What is the role of brain mechanisms underlying arousal in recovery of motor function after structural brain injuries?

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Purpose of review

Standard neurorehabilitation approaches have limited impact on motor recovery in patients with severe brain injuries. Consideration of the contributions of impaired arousal offers a novel approach to understand and enhance recovery.

Recent findings

Animal and human neuroimaging studies are elucidating the neuroanatomical bases of arousal and of arousal regulation, the process by which the cerebrum mobilizes resources. Studies of patients with disorders of consciousness have revealed that recovery of these processes is associated with marked improvements in motor performance. Recent studies have also demonstrated that patients with less severe brain injuries also have impaired arousal, manifesting as diminished sustained attention, fatigue, and apathy. In these less severely injured patients, it is difficult to connect disorders of arousal with motor recovery because of a lack of measures of arousal that are independent of motor function.

Summary

Arousal impairment is common after brain injury and likely plays a significant role in recovery of motor function. A more detailed understanding of this connection will help to develop new therapeutic strategies applicable for a wide range of patients. This requires new tools that continuously and objectively measure arousal in patients with brain injury, to correlate with detailed measures of motor performance and recovery.

Keywords

arousal regulation, goal-directed behavior, poststroke apathy, poststroke fatigue, sustained attention

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Introduction

Only a small percentage of the variance of motor recovery from stroke, and likely traumatic brain injury (TBI), is explainable by rehabilitation interventions; the remainder falls under the category of 'spontaneous' recovery [1,2]. In the setting of focal stroke, animal model and human imaging studies provide evidence that recovery of movement is associated with peri-lesional brain regions taking over for lost functions [3,4]. On the other hand, in the setting of larger injuries produced by large-vessel strokes or TBI, this local neuroplasticity may play less of a role. In these situations, we propose that a major driver of motor recovery is restitution of brain networks supporting arousal and production of goal-directed behavior.

Below, we briefly review the neuroanatomical basis of level of arousal and the initiation and maintenance of goal-directed behavior. We then review evidence from a variety of brain injury types for the connection of functioning of these networks and recovery of motor function and learning. This connection is strongest in cases of severe brain injury with disorders of consciousness, but there is also evidence for a role of arousal in patients with milder diffuse or focal injuries. Finally, we discuss the steps that can be taken in future work to clarify the role of arousal in recovery of motor function in patients without disorders of consciousness to support the development of appropriate interventions.

Background

Goal-directed movements require, in addition to the typically discussed sensory and motor systems, an adequate level of arousal, and a mobilization of distributed neuronal networks to initiate and sustain the behavior. Arousal level refers to an overall state function of brain activity, and in the intact brain ranges from stage three non-REM sleep, where strong stimuli are required to elicit a response, to states of high vigilance within wakefulness, where subtle stimuli can be detected and acted upon [5,6]. Within the awake state, level of arousal is often termed alertness, and can be measured by speed of response to stimuli, and ability to continue responding

over a period of time (i.e. vigilance or sustained attention) [7]. Initiation and maintenance of goal-directed behavior involves the enhancement of arousal with focused activation of corticothalamic networks involved in task performance. This mobilization of resources [8] is one of the brain's 'executive functions' and is termed arousal regulation [9].

Arousal level and regulation of arousal are supported by a collection of highly interactive cortical, subcortical, and brainstem areas. The core areas for arousal (i.e. the 'arousal system') appear to be glutamatergic and cholinergic neurons in the dorsal tegmentum of the midbrain and pons [10,11]. In humans, these neuronal populations broadly activate the cerebrum predominantly via the basal forebrain and central thalamus (primarily intralaminar nuclei). The basal forebrain and central thalamus subsequently activate the cortex through cholinergic and glutamatergic projections, respectively. The brainstem norepinephrine system also enhances arousal via modulation of the cortex, basal forebrain, and thalamic intralaminar nuclei [12,13]. Other arousal system components include brainstem dopaminergic, and hypothalamic histaminergic and orexin/hypocretin-producing neurons [14–17].

Arousal regulation is primarily implicated in healthy individuals during tasks requiring enhancement of alertness or sustained attention. It is primarily supported by activity in the medial frontal and anterior cingulate cortices, though also relies on the broadly activating neurons of the intralaminar thalamus [18–21]. Further organization of goal-directed behaviors is supported by broadly distributed activity across frontal and parietal systems [22]. Loop connections between the frontal and parietal cortices, basal ganglia, and thalamus (both specific and nonspecific nuclei) are also important to focus and support both arousal regulation and organization of behavior [23–25].

In healthy individuals, arousal and arousal regulation play a major role in motor performance and motor learning. Low arousal states, such as those often produced by sleep deprivation, are well known to impair motor performance and learning [26]. Sleep deprivation is associated with decreased metabolism on FDG PET (fluorodeoxyglucose positron emission tomography) across the frontal lobe, basal ganglia, and thalamic regions that support goal-directed behavior [27,28]. These same regions are also the first to reduce with sleep onset [29], and the last to recover after awakening, associated with an impairment of motor responsiveness known as 'sleep inertia' [30]. A recent study using local-field potential recording in rats provides evidence that the decreased hypometabolism measured during sleep deprivation represents intermittent pauses in firing of cortical neurons [31••]. The authors suggested that these cortical areas are entering a local sleep state despite an overall appearance of wakefulness, and that this local sleep state can impair motor performance.

Key points

- Goal-directed behavior requires an adequate arousal level as well as ability to mobilize neuronal resources, termed arousal regulation.
- Recovery of arousal and arousal regulation in patients with disorders of consciousness can be associated with marked recovery of motor performance.
- Disorders of arousal and production of goal-directed behavior are common in patients with traumatic brain injury and stroke.
- New approaches are needed to document disorders of arousal and goal-directed behavior after brain injury independent of motor dysfunction.

Processes that increase arousal, such as motivation, reward, pain, stimulant medications, and anxiety, improve motor performance and learning to a point, though too high levels of stimulation impair behavior and learning [32,33]. These processes likely improve behavior by enhancing cortical signal-to-noise ratios; but too high levels of arousal can enhance response to all stimuli, preventing detection of salient ones [34].

The effect of brain injury on arousal and production of goal-directed behavior

Diffuse and focal brain injuries can impair goal-directed behavior by directly injuring or disconnecting the networks of brain areas involved in arousal and arousal regulation. The connection between these injuries and recovery of motor performance and learning is clearest in patients with global impairments in brain function, known as disorders of consciousness. For patients with less severe diffuse injuries or focal injuries, there is evidence of deficits in arousal and arousal regulation, but less so for a connection with motor recovery.

The disorders of consciousness arising from structural brain injury include coma, vegetative state, and the minimally conscious state [35]. Three canonical pathophysiologies are widespread neuronal death and/or disconnection from global hypoxia; diffuse axonal injury (DAI) from TBI; and focal destruction of the upper brainstem and thalamus often from top of the basilar stroke. These anatomic pathologies all involve dysfunction of corticothalamic activity from either direct loss of neurons, or overwhelming impairment of arousal system activation. In these conditions, recovery of voluntary movement is by definition associated with recovery of arousal (i.e. recovery of consciousness) [36].

The inverse is not true as deficits of corticospinal [37] or higher order motor systems [38,39••,40••] can prohibit detection of consciousness processing. Evidence for the causal link from improved arousal to motor recovery includes patients with rapid improvements in arousal due to zolpidem [41] and central thalamic deep brain stimulation (DBS) [42], who had marked improvements in movement ability. Recovery of consciousness is also associated with return of motor learning. One extreme example is a patient who recovered consciousness after 19 years in the minimally conscious state, and over the subsequent year transitioned from no lower extremity movement to being able to use his lower extremities to elevate his lower back to help in personal care [43].

A relevant, but less common disorder of consciousness is akinetic mutism [44,45]. Here, the behavioral appearance is that of low-level minimally conscious state, but the injury is restricted to the same areas involved in arousal regulation (medial frontal cortices or connected subcortical nuclei), without loss or disconnection of the brainstem or basal forebrain [46]. One of the hallmarks of the syndrome of akinetic mutism is the occasional appearance of high-level organized behaviors in response to specific stimuli [47]; these marked variations in goal-directed behavior suggest that there are alternate paths to enhance arousal regulation network activity. A recently proposed model [48] suggests that specific variations in the activation of different cell types within the arousal regulation network can alter widespread corticothalamic activity, and thereby explain fluctuations in goal-directed behavior in akinetic mutism and similar syndromes. This model accounts for the role of dopaminergic agents [49–51], zolpidem [41,52], central thalamic DBS [42], and other potential agents that would act on these neuronal subsystems.

In patients with diffuse brain injuries but without disorders of consciousness, deficits in arousal and arousal regulation are common. Excessive daytime sleepiness is relatively common in patients with TBI, even 6 months after injury, [53] and affects ability to sustain attention [54]. These patients also demonstrate daily fluctuations in arousal, that can lead to significant variations in behavior [55,56]. Theories for mechanisms of impaired arousal and arousal regulation include loss of cholinergic neurons [57] and impaired cortical connectivity [58••], possibly from residual axonal injury [59•]. The connection between recovery of arousal and of motor function in this population is not well understood, though is important, as motor recovery can be prolonged and incomplete [60].

In patients with focal brain injury such as from stroke, the clearest cases of impaired arousal are in those with focal injuries to the upper brainstem and thalamus, who may either have a disorder of consciousness (discussed above) or may appear alert, but demonstrate impaired attention and slowed responsiveness [61]. Strokes of the medial frontal lobe or basal ganglia, areas involved in arousal regulation, may result in a milder form of akinetic mutism called abulia [47]. There is also evidence that the syndrome of left-sided neglect can be due to damage to areas involved in arousal regulation, resulting in loss of right greater than left arousal tone, rather than a specific loss of attentional network functioning [62]. These syndromes are clearly relevant to overall function after stroke, but their role in motor recovery still needs to be determined.

In patients with focal stroke but without damage to arousal systems or regions involved in arousal regulation, there is still a significant prevalence of disorders of arousal and production of goal-directed behavior, presenting as fatigue and apathy. Both fatigue and apathy are defined by patient description of a lack of drive to perform goal-directed behaviors, with motivation retained in fatigue, but lost in apathy. Both syndromes have been documented poststroke independent of depression [63,64] and correlate with prolonged disability [65,66]. The connection between fatigue and apathy and the patterns of underlying brain injuries are still poorly defined [67], though one study did find a higher prevalence with brainstem strokes [68]. The lack of a clear pathophysiologic basis is likely due to a combination of small sample sizes in observational studies, multiple other contributing factors (e.g. premorbid depression, infection, medications, sleep disorders, and medical comorbidities), and definition of conditions by use of questionnaires rather than physiological biomarkers. Going forward, it is important to develop objective markers of apathy and fatigue to determine their role in motor recovery and to develop treatment approaches aimed at underlying mechanisms.

There is also evidence that exogenous factors that act on arousal pathways may affect motor performance and recovery from brain injury. Many medications that correlate with slower recovery are known to inhibit arousal level including alpha-2 adrenergic agonists (generally inhibit norepinephrine release), GABA allosteric activators (benzodiazepines and barbiturates), and antiepileptics including phenytoin [69–71]. Benzodiazepines have even been shown to transiently reinstate motor deficits in patients in the chronic stage poststroke [72]. Antidopaminergic agents such as haloperidol also slow recovery from brain injury [69], with potential mechanisms including inhibition of an implicit form of arousal regulation [73] and of skill learning [74]. Conversely, medications that enhance noradrenergic [75] and dopaminergic [74] neurotransmitter levels have been shown in animal studies to improve motor learning and recovery, though

human trials have been inconsistent [76]. Sleep disorders are another common factor after stroke and TBI [77,78] and affect recovery. As with direct effects of brain injury on arousal and initiation, most of the studies on exogenous factors are observational and use nonphysiological outcome measures. An approach focused on mechanism could reveal which patients' recoveries are being impaired by these factors, and which ones would most benefit from interventions to enhance arousal.

An approach to determine the role of arousal in recovery of motor function after structural brain injury

The above review highlighted some of the anatomy of highly interconnected brain networks supporting arousal level and production of goal-directed behavior. We reviewed clinical evidence linking specific patterns of brain injuries, as well as common exogenous factors, that affect the functioning of these networks. However, with the exception of patients with disorders of consciousness, the demonstrated connection between improved arousal and motor recovery is weak. One reason is that the behavioral definitions of arousal and arousal regulation are either based on subjective patient reports or on neuropsychological measures (e.g. vigilance tests) that require movement as the output. By requiring patients to move to respond, deficits in arousal and motor control are confounded. Furthermore, most trials are retrospective, limiting interpretation. To address these limitations to allow for development of new therapeutic strategies, we now offer a framework for future studies to allow for a more direct association between these phenomena.

To objectively document recovery of goal-directed behavior, measures should be objective and continuous so they can track the daily fluctuations in arousal level. Quantitative characterization of arousal using such measures has proven highly successful in animal studies [6]. Wireless wearable devices now offer a solution to monitor patient behavior continuously and without need for direct interaction with research staff. Triaxial accelerometers have been used in the home and rehabilitation setting for patients with stroke and brain injury and can demonstrate overall level of activity [79], as well as more specific actions such as walking speed [80•]. Machine-learning algorithms allow for detection of more complex behaviors such as reaching and grasping [81•]. Once the level of goal-directed behavior can be defined, it can be correlated with measures of arousal and arousal regulation that do not require voluntary movement including eye closures and electroencephalography [82,83,84••,85].

Once the objective markers of arousal and goal-directed behavior are available, they should be incorporated into observational and clinical trials focused on motor recovery from brain injury. Motor outcome measures in these trials should include both impairment and disability measures, as it is important to determine whether measures of arousal and arousal regulation correlate with true recovery at a kinematic level or with compensation behaviors. If such information can be included in clinical trials, it may help reveal some of the unexplained variance in recovery [2], so causative factors can be discovered. Further, it also may help to explain the varied responsiveness to adrenergic agents [75], as these drugs may benefit those who have loss of movement from impaired arousal, rather than loss of motor systems.

Conclusion

Sufficient arousal level and ability to regulate arousal to mobilize neuronal resources are basic requirements for all higher level behaviors. This is shown in our daily lives with variations of motor performance across the sleep–wake cycle and during states of sleep deprivation, and also revealed by the global impairments in behavior in patients with disorders of consciousness. Above, we review evidence that the systems that support goal-directed behavior are dysfunctional in a wide range of brain-injured patients. Experience with patients with disorders of consciousness has revealed that enhancement of activity in systems underlying arousal and arousal regulation can lead to marked improvements in motor recovery. We suggest that a deeper study of the presence and influence of arousal disorders in patients with less severe brain injuries will reveal underlying sources of delayed recovery, as well as identify new targets and approaches to enhance recovery.

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Conflicts of interest

A.M.G. has done consulting work with Johnson & Johnson pharmaceuticals. N.D.S. has no conflicts of interest.

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