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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.

Keywords

sleep inertia; sleep drunkenness; idiopathic hypersomnia; narcolepsy; mood disorders

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

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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 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 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 pre-sleep [33, 34]. This slowing persisted up to 30 minutes 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 minutes [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 increases in brain energy stores to combat the increased sleep inertia following recovery sleep [38].

Experimental manipulation: factors that increase sleep inertia

Numerous studies have evaluated the factors that influence sleep inertia presence and severity. Studies performed prior to 2000 have been reviewed in detail [39] and are not further reviewed here. Taken together, these early studies suggested that sleep inertia was most pronounced when awakenings coincided with the circadian trough of body temperature, was intensified by SWS awakenings and prior sleep deprivation, and was present following both short and long sleep periods. Type of task effects were prominent across studies, with a suggestion that speed was more impaired than accuracy [39].

Because cognition is affected by homeostatic and circadian processes as well as sleep inertia, forced desynchrony protocols offer a unique opportunity to study the relative impact of these processes. In a forced desynchrony protocol designed to tease apart these factors, Burke et al demonstrated that the largest effect sizes from sleep inertia were on selective visual attention (on a spatial search task) and subjective sleepiness [40]. Forced desynchrony studies have confirmed that impaired performance on awakening is most prominent during

the biological night, when awakening at or within 120° before the core body temperature minimum [41, 42]. On a serial addition task, circadian variation in number correct was much more pronounced immediately upon awakening (best-to-worst difference of 2.6 additions) than it was 20 minutes after awakening (best-to-worst difference of only 0.8 correct additions), suggesting an interaction between sleep inertia and circadian rhythm [41]. These forced desynchrony studies have reached discordant findings about the effect of sleep stage at awakening [41, 42], possibly reflecting difference in task or participant age (see Table 1). Other laboratory studies, without forced desynchrony, have also found mixed results on the effect of stage at awakening (see Table 2).

Performance is generally worsened after awakening from recovery sleep compared to baseline sleep [14, 15]. This is thought to reflect increased sleep pressure following sleep deprivation, suggesting that SWS amount during sleep should correlate with cognitive impairment upon awakening [44]. Evidence in support of this hypothesis has been mixed, with some [44, 45], but not all [46–48], studies demonstrating a relationship between SWS amount or percentage and waking cognitive performance (Table 2). Relative little attention has been paid to sleep inertia in children, but nocturnal SWS awakenings impair their behavioral responsiveness considerably [43].

The duration of sleep needed to induce sleep inertia has been evaluated using precise durations of measured sleep (see Table 3). After nocturnal time in bed of 5 hours, daytime nap sleep times up to 20 minutes do not convey sleep inertia effects, while sleep inertia is clearly apparent after 30 minutes of measured sleep [49–51]. However, under more pronounced sleep deprivation, naps shorter than 30 minutes time in bed may sometimes result in sleep inertia [16, 46, 52].

In real-life occupational settings, timing nap duration based on elapsed sleep time is impractical, and thus recommendations about nap duration must be made based on time to spend in bed rather than amount of measured sleep to obtain. In this regard, field studies are particularly valuable (see Table 4). Although on first glance these studies appear to demonstrate a minimal amount of sleep inertia, the design of these studies often resulted in a substantial delay between awakening and testing. Field studies are frequently designed to balance the detrimental effects of sleep inertia on cognition against the subsequent beneficial effects of having napped, in part accounting for these differences. Other laboratory studies of sleep inertia are summarized in Table 5. These studies highlight the degree to which sleep inertia is affected by protocol. For example, using the same measure, an investigative group found different effects of a 10 minute nap opportunity when the nap was taken at 0400 versus 0710 [16, 45].

Experimental manipulation: factors that reduce sleep inertia

Multiple strategies to decrease sleep inertia have been tested. Drinking caffeine just before a nap has been suggested as a useful countermeasure for sleepy drivers [53]. Both caffeine infusion during sleep deprivation (0.3 mg/kg/hr) and caffeine gum chewed for five minutes immediately after awakening (~85 mg caffeine) lessen sleep inertia following naps [12, 54]. Simple exposure to light of varying intensities, either during or immediately after sleep, does

not meaningfully impact sleep inertia as measured subjectively or objectively [55, 56]. In contrast, dawn simulators, which gradually increase the lux of light before awakening, have preliminary promise. Three studies have found improvements in subjective sleepiness on awakening, with modest objective performance benefits in one [57–59]. All three studies reported financial support from the simulator manufacturers. Pink noise at 75 decibels improves performance following a nap at midnight, but may have limited generalizability given that it also worsens performance following a rest at 0400 [60]. Application of a cold wet cloth and fan breeze improves post-nap performance [61] and is consistent with the hypothesis that sleep inertia is modulated by changes in body temperature [17]. Further work is needed to clarify the role of these interventions in dissipating sleep inertia, especially in occupational settings.

Sleep inertia/sleep drunkenness in people with sleep disorders

Sleep inertia has important implications in sleep disorders. Exaggerated sleep inertia is a core feature of IH, a common consequence of DSPS (because patients are required by external commitments to awaken near their core body temperature nadir, when sleep inertia is most pronounced, and because patients tend to be chronically, partially sleep deprived), and a factor that can worsen the NREM arousal parasomnias (by exacerbating confusion upon awakening from deep sleep) [3]. The association with idiopathic hypersomnia will be focused on here.

The syndrome of “hypersomnia with sleep drunkenness” was proposed by Bedrich Roth based on patients examined since the 1940s [62, 63]. In 58 patients, he described sleep drunkenness manifesting as confusion, slowness, incoordination, and a tendency to return to sleep lasting up to 4 hours, which was sometimes more problematic than daytime sleepiness itself [62]. Such sleep drunkenness was much more severe than the physiologic sleep inertia that occurs in healthy individuals, with patients often requiring the assistance of another person to be able to wake up. During the period of sleep drunkenness, hypersomnia patients exhibited ataxia, orthostatic disequilibrium, and hypo-reflexia [63]. Roth ultimately concluded that this syndrome was a variant of IH and reported a frequency of sleep drunkenness of 55.1% in IH [64]. Subsequent clinical series have confirmed the high rate of sleep drunkenness in this disorder (see Table 6).

The reason for sleep drunkenness in IH patients is unknown. It is sometimes characterized as an exaggerated and more severe form of physiologic sleep inertia [3]. Many IH patients have a need for extended sleep times (e.g., >11 hours) that cannot be fulfilled, and so are functionally sleep deprived; this sleep deprivation would be expected to worsen sleep inertia [63]. Additionally, IH patients have a tendency toward delayed sleep phase, which itself worsens sleep inertia [65], and IH patients with sleep drunkenness are more likely to be evening types than IH patients without sleep drunkenness [66]. However, some of the findings of Vernet et al [66] suggest that sleep drunkenness may be a phenomenon that is distinct from sleep inertia. In particular, measured sleep times and sleep efficiency do not differ between those IH patients with and without sleep drunkenness, and SWS near the time of awakening (after 0600) is no more common in those with sleep drunkenness.

Although sleep drunkenness is common in patients with IH, the presence of sleep drunkenness is not specific to this diagnosis. Classically, naps are refreshing in narcolepsy patients [3], while patients with IH may need to avoid naps because of problematic sleep drunkenness. Despite this, performance decrements in choice reaction and subtraction tasks are apparent upon awakening in patients with narcolepsy with cataplexy [68, 69]. Compared to controls, however, patients with narcolepsy with cataplexy have relatively preserved performance on a semantic priming task upon awakening from REM (compared to their own wake baseline) [70]. Clinical series suggest that patients with narcolepsy, with or without cataplexy, sometimes endorse sleep drunkenness (see Table 6). In children with narcolepsy, sleep inertia is reported to occur commonly [71], regardless of the presence of cataplexy [72]. On forced awakening from a three minute sleep episode, hypersomnolent patients frequently show high amplitude, frontal negative visual EP responses or a delayed visual P300 response [73]. Positive findings on this paradigm are common across hypersomnolence diagnoses (86% in narcolepsy, 79% in IH, and 100% in obstructive sleep apnea) but are not seen in controls [73]. Thus, while sleep drunkenness may be more characteristic of IH than narcolepsy with cataplexy, it is neither specific nor necessary for the diagnosis.

Clinical trials in patients with hypersomnolence disorders have typically not assessed sleep drunkenness, so an evidence-based approach to its treatment cannot be proposed. Review of clinicaltrials.gov identified only two studies referencing sleep inertia, both testing pharmacological effects of sedative-hypnotics. However, cases from the literature offer several treatment suggestions, including washing with cold water and dosing of stimulant medication at bedtime or 30 minutes before desired awakening [62]. Both slow-release melatonin (2mg) and protriptyline (10–20mg) at bedtime have decreased sleep drunkenness in small series of hypersomnolent patients, although details of the former series are unpublished [74, 75]. In a larger series of 46 IH patients, sodium oxybate (mean 4.3gm/night) improved sleep drunkenness in 71%, although discontinuation due to side effects was common [76], and this observation needs confirmation in a prospective, controlled trial. Improvement in sleep drunkenness has been reported in individual cases with transdermal and subcutaneous flumazenil, a nicotine patch, and etilefrine (the latter in a patient with comorbid hypotension) [77–80].

Difficulty awakening in people with psychiatric disorders

Individuals with mood disorders often have associated sleep symptomatology, including difficulty with awakening, and confusion upon awakening is strongly associated with psychiatric symptoms at the population level [4, 5]. In nearly 600 people with unipolar depression, having trouble getting out of bed was present in 74% of subjects, similar to difficulty falling asleep (72%), difficulty staying asleep (70%), and feeling sleepy (66%) [81]. Individuals with bipolar disorder and those at high-risk of developing it are also more likely than controls to endorse difficulty waking and getting out of bed [82]. On a 21-item sleep inertia questionnaire, depressed individuals endorsed higher levels of sleep inertia than controls on nearly every item [6].

Although the mechanism of difficulty in awakening in patients with mood disorders is not known, it may be related more to mood symptomatology than to sleep physiology, reflecting

anhedonia or decreased motivation. In support of this, depressed subjects who endorse difficulty getting out of bed also commonly endorse wishing not to awaken [81] and depressed patients are much more likely than controls to endorse dread about starting the day [6]. EP studies also suggest that sleep inertia in mood disorders may differ from that in hypersomnolence disorders. Specifically, in forced awakening protocols, patients with psychiatric hypersomnolence tend to have responses similar to normal controls while sleep disorder patients do not [73, 83]. The relationship between mood and hypersomnolence is complex, however, so further work is needed before firm conclusions can be drawn.

As in IH, evidence-based guidance for sleep inertia treatment in mood disorders is presently unavailable. In children with treatment-refractory bipolar disorder, intranasal ketamine improved symptoms, including difficulty with awakening [84], but this finding may have limited generalizability. In those with subsyndromal winter depression or seasonal affective disorder, use of a dawn simulator improves some measures of sleep inertia (e.g., subjective ease of awakening) but not others (e.g., reported time to get out of bed) [85, 86].

In summary, physiologic sleep inertia is a transient period of decreased cognitive performance during the transition from sleep to wakefulness that is amplified by sleep deprivation, SWS, and awakenings during the biological night. In healthy individuals, its main significance may be in occupational settings, where immediate decision-making is sometimes necessary following abrupt awakenings, or when guidance regarding strategic nap timing and duration is needed. In patients with central disorders of hypersomnolence, especially idiopathic hypersomnia and perhaps narcolepsy type 2, a period resembling exaggerated sleep inertia is common and frequently problematic. In patients with mood disorders, difficulty with awakening is common, but might reflect mood dysregulation rather than an exaggerated form of sleep inertia.

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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

SWS slow wave sleep

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Practice points

1. Shift-workers and those requiring immediate vigilance upon awakening may be particularly affected by sleep inertia, and nap schedules should be chosen carefully.
2. Sleep drunkenness frequently occurs in patients with idiopathic hypersomnia and may be more problematic than sleepiness itself, but is not fully specific for this diagnosis.
3. Difficulty with morning awakening is a common symptom of mood disorders, but may represent a different phenomenon than sleep inertia or sleep drunkenness.
4. Sleep drunkenness treatment in hypersomnolence disorders is based only on small case series, and optimal treatment remains unknown. Even less is known about pharmacotherapy for difficulty with awakening in patients with mood disorders, in whom some of the medications used in hypersomnolent patients may be contraindicated.

Research agenda

1. What are the mechanisms of sleep inertia? If, as suggested by PET imaging, resumption of normal waking cognition on awakening requires reorganization of cognitive networks, can other functional neuroimaging and/or neurophysiologic studies better delineate these necessary network changes?
2. During night shifts and extended operations, what is the optimal nap schedule to balance the conflicting issues of sleep inertia, delayed cognitive benefits from napping, and mitigation of chronic, partial sleep deprivation?
3. How can we best measure sleep drunkenness, subjectively and objectively, for differential diagnosis and response to treatment?
4. Is sleep drunkenness in hypersomnolence disorders an exaggeration of physiologic sleep inertia or does it reflect a different pathophysiology? Are sleep drunkenness in hypersomnolence disorders and difficulty awakening in mood disorders related or distinct?
5. How should sleep drunkenness and difficulty awakening be treated in hypersomnolence and mood disorders?

Table 1

Forced desynchrony studies of sleep inertia

Study	n	Mean age	Design	Factor	Subj	Obj	Time before testing	Findings
Burke TA et al 2015 [40]	6	26.8	28 hour sleep/wake cycle, tested upon awakening and every 2 hours	Awakening time	KSS	PVT, ADD, SDST, SVA, VST, Stroop	immediate	Cognition differentially affected by circadian, homeostatic, and SI effects. SI effect largest on SVA
Scheer FA et al 2008 [41]	12	24	28 hour sleep/wake cycles, with three awakenings during each sleep	Awakening time, preceding sleep amount		ADD	1–2 min	SI worsened performance 17%, most severe during biological night. No effect of stage at awakening; modest effect of % sleep stage
Silva EJ and Duffy JF 2008 [42]	10	64.9	20 hour sleep/wake cycles; data excluded if >10 min wake during last hour	Awakening time		SDST	1–9 min	Performance worst when waking during biological night. Better performance when waking from REM than N1 or N2

Abbreviations: ADD=addition, KSS=Karolinska sleepiness scale, min=minutes, n=number analyzed, N1=state N1 sleep, N2=stage N2 sleep, obj=objective measures, PVT=psychomotor vigilance task, SDST=symbol digit substitution task, SI=sleep inertia, subj=subjective measures, SVA=selective visual attention, VST=visual search task

Table 2
 Studies evaluating the effect of stage at awakening, SWS amount, or sleep deprivation

Study	N	Mean age	Design	Factor	Subj	Obj	Time before testing	Findings
<i>Casagrande M and Bertini M 2008</i> [87]	16	ages 20–27	Woken from N2 & REM early and late in night	Stage and time of waking		FTT	Right away	No difference in FTT between REM and N2 awakenings.
<i>Daya VG and Bentley AJ 2010</i> [88]	14	ages 19–25; men	heat stimulus applied after 2–3 min of N2, N3, and REM, then subject woken	Awakening stage	VAS pain		Right away	pain lower after REM awakening than wake and versus NREM awakenings for some temperatures
<i>Ferrara M et al 2000</i> [14]	10	ages 20–30; men	awoken from N2 after 2, 5, and 7.5 hours of measured sleep on 4 consecutive nights: BL, SWS deprivation x 2 nights, recovery sleep	SWS deprivation versus recovery sleep		DST	< 30 s	For morning awakening: Speed less affected by SI after SWS deprivation. Accuracy more affected after recovery sleep.
<i>Ferrara M et al 2000</i> [15]	9	23.3; men	baseline and recovery sleep (after 40 hours sleep deprivation)	baseline versus recovery sleep	VAS	saccade & smooth pursuit, LCT	30 s	Recovery sleep slowed saccades, worsened LCT & subjective sleepiness
<i>Groeger JA et al 2011</i> [47]	32	22.5	Night TIB 6 hours then randomized to two days of naps (<= 90 min) or rest, once in morning and once in afternoon	nap versus rest	mental work-load	n-back	5 min	Accuracy on 2- & 3-back lower for afternoon than morning nap (but not rest) group, worst on the 3-back. No effect of SWS %/amount on performance.
<i>Hilditch CJ et al 2015</i> [16]	21	24.1	randomized to 0 or 10 min nap ending at 0710	nap versus no nap	Fatigue	3 min PVT, drive simulator	2 min	PVT worse immediately after nap. No effect on fatigue or driving.
<i>Hilditch CJ et al 2015</i> [45]	31	24.3	randomized to 0, 10, or 30 min nap, ending at 0400	nap length & nap versus no nap	KSS, fatigue, self-rated performance	3 min PVT, SDST	2 min	30 min nap worsened PVT & SDST. 10 min nap improved fatigue. More SWS correlated to worse performance in 30 min nap.
<i>Hofer-Tinguely G et al 2005</i> [48]	50	23	assigned to 2 hour afternoon sleep, active wake (movie watching), or quiet rest	Nap, rest or active wake	SSS	ADD, auditory RT	5 min	Addition speed and auditory RT worse with sleep. Some “rest inertia” (worsening in quiet rest group) on ADD. No effect on SSS. Performance not correlated with SWS.
<i>Matchock RL and Mordkoff JT 2014</i> [44]	14	22.6	Counter-balanced to 3 hour sleep (0300–0600) vs 6 hour sleep (MN-0600)	Sleep length		ANT	right away	RTs slowed by both sleep lengths but other ANT measures unaffected; SWS duration associated with RT slowing.

Study	N	Mean age	Design	Factor	Subj	Obj	Time before testing	Findings
<i>Micciofi L et al 2008</i> [89]	15	ages 20–30	crossover 3 conditions: full night sleep, partial or total sleep restriction	Sleep length		RT	< 2 min	RT worse after partial sleep restriction than full night sleep but lapses unaffected by partial sleep restriction
<i>Signal TL et al 2012</i> [46]	24	24.2; all men	Counter-balanced to no nap, 20, 40, or 60 min nap after 20 hrs wake (nap end at 0200) or 30 hours wake (nap end at 1200)	nap duration; sleep deprivation	KSS	n-back	right away	No SI effects on KSS. Impaired speed after most naps. Impaired accuracy after 40 and 60 min naps. No effect of stage at waking or SWS duration.

Abbreviations: ADD=addition task, ANT=attention network task, BL=baseline, DST=descending substitution task, FTT=finger tapping test, KSS=Karolinska sleepiness scale, LCT=letter cancellation task, min=minutes, MN=midnight, n=number analyzed, NREM=non-REM sleep, N1=stage N1 sleep, N2=stage N2 sleep, obj=objective measures, PVT=psychomotor vigilance task, RT=reaction time, SDST=symbol digit substitution task, SI=sleep inertia, subj=sleep inertia, subj=subjective measures, SSS=Stanford sleepiness scale, SWS=slow wave sleep, TIB=time in bed, VAS=visual analog scale

Sleep inertia studies using measured nap sleep time

Table 3

Study	n	Mean age	Design	Factor	Subj	Obj	Time before testing	Findings
<i>Brooks A and Lack L 2006</i> [49]	24	22.5	Nocturnal TIB of 5 hours then 3 pm afternoon nap. Crossover design with naps of 0, 5, 10, 20, 30 min sleep	Sleep duration	SSS	SDST, LCT, visual RT	5 minutes	Improvement in SSS, LCT, and RT lapses after 10 min nap vs no nap; worsening in SSS, SDST, LCT after 30 min nap vs later performance
<i>Tietzel AJ and Lack LC 2001</i> [50]	12	21.8	Nocturnal TIB 5 hours then counterbalanced to 3 afternoon sessions: 0, 10, 30 min sleep	Sleep duration	SSS, POMS	SDST, LCT	5 minutes	SSS worsened only in the no-nap group; vigor and SDS worsened after 30 min nap and rest; LCT worsened after 30 min nap
<i>Tietzel AJ and Lack LC 2002</i> [51]	16	22.5	Nocturnal TIB of 5 hours then counterbalanced to 4 afternoon sessions: 0, 30 s, 90 s, 10 min sleep	Sleep duration	SSS, POMS	SDST, LCT	5 minutes	No effect on SSS, POMS (fatigue/vigor), SDST, or LCT

Abbreviations: LCT=letter cancellation task, n=number analyzed, obj=objective measures, POMS=profile of mood states, RT=reaction time, SDST=symbol digit substitution task, SSS=Stanford sleepiness scale, subj=subjective measures, TIB=time in bed, vs=versus

Field studies of sleep inertia

Table 4

Study	N	Mean age	Design	Factor	Subj	Obj	Time before testing	Findings
<i>Horne J and Moseley R 2011</i> [1]	20	21; men	randomized to awakening at 0300 or 0730	Time of waking, sleep length, delay before testing		enemy attack test	5 min in the 0300 group; 60 min for 0730	8/10 of the 0300 group failed versus 3/10 at 0730
<i>Howard ME et al 2010</i> [90]	8	31.0	Randomized, crossover test of 30 min nap at 1945 or 0400 versus no nap during night shift	0400 nap versus no nap (SI not tested for 1945 nap)	KSS	PVT	Right away	No effect of napping on PVT median RT. Authors report study under-powered.
<i>Purnell MT et al 2002</i> [52]	24	34.8; men	Counter-balanced crossover design of 20 min nap or break (0100 to 0300)	nap versus no nap	VAS fatigue	visual RT, VVT	30 min	No reported sleep in 1/2 of cases. Fatigue & VVT worse with nap on 1 of 2 nights. Visual RT unaffected.
<i>Signal TL et al 2009</i> [91]	28	35	4 conditions: 40 min nap or break at 0030 or 0230	time of nap; nap versus no nap		PVT	average 53–57 min	No evidence for SI by the time of testing.
<i>Smith SS et al 2007</i> [92]	9	45.7	Randomized, crossover test of 30 min nap break versus continued work (0200 to 0300)	nap versus no nap	VAS sleepy, task load index	PVT	10–30 min	Napping improved sleepiness at 0300 and had no effect on PVT.
<i>Smith-Coggins et al 2006</i> [2]	49	30	Randomized to 40 min nap or continued work at 0300	nap versus no nap	KSS	PVT, PM, IV place	up to 20 minutes	No effect on PVT, IV place, or KSS. PM worse after nap.

Abbreviations: IV place=CathSim intravenous line insertion, KSS=Karolinska sleepiness scale, min=minutes, n=number analyzed, obj=objective measures, SI=sleep inertia, subj=subjective measures, RT=reaction time, PVT=psychomotor vigilance task, RT=reaction time, VAS=visual analog scale, VVT=visual vigilance task

Table 5

Additional laboratory studies of sleep inertia

Study	N	Age	Design	Factor	Subj	Obj	Time before testing	Findings
<i>Asaka S et al 2010</i> [31]	9	24.0	Counter-balanced to one hour nap or rest (14:00–15:00)	nap versus rest	rating of performance	spatial Stroop	90 s	Objective measures not different, but nappers rated performance better.
<i>Kubo T et al 2010</i> [93]	12	21.6	Counter-balanced to no nap versus four nap types (60 or 120 min, MN or 0400 am)	nap timing and length	VAS sleepy	VVT	Right away	Late 60 min nap worsened RT and lapses on VVT versus no-nap. No effect of any nap on VAS.
<i>Lovato N et al 2009</i> [94]	22	22.5	Counter-balanced to 0 vs 30 min nap at 02:30; afternoon nap for all	nap versus no nap	SSS, KSS, POMS, VAS sleepiness	SDST, LCT, PVT	10 min	SSS & KSS worse after nap; no objective differences
<i>Matchock RL and Mordkoff JT 2007</i> [95]	15	21.6	Counter-balanced to wake times: 2:40 (after 1 hour TIB), 03:00 (4 hrs TIB), 06:00 (7 hours TIB)	Wake time, prior TIB	VAS arousal	Flanker	< 3 min	Energy & tiredness worse after all awakenings. Flanker task RT's worse after waking at 0300 and 0600
<i>Takeyama H et al 2004</i> [96]	6	ages 19–22; men	Counter-balanced to no-nap, 60 or 120 min at MN, 60 or 120 min at 0400	Nap length & timing	fatigue	logical reason, CRT, VVT	not stated	No sleep inertia after any nap except worsened VVT RT after late 60 min nap.
<i>Wakasa M et al 2016</i> [97]	14	64.5	Nocturnal sleep of 5 hours		SSS	TUG, FRT, balance	after waking	TUG and SSS worse upon awakening
<i>Wertz AT et al 2006</i> [98]	9	29.1	Testing upon am awakening (after 8 hrs sleep) then testing for 26 hours			ADD	mean 73 s	Testing upon awakening worse than during subsequent sleep deprivation.

Abbreviations: CRT=choice reaction test, FRT=functional reach test, KSS=Karolinska sleepiness scale, LCT=letter cancellation task, min=minutes, MN=midnight, n=number analyzed, obj=objective measures, POMS=profile of mood states, PVT=psychomotor vigilance task, RT=reaction time, SDST=symbol digit substitution task, subj=subjective measures, SSS=Stanford sleepiness scale, TIB=time in bed, TUG=timed up and go, VAS=visual analog scale, VVT=visual vigilance task

Table 6

Frequency of sleep drunkenness in patients with hypersomnolence disorders

Publication	Definition	IH	N-C	N+C	N unspecified
<i>Anderson KN et al 2007</i> [99]	difficulty with awakening, confusional behavior \geq 30 minutes	42/77 (55%)		2/63 (3%)	
<i>Bassetti C and Aldrich MS 1997</i> [100]	confusion on awakening with nonsensical/slurred speech, ataxia, or amnesia	9/42 (21%)			
<i>Bassetti C et al 2003</i> [101]	> 30 min before full wakefulness, with dysarthria or imbalance	3/5 (60%)	3/4 (75%)	1/4 (25%)	
<i>Martinez- Rodriguez JE et al 2007</i> [102]		1/8 (12.5%)	4/11 (36%)	7/52 (22%)	
<i>Roth B 1980</i> [64]		92/167 (55.1%)			57/360 (15.8%); 37.7% in monosymptomatic narcolepsy and 11.3% in polysymptomatic narcolepsy
<i>Vernet C and Arnulf I 2009</i> [103]		27/75 (36.5%)			
Total		174/374 (47%)	7/15 (47%)	10/99 (10%)	57/360 (15.8%)

Abbreviations: IH=idiopathic hypersomnia, N-C=narcolepsy without cataplexy, N+C=narcolepsy with cataplexy, N=narcolepsy