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The electroencephalographic features of the sleep onset process and their experimental manipulation with sleep deprivation and transcranial electrical stimulation protocols

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ABSTRACT

The sleep onset (SO) process is characterized by gradual electroencephalographic (EEG) changes. The interest for the possibility to manipulate the electrophysiological pattern of the wake-sleep transition is recently growing.This review aims to describe the EEG modifications of the SO process in healthy humans and the evidence about their experimental manipulation. We provide an overview of the electrophysiological changes during the wake-sleep transition, considering several methods to study the EEG signals. We then describe the impact of sleep deprivation (SD) on the electrophysiology of SO. Finally, we discuss the evidence about the possibility to modulate the local EEG activity through transcranial current stimulation protocols with the aim to promote, hinder, or manipulate the electrophysiological mechanisms of the wake-sleep transition. The reviewed findings highlight the local nature of the EEG processes during the SO and their intensification and speedup after SD. The evidence about the possibility to non-invasively affect the EEG pattern of the wake-sleep transition may have important implications for clinical conditions that would benefit from its prevention or promotion.

1. Introduction

Sleep and wakefulness have been classically considered global, mutually exclusive behavioural states. Research in the last decades challenged this paradigm, supporting the notion of sleep as a locally regulated phenomenon, and suggesting that neurobiological signs of sleep and wakefulness can co-exist in different cerebral regions (for review, see Ferrara and De Gennaro, 2011; Siclari and Tononi, 2017).

Sleep onset (SO) can be defined as a complex process of transition from wakefulness to sleep, characterized by progressive subjective, behavioural, cognitive, and physiological modifications (for review, see Ogilvie, 2001; Merica and Fortune, 2004; Gorgoni et al., 2019a). Its intrinsic nature of transitory process between different states of consciousness makes the SO period an ideal scenario to assess the co-existence of local hallmarks of sleep and wakefulness. Indeed, the study of the brain dynamics underlying the wake-sleep transition depicted an orchestrated pattern of progressive changes in local EEG activity and in the communication between functionally distinct cortical regions, in which several areas exhibit sleep hallmarks when others still show wake-like EEG features (Gorgoni et al., 2019a). Moreover, a dissociation of the EEG pattern at SO has also been observed between cortical and deep brain structures (Magnin et al., 2010; Sarasso et al., 2014a, 2014b).

The sleep EEG pattern can be locally modulated with experimental manipulations like sleep deprivation, cognitive and behavioural tasks, or stimulation techniques (for review, see Ferrara and De Gennaro, 2011; Siclari and Tononi, 2017; D'Ambrosio et al., 2019; Annarumma et al., 2018). Starting from this consolidated evidence, the research interest for the possibility to experimentally affect, induce or prevent the EEG pattern of the wake-sleep transition is progressively growing. In this context, one line of research concerns the assessment of the effect of sleep deprivation (SD) on the falling-asleep process. Indeed, since SD has a dramatic impact on the EEG activity of both wakefulness and recovery sleep (for review, see D'Ambrosio et al., 2019), several studies have been conducted with the aim to understand how the increased homeostatic sleep pressure modulates the topography, timing, and intensity of the spatiotemporal EEG pattern characterizing the wake-sleep transition. Another line of research concerns the possibility to use electrical stimulation to non-invasively boost or hinder the EEG features associated with the SO process, modulating the intensity of sleep pressure (for review, see Annarumma et al., 2018). Albeit studies on the application of electrical current to modulate sleep and

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arousal have a long history (for review, see Guleyupoglu et al., 2013), the development of novel transcranial current stimulation (tCS) techniques with neuromodulatory properties recently renewed the research interest in this field.

The aim of the present review is to systematize the current knowledge about the electrophysiological mechanisms of the falling asleep process in healthy human subjects and the empirical findings concerning the possibility to influence them. First, we will summarize the main techniques for the analysis of the EEG signals used to study the SO process. Then, we will provide an exhaustive description of the electrophysiological changes that characterize the transition from wakefulness to sleep, considering both studies on scalp and intracerebral recordings. Finally, we will focus on the experimental techniques used to modulate the wake-sleep transition. In particular, we will report the present knowledge about the effect of SD on the SO process, and we will describe the recent attempts to manipulate the EEG activity with tCS protocols during wakefulness with the aim to affect (i.e., promote, prevent, modulate) the electrophysiological processes that characterize SO.

2. The assessment of the electrophysiological pattern of the wake-sleep transition

The SO process is characterized by a complex pattern of local electrophysiological changes (Marzano et al., 2013). Such modifications concern different aspects of the EEG activity, assessed with different techniques:

a) EEG spectral analysis: it represents the most frequently used method for the quantitative analysis of the EEG. It consists of the transfer of the EEG data from a time-domain to a frequency-domain, obtaining the spectral power for each EEG frequency band of interest. EEG power spectra have been widely assessed during the SO process (for a review, see Gorgoni et al., 2019a), albeit only a few studies described its topographical pattern with a satisfactory spatial resolution (Marzano et al., 2013; Gorgoni et al., 2019b);

b) Rhythmic oscillatory activity: the assessment of the EEG power does not necessarily highlight genuine rhythmic oscillations in the specific frequency range of interest. On the other hand, the SO process mainly involves modifications in oscillatory activity, and it has been described with the Better OSCillation (BOSC) detection method (Marzano et al., 2013; Gorgoni et al., 2019b), that considers the functional form of a background non-rhythmic portion of the signal to detect deviations from the background (Caplan et al., 2001), or assessing the event ratio, that is the sum of the duration of oscillatory events divided by the total time in a given window (Achermann et al., 2019).

c) Cortical sources: it consists of the assessment of the strength and distribution of the intracranial sources of scalp electric potential differences. A recent study provided a comprehensive description of the brain dynamics using a technique of EEG source localization (LORETA) during SO in baseline and post-SD recovery nights (Fernandez Guerrero and Achermann, 2019);

d) Detection of SO-related EEG events: it consists in the automatic detection of selected electrophysiological markers of sleep, and their description in terms of morphological features, scalp topography, and cortical sources. In the context of the SO process, slow waves (Siclari et al., 2014; Spiess et al., 2018) and sleep spindles (Sarasso et al., 2014a, 2014b; Siclari et al., 2014) have been recently described in detail;

e) Cortical connectivity: it includes a set of techniques used for the assessment of the dynamic interactions between cerebral regions. Among these techniques, the most frequently adopted to describe the SO process are functional connectivity measures like coherence or direct transfer information analyses, evaluating synchrony and mutual information in terms of consistency in phase and amplitude of cortical oscillations in different areas (for a review, see Gorgoni et al., 2019a), effective connectivity measures, quantifying the causal influence of activity in one area over the activity of another region, and network functional organization methods, based on the graph theory and describing cortical dynamics in terms of local specialization (segregation) and global integration (Watts and Strogatz, 1998) of the functional network.

3. The electrophysiology of the sleep onset process assessed with scalp recordings

In this section, we will review the present knowledge about the electrophysiological changes during the SO process in the main EEG frequency bands. The key findings are summarized in Table 1.

3.1. Delta activity

EEG spectral power: the upper panel of Fig. 1 depicts the post- vs. pre-SO ratio of the EEG power of a baseline night. It clearly describes that the most intense change in the EEG power during the SO process is represented by the rise of the delta activity (<4 Hz) (De Gennaro et al., 2001a, 2001b; Marzano et al., 2013), a well-known marker of sleep pressure and intensity that characterizes NREM sleep (Achermann and Borbély, 2011; Finelli et al., 2000). The EEG power in the delta range exhibits a progressive intensification during the transition from wakefulness to sleep that begins just before SO (De Gennaro et al., 2001a, 2001b; Marzano et al., 2013). The anterior brain areas show the earliest and strongest enhancement of the delta activity (De Gennaro et al., 2001a, 2001b; Marzano et al., 2013; Siclari et al., 2014; Tanaka et al., 2000; Werth et al., 1997), as well as the steepest rise rate of the delta activity (Marzano et al., 2013). In other words, the fronto-central regions show electrophysiological signs of sleep when the sensorial posterior areas still exhibit a wake-like EEG activity, suggesting higher sleep need of the anterior part of the cortex. The coexistence of these distinct EEG patterns in anterior and posterior regions may probably explain peculiar perceptual experiences that may be observed at SO, like hypnagogic hallucinations (Mavromatis, 1987) or sleep misperception (Bonnet and Moore, 1982; Sewitch, 1984).

Oscillatory activity: the spatiotemporal pattern of the genuine oscillatory activity confirms the fronto-central prevalence of the delta activity during the entire wake-sleep transition (Marzano et al., 2013). The oscillatory rhythm in the delta frequency peak globally increases after SO, reaching its maximum at the midline central area (Marzano et al., 2013).

Cortical sources: delta activity averaged across the brain shows a progressive post-SO enhancement (Fernandez Guerrero and Achermann, 2019). The highest delta activity is found in correspondence of the frontal (prefrontal cortex) and parietal (postcentral gyrus) lobes.

Morphology, origin, and topography of the slow waves: two types of slow waves have been identified during the SO process (Siclari et al., 2014). The earliest slow waves (Type I) have been described as large, sporadic, and characterized by a steep slope, long duration, and few negative peaks. Their sources have been identified in the sensorimotor area and the postero-medial parietal cortex, with the involvement of an extensive fronto-medial region. Type I slow waves, which probably include the classical K-complexes (Halász, 2005), have been observed in association with a severe decrease of the gamma power. The later slow waves detected during the wake-sleep transition (Type II) exhibit reduced amplitude, slope, and duration, higher density and an increased number of negative peaks. Their origin can occur in any cortical location. Type II slow waves can involve posterior and lateral regions, and they are associated with a weakened reduction of gamma activity. It has been proposed that Type I and Type II slow waves represent, respectively, a "bottom-up" and a "horizontal" cortico-cortical synchronization process (Siclari et al., 2014).

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Table 1
Key findings about the electrophysiological modifications observed during the sleep onset (SO) process, as assessed with EEG scalp recordings in both baseline and post-sleep deprivation recovery nights.

	Delta activity	Theta activity	Alpha activity	Sigma activity	Beta and Gamma activity
Spectral power					
BSL	Early and generalized increase, particularly in the anterior areas (De Gennaro et al., 2001a, 2001b; Marzano et al., 2013; Siclari et al., 2014; Tanaka et al., 2000; Werth et al., 1997)	Global increase (Marzano et al., 2013; Siclari et al., 2014; Wright et al., 2015), with an occipital peak (Marzano et al., 2013)	Gradual pre-SO reduction of the occipital alpha, followed by a post-SO increase of fronto-central alpha (De Gennaro et al., 2001b; Hasan and Broughton, 1994; Marzano et al., 2013; Tanaka et al., 1997)	Post-SO increase with a centro-parietal predominance (De Gennaro et al., 2001a, 2001b; Marzano et al., 2013; Siclari et al., 2014)	Global reduction of the beta (De Gennaro et al., 2001a, 2001b; Marzano et al., 2013; Merica et al., 1991; Merica and Gaillard, 1992) and gamma activity (Siclari et al., 2014)
REC	Compared to BSL, global increase of the post- vs. pre-SO ratio (Gorgoni et al., 2019)	Compared to BSL, global increase of the post- vs. pre-SO ratio (Gorgoni et al., 2019)	Compared to BSL, increased post- vs. pre-SO ratio, global at 8–9 Hz and fronto-central at 10 Hz (Gorgoni et al., 2019)	Compared to BSL, absence of quantitative differences (Gorgoni et al., 2019)	Compared to BSL, absence of quantitative differences in the beta range (Gorgoni et al., 2019) Gamma activity not assessed
Oscillatory activity					
BSL	Global increase, that reaches its maximum in the midline central area in the frequency peak (Marzano et al., 2013)	In the frequency peak, strong increase in the temporo-parietal regions (Marzano et al., 2013). Appearance of "fast" delta/theta oscillatory events (1.5–7 Hz) in stage 1 with highest central incidence, that reach their maximum event-ratio immediately after SO and then decrease with time (Achermann et al., 2019)	Transition from a posterior to an anterior predominance (Marzano et al., 2013; Achermann et al., 2019)	Global and progressive increase after SO with a central maximum (Marzano et al., 2013; Achermann et al., 2019). Global frequency reduction with an antero-posterior gradient (Achermann et al., 2019)	Gradual decrease in the beta activity with a maximum in temporo-frontal areas. Post-SO decline in the oscillatory peak in the lateral frontal areas and right occipital region (Marzano et al., 2013). Gamma activity not assessed
REC	Spatio-temporal pattern similar to BSL (Gorgoni et al., 2019)	Spatio-temporal pattern similar to BSL. Appearance of a post-SO fronto-central increase in the oscillatory peak, not observed at BSL (Gorgoni et al., 2019). Increased incidence of "fast" delta/theta oscillatory events (Achermann et al., 2019)	Spatio-temporal pattern similar to BSL. Appearance of a generalized post-SO increase in the oscillatory peak not observed in BSL (Gorgoni et al., 2019). Increased incidence of alpha oscillatory events (Achermann et al., 2019)	Spatio-temporal pattern similar to BSL (Gorgoni et al., 2019). Reduced incidence of sigma oscillatory events (Achermann et al., 2019).	In the beta range, spatio-temporal pattern similar to BSL (Gorgoni et al., 2019). Appearance of a post-SO centro-parietal increase in the beta frequency peak not observed in BSL (Gorgoni et al., 2019). Gamma activity not assessed
Cortical sources					
BSL	Progressive post-SO enhancement of the delta activity, higher in the prefrontal cortex and postcentral gyrus (Fernandez Guerrero and Achermann, 2019)	Progressive increase of the theta activity until the achievement of a plateau, with greater involvement of the precuneus and cuneus (Fernandez Guerrero and Achermann, 2019)	Progressive increase of the alpha activity during the SO process, with highest values in the precuneus (Fernandez Guerrero and Achermann, 2019)	Progressive post-SO enhancement of the sigma activity, with a greater involvement of the parietal lobe and a secondary contribution of the postcentral gyrus, the cuneus, and the lingual gyrus (Fernandez Guerrero and Achermann, 2019)	Progressive reduction of the beta activity, with higher involvement of the parietal and occipital lobes (Fernandez Guerrero and Achermann, 2019). Gamma activity not assessed
REC	Speedup of the brain dynamics observed in BSL, particularly in the frontal cortex (Fernandez Guerrero and Achermann, 2019)	Compared to BSL, higher involvement of the frontal cortex (Fernandez Guerrero and Achermann, 2019)	Compared to BSL, faster and higher increase of alpha activity (Fernandez Guerrero and Achermann, 2019)	Compared to BSL, earlier sigma peak, but reduced activity and decreased number of brain areas involved (Fernandez Guerrero and Achermann, 2019)	Compared to BSL, faster decrease of the beta activity (Fernandez Guerrero and Achermann, 2019). Gamma activity not assessed
EEG events					

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Table 1 (*Continued*)

	Delta activity	Theta activity	Alpha activity	Sigma activity	Beta and Gamma activity
BSL	Early large and sporadic Type 1 slow waves followed by smaller Type 2 slow waves with higher density (Siclari et al., 2014). No dissociation between Type 1 and Type 2 slow waves in children (Spiess et al., 2018)	Not assessed	Not assessed	Early appearance of sparse, fast spindles involving few cortical areas. Then, they become slower and more numerous, involving more regions (Siclari et al., 2014). Higher current source density immediately after SO than at the end of the first NREM sleep cycle, in the SFG and SPL for slow and fast spindles, respectively (Alfonsi et al., 2019).	Not assessed
REC	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Cortical connectivity					
BSL	Gradual increase of cortical coherence within ipsilateral frontal and central areas and between contralateral frontal and central homologues (Morikawa et al., 1997; Tanaka et al., 1998, 1999; 2000). Progressive decrease of antero-posterior synchrony (De Gennaro et al., 2004; Morikawa et al., 1997), with a post-SO switch to an anterior-to-posterior propagation of the information flow (De Gennaro et al., 2004). Increase of effective connectivity from MPFC to the bilateral HPC and lateral prefrontal cortex but weakened connection from DPFC and ipsilateral HPC. Anterior-posterior disconnection of the DMN but increased information flow and connectivity between the PCC and both anterior and posterior cortices (Fernandez Guerrero and Achermann, 2018). Higher local interconnectedness during the transition period (Ferri et al., 2007, 2008; Tagliazucchi et al., 2013) and lower long-range functional connectedness during more stable sleep (Tagliazucchi et al., 2013; Vecchio et al., 2017)	Increased ipsilateral and inter-hemispheric frontal and central coherence (Morikawa et al., 1997; Tanaka et al., 2000). Increased inter-hemispheric temporal and occipital coherence (Tanaka et al., 2000). Progressive decrease of antero-posterior synchrony (De Gennaro et al., 2004; Morikawa et al., 1997), with a post-SO switch to an anterior-to-posterior propagation of the information flow (De Gennaro et al., 2004). After SO, the theta activity mediates bidirectional information flow between the PCC and the bilateral IPL and the HPC, and from the bilateral HPC to the MCC (Fernandez Guerrero and Achermann, 2018)	Progressive decrease of antero-posterior coherence and inter-hemispheric frontal coherence (Cantero et al., 1999; Wright et al., 1995; Morikawa et al., 2002), and increased posterior coherence (Morikawa et al., 2002). Increased coherence in the upper alpha sub-band (11–12 Hz) with the beginning of sleep stage 2 along the antero-posterior axis (De Gennaro et al., 2004; Morikawa et al., 2002; Tanaka et al., 1998). Increased effective connectivity from the PCC to most of the brain (Fernandez Guerrero and Achermann, 2018)	Widespread and sharp ascending pattern in coherence at the beginning of sleep (Morikawa et al., 2002), with a steeper increase in posterior areas. Increased local and global interconnectivity in the frontal regions (Vecchio et al., 2017; Ferri et al., 2008). Increased effective connectivity after SO, with an enhancement of the MCC and PCC connectivity with many brain areas (Fernandez Guerrero and Achermann, 2018)	Inversion of the information flow direction, with increase of beta oscillations propagation from frontal to parieto-occipital areas (De Gennaro et al., 2004). Gamma activity not assessed
REC	Anterior-to-posterior direction of cortical coupling already present in the pre-SO period (De Gennaro et al., 2005). Compared to BSL, generalized post-SO decrease of effective connectivity (Fernandez Guerrero and Achermann, 2018)	Anterior-to-posterior direction of cortical coupling already present in the pre-SO period (De Gennaro et al., 2005). Compared to BSL, generalized post-SO decrease of effective connectivity (Fernandez Guerrero and Achermann, 2018)	Anterior-to-posterior direction of cortical coupling already present in the pre-SO period (De Gennaro et al., 2005). Compared to BSL, generalized post-SO decrease and few local increases of effective connectivity (Fernandez Guerrero and Achermann, 2018)	Anterior-to-posterior direction of cortical coupling already present in the pre-SO period (De Gennaro et al., 2005). Compared to BSL, generalized post-SO decrease and few local increases of effective connectivity. The MCC shows a stronger impact on the left IPL and a reduced one on the right DPFC. The PCC exhibits a increased information flow to the left and right IPL (Fernandez Guerrero and Achermann, 2018)	Anterior-to-posterior direction of cortical coupling already present in the pre-SO period (De Gennaro et al., 2005). Compared to BSL, generalized post-SO decrease of effective connectivity (Fernandez Guerrero and Achermann, 2018). Gamma activity not assessed

Abbreviations: BSL, baseline; DMN, default mode network; DPFC, dorsolateral prefrontal cortex; HPC, hippocampus IPL, inferior parietal lobule; MCC, medial cingulate cortex; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; REC, recovery; SFG, superior frontal gyrus; SPL, superior parietal lobe; SO, sleep onset.

The temporal dissociation between the two types of slow waves has been recently replicated in young adults, but not in children, which exhibits a linear increase of slow waves number and amplitude during SO (Spiess et al., 2018). Moreover, slow waves in children are characterized by a faster increase of number and amplitude in central and posterior areas, respectively, and a larger amplitude in the period that immediately precedes SO (Spiess et al., 2018). It is possible, then, that the separation between two distinct synchronization processes is influenced by maturation.

Connectivity: coherence of cortical activity within the delta range gradually increases within ipsilateral frontal and central areas and between contralateral frontal and central homologues (Morikawa et al., 1997; Tanaka et al., 1998, 1999, 2000) in the transition between wake and sleep, while it starts to decrease during deeper sleep within and between the more posterior regions (Morikawa et al., 1997; Tanaka et al., 2000). Antero-posterior synchrony progressively decreases during the falling asleep period (De Gennaro et al., 2004; Morikawa et al., 1997), and this pattern is associated with the inver-

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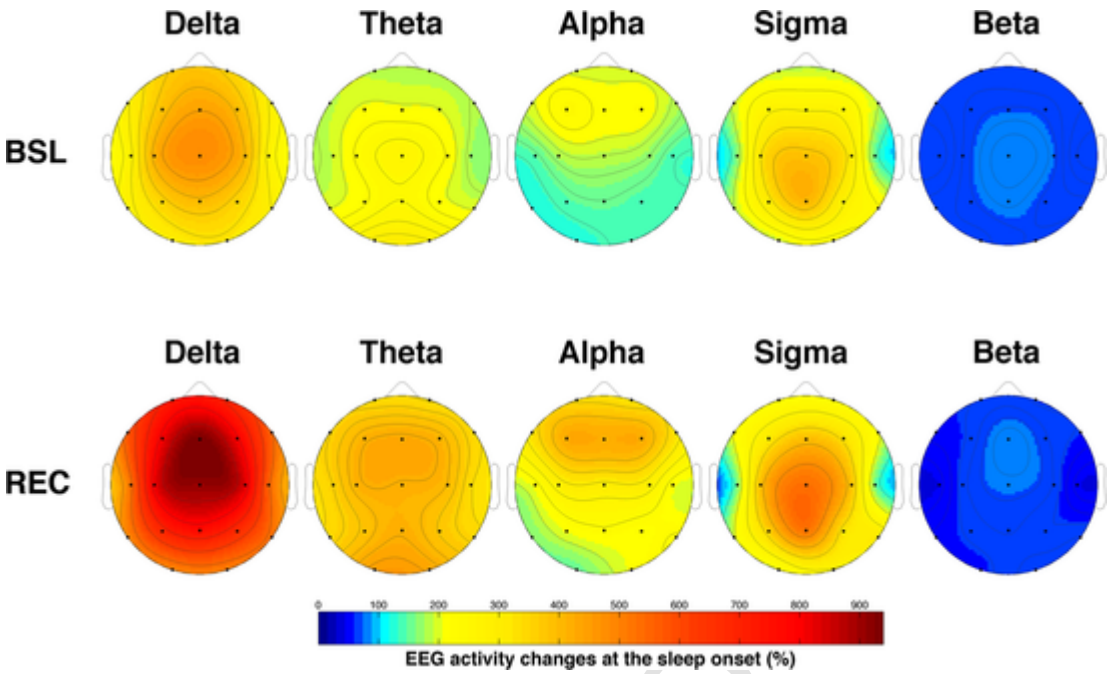

Fig. 1. Scalp topography of the relative EEG power changes during the wake-sleep transition, expressed as the ratio between post-SO and pre-SO periods [(post-SO/pre-SO)*100] in 39 healthy young adults during a baseline (BSL, upper panel) and a recovery night (REC, lower panel). Values are color-coded and plotted at the corresponding position on the planar projection of the scalp surface and are interpolated (biharmonic spline) between electrodes. Values <100 represent a percent reduction of power after the SO. The maps are based on the 19 unipolar EEG derivations of the international 10-20 system with average mastoid reference, and they are plotted for the following frequency bands: delta (0.50-4.75 Hz), theta (5.00-7.75 Hz), alpha (8.00-11.75 Hz), sigma (12.00-15.75 Hz) and beta (16.00-24.75 Hz). Data reported in this figure have been previously published (Marzano et al., 2013; Gorgoni et al., 2019).

sion in the direction of the delta oscillations propagation from the posterior-to-anterior direction of wakefulness to an anterior-to-posterior propagation in the sleeping brain (De Gennaro et al., 2004). Effective connectivity from medial prefrontal cortex to the bilateral hippocampi and lateral prefrontal cortex also increases, while the connections weaken from the dorsolateral prefrontal cortex and the ipsilateral hippocampus (Fernandez Guerrero and Achermann, 2018). Generally, an anterior-posterior disconnection of the default mode network occurs during SO (Fernandez Guerrero and Achermann, 2018). It is worth noting, however, that the posterior cingulate cortex seems to represent a major synchronizer at low frequency also after SO since its information flow and connectivity with both anterior and posterior cortices increases with the switch from the waking to the sleep state (Fernandez Guerrero and Achermann, 2018). Cortical network organization in the delta band during SO has been reported to move towards higher local interconnectedness during the transition period (Ferri et al., 2007, 2008; Tagliazucchi et al., 2013) and lower long-range functional connectedness during more stable sleep (Tagliazucchi et al., 2013; Vecchio et al., 2017).

3.2. Theta activity

EEG spectral power: theta activity (5–7 Hz), another EEG marker of increased sleep pressure (De Gennaro et al., 2007; Finelli et al., 2000, 2001; Gorgoni et al., 2014) exhibits a global power increase during the SO process (Marzano et al., 2013; Siclari et al., 2014; Wright et al., 1995). Its spatiotemporal pattern mirrors that observed in the delta band, with a clear and early fronto-central prevalence (Marzano et al., 2013). On the other hand, the occipital regions, instead of the centro-frontal ones, show the maximum theta power increase after SO (Marzano et al., 2013).

Oscillatory activity: the theta oscillations globally and progressively increase during the wake-sleep transition (Marzano et al., 2013). Rhythmic oscillations in the theta frequency range dramatically increase in the temporo-occipital regions after SO (Marzano et al., 2013).

No changes in the oscillatory theta peak have been found in fronto-central areas after SO (Marzano et al., 2013). This is one of the few remarkable differences observed between EEG spectral power and oscillatory activity at SO. It has been hypothesized that the emergence of genuine fronto-central theta oscillations exceed the short time window used to assess SO in this study (i.e., 5 min) (Marzano et al., 2013), and findings on the effects of sleep deprivation indirectly support this view (see the section "The effect of prolonged wakefulness on the EEG pattern of the sleep onset").

Achermann and co-workers (2019) recently assessed oscillatory events in three derivations (frontal, central, occipital) during the SO process, considering "fast" delta and theta frequencies conjointly (1.5–7 Hz), since they observed that events in these frequency bands have similar properties. The authors found that delta/theta events have the highest incidence in the central location, appear in stage 1, reaching their maximum event-ratio during the first 2 min after SO and then decrease with time. The frequency of these delta/theta events progressively decreases from stage 1 to stage 2.

Cortical sources: the theta activity increases during the SO process until a plateau is reached (Fernandez Guerrero and Achermann, 2019). Two areas in the parietal and occipital lobes (i.e., the precuneus and the cuneus, respectively) seem the most involved in this process.

Connectivity: theta changes in connectivity measures during SO also mirror most of the dynamics described for the delta band: increases in ipsilateral and inter-hemispheric frontal and central coherence (Morikawa et al., 1997; Tanaka et al., 2000), specific increase in inter-hemispheric temporal and occipital coherence (Tanaka et al., 2000), decreased antero-posterior coupling (De Gennaro et al., 2004; Morikawa et al., 1997) and the switch to an anterior-to-posterior direction of the information flow (De Gennaro et al., 2004). Measures of effective connectivity showed that theta activity after SO mediates most of the bidirectional information flow between the poste-

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rior cingulate cortex and the bilateral inferior parietal lobule and the hippocampi, as well as the information flow from the bilateral hippocampi to the medial cingulate cortex (Fernandez Guerrero and Achermann, 2018).

3.3. Alpha activity

EEG spectral power: alpha EEG power (8–12 Hz) exhibits two distinct spatiotemporal patterns before and after SO (Marzano et al., 2013). During the period that precedes SO, alpha power has a clear occipital prevalence that gradually disappears. After SO, alpha activity progressively increases, reaching its peak in the fronto-central regions (De Gennaro et al., 2001b; Hasan and Broughton, 1994; Marzano et al., 2013; Tanaka et al., 1997). It is worth noting that responsiveness to the environment expressed at behavioural level shows a reduction that parallels the fall of alpha activity before SO, but it completely disappears when alpha activity re-emerges after SO (Ogilvie et al., 1991). Together, these findings suggest a different functional meaning of the pre- and post-SO alpha power (De Gennaro et al., 2004; Pivik and Harman, 1995): before SO, the occipital alpha activity reflects the "idle rhythm" characterizing the relaxed eyes-closed wakefulness (Adrian and Matthews, 1934; Niedermeyer, 1997); the fronto-central alpha power after SO should be considered as a component of the complex synchronization process, with possible involvement in sleep-maintaining mechanisms.

Oscillatory activity: at a global level, the alpha rhythm dominates in the pre-SO period, while the post-SO period is dominated by sigma, theta, and delta rhythms (Marzano et al., 2013). Alpha oscillations have maximal parieto-occipital values at the beginning of the pre-SO period, while at the end of the post-SO segment they are prevalent at the anterior locations. However, no significant differences have been detected comparing the pre- and post-SO periods in the alpha oscillatory peak, differently from what has been observed in the EEG power. As for the theta rhythm, it has been hypothesised that a larger time window is needed to observe a boost in genuine alpha oscillations after SO (Marzano et al., 2013).

Consistently with the spatiotemporal pattern described with the BOSC method (Marzano et al., 2013), in the study of Achermann et al. (2019) alpha oscillatory events have been observed during pre-SO wakefulness with an occipital prevalence, showing a dropout in correspondence of the transition to stage 1. Then, the alpha oscillatory activity progressively increased in fronto-central derivations after SO, exhibiting the highest values in the frontal location but with large inter-individual variability. The mean alpha frequency was enhanced at SO but showed an occipital reduction with time spent in sleep.

Cortical sources: alpha activity exhibits a progressive increase during the SO process, reaching a plateau during the first 5 min, with the highest values observed in the precuneus (Fernandez Guerrero and Achermann, 2019).

Connectivity: antero-posterior coherence and inter-hemispheric frontal coherence in alpha activity during the wake-sleep transition reveal a progressive decrease, starting before SO and reaching its minimum at the onset of sleep stage 2 (Cantero et al., 1999; Wright et al., 1995; Morikawa et al., 2002), while the posterior areas tend to increase coherence in the alpha range, mainly after SO (Morikawa et al., 2002). In particular, activity in the upper alpha sub-band (11–12 Hz) shows increasing coherence with the entrance in the sleep period (sleep stage 2) also along the antero-posterior axis, among different regions of the frontal and posterior areas (De Gennaro et al., 2004; Morikawa et al., 2002; Tanaka et al., 1998). Effective connectivity from the posterior cingulate cortex to most of the brain significantly increases in this frequency range after SO, confirming the role of the posterior cingulate cortex as a major driver of the information flow during the transition period (Fernandez Guerrero and Achermann, 2018).

Functional networks in the alpha band show an increased global connectedness and small word network-like organization (Ferri et al., 2008).

The pattern of changes in connectivity described for activity in the alpha range, and even more in the upper alpha, during SO mirrors the dynamics followed by the sigma band activity (see next), suggesting a similar functional role for cortical activity in these two frequency ranges during the entrance into the sleep state.

3.4. Sigma activity/Sleep spindles

EEG spectral power: sleep spindles represent one of the main EEG hallmarks of NREM sleep (De Gennaro and Ferrara, 2003) within the sigma frequency range (~12–15 Hz) and they are usually classified in two categories: slow frontal spindles and fast centroparietal spindles. Sigma power strongly increases after SO (De Gennaro et al., 2001a, 2001b; Marzano et al., 2013), when SO is defined as the beginning of stage 2 sleep (i.e., with the rise of the first sleep spindle and/or K-complex). However, Siclari and coworkers (2014) found similar results defining the beginning of the falling-asleep period as the end of waking alpha activity, and the end of the SO process with the first slow wave sequence. Consistently with classical evidence of sleep spindles topography (De Gennaro and Ferrara, 2003), sigma power at SO exhibits a maximal increase in the centro-parietal locations (Marzano et al., 2013).

Oscillatory activity: the sigma oscillatory activity is the predominant rhythm during the post-SO period (Marzano et al., 2013). It globally and progressively increases after SO, with the exception of the occipital region, and reaches its maximum at the vertex (Marzano et al., 2013). Consistently, sigma oscillatory events occur after SO with a central predominance, showing an initial increase that leads to a plateau (Achermann et al., 2019). The mean sigma frequency is globally reduced with time after SO, exhibiting an antero-posterior gradient (i.e., lower frequency in the frontal location) (Achermann et al., 2019).

Cortical sources: mean sigma activity exhibits a progressive post-SO enhancement, reaching a peak 7 min after SO, with the number of voxels that differed from the pre-SO period peaking 5 min after SO (Fernandez Guerrero and Achermann, 2019). The underlying generators mainly involve the parietal lobe, with a secondary contribution of the postcentral gyrus, the cuneus, and the lingual gyrus.

Morphology, origin, and topography of the sleep spindles: at the beginning of the SO period, sleep spindles are fast and have low density, involving few cortical regions (Siclari et al., 2014). Then, their density progressively increases (with a reduction only at the end of the falling-asleep period) as well as their duration, and they become slower and more diffuse. Slow frontal spindles and fast centroparietal spindles exhibit different patterns of probabilistic origin, the first with more probable origin in the anterior cingulate cortex and medial/lateral prefrontal cortex, the second in the precuneus and posterior cingulate cortex (Siclari et al., 2014). The contribution of frontal and parietal sources for centroparietal and frontal spindles, respectively, increases during the falling-asleep process, highlighting the shift from local to diffuse spindles. The subsequent involvement of fronto-medial areas in centroparietal spindles is enhanced, while the involvement of parietal regions in frontally generated spindles remains unchanged (Siclari et al., 2014). In a recent study, the maximal source activation for slow and fast sleep spindles during a night of sleep has been found respectively in the superior frontal gyrus (BA10) and the superior parietal lobe (BA7), and such observation remains stable across consecutive sleep cycles (Alfonsi et al., 2019). Considering the temporal evolution within the first NREM sleep cycle, it has been observed that the

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current source density was higher at the beginning of the cycle (i.e., immediately after SO) compared to its last intervals for both preferential spindle sources (BA10 and BA7) (Alfonsi et al., 2019).

Connectivity: Cortical activity in the sigma frequency band reveals a widespread and sharp ascending pattern in coherence level at the beginning of sleep, when sleep spindles appear in the EEG recordings (Morikawa et al., 2002), with posterior areas showing the steepest increase. The frontal regions do not undergo main changes in coherence within the sigma band during the transition to sleep, but they significantly enhance their functional connectivity, increasing both local and global interconnectivity (Vecchio et al., 2017; Ferri et al., 2008). Activity in the sigma frequency range does not show modifications in the direction of the information flow (De Gennaro et al., 2004).

Effective connectivity in the sigma band increases significantly with SO, with the mid-cingulate cortex and, to a lesser degree, posterior cingulate cortex enhancing connectivity with most of the brain portions, thus representing the main drivers of information flow (Fernandez Guerrero and Achermann, 2018).

3.5. Fast frequencies

EEG spectral power: beta (16–24 Hz) and gamma (25–40 Hz) EEG frequencies are usually considered markers of arousal and motor/cognitive activation (Basar-Eroglu et al., 1996; Kilavik et al., 2013; Merker, 2013; Neuper and Pfurtscheller, 2001). A global reduction at SO has been observed in both beta (De Gennaro et al., 2001a, 2001b; Marzano et al., 2013; Merica et al., 1991; Merica and Gaillard, 1992) and gamma power (Siclari et al., 2014), without a specific topographical pattern. The decrease of beta activity begins before SO and reaches its maximum in the temporal region, probably mirroring the reduction of the muscular tone (Marzano et al., 2013).

Oscillatory activity: oscillations in the beta range show a gradual decrease that reaches its maximum in temporo-frontal locations and a decline of the oscillatory peak after SO in the lateral frontal areas and the right occipital region (Marzano et al., 2013).

Cortical sources: beta activity shows a reduction with time during the SO process, with the most prominent involvement of the parietal and occipital lobes (Fernandez Guerrero and Achermann, 2019).

Connectivity: Beta and gamma band dynamics during SO have been poorly (beta) or not at all (gamma) investigated by connectivity studies. The few data available suggest that cortical activity in the beta range does not undergo drastic changes in term of coherence (De Gennaro et al., 2004), effective connectivity (Fernandez Guerrero and Achermann, 2019) or functional organization of the networks (Vecchio et al., 2017; Ferri et al., 2008). The most salient variation in this frequency range is represented by the occurrence of the inversion in the direction of the information flow that, after SO, sees beta oscillations propagating from the frontal to the parieto-occipital regions which significantly increase and become dominant (De Gennaro et al., 2004). According to the role of information chunk played by the fast oscillations in cortical communication during both the waking and sleep state (Buzsáki, 2010; Valderrama et al., 2012), minor changes in the same direction of those occurring in the beta band would be expected for the gamma activity.

4. The electrophysiology of the sleep onset process assessed by intracerebral recordings

In a clinical context, it is often required the implantation of intracerebral electrodes in epileptic patients. This procedure offers the unique opportunity to directly measure the local EEG activity in deep and subcortical cerebral structures, and it has also been assessed during the falling-asleep process.

In this way, the antero-posterior gradient of the delta activity observed with scalp electrodes at SO has been confirmed with electrocorticographic recordings, also describing a pattern of temporal changes in the frequency band 0.25–1.25 Hz in the parahippocampal cortex that was comparable to the one found in the anterior cortex (Bódizs et al., 2005).

With Stereo-EEG (SEEG) recordings, it has been observed that the thalamus, a crucial structure for the generation and propagation of cortical sleep rhythms (Steriade et al., 1993), shows physiological signs of deactivation several minutes before the cortex during the wake-sleep transition (Magnin et al., 2010). Moreover, the hippocampus exhibits sleep spindles before SO, as defined on the basis of the scalp EEG, anticipating the cortical spindles with a growing delay along the antero-posterior axis (Sarasso et al., 2014a). This evidence may explain the "mesograde amnesia" phenomenon, which is the alteration of memory for events preceding SO (Perlis et al., 2001a; Wyatt et al., 1997), since the hippocampus has a key role in memory processes. Data from a single subject suggest a thalamo-hippocampal coordination during the wake-sleep transition since hippocampal pre-SO spindles and low-frequency (≤ 2 Hz) activity in the thalamus were related (Sarasso et al., 2014b). Together, these findings underline the existence of a temporal dissociation in the EEG pattern not only between different cortical areas but also between cortical and deep cerebral structures, with the thalamus and the hippocampus exhibiting signs of sleep before the cortically defined SO.

Finally, the assessment of the rhythmic activity in another single patients with intracerebral electrodes showed that the calcarine cortex (but not the parietal and the frontal ones) is dominated by the theta oscillations at SO (Marzano et al., 2013), suggesting that the dominant scalp theta activity detected at SO reflects a peculiar activity of the calcarine cortex, probably mirroring the increased metabolic activity in the visual area at SO found in neuroimaging studies (Fukunaga et al., 2006; Kjaer et al., 2002; Kotajima et al., 2005).

5. The effect of prolonged wakefulness on the EEG pattern of the sleep onset

SD induces marked changes in the EEG activity during wakefulness (Finelli et al., 2000; Tinguely et al., 2006; De Gennaro et al., 2007; Gorgoni et al., 2014; Fattinger et al., 2017) and recovery sleep (Cajochen et al., 1999; Finelli et al., 2001; Tinguely et al., 2006; Marzano et al., 2010). During wakefulness, the SD-dependent modifications in the EEG activity are associated with increased sleepiness (Gorgoni et al., 2014; Bernardi et al., 2015) and impaired performance in cognitive tasks (Gorgoni et al., 2014; Fattinger et al., 2017). Such changes are mainly characterized by a large increase of the slowest EEG frequencies and are widely considered as local electrophysiological markers of the increased homeostatic sleep pressure (for review, see D'Ambrosio et al., 2019). Also, the EEG activity during the process of awakening from recovery sleep is affected by SD (Tassi et al., 2006; Gorgoni et al., 2015). Starting from this consolidated evidence, it is conceivable that SD should affect the EEG pattern during the wake-sleep transition. Still, only recent evidence allowed an exhaustive description of the effect of prolonged wakefulness on the electrophysiological mechanisms underlying the falling-asleep process (Table 1).

In a recent study (Gorgoni et al., 2019b), the spatiotemporal pattern of the EEG spectral power at SO seemed to be unaltered after prolonged wakefulness, but it exhibited an enhanced intensity of the synchronization process (Fig. 1, lower panel). Specifically, compared to the baseline night, the post-SD condition was characterized by a global increase of the post- vs. pre-SO ratio of the EEG power in the frequency bins ≤ 9 Hz, and in fronto-central locations at 10 Hz. Such enhancement in the delta, theta, and alpha bands should be interpreted as an electrophysiological marker of the increased homeostatic sleep pres-

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sure. In the same study, also the rhythmic oscillatory activity has been assessed. While the post-SO period at baseline was dominated by sigma oscillations (Marzano et al., 2013), after prolonged wakefulness it was characterized by a prevalent theta rhythm (Gorgoni et al., 2019b). From a topographical standpoint, the oscillatory peaks in the frequency bands from delta to sigma showed a generalized increase after SO, and a higher beta oscillatory peak has also been observed only in the midline centroparietal area. The main difference from the baseline night, then, is represented by the post-SO enhancement of the global alpha and fronto-central theta oscillatory peaks in the recovery condition. This result supports the hypothesis that the time needed for the rise of such oscillatory rhythms during a normal wake-sleep transition is higher than the 5-minutes window used in previous experiments (Marzano et al., 2013), and the increased homeostatic sleep pressure induces their earlier build-up (Gorgoni et al., 2019b). The surprising centro-parietal increase of the beta oscillatory peak points to the need for a more detailed assessment of its functional meaning, also considering that: a) a beta power enhancement has been observed during a recovery night of sleep after SWS deprivation (Ferrara et al., 2002) and total SD (Marzano et al., 2010), albeit the latter was not significant, b) the depolarizing phase of the slow oscillations during sleep involves fast frequencies (Steriade, 2001), and c) in rats, beta and gamma activity are enhanced during active wakefulness, but in quiet wakefulness, beta activity parallels delta and theta frequencies in tracking the need for sleep, mirrored by changes in the concentration of cortical lactate (a measure of cerebral glucose concentration) (Grønli et al., 2016).

The assessment of the oscillatory events in delta/theta, alpha, and sigma bands showed that SD does not affect the frequencies of these oscillations, while the incidence of the oscillatory events is increased in the delta/theta and alpha bands and reduced in the sigma band (Achermann et al., 2019). However, it is worth noting that this study had a low topographical resolution (only three electrodes).

SD also affects the EEG activity assessed with source localization during the falling-asleep process (Fernandez Guerrero and Achermann, 2019). A speedup of the brain dynamics in the delta frequency after SO has been observed in the recovery condition compared with baseline, with a higher effect of SD on the frontal cortex. As in baseline sleep, theta activity increased mainly in the occipital lobe during the recovery night, but it also involved the frontal areas. Alpha activity exhibited a faster increase and reached a higher level in the recovery compared to the baseline condition. The sigma activity reached its peak quicker in the recovery night, but it was also substantially reduced compared to baseline, involving a lower number of brain areas. Finally, beta activity showed a faster decrease in the recovery condition. Overall, these findings suggest that: a) different brain areas show electrophysiological signs of sleep with different speed, mirroring their level of sleep pressure, and b) the brain dynamics at SO in the recovery night represent a faster version of those observed at baseline (Fernandez Guerrero and Achermann, 2019).

Several studies assessed how the dynamics of the interactions between cortical areas during the wake-sleep transition is affected by SD. Using the DTF technique, it has been observed that the anterior-to-posterior directionality of functional cortical coupling, previously observed after SO in a baseline night (De Gennaro et al., 2004), was already present in the pre-SO period during a recovery night after SWS deprivation (De Gennaro et al., 2005). This result suggests that the increased homeostatic sleep pressure advances the spread of synchronizing signals from the anterior to the posterior regions during the falling-asleep process. More recently, Fernandez Guerrero and Achermann (2018) described the effect of SD on effective connectivity at SO in selected regions of interest assessed with source localization (LORETA). The authors showed that changes in recovery at SO are qualitatively similar to those observed in baseline, corroborating the notion of a crucial role of the mid-cingulate cortex as a prevalent source for sigma activity, and secondary involvement of the posterior cingulate cortex. The SO transition during recovery exhibits a general decrease of connectivity compared to baseline, most conspicuous in the beta band, that would point to a higher degree of network disconnection at SO after prolonged wakefulness. Few local intensifications of connectivity have also been observed in recovery, particularly in the upper alpha and sigma bands, considered as the reflection of spindle synchronization (Fernandez Guerrero and Achermann, 2018). However, SO in the recovery night also exhibits a reduced number of significant connections in the sigma range that may suggest a reduced ability to propagate sleep spindles after SD (Fernandez Guerrero and Achermann, 2018).

Taken together, these findings reveal that SD dramatically affects the electrophysiological pattern of the wake-sleep transition, with a frequency-specific influence in all of the considered measures (i.e., EEG power, oscillatory activity, source localization, connectivity). The increase of homeostatic sleep pressure does not induce substantial qualitative changes, but it is associated with a strong speedup and intensification of the typical electrophysiological changes of the wake-sleep transition, with an earlier emergence of sleep-like brain dynamics and local rhythms already before SO.

6. The effect of tCS techniques on sleep propensity

The evidence that the SO process is characterized by a specific spatiotemporal pattern of local electrophysiological changes, and that the timing and intensity of such changes vary depending on the level of sleep pressure, leads to the following crucial question: can we affect the level of sleep pressure directly modulating the EEG activity during the waking state, with the aim to induce, hinder or manipulate the physiological mechanisms that characterize SO?

An answer to this question may be potentially found applying tCSs, a family of brain stimulation techniques that non-invasively modulate brain physiology and cognitive functioning (Nitsche et al., 2008; Shin et al., 2015). They consist of the delivery of a low-intensity current through the skull by a positive (anode) and a negative (cathode) electrode placed on the scalp. By varying several stimulation parameters (i.e., intensity, frequency, polarity, waveform, duration, site), different effects on brain physiology can be obtained.

When applied during sleep, tCSs revealed the ability to affect NREM sleep EEG rhythms or phasic events (Marshall et al., 2004, 2006; Antonenko et al., 2013; Westerberg et al., 2015; Ladenbauer et al., 2016). Starting from this evidence, recent studies tried to take advantage of the neuromodulatory properties of tCS protocols to promote the EEG pattern distinctive of the wake-sleep transition, enhancing sleep propensity (Table 2). The main protocols used in our laboratory to induce sleep propensity by tCS are depicted in Fig. 2. A first explorative study assessed the effect of oscillatory transcranial direct current stimulation (tDCS) delivered at different frequencies (0.8 Hz, 5 Hz) and polarities (anodal, cathodal, sham) on subjective sleepiness and EEG power during resting wakefulness (D'Atri et al., 2016a). In line with the spatiotemporal dynamics of EEG activity during the SO process (i.e., the anterior region exhibits the earliest signs of synchronization) (Marzano et al., 2013), the stimulation was delivered over the frontal area. Results showed a selective increase of delta power after anodal tDCS at 5 Hz, compared to 0.8 Hz stimulation. Such an increase was not significantly different from the sham condition, but it paralleled the enhancement of subjective sleepiness, and the two phenomena showed a linear correlation in frontal locations perifocal to the stimulation site (D'Atri et al., 2016a). The assessment of the effects on rhythmic activity confirmed the higher efficacy of the theta stimulation compared to the 0.8 Hz stimulation in increasing both theta and slow cortical oscillations (D'Atri et al., 2015). This finding represents the first evidence of a tDCS-induced modulation of the EEG power with a concomi-

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Table 2
Stimulation features and key findings of studies that used transcranial electrical stimulation protocols to promote sleep propensity during wakefulness, and assessed the topographical EEG pattern.

Paper	Stimulation parameters	Key findings
D'Atri et al. (2015)	Type: osc-tDCS (anodal vs. catodal vs. sham)	Local increase of 5.3 Hz and 0.81 Hz rhythmic oscillatory activity after 5 Hz compared to 0.8 Hz osc-tDCS.
	Time: 10 min	
	Frequency: 0.8 Hz vs. 5 Hz	Absence of clear polarity-dependent effects on oscillatory activity.
	Site: Midline frontal cortex with extra-cephalic reference	
D'Atri et al. (2016a)	Type: osc-tDCS (anodal vs. catodal vs. sham)	Selective increase of delta power after anodal osc-tDCS at 5 Hz, compared to 0.8 Hz stimulation, but without significant differences from sham condition.
	Time: 10 min	
	Frequency: 0.8 Hz vs. 5 Hz	
	Site: Midline frontal cortex with extra-cephalic reference	The increase of delta power after 5 Hz osc-tDCS in frontal locations showed a positive linear correlation with the increase of subjective sleepiness.
D'Atri et al. (2017)	Type: tACS (active vs. sham)	Compared to the sham condition, the active stimulation induced a posterior increase of theta power and a fronto-central increase of alpha power, without changes in subjective sleepiness.
	Time: 10 min	
	Frequency: 5 Hz	
	Site: Right and left fronto-temporal locations	
D'Atri et al. (2019)	Type: tACS (active vs. sham)	Absence of differences between active and sham conditions concerning subjective sleepiness and sleep measures.
	Time: 10 min	
	Frequency: 5 Hz	

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Table 2 (*Continued*)

Paper	Stimulation parameters	Key findings
	Site: Right and left fronto-temporal locations	In those subjects that showed an increase of theta power during pre-sleep wakefulness after the active condition, compared to the sham condition, have been observed: a) increased sleep delta power in frontal central and parietal locations; b) larger delta power increase as closer to the sleep onset; c) positive correlation between theta activity during wakefulness and delta activity during sleep.

Abbreviations: oscillatory transcranial direct current stimulation, osc-tDCS; transcranial alternate current stimulation, tACS.

tant increase of sleepiness. The direction, location, and frequency of the EEG changes induced by the stimulation (i.e., increased frontal delta activity) is consistent with the synchronization process typically observed at SO (Marzano et al., 2013). However, the magnitude of the local effect found in this study was substantially small (D'Atri et al., 2016a). In a second study, the effects of a bilateral (i.e., active electrodes placed on the left and right fronto-temporal areas) transcranial alternated current stimulation (tACS) at 5 Hz applied during resting state has been assessed (D'Atri et al., 2017). The bilateral montage has been chosen because the radial direction of the current flow across the brain should have a higher ability to target deep brain structures (i.e., thalamus and hippocampus) that promote the synchronization process at SO before the cortex (Magnin et al., 2010; Sarasso et al., 2014a, 2014b), enhancing the possibility to increase sleep propensity. Compared to the sham condition, bilateral 5-Hz tACS induced a posterior increase of theta activity and a fronto-central boost of alpha activity, an EEG pattern typical of the SO period (Marzano et al., 2013), but no changes have been found in subjective sleepiness (D'Atri et al., 2017). Therefore, the bilateral tACS protocol seems to induce a process of EEG synchronization with a cortical topography consistent with the one observable at SO. Still, no causal relation between such electrophysiological pattern and sleepiness was observed. Crucially, the effect of bilateral tACS at 5 Hz has been assessed not only on resting wakefulness but also on the EEG of a following nap (D'Atri et al., 2019). The direct comparison between active and sham conditions showed no differences in subjective sleepiness and sleep measures. Notwithstanding, in those subjects (responders) that actually exhibited a stimulation-dependent modulation of the EEG activity during wakefulness (i.e. an increase of theta activity during wakefulness after the active theta stimulation), a significant enhancement of sleep has been obtained (D'Atri et al., 2019). Altogether, results pointed to an influence of tACS on the EEG activity after SO in the responders when compared to the sham condition, showing: (a) an increase of sleep delta activity in frontal, central and parietal areas, index of increased sleep pressure; (b) a time course of the EEG activity revealing that the enhanced delta activity was much larger as closer to the SO and, as a consequence, to the stimulation; (c) a positive correlation between theta activity during wakefulness and sleep delta activity in a wide area that encompasses frontal, central, parietal and temporal locations (D'Atri et al., 2019). These results go in the direction of an increase of sleep pressure induced in the responders by bilateral tACS at 5 Hz, suggesting that when the stimulation is efficient during wakefulness, it has an influence also on subsequent sleep, particularly in the first period after SO. However, It is not clear what discriminates responders from non-responders since the baseline EEG did not show between-group differences, except for a non-significant trend of higher alpha power in the responders (D'Atri et al., 2019).

Overall, albeit these findings should be taken with caution, they suggest that bilateral tACS at 5 Hz may represent an optimal candidate to affect the EEG dynamics of the SO process, increasing sleep propensity. Future studies should be directed to understand which factors affect the efficacy of the stimulation, assessing the individual differences in EEG oscillatory activity, cortical connectivity, and propensity to sleep deprivation. Moreover, the effect of tCS techniques applied during the SO process should be directly assessed.

Another research interest concerns the possibility of using tCS techniques to prevent the SO process, enhancing the EEG pattern associated with vigilance and arousal (i.e., reduction of slow EEG frequencies and enhancement of fast frequencies). At present, only a few and indirect findings are available in this field. From a behavioural standpoint, frontal tDCS applied during a vigilance task can improve performance (Gladwin et al., 2012) and reduce the time-dependent reduction of vigilance (Nelson et al., 2014). Moreover, frontal anodal tDCS can compensate for the impairment of vigilance induced by SD better than caffeine (McIntire et al., 2014, 2017). Dalong et al. (2018) found that frontal anodal tDCS reduced sleepiness after SD better than a sham condition and induced higher thalamocortical connectivity. On the other hand, Borragán et al. (2018) found that frontal anodal tDCS was not able to counteract task-induced cognitive fatigue and induced a delayed (16 min) increase of sleepiness. However, the assessment of the cerebral oxygen exchange pointed to a tDCS-dependent inter-hemispheric shift of oxygenation levels after the induction of cognitive fatigue, interpreted as a possible transitory compensatory mechanism to cognitive fatigue induced by the stimulation (Borragán et al., 2018). When applied before sleep, frontal anodal tDCS induces a decrease of total sleep time, with an increase of intra-sleep wake and a reduction of sleep efficiency in the second part of the night, and higher gamma activity in the morning (Frase et al., 2016). Finally, in a recent pilot observation, while a sham condition induced increased sleepiness and higher delta power, a frontal tACS at 30 Hz seemed to inhibit such responses, also exhibiting a weak increase of gamma power, suggesting the possibility that this kind of stimulation may prevent the EEG markers of sleepiness (D'Atri et al., 2016b). Taken together, these results suggest that different tCS protocols may reduce sleepiness, but electrophysiological evidence is scarce, and the direct effect on the process of SO has never been studied.

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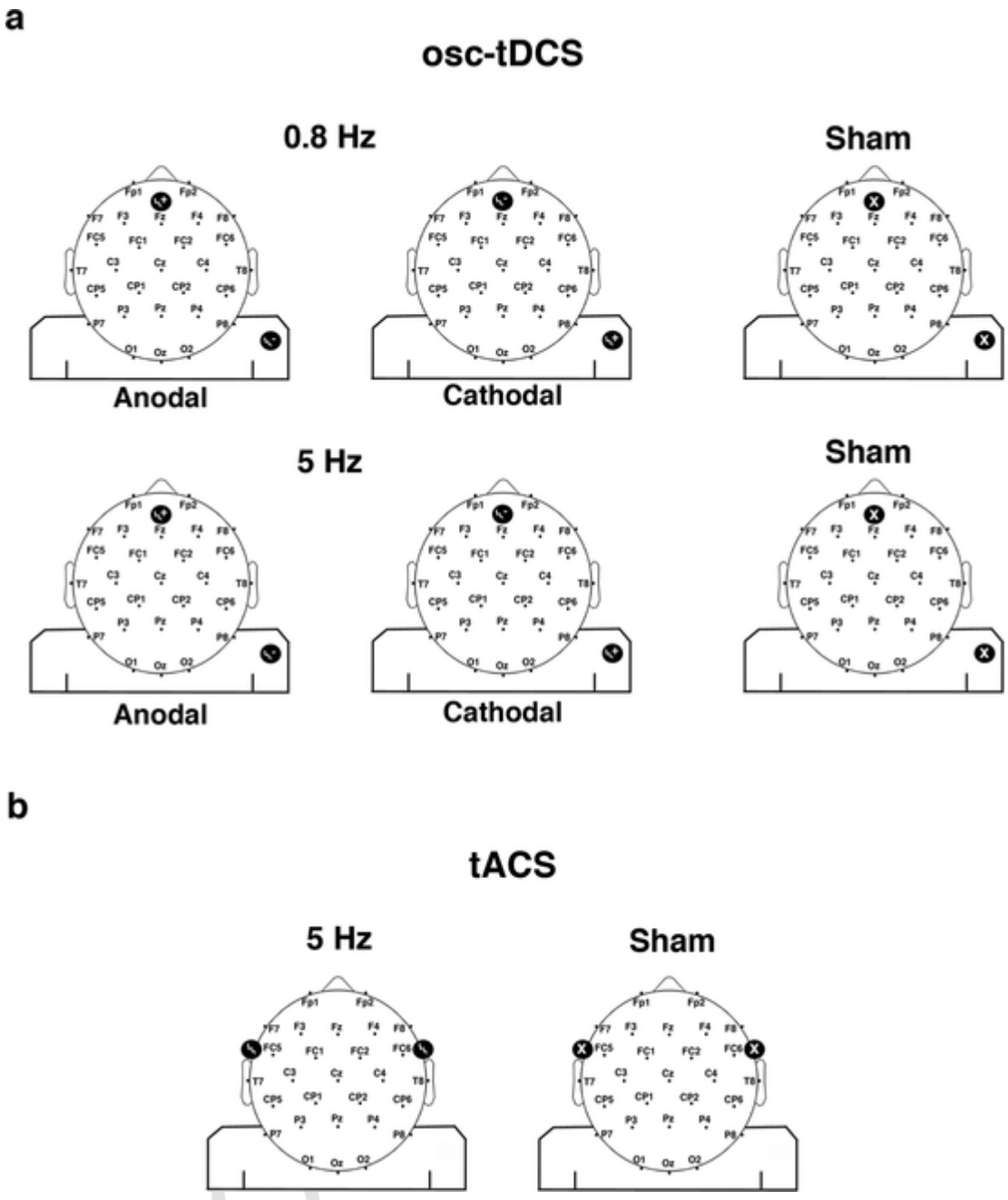

Fig. 2. Protocols with transcranial electrical stimulation used to promote the topographical EEG pattern associated with sleep propensity: (a) oscillatory transcranial direct current stimulation (osc-tDCS) protocol used in D'Atri et al. (2015) and D'Atri et al. (2016a); (b) transcranial alternate current stimulation protocol (tACS) used in D'Atri et al. (2017) and D'Atri et al. (2019). Large black circles indicate the stimulation electrodes position.

7. Conclusion

The possibility to record the EEG activity simultaneously from multiple scalp and deep cerebral locations, and the evolution of several techniques to analyse the EEG signals allowed a broader understanding of the neurobiological mechanisms underlying SO. Studies in this field described a complex scenario of local and gradual electrophysiological changes that guide the progressive transition from wakefulness to sleep, in which regional sleep-like and wake-like activity coexist.

The understanding of the functional meaning of such EEG pattern and the assessment of the modalities in which it can be modulated are the essential starting points to conceptualize the alteration of the SO process and hypothesize possible interventions.

The observation that prolonged wakefulness induces a speedup and an enhancement of the wake-sleep transition, with an intrusion of sleep-like EEG features before SO, provides a description of the physiological mechanisms that probably cause working and car accidents due to excessive daytime sleepiness. In a society in which the reduction of sleep duration and quality is extremely diffuse (Dinges, 1995; Krueger and Friedman, 2009; Maric et al., 2017), this evidence should be used as a core argument for prevention campaigns about the risks of SD, and it should represent the neural basis to develop efficient countermeasures against excessive daytime sleepiness.

The opportunity to bidirectionally affect the human EEG during wakefulness with tCS techniques is a promising way to non-invasively counterbalance the alterations of the falling-asleep process. On the one

hand, the direct induction of EEG synchronization may represent a possible tool for the treatment of insomnia patients and, generalizing, all the conditions characterized by an impaired ability to fall asleep. It is worth noting that patients with insomnia have a high level of arousal at SO that makes them hypervigilant, and such a phenomenon is expressed at a physiological level by enhanced EEG fast frequencies (Merica and Gaillard, 1992; Perlis et al., 2001b). The development of tCS protocols able to boost the EEG synchronization process (D'Atri et al., 2015, 2016, 2017, 2019) may reduce the cortical arousal and promote sleep in these patients. The application of tCS protocols during sleep in patients with insomnia (Saebipour et al., 2015) and during wakefulness in other conditions characterized by sleep disruption (Acler et al., 2013; Minichino et al., 2014; Roizenblatt et al., 2007) mainly goes in the direction of better sleep quality, but it is worth noting that Frase et al. (2019) recently showed that different tDCS protocols did not affect sleep continuity and architecture in patients with insomnia. On the other hand, tCS techniques able to heighten EEG desynchronization may be useful in conditions characterized by high sleep pressure, like SD due to high workload or maladaptive behaviours, obstructive sleep apnea syndrome and idiopathic hypersomnia. Encouraging results on the possibility to enhance vigilance and reduce sleepiness with tCS protocols in a clinical context have been obtained in patients with hypersomnia (Frase et al., 2015; Galbiati et al., 2016) and multiple sclerosis (Hanken et al., 2016), but not in Parkinson's disease (Forogh et al., 2017). However, in both conditions of increased and reduced sleep pressure, studies are scarce, mainly based on behavioral methods and not directly focused on the SO process and its electrophysiological pattern. More important, the findings on healthy subjects reviewed in the present paper describe a scenario in which results are promising but actually insufficient: the number of studies in this field is small, direct evidence of tCSs effects (in the direction of both an enhancement and a reduction of sleep pressure) on the electrophysiology of the SO process is lacking, and we are far from a clear understanding of the variables that influence the efficacy of these protocols. A further effort is needed to enhance knowledge about the possibility of modulating the electrophysiology of the SO process.

Declaration of Competing Interest

None.

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