subjective sleep quality in relation to objective sleep estimates: comparison, gender differences and changes between the acute phase and the six-month follow-up after stroke. *J Adv Nurs*. 2013.
- 69 Bakken LN, Lee KA, Kim HS, Finset A, Lerdal A. Sleep-Wake Patterns during the Acute Phase after First-Ever Stroke. *Stroke Res Treat*. 2011;2011:936298.
- 70 Gottselig JM, Bassetti CL, Achermann P. Power and coherence of sleep spindle frequency activity following hemispheric stroke. *Brain*. 2002, 125:2.
- 71 Poryazova R, Huber R, Khatami R, et al. Topographic sleep EEG changes in the acute and chronic stage of hemispheric stroke. *J Sleep Res*. 2015, 24:1.
- 72 Hermann DM, Siccoli M, Brugger P, et al. Evolution of neurological, neuropsychological and sleep-wake disturbances after paramedian thalamic stroke. *Stroke*. 2008, 39:1.
- 73 Santamaria J, Pujol M, Orteu N, et al. Unilateral thalamic stroke does not decrease ipsilateral sleep spindles. *Sleep*. 2000, 23:3.
- 74 Hachinski V, Mamelak M, Norris J. Prognostic value of sleep morphology in cerebral infarction. *Amsterdam: Excerpta Medica*. 1978.
- 75 Urakami Y. Relationships between sleep spindles and activities of the cerebral cortex after hemispheric stroke as determined by simultaneous EEG and MEG recordings. *J Clin Neurophysiol*. 2009, 26:4.
- 76 Bassetti CL, Aldrich MS. Sleep electroencephalogram changes in acute hemispheric stroke. *Sleep Medicine*. 2001, 2:3.
- 77 Beldarrain MG, Astorgano AG, Gonzalez AB, Garcia-Monco JC. Sleep improves sequential motor learning and performance in patients with prefrontal lobe lesions. *Clinical neurology and neurosurgery*. 2008, 110:3.
- 78 Li Pi Shan RS, Ashworth NL. Comparison of lorazepam and zopiclone for insomnia in patients with stroke and brain injury: a randomized, crossover, double-blinded trial. *Am J Phys Med Rehabil*. Jun 2004, 83:6.
- 79 Sunami E, Usuda K, Nishiyama Y, Otori T, Katsura K, Katayama Y. A preliminary study of fluvoxamine maleate on depressive state and serum melatonin levels in patients after cerebral infarction. *Internal medicine*. 2012, 51:10.
- 80 Kim CR, Chun MH, Han EY. Effects of Hypnotics on Sleep Patterns and Functional Recovery of Patients with Subacute Stroke. *American Journal of Physical Medicine & Rehabilitation*. 2010, 89:4.
- 81 Gao B, Kilic E, Baumann CR, Hermann DM, Bassetti CL. Gamma-hydroxybutyrate accelerates functional recovery after focal cerebral ischemia. *Cerebrovasc Dis*. 2008, 26:4.

- 82 Hodor A, Palchykova S, Gao B, Bassetti CL. Baclofen and gamma-hydroxybutyrate differentially altered behavior, EEG activity and sleep in rats. *Neuroscience*. 2015, 284:18.
- 83 Hodor A, Palchykova S, Baracchi F, Noain D, Bassetti CL. Baclofen facilitates sleep, neuroplasticity, and recovery after stroke in rats. *Annals of clinical and translational neurology*. 2014, 1:10.
- 84 Walsh JK. Enhancement of slow wave sleep: implications for insomnia. *J Clin Sleep Med*. 2009, 5:2.
- 85 Landmann N, Kuhn M, Piosczyk H, et al. The reorganisation of memory during sleep. *Sleep medicine reviews*. 2014, 18:6.
- 86 Butler AJ, Shuster M, O'Hara E, et al. A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. *Journal of Hand Therapy*. 2013, 26:2.
- 87 Hsu W-Y, Cheng C-H, Liao K-K, et al. Effects of Repetitive Transcranial Magnetic Stimulation on Motor Functions in Patients With Stroke A Meta-Analysis. *Stroke*. 2012, 43:7.
- 88 Saeki T, Nakamura M, Hirai N, et al. Localized potentiation of sleep slow-wave activity induced by prefrontal repetitive transcranial magnetic stimulation in patients with a major depressive episode. *Brain stimulation*. 2013, 6:3.
- 89 Huber R, Esser SK, Ferrarelli F, Massimini M, Peterson MJ, Tononi G. TMS-induced cortical potentiation during wakefulness locally increases slow wave activity during sleep. *PLoS One*. 2007, 2:3.