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Network controllability analysis of awake and asleep conditions in the brain

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The difference between sleep and wakefulness is critical for human health. Sleep takes up one third of our lives and remains one of the most mysterious conditions; it plays an important role in memory consolidation and health restoration. Distinct neural behaviors take place under awake and asleep conditions, according to neuroimaging studies. While disordered transitions between wakefulness and sleep accompany brain disease, further investigation of their specific characteristics is required. In this study, the difference is objectively quantified by means of network controllability. We propose a new pipeline using a public intracranial stereo-electroencephalography (stereo-EEG) dataset to unravel differences in the two conditions in terms of system neuroscience. Because intracranial stereo-EEG records neural oscillations covering large-scale cerebral areas, it offers the highest temporal resolution for recording neural behaviors. After EEG preprocessing, the EEG signals are band-passed into sub-slow (0.1–1 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz) band oscillations. Then, dynamic functional connectivity is extracted from time-windowed EEG neural oscillations through phase-locking value (PLV) and non-overlapping sliding time windows. Next, average and modal network controllability are implemented on these time-varying brain networks. Based on this preliminary study, it appears that significant differences exist in the dorsolateral frontal-parietal network (FPN), salience network (SN), and default-mode network (DMN). The combination of network controllability and dynamic functional networks offers new insight for characterizing distinctions between awake and asleep stages in the brain. In other words, network controllability captures the underlying brain dynamics under both awake and asleep conditions.

Sleep and wakefulness act as a double onion-like framework in the brain (Ioannides, 2018). Entanglement of sleep and wakefulness is accompanied with neural pathology (Ioannides, 2018; Sarasso et al., 2020; Andrillon et al., 2021). For example, one main cause of attentional lapses is the appearance of sleep-like slow waves in the awake state (Andrillon et al., 2021). In focal brain injury, neural activity is disturbed by local sleep-liked behavior while awake (Sarasso et al., 2020). Sleep problems can cause aberrant neural behaviors to appear in the DMN, central executive network (CEN), and SN in many psychiatric disorders (Ioannides, 2018). Attention deficiency is closely linked to occurrences of sleep-like activity under awake condition (Andrillon et al., 2021). In obstructive sleep apnea, aberrant neural activity appears during wakefulness, and its severity is related to the status of the insula and prefrontal cortex (Wu et al., 2020).

Multiple brain areas are involved in sleep and wakefulness, and it is necessary to look at the brain from the perspective of system neuroscience. Network representation depicts paramount interactions among neuron populations in the brain (Liao et al., 2018; Xue et al., 2018). Graph theory is generally adopted as an important theoretical architecture because of its capability to estimate, model, and simulate the brain network.

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Structural connectivity represents the white matter wiring derived from diffusion tensor imaging, while functional connectivity emphasizes the synchronous reaction of separate brain areas in general. The latter also reflects the information flow of neural oscillations, and will be our focus in this paper.

Network control detects the navigation of global dynamics through local perturbation along certain trajectories, and has attracted much attention in the area of brain network investigation (Gu et al., 2015). Empirical evidence has shown the relationships between network controllability and working memory (Beynel et al., 2020), language perception (Medaglia et al., 2021), cognitive control function (Gu et al., 2015), creativity and intelligence (Kenett et al., 2018), executive function (Cornblath et al., 2019), psychosis symptoms (Parkes et al., 2021), and schizophrenia (Tang et al., 2022). While network control theory offers great help for exploiting working mechanisms, it mainly focuses on structural connectivity in the brain. More attention should be paid to the role of network controllability in functional interactions.

The proposed pipeline is illustrated in Fig. 1. We derived time-varying functional connectivity to evaluate network controllability, and the involved cerebral areas were the SN, FPN, and DMN. Particularly, SN is comprised of the anterior insula (AI) and anterior cingulate cortex (ACC), FPN contains the middle frontal gyrus (MFG) and supramarginal gyrus (SMG), and DMN is constituted with the posterior cingulate cortex (PCC) and precuneus in this work. Neural oscillations offer subjective monitoring of the brain (Doelling et al., 2021). All EEG signals were band-passed into six separate sub-bands; we paid special attention to sub-slow (0.1–1 Hz) band oscillations, as they play critical roles in non-rapid eye movement stage 3 (N3) sleep. When phase-locking value and time windows were combined, we regarded the strength of instantaneous phase-locking as representing the adjacency elements in the brain networks. Both average controllability

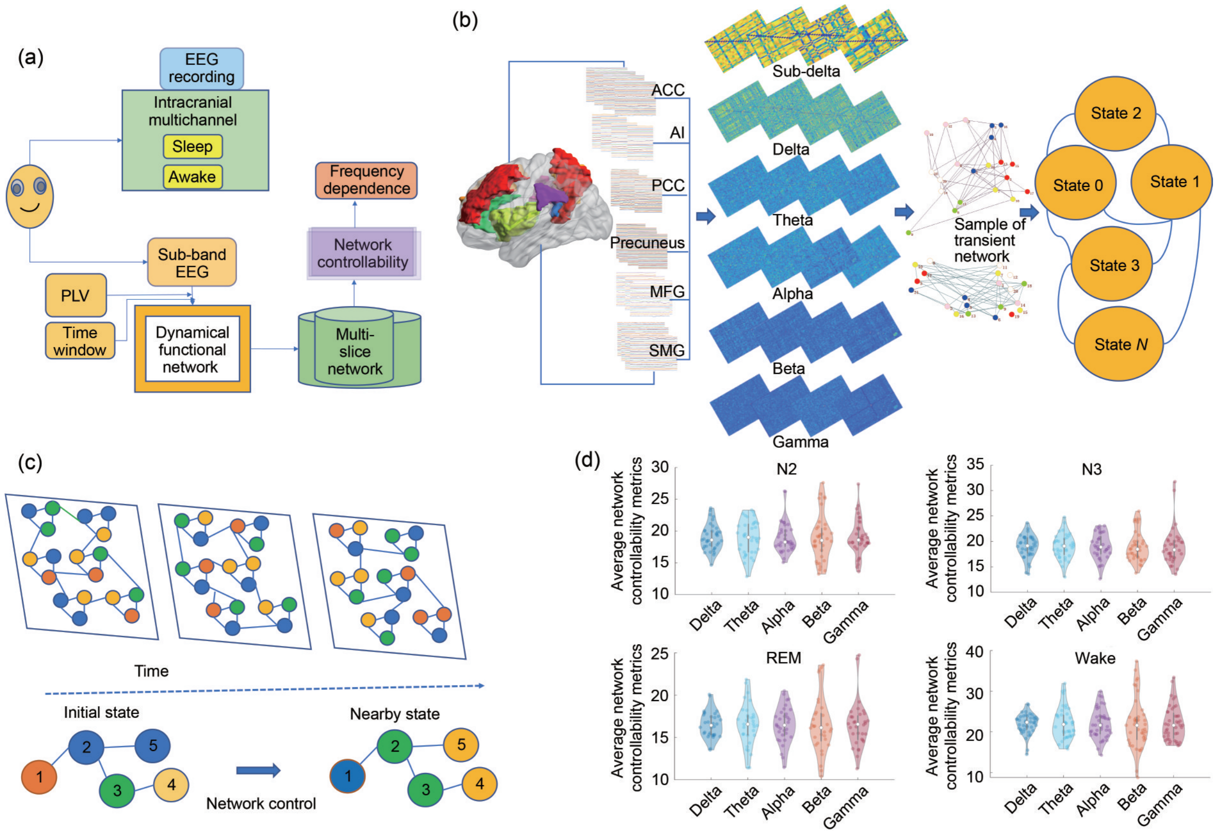

Fig. 1 Framework illustration of the proposed pipeline. (a) The involved techniques; (b) Large spatial time-varying network states under awake and asleep conditions; (c) Schematic diagram of network control; (d) Violin plot of average network controllability metrics in the precuneus under awake and asleep conditions. EEG: electroencephalography; PLV: phase-locking value; REM: rapid eye movement; N2: non-rapid eye movement stage 2; N3: non-rapid eye movement stage 3; ACC: anterior cingulate cortex; AI: anterior insula; PCC: posterior cingulate cortex; MFG: middle frontal gyrus; SMG: supramarginal gyrus.

and modal controllability metrics were adopted to track and quantify brain dynamics under the corresponding four conditions as follows: rapid eye movement (REM), non-rapid eye movement stage 2 (N2), N3, and awake. The detailed methods are provided in the electronic supplementary materials for this paper.

As demonstrated in Table S1, significant differences existed among all six frequency components in the targeted areas, based on modal controllability metrics (P<0.001). The PCC and precuneus demonstrated the frequency-dependent variations covering all four different conditions. Significant differences appeared in the AI under asleep condition but not awake condition.

Since average controllability and modal controllability in turn depict easy and hard-to-attain states, respectively, in the frame of network control theory, we calculated the correlation between them. We carried out an analysis of variance (ANOVA) test to explore distinctions between them. As described in Table S2, there were significant differences among networks that were derived from six sub-band frequency components, when considering modal and average controllability metrics. Specifically, ACC, AI, MFG, and PCC all showed significant differences, especially under awake condition.

In view of the brain state of certain areas that can be defined as the power of amplitude in recorded EEG signals, we calculated the power in all six sub-band EEG signals, and compared their ratios with each other. We found that there was a tiny sub-slow band EEG signal owing a ratio one ten-thousandth of that was derived from beta- or gamma-band EEG oscillation. Therefore, we removed sub-band EEG signals, and implemented average controllability on the networks derived from the remaining five sub-band EEG signals. Significant differences appeared in almost all six brain areas under all four conditions, as presented in Table S3. Exceptions were: MFG under N2 or REM conditions, SMG under REM, and AI under awake condition, where no significance appeared. Specifically, non-significant difference appeared in the MFG under N2 (P=0.0821) or REM (P=0.3076) condition, while the SMG (P=0.0211) or precuneus (P=0.0022) showed no significant differences under REM condition.

Ultimately, we took three spatial levels of network connectivity into consideration for network controllability evaluation. It is found out that average network controllability is not only frequency-dependent but also spatially dependent. At the first level, individual brain areas were considered, including the AI, ACC, MFG, SMG, PCC, and precuneus. Then, at the second level, network controllability was estimated for the SN, FPN, and DMN, which are constituted by the AI and ACC, MFG and SMG, and PCC and precuneus, respectively. Finally, at the third level, the SN, FPN, and DMN made up the largest spatial SN-FPN-DMN network. Average controllability was implemented on the corresponding networks. Based on the preliminary results, we determined that extensive frequency-dependent network controllability existed in most enrolled individual brain areas. At the medial spatial network level, significant differences only existed in the SN network under REM, N3, and awake condition, while no significant difference appeared in the large SN-FPN-DMN network.

To sum up, all six cerebral areas had certain frequency-dependent differences in network controllability under awake condition at the small spatial network level, whereas no such significant frequency-dependent differences emerged in the large spatial SN-FPN-DMN network.

Normally, the brain is optimized to easily transition from sleep to wakefulness or vice versa. Awake and asleep states are apparently different from each other, and entanglement between them signifies brain disorder to some extent. However, quantified biomarkers to distinguish between the states are lacking. Klimesch (2018) proposed the frequency framework of neural oscillations in the brain. According to our preliminary results, the existence of frequency-dependent network controllability provides one available biomarker, and reveals the foundation for seemingly effortless wake-to-sleep manipulation. As previously illustrated, a densely connected DMN controls easy tasks, while a weakly linked cognitive control network is responsible for difficult control issues. As nonstationary neural oscillations interact with each other across the large-scale cerebral cortex, trajectory controlling refers to driving the system from one condition to another desired condition, such as moving to the nearby states or distant states. The way in which they are integrated and segregated exhibits controlling trajectories under diverse cognitive conditions. With the assistance of network control theory, our results demonstrate the distinctions among frequency components, signifying their diverse roles in network adaption and manipulation.

In general, modal controllability and average controllability are believed to act differently, as the former handles difficult tasks and the latter easy ones. The former requires integration and cooperation among more brain areas, while the latter brings neighboring areas together in order to achieve the goal. Certain brain areas prefer solving difficult problems, while others favor easy ones. Cheng et al. (2018) reported that the PCC is critical in sleep and depressive problems. In modal controllability, when all six sub-band EEG signals are considered, the PCC exhibits significant differences under all four conditions, including asleep and awake states. Meanwhile, the precuneus shows significant differences from the N3 condition, while one distinction of N3 sleep is its dominance in slow-wave EEG oscillation. Kinreich et al. (2014) suggested that the AI plays important roles in the transition between wakefulness and sleep; it reflected significant differences among the three conditions other than the awake condition in this study. When modal controllability and average controllability are combined, the ACC, MFG, PCC, and precuneus show significant differences among brain networks; these differences are most apparent under awake condition. Besides, five sub-band EEG signals are enrolled while the sub-slow (0.1–1 Hz) band is removed due to its low amplitude. Average controllability shows significant differences in almost all six brain areas under the four distinct brain conditions.

In this work, we employed intracranial stereo-EEG recordings and network controllability to investigate the roles that frequency components play in the brain. The difference between awake and asleep conditions is revealed in terms of network controllability. Frequency-dependent network controllability provides new insights into understanding the working mechanisms of the brain. Because stereo-EEG can detect temporal variations of neuron populations in large-scale brain areas, it offers a gold standard for evaluating neural activity. In detail, individual cortical regions demonstrate frequency-dependent network controllability to a greater extent than inter-regional interactions. Our findings demonstrate that network control theory offers a distinct systematic way of understanding frequency components in the brain. In consequence, system science should be considered as a future means of uncovering the network dynamics of frequency components in neural oscillation, which could lay a theoretical foundation for electrical neuromodulation in clinics. However, due to the limited number of participants involved in this study, more participants should be recruited to unravel the network control mystery of the brain in future work. Further investigation is necessary to uncover the individual systematic role that frequency components play in different brain regions for certain complex cognitive tasks.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

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Author contributions

Yan HE performed the data analysis and manuscript writing. Zhiqiang YAN performed the statistical analysis. Wenjia ZHANG contributed to the editing of the manuscript. Jie DONG contributed to the data analysis. Hao YAN contributed to the study design. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Yan HE, Zhiqiang YAN, Wenjia ZHANG, Jie DONG, and Hao YAN declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

References

Andrillon T, Burns A, Mackay T, et al., 2021. Predicting lapses of attention with sleep-like slow waves. *Nat Commun*, 12: 3657.
https://doi.org/10.1038/s41467-021-23890-7

Beynel L, Deng LF, Crowell CA, et al., 2020. Structural controllability predicts functional patterns and brain stimulation benefits associated with working memory. *J Neurosci*, 40(35):6770-6778.
https://doi.org/10.1523/JNEUROSCI.0531-20.2020

Cheng W, Rolls ET, Ruan HT, et al., 2018. Functional connectivities in the brain that mediate the association between

depressive problems and sleep quality. *JAMA Psychiatry*, 75(10):1052-1061.
https://doi.org/10.1001/jamapsychiatry.2018.1941

Cornblath EJ, Tang E, Baum GL, et al., 2019. Sex differences in network controllability as a predictor of executive function in youth. *NeuroImage*, 188:122-134.
https://doi.org/10.1016/j.neuroimage.2018.11.048

Doelling KB, Assaneo MF, 2021. Neural oscillations are a start toward understanding brain activity rather than the end. *PLoS Biol*, 19(5):e3001234.
https://doi.org/10.1371/journal.pbio.3001234

Gu S, Pasqualetti F, Cieslak M, et al., 2015. Controllability of structural brain networks. *Nat Commun*, 6:8414.
https://doi.org/10.1038/ncomms9414

Ioannides AA, 2018. Neurofeedback and the neural representation of self: lessons from awake state and sleep. *Front Hum Neurosci*, 12:142.
https://doi.org/10.3389/fnhum.2018.00142

Kenett YN, Medaglia JD, Beaty RE, et al., 2018. Driving the brain towards creativity and intelligence: a network control theory analysis. *Neuropsychologia*, 118(Pt A):79-90.
https://doi.org/10.1016/j.neuropsychologia.2018.01.001

Kinreich S, Podlipsky I, Jamshy S, et al., 2014. Neural dynamics necessary and sufficient for transition into pre-sleep induced by EEG NeuroFeedback. *NeuroImage*, 97:19-28.
https://doi.org/10.1016/j.neuroimage.2014.04.044

Klimesch W, 2018. The frequency architecture of brain and brain body oscillations: an analysis. *Eur J Neurosci*, 48(7): 2431-2453.
https://doi.org/10.1111/ejn.14192

Liao ZL, Tan YF, Qiu YJ, et al., 2018. Interhemispheric functional connectivity for Alzheimer's disease and amnestic mild cognitive impairment based on the triple network model. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 19(12):924-934.
https://doi.org/10.1631/jzus.B1800381

Medaglia JD, Harvey DY, Kelkar AS, et al., 2021. Language tasks and the network control role of the left inferior frontal gyrus. *eNeuro*, 8(5):ENEURO.0382-20.2021.
https://doi.org/10.1523/ENEURO.0382-20.2021

Parkes L, Moore TM, Calkins ME, et al., 2021. Network controllability in transmodal cortex predicts positive psychosis spectrum symptoms. *Biol Psychiatry*, 90(6):409-418.
https://doi.org/10.1016/j.biopsych.2021.03.016

Sarasso S, D'Ambrosio S, Fecchio M, et al., 2020. Local sleep-like cortical reactivity in the awake brain after focal injury. *Brain*, 143(12):3672-3684.
https://doi.org/10.1093/brain/awaa338

Tang BQ, Zhang WJ, Deng SK, et al., 2022. Age-associated network controllability changes in first episode drug-naïve schizophrenia. *BMC Psychiatry*, 22:26.
https://doi.org/10.1186/s12888-021-03674-5

Wu Y, Zhao WR, Chen XY, et al., 2020. Aberrant awake spontaneous brain activity in obstructive sleep apnea: a review focused on resting-state EEG and resting-state fMRI. *Front Neurol*, 11:768.
https://doi.org/10.3389/fneur.2020.00768

Xue SW, Lee TW, Guo YH, 2018. Spontaneous activity in medial orbitofrontal cortex correlates with trait anxiety in healthy male adults. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 19(8):643-653.
https://doi.org/10.1631/jzus.B1700481

Supplementary information

Materials and methods; Tables S1–S3