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The neurophysiological basis of excessive daytime sleepiness: suggestions of an altered state of consciousness

P. K. Hitchcott[1] · D. Menicucci[1] · S. Frumento[1] · A. Zaccaro[1] · A. Gemignani[1,2,3]

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Abstract

Excessive daytime sleepiness (EDS) is characterized by difficulty staying awake during daytime, though additional features may be present. EDS is a significant problem for clinical and non-clinical populations, being associated with a range of negative outcomes that also represent a burden for society. Extreme EDS is associated with sleep disorders, most notably the central hypersomnias such as narcolepsy, Kleine-Levin syndrome, and idiopathic hypersomnia (IH). Although investigation of these conditions indicates that EDS results from diminished sleep quality, the underlying cause for this impairment remains uncertain. One possibility could be that previous research has been too narrow in scope with insufficient attention paid to non-sleep-related aspects. Here, we offer a broader perspective in which findings concerning the impact of EDS on cortical functioning are interpreted in relation to current understanding about the neural basis of consciousness. Alterations in the spatial distribution of cortical activity, in particular reduced connectivity of frontal cortex, suggest that EDS is associated with an altered state of consciousness.

Keywords Sleep · Hypersomnia · Excessive daytime sleepiness · Altered state of consciousness

Introduction

EDS in the general population

Excessive daytime sleepiness (EDS) is characterized by persistent difficulty staying awake during the daytime and can be associated with additional features ("sleep drunkenness") though these are more common in clinical populations. Severity typically varies over time, though a significant minority experience persistent, clinically significant EDS lasting years [1, 2]. EDS is a relatively common complaint which negatively impacts both individuals and society in general. Studies have shown that EDS is associated with a wide range of negative effects related to all aspects of health (somatic, neurological and psychological), including disability, morbidity, and mortality. Beyond its health consequences, EDS is implicated in poor academic and workplace performance and is a major determinant of road traffic accidents [3–8].

Reported prevalence rates for EDS vary widely, ranging from < 1% to > 30% [see 9]. This variability relates to several factors, including how EDS is defined and operationalized. One significant issue is the need to reliably contrast between EDS and fatigue. Though both states are associated with subjective feelings of physical and/or mental tiredness, a core distinction is that EDS is related to increased sleep propensity whereas fatigue is not. Thus, fatigue resolves with rest, without a need for sleep whereas EDS does not [10, 11]. Epidemiological surveys assessing EDS based on less stringent criteria (the use of 1 or 2 basic self-report items is not uncommon) necessarily struggle to discriminate EDS from fatigue. Moreover, although objective assessment of sleep propensity is possible (the Multiple Sleep Latency Test) [12], this methodology is impracticable for epidemiological survey since it requires attendance at a sleep laboratory. Consequently, standardized questionnaires, the Epworth Sleepiness Scale (ESS) [13] being the most popular, represent a suitable compromise. The ESS attempts to capture sleep propensity by specifically assessing participants' tendency to

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✉ A. Gemignani
angelo.gemignani@unipi.it

[1] Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy

[2] National Research Council, Institute of Clinical Physiology, Pisa, Italy

[3] Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

fall asleep in several common situations, and a cut-off score > 10 identifies clinically significant EDS [13]. Similar alternative instruments include the Stanford Sleepiness Scale [14] and the Karolinska Sleepiness Scale [15].

Although most estimates of EDS prevalence fall within the range of 5–15% [9], not all surveys have been performed in samples representative of the general population. This is significant since demographic variables, for example age [16], can substantially affect prevalence estimates. Reports of sizeable same-study differences in EDS rates from different countries (e.g., 25% in the UK vs 3.5% in Spain) [17] and of a ~ 30% increase in prevalence between 2002 and 2012 [18] further complicate this picture. Studies with more rigorous methodologies conducted in larger, representative samples may be more accurate, and these would seem to suggest that EDS prevalence is higher than sometimes stated. For example, in a study of almost 16,000 adults, aged 18–102, Ohayon, Dauvilliers, and Reynolds [2] estimated the overall prevalence of EDS at 27.8%. This value is close to that obtained by Jaussant et al. [19] who reported an overall EDS prevalence of 33% in a study of > 2000 individuals aged 18–89 years using the ESS. While not all similar previous research has yielded such high estimates, rates of ~ 20% are not uncommon [20, 21].

EDS has been reported to be significantly associated with a diverse array of factors. These include sociodemographic (e.g., age, gender, educational level), lifestyle (e.g., caffeine and nicotine use, physical exercise), health (e.g., sleep disorders, neurological and somatic diseases), and psychological (e.g., anxiety and depression symptoms) variables [22]. One significant gap in the literature relates to which of these causes, or affect the progression of, EDS since little longitudinal research has been conducted. However, one recent prospective investigation [19] noted that while the severity of EDS fluctuates in the majority of individuals, it exists in a more severe or persistent form in some. Whereas fluctuations in EDS severity were related to lifestyle and psychological influences, chronic ill health was the main cause of persistent EDS. Replication and extension of these findings would be especially valuable for consolidating understanding about both the nature and causes of EDS within the general population.

EDS and primary hypersomnias

Although there is an obvious relationship between EDS and chronic sleep loss (or poor sleep quality), it occurs with highest frequency (and is a defining feature) of several chronic hypersomnias, including narcolepsy (with and without cataplexy), idiopathic hypersomnia (IH), and Kleine-Levin syndrome. While EDS is a shared symptom, a small number of distinctive clinical features distinguish these disorders. Narcolepsy with cataplexy is characterized by rapid entries into rapid-eye-movement sleep (SOREMPs), the presence of cataplexy (episodes of muscle atony triggered by emotional stimulation), and a deficit of hypocretin-1 in the cerebrospinal fluid. Kleine-Levin syndrome is extremely rare (~ 200 cases have been reported) and characterized by recurrent hypersomnia accompanied by hyperphagia and hypersexuality [1, 23, 24]. The exact prevalence of IH is unclear because of changeable diagnostic criteria but affects ~ 5% of patients with clinically significant EDS. A rough estimate of $50/10^6$ has been suggested based on the 5–10 times lower frequency of IH relative to narcolepsy [1], although some studies have suggested much higher rates [25–27]. There is, moreover, uncertainty about whether IH is a unitary condition. Until quite recently, two forms of IH were distinguished according to whether individuals display prolonged (> 10 h) or normal (> 6 h and < 10 h) nocturnal sleep [28, 29].

While EDS is a shared feature of all hypersomnias, IH is the quintessential EDS disorder. This is evident from the most recent diagnostic classification criteria [23] and from detailed characterizations of IH [e.g., 30]. The latter indicate that relative to healthy controls, individuals with IH are more likely to report unrefreshing sleep despite normal or unusually long (> 10 h) sleep and problematic transition from sleep to wakefulness. Difficulties waking without return to sleep are common and in ~ 30–40% of individual symptoms of sleep drunkenness, such as motor discoordination, confusion, and automatic behavior may be present. Patients also report reduced alertness and ability to focus/concentrate throughout the day with an increased need to lay down/nap, though as with nocturnal sleep, this tends not to be refreshing. Few non-EDS features are evident though psychological (anxiety and depression) and somatic (e.g., temperature dysregulation, digestion problems) symptoms are more common. In addition, the diagnosis of IH requires not only that there should be almost daily EDS lasting ≥ 3 months but also the exclusion of any other of the known causes of EDS [23]. This includes hypersomnia due to mental disorder. Although differential diagnosis may be problematic, based on differential changes in polysomnographic parameters, it has been suggested that whereas psychiatric hypersomnia is a disorder of hyperarousal, primary hypersomnia is a disorder of hypoarousal [31]. Overall, as IH is near-exclusively a disorder of EDS, it may be an ideal population in which to probe the neurophysiological basis of EDS. Previous authors have drawn the same conclusion [32].

To date, no biological mechanism selective for EDS has been identified. Despite considerable excitement about human and animal evidence indicating hypocretin deficiency as a key substrate for narcolepsy with cataplexy [33, 34], CSF hypocretin levels are normal in several other sleep disorders including IH [35–37]. Moreover, the exact role of hypocretin dysfunction in the pathophysiology of narcolepsy is unclear [see 38] with some indications that it is related to non-EDS features of the disorder [37, 39]. Although isolated reports [40] have identified alternative potential causes of EDS, definitive evidence remains absent. Given the highly complex

chemical neuroanatomy of sleep/wake control mechanisms [41], a pragmatic starting point for investigating the neurophysiological basis of EDS is more likely to be in terms of macro brain activity related to the known functions of sleep.

The function(s) of sleep

Sleep is defined as a rapidly reversible state characterized by reductions in responsiveness to sensory stimuli, motor activity, and metabolism. The conservation of sleep across species [42] and the profound consequences of prolonged deprivation [43, 44] are widely interpreted to indicate that it subserves one or more vital functions. Although no single unifying explanation is available, several theories have emerged that provide partially overlapping explanations related to subsets of the available evidence. This fragmentation reflects, in part, the fact that two distinctive sleep states exist in humans: rapid eye movement (REM) and non-REM (NREM). These states are differentiated based on electroencephalographic (EEG) and electromyographic (EMG) parameters and, in addition, possess distinct underlying neurophysiological control mechanisms. In NREM, most bodily functions slow and there is diminished responsivity to sensory stimuli and reduced muscle tone though thermoregulation remains. Breathing is slow and regular, accompanied by reduced heart rate and heat production with slight temperature reduction. The NREM EEG is characterized by high voltage, low frequency (delta and theta) activity, and the presence of spindles and k-complexes (isolated high voltage waves occurring spontaneously or after sensory stimulation). One hallmark of slow wave sleep (SWS) is the presence of slow (< 1 Hz) oscillations [45, 46] that reflects widespread, synchronicity of neuronal up (depolarized) and down (hyperpolarized) states thought to derive in vivo from thalamo-cortical interplay [47]. During REM sleep, there is deep muscular relaxation and sensory thresholds are increased; sudden eye movements, muscular twitches, and dreaming occur. Homeostatic regulation declines as indicated by increased heart rate variability, irregular respiration, and poikilothermy. The REM EEG appears similar to that during waking with low-voltage mixed frequencies [41, 48]. The marked differences between REM and NREM sleep suggest that they may promote separate functions [49].

Most, but not all, theories of sleep function assume that it has adaptive physiological significance. An alternative view is that sleep is primarily an adaptive behavioral state that promotes dormancy (reducing energy expenditure) when waking activity is not beneficial [50]. The more common concept, that sleep performs an essential physiological function, centers on two main themes: nervous system recuperation and synaptic plasticity. NREM sleep is most closely associated with theories of physiological recuperation as brain energy metabolism reaches a minimum during its deepest stages, i.e., during SWS. In contrast, brain metabolism during REM sleep is similar to that during wakefulness [51, 52]. It has been suggested both that sleep restores key macromolecules in preparation for wakefulness [53] and that it aids the removal of toxic by-products of increased waking activity [54, 55]. The former idea is supported by evidence that rates of protein synthesis are highest during SWS [56]. Findings consistent with the latter theme include reports that sleep deprivation causes neuronal degradation and that this is more marked in brain regions with high metabolic activity [57, 58]. One crucial development in this area is the demonstration of a ~ 60% increase in cortical interstitial space during sleep that facilitates clearance of potentially harmful degradation products accumulated during wakefulness. This effect is believed to be mediated by noradrenergic effects on astroglial cell morphology [55, 59]. Such findings add to growing evidence implicating neuronal-glial interactions as an important source of sleep/wake control [60, 61].

A second mainstream theory is that sleep is related to memory consolidation. During consolidation, memory engrams that are initially labile traces susceptible to interference are progressively stabilized ("synaptic consolidation") and integrated into existing information networks ("systems consolidation") by serial neurobiological processes operating over widely varying time spans [62, 63]. The fundamental basis of synaptic consolidation is the alteration of synaptic strengths within the neural networks within which the memory trace is held. The main ways in which learning changes synaptic strengths are via long-term potentiation (LTP) and long-term depression (LTD). Key cellular processes include the activation of glutamatergic synapses and, via their activation, the triggering of various signal transduction cascades, protein synthesis, and pre- and post-synaptic morphological changes [64]. Whereas synaptic consolidation occurs within a timeframe of seconds-hours, systems consolidation requires days-months and its underlying substrates are less well understood. However, sleep is believed to play a key role [65].

It has long been recognized that when sleep follows a learning event, subsequent recall is improved [66]. Explanations for this effect have evolved. It was at first suggested that sleep protected recently encoded memories from retroactive interference; that during sleep, new learning was prevented and thereby ongoing consolidation would continue undisrupted. Thus, memory facilitation was seen as a corollary of sleep unrelated to any direct impact on memory consolidation processes per se. This view has been superseded in light of evidence suggesting that sleep actively promotes consolidation. One significant line of research supporting this hypothesis has demonstrated that high-speed, distributed replay of waking experiences takes place during SWS [67]. This and related evidence have led to proposals that sleep facilitates various facets of system consolidation including the integration of new and existing knowledge [68] and insight [69]. Although the neurophysiological bases of such effects are not yet fully

clear, one key finding is that boosting slow oscillations during sleep by means of transcranial electrical stimulation potentiates memory [70]. Additional evidence suggests that sleep may also play an active role in synaptic consolidation [71]. In this case, REM sleep and specific associated features (e.g., theta activity), rather than NREM sleep, is implicated.

The neurophysiological basis of EDS

While there may be no consensus about the function of sleep, the primary contemporary hypotheses described above nevertheless suggest useful starting points from which to explore the neurophysiological basis of EDS. Most obviously, EDS can be considered as a dysregulation of normal sleep regulatory processes and these can be explored in relation to main functions of sleep. The following section will commence in this manner. However, in an attempt to diversify thinking on this topic, we will explore the possibility that EDS might also be a state of altered consciousness. The foundation for this hypothesis relates to tantalizing hints that neurophysiological dysfunction in EDS occurs within similar neuronal circuitry demonstrated to be involved in consciousness. Our aim is to conduct an open inquiry of this possibility and various gaps in the literature will be over-looked in favor of describing some intriguing, albeit speculative, connections.

Several studies have investigated the possibility that EDS is caused by dysfunction of normal regulatory sleep processes. Three basic processes have been hypothesized to underlie sleep regulation, one of which (process S) is a homeostatic mechanism that increases in strength as a function of time awake and dissipates during sleep. Sforza et al. [72] tested two hypotheses linking EDS to either over- or under-activity of process S. The former idea relates EDS to an excessive build-up of process S during the daytime and/or insufficient dissipation during sleep. The latter postulate considers EDS a product of deficient recuperative sleep caused by hypofunctioning process S. These contrary hypotheses were tested by assessing slow wave activity (SWA; 0.75–4.5 Hz) during the first two sleep cycles as an index of the level of process S activity. The results showed reduced SWA in IH patients compared to healthy controls implying EDS results from a deficit in recuperative sleep. This conclusion is reinforced by the observation of altered sleep microstructure, including increased sleep fragmentation and decreased delta power in IH [29, 32]. Thus, increased sleep duration and EDS can be seen as the consequences of impaired sleep quality. Findings about changes in sleep structure are less clear. Most studies have not found polysomnographic differences in either REM or NREM sleep percentages [28, 32, 72]. In contrast, one previous report [29] observed decreased stage 3–4 sleep percentage and increased REM sleep percentage in IH. Despite this discordance, these studies are consistent in indicating that there are no changes in NREM (or SWS), for example increased NREM duration, which might compensate for impaired sleep quality.

A reasonable conjecture is that the deficit in NREM sleep quality in IH is associated with the high frequency of cognitive complaints in this population. However, it is well established that subjective cognitive complaints are an unreliable index of objective cognitive impairment [73, 74]. One pertinent issue is that subjective complaints are amplified by depressive symptomatology, which is increased in IH [28]. Too few studies profiling cognitive impairments using objective measures have been conducted to identify which specific cognitive processes are actually impaired. Occasional reports of attentional deficits exist [75, 76], and these are consistent both with the problems self-reported by IH patients [30] and broader evidence concerning objective deficits in narcoleptic patients [77]. However, too little data about objective cognitive impairment in hypersomnic patients is available to draw any firm conclusions. Overall, the limited available data suggest impairments in frontal cortical substrates of executive function might be present but whether the profile of cognitive impairment in IH mirrors the selective deficit pattern observed in narcoleptic patients [77] or following sleep deprivation in healthy subjects [78] is unknown. Despite this uncertainty, the existence of working memory/executive impairment would be consistent with additional evidence concerning structural and functional alterations of frontal cortex in IH.

Several studies have examined structural and functional brain alterations in hypersomnic patients and healthy sleep-deprived subjects. Crucially, alterations extraneous to the hypothalamus, both in cortical and subcortical areas, potentially indicative of abnormalities within the default-mode network, have been documented [79]. Whether similar changes are present in the brains of IH patients is less clear as comparatively few studies have been performed. However, growing evidence points to a role of the frontal cortex in EDS. Reduced gray matter volume within the ventromedial prefrontal (vmPFC) and orbital (OFC) regions of frontal cortex is both common to a number of sleep disorders and associated with increased daytime sleepiness (higher ESS scores) in healthy individuals [80]. Measurements of regional glucose metabolism and blood flow are also consistent with a relationship between the prefrontal cortex and EDS. Relevant observations include reports of reduced activity within the vmPFC following overnight sleep deprivation [81] and of a negative correlation between ESS scores and cerebral blood flow in the medial prefrontal cortex [82]. Of particular interest are indications that the pattern of daytime regional cerebral blood flow (rCBF) in IH patients closely resembles that seen in sleeping healthy subjects [83]. As others [82] have noted, this suggests that during wakefulness, IH patients experience an NREM-like metabolism pattern. It seems reasonable to associate this observation with the evidence (described above) on reduced sleep quality (decreased delta power) and the normal or

decreased percentage of NREM sleep in IH. Moreover, these data, along with the specific correlation between delta power and rCBF within the vmPFC [83], reinforces the view that vmPFC disturbances are a central feature of EDS. These reflect a key feature of broader deficits affecting default-mode network structures are related to EDS, a common feature of central hypersomnias.

Can EDS be considered an altered state of consciousness?

It has been argued that consciousness has two main components: wakefulness and awareness, the levels of which are positively correlated in most circumstances [84]. Altered states of consciousness are, therefore, normally reflected in continuous variation along the regression between these components. Though normally correlated, wakefulness and awareness can be dissociated at multiple levels, including neuroanatomically. Wakefulness is controlled principally by subcortical arousal systems including monoamine and cholinergic nuclei located in the region of the upper brainstem [85] and chemically diverse mechanisms originating in the hypothalamus [86]. In contrast, brain areas involved in awareness include several cortical regions including the insula, medial prefrontal, and cingulate cortices, though several non-cortical regions are also critically involved [87]. This broader anatomical distribution is most likely related to the existence of multiple networks that subserve distinct aspects of awareness.

During sleep, there is a substantial decrease in connectivity across cortical regions with frequent breakdowns of temporal integration linked to the occurrence of spontaneous slow oscillations. This phenomenon is thought to explain why sleep is associated with a loss of consciousness despite continued, though decreased, neuronal activity [88, 89]. Crucially, various studies indicate that sleep deprivation also disturbs functional connectivity. Moreover, this occurs within areas or networks implicated in consciousness. Findings derive from investigations employing various techniques including functional magnetic resonance imaging (fMRI) [90, 91] and high-density EEG [92]. Collectively, the results of such studies consistently indicate that sleep deprivation results in decreased connectivity within different brain networks including the default-mode network (DMN). In addition, the study by Verweij et al. [92] detected alterations in both alpha and theta EEG bands indicating reduced local and global efficacy within the frontal aspects of the DMN. This observation is significant given the critical role of frontal cortex in various functions including cognition [93], emotion [94], and as a site associated with the neural representation of self [95]. Thus, sleep deprivation-related changes in cortical connectivity are unlikely to reflect altered wakefulness solely. Moreover, such functions are considered central for self-conscious awareness which is lost or at least greatly diminished by deactivation of the prefrontal cortex during sleep [96]. Indeed, substantial sleep-related changes in blood flow occur within the prefrontal cortex although selective reactivations within posterior and ventromedial prefrontal areas are present during REM sleep. The continued deactivation of dorsolateral PFC has been suggested to underlie illogical (non-executive) thinking during dreaming [97] whereas prefrontal reactivation during REM sleep is linked with consolidation of emotional memories [98].

Overall, the prefrontal cortex appears to be highly sensitive to sleep deprivation and subjective sleepiness, in healthy controls, is associated with altered EEG patterns involving the PFC. In particular, sleepiness correlates both with increased theta and decreased alpha activity and the former correlates with cognitive task performance [99, 100]. Increased theta activity following sleep deprivation has attracted much attention because of evidence that it could be a marker for "local sleep," i.e., transient neuronal off periods [101]. These events have been linked with performance errors in humans, the nature of which depend on the location of the off period within the cortex [102]. Although such data identifies increased frontal theta activity as a correlate of EDS in healthy individuals, similar studies do not appear to have been conducted in IH subjects. Investigations of resting-state cerebral metabolism are unhelpful since this is reported both to be increased [103] and decreased [82] in IH though dissociated alterations in distinct cortical networks (e.g., salience vs default-mode networks) might explain this disparity. Nonetheless, it is worth noting that when cortical theta activity is modified in healthy non-sleep-deprived subjects, either by mechanical stimulation of the olfactory epithelium [104] or slow nasal breathing [105], shifts in consciousness, more specifically, shifts in awareness have been observed.

Summary and conclusions

Although there are many unresolved issues, a reasonable assumption is that EDS, similar to drowsiness, is not only a state of reduced wakefulness but also of reduced awareness. This tentative conclusion derives from diverse and incomplete lines of evidence, and future research may yet contradict this idea. However, studies conducted both in healthy sleep-deprived and hypersomnic subjects are concordant with respect to an impact of sleepiness on frontal cortical activity. As this region is implicated in various aspects of consciousness, one possibility is that alterations in consciousness may accompany pathological or non-pathological sleepiness. While no definitive answer is available, evidence consistent with this view is emerging. Future research is needed on several fronts, some of which have been highlighted in this article. Novel approaches, for example, exploring altered consciousness following natural (slow-breathing) or artificial (mechanical stimulation of the olfactory epithelium) manipulations of cortical activity and connectivity can supplement traditional paradigms. These

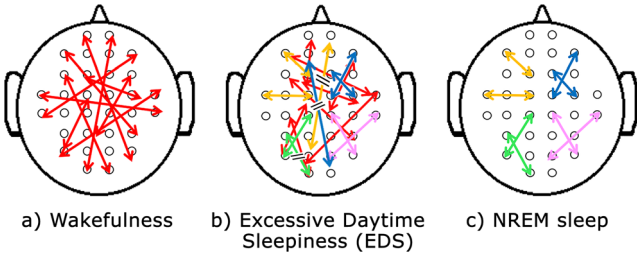

Fig. 1 Schematic representation of the hypothetical functional connectivity in EDS (**b**), compared to wakefulness (**a**) and NREM sleep (**c**): in this model, the EDS pattern shares features of both wakefulness and sleep but displays augmented segregation. Such a model suggests an intermediate state of consciousness is present in EDS

may have important advantages including avoidance of the confounding impact of stress that is inevitably associated with sleep deprivation and sleep disorders. Methodological diversification may also aid conceptual development in this field. There is growing appreciation that core psychological processes are modulated by changes in somatic physiology. Cortical processing and integration of these interoceptive signals is believed to be fundamental to higher level aspects of consciousness including self-awareness [106]. Respiratory feedback is of particular interest given that, unlike many other vital somatic functions (e.g., digestion), it can be brought under conscious control. Recent evidence shows that respiration can alter the balance between long-range vs local connectivity by modulating theta and delta oscillations, respectively [107]. Such effects not only invite comparison with the well-described changes in brain connectivity associated with altered states of wakefulness but lend further support to the hypothesis that EDS represents an intermediate state of consciousness (see Fig. 1).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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Comments

Excellent synthesis of the network neuroscience that is relevant to this challenging and poorly characterized disease. The authors do a nice job citing what evidence is available while constructing a hypothesis framework for discussion about underlying etiology.

Kent Werner

MD, USA