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Sleep EEG functional connectivity varies with age and sex, but not general intelligence

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A B S T R A C T

Variations in the anatomical and functional connectivity between brain areas underlie both healthy and pathological variation in psychological measures. Largely independent from external stimuli, the sleep EEG is particularly well suited to measure individual variations in functional brain connectivity. In this study of 172 healthy individuals (17–69 years old), we show that functional connectivity between distant brain areas—reflected by the weighted phase lag index of the sleep EEG—is strongly affected by the age and sex of participants. Both NREM and REM connectivity in the theta and beta range increased with age, whereas a decrease was seen in the sigma range. Connectivity was substantially greater in females than in males in the high sigma frequency range, but an opposite pattern was seen in the alpha/low sigma and beta range. General intelligence was not significantly associated with connectivity in either sex. Our results confirm strong age effects on sleep spindle-frequency activity, which loses synchrony as a function of aging. Furthermore, we found support for a vigilance state–independent age-related increase in high beta power, previously demonstrated in waking EEG studies. The results highlight that future studies establishing sleep EEG connectivity measures as psychological or psychiatric biomarkers should take into account that sleep EEG synchronization is strongly affected by age and sex, and clinical thresholds must be adjusted accordingly.

1. Introduction

The concept of functional connectivity originally arose from functional multiunit recordings (Aertsen and Preissl, 1991; Gerstein and Perkel, 1969), and it was adapted to fMRI methodology (Biswal et al., 1995; Friston, 2011), referring to clusters of brain regions whose activity is consistently correlated: brain regions generating similar biological signals over time are considered functionally connected, even without directly observing their anatomical connections. The functional connectivity approach has been extended to the electroencephalogram (Thatcher et al., 1987), using coherence or similar metrics (e.g., phase lag indices, entropy, synchronization likelihood, etc.) between pairs of scalp EEG derivations as a simple and cost-efficient way of estimating the functional connectivity between the activity of the underlying cerebral regions. EEG-based functional and diffusion tensor imaging (DTI)-based anatomical connectivity are substantially, but not perfectly, correlated (Chu et al., 2015). DTI may fail to capture functionally relevant unmyelinated fibers or indirect connections between functionally related activity clusters such as common innervation from brainstem areas, while EEG connectivity has substantially lower spatial resolution and it is subject to spatial filtering artifacts due to the distance of the EEG electrodes from signal sources (Chu et al., 2015). Thus, while EEG-based functional connectivity is not without its shortcomings, it may capture couplings between brain areas which are missed by structural imaging approaches and may therefore be relevant as a supplementary diagnostic marker in the wide variety of neurological and psychiatric conditions where the disease of the white matter system is at least a partial cause (Fields,

All data used in the described analyses is available upon request.

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2008; Nunez et al., 2015). In line with this theory, alterations in EEG connectivity were found in many clinical conditions, including Alzheimer's disease and dementia (Blinowska et al., 2017; de Haan et al., 2009), major depressive disorder (Olbrich et al., 2014; Tas et al., 2015), bipolar depression (Kam et al., 2013; Ozerdem et al., 2011; Tas et al., 2015), autism (Goldani et al., 2014; O'Reilly et al., 2017), and schizophrenia (Uhlhaas and Singer, 2010). A subset of studies (Armitage et al., 2006; Augustinavicius et al., 2014; Morehouse et al., 2002; Yeragani et al., 2006) found alterations specifically in sleep EEG connectivity measures in psychiatric conditions, highlighting the utility of using EEG measures in various vigilance states.

To use EEG functional connectivity as a marker of disease (or any other condition of interest), physiological sources of its individual variability must be known. Although wake EEG measurements—usually lasting only a few minutes—are more feasible for most purposes, especially in clinical settings, such recordings are subject to biases due to external stimuli, circadian effects, muscle artifacts, imperfect representativeness of the short recorded session, or contamination due to ongoing mentation (Tarokh et al., 2010). Sleep EEG parameters, on the other hand, are free from most of such wakefulness-specific artifacts, while they show substantial intraindividual stability (De Gennaro et al., 2005; Finelli et al., 2001), strong genetic determination (Adamczyk et al., 2015; De Gennaro et al., 2008), and direct reliance on the underlying anatomical structure of the brain (Piantoni et al., 2013; Saletin et al., 2013; Smit et al., 2012), rendering them good putative markers of interindividual differences with easily controllable sources of confounding variance. Relatively few studies are available about the sources of normal sleep EEG connectivity variability, despite ample literature about at least sex (Åström and Trojaborg, 1992; Carrier et al., 2001; Colrain et al., 2011; Driver et al., 1996; Huupponen et al., 2002; Ujma et al., 2014) and age (Carrier et al., 2001, 2011; Dijk et al., 1989; Fogel et al., 2012; Guazzelli et al., 1986; Landolt et al., 1996; Martin et al., 2013; Principe and Smith, 1982) effects on many other sleep EEG parameters. In childhood (Kurth et al., 2013) and adolescence (Tarokh et al., 2014), a linear, age-dependent increase in sleep EEG coherence in both REM and NREM sleep has been reported. In addition, children and young adults with Williams syndrome and Asperger syndrome were characterized by atypical sleep EEG synchronization patterns (Gombos et al., 2017; Lázár et al., 2010). However, no such data are available about healthy young, and middle-aged adults. To our knowledge, sex differences in sleep EEG connectivity have never been investigated, except for an early negative report with a total of 12 participants (Nielsen et al., 1990).

Parameters of the sleep EEG were previously found to be associated with general cognitive ability (Geiger et al., 2011; Ujma, 2018; Ujma et al., 2017). One study (Tarokh et al., 2014) found no correlation between EEG coherence and baseline performance on 3 neurocognitive tasks with reasonable g-loadings (the Stroop test, Trail Making, and the FAS verbal fluency task) in adolescents, but no previous study investigated the relationship between intelligence and the functional connectivity of the sleep EEG of adults, although wake EEG coherence and complexity measures were much better predictors than spectral power (Thatcher et al., 2005, 2008).

Our study aimed to fill these gaps and investigated age and sex effects on sleep EEG functional connectivity in an adult data set which was substantially larger than previous ones (N = 172). Both age and sex effects on sleep EEG connectivity were substantial. Furthermore, our study is the first to extend a previous wake EEG study design of coherence analysis (Thatcher et al., 2005) to sleep EEG and investigate the relationship between sleep EEG connectivity and general intelligence. This relationship, however, was not found to be statistically significant.

2. Methods

2.1. Participants and psychometric data

Our analyses were performed in an existing multicenter database of full-night polysomnography recordings of adult (Pótári et al., 2017; Ujma et al., 2014, 2015) participants. The absence of a diagnosis of any neurological or psychiatric disease was a requirement for inclusion, and participants were free of any current drug effects, excluding contraceptives. Eight participants were light to moderate smokers, whereas the rest of the participants were nonsmokers. For the participants, small, habitual doses of caffeine (max. 2 cups of coffee before noon) were allowed. Procedures were approved by the ethical boards of the involved institutions (Semmelweis University, Budapest, and the Ludwig Maximilian University, Munich). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. All participants spent 2 nights in a sleep laboratory, of which the first night served as an adaptation night and data from the second night was used in subsequent analyses.

Participants with poor-quality EEG data (characterized by the presence of wide frequency band artifacts and/or multiple electrode failures within the same electrode cluster; see under Data processing) were excluded, and 15 novel recordings with available sex and age data, but without cognitive ability test scores, were added, yielding a total sample size of N = 172 (94 males, 78 females, mean age: 29.74 years, SD = 10.71 years, range 17–69 years). A histogram of the distribution of participant ages is given on Supplementary Fig. 1. For analyses involving cognitive ability scores, only participants with such scores (N = 157) were used.

The sex, age in years, and general cognitive ability of each participant were recorded. General cognitive ability was assessed using either Raven's Advanced Progressive Matrices (N = 86) (Raven et al., 2004), the Culture Fair Test (N = 113) (Cattell, 1973), and/or the Number Connection Test (Zahlen-Verbindungs-Test) (N = 106) (Oswald and Roth, 1987). For each subject with multiple general cognitive ability scores, we converted the scores from CFT and/or ZVT raw scores to Raven equivalents by looking up the Raven APM score corresponding to the same IQ as the participant obtained using the other test (CFT or ZVT), taking into account the participant's age. We used the 1993 Des Moines (Iowa) standardization of the Raven APM (Raven et al., 2004) as a reference. IQ test raw score intercorrelations were the following: $r_{Raven\text{-}CFT} = 0.69$, $r_{Raven\text{-}ZVT} = -0.57$, $r_{CFT\text{-}ZVT} = -0.66$. If multiple test scores were available, their Raven equivalents were averaged (Pótári et al., 2017; Ujma et al., 2014).

Males and females did not significantly differ in their age and Raven's APM equivalent scores ($t_{Raven} = 0.84$, $p_{Raven} = 0.4$; $t_{age} = 0.68$, $p_{age} = 0.49$).

2.2. Polysomnography

Polysomnography data were obtained at multiple recording centers (Pótári et al., 2017; Ujma et al., 2014, 2015) with the common recording sites across studies and laboratories being: Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, T3, T4, T5, T6, O1, and O2, electrooculography, bipolar submental electromyography, as well as electrocardiography. Impedances for the EEG electrodes were kept below 8 kΩ. The sampling frequency was either 249 Hz, or 250 Hz, or 1024 Hz, depending on recording site.

All recordings were referenced to the mathematically linked mastoids. Sample sizes, age distributions, and further recording apparatus details are provided in Supplementary Table 1.

2.3. Data processing

All polysomnography recordings were visually scored by expert raters using standard criteria (Iber et al., 2007). Artifacts were rejected by visual inspection on a 4-second basis. In case of electrode failure, data from the affected electrodes were treated as missing data. However, if multiple electrodes from the same cluster failed (see later for the definition of electrode clusters), the subject was dropped from further analysis.

To calculate functional connectivity for each subject, EEG data were first separated into NREM (excluding N1) and REM data. The weighted phase-lag index (WPLI [Vinck et al., 2011]), defined as the phase leads or lags weighted by the magnitude of the imaginary part of the complex cross-spectrum of the series (based on the fast Fourier transform), was calculated between all possible electrode pairs from the resulting time-frequency data and finally averaged across all data segments and electrode pairs belonging to the same cluster, respectively. WPLI was chosen as a measure of functional connectivity because it penalizes exact in-phase and antiphase patterns between signals, which are likely the result of mass conductance rather than actual functional coupling.

WPLI was averaged within electrode clusters to reduce the complexity of calculations and to smoothen out potentially spurious effects resulting from a single signal pair. Electrode clusters were the following: frontal (Fp1/2, F3/4, F7/8), centrotemporal (C3/4, T3/4), and posterior (P3/4, O1/2, T5/6) (Lázár et al., 2010). Analogous regions were defined over both the left and the right hemisphere, except for the central region, yielding a total of 6 electrode clusters. Central electrodes (Cz, Fz, and Pz) were not included in any of the electrode clusters due to their lack of assignment to either hemisphere. WPLI was averaged for all possible signal pairs between electrodes in a certain electrode cluster and all other electrodes in the ipsilateral (intrahemispheric WPLI) or contralateral (interhemispheric WPLI) hemisphere for both REM and NREM sleep, yielding a total of 24 connectivity measures for each subject. Central electrodes (Fz, Cz, and Pz) were not included in any electrode cluster, but they were included in both intrahemispheric and interhemispheric analyses as ipsilateral and contralateral electrodes, respectively, unless they were topographically included in the electrode cluster for which connectivity was calculated: that is, Fz was excluded from frontal, Cz from central, and Pz from posterior measures. For example, NREM posterior left intrahemispheric WPLI was defined as the grand average of the mean WPLI values (averaged across all 4-second segments in NREM sleep) between P3 and all non–posterior ipsilateral electrodes, O1 and all non–posterior ipsilateral electrodes, and T5 and all non–posterior ipsilateral electrodes. Non–posterior ipsilateral electrodes in this case did not include Pz because of its posterior position but did include Fz and Cz. A precise description of our connectivity measures is provided in Supplementary Table 2.

2.4. Statistics

WPLI values are, by definition, bounded between 0 and 1. To normalize variances across this range and permit scale-level statistics, all connectivity measures were transformed using the Fisher Z-transform before statistical analysis (Fisher, 1915). We computed independent-sample t-tests (or the equivalent Welch t-test in case of unequal variances) to assess sex differences in connectivity, Pearson's point-moment correlations to assess the correlation between connectivity and age, and Pearson's partial correlations (corrected for age) to assess the correlation between connectivity and general cognitive ability. We applied the Benjamini-Hochberg method (Benjamini and Hochberg, 1995) across all frequencies for each connectivity measure to control for multiple comparisons. Statistical analyses were performed in Statistica (StatSoft Inc, Tulsa, OK), IBM SPSS Statistics (IBM Corporation, Armonk, NY, USA), and MATLAB (The MathWorks, Natick, MA, USA).

3. Results

3.1. Age effects on connectivity

Age was associated with decreased connectivity in the NREM sigma range (10.25–14.75 Hz) and increased connectivity in both NREM theta (4.25–5.5 Hz) and beta (30.75–40 Hz) and REM theta (2.5–5.25 Hz) and beta (26.75–40 Hz) ranges. The topography of these effects (age-related increases in NREM and REM beta, as well as of REM theta WPLI), extended to most (at many frequencies, all) connectivity measures, with the exception of age-related increase in NREM theta synchronization. The latter was restricted to the age-related increases in the connectivity of the posterior regions with the other areas of the brain (Fig. 1). These effects were similar in males and females (Supplementary Fig. 2).

3.2. Sex differences in connectivity

Several significant sex differences of functional connectivity were found, many of which were independent of scalp topography and sleep state (Fig. 2). The most prominent differences were found in the NREM sigma range (13.5–14.5 Hz) with higher values in females, and in the beta range of both NREM (15.75–27.25 Hz) and REM (12.25–24.75 Hz) sleep, where higher values were seen in males. Higher connectivity in the NREM high alpha/low sigma range (10.25–11.75 Hz) was also found in males. The effect size of these differences was relatively large: the maximal magnitude of the higher female connectivity (at 14 Hz in the NREM intrahemispheric left centrotemporal connectivity measure) corresponded to a Cohen's d of 0.73, whereas the maximal magnitude of the higher male connectivity (at 18.75 Hz in the REM intrahemispheric right frontal connectivity measure) corresponded to a Cohen's d of 1.03, slightly lower than typical sex differences in body mass and body height, respectively (Conroy-Beam et al., 2015).

3.3. Connectivity and general cognitive ability

General cognitive ability, assessed through a composite score of 3 nonverbal tests, was not significantly associated with connectivity patterns of the sleep EEG after correcting for multiple comparisons (Fig. 3), either in the whole sample or within sexes (except for a total of 7 discontinuous frequency bins reaching significance in males, all in the NREM posterior interhemispheric measure at 31.25, 31.5, 32.75, 39.25, 39.5, 39.75, and 40 Hz, data not shown). Supplementary Fig. 3 shows the association between connectivity and general cognitive ability by sex.

The strongest sex and age effects are illustrated on Fig. 4.

3.4. Additional analyses

With additional analyses (Supplementary Text), we found that natural logarithmic and quadratic models yielded a worse fit than a linear model, and a cubic model was only minimally superior, confirming the linear nature of the age-connectivity relationship. We also assigned statistical weights to our participants to enforce to simulate a true population distribution of age and found that our

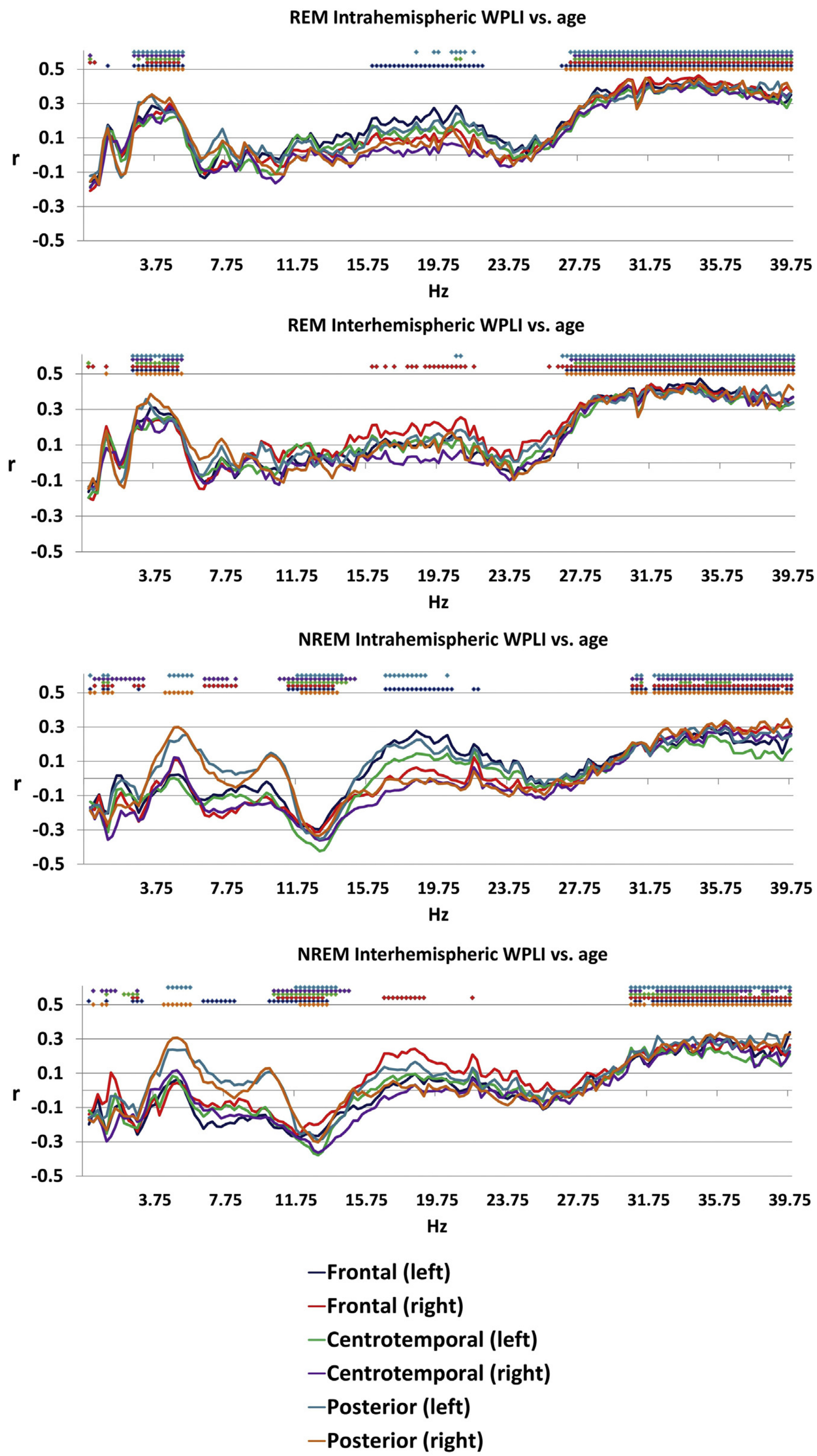

Fig. 1. Pearson's correlation coefficients between age and connectivity. Colored dots indicate that the correlation coefficient for the given frequency was significant after Benjamini-Hochberg correction for multiple comparisons. Abbreviation: WPLI, weighted phase-lag index.

results are robust to the restriction of the age range of participants, with the possible exception of the 3.5 Hz REM oscillation.

Finally, to test the hypothesis whether general effects are caused by small clusters of actual connectivity, we increased the resolution of our analysis by averaging WPLI between all possible pairs of clusters, yielding 6*6 = 36 connectivity measures, including connectivity within different electrodes in the same cluster. We averaged WPLI values within traditional EEG bands: 1–3 Hz (delta), 3.25–7.75 Hz (theta), 8–10.75 Hz (alpha), 11–15.75 Hz (sigma), 16–25 Hz (beta), and 25.25–48 Hz (gamma)

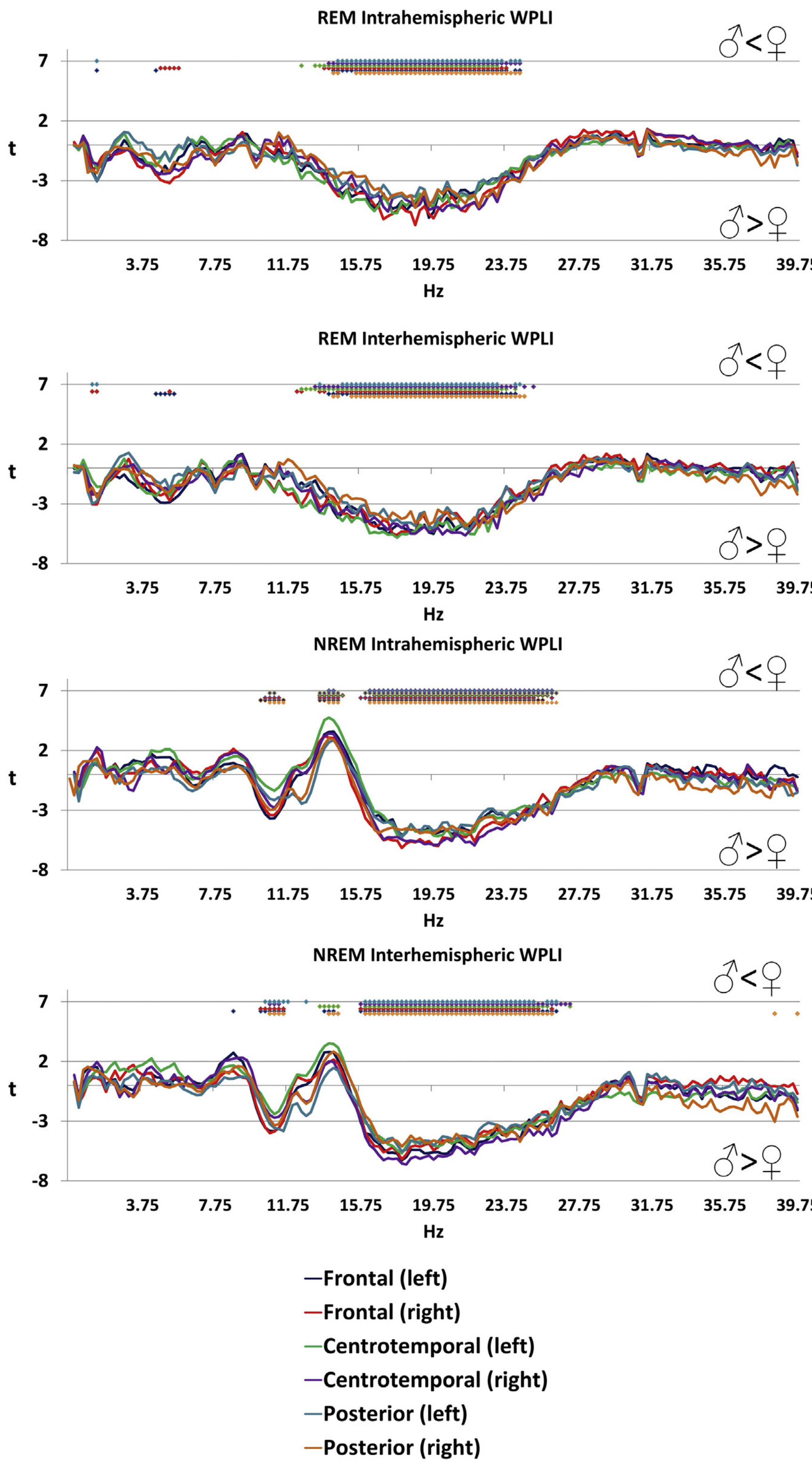

Fig. 2. Sex differences in connectivity. Positive t-values indicate higher values in females, whereas negative t-values indicate higher values in males. Colored dots indicate that the independent-samples *t*-test for the given frequency was significant after Benjamini-Hochberg correction for multiple comparisons. Abbreviation: WPLI, weighted phase-lag index.

separately in REM and NREM sleep. We calculated the correlation of these measures with age and their differences between the sexes. These results are shown in Fig. 5 and reported in detail in Supplementary Tables 3 and 4, which also contain same-cluster connectivity effects. Our results indicate that age-related decreases in low-frequency activity are concentrated in frontal and central areas, and age-related increases in theta activity are concentrated in posterior areas. However, our main age-related findings—a reduction in sigma connectivity and an increase in gamma connectivity—were present with a widespread and

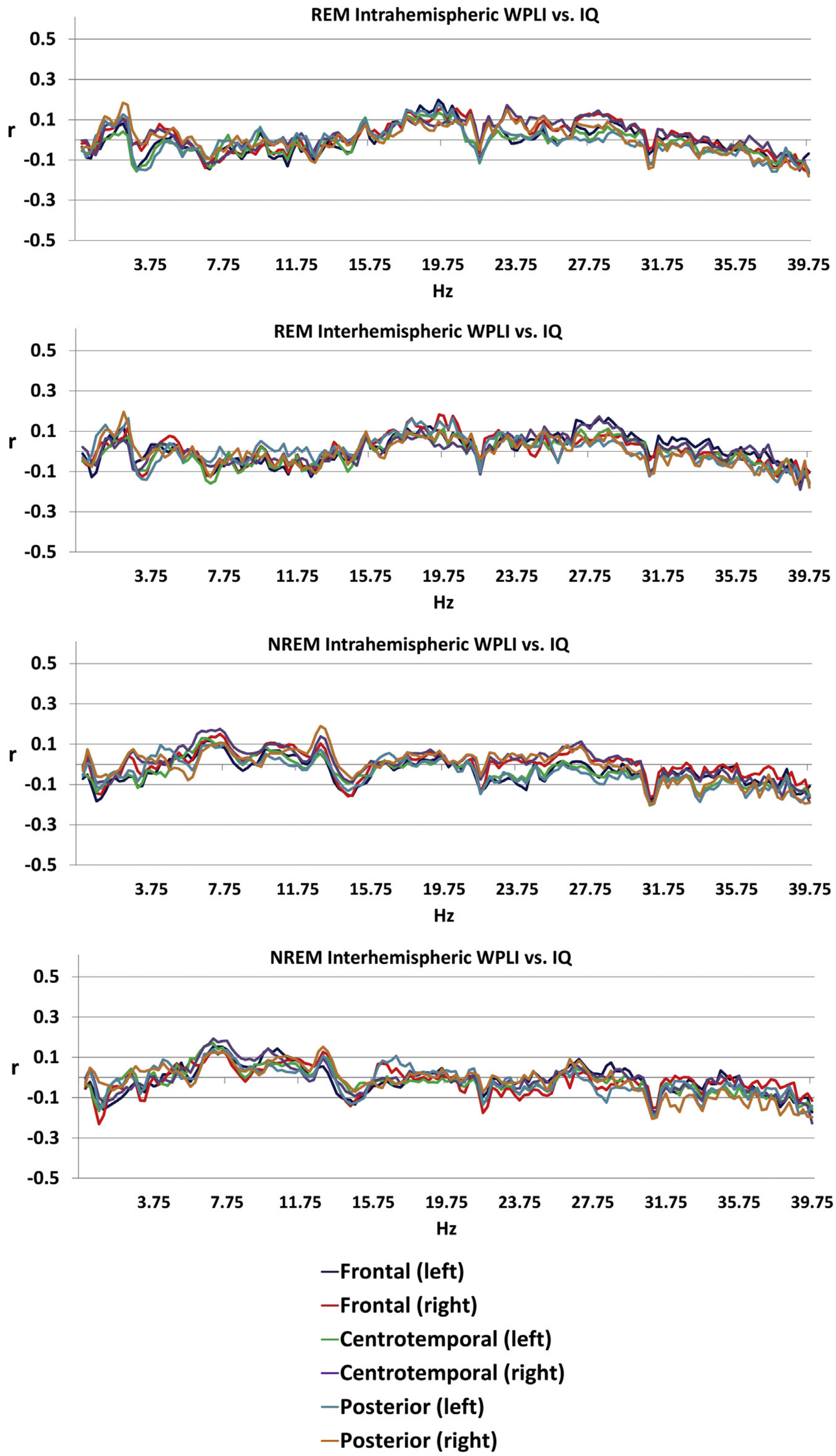

Fig. 3. Age-corrected Pearson's correlation coefficients between general cognitive ability and connectivity. Correlation coefficients were not significant after Benjamini-Hochberg correction for multiple comparisons. Abbreviation: WPLI, weighted phase-lag index.

general topography. Higher female connectivity was most prominent in frontal and central intrahemispheric comparisons, but higher male beta and gamma connectivity were topographically widespread. Note that sex effects were heterogeneous within the broad sigma range (Fig. 2), limiting the power of bandwise comparisons.

4. Discussion

Our main results can be summarized as follows: (1) NREM sleep EEG connectivity in the sigma frequency range increases decreases with aging, while aging is also associated with a sleep state–independent increase in sleep EEG beta and theta-range

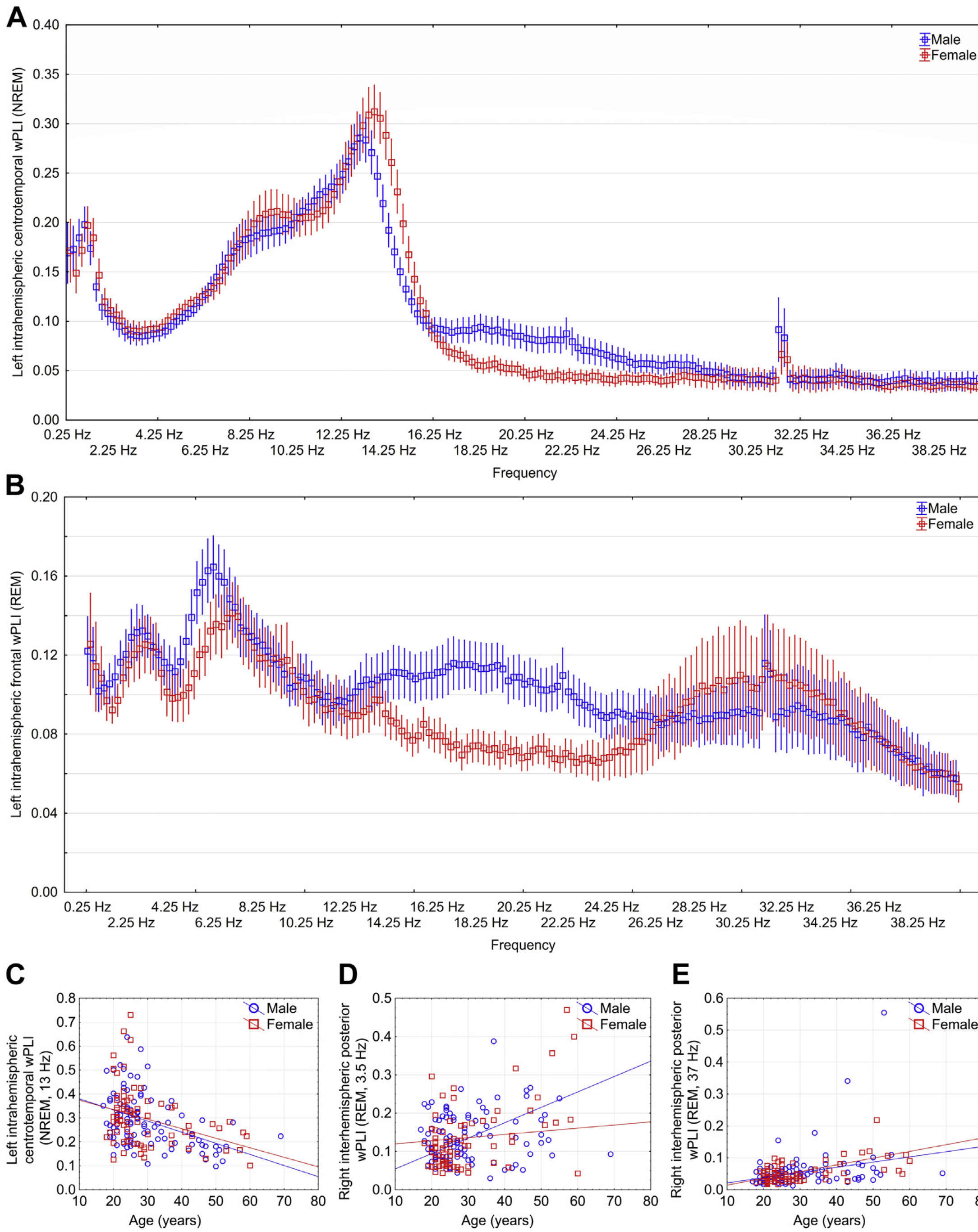

Fig. 4. Sex differences and age dependence of sleep EEG connectivity. Panels A and B depict male and female mean WPLI values in NREM and REM sleep, respectively, with 95% confidence intervals in each 0.25 Hz bin. Values are shown for the connectivity measures where sex differences were maximal. Panels C–E depict the correlation between age and WPLI values, with separate regression lines by sex. 13 Hz and 37 Hz effects were not significantly different between males and females ($p = 0.07$ and $p = 0.52$), but 3.5 Hz effects were significantly larger in males ($p = 0.004$, all analyses based on the comparison of correlation coefficients using Fisher's r-to-z method). All data are shown for the connectivity measure and frequency where the correlation was maximal. Abbreviation: WPLI, weighted phase-lag index.

connectivity; (2) NREM sleep EEG connectivity in the high sigma frequency range is higher in females, but in the alpha/low sigma and beta frequency range (in the latter partially also in REM sleep), it is larger in males. We did not find a significant association between connectivity and general intelligence in either sex.

The association between sleep EEG connectivity and age is well in line with the previously reported gross reduction in sleep spindle activity (Carrier et al., 2001, 2011; Martin et al., 2013; Principe and Smith, 1982) and an increase in beta activity (Carrier et al., 2001). As expected, reductions in the sigma range are confined to NREM sleep where sleep spindles are present and where characteristic peaks were reported not only for the power spectrum, but also for coherence (Achermann and Borbely, 1998a, b). Beta increases were, however, observed in both NREM and REM sleep, indicating a state-independent effect. Importantly, a very similar effect—including the loss of coherence at lower frequencies—has been reported in a very large sample of wake EEGs (Vysata et al., 2014), indicating that higher beta-range connectivity is a vigilance state–independent

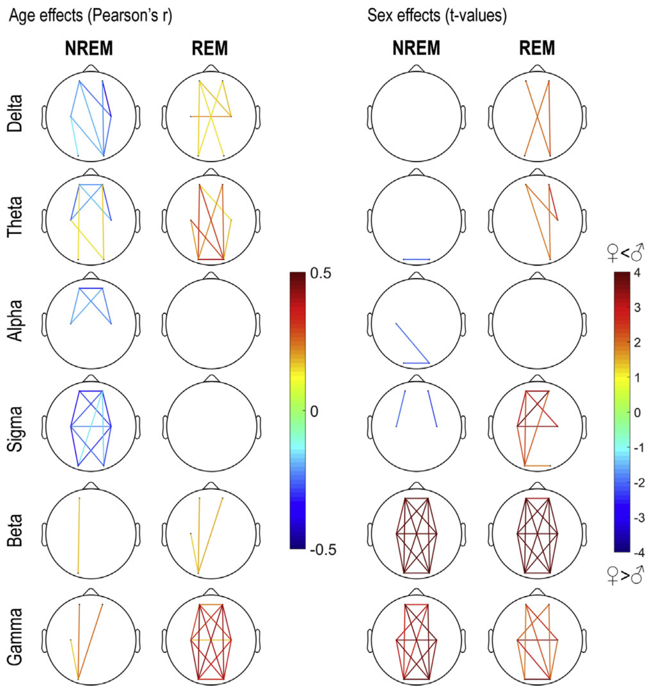

Fig. 5. Pearson correlation coefficients between age and WPLI values (left) and t-values of male-female differences in WPLI (right). WPLI values averaged between all frequency bins in a frequency band and between all possible electrode pairs in the 2 electrode clusters. Positive t-values indicate higher values in males. Only connectivity measures with at least nominally significant age or sex effects are shown. Abbreviation: WPLI, weighted phase-lag index.

correlate of aging. Because the spatial extent of neural activity synchronization decreases as a function of frequency (Baria et al., 2011; Chu et al., 2015; Tallon-Baudry, 2009), and high-frequency oscillations remain especially local without the support of prominent white matter connections (Chu et al., 2015), it is likely that the age-related loss of white matter (Yap et al., 2013) causes a breakdown of low-frequency connectivity over distant areas and an increase of synchronization in local networks. Notably, most age effects on connectivity had a very general topography, indicating that age-related changes in functional connectivity are widespread. However, age-dependent increases with relatively restricted topography were found for NREM sleep EEG theta connectivity. The latter was confined to paths binding posterior sites with more rostral ones.

Our findings regarding the age-associated increase in REM and NREM sleep EEG theta connectivity are without antecedents in the literature. All available reports on age-relatedness of EEG connectivity focus on wakefulness (Duffy et al., 1995; Vysata et al., 2014), and all report an age-related decrease in low frequency wake EEG coherence. Our current findings suggest the state specificity of these correlations as well as the importance of distinguishing (REM) sleep EEG theta synchronization from that of theta connectivity in the state of wakeful rest, particularly as low-frequency waves in REM sleep, NREM sleep and wakefulness have different neural generators (Bodizs et al., 2001; Montplaisir et al., 1998). Another possible reason for the diverging results may be methodological one: although coherence (used in older studies) is sensitive to amplitude covariation and volume conduction, WPLI (used by our study) is completely free of these shortcomings. In short, a high zero-phase synchrony in the theta frequency range could result in high coherence but low WPLI.

Regarding sex differences, higher female sigma connectivity and higher male alpha/low sigma and beta connectivity were found. Sleep spindling is arguably more prominent in females in general, as higher sleep spindle amplitude and sigma EEG power have been previously reported in females (Ujma et al., 2014). Functional connectivity is generally higher in females (Duffy et al., 1995; Gong et al., 2009; Tomasi and Volkow, 2012). A large study (Ingalhalikar et al., 2014) also found substantial sex differences in DTI-derived structural connectivity, with higher long-distance interhemispheric connectivity in females. In light of these reports, greater female connectivity is unsurprising and it may reflect both higher sleep spindle generation and long-distance connectivity in females. It must be noted, however, that an even larger study of an older (>45 year old) sample (Ritchie et al., 2017) found higher fractional anisotropy values in males instead of females, although higher white matter complexity was still found in females.

Higher male NREM and REM low beta connectivity in males is a novel finding. Notably, it is in a different frequency range than the one affected by age (≤25 Hz, while age-related effects are usually at ≥25 Hz, see Figures 1 and 2). It is unlikely to be caused by a reduction in sleep quality because no sex differences are seen in the current data set when sleep macrostructure is compared (Ujma et al., 2017). In the absence of relevant previous literature, it is not possible to interpret the functional significance of this oscillation, although its frequency is the same as that of REM beta oscillations recently described in the frontal cortex (Vijayan et al., 2017), the characteristic power of which we found to positively correlate with intelligence (Ujma et al., 2017).

A further finding without antecedents in the literature is the increased NREM sleep EEG alpha/low sigma connectivity in males as compared to females. This finding might be interpreted as another case of state-specific oscillatory phenomena, perhaps involving the physiological mechanisms of slow sleep spindles during NREM sleep as well. To discern the potential routes of this higher male NREM sleep EEG alpha/low sigma connectivity, further studies focusing on sleep stage and cycle effects, as well as an individualization of sleep spindle frequencies are needed.

Our study failed to find an association between sleep EEG connectivity patterns and general cognitive ability, at odds with waking EEG results (Thatcher et al., 2005, 2008). The most likely reason for this is that reasoning in wakefulness may be supported by synchronization patterns that are disengaged during sleep and therefore not detectable using the sleep EEG.

Overall, our findings therefore confirm previous studies about the dependence of sleep EEG features on sex (Åström and Trojaborg, 1992; Carrier et al., 2001; Colrain et al., 2011; Driver et al., 1996; Huupponen et al., 2002; Ujma et al., 2014) and age (Carrier et al., 2001, 2011; Dijk et al., 1989; Fogel et al., 2012; Guazzelli et al., 1986; Landolt et al., 1996; Martin et al., 2013; Principe and Smith, 1982), extending results about spectral power and microstructural features into connectivity. Our results are of particular importance for future clinical applications.

In 2010, the National Institute of Mental Health called for an evidence-based classification of psychological phenomena and mental disorders, labeled Research Domain Criteria (Insel et al., 2010). Research Domain Criteria aims to classify psychological constructs and their relationship with mental disorders based on objective measurement instead of the traditional nomenclature of the DSM-V. Electrophysiological measures are listed as possible biomarkers, foreshadowing their importance in future psychological and psychiatric classification systems. However, the search for actual biomarkers in several neurological and especially psychiatric disorders is still ongoing (Boksa, 2013; Venkatasubramanian and Keshavan, 2016), and the currently available biomarkers for—among others—psychosis (Prata et al., 2014), autism (Goldani et al., 2014), and even Alzheimer's disease (Wurtman, 2015) are not satisfactory. Functional connectivity, estimated by scalp EEG measures, is an indirect and imperfect approximation of the actual connectivity patterns of the brain: however, its agreement with anatomically derived connectivity measures is not trivial (Chu et al., 2015), it likely captures meaningful functional coupling between brain regions even if DTI fails to discover a supporting anatomical pathway (Chu et al., 2015; Nunez et al., 2015) and the simple and cost-efficient way in which it can be measured renders it a particularly attractive clinical marker even if the physiological details of its generation are poorly understood. Alterations in EEG connectivity were found in various psychiatric and neurological conditions (Babiloni et al., 2016; Blinowska et al., 2017; de Haan et al., 2009; Fields, 2008; Kam et al., 2013; Li et al., 2016; O'Reilly et al., 2017; Olbrich et al., 2014; Ozerdem et al., 2011; Tas et al., 2015; Uhlhaas and Singer, 2010), supporting its potential role as a clinical biomarker which can be used to indicate the risk, severity, or treatment response of various conditions. Most previous clinical EEG connectivity studies investigated EEGs recorded in short wakeful resting periods. Because of its high individual stability and strong reliance on an anatomical and genetic scaffold (De Gennaro et al., 2008; Landolt, 2011; Piantoni et al., 2013; Saletin et al., 2013; Smit et al., 2012), the sleep EEG is an even more interesting potential clinical biomarker, which is harder to obtain from patients but shows even more promise (Al-Qazzaz et al., 2014; Olbrich and Arns, 2013; Steiger et al., 2015; Steiger and Kimura, 2010; Tsolaki et al., 2014). However, our results indicate that connectivity measures in the sleep EEG are subject to robust physiological variation as a function of both age and sex: therefore, connectivity-based biomarkers must be carefully tailored based on age and sex.

Our study suffers from a number of shortcomings. We calculated connectivity between electrode clusters defined by a previous study (Lázár et al., 2010), reducing the spatial resolution of our estimations of functional connectivity. However, we found age and sex effects on connectivity to be quite general instead of limited to certain specific connectivity measures, indicating that low spatial resolution was likely not an issue for the detection of these effects. We further investigated this by using bandwise comparisons between specific electrode clusters, which mostly confirmed the hypothesis of topographically widespread effects. Our sample did not involve a healthy older adult population, the oldest participant being 69 year old, and most of the older half of the sample being only in their 40s; therefore, our findings about sleep EEG connectivity alterations as a function of age are only representative of a limited section of the human lifespan. We attempted to partially correct for this by weighting subjects to enforce a representative age distribution, which resulted in the replication of most key findings. Furthermore, it must be also noted that sex and age effects may not be direct but instead mediated by environmental exposures correlated to these variables. Therefore, it is possible that these correlates of age and sex are not uniform across all environments.

Disclosure

The authors declare that they have no conflict of interest.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.02.007.

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