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CLINICAL REVIEW

Waking up is the hardest thing I do all day: Sleep inertia and sleep drunkenness

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SUMMARY

The transition from sleep to wake is marked by sleep inertia, a distinct state that is measurably different from wakefulness and manifests as performance impairments and sleepiness. Although the precise substrate of sleep inertia is unknown, electroencephalographic, evoked potential, and neuroimaging studies suggest the persistence of some features of sleep beyond the point of awakening. Forced desynchrony studies have demonstrated that sleep inertia impacts cognition differently than do homeostatic and circadian drives and that sleep inertia is most intense during awakenings from the biological night. Recovery sleep after sleep deprivation also amplifies sleep inertia, although the effects of deep sleep vary based on task and timing. In patients with hypersomnolence disorders, especially but not exclusively idiopathic hypersomnia, a more pronounced period of confusion and sleepiness upon awakening, known as "sleep drunkenness", is common and problematic. Optimal treatment of sleep drunkenness is unknown, although several medications have been used with benefit in small case series. Difficulty with awakening is also commonly endorsed by individuals with mood disorders, disproportionately to the general population. This may represent an important treatment target, but evidence-based treatment guidance is not yet available.

Introduction

"Sleep inertia" refers to the transitional state between sleep and wake, marked by impaired performance, reduced vigilance, and a desire to return to sleep. The intensity and duration of sleep inertia vary based on situational factors, but its effects may last minutes to several hours. Sleep inertia is a normal phenomenon, but one with potentially dangerous ramifications, e.g., in health care workers or military personnel who are woken abruptly in the night and required to make cognitively-taxing decisions [1,2]. In some disease states, a transitional period akin to markedly pronounced sleep inertia is present and is sometimes referred to as "sleep drunkenness". Such pronounced sleep inertia is a core feature of idiopathic hypersomnia (IH), a potential consequence of delayed sleep phase syndrome (DSPS), and a contributor to non-REM (NREM) arousal parasomnia severity [3]. Difficulty awakening is also common in people with mood disorders and may be an important treatment target [4–6].

For this review, PubMed was searched for "sleep inertia", "sleep drunkenness", "sleep–wake transition", "sleep–wake transitions", "wake up", "wake-up", "waking up", "waking-up", "awaken", "awakening", "neural inertia", "sleep offset", and "sleep-offset". The former two terms were also queried at clinicaltrials.gov. Reference lists were reviewed to identify additional manuscripts.

Epidemiology of sleep inertia

Assessment of subjective sleep inertia at the population level suggests that difficulty awakening is a common experience. Difficulty getting up almost every morning is reported by 42% of adolescents [7], although confusion on awakening lessens with age in adulthood [4,5]. Men and women endorse similar difficulties with awakening [8] and similar rates of confusion upon awakening [4,5]. Chronotype influences difficulty with awakening through interaction with sleep time, such that night owls report more sleep inertia on workdays but sleep inertia is independent of chronotype on

Abbreviations: DSPS, delayed sleep phase syndrome; EEG, electroencephalography; EP, evoked potentials; fMRI, functional magnetic resonance imaging; IH, idiopathic hypersomnia; NREM, non-REM sleep; PET, positron emission tomography; PVT, psychomotor vigilance task; REM, rapid eye movement sleep; SWS, slow wave sleep.

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non-work days [9]. Shift and night work increase the risk of confusion on awakening [4].

Neurophysiology and neuroimaging of sleep inertia

From an evolutionary standpoint, sleep inertia is counterintuitive, as sudden transitions to wakefulness seem clearly more adaptive. To some extent, the potential harm of slow transitions to cognitive baseline may be mitigated by changes in sleep inertia intensity based on sleep timing, composition, and duration (see below), such that there are times when a sudden awakening impairs cognition to a lesser extent. Despite this, worsened cognitive performance after even some awakenings is still potentially problematic. Sleep inertia is thus hypothesized to reflect the contradictory needs of maintaining sleep and allowing behavioral responsiveness [10] or the brain's need for a more gradual awakening process due to its complexity [11]. Mechanistically, it has been hypothesized that awakening may occur before adenosine is fully cleared, resulting in sleep inertia [12]. Because adenosine levels are increased by sleep restriction and gradually decrease over hours of subsequent sleep, especially in the basal forebrain [13], such a hypothesis could account for the finding of more intense sleep inertia following awakenings from recovery sleep than from baseline sleep [14,15]. An adenosine-sleep inertia hypothesis is concordant with the widespread practice of drinking coffee (containing the adenosine antagonist caffeine) upon awakening [12], but morning caffeine ingestion could alternatively reflect only a response to caffeine-withdrawal. Additionally, an adenosine hypothesis does not well account for the finding that performance after a short nap can be worse than performance immediately prior to the nap during sleep deprivation [16]. The decay of subjective sleepiness after awakening closely parallels the time courses of both extremity cooling and the cortisol awakening response, suggesting possible links of both thermoregulation and the hypothalamic-pituitary-adrenal axis to sleep inertia [17,18]. However, the substrate for sleep inertia remains incompletely understood [19,20].

Electroencephalography (EEG) studies

Immediately upon awakening, slow EEG activity (1–9 Hz) is persistent, and this carryover of sleep-like EEG features has been proposed as a signature of sleep inertia [20–22]. EEG analyses suggest an anterior-to-posterior gradient of awakening, as parieto-occipital regions demonstrate more slow activity than frontal regions [20,22]. Decreased beta activity on awakening is also present but is more global [20,22].

Recovery sleep after sleep deprivation may intensify sleep inertia [14,23] and similarly results in more persistent slow (theta) activity in the first hour after awakening [24]. With longer periods of sleep deprivation, post-waking reduction in fast activity (frontal beta and alpha) is pronounced [25]. Despite this suggestion that recovery sleep increases the carryover of EEG features characteristic of sleep, an early study found poor correlation between pre- and post-awakening EEG spectral power after recovery sleep (compared to baseline sleep) [24]. Subsequently, however, regionally-specific correlations between pre- and post-awakening EEG power were identified using additional EEG derivations following recovery sleep [25].

EEG analysis of arousals from sleep further confirms that the transition from sleep to wake is not a sudden, off-on process [10]. In particular, stereotyped thalamic EEG activity during arousals (measured by intracranial electrodes) suggests a state intermediate to sleep and wake, while cortical EEG during arousals is more dependent on preceding sleep stage but still represents a state clearly different from wakefulness [10]. In rodents, there is a low neuronal firing rate immediately upon spontaneous awakening, reaching baseline rates within ten minutes [11]. Off periods, characterized by global cessation of spiking, are more frequent immediately upon awakening than subsequently, suggesting that off periods or decreases in firing rate could be the neurophysiologic marker of rodent sleep inertia [11].

Evoked potential studies

Sensory evoked potentials (EP) are low amplitude EEG responses to stimuli that are normally obscured by background EEG activity but correlate with specific cognitive processes. Visual EP responses characteristic of sleep have been observed in early wakefulness [26]. Factors that amplify sleep inertia, such as awakening from recovery sleep [14,23], also accentuate auditory EP abnormalities (i.e., reduced amplitude of N1-P2, thought to reflect vigilance) [27,28]. Factors that lessen sleep inertia, such as self-awakening [29], mitigate the effects of waking on EPs (i.e., resulting in a higher amplitude visual P300 than forced awakening) [29,30]. Reduction in the amplitude of error-related EPs following an hour-long afternoon nap has been implicated as the neurophysiologic correlate of reduced motivation or significance related to errors in the period of sleep inertia [31]. Sleep stage at awakening may affect EPs, such that sleep-like responses and response delays are observed on visual EPs after slow wave but not rapid eye movement sleep (REM) awakenings [26]. Analogously, waking motor evoked potentials (recorded over the abductor digiti minimi muscle) following transcutaneous magnetic stimulation also demonstrate effects of stage at awakening, with greater facilitation apparent upon awakening from REM than from slow wave sleep (SWS) [32].

Cerebral blood flow and PET studies

Cerebral blood flow is a surrogate measure of cerebral activity. Early studies demonstrated decreased blood flow velocity in the middle cerebral artery immediately after waking compared to presleep [33,34]. This slowing persisted up to 30 min after awakening, closely paralleling the decay of sleep inertia in other studies [33,34]. In partially sleep-deprived controls, positron emission testing (PET) allowed regional evaluation of blood flow and demonstrated normalization of flow to the brainstem, basal ganglia, and thalamus within five minutes of awakening, while normalization of flow to the prefrontal cortex and other neocortical areas took 5–30 min [35]. The authors hypothesized that the recovery from sleep inertia requires reorganization of waking cognitive networks, which is demonstrated by the delay in resumption of waking levels of cortical blood flow [35].

Magnetic resonance imaging (MRI) studies

On functional MRI, connectivity within the sensory motor network is lower on awakening than prior to sleep onset, resembling connectivity patterns seen in NREM sleep [36,37]. This decreased connectivity could result in poor sensorimotor performance on awakening, i.e., sleep inertia [36,37]. Post-sleep connectivity changes do not differ based on the presence of deep sleep, although deep sleep correlates with regionally reduced EEG spectral power on awakening, consistent with earlier studies [37].

With magnetic resonance spectroscopy, elevated levels of nucleoside triphosphate are demonstrated in the basal ganglia and anterior cingulate on awakening from recovery sleep compared to baseline sleep [38]. Rather than being a potential cause of sleep inertia, this finding was hypothesized to reflect compensatory