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The slow-wave components of the cyclic alternating pattern (CAP) have a role in sleep-related learning processes

Raffaele Ferri [a,*], Reto Huber [b], Debora Aricò [a,c], Valeria Drago [a,d], Francesco Rundo [a], M. Felice Ghilardi [e], Marcello Massimini [b], Giulio Tononi [b]

[a] *Sleep Research Centre, Department of Neurology I.C., Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Via Conte Ruggero 73, 94018 Troina, Italy*
[b] *Department of Psychiatry, University of Wisconsin, Madison, Madison, WI, USA*
[c] *Department of Neurological Sciences, University of Bologna, Bologna, Italy*
[d] *Department of Neurology, University of Florida, Gainesville, FL, USA*
[e] *City University of New York, New York, NY, USA*

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Abstract

Slow waves, a key feature of the EEG of NREM sleep, may be causally involved in producing a sleep-dependent, progressive downscaling of synaptic strength, which would lead to several benefits in terms of both cellular function and network performance. Also the A1 subtypes of the so-called cyclic alternating pattern (CAP) are composed mostly of slow waves and map over the frontal and prefrontal regions of the scalp. The aim of this study was to evaluate the eventual changes of CAP induced by an implicit learning paradigm which has already been shown to be able to increase locally sleep slow-wave activity (SWA). Our hypothesis was that learning is accompanied by a change in the components of CAP characterized by SWA (0.5–2.5 Hz), i.e. its A1 subtypes. For this reason, in the present study we evaluated sleep recordings obtained in 10 healthy young normal subjects (mean age 25.8 ± 1.8 years) who were asked to perform a motor learning task just before going to sleep. Sleep EEG was recorded for 2 h and subjects were also tested after the night following the rotation task. Sleep stages and CAP (classified into three subtypes: A1, A2, and A3) were identified in the first hour of each recording. We found a significant increase in the number of CAP A1 subtypes per hour of NREM sleep on the night following the rotation test; the correlation between the change in A1 index and the post-sleep performance improvement after the rotation task was positive. These results confirm our hypothesis that CAP slow components are modified by a learning task during the day preceding sleep and support the idea that these components may play a role in sleep-related cognitive processes.

Keywords: Cyclic alternating pattern; Sleep slow-wave activity; Sleep-related cognitive processing; Synaptic downscaling hypothesis

Slow waves are a key feature of the EEG of NREM sleep. Moreover, sleep slow-wave activity (SWA, frequency range between 0.5 and 4 Hz) is homeostatically regulated, increasing in proportion to the duration of wakefulness and decreasing in the course of sleep [3,2]. Although the physiological processes underlying the homeostatic regulation of slow waves are still unknown, it has recently been suggested that sleep SWA may reflect the net strength of synapses in cortical circuits, which would therefore increase with wakefulness and decrease with sleep [3,2,37]. Also, slow waves may also be causally involved in producing a sleep-dependent, progressive downscaling of synaptic strength, which would lead to several benefits in terms of both cellular function and network performance [37,19,23], and some recent studies seem to confirm this hypothesis [19,38,18,32,21,26].

According to Terzano et al. the so-called cyclic alternating pattern (CAP) [34,20,35] is a periodic EEG activity of NREM sleep characterized by repeated spontaneous sequences of transient events (phase A) which clearly breaks away from the background rhythm of the ongoing sleep stage, with an abrupt frequency/amplitude variation, recurring at intervals up to 1 min long. The return to background activity identifies the interval that separates the repetitive elements (phase B). CAP sequences are defined as three or more A phases separated from each other by no more than 60 s. The percentage of NREM occupied by CAP sequences defines the CAP rate. All the remaining NREM sleep, not occupied by CAP sequences is called NCAP. Three main

* Corresponding author. Tel.: +39 0935 936111; fax: +39 0935 936694.
E-mail address: rferri@oasi.en.it (R. Ferri).

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EEG patterns have been described according to the prevalence of EEG synchronized slow-waves (subtype A1), prevalence of EEG fast rhythms (subtype A3), or a combination of both (subtype A2) [35]. The hierarchical activation from the slower EEG patterns (moderate autonomic activation without sleep disruption) [5,10,28] to the faster EEG patterns (robust vegetative activation associated with visible sleep fragmentation) can have different meanings: A1 subtypes are involved in the build-up and maintenance of deep NREM sleep and can have a protective role for sleep continuity; A2 and A3 can have the function of maintaining the subject arousability [33].

Importantly, the A1 subtypes of CAP [34,20] are composed mostly of slow waves [35,7] and map over the frontal and prefrontal regions of the scalp [8,12]. This makes CAP slow waves good candidates for a role in sleep-related cognitive processing [6] and some preliminary indication has already been found [25,9,24].

The aim of this study was to evaluate the eventual changes of CAP induced by an implicit learning paradigm which has already been shown to be able to increase locally sleep SWA [19]. Our hypothesis was that learning is accompanied by a change in the components of CAP characterized by SWA (0.5–2.5 Hz).

For this reason, in the present study we reevaluated the same recordings obtained for a previous study [19] in 10 healthy young normal subjects (mean age 25.8 ± 1.8 years). Subjects were asked to perform a motor learning task just before going to sleep. In this task, subjects reached for visual targets using a hand-held cursor while unconsciously adapting to systematic rotations imposed on the perceived cursor trajectory [19,16]. This rotation adaptation task was chosen because it is an implicit learning paradigm; it is suitable for extended sessions; it permits accurate parameterization of both performance improvement and noise reduction; it can be contrasted with a no-rotation task that has the same kinematic requirements and is subjectively indistinguishable from it. Finally, this task, in contrast with the no-rotation task, activates circumscribed brain regions (that is, right parietal areas 40 and 7 [16]).

Over a number of movements, all subjects adapted to the imposed rotation by progressively reducing the directional error of their trajectory as well as its variance. Immediately after the rotation adaptation task, the sleep EEG was recorded using a 256-channel system (Electrical Geodesics) inside a soundproofed room; for the present study 19 channels were selected and used, according to the international 10–20 system (Fp2, F4, C4, P4, O2, F8, T4, T6, Fz, Cz, Pz, Fp1, F3, C3, P3, O1, F7, T3, T5). As whole night recordings with the available high-density EEG was not possible, the cap was removed after 2 h and subjects were then allowed to sleep undisturbed for the rest of the night (all reported satisfactory, restful sleep). Subjects were also tested after the night following the rotation task; in this condition, the directional error decreased further, corresponding to a performance enhancement of $11.1 \pm 3.0\%$ above and beyond the level achieved at the end of awake training [19].

As a control condition, 1 week earlier or later, subjects performed the no-rotation task, where the requirements were kinematically identical but the cursor was not rotated [16,17].

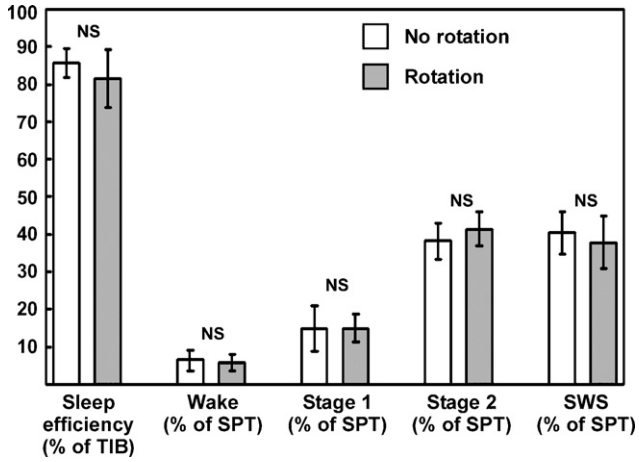

Fig. 1. Sleep efficiency and stages after the rotation and no rotation conditions; values are shown as mean (bar) and SE (whiskers). Sleep stages were scored on the C3-A2 and C4-A1 EEG channels [27].

In the present study, CAP and sleep stages were identified in the first hour of each recording after lights out because the previous investigation showed significant changes of the sleep slow-wave activity mostly during this period of time [19]. Sleep stages were scored by the first author following standard criteria [27] on 30 s epochs. Subsequently, all CAP A phases were detected in each recording, during NREM sleep, and classified into three subtypes (A1, A2, and A3), according to the rules defined by Terzano et al. [36]. CAP A phases were visually marked on screen by means of the sleep analysis software Hypnolab 1.2 (SWS Soft, Italy), taking into account the 19 EEG channels listed above. This process allowed us to obtain a complete characterization of the sleep macrostructure (stages) and microstructure (CAP).

Fig. 1 shows the results of sleep staging; sleep efficiency and stages after the rotation and no rotation conditions are substantially the same and show no statistically significant differences (nonparametric Wilcoxon test for paired data sets); no REM sleep was detected during the first hour of recording. On the contrary, when CAP parameters were considered (Fig. 2), we

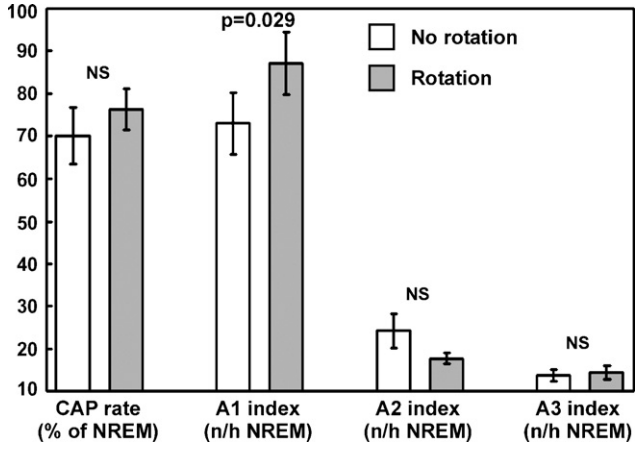

Fig. 2. CAP parameters after the rotation and no rotation conditions; values are shown as mean (bar) and SE (whiskers). CAP was scored as an average on all 19 channels visualized on screen (see text).

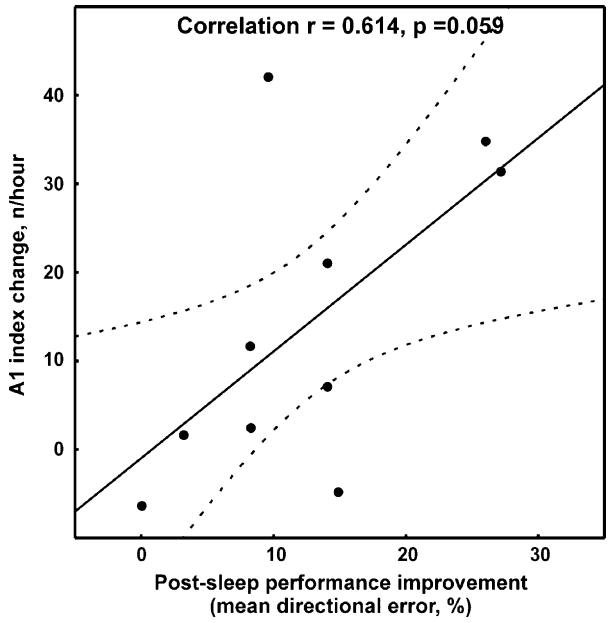

Fig. 3. Correlation between the change in CAP A1 index and performance improvement at the rotation test in the 10 normal subjects included in this study.

found a significant increase in the number of CAP A1 subtypes per hour of NREM sleep (A1 index) in the first hour of recording of the night following the rotation test, as compared to that following the no-rotation condition. This increase was accompanied by a nonsignificant increase in CAP rate and a decrease in A2 index. Finally, the correlation between the change in A1 index and the post-sleep performance improvement after the rotation task (Fig. 3) was positive and almost reached statistical significance (Pearson correlation coefficient).

The results of this new analysis confirm our original hypothesis that CAP components characterized by sleep SWA are modified by a learning task during the day preceding sleep. These results also support the idea that these components may play a role in sleep-related cognitive processes favoring performance improvement after learning.

We have shown previously that A1 CAP subtypes are generated mostly in the anterior frontal regions of the brain [8] and are characterized by a high spatial synchronizing effect [11] which involves probably cortico-cortical pathways connecting the frontal regions of the two hemispheres [12]. Cortico-cortical regulation of SWA is implicated in the local regulation of sleep, as suggested also by a series of other studies which have analyzed the mechanisms of generation and propagation of sleep slow waves [23,18,22]. However, the new clues obtained from the present analysis point to the need to take into account not only the spatial arrangement of SWA but also its dynamic time structure, as shown by the evident involvement of CAP.

An interesting way to take into consideration both the local spatial and temporal organization of SWA during sleep was recently suggested in a paper reporting that sleep SWA shows a small world-like network architecture [13]. The term "small-world" network derives from the graph theory and defines an organization with many local connections and a few random long distance connections, with intermediate features between ordered and random networks [40]. This means that although most of the connectivity is local, the network remains highly integrated due to a small number of long distance connections. It has been suggested that a small-world network architecture may be optimal for synchronizing neural activity between different brain regions and for information processing in complex systems [40,30].

With the results of this study, we can speculate that a particular learning task during the day might be followed, during the night, by an increased SWA regulated by a complex mechanism integrating local and long distance connectivity, needed for processing new information and consolidating memory and learning, and based on the formation of synchronized neuron assemblies. The integration of information processed in widely distributed neural systems in the brain is thought to depend, at least in part, upon the formation of synchronized cell assemblies; however, flexible information processing requires not only the formation, but also the dissolution of synchronous cell assemblies. This idea of consecutive synchronization and desynchronization processes underlying higher brain function has been suggested by several authors [29,31,4,15,39] and might be an important mechanism of NREM sleep probably reflected by SWA and CAP in the scalp EEG.

Finally, our findings should be considered in the more general framework of sleep-related memory and learning processes which seem to be regulated by more complex mechanisms involving in coordinated, differential and specific ways wakefulness, REM and NREM sleep [1,14].

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