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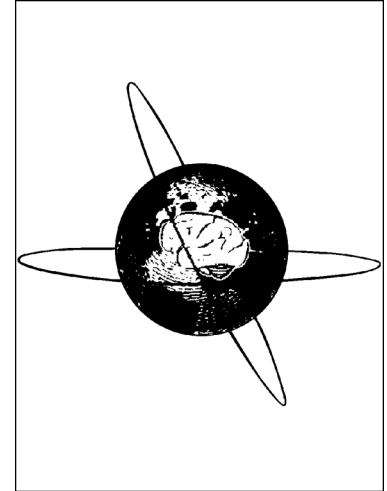
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**The brain network organization during sleep onset after deprivation**

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**Abstract**

**Objective** Aim of the present study is to investigate the alterations of brain networks derived from EEG analysis in pre- and post-sleep onset conditions after 40 hours of sleep deprivation (SD) compared to sleep onset after normal sleep in 39 healthy subjects.

**Methods** Functional connectivity analysis was made on electroenceelographic (EEG) cortical sources of current density and small world (SW) index was evaluated in the EEG frequency bands (delta, theta, alpha, sigma and beta).

**Results** Comparing pre- vs. post-sleep onset conditions after a night of SD a significant decrease of SW in delta and theta bands in post-sleep onset condition was found together with an increase of SW in sigma band. Comparing pre-sleep onset after sleep SD versus pre-sleep onset after a night of normal sleep a decreased of SW index in beta band in pre-sleep onset in SD compared to pre-sleep onset in normal sleep was evidenced.

**Conclusions** Brain functional network architecture is influenced by the SD in different ways. Brain networks topology during wake resting state needs to be further explored to reveal SD-related changes in order to prevent possible negative effects of SD on behaviour and brain function during wakefulness.

**Significance** The SW modulations as revealed by the current study could be used as an index of an altered balance between brain integration and segregation processes after SD.

**Keywords:**

EEG; sleep; brain network; small world; graph theory.

**Highlights**

- A night of sleep deprivation affects EEG during the subsequent recovery sleep.
- Brain networks organization is modified during the wakefulness-to-sleep transition.
- During sleep, EEG connectivity resembles more a small-world network organization.

## 1 Introduction

Sleep deprivation (SD) is associated to substantial cognitive impairment of attention, memory, executive function and reflexes during wakefulness, with a detrimental impact on multiple domains of functioning in the following day wakefulness activities (Chee et al., 2010, Cirelli and Tononi, 2008, Goel et al., 2009, Lei et al., 2017, Mu et al., 2005, Tkachenko and Dinges, 2018). Functional neuroimaging has shown that sleep loss produces changes in hippocampal, thalamic, amygdaloid circuits (Shao et al., 2014, Shao et al., 2013, Yoo et al., 2007) and in the dorsolateral prefrontal cortex (Bosch et al., 2013). The electroencephalogram (EEG) is also extensively affected by SD (Borbély, 1990, Borbély et al., 1981, Dijk and Beersma, 1989). Some studies demonstrated that EEG modifications in consciousness in the descent to sleep are characterized by a lower thalamo-cortical connectivity during sleep onset (Spoormaker et al., 2010) and by a general connectivity interruption in the slow-wave sleep, limiting the brain ability to integrate information through functional modules. Moreover, as a measure of a homeostatic response, EEG power increases in the whole low frequency (<8 Hz) range during both REM and NREM sleep in most brain regions, with the exception of temporal areas (Marzano et al., 2010). Despite such a bulk of evidence on the massive cortical and subcortical changes consequent to SD clearly suggest a perturbed functional brain connectivity as compared to that of wakefulness, still few studies have explored eventual changes of brain network architecture after SD with graph theoretical measures.

The graph theory – that has been lately used to describe the dynamics of the networks- has offered an insightful framework of brain modulation in several conditions including SD. In fact, empirical evidence suggested that the small worldness – that is an index of balancing of (global) integration and (local) segregation of the cerebral connections- significantly changed during wakefulness after SD (Koenis et al., 2013, Liu et al., 2014).

Few studies have been devoted so far to cortical connectivity during sleep; they reported that brain networks exhibit *small world (SW)* characteristics in sleep and in normal wakefulness, and that EEG functional connectivity during sleep moves toward a small-world network organization (Ferri et al., 2008).

A study of functional magnetic resonance imaging (fMRI) by Liu and colleagues showed that the SW significantly increased after SD (Liu et al., 2014) as a compensatory effect, and Koenis and colleagues observed that after SD, the networks presented a more random architecture in the EEG alpha band and a more ordered one in the gamma band (Koenis et al., 2013).

However, the mentioned studies have only evaluated connectivity during wakefulness after SD, without any evaluation of its impact on normal sleep in the following night(s). If SD induces changes in network architecture and provokes alteration of the SW characteristics of brain connectivity during the subsequent resting wake, how does the brain connectivity change during the first sleep experience subsequent to a prolonged SD? In this scenario, a massive local brain heterogeneity characterizes the shifts between states of vigilance and, especially, sleep onset [i.e., concerning regional EEG differences in temporal (Marzano et al., 2010) and spatial (Broughton and Hasan, 1995, Marzano et al., 2010, Wright et al., 1995) changes across the transition]. After some pioneering studies (Ogilvie and Harsh, 1994, Ogilvie et al., 1991, Ogilvie et al., 1989, Santamaria and Chiappa, 1987), the quantitative indices of EEG activity have revealed an uniform increase of EEG power in the frequency range between 1 and 16 Hz after sleep onset which was considered as the first epoch of stage 2 (De Gennaro et al., 2001a). Furthermore, low-frequency EEG rhythms are more activated in the anterior brain regions, while higher frequencies (> 8 Hz) are prominent in the occipital areas over pre-sleep wake (De Gennaro et al., 2001b, Marzano et al., 2010). It was further demonstrated that the alpha activity (i.e., in the frequency range 8-12 Hz) spreads toward the frontal areas, and that the progressive EEG synchronization over NREM sleep is characterized by an increase of low-

frequency activity in the centro-frontal areas, and by a prevalence of centro-parietal maxima in the sigma band (i.e. in the frequency range 12-14 Hz) (De Gennaro et al., 2001b, Marzano et al., 2010). Moreover, it is worth mentioning that changes in fronto-posterior functional EEG coupling characterize sleep onset (De Gennaro et al., 2004). Further studies on electrocorticographic data of epileptic patients (Bódizs et al., 2005) have outlined a dynamic involvement of multiple brain areas and of several EEG frequencies from an organized series of cortical changes, and have shown that wide cortical regions can preserve several minutes of activated patterns after the deactivation of the hippocampal (Sarasso et al., 2014) and thalamic (Magnin et al., 2010) structures. The temporal decoupling of neuronal oscillations among various cortical areas and between cortical and subcortical relays is further suggested by the simultaneous presence of wake-like and sleep-like EEG patterns in various cortical regions over sleep (Nobili et al., 2011).

On this respect, we recently outlined that the EEG networks organization changed during the wakefulness to sleep transition (Vecchio et al., 2017).

An EEG study by Verweij and colleagues (Verweij et al., 2014) demonstrated that – as revealed by global and local network parameters (as Characteristic Path Length and Clustering Coefficient) – SD more heavily influenced the functional connectivity of the prefrontal areas and that the maintenance of functional connectivity of the prefrontal brain regions takes a remarkable advantage for the restorative effect of sleep (Verweij et al., 2014). This mechanism could be of pivotal importance to understand whether brain functional networking could be down-graded by SD. The SW index – which represents a balance between local and global networks' modulation (Runinov and Sporns, 2010) – could provide a complex measure of the restorative effect of sleep on waking brain activity and might retrieve the ideal organization of the neuronal network architecture.

Within the track of this theoretical framework, the current study aimed to explore the brain networks modulation during the sleep onset, both after a night of normal sleep and after a night of sleep deprivation.

## 2 Methods

### 2.1 Participants

The study considered a database (Marzano et al., 2010) of 39 healthy subjects right-handed (20 females and 19 males; mean age=  $23.8 \pm 2.88$  yrs) and was conformed to the Declaration of Helsinki and national guidelines. The local Ethics Committee approved the experimental protocol and the informed consents were obtained from each participant.

The EEG data were recorded during the sleep onset in two conditions: after a night of normal sleep (NS) and after 40 hours of SD (Figure 1).

#### **Please add Figure 1**

During the experiment, participants were steadily under the supervision of at least one experimenter. They were free to carry on their favorite activities during the day, such as listening to music, reading, playing games or watching TV. Lying down, sleeping and strong physical activity were not allowed. Meals were scheduled at 08:30 am, 2:30 pm, and 7:30 pm. During the deprivation protocol, subjects were granted to have no-planned light snacks, while beverages with caffeine, alcohol, chocolate and medications that can alterate sleepiness were not allowed. Concerning the current study, 5 minutes of EEG were selected before and after sleep onset in a night of NS and after a night of SD. This interval was chosen according to the previous study on baseline sleep (Vecchio et al., 2017). Each subject underwent 19 EEG electrodes registration in a soundproof, temperature-controlled room. During the entire experimental procedure, the impedances between skin and

electrodes were maintained under 5 K $\Omega$ , and the system acquisition was settled up at 128 Hz sampling rate.

## 2.2 Preprocessing analysis

EEGs evaluation was carried out by means of the comparison between the 5-min pre sleep onset and the 5-min post sleep onset intervals. The time series of EEG power values were aligned based on the first sleep epoch, starting as soon as the first k-complex or sleep spindle appeared. Indeed, the first epoch of stage 2 sleep has been previously revealed to represent an unambiguous feature of the starting of sleep (De Gennaro et al., 2000; 2001).

In order to remove the very low and very high frequency artifacts (i.e., line artifacts), EEG signals were filtered from 0.1 to 47 Hz with a Finite Impulse Response (FIR) filter as implemented in Matlab R2018b (MathWorks, Natick, MA) (Vecchio et al., 2017b, Vecchio et al., 2015). Then, aiming to eliminate the residual artifacts (i.e. cardiac activity, eye movements, contractions of scalp muscles), for each subject's condition 2 seconds epochs were extracted and concatenated from continuous data, visually inspected and processed with Independent component analysis (ICA) by Infomax algorithm (Iriarte et al., 2003), with EEGLAB solution (EEGLAB 14.1.2b software, [www.sccn.ucsd.edu/eeglab](http://www.sccn.ucsd.edu/eeglab)). An expert EEGer analyzed components' properties and labeled for rejection (i.e. identifying EEG segments to subtract from the data). ICA was chosen because it resulted an efficient procedure for dividing artifact sources, such as blinking and eyes movements, from EEG data (Caliandro et al., 2017, Jung et al., 2000, Vecchio et al., 2014).

## 2.3 Functional connectivity analysis



The functional coupling between distinct brain regions can be evaluated by the functional connectivity, which represents the statistical interdependence of time-varying signals generated in such areas. Connectivity can be analyzed through different methods, for example with the study of the EEG coherence (Melgari et al., 2013, Zito et al., 2014). The total coherence is represented by instantaneous and lagged coherence. The lagged coherence is considered one of the most suitable methods for the evaluation of functional connectivity. The EEG connectivity depends on the timing and structure of the “excitable medium”, and does not occur instantaneously, due to axonal and synaptic conduction (Pascual-Marqui, 2007). The lagged coherence index allows to obtain reliable values of phase synchronization, as it is not affected by the effect of volume conduction or low spatial resolution and by the presence of active reference electrode. For these reasons, it is considered one of the most adequate measures of electrophysiological connectivity (Pascual-Marqui, 2007, Pascual-Marqui et al., 2011).

Functional connectivity analysis was made on EEG cortical sources of current density extracted by exact low resolution brain electromagnetic tomography (eLORETA) algorithm ([www.uzh.ch/keyinst/NewLORETA/LORETA01.htm](http://www.uzh.ch/keyinst/NewLORETA/LORETA01.htm)).

eLORETA provides a three-dimensional linear, distributed, discrete and weighted minimum norm inverse solutions. The exact localization to test point sources tomography is obtained by the specific weights applied in eLORETA, providing pictures of current density with proper localization, as well as affected by low spatial resolution (the closer neuronal sources are particularly correlated). The eLORETA solution was chosen as it provides a linear inverse solution for EEG signals with no localization error to point sources in noise-free situations (Pascual-Marqui, 2007).

In the current implementation of eLORETA, computations were made in a realistic head model, using the Montreal Neurological Institute (MNI) 152 template, with the three-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic Talairach atlas. The

standard electrode positions were taken on the MNI152 scalp. The intracerebral volume is divided in 6239 voxels with 5 mm of spatial resolution. Therefore, eLORETA images express the electric activity at each voxel in the MNI space as the proper magnitude of the evaluated current density. Anatomical labels as Brodmann areas are also reported using MNI space, with correction to Talairach space. Regions of Interest (ROIs) are used for the computing of the electric neuronal activity for the brain functional connectivity analyses. In order to evaluate the functional connectivity among brain areas, the cortical areas under the 19 EEG electrodes Fp1/2, F3/4, F7/8, C3/4, Fz, Cz, Pz, T3/T4, T5/6, P3/4, O1/2 of the international 10/20 system were considered. The signal of each ROI is the mean electric neuronal activities of all the voxels that belong to that ROI, as evaluated by eLORETA. The EEG data were divided in time points of 2 seconds length (2 sec epochs) and all of them were taken to construct the cortical source images of each subject.

In each subject, Intracortical Lagged Linear Coherence ( $LagR^2_{xyw}$ ) was computed on 84 ROI, 42 Brodmann Areas (BAs) of which belonging to the right emisphere and 42 BAs to the left one.

Started from the definition of the complex value of coherence (Nolte et al., 2004), between the two time series -  $x$ ,  $y$  - in the frequency band  $\omega$ :

$$r_{xyw} = \frac{ReCov(x,y) + iImCov(x,y)}{\sqrt{Var(x) \times Var(y)}}$$

is a function of the cross-spectrum obtained by the variances and covariance of the signals, with  $i$  the imaginary unit, the coherence squared modulus is:

$$r_{xyw}^2 = \frac{[ReCov(x,y)]^2 + [ImCov(x,y)]^2}{Var(x) \times Var(y)}$$

and the lagged linear coherence (Pascual-Marqui, 2007, Pascual-Marqui et al., 2011) is:

$$LagR_{xyw}^2 = \frac{[ImCov(x,y)]^2}{Var(x) * Var(y) - [ReCov(x,y)]^2}$$

where  $x$  and  $y$  are the time series between two BAs,  $Re$  is the real and  $Im$  is the imaginary part,  $Cov$  is the covariance and  $Var$  is the variance of the EEG time series (Vecchio et al., 2018c).

The lagged linear connectivity values evaluated between all pairs of ROIs are the weights of the graphs, as described below.

## 2.4 Networks analysis

When applying the graph theory to the study of the brain, nodes and edges of the graph should be associated to brain characteristics and/or functions. Brain networks can be weighted or unweighted, directed or undirected. In the present study, undirected and weighted networks were built: in particular, the graph nodes are represented by the 84 BAs and the edges are weighted by Lagged Linear Coherence values (Vecchio et al., 2018b, Vecchio et al., 2016).

Once designed the network architecture, parameters that describe network modulations should be computed. The parameter, which well designed anatomical and functional network, is described by the SW index. The SW networks combine the presence of functionally specialized (segregated) modules with a robust number of intermodular (integrating) links (Watts and Strogatz, 1998). The SW parameter is an indicator of the balance between global integration and regional connectedness of a network and it has been demonstrated that the SW network architecture might be ideal for the information processing in the complex systems (Watts and Strogatz, 1998). SW is an intermediate organization between that of regular neuronal assemblies, characterized by high network Clustering and long Path Length, and the random networks one, associated with shorter Path Length and lower level of Clustering (Rossini et al., 2016, Vecchio et al., 2018a).

SW is typically obtained calculating the ratio between the normalized Coefficient (C) and the normalized Characteristic Path Length (L). In this study the normalization was performed by dividing

C and L with the average values of C and L computed in all the EEG frequency bands for each subject (Miraglia et al., 2016, Miraglia et al., 2020, Miraglia et al., 2017, 2018, Tecchio et al., 2016, Vecchio et al., 2017, Vecchio et al., 2018b, Vecchio et al., 2019).

In weighted graphs, the weighted Clustering ( $C^w$ ) Coefficient is computed. It measures the local interconnection and is obtained by the sum of triangle intensities in which the  $i$ -th vertex participates, normalized with the higher possible number of triangles (Onnela et al., 2005, Rubinov and Sporns, 2010):

$$C^w = \frac{1}{n} \sum_{i \in N} \frac{2t_i^w}{k_i(k_i - 1)}$$

in which

$$t_i^w = \frac{1}{2} \sum_{j,h \in N} (w_{ij}w_{ih}w_{jh})^{1/3}$$

is the geometric mean of triangles around  $i$ ,  $w_{ij}$  are the connection weights related to links  $(i,j)$ .

Weights are normalized such that for all  $i$  and  $j$ ,  $0 \leq w_{ij} \leq 1$ .

The weighted Characteristic Path Length ( $L^w$ ) is an index of global integration and is computed as (Onnela et al., 2005, Rubinov and Sporns, 2010):

$$L^w = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^w}{n - 1}$$

where

$$d_{ij}^w = \sum a_{uv} \in g_{i \leftrightarrow j}^w(w_{uv})$$

corresponds to the shortest weighted Path Length among  $i$  and  $j$ .

Accordingly,  $C^w$  and  $L^w$  were normalized, and the SW index was computed as the ratio between the normalized  $C^w$  and the normalized  $L^w$ .

## 2.5 Statistical evaluation

Analysis of variance (ANOVA) was performed with Statistica v.7. ANOVA was chosen because it is considered a robust method with respect to the departure of normality and homoscedasticity of data being treated (Zar, 1984).

The first analysis was a two way ANOVA among the parameters of graph theory (SW, L, C) and the factors Time (pre-sleep onset, post-sleep onset) and Band (delta, theta, alpha, sigma, beta) aiming to study the differences before sleep onset and after it, when the subjects underwent a SD night.

The second analysis was a three way ANOVA between the parameters of graph theory (SW, L, C) and the factors Condition (NS, SD), Time (pre-sleep onset, post-sleep onset) and Band (delta, theta, alpha, sigma, beta) with the aim of studying the differences before and after sleep onset, both in the NS and SD nights.

Finally, a two way ANOVA was computed to compare pre-sleep onset in NS (pre-sleep onset in NS) and pre-sleep onset 40 hrs of SD (pre-sleep onset in SD).

Greenhouse and Geisser correction was applied in order to avoid the sphericity assumption violation in the repeated-measure ANOVA. Significance level was fixed at 0.05 in posthoc Duncan's test.

A further analysis was carried out in order to compare the pre-sleep and post-sleep onset conditions by means of their Lagged linear connectivity values. It was obtained by the statistical non-parametric mapping (SnPM) procedure Fisher's permutation test provided by the eLORETA solution. The maximum  $F$  statistic –represented by an empirical probability distribution– was evaluated with randomization, considering the null assumption that the Lagged linear connectivity values pre- and post-sleep onset were equal, for all the discrete bins of frequency within the groups. For each randomization test a total of 5000 permutations were utilized. The procedure is non-parametric, accordingly it is not require to meet any hypothesis of Gaussianity for its validity (Nichols and Holmes, 2002). Significance level was fixed at 0.05.

### 3 Results

Comparing pre-sleep vs. post-sleep onset after SD, the ANOVA showed a statistically significant interaction) among the parameters of graph theory (SW, L, C) and the factors Time and Band.

In particular, for the SW index ( $F(4,152)=15.974$ ;  $p=0.00001$ ), the Duncan post-hoc computations showed that in delta ( $F(4,152)=15.974$ ;  $p=0.000010$ ) and theta ( $F(4,152)=15.974$ ;  $p=0.000672$ ) bands the SW index decreased in post-sleep compared to pre-sleep onset, while in sigma band ( $F(4,152)=15.974$ ;  $p=0.000003$ ) the SW index increased in post-sleep (Figure 2) compared to pre-sleep onset (Table 1).

L ( $F(4,152)=18.410$ ;  $p=0.00001$ ) and C ( $F(4,152)=18.410$ ;  $p=0.00001$ ) showed significant interactions in the sigma and beta bands. In particular, the Duncan post-hoc comparisons revealed that in the sigma band L ( $F(4,152)=18.410$ ;  $p=0.00001$ ) and C ( $F(4,152)=19.175$ ;  $p=0.00001$ ) increased in post-sleep compared to pre-sleep onset, while in beta band L ( $F(4,152)=18.410$ ;  $p=0.00002$ ) and C ( $F(4,152)=19.175$ ;  $p=0.00003$ ) decreased in post-sleep compared to pre-sleep onset.

As control analysis, we computed the percentage of increase of L and C in the pre- and post-sleep onset conditions for sigma and beta EEG frequency bands. Results showed that the increase of C was a little higher (40.26%) than that of L (37.12%) in the sigma band, while the decrease of C (24.4%) and L (23.9%) were similar in the beta band. The current findings can explain which parameter between C and L was responsible for the SW modulation, and that the final increase of the SW depends on the fact that the increase of C was a little higher (40.26%) than that of L (37.12%) in the sigma band, while the similar decrease of C and L in beta band did not affect on the SW index significant difference in the beta band.

**Please add Figure 2**

Results of Lagged Linear Connectivity statistics showed significant differences ( $p < 0.05$ ) only at 12.5 Hz frequency, in the sigma band (exactly when the 0.5 Hz bin is centered at 12.5 Hz) in pre vs. post-sleep onset after SD. They are displayed by maps of the sources of EEG cortical activity in which the statistically significant differences between the conditions are indicated by the red lines (Figure 3). All the bins of the sigma frequency range have been subjected to the same analyses, without considerable differences.

**Please add Figure 3**

Comparing pre-sleep onset and post-sleep onset in NS and in SD, ANOVA showed no significant results. Comparing pre-sleep onset after SD versus pre-sleep onset after NS, the ANOVA showed statistically significant interaction ( $F(4,152)=4.7359$ ;  $p=0.00127$ ) between the factors Condition and Band for SW index only (Table 1). The Duncan planned post-hoc comparisons showed a decreased of SW index in beta band ( $F(4,152)=4.7359$ ;  $p=0.000563$ ) in sleep onset after SD compared to sleep onset in NS condition (Figure 4).

**Please add Figure 4**

Results of Lagged Linear Connectivity statistics showed significant differences ( $p < 0.05$ ) at 18 Hz frequency, in the beta band (exactly when the 0.5 Hz bin is centered at 18 Hz) in pre-sleep after SD vs pre-sleep onset after NS. Again, they are displayed by maps of the sources of the EEG cortical activity in which the statistically significant differences between the conditions are indicated by the red lines (Figure 5). All the bins of the beta frequency range have been subjected to the same analyses, without considerable differences.

**Please add Figure 5**

#### 4 Discussion

The present study has explored brain networks modulations in pre- and post-sleep onset conditions after 40 hours of sleep deprivation with respect to sleep onset in regular sleep condition.

Our results suggested that the SW parameter evaluated in pre and post-sleep onset condition after SD provoke significant changes of the SW index during baseline sleep onset. As previously reported (Vecchio et al., 2017), we have observed that in the low frequency bands (delta and theta) the SW index decreased in post-sleep onset vs pre-sleep onset interval, while in the higher frequencies (the sigma band) the SW presented the opposite trend.

Moreover, the current results demonstrated that the pre-sleep onset interval in SD, which precedes the recovery sleep after 40-h of prolonged wakefulness, is associated to a decrease of SW index in the beta band compared to normal sleep. The effect is maximally expressed in the parieto-occipital brain regions, as already previously observed in power distribution of beta parieto-occipital EEG rhythms (De Gennaro et al., 2007). Notably, differences between sleep and recovery sleep are not maintained after sleep onset. While the SW index modulation in the low EEG frequency bands and in the sigma bands is a substantial confirmation of changes of connectivity when subjects fall asleep, the effect on the beta frequency was not previously described.

With a different approach (i.e., using the directed transfer function (DTF), which provides a measure of the information flow direction supporting cortico-cortical functional coupling), we found a similar phenomenon during sleep onset. In that case, the beta band exhibited a significant flow from frontal- to parieto-occipital direction before sleep onset, suggesting that the effect of anterior-to-posterior direction of functional cortical coupling was already present in the pre-sleep onset period (De Gennaro et al., 2005) and that part of changes in cortical connectivity associated to falling asleep are anticipated when sleep pressure is raised by SD. Similarly, the topographical pattern detected



during baseline sleep was reproduced by a recent EEG study (Gorgoni et al., 2019) but with more intense changes at sleep onset in the frequencies  $\leq 10$  Hz, showing that the spatio temporal modulation of EEG activity during the process of falling-asleep is affected from sleep deprivation and induces the earlier emergence of sleep-related cortical oscillations.

Our results are in agreement with the assumption that a prolonged SD induces brain networks architecture to diverge from the ideal SW organization that is observed after a normal sleep night (Koenis et al., 2013). Indeed, brain network architecture after a night of sleep deprivation exhibits a shift towards a more regular organization with reduced small worldness presumably due to fact that the functional neuronal network is not able to “reset” to its optimal condition. The decrease of cognitive performance during wakefulness after SD (Chee et al., 2010, Goel et al., 2009, Lei et al., 2017, Mu et al., 2005) implies that the preservation and the restoration of an optimal network architecture for information processing is affected by sleep deprivation. Following the idea that sleep is a complex process where brain networks dynamically move across different states, compared to the state before the onset of sleep, in the current study we have performed the graph theory analysis because it is able to characterize complex networks through the SW index.

Current results are in line with previous evidences which suggested that after SD the network organization of the EEG signals move forward a more ordered architecture in the higher frequency bands (Koenis et al., 2013).

Moreover, others have demonstrated that the SD mainly affects a set of brain areas involved in the executive functions and in self-awareness processes, reducing long-/short-range functional connectivity density, and acts to other brain regions engaged in regulating arousal and sensory integration, increasing long-/short-range connectivity density, globally suggesting an altered integration/segregation ratio of the brain networks (Yang et al., 2018). This kind of

increase/decrease activation ratio might be at the basis of the modulation of SW as revealed by the current study.

Our findings in the beta band confirm the hypothesis of previous evidences that suggested that changes in the network of beta rhythms are related to worsened memory function and attentional lapses typical of sleep deprived people. Indeed, this band of frequency is implicated in memory activities (Axmacher et al., 2008, Herrmann et al., 2004) and in the binding processes needed for stimulate the achievement of consciousness (Gray et al., 1989, Nase et al., 2003). Sleep loss also induces deficits in many high-level cognitive functions, including working memory and decision-making (Harrison et al., 2000, Killgore et al., 2006) suggesting that sleep deprivation and aging have similar effects as decreased cognition performance and impaired brain function (Zhou et al., 2017). A growing evidence demonstrates that during an audiovisual task, the age-related differences are selectively evident in the EEG beta band (von Stein and Sarnthein, 2000), suggesting that the beta band connections have an important role in the communication track between far cortical regions engaged in visual, audiovisual and auditory processes (Sakowitz et al., 2005, Senkowski et al., 2008, Wang et al., 2017). The SD also generates a decrement of beta power frequency range in recovery from SD (Endo et al., 1998). The decrease of the beta activity which has been revealed over prolonged wakefulness (De Gennaro et al., 2007) and the reduction of the SW index following SD, suggested that highly integrated networks become less integrated during SD, whereas highly segregated networks become less segregated during SD (Yeo et al., 2015). Even if we found nearly significant differences when we compared SW changes in post-sleep conditions (normal vs recovery), future studies should include a sleep-deprived time point, in order to find new insights in SD effects on brain networks modulation.

As methodological remark, the low number of EEG channels recordings could be reported as a general limitation of this study. Certainly, EEG recordings with 32 or more channels represent a

research tool, but with difficulty can be introduced (and actually have not been introduced so far) in the clinical routine for recordings during wakefulness. This applies even more during sleep when the risk of electrocution is greater than the uncooperative state of the subject. Future insights could also try to extend the aims of the current study to EEG recordings with a larger number of electrodes.

Finally, future studies could extend the present results by describing the contrast maps using hierarchical modularity features in order to enhance the interpretation of the results revealing interesting hub areas related to NS and SD.

## 5 Conclusions

On the basis of the present results it is evident that sleep deprivation affects the functional brain network in different ways and its effects are linked to the different cognitive processes in which the EEG frequency bands are implicated (von Stein and Sarnthein, 2000).

Based on the current study and on previous evidences suggesting that EEG beta activity represents a marker of cortical arousal and EEG sleep sigma activity is an index of sleep protective mechanisms (De Gennaro and Ferrara, 2003, Spiegelhalder et al., 2012), functional brain networks topology over wake resting condition needs to be further explored to reveal and prevent possible negative effects of SD on behaviour and brain. In fact, most changes in cortical connectivity associated to falling asleep are anticipated when sleep pressure is heightened by SD, and our finding for the beta activity of a decreased SW index in pre-sleep onset after SD compared to pre-sleep onset after NS also supports the hypothesis that changes in the network of beta are related to attentional lapses following SD.

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**Research involving Human Participants and/or Animals:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Institutional Ethics Committee of the Department of Psychology of “Sapienza” University of Rome) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

**Data Accessibility Statement** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Figure legends**

**Figure 1.** The EEG data were recorded during the sleep onset in two conditions: after a night of normal sleep (i.e., in baseline sleep) and after a sleep deprivation (SD) of 40 hours (i.e., in sleep recovery).

**Figure 2. Small world (SW) index results in pre-sleep onset and post-sleep onset conditions following sleep deprivation (SD).** The SW index values are reported in the delta, theta, alpha, sigma and beta bands in pre-sleep onset (blu line) versus post-sleep onset (red line) after SD. The Duncan post-hoc computations showed that in delta ( $F(4,152)=15.974$ ;  $p=0.000010$ ) and theta ( $F(4,152)=15.974$ ;  $p=0.000672$ ) bands the SW index decreased in post-sleep compared to pre-sleep onset, while in sigma band ( $F(4,152)=15.974$ ;  $p=0.000003$ ) the SW index increased in post-sleep compared to pre-sleep onset.

**Figure 3. Lagged linear connectivity in pre-sleep onset and post-sleep onset state following sleep deprivation (SD).** Significant differences for lagged linear connectivity in the sigma band mapped by eLORETA, in which the red tract representation belongs to ROIs well connected over a cut-off threshold.

**Figure 4. Small world (SW) index in pre-sleep onset after sleep deprivation (SD) versus pre-sleep onset after normal sleep (NS).** The SW index values are reported in the delta, theta, alpha, sigma and beta bands in pre-sleep onset after NS (redline) vs. pre-sleep onset after SD (blueline). The Duncan planned post-hoc comparisons showed a decreased of SW index in beta band ( $F(4,152)=4.7359$ ;  $p=0.000563$ ) in sleep onset after SD compared to sleep onset in NS condition.

**Figure 5. Lagged linear connectivity in pre-sleep onset after sleep deprivation (SD) versus pre-sleep onset after normal sleep (NS).** Lagged linear connectivity significant differences in the beta band mapped by eLORETA, in which the red tract representation belongs to ROIs well connected over a cut-off threshold.

**Table 1.** Mean and standard error (SE) of small world (SW) index, Characteristic Path Length (L), Clustering Coefficient (C) in the EEG bands (delta, theta, alpha, sigma, beta) in Recovery and in Normal sleep, in pre and post sleep onset conditions.

		Pre					Post				
		Delta	Theta	Alpha	Sigma	Beta	Delta	Theta	Alpha	Sigma	Beta
<b>SW</b>											
<b>Recovery</b>	Mean	1.0531	1.0028	1.0024	0.9801	0.9803	1.0344	0.9890	1.0031	1.0010	0.9754
	SE	0.0033	0.0027	0.0020	0.0025	0.0025	0.0029	0.0026	0.0023	0.0025	0.0042
<b>Normal sleep</b>	Mean	1.0474	0.9997	0.9960	0.9844	0.9942	1.0394	0.9883	0.9952	1.0034	0.9899
	SE	0.0036	0.0019	0.0018	0.0016	0.0018	0.0027	0.0026	0.0022	0.0021	0.0036
<b>L</b>											
<b>Recovery</b>	Mean	0.6276	0.9601	1.4526	1.0061	0.9536	0.6011	0.9739	1.3201	1.3796	0.7254
	SE	0.0443	0.0343	0.0654	0.0239	0.0248	0.0254	0.0249	0.0390	0.0385	0.0253
<b>Normal sleep</b>	Mean	0.6791	0.9698	1.2829	1.0465	1.0218	0.6083	1.0494	1.1725	1.3026	0.8672
	SE	0.0343	0.0213	0.0431	0.0183	0.0208	0.0291	0.0257	0.0288	0.0369	0.0287
<b>C</b>											
<b>Recovery</b>	Mean	0.6580	0.9624	1.4587	0.9860	0.9350	0.6218	0.9632	1.3261	1.3829	0.7059
	SE	0.0442	0.0343	0.0674	0.0237	0.0245	0.0262	0.0246	0.0408	0.0409	0.0239
<b>Normal sleep</b>	Mean	0.7079	0.9691	1.2779	1.0295	1.0156	0.6312	1.0368	1.1668	1.3085	0.8568
	SE	0.0334	0.0208	0.0430	0.0174	0.0206	0.0293	0.0252	0.0284	0.0385	0.0280

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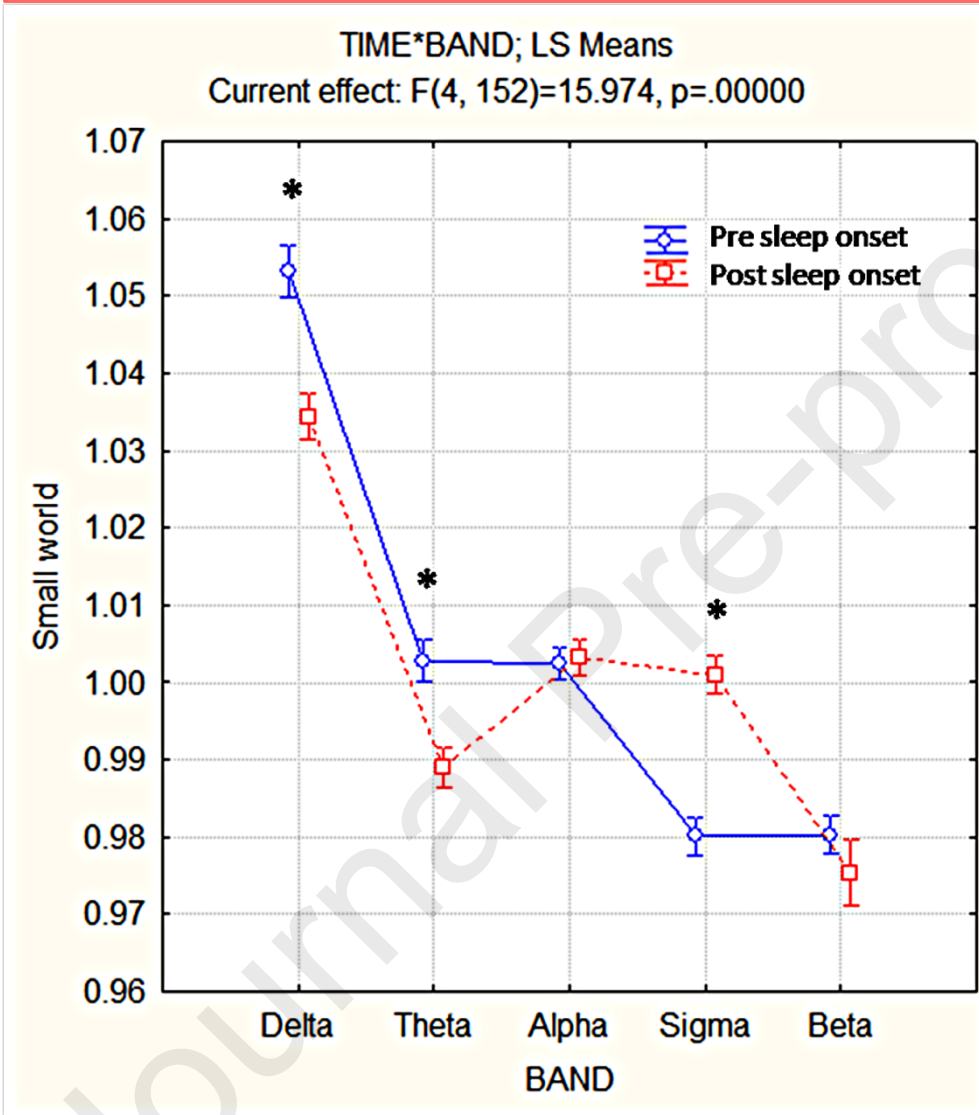
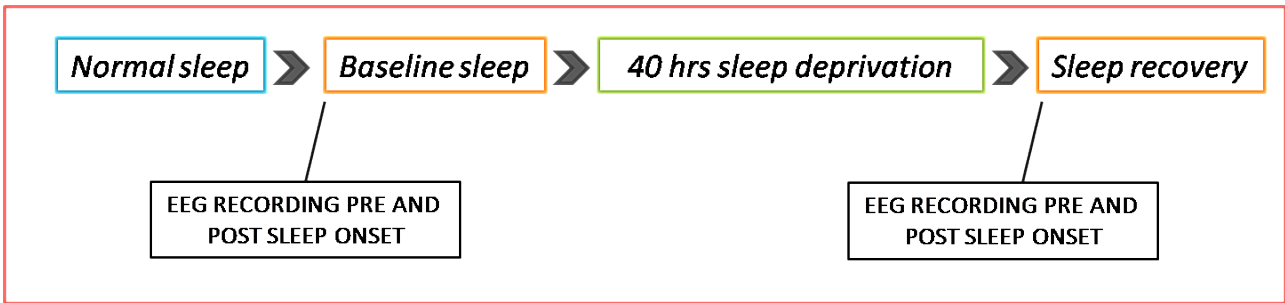


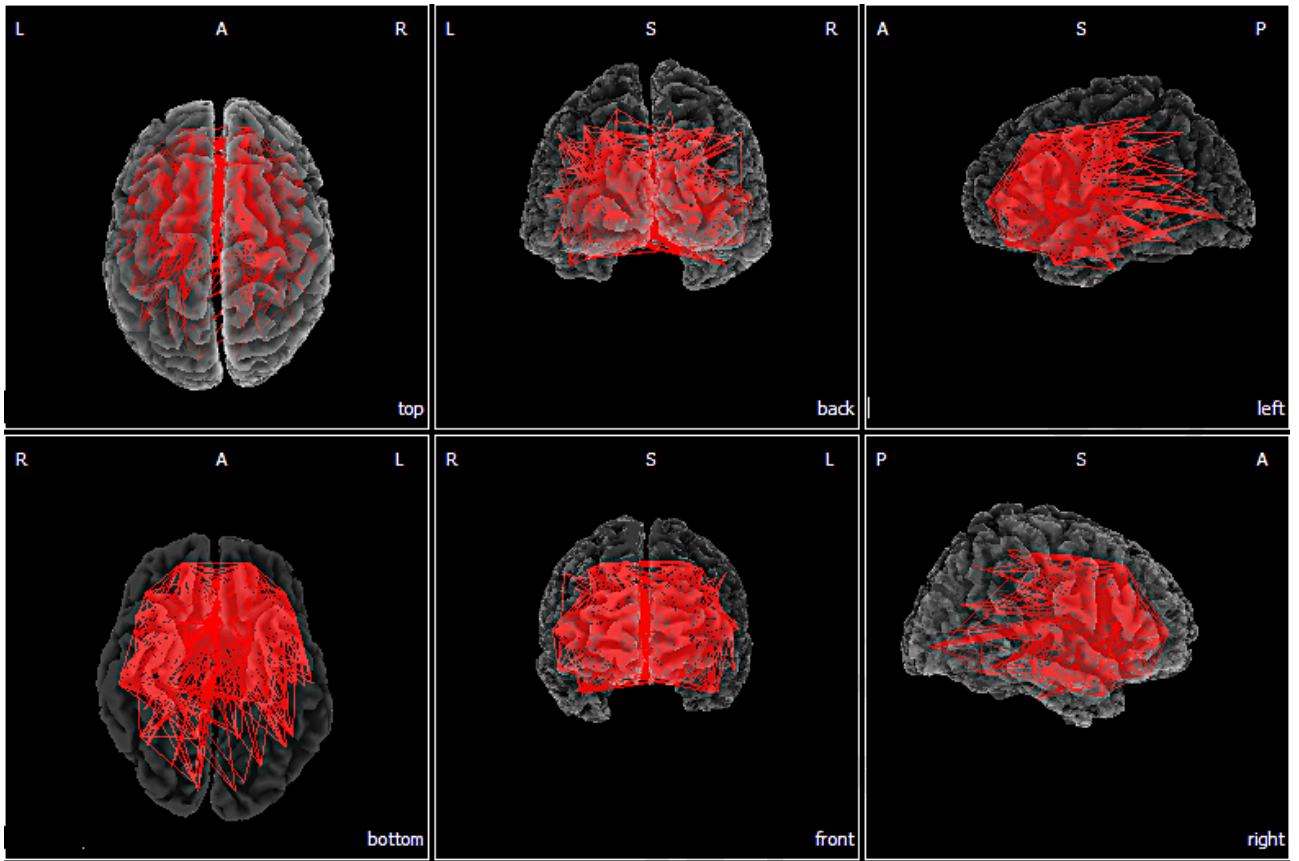
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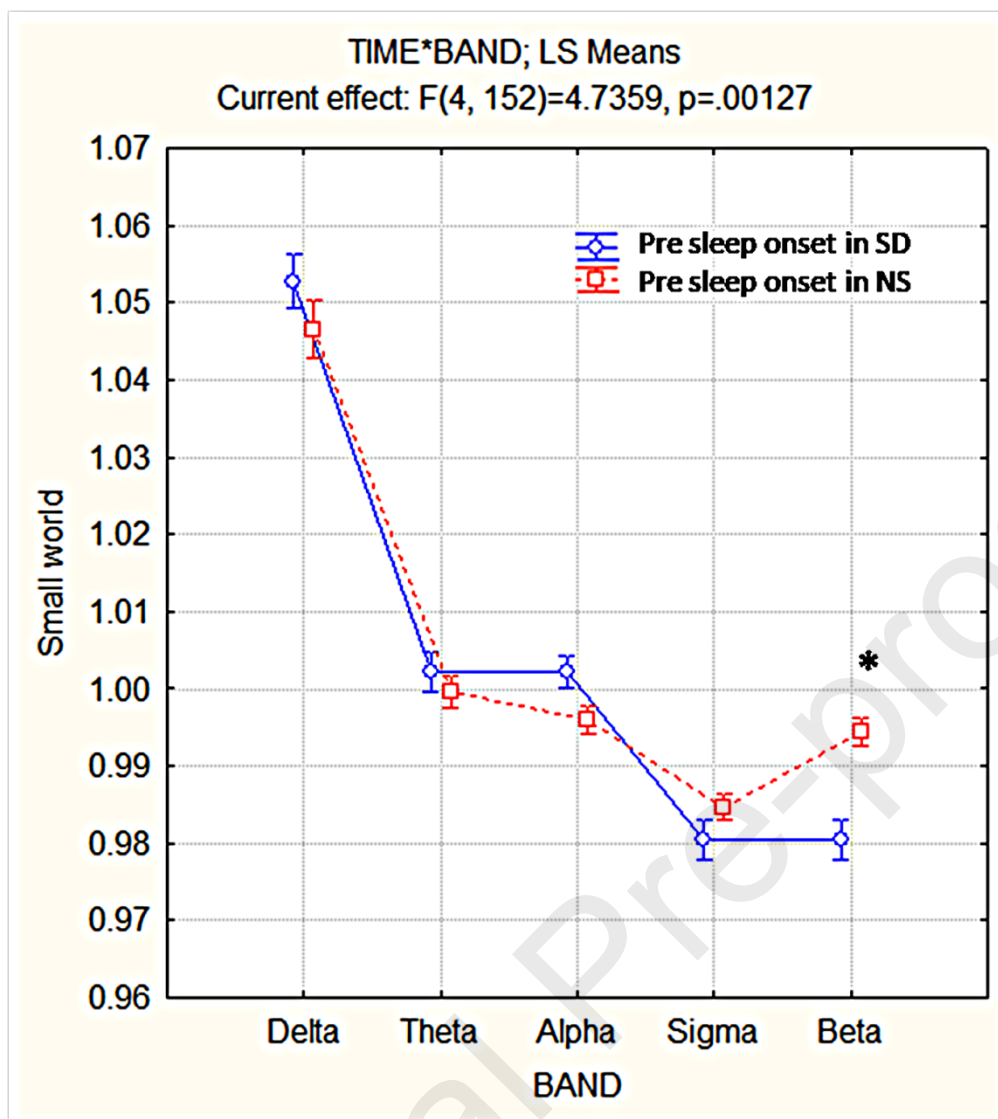
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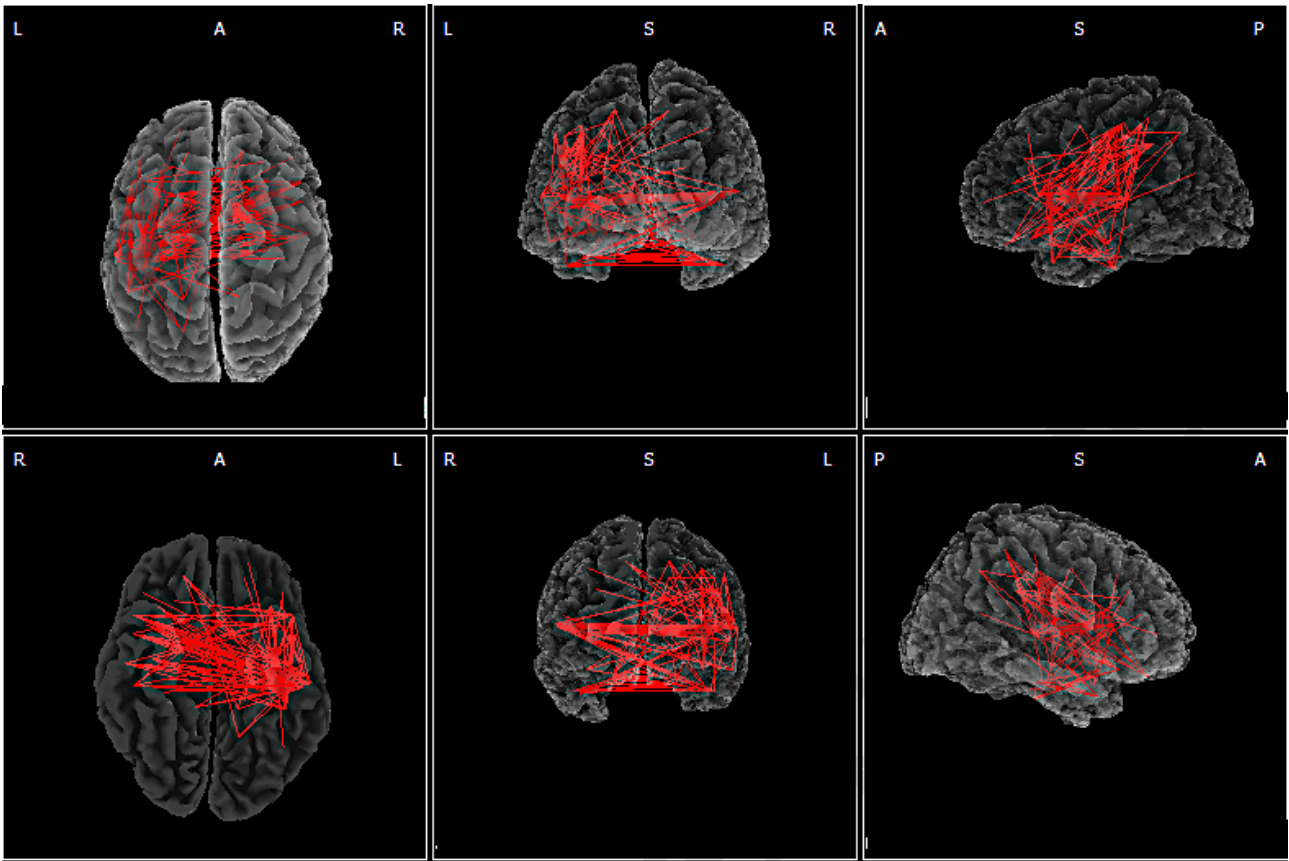
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