Title: Loss of integration of brain networks after one night of sleep deprivation underlies worsening of attentive functions

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Abstract

The topological characteristics of brain networks changes according to environmental demands and can be described under the framework of graph theory. We hypothesized that 24-hours long sleep deprivation (SD) causes functional rearrangements of the brain topology so as to impair optimal communication, and that such rearrangements relate to changes in specific cognitive tasks, especially the ones requiring attention. Thirty-four young men underwent MEG recording and assessments of attention and switching abilities before and after SD. We found loss of integration of brain network and a worsening of attention but not of switching abilities. This results showed that brain network changes due to SD selectively impaired attention and forced the brain to put in place a compensatory mechanism to preserve the switching ability as the nature of the presented stimuli involved differently the top-down and bottom-up processing.

Introduction

The introduction of neuroimaging techniques has allowed us to overcome the concept according to which cognitive functioning is under the control of specific brain areas, rather identifying it as a distributed property. Historically, behavioural functions have been associated to localized brain structures (e.g. the Broca area for language production). More recently, converging evidence has showed that more complex, associative functions, cannot be as easily associated to localized areas, but rather need distributed coordinated activity across multiple, diffuse areas (McGonigle et al., 2000, Ascoli et al., 2004). Hence, complex functions such as

attention, memory and reasoning are modulated by a "multifocal neural system" formed by multiple interacting areas (McIntosh, 2000; Mesulam, 1990). As a consequence, capturing the complex patterns of coordinated activity is necessary in order to explain higher cognitive functions. To this regard, mathematical tools such as "Graph Theory" lands themselves nicely to the study of the brain (Sporns, 2018). Under this framework the brain is conceptualized as a complex system of interacting units (Medaglia et al., 2015), represented as nodes (brain areas) linked by edges (structural, functional or causal interactions) (Bullmore & Sporns, 2009; Friston, 2011). This way, some topological features of the macroscopic, long-range connections, have been described consistently, such us "small-worldness" (Watts & Strogatz, 1998) and "scale-freeness" (Barabási & Albert, 1999). Such topological structure allows an optimal and efficient communication under spatial and energetic constraints. Consequently, pathological conditions that disrupt this optimally tuned configuration are deleterious, both as excessive disconnections (as happens in Alzheimer disease; (Heringa et al., 2014)) and in terms of hyperconnectedness (as it occurs in epilepsy and amyotrophic lateral sclerosis (Sorrentino et al., 2018). In fact, while, on the one hand, disconnectedness hinders efficient communication, hyperconncetedness, on the other hand, impairs brain flexibility and re-adaptation (Sorrentino et al., 2020).

Sleep is an active physiological process during which the body recovers, and it is essential for the well-being and for optimal behavioral and cognitive performance. For example, both NREM and REM sleep promote learning and memory consolidation (Klinzing et al., 2019; Tononi & Cirelli, 2014). In particular, non-REM (NREM) sleep is relevant to many cognitive functions (Anderson & Horne, 2003; Lafortune et al., 2014; Walker, 2009; Wilckens et al., 2016, 2017): increases in amplitude of low-frequency slow wave activity (SWA) during NREM sleep is associated with improved executive functions (Wilckens et al., 2016), while the increase of SWA during NREM sleep is crucial for memory consolidation (Staresina et al., 2015). Wilckens showed that higher delta EEG power (0.5–4.0 Hz), particularly within NREM period, has been associated with better working memory, set-shifting, and reasoning in older adults (Anderson & Horne, 2003; Wilckens et al., 2016). Furthermore, Clark et al. (1998) reported that the relative power in the low frequencies in the frontal EEG channels during the NREM phase was directly related to the performance in neuropsychological tests assessing prefrontal functions.

Accordingly, insufficient or poor sleeping negatively affect mood and cognition, and the effects of sleep deprivation (SD) are evident at both the behavioral and physiological level. In fact, SD affects memory, executive functions and attention (Tomasi et al., 2009; Chee & Chuah, 2008; Lim & Dinges, 2012). In particular, SD selectively impairs top-down but not bottom-up processing (Gevers et al., 2015), two mechanisms underlying adaptative behavior (Moore & Zirnsak, 2017). On the one hand, top-down processing is internally induced, and information is sought out voluntarily. On the other hand, bottom up processing is driven by the salient features of the stimuli (Katsuki & Constantinidis, 2014) .

EEG-based and neuroimaging evidence indicate that sleep loss affects primarily the frontal lobes. For instance, studies have shown that sleep pressure (i.e. the felt urge to sleep), reflects itself in increased theta power density mostly in the frontal areas (Cajochen et al., 2001; Finelli et al., 2000).

Neuroimaging researches have thoroughly investigated the effects of SD on cognition and brain connectivity, and several fMRI studies reported a change in network topology. SD is often associated with reduced connectivity within the dorsal attention network, the visual network and especially the default mode network (DMN) (Gao et al., 2015; Kaufmann et al., 2016; Yeo et al., 2015). A prolonged wakefulness acts against the physiological decoupling between DMN and attentional networks (Fox et al., 2005), and this feature is associated with the worsening of cognitive performances. In particular, impairment of vigilance and attention (Lim & Dinges, 2008) are related to the alteration of the changes in the salience and attentional network (Ma et al., 2015).

While fMRI offers optimal spatial resolution, it is suboptimal in terms of temporal resolution. Furthermore, the estimation of functional connection in fMRI is done by correlating the amplitudes of the signals. However, typical electrophysiological activity unfolds in faster frequency bands, and is partly expressed as neuronal oscillations. While EEG has optimal temporal resolution, it shows poor spatial resolution, given that the electric fields are distorted by the layers surrounding the brain. To that regard, MEG is a useful complementary neuroimaging technique as it allows an optimal trade-off between spatial and temporal resolutions, capturing part of the activity that goes undetected with fMRI and EEG (Baillet, 2017; Lopes da Silva, 2013). Based on source-reconstructed magnetoencephalography signals, we built a functional network where the links represent the extent to which two signals are synchronized. To estimate synchronization, we choose the phase linearity measurement (PLM), a purely phase-based metric designed to be robust to noise and insensitive to volume conduction (Baselice et al., 2019) of the network (van Wijk et al., 2010). In order to avoid potential biases induced by different edge densities or average degrees (van Wijk et al., 2010), we used the minimum spanning tree (MST; Tewarie et al., 2015), obtaining comparable networks (Tewarie et al., 2015).

To the best of our knowledge, this is the first MEG-based study on SD. Therefore, here we present an experimental design to evaluate the physiological and behavioral effects of 24-hour long SD. On the basis of the available evidence, we hypothesized that SD modifies brain oscillatory activity, leading to modified topology and less efficient communication. We further hypothesize that such topological rearrangements would relate to cognitive performance. To this end, 34 young adults underwent MEG recordings and assessments of attentional functions and switching abilities before and after 24h of SD. Observed topological changes were then correlated to cognitive performance.

Results

Cognitive assessment

Letter Cancellation task (LCT)

In order to evaluate the attentional function, the LCT was performed by participants. Participants must identify and mark 3 target letters within an array of distracting letters.

Accuracy: on average, dependent *t*-test showed a better performance (t_{33}=2,8; p=.009) during T0 (mean ± sd = 142.18 ± 24.01) than T1 (mean ± sd = 130.94 ± 33.67) (Fig.1a).

Speed: With regard to the number of rows, that is the number of lines inspected within the task time limit, the dependent *t*-test revealed a significant difference between the two different experimental sessions (t_{33}=3,2; p=.003), indicating a faster time to complete the test during T0 (mean ± sd = 18,97 ± 3.58) than T1 (mean ± sd =17.58 ± 3,92) (Fig.1b).

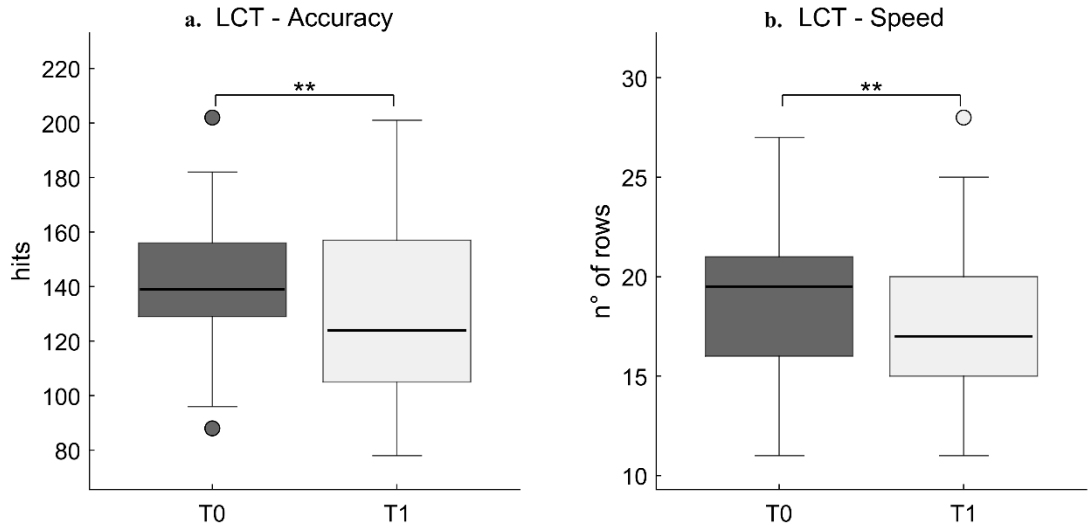

Fig.1 Letter Cancellation Test (LCT). *Performance in LCT show the worsening of attentional funciton: accuracy (Fig.1a) and speed (Fig.2b) were reduced in T1 in respect to T0. ** = p<.01*

Task Switching (TS)

In order to evaluate the switching abilities, the participants performed the TS. This task requires selecting the appropriate response based on the type of stimulus presented. Reaction times, switch cost (as measure of executive control) and errors were assessed.

Reaction times (RT): surprisingly, two-factor repeated-measures ANOVA revealed a significant main effect of Time on RT ($F_{1,33}$ = 15.82; p < .0001; ηp2 = 0.32), indicating, regardless of the trial, a higher RT at T0 (mean ± se = 758.18 ± 34.49) than T1 (mean ± se = 706.5 ± 28.73).

There was also a significant main effect of Trial on RT ($F_{1,33}$ = 39.4; p < .0001; ηp2 = 0.54), revealing a faster RT in Repetition trials (mean ± se = 704.45 ± 28.6) than Switch trials (mean ± se = 787.23 ± 33).

Finally, a significant interaction effect was found between Time and Trial ($F_{1,33}$ = 12.74; p = .001; ηp2 = 0.28; Repetition trials: T0 (mean ± se) = 729.25 ± 32.24; T1 (mean ± se) = 679.66 ± 27.77 (Fig.2a); Switch trials: T0 (mean ± se) = 841.1 ± 38.94; T1 (mean ± se) = 733.37 ± 30.71 (Fig.2b).

Error proportion (EP): two-factor repeated-measures ANOVA revealed a significant main effect of Trial on EP ($F_{1,33}$ = 8.79; p = .006; ηp2 = 0.21), indicating, regardless of the time, a higher accuracy during repetition (mean ± se =1.49 ± .01) than switch trials (mean ± se =1.44 ± .02). No other significant effects were observed.

Switch cost (SC): dependent *t*-test showed, on average, a higher SC (t_{33}=3,57; p=.001) at T0 (mean ± se = 111.85 ± 18.81) than T1 (mean ± se = 53.7 ± 11.24) (Fig.2c).

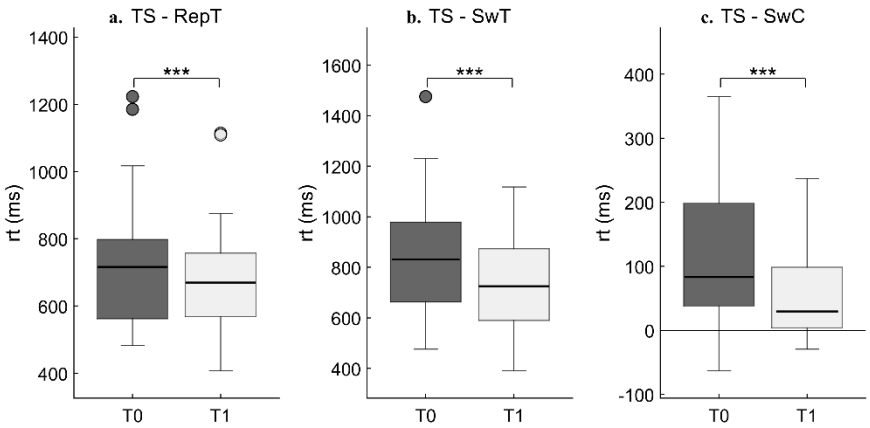

Fig.2 Task Switching. *Task switching (TS) show a reduction in time reaction (rt) both in repetition trial (RepT; Fig.2a) and Switch trial (SwT; Fig.2b). Even the Switch cost (SwC; Fig.2c) was reduced after 24h of sleep deprivation. *** = p<.001*

Subjective evaluations

KSS and NASA have been used to assess the level of subjective sleepiness and perceived cognitive load. KSS results showed an increased level of sleepiness after 24 hours of sleep deprivation (Fig.3a; mean ± se; T0: 4,73±0,31, T1:7,82±0,24; *p*<.001) and the NASA index reported an increase in the score in T1 compared to T0 (Fig.3b; mean ± se; T0: 46±2,80, T1:54,91±3,63; *p*<.05).

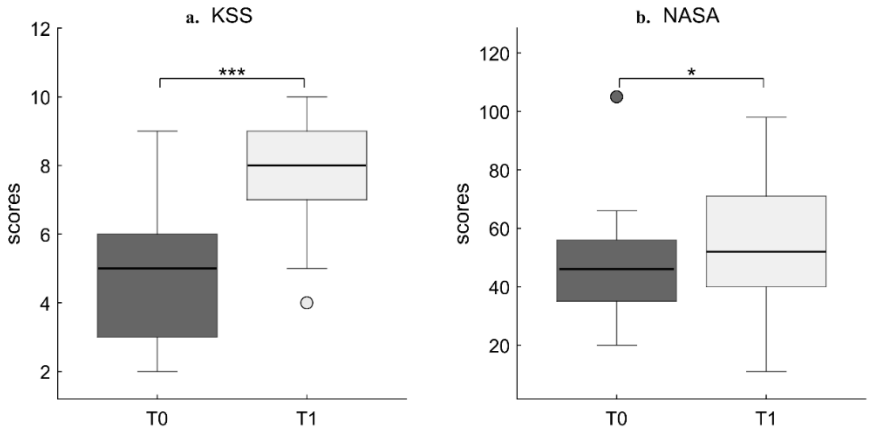

Fig.3 Subjective evaluation. *Participants reported a significant increase in the subjective level of sleepiness (KSS; fig.3a) and cognitive load perceived (NASA; fig.3b) in T1 compared to T0. * = p<.05, *** = p<.001*

Topological analysis

Analysis for the global parameters showed an increase of the Diameter in Alpha (Fig.4a; median ± IQR; T0: 8,66 ± 1,44; T1: 9,33, 1,15; *p*<.001) and Delta (Fig.4b; median ± IQR; T0: 6,82±0,97, T1: 7,40±1,23; *p*<.05) band in T0 compared to T1. No other global parameter (leaf fraction, degree divergence, eccentricity and three hierarchy) was different between the two group. Among nodal parameters, there was a decrease in the alpha band of the degree in T0 with respect to T1, in particular in the right Superior Occipital gyrus (Fig. 5a; median

± IQR; T0: 1,94±1,06, T1: 1,57±0,53; *p*<.05) and right the Middle Occipital gyrus (Fig.5b; median±IQR; T0: 2,23±0,84, T1: 1,83±0,75; *p*<.05). No significant difference was found in BC.

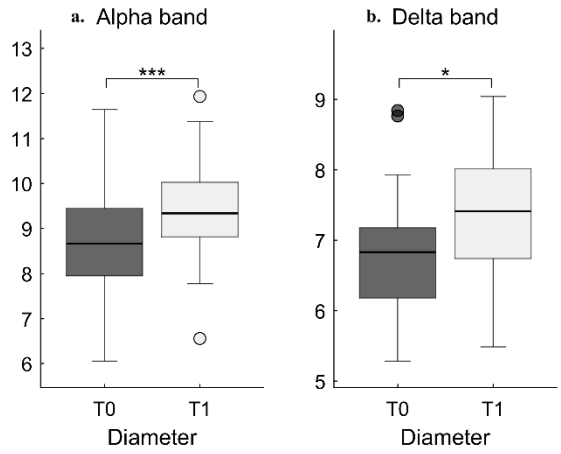

Fig.4 Topological analysis; Diameter. *Statistical comparison between T0 and T1 show a significant increase in diameter in alpha (fig.4a) and delta (fig.4b) bands after 24h of sleep deprivation. * = p<.05, *** = p<.001*

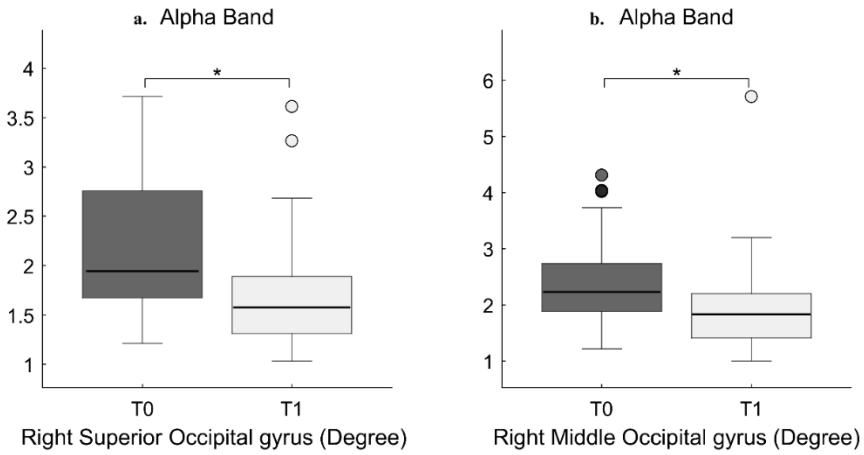

Fig.5 Topological analysis; Degree. *Statistical comparison between T0 and T1 show a significant decrease in degree in alpha band in right superior occipital gyrus (fig.5a) and right middle occipital gyrus (fig.5b). * = p<.05*

Correlation between brain topology, performance and sleepiness

In order to evaluate a possible relationship between network rearrangements and cognitive functioning, we carried out a correlation between topological parameters, test performance and subjective evaluations. Specifically, Pearson's correlation analysis showed a positive correlation between KSS and diameter in alpha (Fig.6a; *p*=.035; r=0,255) and delta (Fig.6b; *p*=.037; r=0,252) bands, highlighting that prolonged wakefulness causes a rearrangement of the brain network topology which becomes less integrated and efficient. Conversely, a reverse correlation was found between KSS and degree in right Superior Occipital gyrus (Fig.6c; *p*=.009; r=-0,311) and right Middle Occipital gyrus (Fig.6d; *p*=.003; r=-0,351) in alpha band, showing that SD affects specific areas that decrease connectivity within the brain network. However, despite the worsening of the topological characteristics of the network, the performance in the switching ability improves after the SD, as

showed by the reverse correlations between diameter in alpha band and Repetition trial time reaction (rt RepT) (Fig.6e; *p*=.008, r=-0,316) and between diameter in alpha band and Switch trial time reaction (rt SwT) (Fig.6f; *p*=.004, r=-0,344).

LCT performance and NASA score were not correlated with topological data.

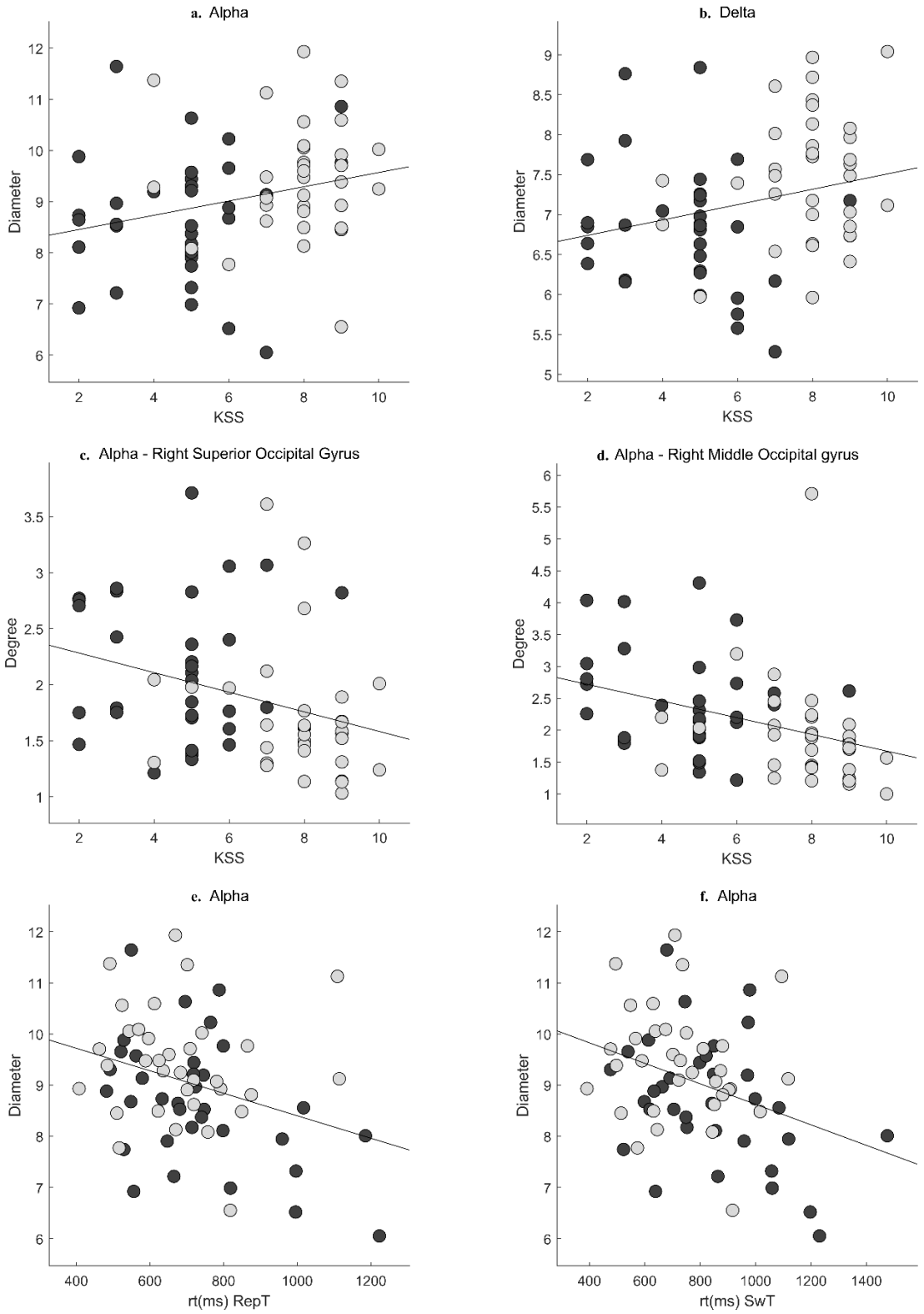

Fig.6 Correlation analysis. *Pearson's correlation between topology, performance and sleepiness. T0● ; T1●*

Discussion

SD is a typically harmful condition for the brain. With regard to moderate sleep deprivation the main cognitive effects concern attentional functions and higher order cognition. Moreover, SD is known to cause changes in neurophysiological activity.

In this paper, we set out to test the hypothesis that sleep deprivation causes functional rearrangements in the brain so as to impair optimal communication, and that such rearrangements relate to changes in specific cognitive tasks, especially the ones requiring (active engagement) sustained attention.

SD negatively influences attentional functions as evident from the worsening in the speed and accuracy of the LCT. Our data are in line with Casagrande et al., (1997) showing that the effect of SD on cognitive performance are prominent in tasks requiring high attentional load (in both short and long tasks). In our study, the impairment of attentional functions was demonstrated by the worsening in the three letter searching task. Accordingly, several authors (Lanteaume et al., 2016; Lim et al., 2010; Lim & Dinges, 2008) reported that attention is among the firsts functions affected by SD. Given the nature of the task, the attention deficit was possibly due to the weakening of the top-down processing, an internally induced process in which information is sought on voluntarily chosen factors.

A counterintuitive scenario was observed in the TS task where performance appeared worse at T0 than at T1, as shown by both higher RTs and SCs. Coherently, also SCs appeared to be reduced as a consequence of sleep deprivation. This unexpected effect of a single night of sleep loss cannot be ascribed to data instability. In fact, as an indirect measure of data goodness, statistical comparison of reaction times and error proportions at task switching highlighted faster RTs and reduced EP in repetition than switch trials, as expected on the light of previous literature, and this trend was confirmed in both pre- and post-sleep deprivation sessions.

The topological results obtained show that after SD the brain network undergoes topological rearrangements both at the global and the nodal level. Global metrics allow to characterize the widespread remodelling of large-scale brain activity. We found increased diameter after SD in the alpha and delta bands. The diameter is defined as the longest shortest path of a graph (Tewarie et al., 2015); a network characterized by a low value of this property presents a functional configuration with a few central nodes mediating long-range communication (Bullmore & Sporns, 2009; Van Den Heuvel et al., 2009; Van Den Heuvel & Sporns, 2011); this arrangement is advantageous as it allows efficient communication throughout the entire network, at the cost of increased risk of node overload (Stam, 2014). Conversely, a higher diameter implies a less compact topology with, on average, longer paths to go between any two nodes. This implies that the relative importance of nodes is more homogeneous (Rubinov & Sporns, 2010). Given the redistribution of the workload across the brain network, the node overload risk might be reduced. The nodal parameters showed a decrease in the degree in the alpha band in the right Superior occipital gyrus and in the right Medial occipital gyrus in T1 with respect to T0. The degree is defined as the number of connections for a given node (Tewarie et al., 2015), and a high degree indicates that a specific area is connected to many other areas, likely playing a central role. In our case, the SD caused a reduction in the degree on the right Superior and Medial Occipital gyrus. Evidence supporting the incidence of SD on the occipital lobe has been highlighted by EEG studies that reported a reduction in the

amplitude of the ERP/ERF N1 component, associated with the processing of stimuli in primary sensory areas, particularly for visual–evoked potential (Arce & Guevara, 1999). Boonstra et al. (2005) showed a posterior-anterior shift in which alpha power decreased in the occipital regions and increased in the frontal regions. One intriguing interpretation of our findings could be that the system parallelises the information processing onto more nodes, hence reducing the workload on overloaded areas, at the cost of reducing global network efficiency. However, such interpretation remains purely speculative. Top down attention is important for the identification of the characteristics of a relevant object in relation to irrelevant stimuli and it is not by chance that it has been shown to be a process also, but not only, related to the activation of visual areas (Noudoost et al., 2010). In support of this, Tomasi et al. (2009) reported a reduced activation of dorsal fronto-parietal attention network, occipital area and most importantly an altered thalamo-cortical activity.

Finally, we found that the changes in the network relate to the perceived sleepiness, as evidenced by the direct correlation between the diameter and KSS and the inverse correlation between the degree and KSS.

The inverse correlation between the diameter and the TS performance showed that topological rearrangements are related to cognitive performance. In particular, the sleep-deprived subjects have a less integrated topology and, it is also the case that the more they do, the better they perform the reaction times at TS. One possible interpretation would be that topological rearrangements are put in place to respond to sleep deprivation by redistributing the computational load across the network, which in turn results in a better performance. However, caution should be used when interpreting the data, given that the brain measures are made at rest and not during the execution of the task.

It is well known that a correct balance between global and local efficiency is important (Sporns et al., 2000). After 24 hours of prolonged wakefulness, the brain networks appeared to have modulated its overall integration. Recently, the achievement of the correct balance between integration and segregation has been related to neurotransmitter-specific pathways. More specifically, cholinergic neurons have a strong influence in promoting segregation. Cholinergic tone is known to be modulated by wakefulness via the inhibition induced by adenosine (AD) on acetyilcholine (ACh) (Boonstra et al., 2007; Shine, 2019). In fact, during SD, the increase in AD causes an inhibition of the cholinergic system that, from the basal forebrain, project widely towards subcortical and cortical structures including the visual, somatosensory and prefrontal cortex controlling the selective visual attention (Moore & Zirnsak, 2017; Noudoost & Moore, 2011). These are the areas that we found to be altered. In addition to Ach, noradrenaline (NA) is another neuromodulator that macroscopically influences the network topology. Noradrenergic projections from the locus coeruleus are widespread to the whole brain and recent studies using whole-brain functional neuroimaging support the role of NA as a promoter of network integration (Shine, 2019). Furthermore, high levels of NA have been associated with the ability to shift between different task sets (Aston-Jones & Cohen, 2005) and other higher order functions such as cognitive control. Despite the decreased integration that makes the network less efficient, it is surprising that after 24h of SD the participants performed better the TS. Our interpretation of this evidence is that this type of task is more engaging: in this case, the processing of information is externally induced by the stimuli presented which are elaborated through a bottom up mechanism that does not seem to

suffer from the effects of SD. In fact, selective damage to top down versus bottom up mechanisms after sleep deprivation has been demonstrated by Gevers et al. (2015). Thus, the brain network, was able to support optimal performance by compensating through greater cognitive effort as suggested by the increased cognitive load detected through NASA. The increase in cognitive load compared to an unchanged performance is in line with Tomasko et al., (2012) that showed that SD increases the cognitive load of learning surgical procedures that were otherwise well performed.

In conclusion, the current work shows that 24h of SD affect the topology of the brain network making it less integrated. The less integrated brain network causes selective damage to the attentional function but not to the switching ability. This is probably related to the fact that the stimuli of the two different tasks are processed in different ways through bottom-up and top-down processing, which are affected differently by sleep deprivation. This way while unable to cope with attentional requests, the brain puts in place compensation mechanisms to facilitate the response to more engaging stimuli.

Material and Methods

Participants

Thirty-four young adult males were recruited (mean age ± SD, 24,8 ± 2,83 years) from the neurology course. All participants were right-handed and none of them had a history of medical, neurological or psychiatric illness nor of medication or drug intake. Requirement of inclusion were normal sleep duration and no excessive daytime sleepiness. Quality and quantity of participants usual sleep and daytime sleepiness were assessed by Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989), the Epworth Sleepines Scale (ESS; Johns, 1991) and Karolinska Sleep Diary (KSD; Akerstedt et al., 1994). From the third day before the beginning of the experimental procedure each participant was required to maintain a regular sleep-wake cycle and actigraphic recordings (wActiSleep-BT, ActiGraph-BT, Pensacola, Florida) were collected to control subjects compliance. The intake of coffee, beverages containing stimulating active ingredients and intense physical activity were prohibited starting from 24 hours before the experimental procedure which was performed during the week to avoid changes related to weekend activities.

All subjects gave their written informed consent. The study was approved by Ethical Committee of Psychological Research of the Department of Humanities of the University of Naples Federico II (n prot 11/2020) and was conducted in accordance with the Declaration of Helsinki.

Cognitive assessment

Letter Cancellation Task (LCT)

The Letter Cancellation Task (M. Casagrande et al., 1999; Maria Casagrande et al., 1997) requires participants to search and sign sequentially (from left to right and from top to bottom), as fast and as accurately as possible, three target letters within a 36 x 50 matrix of capital letters (fonts: New York, 12”) printed on an A4 paper sheet. A maximum completion time of 3 minutes was allowed. Every target appeared 100 times in a random sequence; for each matrix, 300 hits were possible. To avoid learning effects, different parallel forms were used.

The following dependent variables were considered: number of hits (as measures of accuracy) and number of rows completed (as index of speed).

Task Switching (TS)

In task-switching, two different tasks are performed in rapid succession and according to a random sequence of task presentation, so that the task to be executed might change from one trial to the next ("switch" trial), or be repeated ("repetition" trial). Task switches are usually slower and less accurate than task repetitions, and this difference is often referred to as the "switch cost" (SC). This cost is thought to reflect the time needed for the executive control processes to reconfigure the cognitive system for the execution of a new task (Rogers & Monsell, 1995; Rubinstein et al., 2001) so that it can be considered an operational measure of the executive control (Couyoumdjian et al., 2010).

All the participants were individually tested in a well-lit, sound-proof room. They were seated in front of a 15-inch computer monitor, at a distance of 50 cm, and at the beginning of each session, task instructions were both displayed on the screen and explained verbally by the experimenter, emphasizing the need for both accuracy (avoiding errors) and speed (minimize reaction times). In this study, the two tasks require deciding if a digit stimulus was odd or even (task A), or if it was greater or smaller than 5 (task B). In each trial of the two tasks, a cue (the "square" or "diamond" respectively) indicated the specific task (A or B) to perform on the subsequent target stimulus that appeared inside the cue. Experimental subjects used their left and right index fingers to provide your response: odd digits and digits smaller than 5 were mapped onto the left index finger response, whereas even digits and digits larger than 5 were mapped onto the right index finger response. The same two response keys on the computer keyboard ('A' for left and 'L' for right index finger) were used for both tasks. Stimuli presentation and response recordings were managed to employ custom software (Superlab, version 4.0.4 for Windows, Cedrus Corporation). Each participant initially performed a training session (1 block of 80 trials) followed by an experimental session consisting of 320 trials, arranged in 4 blocks of 80 trials each. On each trial, a cue was presented for 1000 ms, and then it was followed by a target stimulus that remained on the monitor until the participant's response. A schematic description of the present task-switching paradigm is reported in Figure 7.

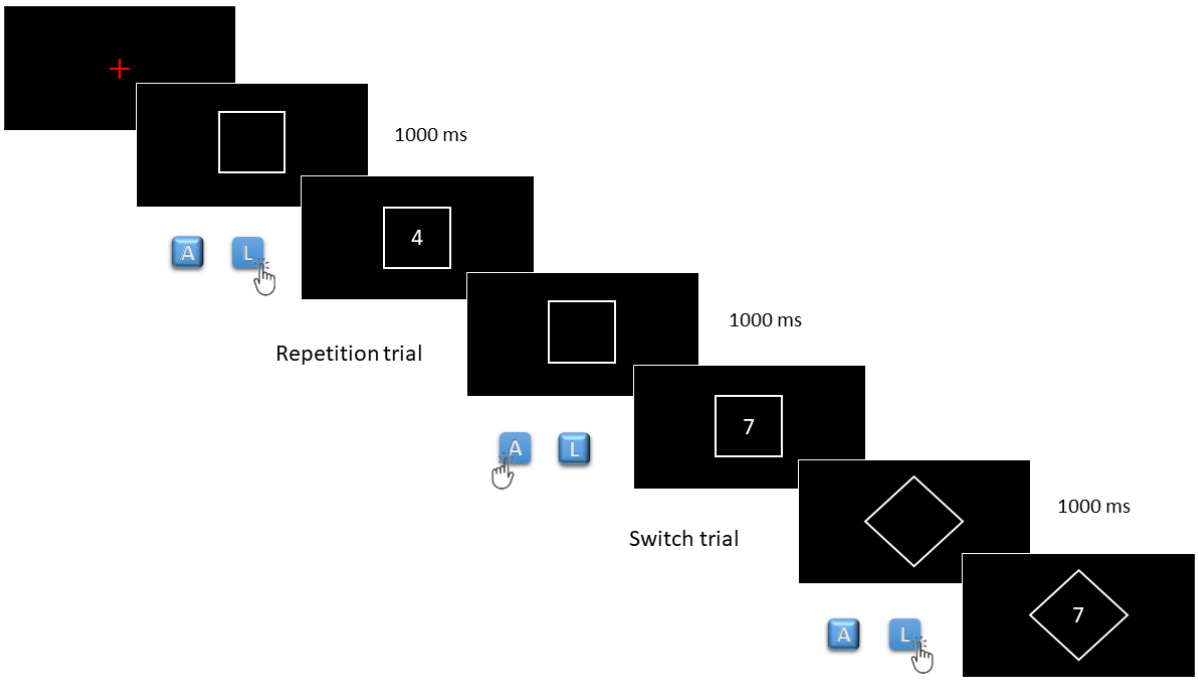

Fig.7 Schematic representation of Task Switching. *The two tasks require deciding if a digit stimulus was odd or even (task A), or if it was greater or smaller than 5 (task B). In each trial of the two tasks, a cue (the "square" or "diamond" respectively) indicated the specific task (A or B) to perform on the subsequent target stimulus that appeared inside the cue. The "L" key (right index finger) of the keyboard key was used provide the response "even" or "larger than 5", while the "A" key (left index finger) was used to respond "odd" or "less than 5". Each participant initially performed a training session (1 block of 80 trials) followed by an experimental session consisting of 320 trials, arranged in 4 blocks of 80 trials each. On each trial, a cue was presented for 1000 ms, and then it was followed by a target stimulus.*

Subjective evaluations

In both sessions we assessed the perceived subjective state of sleepiness through the administration of the Karolinska Sleepiness Scale (KSS; Akerstedt et al., 1994), and the cognitive load by mean the NASA Task Load Index (NASA**;** Hart, 2006**).**

MEG acquisition

The MEG system was developed by the National Research Council, Pozzuoli, Naples, at Institute of Applied Sciences and Intelligent Systems "E. Caianiello" (Granata et al., 2018). This tool is equipped by 154 magnetometers and 9 reference sensors located on a helmet, useful, respectively, to reveal the magnetic fields produced by the electrical activity of neurons and for detecting environmental noise. The MEG system was placed inside a room shielded from external magnetic fields (AtB Biomag UG - Ulm – Germany). Before signals recording, four position coils were placed on the participant's head and digitized by using Fastrak (Polhemus®). The coils were activated and localized at the beginning of each segment of registration. The magnetic fields were recorded for 7 minutes, divided into two time intervals of 3'30", while the participants were sitting comfortably in an armchair in the cabin with their eyes closed without sleep. Before the

acquisition, for each participant, a standardized instruction to stay with eyes closed was communicated through intercom. Electrocardiogram (ECG) and electro-oculogram (EOG) signals were also recorded during the aquisition. The data were sampled at fs=1024 Hz and a pass-band filter between 0.5 and 48 Hz was applied offline, during data pre-processing after the recording phase.

After recording phase, the brain magnetic fields were cleaned through an automated process as described in our previous article (Sorriso et al., 2019). The FieldTrip software tool (Oostenveld et al., 2011), which is based on Mathworks® MATLAB™ environment, was used to implement two calculation functions: the principal component analysis (PCA) to reduce the environmental noise and the independent component analysis (ICA) to remove the physiological artefacts such as cardiac noise or eyes blinking (if present). For each participant, the cleaned trials longer than 4s were selected. On the letter a beamforming procedure was performed using the Fieldtrip toolbox. Based on a magnetic resonance imaging (MRI), the volume conduction model proposed by Nolte was considered and the Linearity Constrained Minimum Variance (LCMV) beamformer was implemented to reconstruct time series related to the centroids of 116 regions-of-interest (ROIs), derived from the Automated Anatomical Labeling (AAL) atlas. Subsequently the Phase Linearity Measurement (PLM) was performed to provide an adirectional estimate of the connectivity that is purely based upon the phases of the signals, indeed this metric detects if the signals evolve linearly over time. The PLM is defined by the following equation:

$$PLM = \frac{\int_{-B}^{B} \left| \int_{0}^{T} e^{i\Delta\emptyset(t)}\, e^{-i2\pi f\, t} dt \right|^{2} df}{\int_{-\infty}^{\infty} \left| \int_{0}^{T} e^{i\Delta\emptyset(t)}\, e^{-i2\pi f\, t} dt \right|^{2} df}$$

where the $\Delta\emptyset(t)$ represent the phase difference between two signals, the 2B is the frequency band range, f is the frequency and T is the observation time interval.

By computing PLM for each couple of brain regions, we obtained a 90×90 weighted adjacency matrix for each epoch and for each subject, in all of the frequency bands: delta (0.5–4 Hz), theta (4.0–8.0 Hz), alpha (8.0–13.0 Hz), beta (13.0–30.0 Hz) and gamma (30.0–48.0 Hz). The weighted adjacency matrix was used to reconstruct a brain network, where the 90 areas of the AAL atlas are represented as nodes, and the PLM values form the weighted edges. For each trial longer than 4s and for each frequency band, through Kruskal's algorithm, the minimum spanning tree (MST) was calculated. The MST is a loop less graph with N nodes and M= N-1 links. The MST was computed to obtain topologic measures that are unaffected by the degree distribution, matrix density, or arbitrary thresholds.

Later, we calculated both global and nodal parameters. The global parameters include: the *diameter* (D), is the longest shortest path of an MST; the *leaf fraction* (L), providing an indication of the integration of the network and is defined as the fraction of nodes with a degree of 1; the *degree divergence* (K) a measure of the broadness of the degree distribution, related to the resilience against attacks; the *tree hierarchy* (Th) defined as the number of leaf over the maximum betweenness centrality. The nodal parameters include: the *degree* (k), defined as the number of connection incident on a given node; the *betweenness centrally* (BC) described as the number of

the shortest paths passing through a given node over the total of the shortest paths of the network. Before moving to the statistical analysis, all the metrics were averaged across epochs in order to obtain one value for subject. A pipeline of the processing MEG data is illustrated in Figure 8.

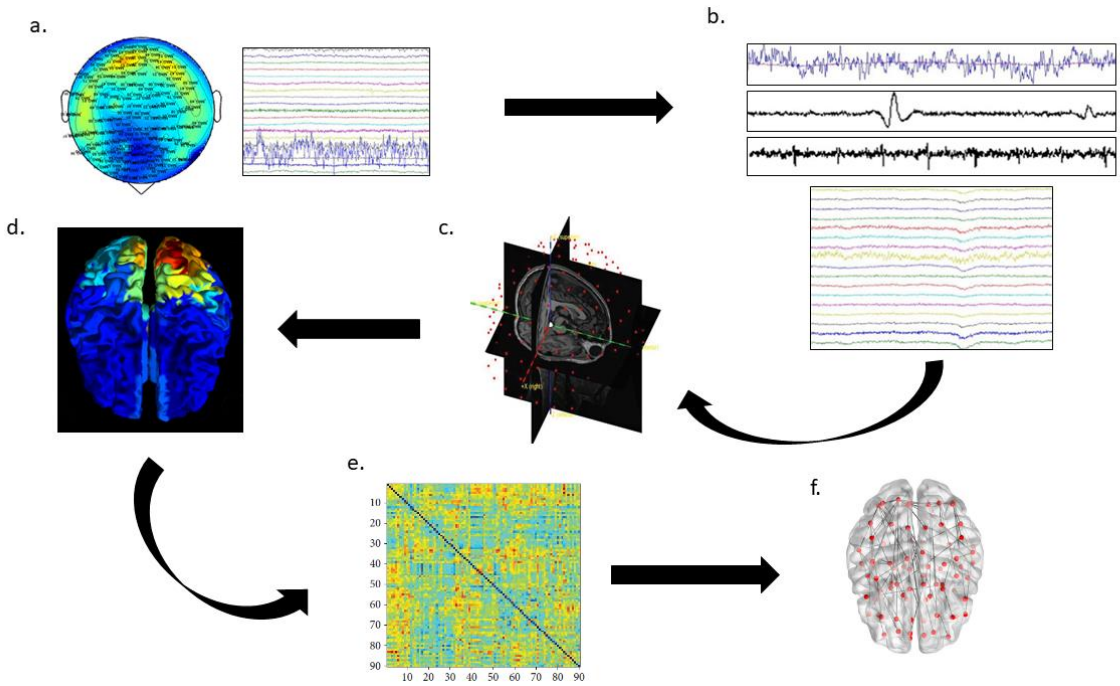

Fig.8 Data analysis pipeline: *a) MEG signal recorded by 154 sensors; b) noisy channels, cardiac and blinking artifacts (upper) are removed to obtain the cleaned signals (lower); c) MRI and MEG sensors are coregistered (beamforming); d) model of brain volume: the activity on the sensor level is projected onto brain regions (based on the AAL atlas); e) connectivity matrix estimated using the PLM; f) brain network representation based on the MST.*

Procedure

Experimental protocol included two sessions which took place at 09.00 a.m. at day 1 (T0) and 24 hours later at day 2 (T1). The participants underwent to: MEG recordings; KSS; TS; LCT; NASA. During experimental sessions, participants were seated on a comfortable chair in a soundproof room. After the first session the participants were free to return to their daily life activities. At 09.00 p.m. they returned to the laboratory to begin the sleep deprivation night under the supervision of the experimenters. Lying down and sleeping were not permitted.

MRI acquisition

MRI images of thirty-four young adult males were acquired on a 1.5-T Signa Explorer scanner equipped with an 8-channel parallel head coil (General Electric Healthcare, Milwaukee, WI, USA). MR scans were acquired after the MEG recording. In particular, three-dimensional T1-weighted images (gradient-echo sequence Inversion Recovery prepared Fast Spoiled Gradient Recalled-echo, time repetition = 8.216 ms, TI = 450 ms, TE = 3.08 ms, flip angle = 12, voxel size = 1×1×1.2 mm1; matrix =256x256) were acquired.

Statistical analysis

In order to assess the potential variations of participant's executive performance during the two experimental sessions (T0 vs T1), and to assess how both the sleep deprivation and the consequent increase in sleepiness can affect their performance, we run a two different statistical analysis, respectively two-factor repeated-measures ANOVA, with Time and Trial as within factor, and paired *t*-test.

In particular, with regards to TS, median reaction times (in ms; median RT) to both repetition and switch trials, and angular transformations of the proportion of errors resulting from the two experimental sessions were submitted to two-factor repeated-measures ANOVA, instead, SC as well as all dependent variables obtained from LCT (number of hits and number of rows completed), were submitted to paired *t*-test. SCs were computed as the difference between median switch RT and median repetition RT. Proportions of errors were computed by including both incorrect and missing responses. Before statistical analysis, this variable was submitted to an angular transformation, y=arcsen [sqr(p)], where sqr(p) is the square root of the proportion. All statistical analyses were performed using IBM SPSS Statistics for Macintosh, version 25.0 (IBM Corp., Armonk, NY, USA).

As regard the topological data, statistical analysis was performed in Matlab (Mathworks®, version R2018b). Non parametric Wilcoxon test was performed to compare T0 and T1 in all frequency bands, after check the normal distribution of variables through the Shapiro-Wilk test; all *p*-values were corrected for multiple comparison using the false discovery rate (FDR).

Subsequently, Pearson's correlation index was used to find possible correlations between topological data and behavioral performances. Therefore, the correlation analysis was carried out between topological parameters and scores at cognitive tests (LCT, TS) and subjective evaluation (KSS, NASA). Alpha level was fixed at 0,05.

Competing interest

All authors declare no competing interest.

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