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The role of sleep in recovery following ischemic stroke: A review of human and animal data

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ABSTRACT

Despite advancements in understanding the pathophysiology of stroke and the state of the art in acute management of afflicted patients as well as in subsequent neurorehabilitation training, stroke remains the most common neurological cause of long-term disability in adulthood. To enhance stroke patients' independence and well-being it is necessary, therefore, to consider and develop new therapeutic strategies and approaches. We postulate that sleep might play a pivotal role in neurorehabilitation following stroke. Over the last two decades compelling evidence for a major function of sleep in neuroplasticity and neural network reorganization underlying learning and memory has evolved. Training and learning of new motor skills and knowledge can modulate the characteristics of subsequent sleep, which additionally can improve memory performance. While healthy sleep appears to support neuroplasticity resulting in improved learning and memory, disturbed sleep following stroke in animals and humans can impair stroke outcome. In addition, sleep disorders such as sleep disordered breathing, insomnia, and restless legs syndrome are frequent in stroke patients and associated with worse recovery outcomes. Studies investigating the evolution of post-stroke sleep changes suggest that these changes might also reflect neural network reorganization underlying functional recovery. Experimental and clinical studies provide evidence that pharmacological sleep promotion in rodents and treatment of sleep disorders in humans improves functional outcome following stroke. Taken together, there is accumulating evidence that sleep represents a "plasticity state" in the process of recovery following ischemic stroke. However, to test the key role of sleep and sleep disorders for stroke recovery and to better understand the underlying molecular mechanisms, experimental research and large-scale prospective studies in humans are necessary. The effects of hospital conditions, such as adjusting light conditions according to the patients' sleep-wake rhythms, or sleep promoting drugs and non-invasive brain stimulation to promote neuronal plasticity and recovery following stroke requires further investigation.

1. Introduction

Investigating the impact of sleep on functional recovery following stroke is of major importance given the potential clinical implications for patient management. Stroke affects approximately 2–3 individuals per 1000 per year (Bassetti, 2016). Despite improved knowledge about its pathophysiological mechanisms and acute treatment by thrombolysis or thrombectomy, stroke remains the most common neurological cause of hospitalization and disability in adulthood (www.strokecenter.org; Bassetti, 2016). There is growing compelling evidence that sleep disorders such as sleep disordered breathing (SDB), insomnia, and restless legs syndrome (RLS) are frequent in stroke survivors and are associated with worse stroke recovery outcomes and increased cardiocerebrovascular morbidity (Johnson and Johnson, 2010; Medeiros et al., 2011; Tang et al., 2015; Wu et al., 2014; Yan-fang and Yu-ping, 2009). Experimental and clinical studies in animals and humans suggest that healthy sleep promotes neuroplasticity resulting in improved learning and memory (e.g., Krueger et al., 2016; Rasch and Born, 2013; Yang et al., 2014). Accordingly, studies found that promoting sleep after stroke facilitates neuroplasticity and stroke recovery in both animals and humans (e.g., Hodor et al., 2014; Parra et al., 2011; Zunzunegui et al., 2011). These findings emphasize the importance of multidisciplinary approaches in stroke management integrating sleep-related therapeutic strategies. This review examines

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the role of sleep in recovery and compensation of impaired physical and cognitive functions associated with stroke.

2. Neuroplasticity and stroke recovery

Stroke is the result of cell death due to sudden insufficient oxygenation and energy supply from impaired blood flow that originates from either thrombotic or embolic obstruction (ischemic event) or from hemorrhagic rupture (hemorrhagic stroke) of a supplying cerebral artery. Most strokes are ischemic strokes and lead to lasting neurological deficits. Hemorrhagic strokes, representing about 15% of all events, are beyond the scope of this article given the marked differences in pathophysiology. For example, the degree of cell damage surrounding a hemorrhage is highly variable and the mass effect from the hematoma introduces additional complications secondary to increased intracranial pressure.

In the acute phase of ischemic stroke, two main dysfunctional areas can be differentiated: (a) the *core lesion* where the lack of blood supply results in irreversible cell death and (b) the surrounding *ischemic penumbra* which consists of hypo-perfused yet viable tissue. Functional deficits from stroke are not only secondary to focal brain damage in a core lesion and surrounding penumbra but result also from a dysfunction of corresponding neural networks responsible for a given behavior/function. The disturbance of the interplay between the ischemic core and adjacent and remote brain areas is called *diaschisis;* the reduced neuronal connectivity and excitatory input leads to a decreased metabolism in these remote structures (Kwakkel et al., 2014).

After the acute phase of stroke the human brain, in the absence of (significant) neuronal regeneration, undergoes a (spontaneous) functional reorganization in order to improve function (Kwakkel et al., 2014). This process of neuroplasticity can be promoted by neurorehabilitation.Neurorehabilitation, including physical therapy, occupational therapy, speech therapy, and neuropsychological therapy, aims at improving activities of daily living and cognitive functioning by extensive exercise and training. Both restoration and compensation of a lost function are important in neurorehabilitation and are usually differentiated (Kwakkel et al., 2014; Levin et al., 2009; Warraich and Kleim, 2010). *Restoration*, also called true recovery, is based on re-engaging brain areas that were initially impaired or dysfunctional due to the stroke. *Compensation*, in contrast, involves either recruitment of brain areas not initially specialized but capable of contributing to taking over the lost function or retraining of other brain areas initially specialized for a different function.

Fig. 1 illustrates an approach to classify temporal and spatial changes in spontaneous and training-induced post-stroke neuroplasticity from the molecular to the network level (adapted from Duss et al. (2015)).

2.1. Animal data

In the acute phase of stroke, brain excitability in the ischemic core is increased by a glutamatergic overactivation further increasing the process of ischemic cell death. Blocking glutamatergic and enhancing GABAergic signaling was shown to be neuroprotective (Carmichael, 2012). After the acute phase, neuroplasticity processes take place in surviving perilesional as well as distant brain areas.Three phases of post-stroke plasticity are observed during functional recovery in rodents (Wieloch and Nikolich, 2006). In a first phase, neurons in the peri-infarct tissue are hypo-excitable because of an impaired reuptake of the inhibitory neurotransmitter GABA by damaged astrocytes (Carmichael, 2012; Krakauer et al., 2012). A cascade of repair- and growth-related processes including axonal sprouting take place at the molecular and cellular levels in the peri-infarct area and ipsilesional hemisphere, but also contralesionally (Carmichael, 2006; Carmichael et al., 2005; Cramer, 2008; Nudo, 2013; Wieloch and Nikolich, 2006). Axonal sprouting is associated with synchronous low-frequency oscillations in peri- and contralesional cortical areas, that are comparable in frequency to slow oscillations seen during slow wave sleep (Carmichael and Chesselet, 2002; Murphy and Corbett, 2009).

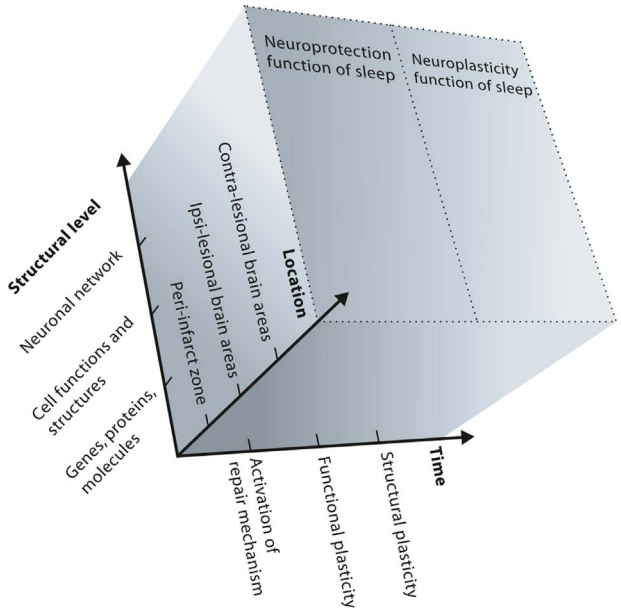

Fig. 1. Schematic approach to classify temporal and spatial changes in post-stroke neuroplasticity covering changes from the micro- to macroscopic levels. Within the first days of stroke genes promoting growth and structural changes at the dendrites, synapses and axons of neurons are upregulated and inhibitory genes are reduced in the peri-infarct zone (Carmichael, 2006; Carmichael and Chesselet, 2002). The post-ischemic brain enters a state of hyperexcitability. Post-ischemic long-term potentiation (LTP) due to enhanced glutamergic transmission is postulated to occur and foster structural neuroplasticity (i.e. synaptic, dendritic and axonal growth) and reorganization of the disrupted neuronal network (Di Filippo et al., 2008; Krakauer et al., 2012). In the acute phase of stroke sleep may be neuroprotective as suggested from studies showing that fostering inhibitory GABA-ergic activity increases functional recovery (Gao et al., 2008; Hodor et al., 2014), whereas reducing excessive GABA-ergig activity, premature use-dependent neuronal activation and sleep disruption, have adverse effects on infarct size and post-stroke recovery (Clarkson et al., 2010; Dromerick et al., 2009; Gao et al., 2010). In the subchronic and chronic phases, sleep is assumed to promote use-dependent neuroplasticity and improve learning and stroke recovery (Siengsukon et al., 2015).

In the second phase, the brain enters a highly excitable state, resulting from changes in the properties of undamaged neuronal pathways. This increased excitability provides a permissive environment for changes in synaptic transmission important for learning (Cramer, 2008; Wieloch and Nikolich, 2006).

The foundation laid by this second phase likely plays a key role for the third phase which is characterized by neuroanatomical plasticity through structural changes at the cellular level. Growth of synapses, dendrites and new synaptic connections between cells occur in the peri-infarct zone and remote brain areas and are essential for the recovery of neural circuits (Nudo, 2013; Wieloch and Nikolich, 2006). In addition to the remodeling of surviving neurons, new cells, including glial cells and neuroblasts, are generated in the subventricular zone of the brain and migrate into the peri-infarct area up to several month after stroke. The cytokine erythropoietin, induced near the infarct zone after stroke, is one of these molecular signals that promotes neuroblast migration (Carmichael, 2006). Whether these new cells are integrated into the neocortical networks or serve as guideposts for remodeling of connections between surviving neurons by releasing signaling molecules is unclear.

2.2. Human data

Interpretation of data gained from human stroke research compared to animal work is complicated by several factors, including

Box 1. Challenges and directions in translational stroke research.

Animal models of stroke have advanced our understanding of stroke pathophysiology (Casals et al., 2011; Dirnagl and Endres, 2014), however the pathophysiological mechanisms of stroke and stroke recovery await further investigation for a complete translation into successful and innovative treatments to improve stroke patients' recovery. Limitations of experimental research include the insufficient consideration of the heterogeneity characterizing human stroke patients (Casals et al., 2011; Turner et al., 2011). Lesion location, stroke severity, risk factors and comorbidities (e.g., hypertension, diabetes, atrial fibrillation), etiology (thrombosis, embolism, systemic hypoperfusion) and subscribed medication widely differ among ischemic stroke patients. Patients also differ in age and weight affecting among others metabolism, arterial stiffness and endothelial function. Such factors are often still neglected in animal studies but could be controlled for or systematically examined in properly performed experiments. In contrast, animal samples are usually highly homogenous and often include young males of the same genetic background and utilize identical stroke induction protocols and treatment methods (Fisher et al., 2009; Lapchak et al., 2013). Another important difference is that most animal studies utilize anesthesia when inducing stroke which is not the case in humans (Turner et al., 2011). A frequently raised criticism is that animal samples are also often small and experimental designs are imperfect (e.g., lack of randomization and of allocation concealment to the experimental and control conditions) decreasing validity of the statistical inferences (Dirnagl, 2016; Fisher et al., 2009; Lapchak et al., 2013). However, important translational studies have identified thrombolytic tissue plasminogen activator (tPA) as a highly efficient treatment of ischemic stroke that is now widely used in human stroke patients (Dirnagl and Endres, 2014; Turner et al., 2011). Hence pessimism regarding stroke models' benefit for patients treatment is not be appropriate.

To improve translation of findings from animal stroke research but also from human observational research into new treatment approaches we refer to the recommendations that emerged from the Stroke Therapy Academic Industry (1999) Roundtable (STAIR) consensus conferences and other initiatives such as STEPS (Stem Cell Therapy as an Emerging Paradigm for Stroke (Savitz et al., 2011)) and RIGOR (Guidelines based on a workshop by the National Institute of Neurological Disorders and Stroke (Landis et al., 2012; Lapchak et al., 2013)). Important common recommendations are (a) randomization of animals and patients to the experimental conditions, (b) blinding of investigators regarding group allocation when performing experiments and when assessing outcome measures, (c) transparency regarding calculated power analysis, inclusion and exclusion criteria, dropouts and potential conflicts of interest. Moreover, replication and validation of results within and between research group and initiatives to share data with other researchers of the field should be pursued (Dirnagl et al., 2013).

An opportunity for more successful translations of preclinical and clinical findings into treatment trials is offered by improved neuroimaging technologies and new tools of non-invasive brain stimulation, such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), that can be applied in humans and animals. After having observed robust markers for positive stroke recovery, they should be systematically manipulated in interventional studies to test whether their reduction or induction is beneficial for stroke recovery.

patients' heterogeneity regarding lesion location, stroke severity, variations in risk factors and comorbidities (e.g., hypertension, diabetes, atrial fibrillation), etiology (thrombosis, embolism, systemic hypoperfusion) and concomitant medication use. Moreover, the time window during which the patients receive treatment, in addition to the choice of treatment, differs markedly across patients. This heterogeneity is assumed responsible for failures in translating findings in animal models of stroke to human stroke and developing effective treatments to enhance stroke recovery (see Box 1 for some considerations in translational research). Despite the large sources of heterogeneity in human stroke patients, there are consistent findings regarding neuroplasticity changes in humans post stroke recovery paralleling evidence gained from animal stroke research. For example, evidence for ipsi-and contra-lesional cortical reorganization following stroke is also provided by human data investigating recovery of motor and language functions using neuroimaging or non-invasive brain stimulation. The bigger the ischemic lesion, the more the contralesional hemisphere is recruited to compensate for a lost function. Compensation by contralesional activation is often associated with worse functional recovery compared to restoration of the lost function (Di Pino et al., 2014; Hamilton et al., 2011; Murphy and Corbett, 2009). The time course of post-stroke recovery of motor and language functions in patients can be characterized by decreased neuronal activity within the affected hemisphere during the acute phase of stroke (first days post-stroke) consistent with evidence from animal data. Then, in the subacute phase of stroke, increased neuronal activity can be measured in the peri- and contralesional hemisphere involving contralesional homologue brain areas and brain areas forming the neural network responsible for the impaired motor or cognitive function (Buma et al., 2010; Hamilton et al., 2011). There is evidence that this activity increase is associated with improved neurological recovery (Di Pino et al., 2014; Saur et al., 2006). In the chronic phase of stroke, especially in case of good recovery, neural activity shifts back towards the ipsilesional hemisphere involving perilesional brain areas suggestive of restoration (Buma et al., 2010; Hamilton et al., 2011; Saur et al., 2006).

Human data show that a very early start of intensive movement training of the affected arm while constraining the unaffected arm by a mitten (constraint-induced movement therapy) is not beneficial for post-stroke motor recovery compared to a less intensive training and standard occupational therapy (Dromerick et al., 2009). In the subacute and chronic phases of stroke, few approaches may modulate neuroplasticity and improve functional recovery through putative neuronal network reorganization. Non-invasive brain stimulation such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) are used to either decrease activity in the contralesional hemisphere or to increase activity over the perilesional regions with mixed findings of no to moderate effects on stroke recovery (Di Pino et al., 2014). For example in one study, facilitating synaptic plasticity over the motor cortex in hemiparetic stroke patients by tDCS-mediated decrease of neuronal excitability thresholds, improved paretic hand function (Hummel et al., 2005). On the other hand, theta burst TMS decreasing the heightened excitability of the contralesional hemisphere considerably improved spatial neglect after subacute right-hemispheric stroke (Cazzoli et al., 2015). The rationale behind the inhibition of the contralesional hemisphere is that persistent post-stroke overactivation of the contralesional hemisphere with simultaneous decreased activation of the ipsilesional hemisphere following stroke results in interhemispheric inhibition of the affected hemisphere hampering functional restoration. A fine-tuned combination of inhibitory and excitatory stimulation approaches over the contra- and ipsilesional hemisphere to improve motor and cognitive rehabilitation following stroke is suggested to be most efficient (Di Pino et al., 2014). Sleep following non-invasive brain stimulation combined with neurorehabilitative training may have an additive positive benefit on the synaptic strengthening and use-dependent remodeling of neuronal networks underlying consolidation of trained skills (as illustrated in Fig. 1, see also Section 5).

3. Experience-dependent neuroplasticity in sleep

Although the function of sleep is not yet fully understood, a great body of literature suggests an important role for sleep in neural network reorganization and repair, particularly with respect to learning and memory (e.g., Krueger et al., 2016; Rasch and Born, 2013; Walker and Stickgold, 2006). Despite growing evidence for the importance of sleep in neuroplasticity and learning, promotion of sleep is generally not considered in stroke management and rehabilitative protocols. With the aim of elucidating the role of sleep-dependent plasticity in functional recovery following stroke, we first summarize evidence suggesting that sleep (SWS and Rapid-Eye-Movement (REM) Sleep) promotes consolidation of declarative and procedural memory. We then review three pertinent theories of sleep function concerning experience-dependent plasticity mechanisms underlying learning and memory: the active system consolidation theory (Diekelmann and Born, 2010; Rasch and Born, 2013), the synaptic downscaling theory (Tononi and Cirelli, 2014) and the energy allocation model of sleep and wakefulness (Schmidt, 2014; Schmidt et al., 2017). Whereas the active system consolidation and the synaptic downscaling theories describe how sleep may contribute to learning and memory by strengthening experience-dependent neural pathways, the energy allocation model provides an explanation for why sleep might be important for neuronal plasticity processes in general and after stroke in particular.

3.1. Sleep promotes learning and memory

Sleep is not a homogenous phenomenon but consists of different sleep stages characterized by a specific pattern of neural activity measurable with electroencephalography (EEG) over the scalp and by differences in muscle tonus measured by electromyography (EMG) at the chin. Although, rodents do have some differences compared to humans regarding the sleep-wake cycle distribution across the 24 h, the main regulatory mechanisms are maintained across both species (see Box 2 Sleep and sleep stages in humans and rodents).

The ultradian rhythmicity of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep stages defines the macrostructure of sleep. Human NREM sleep comprising three different stages ranging from light (stage 1) to deep slow wave sleep (SWS, stage 3) is characterized by typical microstructural elements: slowing of cortical oscillations and appearance of theta activity is observed in stage 1 sleep; sleep spindles, i.e. waxing and waning activity over ≥0.5 s between 11 and 16 Hz, and K-complexes in stage 2; and neocortical slow wave activity (SWA, 1–4.5 Hz) and slow oscillations (< 1 Hz) in stage 3 that predominate in the first part of the night. This slowing of activity in NREM sleep is in contrast to the relatively activated pattern seen during REM sleep, characterized by wake-like fast and low-amplitude oscillatory brain activity predominating in the second part of the night.

Particularly in humans SWS and REM sleep have been suggested to promote different types of memories (Rasch and Born, 2013). Whereas SWS is thought to support consolidation of declarative memory, the memory for episodes and sematic knowledge dependent on intact structures of the medial temporal lobe; REM sleep is assumed to support procedural memory, the memory for motor and perceptual skills not depending on medial temporal lobe structures. This assumption is supported by night studies showing better recall performance or declarative memories (e.g., word pairs) following the first half of the night rich in SWS and improved performance in a skill task (e.g. mirror tracing) after the second half of the night rich in REM sleep compared to a wake control condition (e.g., Plihal and Born, 1997). Further evidence is provided by nap-studies. Day-time naps following learning of word pairs and training of the mirror tracing task containing NREM sleep only result in better retrieval performance of word pairs but do not improve mirror tracing performance (Tucker et al., 2006). However, perceptual skill learning only improved following naps containing REM and NREM sleep (Mednick et al., 2003). In animal studies evidence for a causal role of REM and NREM sleep for learning is provided (Boyce et al., 2016; Yang et al., 2014). For an extensive review on the role of sleep for learning and memory see Rasch and Born (2013).

Although only a few studies have systematically investigated the effect of sleep on learning in stroke patients, they suggest that sleep enhances motor task performance (Siengsukon and Boyd, 2008, 2009). In a recent study, improved offline motor learning in stroke patients was associated with more time spent in REM sleep (Siengsukon et al., 2015), supporting theories postulating REM sleep to be important for procedural memory. Independent thereof, the question about the underlying mechanism of the motor improvement, such as through neuronal reactivation in active consolidation versus enhanced neural selectivity in synaptic downscaling (see below), cannot be conclusively answered. Nevertheless, the above results, highlight the potential importance of sleep for memory consolidation in neurorehabilitation.

3.2. Potential mechanisms of experience-dependent neuroplasticity in sleep

Theories of experience-dependent plasticity during sleep assume different synaptic mechanisms. Whereas the *synaptic downscaling theory* postulates a down-regulation of synaptic plasticity during sleep, the *active system consolidation theory* assumes that synaptic connections are strengthened during sleep. Both theories are introduced here, as well as the *energy allocation model of sleep and wakefulness* that postulates a clear division of labor occurring during wakefulness and

Box 2. Sleep and sleep stages in humans and rodents.

Sleep is a reversible state of reduced responsiveness to external stimuli. In humans and rodents (mice and rats) waking and sleep stages are defined by electroencephalography (EEG) combined with electromyography (EMG) and electrooculogram (EOG). Sleep architecture is characterised by three different vigilance states: wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep which alternate cyclically. Each state has its unique microstructural characteristics including variations in brain wave patterns, eye movements, and muscle tone.

Sleep architecture is relatively conserved across species, together with the circadian and neurochemical regulations; however, there are few differences between human and rodent sleep. For example, sleep in both humans and rodents is regulated by circadian time, but the organization of the sleep-wake cycle is in the opposite phase in rodents compared to humans. Specifically, most rodents are nocturnal animals; they are awake during the dark phase and asleep during the light phase. Another difference between humans and rodents is that humans have monophasic sleep, meaning that, sleep is usually taken in one session during a 24-h period (i.e. during night). Conversely, rodent sleep is polyphasic and relatively fragmented (Paterson et al., 2011; Toth and Bhargava, 2013) (Fig. 1). In humans non-REM-REM sleep pass through 4 to 6 cycles within a night's sleep; these sleep cycles have a fairly constant period with a duration of around 90 min (Hobson and Pace-Schott, 2002). Conversely, in rodents, the non-REM-REM sleep cycle is much shorter and lasts about 12 min in rats (McCarley, 2007) and less than 5 min in mice (Toth and Bhargava, 2013), occurring periodically throughout the 24-h day. Finally, non-REM sleep in humans is conventionally divided into 3 stages, whereas in rodents this distinction is not used (Rasch and Born, 2013).

sleep to explain why certain functions predominantly occur in either the wake or the sleep state.

3.2.1. Synaptic downscaling during sleep

During wakefulness living organisms incidentally or intentionally acquire new knowledge and skills to flexibly adapt to the environmental needs. This experience-dependent learning involves long-term potentiation (LTP) resulting in strengthened synaptic connections between commonly activated neurons (Gorgoni et al., 2013; Tononi and Cirelli, 2014). As hypothesized by Tononi and Cirelli (2014) potentiated synapses consume more energy and lose their selectivity of firing patterns, increasing the likelihood of neurons to fire by chance and detect spurious instead of relevant coincidences. Synaptic downscaling may provide an effective countermeasure according to this theory. This process is believed to be driven by slow oscillations during SWS, an ideal climate for synaptic long-term depression (LTD). Synaptic strength may then be restored to a sustainable energy level while improving neuronal selectivity which benefits consolidation of newly acquired skills and knowledge.

SWA is homeostatically regulated, i.e., enhancement or reduction of SWA over a particular brain region during sleep is dependent on the prior use of this brain region during wakefulness. Whereas visuo-motor and declarative learning results in an increase of SWA over the brain areas recruited during training that correlates with improved post-sleep performance (Huber et al., 2004; Schmidt et al., 2006), reduced motor experience due to immobilization of an extremity is associated with reduced SWA during sleep and worse post-sleep motor performance (Huber et al., 2006). While these studies suggest a direct link between cortical plasticity and sleep regulation, as well as between SWA and post-sleep task performance, they do not provide direct evidence for the function of sleep in synaptic downscaling. Here evidence is more contradictory. Whereas some studies in rats and flies suggest upregulation of molecular and structural changes fostering synaptic potentiation and spine formation during wakefulness and net downscaling during sleep (e.g., Bushey et al., 2011; Vyazovskiy et al., 2008), other studies suggest that not only during waking but also during sleep, plasticity-inducing molecular mechanisms are upregulated and synaptic spines are formed (Calais et al., 2015; Yang et al., 2014). These latter studies support the active system consolidation theory during sleep covered in the next section.

3.2.2. Active system consolidation in sleep

The active system consolidation theory assumes that strengthening of newly acquired knowledge or skills results from repeated reactivation of the neuronal network involved in encoding during subsequent sleep. The theory accounts for consolidation of initially hippocampal-dependent memories and postulates a shift during sleep of the memory representation from the hippocampal short-term store to the neocortical long-term store (Diekelmann and Born, 2010; Rasch and Born, 2013).

The active system consolidation theory is supported by intracranial EEG studies in animals and combined scalp EEG and functional magnetic resonance imaging (fMRI) studies in humans. Intracranial EEG recordings of hippocampal place cells in rats that code the spatial position relative to a given landmark while navigating through an environment, provide evidence for reactivation of these cells during sleep (Pavlides and Winson, 1989). Following a visuo-spatial encoding task, the spatial and temporal firing pattern of hippocampal place cells and cells in the visual cortex during NREM sleep was highly similar to the firing pattern observed during encoding (Ji and Wilson, 2007; Wilson and McNaughton, 1994). Importantly, no similar spatial-temporal firing pattern was observed during rats' sleep prior to the encoding task. Suggestive for a causal role of sleep-related neural reactivation for neural plasticity is the finding that its disruption prevents dendritic spine formation following motor training in mice (Yang et al., 2014). Also, studies in humans provide evidence for hippocampal reactivation and fostering of learning-dependent neuroplasticity during SWS. Participants were exposed to an odor of a rose during learning of card-pair locations. Exposure of participants to this odor during subsequent SWS reactivated the hippocampus and enhanced retrieval performance following sleep (Rasch et al., 2007).

Further studies are necessary to clarify whether up- or down-regulation of synaptic plasticity occurs during sleep, although both mechanisms likely occur in parallel. The investigational designs for both theories differ in one potentially relevant aspect. Studies supporting down-regulation of synaptic plasticity during sleep investigated neuroplasticity in freely behaving animals whereas studies providing evidence for up-regulation engaged animals in prior learning of new tasks. This later setting also applies to post-stroke neurorehabilitation.

3.2.3. The energy allocation model of sleep and wakefulness

The energy allocation (EA) model proposes that the ultimate (evolutionary) function of sleep is energy conservation through repartitioning of biological operations (Schmidt, 2014; Schmidt et al., 2017), also referred to as a state-dependent division of labor (DOL). Although metabolic rate decreases during sleep compared to quiet wakefulness and may augment energy savings in the model, DOL and the associated upregulation of unique biological operations during sleep plays a comparatively greater role. These upregulated functions coupled with sleep are many, including macromolecule biosynthesis (Mackiewicz et al., 2009; Ramm and Smith, 1990), intracellular transport and membrane repair (Cirelli et al., 2005; Mackiewicz et al., 2009), myelin formation (Bellesi et al., 2013; Cirelli, 2005), neural network reorganization and memory consolidation (Smith, 2001; Walker and Stickgold, 2004), immune function (Imeri and Opp, 2009) and other restorative processes (Everson et al., 2014; Xie et al., 2013). Importantly, these same processes are downregulated during waking at a time when other biological functions are specifically upregulated, including excitatory neurotransmission, energy metabolism and cellular stress (Cirelli, 2009; Mackiewicz et al., 2009). As a result of state-dependent DOL, the EA model calculates actual energy savings achieved from an 8 h sleep quota to be approximately 4-fold greater than previous estimates based only on metabolic rate reduction (Schmidt et al., 2017). The EA model thus identifies a selective advantage for metabolic repartitioning and provides a unifying perspective to understand why such a great diversity of central and peripheral biological processes across species of the animal kingdom are specifically coupled with sleep.

Biological systems face trade-offs related to state-dependent metabolic repartitioning (Schmidt, 2014; Schmidt et al., 2017). Although energy savings is amplified by coupling unique operations with behavioral state as the EA model identifies, cellular stress and dysfunction are anticipated when sleep-dependent processes are constrained through sleep restriction. Moreover, energy requirements must increase if cellular operational integrity is to be maintained at a time when waking bout durations lengthen and a greater proportion of biological processes may be required simultaneously. In contrast, longer sleeping bouts provide proportionally greater calculated energy savings in the model (Schmidt et al., 2017).

4. Sleep disruption/loss and stroke outcome

In the first part of this section we discuss how sleep disruption/loss affects post-stroke neuroplasticity and functional recovery in animal models of stroke. In the second part we present human data on the effects of sleep disorders post-stroke and their impact on stroke outcome (for a comprehensive review see Hermann and Bassetti (2016)). In the third part, we address changes in sleep EEG following stroke that might reflect not only damage in a neuronal network, but also neuroplasticity processes underlying stroke recovery.

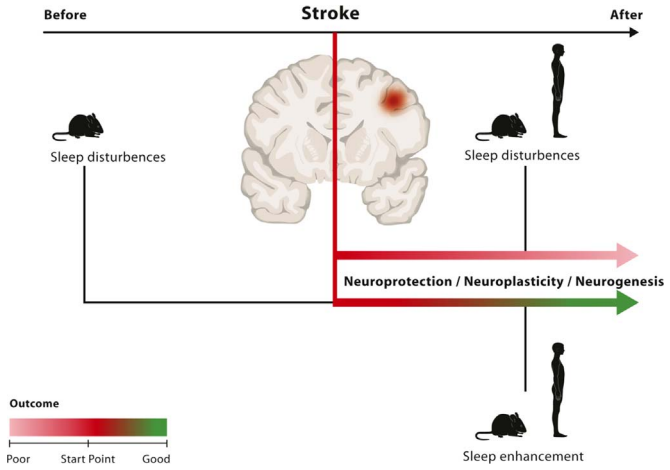

Fig. 2. Multiple facets of sleep intervention on recovery following ischemia. This diagram shows how sleep may differently modulate functional recovery after stroke depending on the time window when sleep alteration occurs (before or after ischemic stroke) and also by kinds of sleep alterations (deprived or enhanced). Particularly, sleep disturbances after stroke are detrimental in preclinical and clinical studies; enhancement of sleep following stroke is beneficial by increasing neuroplastic and neurogenic processes in preclinical studies; in humans post-stroke treatment of sleep disorders is suggested to improve stroke outcome (see Section 5). Sleep deprivation before stroke as a form of preconditioning treatment is neuroprotective, likely by increasing sleep homeostatically following ischemia. The neuroprotective effect of sleep deprivation pre-ischemia has been observed in preclinical studies.

4.1. Animal data

Studies in animal models of stroke have the distinct advantage of being able to actively manipulate sleep (disrupt versus enhance) while investigating the impact of this manipulation at the cellular and behavioral levels (see Fig. 2).

Data from animal studies show that increasing the length and repetition of sleep deprivation during the acute phase of ischemia has detrimental effects on both stroke evolution and functional recovery (Gao et al., 2010; Zunzunegui et al., 2011). For instance, 12 h of sleep deprivation for one or three consecutive days after stroke increases infarct volume in comparison to either non-sleep deprived animals or animals sleep deprived for 6 h post-stroke (Gao et al., 2010). Interestingly, the amount of wakefulness the first day after stroke was associated with increased infarct size, whereas higher amount of SWS was associated with smaller infarct size (Gao et al., 2010). Additionally, sleep deprivation has an adverse impact on neuroplasticity as seen by a reduction in axonal sprouting and neurogenesis (Zunzunegui et al., 2011), a finding possibly mediated through higher post-stroke expression of neurocan in sleep disturbed animals given the known role of this molecule in the inhibition of axonal extension (Carmichael, 2006; Gao et al., 2010). Finally, post-stroke functional motor recovery appears adversely affected by sleep deprivation as demonstrated with the single pellet-reaching task, a behavioral test commonly used to assess functional outcome in rats in preclinical studies of stroke (Zunzunegui et al., 2011).

Noteworthy, pretreating animals with sleep deprivation before an ischemic event has the opposite effect compared to post-stroke sleep deprivation. Pre-ischemic sleep deprivation leads to a sleep rebound, significantly increasing total sleep time during the first 24 h following ischemia compared to animals that did not undergo pre-ischemic sleep deprivation (Cam et al., 2013). Moreover, sleep deprivation prior to ischemia led to better outcomes when compared to animals undergoing ischemia alone; showing a significant reduction in infarct volume at 7 days following ischemia (Cam et al., 2013; Moldovan et al., 2010), as well as an improvement in sensorimotor performance and motor coordination (Moldovan et al., 2010). In a recent study in rats, more REM sleep during the first 24 hours following ischemic injury was associated with a reduced infarct volume assessed 7 days post-stroke, suggesting a neuroprotective role of REM sleep in acute stroke (Pace et al., 2017).

Sleep deprivation, e.g., by gentle handling, is a simple and frequently utilized approach to perturb sleep in animals. To our knowledge other animal models of sleep disturbances, such as models of obstructive sleep apnea, have not been applied to investigate the link between sleep disorders and stroke recovery. The development of a reliable model of obstructive sleep apnea faces diverse challenges, e.g., differences in upper airway anatomy and physiological reactions to intermittent hypoxemia between rodents and humans (Davis and O'Donnell, 2013; Toth and Bhargava, 2013). Moreover, induction of sleep apneas should be synchronized with the sleep-wake-rhythm of the animals, which is technically challenging (Davis and O'Donnell, 2013; Toth and Bhargava, 2013). Nevertheless, reliable and easily applicable animal models of sleep disturbances would offer a unique opportunity to better understand the pathophysiological mechanisms of common sleep disorders on stroke recovery.

4.2. Human data

Sleep disorders, such as insomnia, sleep disordered breathing (SDB), and restless legs syndrome, are frequent after stroke and may affect >50% of patients. In some cases sleep disturbances are pre-existing and may even represent a risk of stroke (Hsu et al., 2015; Loke et al., 2012; Szentkiralyi et al., 2013; Wu et al., 2014). In other cases sleep disorders appear "de novo" as a direct consequence of brain damage. For example strokes affecting the brainstem may give rise to specific forms of SDB (Bassetti, 2016). Finally, sleep disorders may be caused by stroke-related complications other than brain damage such as immobilization/hospitalization in a stroke unit, infections (e.g. pneumonia), pain, depression, and drugs.

Sleep disorders after stroke may have detrimental effects during the acute phase of stroke (and evolution of the penumbra). The possible mechanisms linking insufficient or fragmented sleep with worse outcomes are multiple and include elevated sympathetic activation, intermittent hypoxemia, oxidative stress and inflammatory changes likely due to frequent arousals and disturbed sleep-wake regulation (Arnardottir et al., 2009; Bassetti, 2016; Libby, 2002; Shamsuzzaman et al., 2003).

Sleep disorders after stroke may also have a detrimental effect during the subacute and chronic phases of stroke (and neuroplasticity processes). Sleep disorders are typically associated with decreases in SWS and REM sleep and have been associated with decreased attentional and cognitive performance (Decary et al., 2000). As a result, neuroplasticity-dependent consolidation of newly acquired procedural and declarative memories may be compromised (Kim et al., 2015; Siccoli et al., 2008; Siengsukon et al., 2015).

4.2.1. Sleep disordered breathing (SDB)

SDB is frequent after stroke and affects over 50% of such patients as defined by an Apnea-Hypopnea-Index (AHI) >10 (Johnson and Johnson, 2010). Observational studies suggest that the presence of SDB in stroke patients predicts slower recovery, higher degree of dependence and increased mortality (Good et al., 1996; Kaneko et al., 2003; Yan-fang and Yu-ping, 2009). Detrimental effects of SDB on stroke recovery may result from hemodynamic changes due to apneas resulting in a decrease of oxygenated hemoglobin and increase of deoxygenated hemoglobin in the brain measured by near infrared spectra (Pizza et al., 2012). Changes in cerebral blood flow velocity and arterial blood pressure are also observed during apneas (Pizza et al., 2010; Selic et al., 2005). In addition to repetitive nocturnal hypoxia, fragmented sleep and reduced SWS due to SDB, the sympathetic overactivity observed in these patients may further hinder stroke rehabilitation (Abboud and Kumar, 2014). Moreover, SDB is associated with cognitive deficits, including reduced attentional and executive func-

tions, decreased learning and memory abilities, and daytime sleepiness (Decary et al., 2000). These factors may adversely affect performance during rehabilitation training and, by extension, neural plasticity.

4.2.2. Insomnia

Insomnia is frequent in stroke survivors. Thirty eight to 50% report poor sleep quality and insomnia complaints, including difficulty initiating or maintaining sleep, or early morning awakening (Kim et al., 2015; Leppavuori et al., 2002). De novo insomnia post-stroke onset was found in one study in 18% of patients (Leppavuori et al., 2002). A recently published systematic review of 15 studies, where 9 were also used for a meta-analysis included in the same publication, also reveals objective evidence for poorer sleep in predominantly subacute stroke patients compared with healthy controls, including significantly decreased sleep efficiency and total sleep time (Baglioni et al., 2016). Most studies included in this systematic review with integrated meta-analysis have investigated sleep within the first 16 days of stroke. Taking into consideration the disrupting environmental factors on a stroke unit, such as noisy and illuminated hospital rooms or concomitant medical conditions (e.g., pain) and the fact that patients are bedridden, new onset insomnia in such conditions is not surprising. However, it must always be considered that insomnia complaints may often occur secondary to an underlying sleep disorder, such as SDB or restless legs syndrome.

Large-scale studies on the impact of insomnia on stroke outcomes in humans are lacking. However, some studies provide evidence that insomnia patients and poor sleepers show worse stroke recovery measured by functional independence scores, scores assessing activities of daily living, and health-related quality of life (Leppavuori et al., 2002; Tang et al., 2015). A recent study also found that higher scores on the Insomnia Severity Index within the first two weeks of stroke were associated with inferior upper extremity motor function (Kim et al., 2015). Moreover, insomnia is frequently associated with decreased quality of life and depression, conditions that may interfere with rehabilitation.

4.2.3. Restless legs syndrome (RLS)

In about 12% of stroke survivors RLS is documented, including the possibility of de novo symptom onset after stroke (Lee et al., 2009; Medeiros et al., 2011). The impact of de novo or preexisting RLS on stroke recovery are sparse and sometimes contradictory (Hermann and Bassetti, 2016). Lee et al. (2009) investigated the relationship between lesion location and RLS in 137 ischemic stroke patients. All but one out of 17 patients diagnosed with RLS had subcortical lesions affecting the pyramidal tract and basal ganglia-brainstem axis. Medeiros et al. (2011) found that stroke recovery at 12 months, as assessed by clinical scores of functional independence and activities of daily living, was worse in RLS patients versus patients without RLS, even after adjusting for diabetes and BMI. These data underline the need for further studies to better understand the interplay between RLS and stroke, or the potential role of RLS in adversely affecting stroke recovery.

4.3. Sleep EEG and stroke outcome (human and animal data)

Sleep EEG changes may result from multiple causes. First, they can be the result of a disruption of the sleep-wake machinery reflecting the underlying damage. Second, they may be caused by pre-existing or de novo sleep disturbances. Third, sleep EEG changes ipsi- and contralesionally may reflect the neuroplasticity processes taking place after stroke, and therefore reflect neuroplasticity and functional reorganization.

In this section we will review current human and animal data on macro- and microstructural post-stroke sleep EEG changes.

4.3.1. Post-stroke changes in sleep's macrostructure and stroke outcome

Macro- as well as microstructural sleep changes following stroke are likewise an expression of the severity and location of brain damage but also represent a marker for neurological recovery depending on the localization and time of their appearance during recovery. Environmental factors on Stroke Units and co-morbidities (sleep disorders, medication) also likely have an influence.

Stroke patients most consistently show a reduction in total sleep time and sleep efficiency as reported in a recent meta-analysis of nine studies investigating stroke patients' sleep EEG at different stages of chronicity, but predominantly within the first 16 days of stroke (Baglioni et al., 2016). Reports on post-stroke changes in the quantity of NREM sleep stages are less consistent, especially concerning light sleep (NREM stages 1 and 2). However, most studies have observed a decrease in SWS (NREM stage 3) during the acute phase following either supratentorial or brainstem strokes (Autret et al., 1988; Bassetti et al., 1996; Bassetti and Aldrich, 2001; Korner et al., 1986; Terzoudi et al., 2009). Prolonged sleep, especially due to increased NREM stage 1, is also reported, particularly in patients after bilateral paramedian thalamic strokes (Bassetti et al., 1996; Bassetti, 2016; Hermann et al., 2008) and persistence of higher sleep needs one year after is associated with incomplete recovery (Hermann et al., 2008). Also REM sleep is frequently decreased in acute supratentorial as well as in brainstem strokes (Autret et al., 1988; Bassetti and Aldrich, 2001; Cummings and Greenberg, 1977; Giubilei et al., 1992; Korner et al., 1986; Muller et al., 2002; Terzoudi et al., 2009).

Similar post-stroke changes in REM and NREM sleep found in patients are also observed in animal models of stroke. Most consistently, REM sleep is decreased in the acute phase of ischemic stroke, whereas post-stroke increases and decreases of NREM sleep in rodents and rabbits are reported (Ahmed et al., 2011; Baumann et al., 2006; Sainio and Putkonen, 1975). Interestingly, higher amounts of REM sleep are linked with lower infarct volumes in rodents (Pace et al., 2017).

Although not many studies have so far investigated the relationship between post-stroke sleep changes (including evolution of sleep changes over time) and neurological recovery, less disturbed sleep following stroke and better recovery of sleep architecture over time appears associated with better neurological and cognitive recovery (see Fig. 2). Stroke patients with better short-term outcome at hospital dismissal, i.e., lower degree of disability or dependence in daily activities, also show higher sleep efficiency and more NREM sleep (significant increase in stage 2 and a non-significant increase in stage 3 sleep) recorded as early as possible after stroke (Bassetti and Aldrich, 2001). It also appears that improved sleep efficiency during the acute and subacute phases of stroke is important for good short- and long-term recovery (Vock et al., 2002). In a study by Siccoli et al. (2008) a positive association between verbal and non-verbal memory and amounts of SWS, REM sleep, and total sleep efficiency was observed in the recovery phase after stroke, supporting the perspective that recovery of consolidated sleep is crucial for cognitive rehabilitation following stroke.

Taken together, these findings are consistent with a widely distributed neural network regulating sleep-wake control, in that damage to one area of the network may cause transient perturbations in the expression, timing or maintenance of the states of sleep and wakefulness. Studies suggest that sleep macrostructure, as well as microstructure as reviewed in the next section, tends to be most altered primarily during the first few days after stroke, showing a trend towards normalization during subsequent months of recovery which is related to stroke outcome (Bassetti and Aldrich, 2001; Gottselig et al., 2002; Hermann et al., 2008; Siccoli et al., 2008; Vock et al., 2002). Hence, post-stroke sleep changes and evolution over time not only occur in parallel with recovery, but also appear to support post-stroke neuronal plasticity underlying recovery (see Fig. 3).

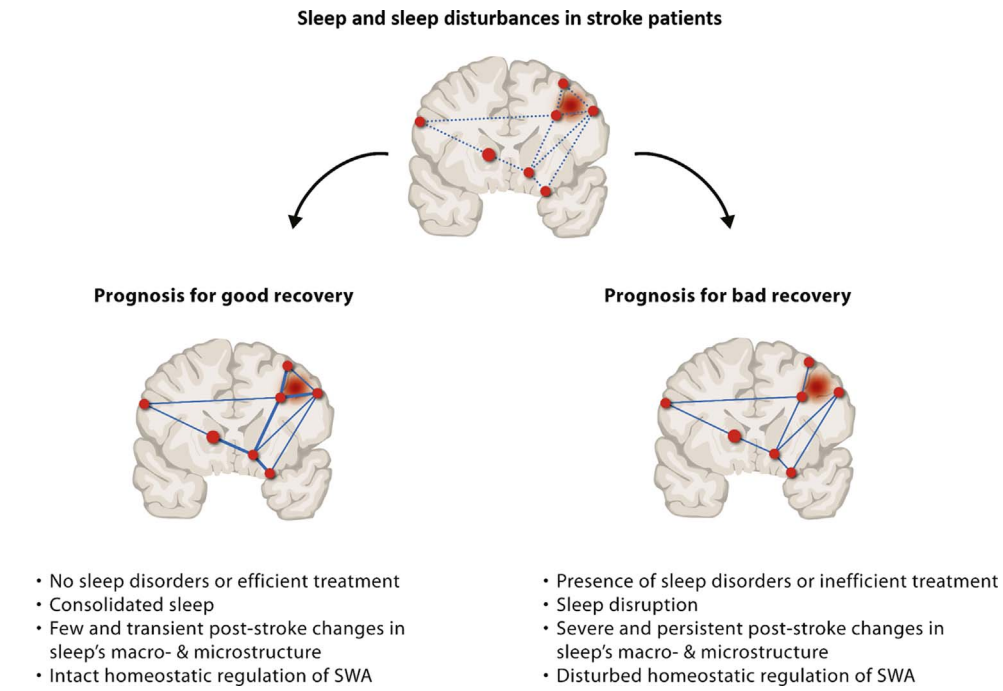

Fig. 3. Sleep and sleep disturbances in stroke patients and prognosis of recovery. Good or bad prognosis of stroke recovery can depend on the presence or absence of sleep disturbances and on the severity and persistence of post-stroke changes in sleep's micro- and macrostructure.

4.3.2. Post-stroke changes in sleep's microstructure and stroke outcome

Reduction of sleep spindles is observed after thalamic (paramedian) and supratentorial (large) strokes, but only rarely after brainstem stroke (Bassetti and Hermann, 2011). Larger lesions are associated with a more pronounced spindle reduction (Bassetti and Aldrich, 2001), but also smaller and even subcortical lesions show similar effects (Reeves and Klass, 1998). Gottselig et al. (2002), in accordance with Poryazova et al. (2015), observed lower spindle frequency range power and reduced spindle peak sizes in the power spectra, a measure aimed at quantifying the amount of spindles, within the first 10 days after hemispheric stroke, whereas spindles reappeared in the more subacute and chronic phases of stroke. Using high density EEG, Poryazova et al. (2015) identified lower power in the spindle frequency range in stroke patients compared to control participants within the peri-infarct area. Over the contralesional hemisphere, however, they found an increase in spindle frequency power that decreased again during the more chronic phase of stroke. This initial increase and then decrease in spindle frequency power possibly reflects a compensatory mechanism or a marker of ongoing contralateral neuroplastic changes consistent with the initially increased and then decreased activity measured in imaging studies over the contralesional hemisphere during recovery of motor and language functions (Buma et al., 2010; Hamilton et al., 2011). Supporting this idea of an effect of sleep spindles for stroke recovery, Gottselig et al. (2002) have even measured a positive correlation between ipsilesional spindle peak size in the acute stroke-phase and functional outcome after twelve months.

Local SWA changes are a second microstructural characteristic identified after stroke (Poryazova et al., 2015). Local SWA has gained special interest, in part because of its non-specific appearance after brain injury (see e.g., van Dellen et al. (2013)), but also in light of the accumulating knowledge about its role in sleep-related learning and memory processes potentially relevant for successful neurorehabilitation after stroke (Diekelmann and Born, 2010; Tononi and Cirelli, 2014). Poryazova et al. (2015) measured an increase in SWA over the infarct area and a decrease in SWA over the peri-infarct area during sleep in the acute phase after stroke and three months thereafter. They interpreted the increase in SWA over the infarct as a sign of neuronal deafferentation and hence of neuronal dysfunction. This interpretation is in accordance with studies showing delta activity in wakefulness to result from cortical deafferentation (corticocortical and thalamocortical disconnection; see e.g., Topolnik et al. (2003)). The decrease of SWA over the peri-infarct area might reflect a marker of decreased neuronal synchronization during sleep which possibly further hinders sleep-related stroke recovery. This perspective is consistent with the correlation between poorer functional stroke outcome after three months and the combined finding of SWA increase over the infarct and SWA decrease over the peri-infarct area Poryazova et al. (2015). Additional evidence that persistent decrease in SWA over the peri-infarct area in the chronic phase of stroke might be maladaptive for recovery, whereas an increase seems beneficial, is provided by a study of Sarasso et al. (2014). They recorded chronic stroke patients' sleep using high density EEG following an imitation-based speech training. Interestingly, an increase in SWA in the left precentral perilesional areas of the brain was associated with better post-training language performance. This suggests that patients regaining a good homeostatic regulation of SWA in prerilesional areas, assumed to reflect greater learning-induced neuroplasticity, show better performance and functional recovery.

5. Sleep promotion to improve stroke recovery

5.1. Animal data

Studies on timing of rehabilitation in animal models investigating GABAergic inhibition in the peri-infarct zone of stroke suggest that sleep provide a protective environment that facilitate neuronal survival and activation of repair mechanisms during the first days following stroke. GABA receptor agonists do not only improve sleep, but also stroke recovery (Hodor et al., 2014).

Administration of GABA antagonists in the acute phase of stroke, as well as premature use-dependent neuronal activation, have adverse effects on infarct size and post-stroke recovery (Clarkson et al., 2010; Krakauer et al., 2012). In contrast, one week to several months following stroke, reduction of GABAergic activity in the peri-infarct zone and use-dependent neuronal activation is beneficial for neuro-

plasticity and improves stroke recovery (Clarkson et al., 2010; Krakauer et al., 2012).

Few experimental data suggest positive effects of sleep promoting medications on stroke outcomes (Gao et al., 2008; Hodor et al., 2014). Mice undergoing treatment with γ-hydroxybutyrate (used in treatment of narcolepsy) show faster recovery in grip strength in the paretic forelimb as compared with those treated with saline (Gao et al., 2008). In treated mice the neuroplasticity-associated genes neurocan, thought to inhibit axonal outgrowth, and c-jun, associated with neural survival and death, were found to be down-regulated. Consistent with these data, consecutive injections of Baclofen, a γ-aminobutyric acid (GABA) B receptor agonist used to promote NREM sleep, compared to saline injections induced post-stroke axonal sprouting from the contra- to the ipsilesional hemisphere and cell proliferation in the peri-infarct zone in rats and resulted in improved functional outcomes (Hodor et al., 2014).

5.2. Human data

During the acute phase after stroke, conditions on stroke units must be optimized, as much as possible, to help patients maintain a well-regulated sleep-wake rhythm, particularly with respect to light and noise exposure. As suggested by human and animal studies, the point in time when post-stroke rehabilitative training is started provides crucial – to early and to late post-stroke onset of training might deteriorate recovery (Dromerick et al., 2009; Krakauer et al., 2012). Allowing for prolonged sleep during the acute phase of stroke might be beneficial (neuroprotective function of sleep), whereas sleep may become important to foster training-induced neuroplasticity during the subacute and chronic phases (Fig. 1).

Early recognition and treatment of sleep disorders is important. Until now, research has predominantly focused on post-stroke treatment of SDB. Five randomized studies have investigated treatment of SDB with continuous positive airway pressure (CPAP) in the acute phase of stroke and at least partly suggest a beneficial effect on neurological recovery (see Hermann and Bassetti (2016) for a systematic review). In a sample of stroke patients not randomly assigned to the treatment (N=11) and control group (N=13), Benbir and Karadeniz (2012) even found that in a greater number of treated than untreated stroke patients the lesion sizes decreased, suggesting a protective effect for the penumbra due to SDB treatment.

Post-stroke insomnia and RLS may be pharmacologically managed. Care should be taken with benzodiazepines frequently used to treat insomnia because they may worsen SDB and even neurological deficits and alter sleep architecture (Feld and Diekelmann, 2015; Hermann and Bassetti, 2016).

As alternative to drugs, less invasive strategies and techniques to promote sleep exist (see Fig. 4). These comprise noninvasive brain stimulation tools, such as tDCS and rTMS. Both techniques have been evaluated as a tool to improve stroke recovery with mixed findings of no to moderate effects on stroke recovery (Di Pino et al., 2014). However, the application of noninvasive brain stimulation combined with sleep as a tool to modulate the efficacy of neuroplasticity and influence functional stroke outcome has not yet been addressed. In a recent review by Nissen and Sterr (Ebajemito et al., 2016) the potential of sleep in modulating the efficiency of tDCS in rehabilitation from stroke is discussed. In simple terms, tDCS can be used to facilitate and thus enhance synaptic plasticity in the perilesional cortex during training of a lost motor skill or cognitive function (anodal excitatory tDCS) and/or to reduce compensatory activity in the contralesional hemisphere (cathodal inhibitory tDCS) (Ebajemito et al., 2016). Enhanced synaptic plasticity during learning may increase homeostatic sleep regulation as proposed by Tononi and Cirelli (2014), measurable by an increase in local SWS over the brain regions involved in learning. Moreover, tDCS can be applied during SWS to potentially stabilize or even increase slow oscillations suggested to benefit memory consolidation (Marshall et al., 2004). However, before clinical application of

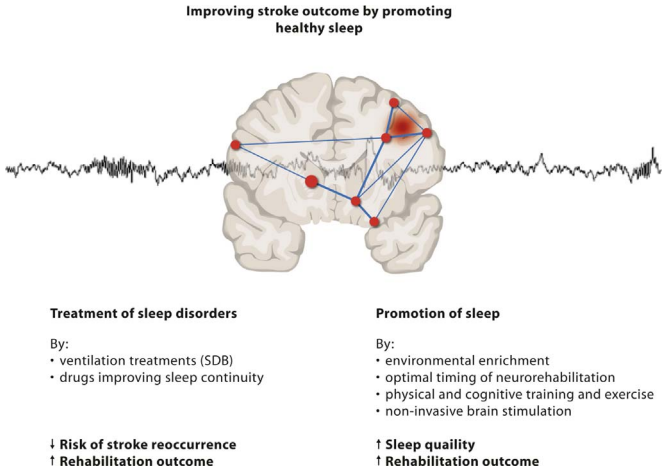

Fig. 4. Improving stroke outcome by promoting healthy sleep. Treatment of post-stroke sleep disorders is associated with better stroke outcome and decreased risk for stroke reoccurrence. As suggested by animal studies promotion of sleep by drugs following a stroke is associated with increase neuroplasticity processes and better motor recovery. In stroke patients sleep might be promoted by increasing the homeostatic sleep drive, e.g. by environmental enrichment and optimized rehabilitative trainings or by non-invasive brain stimulation during training and during sleep.

tDCS, its potentially beneficial effect on sleep homeostasis, whether applied during waking while learning or during sleep, must be systematically investigated in the context of stroke rehabilitation. As waking cognitive and motor activities can increase local EEG SWA during subsequent sleep, it is important to note that currently practiced interventions following stroke such as physical and cognitive training with enriched rehabilitative care may naturally increase local homeostatic sleep drive and the associated neuroplastic processes during sleep.

6. Conclusion and future directions

The accumulating data documenting increased neuroplasticity during either healthy sleep or in the process of spontaneous functional recovery after stroke across species suggests that sleep (and its modulation) may influence the outcome after stroke.

Experimental data in rodent models of stroke and clinical observations in stroke patients have indeed shown a detrimental effect of sleep disruption/loss (sleep deprivation protocols in animals; sleep disturbances in humans) on stroke evolution. On the other hand, first data suggest a favorable effect on stroke outcome from pharmacological (and possibly also non-pharmacological) sleep promotion in rodents and from treatment of sleep disordered breathing (and possibly also other sleep disorders) in humans with stroke. Finally, animal and human EEG studies performed after stroke show that the neuroplasticity processes underlying functional recovery can be documented and monitored by t sleep EEG changes.

More data are necessary to test the basic hypothesis of a direct/causal link between sleep (and its modulation) and stroke recovery. In animals and humans, the evolution of sleep EEG over the damaged area in both the peri- and contralesional areas of the brain should be studied longitudinally and correlated with functional recovery. In this context, the differentiation between sleep EEG changes due to brain damage/cortical disconnection (“bad waves”) and those reflecting enhanced sleep processes/neuroplasticity (“good waves”) is crucial. The impact of early diagnosis and effective treatment of sleep disorders after stroke (as currently done in the context of the SAS-CARE (Cereda et al., 2012) and eSATIS trials (ClinicalTrials.gov, NCT02554487)) should be tested systematically and prospectively in large patient populations. In both humans (e.g., using TMS or tDCS) and animals (e.g., using optogenetic approaches) after stroke, non-pharmacological strategies to promote sleep should be assessed in terms of their

potential to enhance the effects on spontaneously occurring, or neurorehabilitation-related functional recovery. This is currently done in the context of a Swiss National Science Foundation (Sinergia) Project entitled "Sleep as a model to understand and manipulate cortical activity in oder to promote neuroplasticity and functional recovery after stroke" and performed between the Universities of Bern and Zurich in Switzerland and the University of Milano in Italy ("http://p3.snf.ch/project-160803).It is to be anticipated that the effects of similar interventions could have different, if not opposite, effects depending on the exact time of their use (i.e., before stroke, or in the acute or the subacute-chronic phase after stroke). A better understanding of the molecular mechanisms underlying the interactions between sleep and stroke will improve the possibility for tailored pharmacological and non-pharmacological interventions to improve functional recovery.

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Conflicts of interest

All authors have contributed to this manuscript and have no interest of conflict to declare.

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