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Overall Population Generalities, Sex Differences, and Individual Differences in Sleep Electroencephalography Functional Connectivity

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ABSTRACT Sleep is indispensable for humans to maintain normal life activities. Sex and individual differences in sleep patterns and quality of sleep cannot be ignored. Nevertheless, the overall population generalities and sex- or individual- differences in cerebral cortical functional connectivity (FC) during sleep have not been well described. Here, we evaluated the characteristic patterns of FC based on whole-night sleep electroencephalography (EEG) recordings. An improved weighted phase lag index (WPLI) algorithm was applied to obtain the FC in delta (0.5-4Hz), theta (4-8Hz), alpha (8-12Hz) and beta band (12-32Hz). FC strength, short-term stability and inter-regional imbalance of FC were studied. We found that the variations in FC-related parameters among sleep stages had overall population commonalities, and these parameters also showed stage- and frequency band-dependent sex differences. With the deepening of no-rapid eye movement (NREM), increased delta and beta FC strength were observed. Rapid eye movement (REM) showed weaker FC strength, higher FC stability, and higher anterior-posterior FC anisotropy than NREM in beta band. Meanwhile, females exhibited higher sleep EEG synchronization and higher delta FC stability in deep NREM sleep than males. Moreover, the dominant hemisphere in terms of FC did not show group generality or stage- and frequency-dependence. Our results add to the understanding of sleep staging function and may provide clues to sex differences in sleep patterns and quality as well as the prevalence and clinical manifestations of sleep-related illness. Short-term stability offers a new perspective in analyzing FC, which cannot be ignored.

INDEX TERMS Overall population generalities, sex differences, sleep stages, sleep EEG, functional connectivity.

I. INTRODUCTION

Sleep is one of the most widespread biological processes, occupying one-third of our life [1]. Using tracing by electroencephalography (EEG) during sleep, it has been observed that a healthy individual will experience rapid eye movement (REM, R) and no-REM (NREM) sleep, with occasional transitions to wakefulness (WAKE, W) [2]. NREM can be further divided into N1, N2, and N3 stages [2]. Despite the relatively good understanding of sleep behavior and mechanism, the exact functional significance of sleep remains enigmatic. Sleep plays a key role in psychiatric comorbidity processes [3], and the degree of sleep disturbance in patients with certain psychiatric disorders can predict future treatment outcomes to some extent [4]. Basic research on different stages of normal sleep is important for understanding sleep function and how sleep affects mental states. Functional connectivity (FC) in human brain networks, which objectively

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describes the communication between different brain regions, has also been introduced to the field of sleep research [5]–[7]. Some studies have described the FC during normal sleep [8]–[10]; however, they focused on the generalities of overall normal groups and seldom mentioned differences between groups with different characteristics (such as different sex) or among individuals.

The existence of sex differences at all levels of the central nervous system (CNS), including genetic, systemic, and behavioral level, are generally accepted [11], [12]. There are significant differences in sleep patterns and quality between females and males [13]. Some sleep-related disorders, and some neuropsychiatric disorders linked to sleep also show sex differences regarding clinical phenotype and prevalence. Based on demographic data, males are more susceptible to narcolepsy, schizophrenia, REM sleep behavior disorder, and attention-deficit/hyperactivity disorder, while insomnia, anxiety, depression, and restless leg syndrome affect females more than males [14]–[16]. Moreover, sex differences are also found in FC variants associated with mental diseases [17], [18]. Such examples demonstrate the importance of sex as a group-specific variable when studying sleep FC, which may explain sex differences regarding the risk of psychiatric and sleep-related disorders. However, this remains unexplored.

EEG is commonly used to study cerebral cortex activity during sleep owing to its high temporal resolution. EEG FC can capture the coupling between brain regions missed by structural imaging [6], [19], so it may be used as an evaluation criterion for various psychiatric diseases and mental conditions. Many studies have shown that changes in EEG connectivity have been found in a variety of clinical diseases, such as depression [20] and schizophrenia [21]. EEG FC are generally evaluated using coherence or similar indicators (e.g., spectral coherence, synchronization likelihood, phase lag index, etc.) between EEG channel pairs. However, many traditional coherence and similarity evaluation algorithms are susceptible to the influence of volume-condition, reference electrode and noise source, resulting in serious false positive [22], [23]. In order to overcome these problems, Stam *et al.* [23] introduced the phase-lag-index (PLI) to estimate the phase lags between signals. Further, the weighted phase lag index (WPLI) has been developed to increase the capacity to detect phase synchronization changes of small magnitude [24] by introducing phase-difference weighting normalization and has been widely used recently [25], [26].

Temporal variability in FC and short-term stability of EEG FC have attracted the attention of some researchers [25], [27]–[29], as phase synchronization in EEG has been reported to be associated with the exact timing of neural connectivity among different cortical areas [30]. EEG FC stability reflects the stability of information communication between neuronal populations [27], and it is well known that physiological sex and sex hormones affect brain functional asymmetry [31]. Therefore, besides FC strength, it is necessary to describe other FC dimensions, including short-term stability and inter-regional differences.

A number of studies have analyzed the normal sleep EEG FC [8]–[10], and found that EEG FC strength [8], [10] and predominant area [9] changes with the sleep deepens. Although these researches only deal with the strength of FC, we also speculate that the short-term stability of FC may change across sleep stages. And several studies indicated that gender is an independent factor in the division of normal sleep [32]–[35]. In terms of sleep structure, women spend more time in deep sleep (slow-wave sleep) than men in the middle-aged and elderly group [34]. According to the EEG, women's brain power is higher than men's during the sleep [32], [33]. These differences may be due to hormone levels [35], which also greatly affect brain connections [36]. However, there were gaps in the study of sex differences in EEG FC.

In this study, we attempted to find commonalities in sleep EEG FC in the general healthy population, significant congenital differences between males and females, and possible individual differences. To this end, we made some improvements to the WPLI algorithm and used it to evaluate FC. Besides the FC strength, we also investigated short-term stability and inter-regional differences of FC.

II. METHODS AND MATERIALS

A. PARTICIPANTS

Fifty healthy volunteers (21 females and 29 males) aged between 17 and 63 years (mean age 36 ± 12 years) were eventually enrolled in the analysis. They were diagnosed as being free of neurological or psychological disorders, epilepsy, sleep apnea syndrome (apnea-hypopnea index, AHI < 5), or other sleep disturbances. All participants were recruited in the Sleep Disordered Breathing Center of the 6th Affiliated Hospital of Sun Yat-sen University, and this study was approved by the ethics committee of the aforementioned hospital. Informed consent was obtained from all individual participants included in the study.

B. POLYSOMNOGRAPHY

Each participant underwent polysomnographic (PSG) all-night recordings for one night. All recordings started at the participants' usual bedtime and ended at their usual time of getting up in the morning. PSG recording included six EEG channels (F3, F4, C3, C4, O1 and O2, placed according to the 10-20 system), two electrooculogram (EOG) channels, submental electromyogram (EMG) , EMG recorded from electrodes placed at the musculus anterior tibialis of the left or right leg, electrocardiogram (ECG) and respiratory signals (airflow, movements of the chest wall and abdomen, O2 saturation of arterial blood). The recorded EEG, EOG, and EMG signals were digitized at 500 Hz. Respiratory signals were sampled at 100 Hz, and O2 saturation at 10 Hz. Sleep stages were scored by registered sleep technicians according

to standard American Academy of Sleep Medicine (AASM) Criteria.

C. EEG SIGNAL PROCESSING

We first segmented EEG signals according to the sleep stage (into 30-s epochs), and extracted a 10-s epoch from the middle of each 30-s epoch. Then, some 10-s epochs were removed due to the artifacts identified by visual inspection. Finally, 39,114 epochs were obtained (4345 W epochs, 6048 R epochs, 5,822 N1 epochs, 17,424 N2 epochs, and 5,755 N3 epochs) for all 50 participants. In addition to the brief awakening that occurred between two sleep stages, the epochs that occurred within 30 min before the first phase of night sleep and less than 30 min after the last sleep phase were also enrolled into the 4094 W epochs. De-noising was performed to raw EEG signals using wavelets.

D. PHASE SYNCHRONIZATION ESTIMATION

As explained by Vinck *et al.* [24], WPLI is used to estimate inter-regional phase synchronization. In this study, we improved the calculation algorithm of WPLI. A combined Morlet wavelet was introduced for high-precision frequency division. By this method, the instantaneous phase of each sampling point of each channel was obtained.

Complex Morlet wavelet was defined as:

$$\delta(t) = \frac{1}{\sqrt{\pi f_b}} e^{2i\pi f_c t} e^{-\frac{x^2}{f_b}} \tag{1}$$

where f is the center frequency of the wavelet, and f_b is the bandwidth parameter. Combined Morlet wavelets were obtained by superimposing multiple Morlet wavelets with different central frequencies in the time domain. If the combined Morlet wavelet is composed of M Morlet wavelets, the central frequency of the first wavelet is f_L and of the last is f_H, by increasing Δf. Thus, the central frequency of each Morlet wavelet in the combined Morlet wavelet is

$$f_m = f_L + m \cdot \Delta f, \quad m = 0 \ldots M1 \ldots \tag{2}$$

The passband of the Morlet combination is stable and the transition band is relatively narrow. Thus, there is no need to filter the signal in advance when different frequency bands need to be analyzed.

The Morlet combination is defined as:

$$\psi_c(t) = \frac{1}{C} \sum_{m=0}^{M1} \sigma_{f_m}(t) = \frac{1}{C\sqrt{\pi f_b}} e^{-\frac{x^2}{f_b}} \sum_{m=0}^{M1} e^{2i\pi f_m t}, \tag{3}$$

where $f_b = 1$, and C is the correction coefficient that makes the amplitude-frequency characteristic passband of the combined wavelet to be 1.

We set $\Delta f = 1$. The phase of delta band (0.5-4 Hz) was calculated by the parameters $f_L = 1$ and M = 39, of theta band (4-8 Hz) by $f_L = 4$ and M = 40, alpha band (8-12 Hz) by $f_L = 8$ and M = 40, and beta band (12-32 Hz) by $f_L = 12$ and M = 200. Due to the great centralization of the Morlet wavelet in the time and frequency domains, the phase information within the fixed frequency band is more accurate.

For signal S(t) recorded from the electrode, wavelet coefficients at time τ were defined as:

$$W_S(\tau) = \int_{-\infty}^{+\infty} S(t)\, \psi_c^*(t) = A(\tau)\, e^{i\varphi(t)}. \tag{4}$$

The phase difference between a pair of nodes, i and j, was calculated using the formula

$$\Delta\varphi_{i,j,t} = \varphi_i(\tau) - \varphi_j(\tau). \tag{5}$$

Then the phase synchronization was obtained according to the formula

$$\mathrm{WPLI}_{i,j,t} = \frac{\left|E\left\{\sin\left(\Delta\varphi_{i,j,\tau}\right)\right\}\right|}{E\left\{\left|\sin\left(\Delta\varphi_{i,j,\tau}\right)\right|\right\}} \tag{6}$$

with $0 \le \mathrm{WPLI} \le 1$ and E{.} being the expected value operator. The advantage of this algorithm is that it does not rely on Fast Fourier Transform-based power spectrum, making the instantaneous synchronization calculation more reliable.

E. THE INTENSITY AND STABILITY OF WPLI

The WPLI was calculated for each 1-s sliding time-window. Therefore 10 WPLI values would be obtained for every 10-s epoch. We used the mean value of these 10 WPLIs to represent the intensity of phase synchronization, namely WPLII. The ratio between standard deviation and mean value was used to estimate the stability of this 10 s epoch, considered to be WPLIS. WPLII and WPLIS were calculated as follows:

$$\mathrm{WPLI}I_{i,j,t} = E\left\{\mathrm{WPLI}_{i,j,t-10s\ldots\ldots}\mathrm{WPLI}_{i,j,t}\right\} \tag{7}$$

$$\mathrm{WPLI}S_{i,j,t} = \frac{STD\left\{\mathrm{WPLI}_{i,j,t-10s\ldots\ldots}\mathrm{WPLI}_{i,j,t}\right\}}{E\left\{\mathrm{WPLI}_{i,j,t-10s\ldots\ldots}\mathrm{WPLI}_{i,j,t}\right\}} \tag{8}$$

A higher value of WPLII reflects the stronger connection strength. Since WPLI is a measurement of the functional flow of information between two brain regions (mapped to EEG channels in this case) [24], a low WPLIS reflects continuous and uniform information flow. Conversely, if WPLIS is high, an irregular and unstable dynamic information flow is implied [22].

F. INTERHEMISPHERIC FC ASYMMETRY AND ANTERIOR-POSTERIOR FC ANISOTROPY

Based on WPLII, interhemispheric FC asymmetry and anterior-posterior FC anisotropy were studied to describe FC inter-regional differences, using the parameters LR and AP, respectively.

LR was obtained by

$$LR = \frac{STD\left\{R_{tot}, L_{tot}\right\}}{\mathrm{E}\left\{R_{tot}, L_{tot}\right\}}, \tag{9}$$

where R_{tot}/L_{tot} is the average weight from all the connection-strengths WPLII among the nodes restricted in the right/left side of the topographic arrangement. Higher LR index values indicate higher asymmetry between left and right hemisphere FC.

TABLE 1. Anthropometric polysomnography characteristics of the overall healthy population and of males and females.

Variables	Male (n=29)		Female (n=21)		General (n=50)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	34.2	9.8	37.5	14.0	37.5	12.0
Total Sleep Time (min)	401.3	60.5	380.7	67.3	392.7	63.6
N1 Time (min)	54.8	13.1	47.5	15.3	51.8	14.4
N1 Proportion (%)	13.8	2.8	12.4	3.1	13.2	3.0
N2 Time (min)	196.8	40.4	197.8	35.5	197.2	38.0
N2 Proportion (%)	49.2	7.4	52.3	5.9	50.5	6.9
N3 Time (min)	63.4	19.2	65.4	26.8	64.3	22.5
N3 Proportion (%)	16.0	4.8	17.0	5.6	16.4	5.1
REM Time(min)	78.4	284	71.0	21.4	75.3	25.7
REM Proportion (%)	19.3	5.7	18.5	3.6	19.0	4.9
REM Cycle (n)	4.5	1.0	3.9	1.3	4.3	1.2

AP was calculated as follows:

$$AP = \frac{\mathrm{STD}\{FC_{\mathrm{tot}}, CO_{\mathrm{tot}}, FO_{\mathrm{tot}}\}}{\mathrm{E}\{FC_{\mathrm{tot}}, CO_{\mathrm{tot}}, FO_{\mathrm{tot}}\}} \tag{10}$$

where FC_{tot}, CO_{tot}, FO_{tot} indicate the average WPLII or WPLII^* within the frontal-central {F3,F4,C3,C4}, the central-occipital {C3,C4,O1,O2}, and the frontal-occipital {F3,F4,O1,O2}. Higher AP index values indicate higher anterior-posterior anisotropy.

Possible asymmetries between the left and right hemisphere and anisotropies of the anterior-posterior axis were investigated in all sleep stages and frequency bands.

G. STATISTICAL ANALYSIS

Since group commonalities in the general healthy population may be hidden in the variation trends among stages, we would like to determine the stage-dependent significant differences. The parameters defined above were normalized from 0 to 1 within individuals by equation (11), where x^* representing a normalized value and x the original value. In order to avoid false significance, data at different sleep stages were regarded as statistically dependent samples. Therefore, we randomly selected 30 epochs at each stage from every subject to form data set for statistical analysis. As the samples of WPLII^*, WPLIS^*, LR^* and AP^* values did not fit Gaussian distribution (determined by Kolmogorov-Smirnov test, $p < 0.05$), nor homogeneity of variance (determined by Levene test, $p < 0.05$), Friedman test with Dunn-Bonferroni post-hoc test were used to evaluate stage-dependent significant differences. The threshold for significance was set as $p< 0.05/C_5^2$.

$$x^* = \frac{x - x_{\min}}{x_{\max} - x_{\min}} \tag{11}$$

Samples from different sexes were considered independent. Similarly, Gaussian distribution (determined by Kolmogorov-Smirnov test), or homogeneity of variance (determined by Levene test) were not valid in the samples of WPLII, WPLIS, LR and AP values ($p < 0.05$). Therefore, we used Kruskal-Wallis test to compare sex-differences at different stages, and a Dunn-Bonferroni test were conducted for post hoc comparisons. Differences were considered significant at $p< 0.05/C_{10}^2$.

To determine the relative distribution of FC intensity within each individual, statistically significant differences between R_{tot} and L_{tot} and among FC_{tot}, CO_{tot}, and FO_{tot} were calculated for each frequency band and sleep stage. As not all samples meet Gaussian distribution (determined by Kolmogorov-Smirnov test, $p < 0.005$) and homogeneity of variance (determined by Levene test, $p < 0.05$), we also used non-parametric tests. The Wilcoxon signed rank non-parametric test was used to compare R_{tot} and L_{tot} ($p < 0.05$). Friedman test with post hoc analysis by Dunn-Bonferroni test were performed to determine significant difference among FC_{tot}, CO_{tot}, and FO_{tot} ($p< 0.05/C_3^2$).

These analyses were performed using the IBM SPSS statistics software version 22.0 (SPSS Inc.; New York, USA).

III. RESULTS

Variation trends of WPLII^*, WPLIS^*, LR^*, and AP^* across W, R, N1, N2, and N3 stages showed commonalities between males and females and among the general study population. These commonalities related to stage-dependent differences in the general population and are discussed below as an example. Nevertheless, we also found differences in the unnormalized parameters WPLII, WPLIS, LR, and AP between

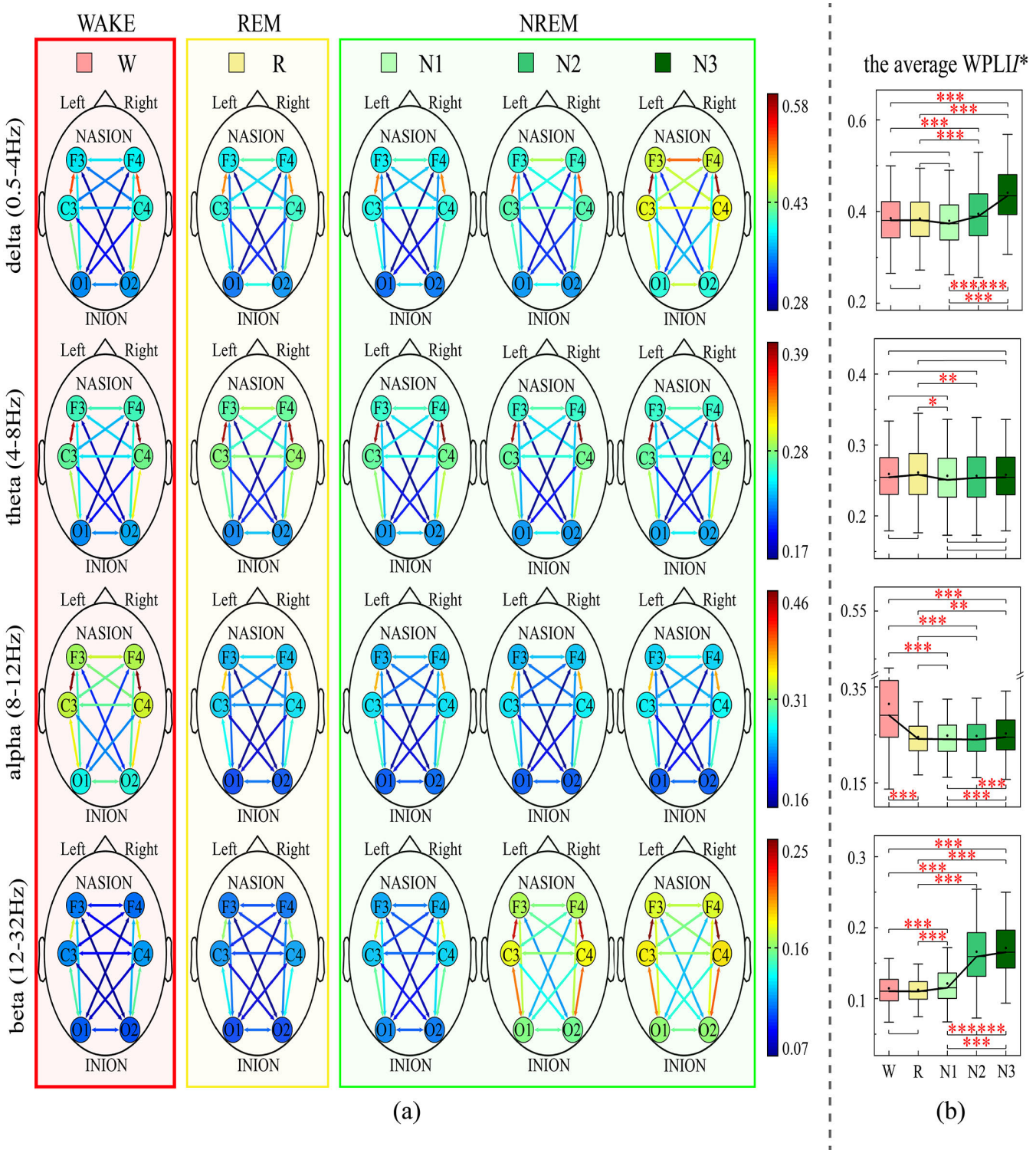

FIGURE 1. **Functional connectivity (FC) intensity during the five sleep stages and in the four frequency bands. (a) FC intensity graphs of six cortical electrodes are displayed. The small circles represent the FC intensity of electrodes [quantified by the mean weighted phase lag index I* (WPLI *I**) value between that electrode and all other electrodes]. The double-headed arrows denote electrode-pair FC intensities. The warmer color of the small circles and arrows represent stronger FC intensity. The circles and lines within one frequency band share the same color bar, which is located on the right of the FC graph of N3. (b) Significant differences in WPLII* averaged across all electrode pairs among the five sleep stages. The asterisks specify that the two distributions designated by the brackets are significantly different. *, $p < 0.05/10$; **, $p < 0.01/10$; ***, $p < 0.001/10$.**

different sexes, which are described in the following sections. Individual differences are explained in the final part of the results as a supplement to the group commonalities and sex differences.

A. SUBJECT CHARACTERISTICS

The data from 50 healthy subjects without sleep-related illnesses were analyzed. Table 1 provides summary statistics of demographic data, including age and sleep quality. There were no significant differences in ages ($p = 0.561$), total sleep time ($p = 0.297$), N1 time ($p = 0.130$), N1 proportion ($p = 0.175$), N2 time ($p = 0.945$), N2 proportion ($p = 0.105$), N3 time ($p = 0.976$), N3 proportion ($p = 0.461$), REM time ($p = 0.275$), REM proportion ($p = 0.361$), and REM cycles ($p = 0.086$) between males and females, as assessed using the Mann-Whitney U test.

B. COMMONALITIES IN THE OVERALL STUDY POPULATION

1) FC INTENSITY

Based on WPLII^* values, we obtained the overall-averaged connectome (averaged WPLII^* of the selected epochs of all subjects) within each frequency band and each stage, yielding a series of FC graphs (Fig. 1). The average WPLII^* of all FC lines indicated significant stage-dependent changes in all four bands. With the deepening of NREM sleep (N1->N2->N3), FC intensity significantly increased in delta and beta bands, whereas it was higher in N3 than in N1 and N2 in alpha band, and no significant differences could be observed in theta band among NREM stages. Furthermore, FC intensity in R stage was relatively low in delta, alpha, and beta bands and significantly lower than that in N3 sleep stage in these bands. However, FC intensity in theta band was higher in R than in N1 and N2 stages. In W stage, different frequency bands showed inconsistent FC intensity: significantly lower than in NREM sleep stages in beta band, higher than in all sleep stages in alpha band, but relatively low in delta band.

2) FC STABILITY

Stage-dependent FC stability was tested by calculating WPLIS^* (Fig. 2). We found stage-dependent differences in delta, alpha, and beta bands. In delta and alpha bands, the variation in WPLIS^* among different stages was generally opposite to that observed for WPLII^* (Fig. 1). For example, WPLII^* in N3 was higher than that in N1 and N2 stages, whereas WPLI$^S*$ in N3 was lower than that in N1 and N2 stages in delta frequency band. WPLIS* values in W stage was high in delta band and low in alpha band, whereas the opposite was observed for WPLII^* values. However, in beta band, the variation in WPLIS^* was similar to that in WPLII^* (Fig. 1). For example, both WPLIS^* and WPLII^* in W and R stages were significantly lower than those in N2 and N3 stages, and both WPLIS^* and WPLII^* in N1 were significantly higher than in R stage. WPLII^* and WPLIS^* were different during NREM sleep in beta band: WPLII^* increased significantly with the deepening of NREM sleep, while WPLIS^* reached the highest level in N2; no significant difference was seen between N1 and N3.

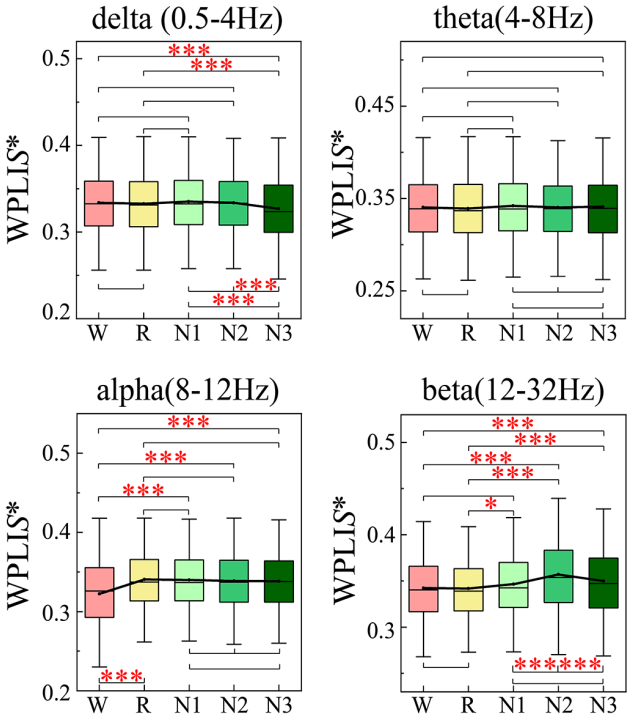

FIGURE 2. Differences in stability of weighted phase lag index (WPLI S^*) among different stages. *, $p < 0.05/10$; **, $p < 0.01/10$; *** $p < 0.001/10$.

3) INTER-REGIONAL DIFFERENCES OF FC INTENSITY

Differences in the degree of interhemispheric FC asymmetry are presented in Fig. 3a; stage-dependent differences were found only in beta band. In beta band, LR^* values were significantly higher in W and R than in N2 and N3 sleep stages, indicating higher interhemispheric FC asymmetry.

Furthermore, differences in AP^* among stages were also studied to illustrate changes in anterior-posterior FC anisotropy (Fig. 3b); significant differences were found in all four bands. In deep sleep stage (N3), AP^* was higher than N1 and N2 stages in alpha band. AP^* in R was significant higher than in NREM stages in beta band, higher than N1 and N3 in theta band, and higher than N1 in alpha band. In delta band, no significant differences were observed between R and N1 or N2. In W stage, AP^* was significantly lower than in other sleep stages in delta and theta bands and was lower than in R stage in beta band. The variations in anterior-posterior FC anisotropy across W, R, N1, N2, and N3 stages were more obvious than those in interhemispheric FC asymmetry (Fig. 3a, Fig. 3b).

C. SEX DIFFERENCES

1) FC INTENSITY

We further explored sex differences in FC intensity, and detected significant differences in WPLII between males and females (Fig. 4). As shown in Fig. 4b, significantly higher average cortical FC intensities were found in females than in males, except in alpha and beta bands in W. Moreover, at all frequencies and sleep stages, most node-pairs showed

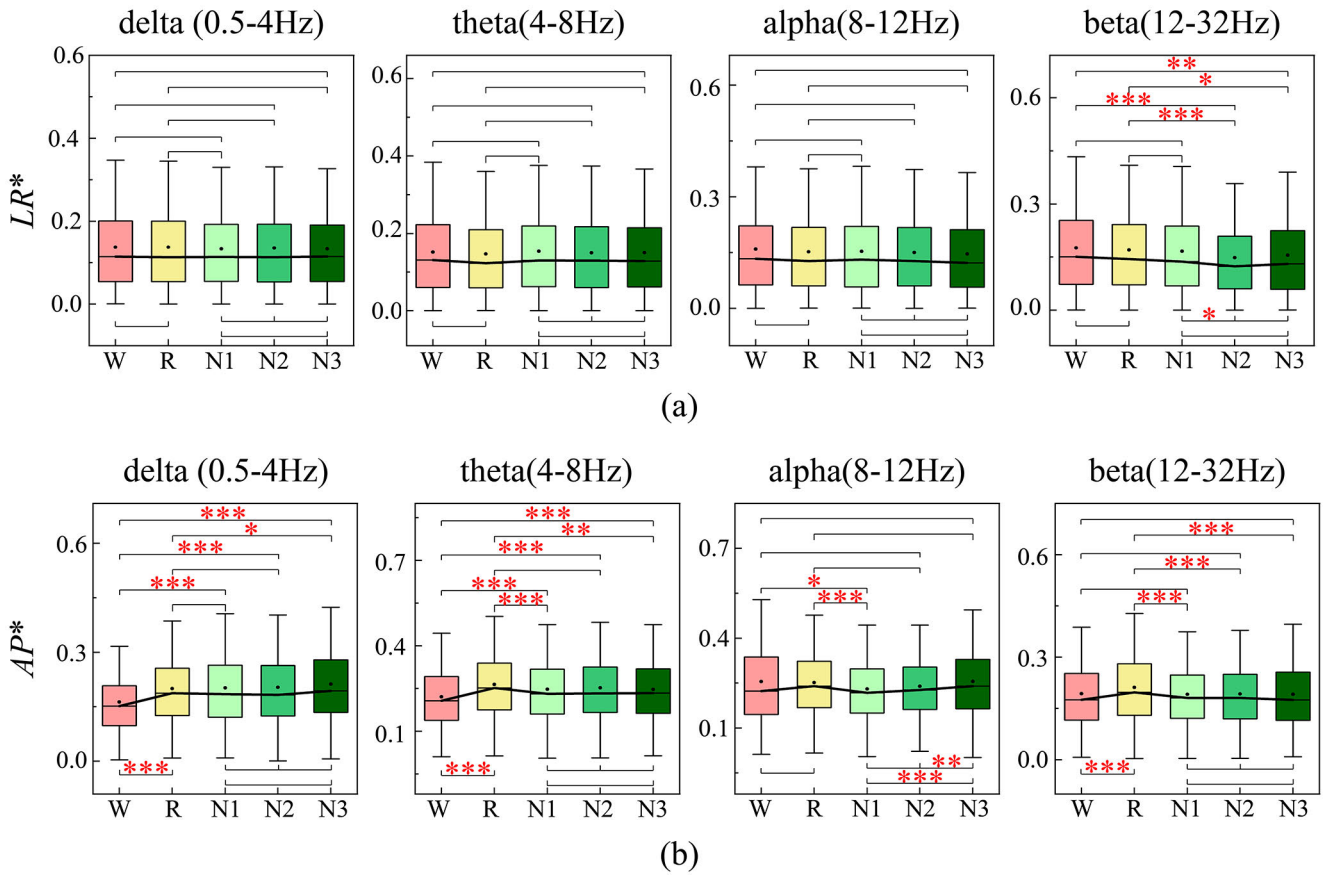

FIGURE 3. (a) Significant differences in *LR** among different stages. (b) Significant differences in *AP** among different stages. *, $p < 0.05/10$; **, $p < 0.01/10$; *** $p < 0.001/10$.

greater FC in females. However, it was worth noting that in theta frequency band, FCs between F3 and F4, F3 and C3, and between F4 and C3 were either not different between sexes or higher in males in different stages. The same was true for FCs between F3 and C3 and between C3 and O1 during REM and WAKE.

2) FC STABILITY

To explore sex differences in FC stability, we measured WPLI*S* (Fig. 5). We found that WPLI*S** in N2 and N3 of delta and alpha bands was significantly higher in males than females, whereas in W of alpha band and N2 of beta band, it was significantly higher in females than in males. Moreover, there was no significant difference in the WPLI*S* values of all node-pairs between males and females in any frequency band during R stage.

3) INTER-REGIONAL DIFFERENCES OF FC INTENSITY

Apart from N3 in alpha band and R in beta band, in all other cases, the proportion of male subjects who showed significantly higher FC intensity in the left hemisphere was higher than that of female subjects (Fig. 6). Moreover, the proportion of female subjects with a significantly higher synchronization in the right hemisphere was higher than that of male subjects.

AP was calculated to evaluate sex differences in anterior-posterior FC anisotropy (Fig. 7). In N2 and N3 stages, we found different results for different frequency bands: for relatively low frequency bands (delta and theta), males presented more obvious anisotropy (higher *AP* values), with no significant difference seen in alpha band. In contrast, for the high frequency band (beta), females presented higher *AP* values. Nevertheless, in N1 and W stages, we found similar results for different frequency bands, with males presented more obvious anisotropy than females, except that there were no significant differences in W of delta band and N1 of beta band. In R stage, no significant difference was observed except a higher value in delta band for males than females.

Sex differences in *LR*, which was used to evaluate the asymmetry in inter-hemispheric FC, are shown in Fig. 7. *LR* was significantly different between sexes only in relatively high frequencies (alpha and beta bands). Significant differences were observed in alpha and beta bands in W. Additional, the results were consistent, with males having higher *LR* value than females.

D. INDIVIDUAL DIFFERENCES

When comparing R_{tot} and L_{tot} in the same individual, we found that if a subject showed significantly higher R_{tot} in

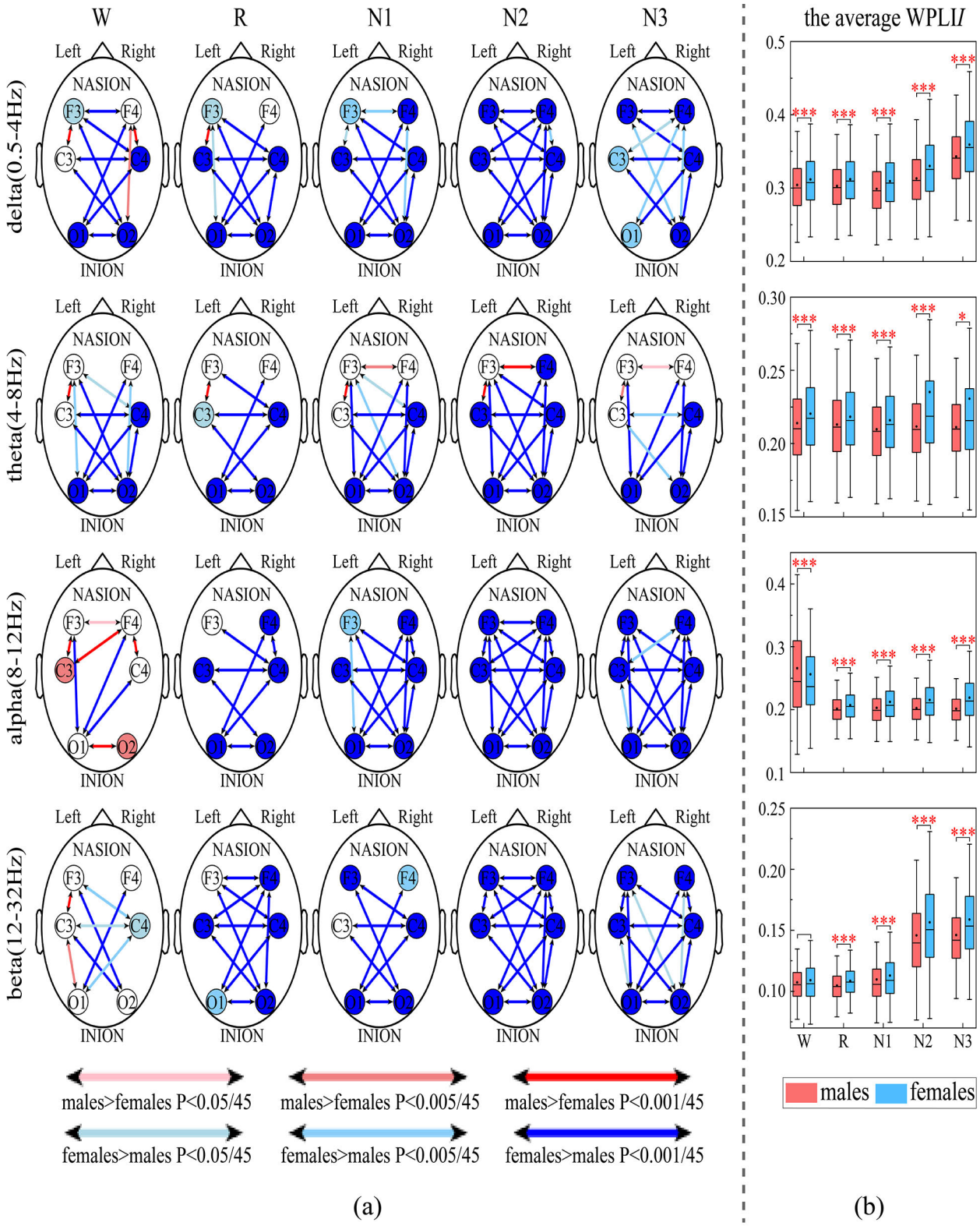

FIGURE 4. (a) Sex differences in FC intensity graphs. The double-headed arrows denote sex differences in node-pair synchronization intensity. The small circles represent the differences of weighted degree of each electrode. Red indicates that males have significantly higher FC intensity than women, and blue indicates the opposite. The darker the color, the smaller the p value is. (b) Sex differences in the averaged FC intensity. *, $p < 0.05/45$; **, $p < 0.01/45$; *** $p < 0.001/45$.

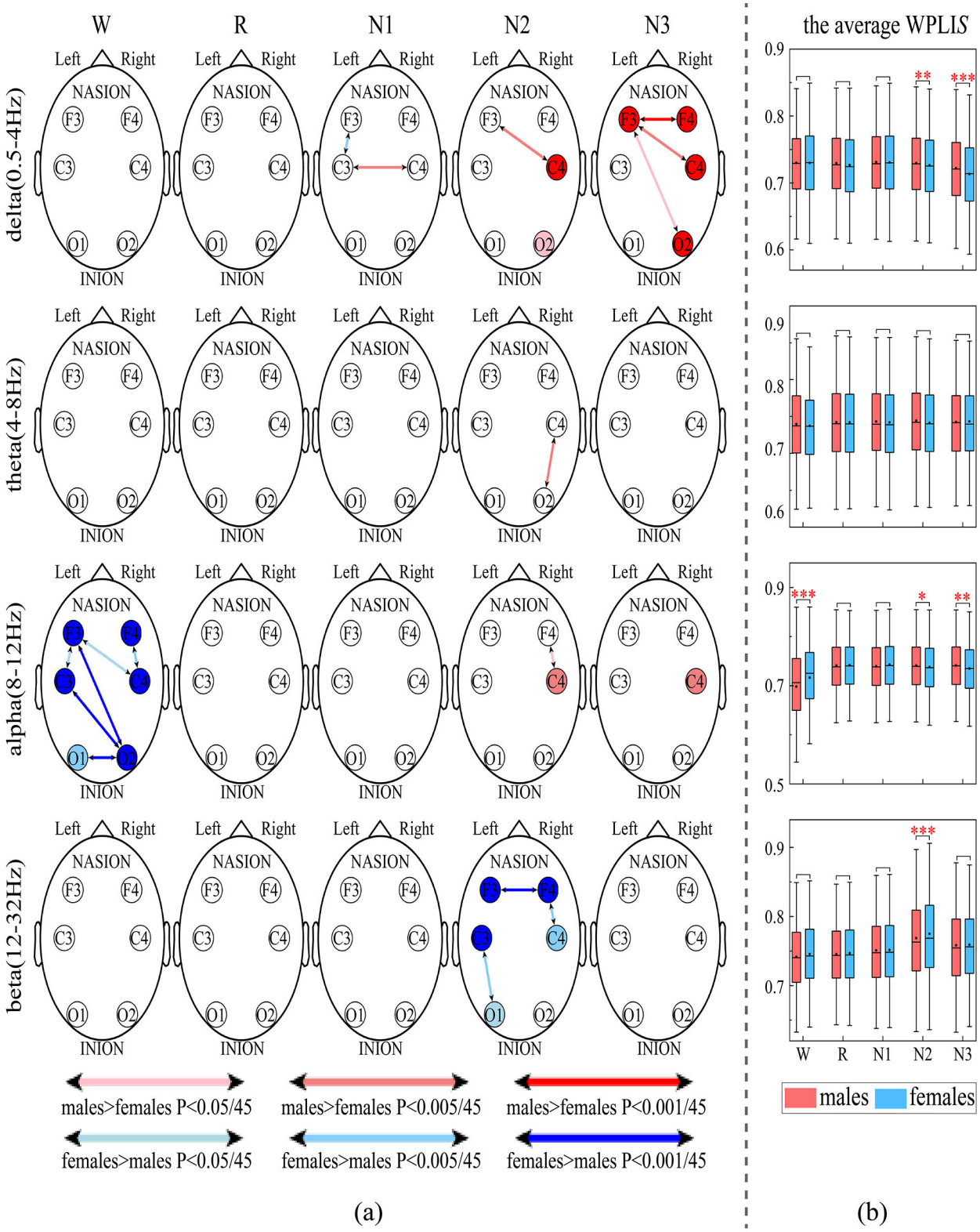

FIGURE 5. Sex differences in functional connectivity (FC) stability during the five sleep stages and in the four frequency bands. (a) Sex differences of FC stability graphs. The double-headed arrows denote sex differences in node-pair synchronization stability. The small circles represent the differences in weighted degree of each electrode. Red indicates that males have significantly higher FC stability than women, and blue indicates the opposite. The darker the color, the smaller the p value is. (b) Sex differences in the averaged FC stability. *, $p < 0.05/45$; **, $p < 0.01/45$; *** $p < 0.001/45$.

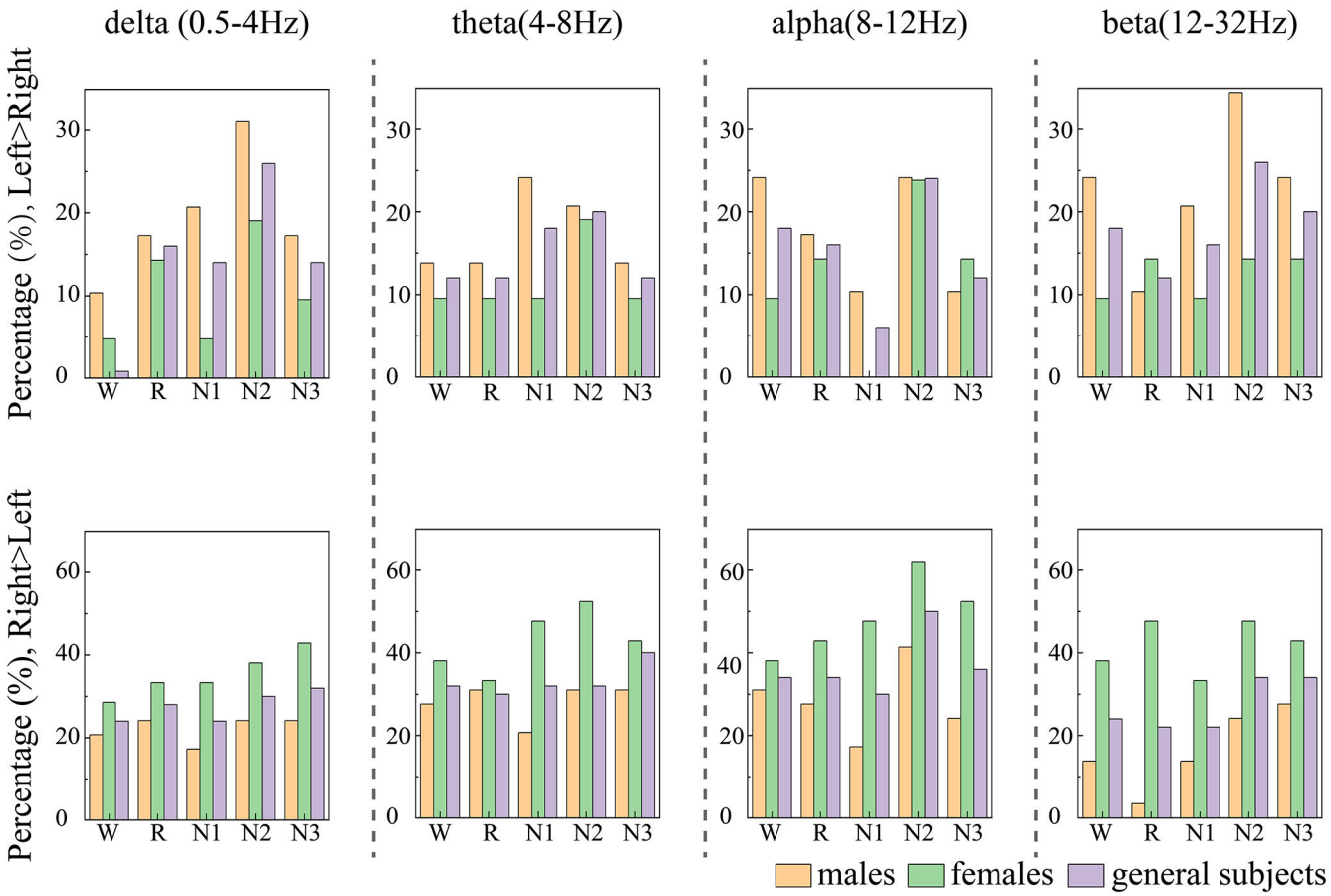

FIGURE 6. The proportion of subjects in the three groups (males, females, and overall population) showing significantly higher left or right hemisphere synchronization in each frequency band and sleep stage.

TABLE 2. Statistical analysis of the number of subjects with differences between R_{tot} and L_{tot} in different frequency bands. Second/third row: L_{tot}/R_{tot} was significantly higher than R_{tot}/L_{tot} in at least one sleep stage. No significant differences was observed in other sleep stages. Fourth row: L_{tot} was significantly higher than R_{tot} in at least one sleep stage but lower in some other sleep stages. Fifth row: No significant differences between L_{tot} and R_{tot} in all four sleep stages.

The differences between R_{tot} and L_{tot}	delta	theta	alpha	beta
L_{tot}>R_{tot}	13	13	14	21
R_{tot}>L_{tot}	24	28	28	23
discordance	2	0	0	0
R_{tot}~L_{tot}	11	9	8	6

a certain frequency band and in a certain sleep stage, the same (i.e., higher R_{tot}) was true in other bands or stages in this subject. The opposite was also true: if L_{tot} was higher than R_{tot} in a certain frequency band and in a certain sleep stage, then R_{tot} would be higher in other bands or stages in the same subject. This suggests that the frequency bands or sleep stages may not determine higher R_{tot} or L_{tot}. Table 2 shows the consistency of the intra-individual dominant FC hemisphere in different sleep stages. Among the 50 subjects, 13 presented significantly higher left hemispheric synchronous intensity in delta band, 13 in theta band, 14 in alpha band and 32 in beta band albeit in only some sleep stages, while no significant interhemispheric differences were observed in other stages. Moreover, 24 of the 50 subjects presented significantly higher right hemispheric synchrony in delta band, 28 in theta band, 28 in alpha band and 23 in beta band in some stages with no significant interhemispheric differences in other stages. Moreover, only in delta band, two subjects showed significantly higher right than left hemispheric synchrony in some sleep stages, but opposite in some others. No subject showed such inconsistency in theta, alpha, or beta frequency bands. It should be noted that the sleep stages did not include W stage. Furthermore, in the case of significant differences between R_{tot} and L_{tot} in at least half of the 16 combinations (4 sleep stages $\times$ 4 frequency bands), 6% of the subjects held higher R_{tot} in some cases and higher L_{tot} in other cases (Fig. 8a), further suggesting that inter-hemispheric differences of FC may not reverse due to the frequency band or sleep stage.

The different proportions of subjects who showed different anterior-posterior FC anisotropies were also calculated (Fig. 8b). For most of the subjects, $FC_{tot} > CO_{tot} > FO_{tot}$ in any frequency band and stage. In more than 80% of the subjects, all or two of the following three conditions were satisfied: FC_{tot} was significantly higher than CO_{tot}, FC_{tot} was

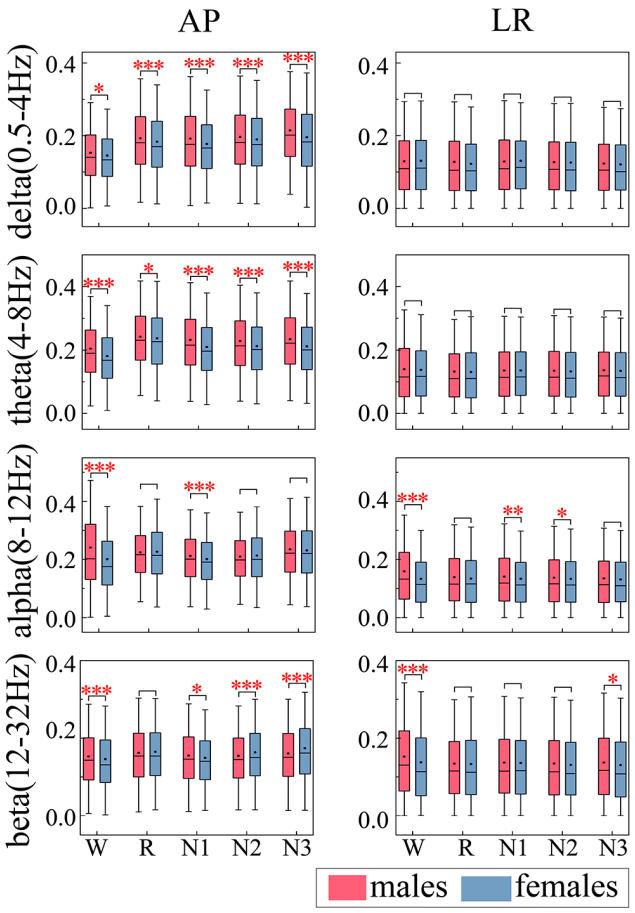

FIGURE 7. Sex differences in anterior-posterior functional connectivity (FC) anisotropy (AP) and interhemispheric FC asymmetry (LR) in each frequency band and sleep stage. *, $p < 0.05/45$; **, $p < 0.01/45$; *** $p < 0.001/45$.

significantly higher than FO_{tot}, and CO_{tot} was significantly higher than FO_{tot}.

IV. DISCUSSION

The purpose of this study was to give a detailed description of overall population commonalities, sex-dependent differences, and individual differences related to sleep EEG FC. In the overall population, the variation in EEG FC parameters in the different sleep stages was similar among subjects. Regarding sex, EEG FC parameters showed significant stage- and frequency band-dependent sex differences. Hemispheric FC dominance did not show obvious overall population commonalities.

A. COMMONALITIES IN THE OVERALL STUDY POPULATION

The variation in EEG FC parameters during different sleep stages was similar among subjects. Although our study was based on different synchronous estimation methods, we observed increased delta synchronization with the deepening of NREM sleep, similar to previous studies [8], [10]. Increased EEG synchronization means increased order in neural networks [37]. The process of falling asleep is accompanied by a loss of conscious awareness [38]. This is consistent with the hypothesis that increased neural network order may lead to unconsciousness [39], [40]. This also explains the low delta FC strength during REM, as REM is still active [41].

The increased FC intensity with NREM deepening was not only confined to the delta frequency range but was also observed for beta band. Beta activity is increased by non-benzodiazepine modulators of receptors for $GABA_A$ [42], the main inhibitory neurotransmitter in the CNS, and it is well established that activation of $GABA_A$ receptors favors sleep [43]. Increased beta FC intensity suggests activation of $GABA_A$ receptors and the cortical inhibition of the CNS system, which is consistent with N3 sleep characteristics. Unlike our results in delta band, FC stability in beta band was higher in W and REM, and lower in NREM sleep stages. This means that the activation of this neural pathway is not stable in NREM stages, which provides the anatomical feasibility for some hypnotics [42] to induce N3 stage.

Furthermore, our study also found that, in beta band, the FC strength hemispheric lateralization was higher in REM than in N2 and N3 sleep stages. The asymmetry of cortical EEG FC strength has an anatomical basis [44] and is influenced by the brain state [45], [46]. Hemispheric FC strength lateralization is closely related to the exchange of information flow between hemispheres [45], [46]. The high hemispheric lateralization in REM stage in beta band reflects that the information flow between left and right hemisphere in REM stage is higher in REM than in NREM sleep stages [47].

Anterior-posterior FC anisotropy during REM was high in theta and beta bands but significantly lower during WAKE than during sleep in delta and theta bands. These results suggest that the transformation of sleep and WAKE is characterized by a coordinated FC of cortical rhythms possibly generated by a frontal-central-occipital network. As $FC_{\text{tot}} > CO_{\text{tot}} > FO_{\text{tot}}$ in all stages and frequency bands, the higher anterior-posterior FC anisotropy may indicate an increased frontal-central synchronization predominance during REM.

B. SEX DIFFERENCES

Several methods have been reported for detecting sex differences using sleep EEG signals, with most utilizing the calculation of energy [32], [33] or entropy [48]. Few studies have focused on sleep EEG FC. Nevertheless, our results showed a clear sex effects in FC.

We found that average FC strengths were higher in females in all sleep stages and frequency bands. Research using magnetic resonance imaging (MRI) has also demonstrated that women tend to have higher FC [49]. Additionally, higher spindle density and intensity [33], and higher slow wave energy [32] are also found in women. Some correlation may exist among these results. Another finding of this study was the sex differences in FC stability. Our results indicated that females exhibit higher FC stability than males in low frequency bands in some NREM stages. Previous statistics

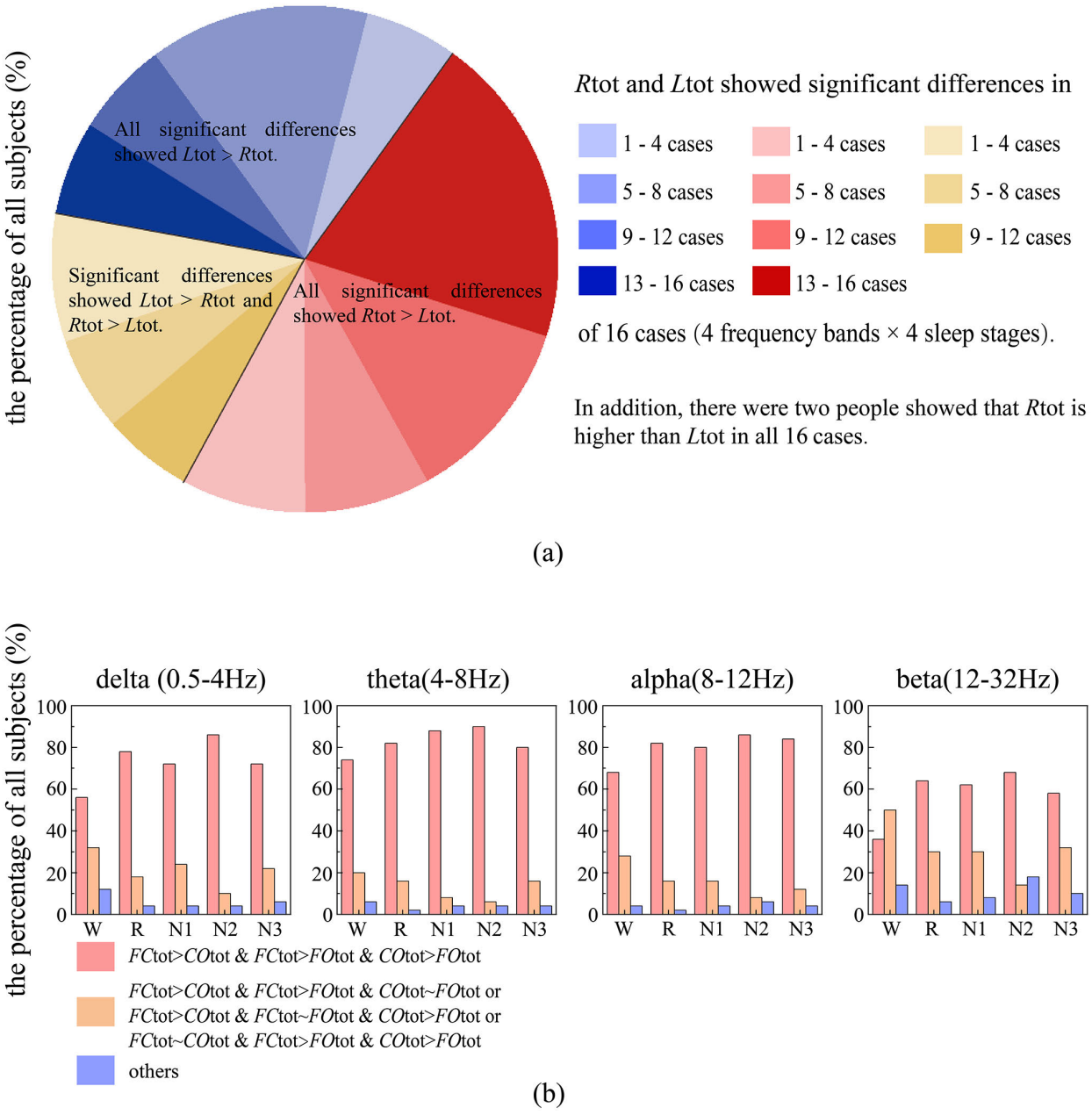

FIGURE 8. (a) The proportion of subjects with higher Rtot or Ltot in all sleep stages and frequency bands, or with higher Rtot in some stages and frequency bands and higher Ltot in other stages and frequency bands, in which there were significant differences between Rtot and Ltot. (b) The proportion of all subjects with different anterior-posterior functional connectivity (FC) anisotropies in different sleep stages and frequency bands. "A > B" means A is significantly higher than B. "A ~ B " means there was no significant difference between A and B.

have shown that sleep quality was different between men and women [50], and that women had more slow-wave content than men during NREM sleep [51]. There may also be some relations among these findings.

For both males and females, we found that $FC_{\text{tot}} > CO_{\text{tot}} > FO_{\text{tot}}$. During WAKE and light sleep (N1 stage), males showed stronger frontal-central synchronization predominance in all four frequency bands. However, during N2 and N3 stages, males showed stronger frontal-central synchronization predominance in delta and theta bands, but weaker in beta band, while there were no sex differences in alpha band. As N1 sleep stage represents the transition between wakefulness and sleep, it is considered 'unstable sleep' [52]. When subjects were awakened from N1 stage, they often report dream-like experiences or claim they were awake [53]. For this reason, we can hypothesize that N2 and N3 can better indicate the EEG differences between different populations in NREM sleep. According to the modern view of cortical oscillations, the alpha frequency range is very uneven, with slow alpha (~8-10 Hz) and a lower band (0.5-7 Hz) mainly located below the cortex and upper alpha (~11-12 Hz) mainly located in the cortex [54]. Beta bands

are more uniform and are considered completely cortical [55]. Beta is usually associated with cortical activation. Thus, this phenomenon might suggest that the subcortical predominance of frontal-central synchronization is evident in men, but the cortical one is more evident in women.

C. INDIVIDUAL DIFFERENCES

Interhemispheric EEG FC in sleep has been analyzed in some studies. However, the results of these studies were divergent or contradictory. Dimitriadis *et al.* [56] reported that REM sleep is associated with higher FC in the right hemisphere whereas NREM involved higher FC in the left hemisphere. In contract, Kamiński *et al.* [8] suggested that the right hemisphere is more coherent. In our study, hemispheric asymmetry was not significantly dependent on sleep stage or frequency band. And the dominant hemisphere of FC did not show group generality. These discrepancies in the results may be due to the calculation or statistical methods used.

V. LIMITATION

In addition to the differences between females and males, a larger sample size is needed to extend this study to different age groups. Due to the lack of imaging data such as MRI, it is difficult to explain individual differences anatomically. We will work on these questions in future experiments. One aspect that requires further examination is the presence of sex or individual differences in FC changes in NREM-REM sleep cycle progression. In addition, our study followed the frequency division of traditional sleep research, and did not involve the high frequency band. However, recent studies have a tendency to shift to the high frequency band. The gamma frequency band will be considered in our further research.

VI. CONCLUSION

In summary, our findings added to the understanding of general sleep characteristics, as well as sex differences in these characteristics. Connectivity measures in sleep are dependent on the sleep stage and sex; therefore, connectivity-based biomarkers must be carefully tailored accordingly, and treatments that induce sleep must also be carefully adjusted based on specific FC characteristics. Except FC strength, we introduced FC short-term stability for studying sleep performance. This parameter provides new insights into the understanding of sleep, and may provide clues to sex differences in regard to the prevalence and clinical manifestations of mental illness. We expect that our study will provide the basis for a more complete understanding of sleep FC.

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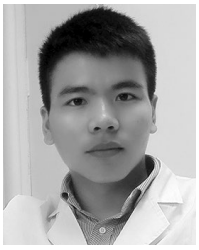

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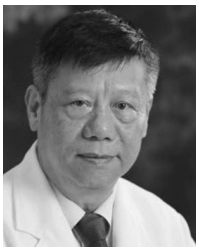

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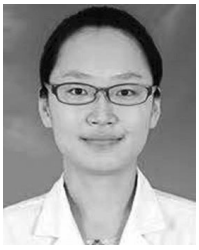

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