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Connectivity analysis of novelty process in habitual short sleepers

Abbas Babajani-Feremi [a,*], Valentina Gumenyuk [b], Thomas Roth [b], Christopher L. Drake [b], Hamid Soltanian-Zadeh [c,d]

[a] Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA
[b] Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI, USA
[c] CIPCE, School of Elec. and Comp. Eng., University of Tehran, Tehran, Iran
[d] Image Analysis Lab., Radiology Department, Henry Ford Hospital, Detroit, MI, USA

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ABSTRACT

Neurophysiological processes underlying auditory memory and attention are impaired in habitually short sleepers. The aim of this study was to use dynamic causal modeling (DCM) to study the mechanisms of these impairments in short sleepers. Eight normal sleepers (total sleep time (TST) = 7–8 h) and nine habitual short sleepers (TST ≤ 6 h) participated. The time in bed was increased from habitual (≤6 h) to extended (~8.5 h) for one week in the short sleep group. Event related potentials (ERPs) were collected using an auditory novelty task in "IGNORE" and "ATTEND" conditions. Fourteen DCM models were considered using different configurations of connections among the following six areas: left and right primary auditory cortices, superior temporal gyri (STG), and inferior temporal gyri (IFG). After fitting the ERPs to the 14 models (separately for the IGNORE and ATTEND conditions), the best model (across subjects) was chosen using the Bayesian model comparison. For both conditions, the connection from right-STG to right-IFG for normal sleepers was significantly greater than habitual short sleepers. This connection did not differ in habitual short sleepers before and after one week of extended sleep time. This connection for normal sleepers was not significantly greater than the habitual short sleepers after one week of extended sleep. These results show that the deficiency of novelty processing, seen in short sleepers, can be explained by the differences in connectivity of the pathway between frontal and temporal brain areas as compared to the normal sleepers. In addition, one week of extended time in bed was not enough to fully normalize this neuronal pathway between STG and IFG in short sleepers.

Introduction

Habitual sleep duration varies significantly among individuals (Aeschbach et al., 2001; Kripke et al., 1979). Short sleepers are typically defined as those regularly report less than 6 h of sleep. Restricting sleep to 6 h or less in healthy individuals increases objective daytime sleepiness, impairs reaction time, and produces impairments in memory (Dinges et al., 1997; Drake et al., 2001; Van Dongen et al., 2003). Impairments of neuronal processing of auditory information are present in short sleepers, but the neurophysiological mechanisms underlying these deficits have not been investigated (Gumenyuk et al., 2011).

Neuronal impairments due to sleep restriction as well as neuronal recovery followed by sleep extension can be evaluated by event related potentials (ERPs) during auditory information processing (Bastien et al., 2008; Devoto et al., 2003; Gosselin et al., 2006; Salmi et al., 2005; Trujillo et al., 2009). It has been shown that the novelty oddball task can be utilized to evaluate the effects of sleep on brain functions underlying attention control process (Halgren et al., 2011). Mismatch negativity (MMN), P3a, and P3b are three ERP components that are indices of the pre-attentive stage, attention-dependent component, and memory-dependent component, respectively (Polich, 2007). These three ERP components were used to evaluate the effects of sleep on brain functions (Gumenyuk et al., 2011).

Given ERPs' high sensitivity to variables related to information processing (e.g., auditory discrimination), it has been shown that the auditory oddball ERPs detect sleep related neurocognitive changes (Raz et al., 2001; Sallinen and Lyytinen, 1997). Recent studies have focused on ERP components that may reflect the activity of the frontal regions, which are critical for memory and attentional functions and importantly that frontal lobe activity declines during sleep. Gosselin et al. by using a variation of the oddball task were able to demonstrate the impact of 36 h of sleep deprivation on frontally distributed ERP (P3a) (Gosselin et al., 2005). They reported that following 36 h of sleep deprivation amplitude of the novelty P3a was decreased in frontal and latency of the novelty P3a was increased at all sites. For the behavioral performance, they reported that total sleep deprivation group had significantly more errors compared to the normal non-sleep-deprived group. However, reaction time was not affected by total sleep deprivation. In Salmi et al. (2005), it was demonstrated that increased

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* Corresponding author at: Washington University School of Medicine, Mallinckrodt Institute of Radiology, 510 S. Kingshighway, Suite 3353, St. Louis, MO 63110, USA. Fax: +1 314 362 6971.
E-mail address: abbasbf@pcg.wustl.edu (A. Babajani-Feremi).

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sleepiness was associated with a decline in P3a amplitude, index of involuntary switching of attention to irrelevant stimuli.

There are few studies in the literature that use ERPs to study short sleepers. Furthermore, the existing studies have limitations. The majority of existing studies are in the sensor-space while the source-space analysis provides more information about the location and power of active sources (Schoffelen and Gross, 2009). Brain connectivity analysis (BCA), in particular dynamic causal modeling (DCM), has not been used in ERP sleep studies. Using the Bayesian model comparison in DCM, one can find the best model over a wide range of models (Stephan et al., 2009). Strengths of the connections among cortical areas of the best model are estimated in DCM. While traditional ERP analyses do not deal with the coupling of the cortical areas, it is possible to investigate changes in the connections of the cortical areas due to sleep deficits or sleep disorders using the effective connectivity analysis in DCM.

Model based BCA of the auditory oddball paradigm provides valuable information about neuronal circuitry underlying auditory attention and memory (Garrido et al., 2007b, 2008; Kiebel et al., 2008). The difference in the time spent in bed (TIB) between short sleepers and normal sleepers may alter the activity of neuronal circuitry underlying attention and memory impairment in short sleepers. The effective connectivity analysis of DCM can be used to assess attention and memory deficits of short sleepers. The aim of this paper is to use DCM and perform effective connectivity analysis on ERP auditory novelty data collected from normal sleepers and habitual short sleepers. Our hypothesis is that the habitual short sleepers have deficit connection to frontal areas.

In recent years, we proposed several methods for effective connectivity analysis (Babajani and Soltanian-Zadeh, 2006; Babajani et al., 2005; Babajani-Feremi and Soltanian-Zadeh, 2010, 2011a, b; Babajani-Feremi et al., 2008, 2011). We developed and evaluated an effective connectivity analysis based on a variational Bayesian approach for the model inversion of our proposed multi-area extended neural mass model (Babajani-Feremi and Soltanian-Zadeh, 2011a, b; Babajani-Feremi et al., 2011). We showed that our effective connectivity approach is able to outperform the DCM (Babajani-Feremi and Soltanian-Zadeh, 2011a, b; Babajani-Feremi et al., 2011). We used the DCM in this study as it has been widely used in neuroimaging.

This study is a reanalysis of a study in which a sensor-based analysis of auditory oddball (novelty) was used to compare amplitudes of MMN, P3a, and P3b components in normal and short sleeping subjects (Gumenyuk et al., 2011). Gumenyuk et al. show that habitually short sleeping individuals have a deficiency in both the MMN and P3a as compared to normal sleeping subjects during passive [IGNORE] and active [ATTEND] tasks. It was also shown that the amplitude of the P3b in short sleeping individuals was elevated on frontal electrodes and decreased on parietal electrodes as compared to normal sleeping subjects in ATTEND condition. Furthermore, Gumenyuk et al. show that one week of sleep extension partially normalized the amplitudes of the MMN (attention/memory dependent brain response) in frontal electrodes but it did not normalize the amplitudes of the P3a and P3b (attention-dependent brain responses). Using a traditional *sensor-space* ERP analysis of novelty processing, Gumenyuk et al. (2011) demonstrated that normal sleeping subjects and short sleeping individuals show different amplitudes of ERPs measured from frontal, central, and parietal electrodes. Differences between these two groups regarding the mechanism of interactions among the cortical areas involved in the processing of novelty require a *source-space* connectivity analysis; this is the focus of the current study.

Methods

Subjects and design

In this study, we compared the network of effective connectivity (in response to the novelty oddball paradigm) of habitual short sleeping individuals with normal sleeping controls and evaluated potential enhancement of the connectivity in short sleepers after one week of sleep extension. Participants were recruited from advertisements posted at the Henry Ford Hospital website. Eight self-reported normal sleepers with total sleep time (TST) = 7–8 h (aged 24–36 years, 6 female) and nine self-defined healthy short sleepers (1-week sleep diary TST ≤ 6 h, aged 25–45 years, 5 females) participated in the study. No participant had history of sleep disorders. Habitually short sleeping participants were free of insomnia and excessive sleepiness based on the Insomnia Severity Index (ISI = 4.9 ± 3.8) and the Epworth Sleepiness Scale (ESS = 3.6 ± 2.2) and the max score for INS and ESS were 28 and 24, respectively. The clock time of each EEG (ERP) session was set between 14:00 and 16:00. Caffeine consumption was based on self-report and subjects were selected if they consumed less than six caffeinated beverages per week. Participants were free of medications, including antihistamines and CNS medications, for the entire period of their participation in the study. The Institutional Review Board (IRB) of the Henry Ford Hospital approved all study procedures and informed consent was obtained from all participants.

The habitual short sleepers increased their TIB to about 8.5 h for one week as part of the sleep extension condition. The habitual and extended sleep conditions were counterbalanced in short sleeping participants and performed for one week prior to the ERP data collection. Participants in the sleep extension study were asked to go to bed earlier by about 1 h and delay their habitual rise time by about 1 h. Habitual sleep was determined by self-report with one week sleep diary prior to participation in the EEG study which was performed on the 7th day of the habitual or extended week of sleep. Details of the measured sleep parameters of the participants have been previously presented (Gumenyuk et al., 2011).

Stimuli, EEG recording, and preprocessing

The auditory oddball task utilizing "IGNORE" and "ATTEND" conditions was used in this study. The sequence of stimuli in the IGNORE task consisted of a "standard tone" (pure tone = 600 Hz, 100 ms duration, probability of occurrence = 70%), a "deviant tone" (pure tone = 700 Hz, 100 ms duration, probability of occurrence = 20%), and a "novel sound" (100 ms duration, probability of occurrence = 10%). The novel sounds were presented as 110 unique environmental sounds (e.g., baby sounds, dog barking, bird sounds) and were randomly interspersed among standard and deviant tones. The tones and novel sounds had a 5 ms rise/fall time. The auditory stimuli were generated and presented by the Visual Auditory Presentation Program (VAPP).

All participants were asked to ignore all sounds during the IGNORE task condition while watching a silent movie. The same stimuli sequence was used in the IGNORE and ATTEND conditions except that a target tone (pure tone = 1000 Hz, duration 100 ms, probability of occurrence = 1.1%) was presented in the ATTEND condition. In the ATTEND condition, participants were asked to fixate their gaze on a cross presented on the screen of a computer, count target tones quietly, and report the total number of the target tones after each session recording. Accuracy of counting the target tone (in the ATTEND condition) was more than 85% for all subjects. The participants in this study listened to tones and sounds using earplugs binaurally at a 75 dB Sound Pressure Level. All stimuli were presented at a constant interstimulus interval of 800 ms. A total of 1100 trials were presented for each of the IGNORE and ATTEND task conditions. It is notable that the visual background is different between the ATTEND and IGNORE conditions. This might be considered as a potential confound if we compared the ATTEND and IGNORE conditions. However, we did not compare these two conditions; we compared Control, Habitual, and Extended in each condition separately.

The EEG data was collected by ASA amplifier (ANT, Netherlands, http://www.ant-neuro.com) via a 64 EEG-channel cap, sampled at 1024 Hz, and initially high-pass filtered (0.1 Hz) before disk storage. The average of all channels was used as the reference. A band-pass filter (0.5–30 Hz) was applied on the EEG raw datasets and then eye movement artifacts were removed. EEG data was segmented separately for each stimulus to calculate ERP epochs from 100 ms before to 500 ms after stimulus onset. For each subject and task condition (IGNORE or ATTEND), ERPs in response to the standard tone and novel sounds were averaged separately to calculate the average datasets containing two events (one for the standard tone and one for the novel sounds). Twenty-six averaged ERPs for eight normal sleeping subjects (Control), nine habitual short sleeping subjects (Habitual), and nine habitual short sleeping subjects after one week sleep extension (Extended) were calculated for each of the IGNORE and ATTEND conditions that generated a total of 52 average ERPs. The time courses of the differences in the ERP amplitudes corresponding to the novel sounds and the standard tone ($ERP_{novel} - ERP_{standard}$) for a normal sleeping subject and a short sleeping individual are illustrated in Fig. 1. Topographic maps of the difference ERP in the three time windows, MMN (110–140 ms), P3a (200–240 ms), and P3b (280–320 ms) are presented for illustration purposes in Fig. 2. Further details of the standard ERP outcomes are described in Gumenyuk et al. (2011).

DCM effective connectivity analysis

Brain function is a consequence of interactions among several cortical regions that are reciprocally interconnected. Connectivity analysis facilitates our understanding of how the brain works, and helps us to assess the roles of different areas in specific cognitive functions. In the neuroimaging literature, the influence that one neural system exerts on another one is defined as effective connectivity which requires a causal model connecting several brain regions (Friston et al., 1993, 2003). Another approach to connectivity analysis is functional connectivity, which measures such as coherence or temporal correlations, which are based on dependencies between two separate time-series.

We used the effective connectivity analysis offered by DCM in this study as we were interested in causal modeling of auditory process comparing short and normal sleepers. DCM is especially useful when causal interactions among cortical areas are the focus of the analysis. It allows one to make inferences about model parameters and investigates how these parameters are influenced by interventions or stimuli. DCM for EEG/MEG data uses neural mass models to explain source activity in terms of the ensemble dynamics of interacting inhibitory and excitatory subpopulations of neurons (David and Friston, 2003). DCM provides a spatiotemporal analysis for evoked responses using the EEG/MEG data (David et al., 2006). It shows advantages over conventional analyses of evoked responses as it uses natural constraints on the inversion, and activity in one source has to be caused by activities in other sources.

DCM estimates the probability of the data, given a particular model, by taking the marginal likelihood over the conditional density of the model parameters. The marginal likelihood or evidence is used in DCM to compare and select the best model amongst alternative models. DCM has been used in several EEG/MEG studies to investigate brain function in the processing of the auditory oddball paradigm (Garrido et al., 2007a, 2007b, 2008, 2009a, 2009b, 2009c; Kiebel et al., 2007, 2009). The connectivity analysis in these studies is based on the established DCM analysis of the auditory oddball paradigm in Garrido et al. (2008, 2009a, 2009c) where differences in the ERPs to standard and deviant sounds were modeled in terms of changes in synaptic connections within and between cortical areas. The selection of network architecture of connections among cortical areas was motivated by the results of previous studies of mismatch negativity generators (Doeller et al., 2003; Grau et al., 2007; Opitz et al., 2002; Rinne et al., 2000). These studies suggest bilateral sources located in the primary auditory cortex (A1), superior temporal gyrus (STG), and inferior frontal gyrus (IFG). Here, A1 represents cortical input stations for the processing of the auditory information. The

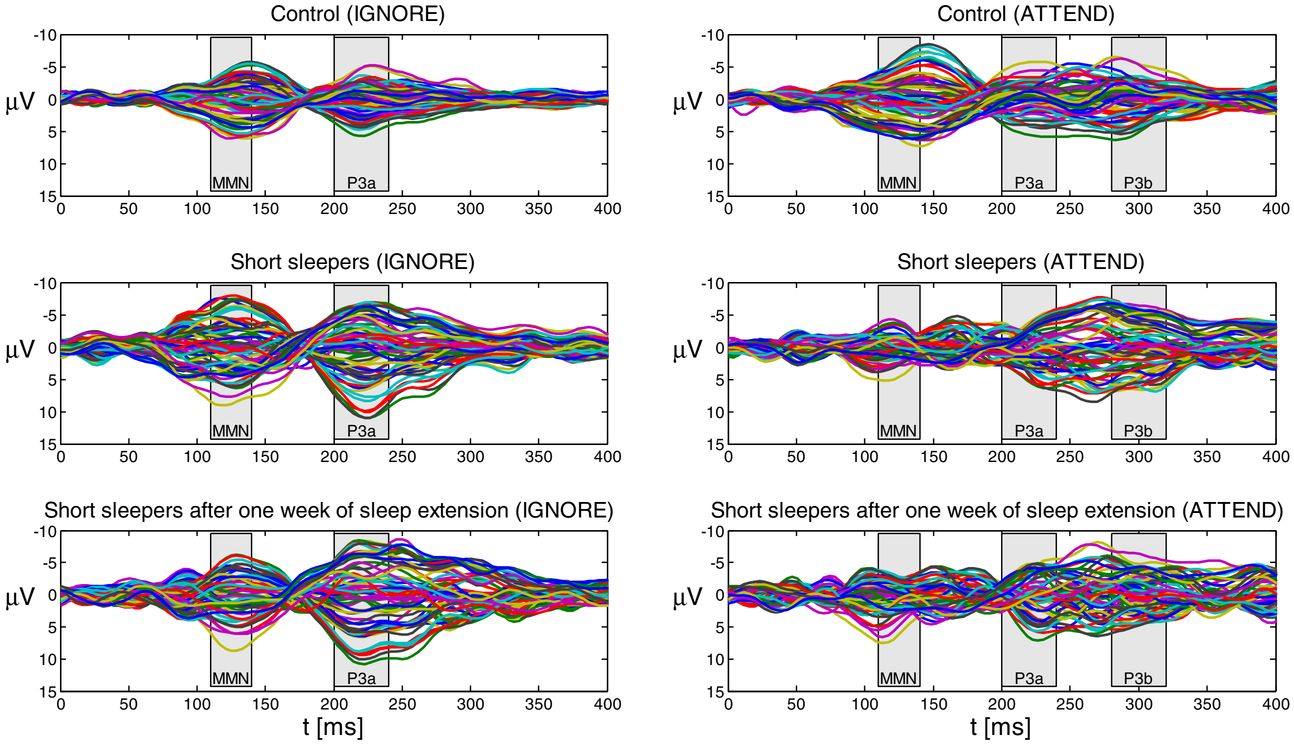


Fig. 1. Time courses of the averaged ERPs in two tasks (IGNORE and ATTEND) for a normal sleeping subject and a habitual short sleeping individual before and after one week of sleep extension. The plotted time courses represent the difference ERP signals generated by novel sounds and standard tone ($ERP_{novel} - ERP_{standard}$). The time intervals of two ERP components (MMN and P3a) in IGNORE and three ERP components (MMN, P3a, and P3b) in ATTEND are highlighted.

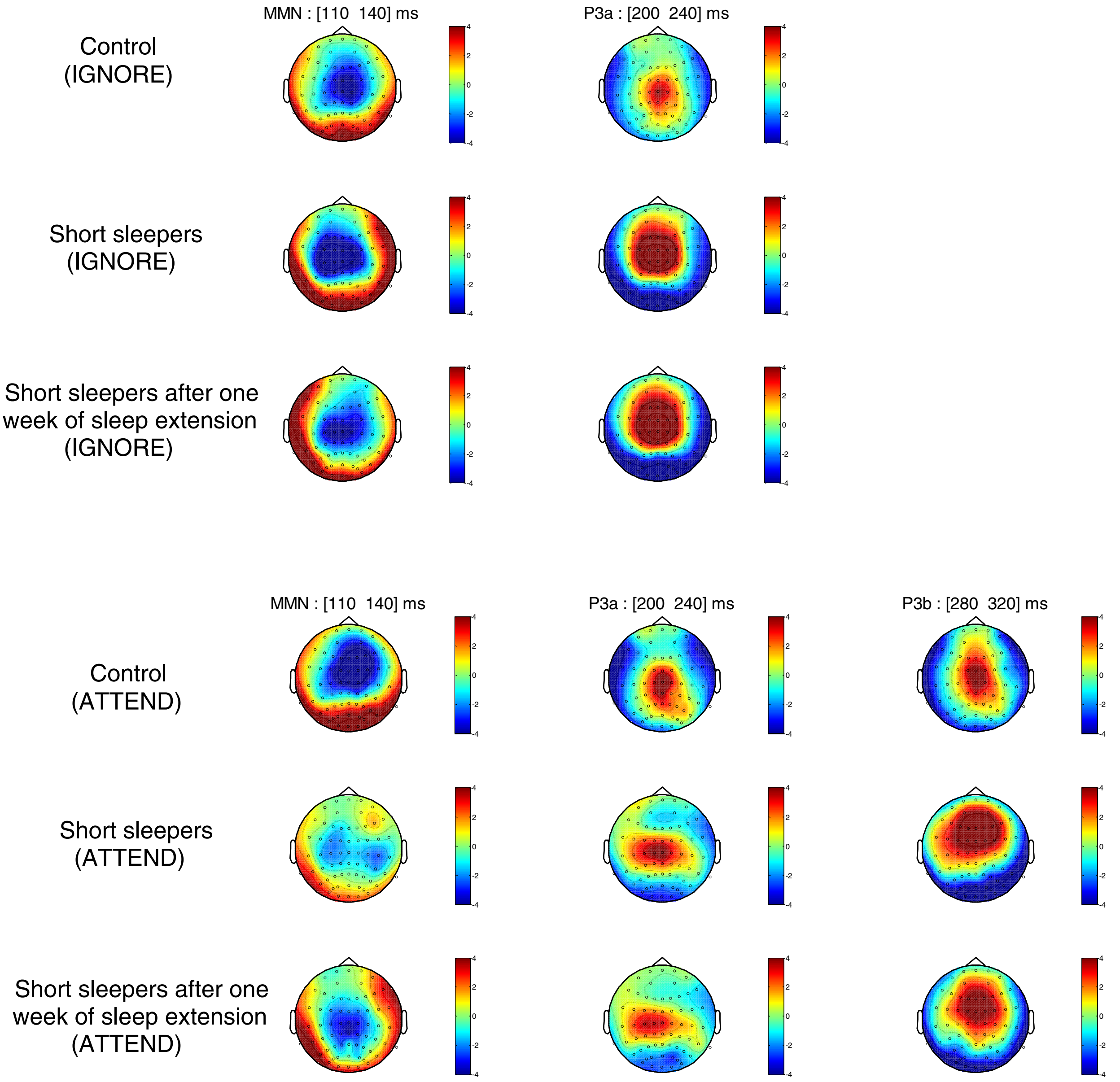


Fig. 2. Topographic maps of the three ERP components MMN (left column), P3a (middle column), and P3b (right column), highlighted in Fig. 1. Maps represent the difference ERP signals generated by the novel sounds and standard tone ($ERP_{novel} - ERP_{standard}$) averaged over time intervals given in the title of subplots.

activity in IFG is usually stronger and found more consistently in the right hemisphere (Garrido et al., 2009a). Each active source can be modeled with a single equivalent current dipole (ECD). The prior source locations in Montreal Neurological Institute (MNI) space are illustrated in Fig. 3-a.

Based on the previous DCM studies of the auditory oddball stimuli (Garrido et al., 2008, 2009a, 2009c), we specify 14 models (see Fig. 3-b) covering different potential mechanisms underlying the auditory oddball process (Doeller et al., 2003; Giard et al., 1990; Jaaskelainen et al., 2004; Naatanen et al., 2005; Opitz et al., 2002; Winkler et al., 1996). Note that considering only the forward connections among six areas, a total of $2^{5\times6} = 1{,}073{,}741{,}824$ models can be theoretically considered. Most of these models are not physiologically plausible and inverting this huge number of models may not be computationally feasible. Thus, we limit the models to the physiologically plausible ones based on existing studies in the literature.

The complexity of models in Fig. 3-b increases from left to right and top to bottom in terms of hierarchical levels (number of sources) and changes in intrinsic connectivity as well as extrinsic connectivity. The intrinsic connectivity in A1 is included in seven models in the bottom-row of Fig. 3-b. Model 1 (M1) is the simplest model which contains a one-level hierarchical model comprising two areas in the left and right primary auditory cortex (A1). This model corresponds to the hypothesis that the ERPs to standard and deviant tones are generated by bilateral activity in primary auditory cortex. M1 does not support any changes in connectivity or consequent changes in ERPs. Model 2 (M2) is similar to M1 but allows change in intrinsic connections within left and right A1. Since the intrinsic interactions are fixed in M1, parameters of this model are fixed for the standard tone and the novel sounds and thus, it cannot explain any ERP differences (between standard tone and novel sounds) that are present in the ERP data.

A second-level hierarchical model comprising four sources is considered in Model 3 (M3) where the left and right superior temporal gyrus (STG) sources are added to M1. There are reciprocal forward and backward connections between STG and ipsilateral A1 which is

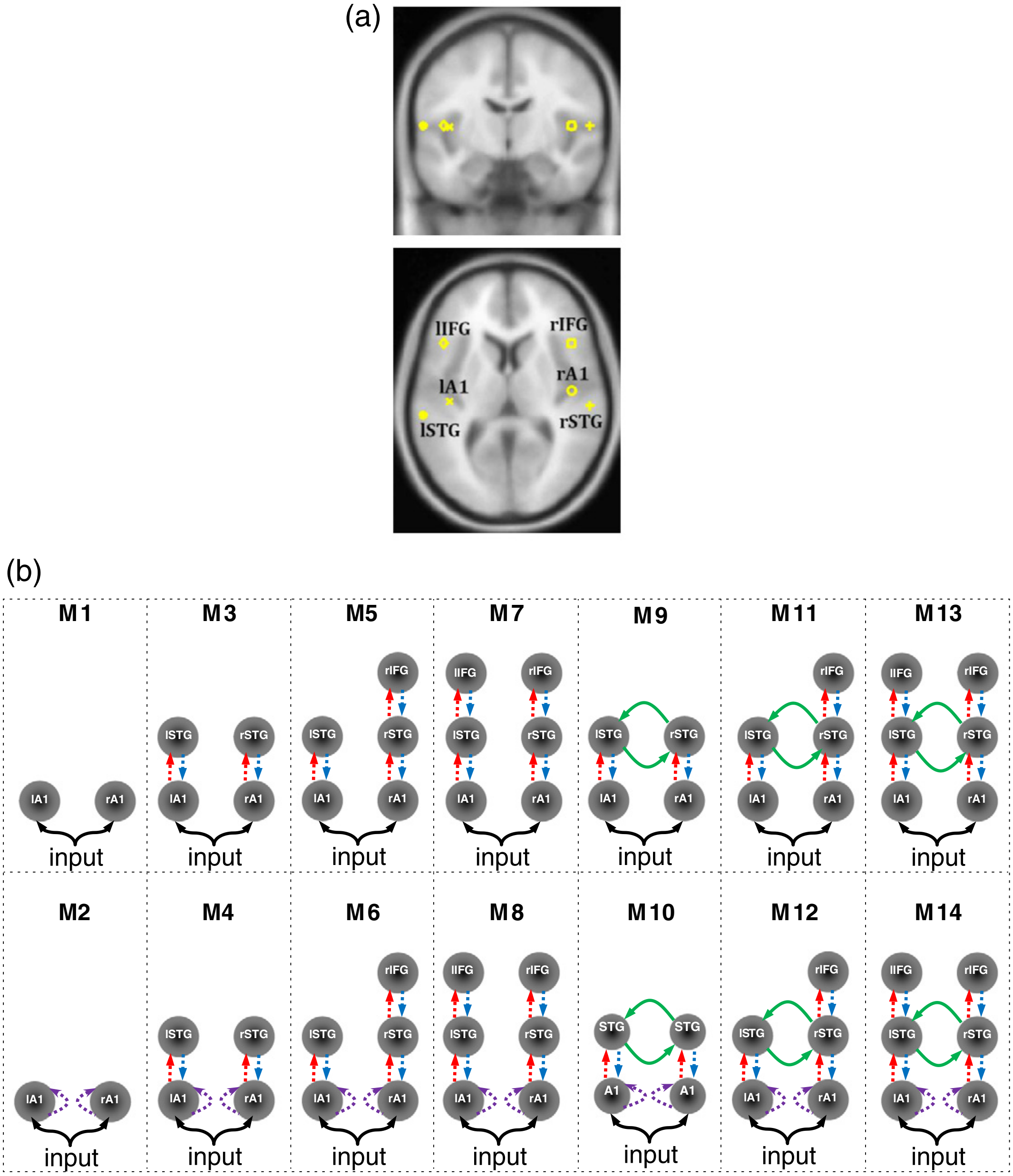


Fig. 3. Model specification for dynamical modeling of active areas involved in the auditory oddball paradigm. (a) Prior locations for the possible active areas in auditory oddball task. Sources of activity are superimposed on an MRI of a standard brain in the Montreal Neurological Institute (MNI) space (Collins et al., 1998). (b) The sources comprising the network are connected with forward (red), backward (blue), lateral (green), or intrinsic (purple) connections. The broken lines indicate the connections that we allowed to change in novelty sound after fitting the standard tone. A1: primary auditory cortex; STG: superior temporal gyrus; IFG: inferior temporal gyrus.

motivated by the general principle of reciprocity in cortico-cortical connections (Felleman and Van Essen, 1991; Rockland and Pandya, 1979). Model 5 (M5) and Model (M7) are third-level hierarchical models in which IFG is reciprocally connected with ipsilateral STG. The reciprocal lateral connections between the left and right STG sources are presented in Model 9 (M9), Model 11 (M11), and Model 13 (M13). M2 resembles local adaptation in which the differences between responses to standard tone and novel sounds are assumed to be caused by changes in left and right A1 activities due to modulations of intrinsic connections within these areas (Garrido et al., 2009a). Models M3, M5, M7, M9, M11, and M13 embody the mechanism that a temporo-frontal network underlies the difference of the responses generated by the standard tone and novel sounds (Garrido et al., 2009a). Models M4, M6, M8, M10, M12, and M14 cover the hypothesis that both interactions within a temporo-frontal network and local adaptation (within primary auditory cortex) underlie the difference of the responses generated by the standard tone and novel sounds (Garrido et al., 2009a). To have a valid model comparison, all 6 areas should be included in the 14 models. However, areas without any connections are not shown in Fig. 3-b because their activations are zero as they have no input.

Model inversion and comparison

After preprocessing of the collected EEG data, 52 averaged ERPs (eight Control, nine Habitual, and nine Extended in two IGNORE and ATTEND conditions) were calculated. Then the 14 dynamical models shown in Fig. 3-b were fitted to each of the 52 averaged ERPs using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). A realistic head model based on the boundary elements method was used for the forward problem (Mosher et al., 1999). The positions of EEG electrodes were taken from the standard 10–10 system in the MNI coordinates (Oostenveld and Praamstra, 2001). We used a patch on the cortical surface ("IMG" option in SPM8) to spatially model the source in each area (Daunizeau et al., 2009). It has been shown that this method of modeling the active cortical sources outperforms the equivalent current dipole (ECD) formulation and provides more accurate spatiotemporal source estimation for spatially distributed sources (Daunizeau et al., 2009). To reduce the dimensionality of the sensor data in DCM, eight components of the singular value decomposition (SVD) of the data were used. A time window of [0 350] ms after stimulus onset was considered for the model inversion. The selection of this time window was motivated by the fact that it covered most of the EEG signal power generated by the novel and standard stimuli (see, for instance, Fig. 1).

We used the default values of the parameters in SPM8, except the above mentioned parameters, to invert models and estimate the model parameters as well as the "model evidence." In DCM, model m is inverted by optimizing a variational free-energy bound, F, on the model evidence. It provides the model evidence, $p(y|m)$, and the conditional density of the model parameters, $p(\theta|y,m)$. The model evidence is used for model comparison to select the best model before making statistical inferences on the basis of the conditional density. The model with highest log-evidence, $\ln p(y|m)$, is the best model (assuming a uniform prior over models) given the data. Two models m_1 and m_2 can be compared by computing the relative log-evidence $\ln p(y|m_1) - \ln p(y|m_2)$. There is strong evidence in favor of one model over another model if this difference is greater than three (the relative likelihood is more than 20:1) (Penny et al., 2004).

There are two Bayesian model selection (BMS) approaches for selecting the best (optimal) model at the group-level: fixed-effect analysis (FFX) and random-effect analysis (RFX) (Boly et al., 2011; Campo et al., 2012; Friston and Penny, 2011; Stephan et al., 2009). In the FFX, the sum of the log-evidence of each subject for each model is calculated to find the optimal model with maximum summed log-evidence (Stephan et al., 2009). One assumes in the FFX that the optimal model is the same for each subject in the group. However, this assumption may not be appropriate, for instance, when dealing with cognitive tasks that can be implemented neuronally in different ways with various cognitive strategies (Stephan et al., 2010). In the RFX, the optimal model structure is not assumed to be identical across subjects. It has been shown that the RFX is accurate and outliers have little impacts on its results (Stephan et al., 2009). We performed a group-level BMS to identify the network architecture that best explained EEG data of subjects in each of the IGNORE and ATTEND conditions. BMS using both FFX and RFX was performed to compare 14 models at the group level. In addition, we compared the 14 models at a single subject level (Penny et al., 2004). After selecting the optimal model for each of the IGNORE and ATTEND conditions, the strength of connections among areas of the optimal model for each condition was analyzed using unpaired t-test to investigate significant differences in the Control, Habitual, and Extended subjects. A Bonferroni correction for multiple comparisons is inappropriate because it assumes comparisons to be independent while the statistical inferences about the connections are highly correlated. In the absence of any established method for multiple comparisons in DCM and following previous studies (Benetti et al., 2009; Mechelli et al., 2007), we controlled for Type-I error using a relatively conservative statistical threshold of $P<0.01$ that yields an expected false positive rate of 1%.

Results

For each of the 52 average ERPs (8 Control, 9 Habitual, and 9 Extended in IGNORE and ATTEND conditions), the 14 models shown in Fig. 3-b were inverted. Then the best model at the group (Control, Habitual, and Extended) level for each of the IGNORE and ATTEND conditions was selected using the BMS approach described in the Methods section. Fig. 4 illustrates the BMS results for the FFX and RFX analyses. Model 8 (M8) was the best model for both of the IGNORE and ATTEND conditions. Based on the FFX analysis in the IGNORE condition, the Bayes factor of M8 relative to the second best model (M14) was 1722.52. The FFX analysis in ATTEND revealed that M8 supervened where the Bayes factor relative to the second best model (M6) was 833.02. Since a relative Bayes factor greater than three represents a strong evidence in favor of one model over another model (Penny et al., 2004), the FFX results showed a very strong evidence in favor of M8 for both of the IGNORE and ATTEND conditions. RFX analysis provided similar results where M8 was the best model for IGNORE and ATTEND. Based on the RFX analyses in the IGNORE condition, the exceedance probability for M8 was 0.907 while the exceedance probability for the second best model (M6) was 0.022. In the ATTEND condition, the exceedance probability for M8 was 0.680 and the exceedance probability for the second best model (M7) was 0.172.

We also performed model comparison for each subject individually. Fig. 5 illustrates the log-evidence of the best model relative to the second best model for all subjects. In the IGNORE condition, M8 was superior to all other models in 10 out of 26 subjects while M6 (as the second best model based on RFX) was the best model in 3 out of 26 subjects. In the ATTEND condition, M8 was superior to all other models in 7 out of 26 subjects while M7 (as the second best model based on RFX) was the best model in 5 out of 26 subjects. In summary, the FFX and RFX analyses at the group level as well as the model comparison for each subject individually confirmed that M8 was the best model for both IGNORE and ATTEND.

After selecting the best model, group difference in the strength of connections among areas of the best model was assessed using the estimated parameters of all subjects. Means and standard deviations of the estimated strength of connections among cortical areas of M8 (the best model) for Control, Habitual, and Extended are shown in Fig. 6. Note that for model inversion in SPM8, we used the between trials (events) effect corresponding to two events: the standard tone and the novel sounds. The connections among areas are in fact the estimated change in the strength of connections from the standard tone to the novel sounds.

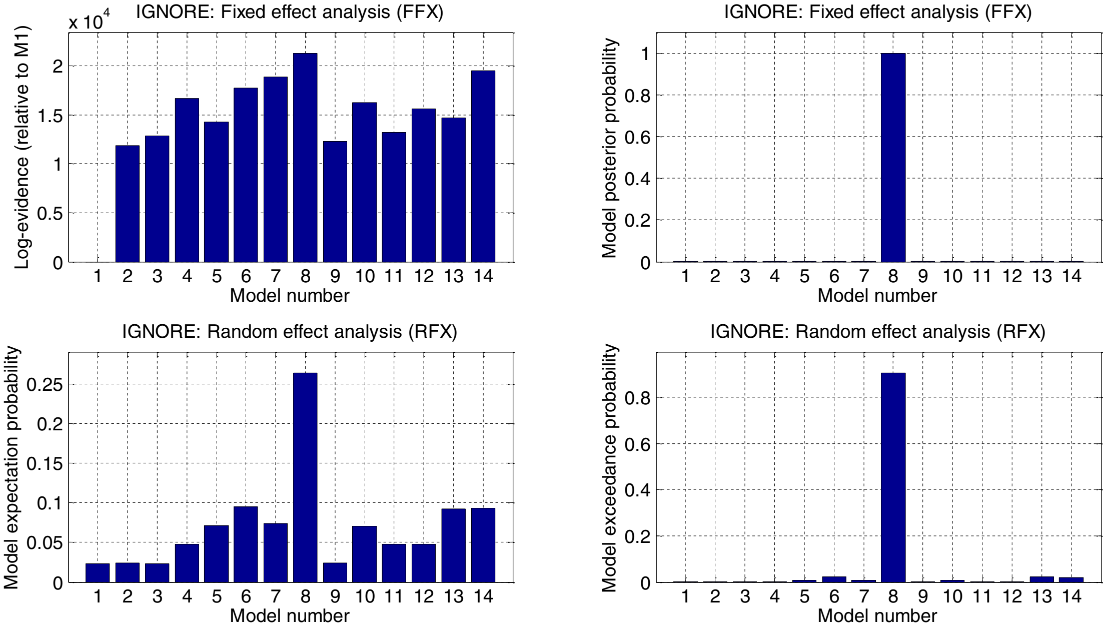
An unpaired t-test revealed that the forward connection from the right STG (rSTG) to right IFG (rIFG) for Control was significantly greater than Habitual in both IGNORE and ATTEND conditions. In IGNORE, the forward connection from rSTG to rIFG was greater for Control (mean = 1.73; SD = 0.52) as compared with Habitual (mean = 0.68; SD = 0.39) [two-sample t-test; $P<0.0092$]. In ATTEND, this connection for Control (mean = 1.70; SD = 0.37) was significantly greater than Habitual (mean = 1.02; SD = 0.14) [two-sample t-test; $P<0.0063$].

In both IGNORE and ATTEND conditions, the forward connection from rSTG to rIFG for Control (IGNORE: mean = 1.73; SD = 0.52 and ATTEND: mean = 1.70; SD = 0.37) was also greater than Extended (IGNORE: mean = 1.04; SD = 0.09 and ATTEND: mean = 0.99; SD = 0.31) [IGNORE: two-sample t-test; $P<0.0175$ and ATTEND: two-sample t-test; $P<0.0161$]. However, using a statistical threshold of $P<0.01$, this connection for Control was not significantly greater than Extended although the p-values were close to the statistical threshold. On the other hand, Habitual and Extended did not significantly differ in terms of the forward connection from rSTG to rIFG in the IGNORE [$P>0.0829$] and ATTEND [$P>0.8326$] conditions. Using a statistical threshold of $P<0.01$, the remaining connections did not significantly differ in Control versus Habitual, Control versus Extended, and Habitual versus Extended (majority of p-values were greater than 0.2).

Discussions

The results of the present study using the oddball auditory paradigm show that short sleepers have a deficiency in the forward connection

(a) IGNORE



(b) ATTEND

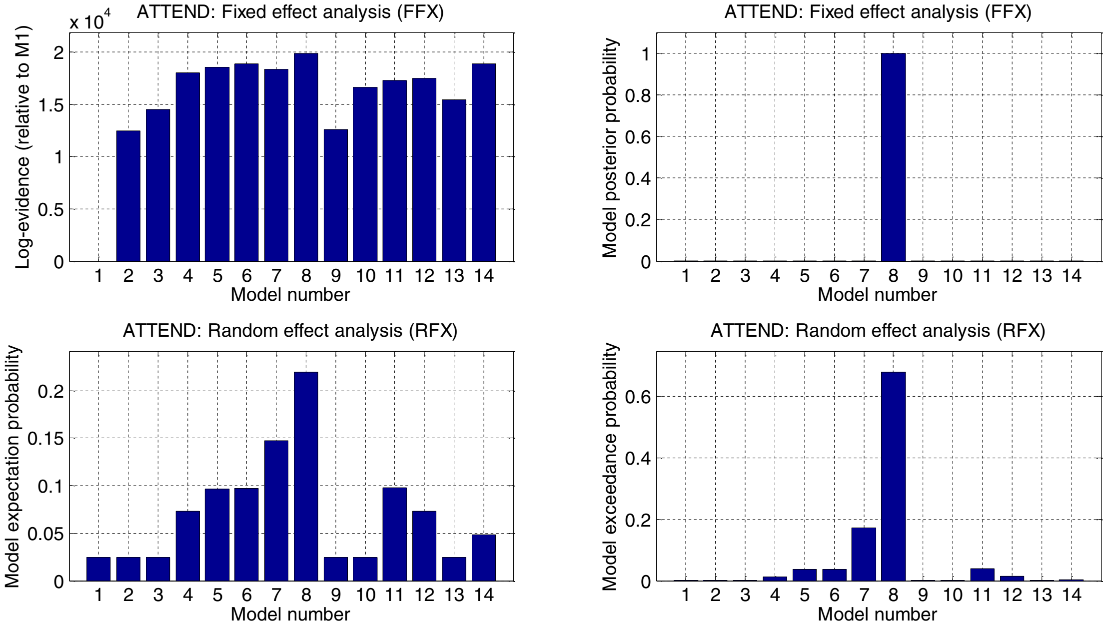


Fig. 4. Group level Bayesian model selection of the 14 tested models shown in Fig. 3. For each of the IGNORE (top) and ATTEND (bottom) conditions, the top-left and the top-right subplots illustrate the log-evidence (relative to M1) and the model posterior probability based on the FFX analysis; the bottom-left and the bottom-right subplots illustrate the model expectation probability and the model exeedance probability. Eight Control, nine Habitual, and nine Extended subjects were considered in one group to find the best model using the Bayesian model selection at the group level. The FFX and RFX results indicate that Model 8 (M8) is the best model in both IGNORE and ATTEND conditions (see Fig. 3 for definition of M8).

from the superior temporal gyrus (STG) to the inferior frontal gyrus (IFG) as compared to normally sleeping subjects. In both IGNORE and ATTEND conditions, the strength of the forward connection from the right-STG (rSTG) to right-IFG (rIFG) in normally sleeping subjects is significantly greater than the habitual short sleepers. To investigate any possible normalization of this connection in the habitual short sleepers after one week of extended sleep, we observed that this connection did not significantly differ in normally sleeping subjects and the habitual short sleepers after one week of extended sleep. On the other hand, we failed to detect difference in this connection between the habitual short sleepers before and after one week of extended sleep. Thus, this connection seems to be partially (not fully) normalized in the habitual short sleepers after one week of extended sleep.

This difference in connectivity between IGNORE and ATTEND conditions in normally sleeping subjects can be explained by attentional input to the pathway from temporal to frontal brain areas. This attentional input may increase the degree of synchrony between activated neuronal sources during the novelty processing in ATTEND condition, orchestrated by thalamus (Frith and Friston, 1996). In habitually short sleeping individuals, the neuronal circuitry underlying both

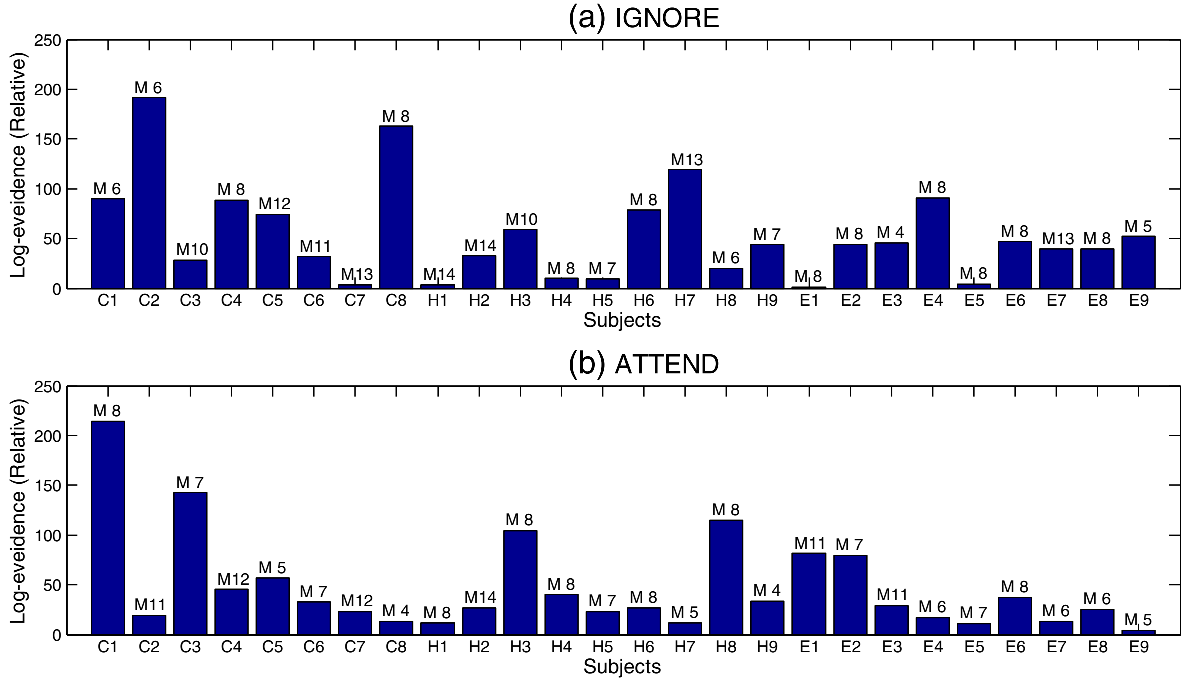


Fig. 5. Model comparison for each subject individually in the IGNORE (top) and ATTEND (bottom) conditions. Each subplot illustrates the log-evidence of the best model relative to the second best model for all subjects. The x-axes of the subplots represent the number of subjects. C1 to C8: eight normal sleeping subjects; H1 to H9: nine habitual short sleeping subjects; E1 to E9: nine habitual short sleeping subjects after one week of extended sleep. In IGNORE and ATTEND, M8 was superior to all other models in 10 out of 26 subjects and 7 out of 26 subjects, respectively.

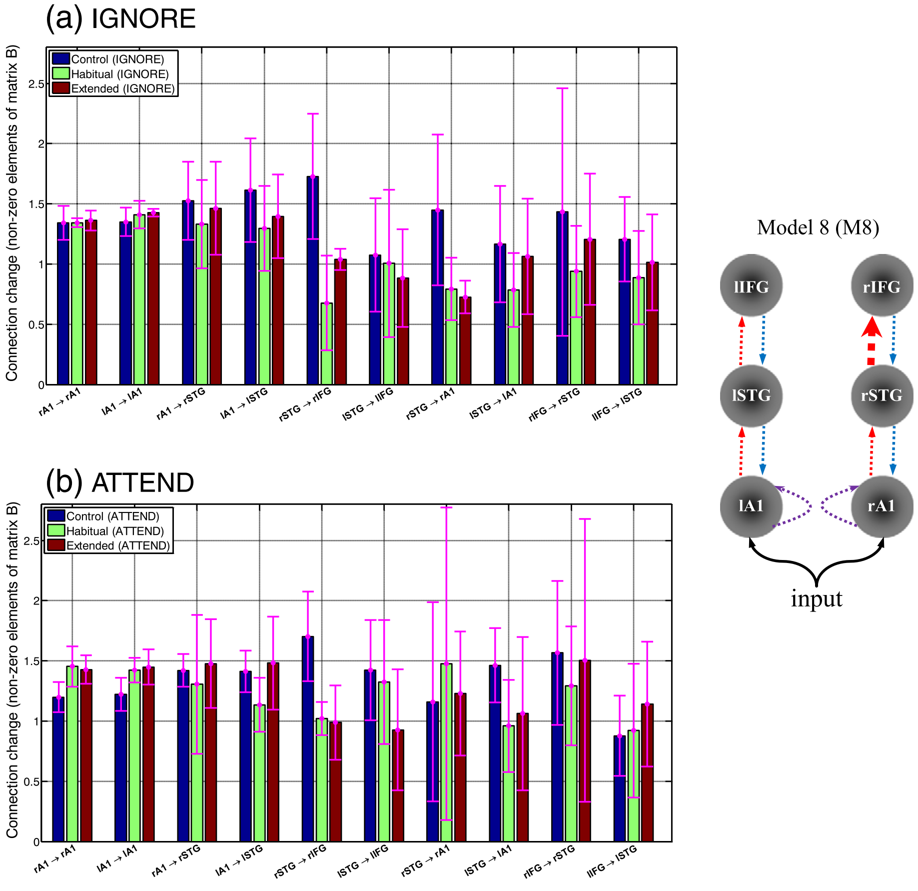


Fig. 6. Estimated means and standard deviations of strengths of connections of the best models (M8) in the three groups (Control, Habitual, and Extended) for two conditions (IGNORE and ATTEND). Note that the forward connection from right STG (rSTG) to right IFG (rIFG) for Control is significantly greater than Habitual in both of the IGNORE and ATTEND conditions.

attentional and passive processing is impacted by sleep loss. The prolonged wakefulness produces a decrease in metabolic rates in widespread cortical and subcortical areas, specifically in the thalamus, hypothalamus, and brainstem reticular formation (Thomas et al., 2000). Thereby, the connections between temporal and frontal areas during novelty processing in short sleepers may be affected by metabolic changes due to sleep loss.

This BCA analysis builds upon the previous ERP analyses (Gumenyuk et al., 2011) and is consistent with the prior studies showing that reduced sleep time negatively affects the performance and function of the brain in cognitive tasks including impaired psychomotor performance (Balkin et al., 2004; Van Dongen et al., 2003), reduced performance in cognitive tasks (Bonnet and Arand, 2005), and decline in alertness (Dinges et al., 1997; Drake et al., 2001). The results of the current study extend the previous findings in (Gumenyuk et al., 2011) by relating the deficits found to particular brain regions involved in auditory processing particularly connections between STG and IFG. These results are also consistent with PET studies in sleep deprived healthy controls where both frontal and thalamic brain areas showed reductions in brain metabolism following sleep deprivation (Thomas et al., 2000).

It has been shown in several previous studies that the temporal and frontal lobes, which are modeled as STG and IFG, respectively, in the current study, have a significant role in the processing of auditory information related to infrequent (novel) tones (Doeller et al., 2003; Grau et al., 2007; Opitz et al., 2002; Rinne et al., 2000). In a recent MEG auditory oddball study (Halgren et al., 2011), the following three phases were found for the processing of the rare (infrequent) tones: First, superior temporal lobe is active during the MMN that may reflect detection of the rare tone; Then the frontal lobe is active during the N2 and P3a that may reflect the orientation of attention; Finally, the temporal lobe is again active during the P3b linking of this phase to working memory. Therefore, there is a back and forth exchange of information (in different time windows) between the temporal and frontal lobes in processing the rare event that is modeled in our approach as the forward and backward connections between the STG and IFG. Halgren et al. show that cortical activity for processing of the rare tone is more prominent in the right hemisphere. Their finding is consistent with other studies (Garrido et al., 2008; Opitz et al., 2002). To distinguish between normal and short sleepers, our results show that the connections between STG and IFG in the right hemisphere are a better discriminating feature compared to these connections in the left hemisphere. Therefore, our finding is consistent with prior studies showing that the right hemisphere is more prominent in the processing of auditory oddball information.

Gumenyuk et al. showed that habitual short sleep is associated with a decline in amplitudes of the frontally distributed ERPs during novelty processing (Gumenyuk et al., 2011). They found that the MMN and P3a in the ATTEND task were significantly reduced in short sleepers compared to controls and this reduction had a spatial distribution over the frontal electrodes. Given that the MMN represents an index of pre-attentive sensory memory operations in detection of changes in the auditory stream, the reduction of the forward connection to frontal areas (primary finding of the current study) suggests that habitual short sleep reduces the efficiency of the frontal mechanism underlying the process of tasks which require attention. Specifically, our results suggest that the connection between IFG and STG is the critical site responsible for the ERP reductions observed by Gumenyuk et al. (2011). The lack of a behavioral performance measure is a limitation of our study and the functional relationship remains speculative.

The results of the current study show that although extension of time in bed for one week increased total sleep time, it did not completely normalize the forward connection to frontal areas in habitually short sleeping individuals. The lack of complete recovery in this connection after one week of sleep extension might be associated with the short period of sleep extension (Gumenyuk et al., 2011). Chronic short sleepers appear to need longer periods of sleep extension to normalize the activity in this connection. It has been shown in one study that two weeks of sleep extension may normalize alertness (Roehrs et al., 1996) while one week of sleep extension does not (Roehrs et al., 1989). In fact, in a primary insomnia fMRI study, the recovery of the prefrontal area after six weeks of behavioral therapy was reported (Altena et al., 2008). Gumenyuk et al. found that the attention-dependent neural processes do not fully recover after one week of sleep extension in habitually short sleeping individuals whereas the neuronal process linked to the automatic change detection may recover after this time (Gumenyuk et al., 2011). Further studies are required to investigate the normalization of the connections between the STG and IFG after a longer sleep extension in habitual short sleeping individuals.

There is no significant difference between the connections among the areas for extended and habitual short sleep. This suggests a potential adaptation effect to chronic sleep restriction in short sleeping individuals compared to the normally sleeping subjects. This is consistent with a study reporting that an adaptive process occurs when sleep is shortened gradually that causes less impairments compared to similar level of sleep loss but experienced at a rapid rate (Drake et al., 2001). As the attentional system is confronted with more challenges in the ATTEND task compared to the IGNORE task, it is expected that the deficits in frontal regions of short sleeping individuals show a greater reduction of the connections to frontal areas in novelty processing of the ATTEND task. Thus, the effects of sleep deprivation are more apparent when there is a demand to perform (which requires greater levels of attentional processing) and therefore, active attention tasks are more sensitive to sleep deprivation.

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