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Review

High-density electroencephalography as an innovative tool to explore sleep physiology and sleep related disorders

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A B S T R A C T

High density EEG represents a promising tool to achieve new insights regarding sleep physiology and pathology. It combines the advantages of an EEG technique as an optimal temporal resolution with the spatial resolution of the neuroimaging. So far its application in sleep research contributed to better characterize some of the peculiar microstructural figures of sleep such as spindles and K-complexes, and to understand the fundamental relationships between sleep and synaptic plasticity, learning and consciousness. Its application is not limited to neurophysiology, being recently also applied to study some sleep related psychiatric and neurological disorders such as depression, schizophrenia, attention-deficit hyperactivity disorder, and stroke. adding some interesting new pieces in the pathophysiological puzzle of these diseases. Due to its non-invasive, repetitive and reliable tempo-spatial resolution it is reasonable that the field of application of this tool will be soon enlarged to other areas of neuroscience.

The present review aims to offer a complete overview regarding the use of high density EEG over the last decade in sleep research and sleep medicine, including its possible future perspective.

1. Introduction

Understanding the mechanisms underlying sleep pathophysiology is one of the most stimulating challenges of modern neuroscience. Both electrophysiology and neuroimaging have provided so far fascinating insights in the field, mainly thanks to the modern techniques such as functional magnetic resonance imaging (fMRI), high density electroencephalography (HD-EEG) and magnetoencephalography (MEG).

Since its development in the 1920s, electroencephalography (EEG) remains the gold standard technique in recording brain activity with high temporal resolution, reaching a sub-millisecond time scale. Standard EEG montages, however, are unable to locate the precise source of the signal, leading to a poor spatial resolution. High-density EEG (HD-EEG) attempts to overcome these spatial limitations by covering the scalp with up to 256 electrodes, a much higher number than used for a standard EEG. The high density of electrodes increases the spatial accuracy, allowing localizing precisely the source of the cortical signal in real-time, or even detecting hidden EEG features (Holmes et al., 2010). Nevertheless, the HD-EEG instrument does not provide any further qualitative information in respect to standard EEG, and the huge amount of data collected requires a post-processing analysis to achieve significant results.

Nowadays, HD-EEG technique is mainly used in clinics to better identify the epileptic focus, usually in the context of pre-surgical screening. However, this tool is well suitable for various applications in brain research and in particular in the field of sleep pathophysiology. Several sleep-related specific EEG figures such as delta waves, spindles and K-complexes have already been addressed by HD-EEG, leading to interesting theories concerning their physiological role. At the moment, the application of HD-EEG in sleep physiology and in sleep disorders should still be considered preliminary, consisting mainly in the comparison of EEG sleep features between healthy subjects and subjects with psychiatric or neuro-degenerative diseases.

The present review aims to provide the state of the art on the most recent results of the application of HD-EEG in sleep research. A systematic research of the most recent literature was conducted on PubMed, using the terms "high-density EEG", "dense-array EEG" and the combination of both with "brain", "sleep", "sleep disorders", "sleep physiology", "sleep slow waves", "sleep homeostasis", "spindles", "K-complex" and "source localization". The first section of the review focuses on sleep neurophysiology (Table 1), while the second one on sleep in some neurological and psychiatric disorders (Table 2). At the end, possible promising future applications of HD-EEG in sleep are briefly discussed.

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Table 1
High-density EEG in sleep physiology.

Authors and year	Topic	Methods	Findings
Huber et al. (2004)	Local sleep and learning	11/10 subjects (sleep/wakefulness group) Learning task and subsequent sleep recording (256 EEG channels)	Local increased on SWA on the right parietal lobe (Brodmann areas 40 and 7) associated with learning
Masimini et al. (2004)	Sleep slow and traveling wave	8 healthy subjects HD-EEG (256 channels)	Anterior–posterior propagation, stable across the night
Massimini et al. (2005)	Cortical connectivity during sleep	6 subjects HD-EEG (60-channels) + TMS	Breakdown of transcallosal and effective connectivity during NREM sleep
Riedner et al. (2007)	Sleep homeostasis and cortical synchronization	7 healthy male subjects HD-EEG (256 channels)	Slow wave downscaling across the night. Markers of downscaling process: SWA, slow-wave slope, increased multi-peak wake wave
Kurth et al. (2010)	SWA and cortical maturation	55 healthy subjects in the first 2 decades of life HD-EEG (256 channels)	SWA posterior–anterior shift, stable across the night.

Abbreviation: SWA = slow wave activity, TMS = Transcranial Magnetic Stimulation (TMS).

1.1. High density EEG background

HD-EEG is a dense array scalp EEG recording system, consisting in pre-cabled cuffs connected to a digital amplifier and preferably to a dedicated computer. The number of electrodes used can vary from 32 to 256. The huge amount of data recorded requires an adequate storage capacity and a post-processing computing. Dense array EEG cannot be inspected visually as standard EEG, but only provides quantitative EEG data. The analysis consists in different steps from the "cleaning" of the signal to data elaboration. Getting rid of the artifacts is one of the challenges approaching HD-EEG: firstly by detecting and rejecting bad channels and then applying different methods based on Blind Source Separation (BSS) and Independent Component Analysis (ICA). Substantially, the aim of the two algorithms is to decompose the signal recognizing different components which can be visually detected separately and removed without affecting the underlying signal, or else analyzed to recognize specific signals. The BSS method has been used mainly in the field of brain computer interface development, in order to recognize scalp EEG signals associated with specific motor tasks or parts of the body. The main application of HD-EEG is in the field of epilepsy, where increased number of electrodes helps to unmask hidden epileptic EEG features and allows a more precise source localization. Therefore, source imaging techniques, already developed for MEG, have been implemented to HD-EEG (as LORETA and LAURA) to localize epileptic focuses. Currently, HD-EEG tool is not proposed for clinical routine but it is restricted to research purposes. Within the research settings, its high costs have to be considered in relationship to the expected results, as it happens for other expensive innovative research techniques (i.e. fMRI).

2. Physiology

Sleep microstructure seems to be a good target for HD-EEG, in particular in characterizing the typical polysomnographic markers of NREM sleep, such as slow waves, spindles, vertex spikes and K-complexes. These phasic sleep-related EEG figures express the fine regulation of brain activity during sleep. The understanding of these basic mechanisms is essential to improve our knowledge about sleep neurophysiology.

2.1. Slow wave activity (SWA)

The NREM sleep-specific slow cortical waves, well described by Steriade in 1993 (Steriade et al., 1993a, 1993b, 1993c), became one of the primary focuses of the research on cortical activity during sleep. The so-called slow wave activity (SWA) shows a frequency band below 4.5 c/s, which appears and progressively increases through the NREM sleep deepening, reaching its maximum representation in stage N3 (frontal EEG frequency ranging between 0.5 and 2 Hz, occupying more than 20% of a sleep epoch) (Silber et al., 2007). Since 1937 it is known that SWA reflects sleep "intensity" (Blake and Gerard, 1937). Further studies confirmed that unresponsiveness to external stimuli increases during SWA (Williams et al., 1964). Moreover, within the entire restorative homeostatic process of sleep, SWA is believed to significantly contribute to learning and memory consolidation (Tononi and Cirelli, 2006; Diekelmann and Born, 2010).

2.1.1. Sleep homeostasis

SWA is intimately linked to the concept of sleep homeostasis, whereby increasing SWA is a function of the prior waking period and decreasing SWA occurs during the course of sleep. SWA runs in parallel to what is called the *sleep pressure* or *sleep need* or *process S*, which is high at the beginning of the sleep episode, after a consistent period of wakefulness, and declines across sleep (Borbély and Achermann, 2000). The amount of SWA is higher during the first part of the night compared to the second part, where sleep encompasses a larger amount of multi-peak slow activity, which represents the decrease in synchronization of neuronal networks throughout the sleep processes. At that point, most of the homeostatic function of sleep is already over, and the need of strong cortical synchronization measurable as SWA is lower. Multi-peak slow waves represent the sum of the asynchronous generation of slow waves among distant cortical sources introducing the concept of "local sleep" consisting in the idea that SWA is an expression of spatially distinct cortical sources oscillating at their own frequency (Esser et al., 2007; Vyazovskiy et al., 2007). This connection between SWA and the restorative role of sleep, in terms of homeostatic function, has been tested in nap and after sleep deprivation. Naps occurring in the early morning (close to the previous night sleep episode) contain less SWA than naps taken in the late afternoon, when the sleep episodes occur after a longer period of wakefulness (Dijk et al., 1987). Eventually, the overall amount of SWA within the nighttime sleep of a subject who took a nap during the day is lower than the one measured in a subject who didn't sleep during the previous day. Moreover, SWA increases for a rebound phenomenon in the recovery night after sleep deprivation (Huber et al., 2000a, 2000b).

HD-EEG allowed a fine characterization of the SWA in terms of spatial resolution providing important pieces of information on the neurophysiological meaning of SWA. Whole night sleep recording by HD-EEG showed that during the first NREM sleep cycle there is a high proportion of large-amplitude slow waves with a steep slope, while in the last NREM cycle the proportion of large-amplitude slow waves was significantly lower and slow-wave slopes were reduced (Riedner et al., 2007). The slope of slow waves during sleep is thought to represent the most direct reflection of synaptic strength available in the EEG signal (Whitlock et al., 2006; Vyazovskiy et al., 2007; Riedner et al., 2007). According to the theory of the homeostatic function of sleep, together with the decrease of SWA across the night, the brain undergoes a downscaling process during sleep period to optimize the synapses gained during wakefulness in