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Natural frequencies of neural activities and cognitions may serve as precise targets of rhythmic interventions to the aging brain

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Rhythmic neural activities are critical to the efficiency of regulatory procedures in brain functions. However, brain functions usually decline in aging as accompanied by frequency shift and temporal dedifferentiation of neural activities. Considering the strong oscillations and long-lasting after-effects induced by rhythmic brain stimulations, we suggest that non-invasive rhythmic brain stimulation technique may help restore the natural frequencies of neural activities in aging to that in younger and healthy brains. Although with tremendous work to do, this technique offers great opportunities for the restoration of normal brain functions in aging, or even in those suffering from neurodegenerative diseases and neuropsychiatric disorders.

KEYWORDS

frequency shift, natural frequency, neurodegenerative diseases, rhythmic brain stimulation, temporal dedifferentiation

Introduction

Rhythmic neural activities are the basic characteristic of brain function (Buzsáki, 2006). In response to various cognitive demands, the human brain functions across multiple frequencies (Soltani et al., 2021) with distinct mechanisms (Brookes et al., 2016) or multi-layer functional networks (Sasai et al., 2020). Intrinsic frequencies have been stressed for local neural activities (Murray et al., 2014), neural circuits (Rosanova et al., 2009), as well as cognitive functions (Palva and Palva, 2018). Neural activities at intrinsic frequencies form spectral fingerprints of brain functions (Siegel et al., 2012). Throughout the human lifespan, frequencies of these neural activities, however, are constantly changing, as presented in the form of the shift of frequency between adjacent frequency bands and/or temporal dedifferentiation among multiple bands (Alcauter et al., 2015; Yang et al., 2018; Ao et al., 2022). For instance, the individual alpha peak frequency slowed from 10 Hz at the age of 20 years (i.e., younger age) to 8.8 Hz

at the age of 70 years (i.e., older age) and from 9.9 Hz in healthy adults aged 18–60 years old to 9.4 Hz in patients with schizophrenia of the same age range (Sally et al., 2018; Ramsay et al., 2021). These altered frequency characteristics due to aging and/or age-related conditions are closely associated with changes in brain functions and behavioral performances, such as cognitive and motor functions, the control of standing and walking (He et al., 2010; Assenza et al., 2017). In other words, such altered frequency characteristics may interfere with neural activities that are related to cognitive and behavioral performances, leading to their non-optimal (less efficient) neural control (Klimesch, 2018; Wolinski et al., 2018).

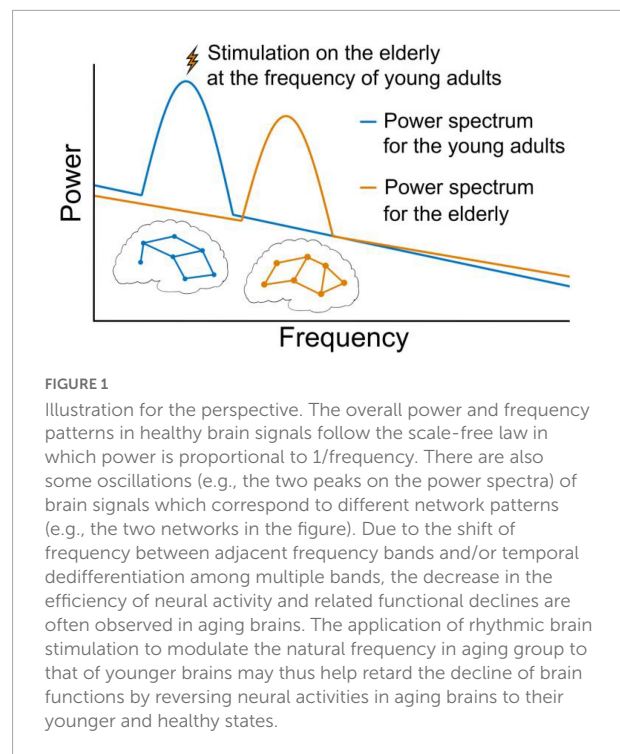
This may be a potential explanation for the findings that though many cognitive training strategies can help improve cognitive performances in relatively older adults, no benefits for the prevention of age-related cognitive decline have been observed (Butler et al., 2018), which may potentially be because those interventions cannot restore the altered frequency behaviors (e.g., frequency shift and/or temporal dedifferentiation), the important factor underlying the etiology of cognitive impairment. Therefore, age-related declines in brain function can be linked to altered frequency characteristics, which may be preserved by strategies targeting the restoration of such frequency characteristics (i.e., rhythmic brain stimulation techniques).

Main perspective

Non-invasive rhythmic brain stimulation techniques have been widely used in the rehabilitation of cognitive and brain functions in relatively older adults (Tatti et al., 2016; Assenza et al., 2017), which facilitate the neural entrainment or resonance (Henry et al., 2017) of the brain activities. These techniques are usually imposed physically or psychologically. The former primarily includes repetitive transcranial magnetic stimulation (rTMS), transcranial alternating current stimulation (tACS), and oscillatory transcranial direct current stimulation (O-tDCS) (Wischniewski et al., 2019; Chou et al., 2020; Qiao et al., 2022); and the latter includes cognitive tasks or sensory stimulations focusing on particular frequencies (Norcia et al., 2015; Wang et al., 2016, 2019).

In the application of these techniques, the selection of appropriate stimulation frequency is critical to maximize their benefits. For instance, the effects of 4 and 7 Hz tACS on working memory are quite different, even though they all belong to the theta rhythm (Wolinski et al., 2018). More precise design of targeting frequency in rhythmic stimulation is critical to improve the efficiency of the intervention (Tatti et al., 2016).

Natural frequencies of neural activities related to particular cognitive functions are defined as the frequencies at which



neural activities and/or cognitive functions can achieve the optimal efficiencies. The optimal efficiencies of neural activities and/or cognitive functions are oftentimes observed in people younger than 40 years old (i.e., young adults) (Edde et al., 2021). For example, the resonant frequencies in Brodmann areas 6, 7, and 19 appeared at about 29, 18.6, and 10.8 Hz, respectively, in people about 30 years old (Rosanova et al., 2009). Another example is that the natural frequency of sustained attention occurred at around 0.05 Hz in children and young adults (Qiao et al., 2022). The resonances at natural frequencies of neural activities (Rosanova et al., 2009) related to sensorimotor or other behavioral performances (Lu et al., 2017; Klimesch, 2018) have been demonstrated. Appropriately characterizing these natural frequencies, which are the promising targets for rhythmic stimulations, is thus important for the design of these techniques. Recently, Qiao et al. (2022) observed that as compared to conventional tDCS, the O-tDCS targeting the potential natural frequency (i.e., 0.05 Hz) of sustained attention may induce significantly greater effects on this function, suggesting that using the natural-frequency-based rhythmic stimulation can further help the higher-order cognitive function. These findings indicate that natural frequencies may serve as precise and efficient targets of rhythmic interventions to improve cognitive and other functions (Lee et al., 2021), holding great promise of retarding the age-related decline of brain functions by reversing frequency shift and temporal dedifferentiation in aging brains (see Figure 1).

Discussion

Rhythmicity is a critical component for the regulation of neural activities related to cognitive and other important functions. Rhythmic brain stimulation techniques have been demonstrated to improve or restore neural activities at particular frequencies (Klink et al., 2020; Qiao et al., 2022), indicating it may be a novel strategy for the restoration of functions in aging by entraining the altered frequencies in aging brain to those in younger and healthy brain. Still, though it is of great promise, future work is highly demanded and warranted to (1) explicitly examine and characterize the efficacy of this kind of technology, helping maximize its benefits at individual level (Knyazeva et al., 2018; Jafari et al., 2020; Wang et al., 2022); and (2) determine the optimal design of this intervention that would be appropriate for different populations (e.g., those with and without neurodegenerative diseases), including the immediate and longer-term effects, dose-response relationship, etc. (Wang et al., 2015; Solomon et al., 2021).

Taken together, the natural-frequency-based rhythmic brain stimulation techniques hold great potential to restore brain functions in aging process with their significant benefits, which may be expanded to benefit those suffering from neurodegenerative diseases and neuropsychiatric disorders (Mingoaia et al., 2013). Future research efforts are warranted to provide critical knowledge and insights into the relationships between natural frequency of brain activities and functional performances, as well as the underlying pathway through which the modulation of such frequency benefits the functions.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

References

- Alcauter, S., Lin, W., Smith, J. K., Goldman, B. D., Reznick, J. S., Gilmore, J. H., et al. (2015). Frequency of spontaneous BOLD signal shifts during infancy and correlates with cognitive performance. *Dev. Cogn. Neurosci.* 12, 40–50. doi: 10.1016/j.dcn.2014.10.004
- Ao, Y., Kou, J., Yang, C., Wang, Y., Huang, L., Jing, X., et al. (2022). The temporal dedifferentiation of global brain signal fluctuations during human brain ageing. *Sci. Rep.* 12:3616. doi: 10.1038/s41598-022-07578-6
- Assenza, G., Capone, F., Biase, L., Ferreri, F., Florio, L., Guerra, A., et al. (2017). Oscillatory activities in neurological disorders of elderly: Biomarkers to target for neuromodulation. *Front. Aging Neurosci.* 9:189. doi: 10.3389/fnagi.2017.00189
- Brookes, M. J., Tewarie, P. K., Hunt, B. A., Robson, S. E., Gascoyne, L. E., Liddle, E. B., et al. (2016). A multi-layer network approach to MEG connectivity analysis. *Neuroimage* 132, 425–438. doi: 10.1016/j.neuroimage.2016.02.045
- Butler, M., McCreedy, E., Nelson, V. A., Desai, P., Ratner, E., Fink, H. A., et al. (2018). Does cognitive training prevent cognitive decline? A systematic review. *Ann. Intern. Med.* 168, 63–68. doi: 10.7326/M17-1531
- Buzsáki, G. (2006). *Rhythms of the Brain*. New York, NY: Oxford University Press. doi: 10.1093/acprof:oso/9780195301069.001.0001
- Chou, Y.-H., That, V. T., and Sundman, M. (2020). A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. *Neurobiol. Aging*. 86, 1–10. doi: 10.1016/j.neurobiolaging.2019.08.020
- Edde, M., Leroux, G., Altena, E., and Chanraud, S. (2021). Functional brain connectivity changes across the human life span: From fetal development to old age. *J. Neurosci. Res.* 99, 236–262. doi: 10.1002/jnr.24669

Author contributions

JQ completed the manuscript writing. SW, YW, and JQ were responsible for the design of the perspective, contributed to the article, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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- He, B. J., Zempel, J. M., Snyder, A. Z., and Raichle, M. E. (2010). The temporal structures and functional significance of scale-free brain activity. *Neuron* 66, 353–369. doi: 10.1016/j.neuron.2010.04.020
- Henry, M. J., Herrmann, B., Kunke, D., and Obleser, J. (2017). Aging affects the balance of neural entrainment and top-down neural modulation in the listening brain. *Nat. Commun.* 8:15801. doi: 10.1038/ncomms15801
- Jafari, Z., Kolb, B. E., and Mohajerani, M. H. (2020). Neural oscillations and brain stimulation in Alzheimer's disease. *Progr. Neurobiol.* 194:101878. doi: 10.1016/j.pneurobio.2020.101878
- Klimesch, W. (2018). The frequency architecture of brain and brain body oscillations: An analysis. *Eur. J. Neurosci.* 48, 2431–2453. doi: 10.1111/ejn.14192
- Klink, K., Paßmann, S., Kasten, F. H., and Peter, J. (2020). The modulation of cognitive performance with transcranial alternating current stimulation a systematic review of frequency-specific effects. *Brain Sci.* 10:932. doi: 10.3390/brainsci10120932
- Knyazeva, M. G., Barzegaran, E., Vildavski, V. Y., and Demonet, J.-F. (2018). Aging of human alpha rhythm. *Neurobiol. Aging* 69, 261–273. doi: 10.1016/j.neurobiolaging.2018.05.018
- Lee, K., Park, Y., Suh, S. W., Kim, S.-S., Kim, D.-W., Lee, J., et al. (2021). Optimal flickering light stimulation for entraining gamma waves in the human brain. *Sci. Rep.* 11:16206. doi: 10.1038/s41598-021-95550-1
- Lu, F. M., Wang, Y. F., Zhang, J., Chen, H. F., and Yuan, Z. (2017). Optical mapping of the dominant frequency of brain signal oscillations in motor systems. *Sci. Rep.* 7:14703. doi: 10.1038/s41598-017-15046-9
- Mingoia, G., Langbein, K., Dietzek, M., Wagner, G., Smesny, S., Scherpiet, S., et al. (2013). Frequency domains of resting state default mode network activity in schizophrenia. *Psychiatry Res.* 214, 80–82. doi: 10.1016/j.psychres.2013.05.013
- Murray, J. D., Bernacchia, A., Freedman, D. J., Romo, R., Wallis, J. D., Cai, X., et al. (2014). A hierarchy of intrinsic timescales across primate cortex. *Nat. Neurosci.* 17, 1661–1663. doi: 10.1038/nn.3862
- Norcia, A. M., Appelbaum, L. G., Ales, J. M., Cottureau, B. R., and Rossion, B. (2015). The steady-state visual evoked potential in vision research: A review. *J. Vis.* 15:4. doi: 10.1167/15.6.4
- Palva, S., and Palva, J. M. (2018). Roles of brain criticality and multiscale oscillations in temporal predictions for sensorimotor processing. *Trends Neurosci.* 41, 729–743. doi: 10.1016/j.tins.2018.08.008
- Qiao, J., Li, X., Wang, Y., Wang, Y., Li, G., Lu, P., et al. (2022). The infraslow frequency oscillatory transcranial direct current stimulation over the left dorsolateral prefrontal cortex enhances sustained attention. *Front. Aging Neurosci.* 14:879006. doi: 10.3389/fnagi.2022.879006
- Ramsay, I. S., Lynn, P., Schermitzler, B., and Sponheim, S. (2021). Individual alpha peak frequency is slower in schizophrenia and related to deficits in visual perception and cognition. *Sci. Rep.* 11:17852. doi: 10.1038/s41598-021-97303-6
- Rosanova, M., Casali, A., Bellina, V., Resta, F., Mariotti, M., and Massimini, M. (2009). Natural frequencies of human corticothalamic circuits. *J. Neurosci.* 29, 7679–7685.
- Sasai, S., Koike, T., Sugawara, S. K., Hamano, Y. H., Sumiya, M., Okazaki, S., et al. (2020). Frequency-specific task modulation of human brain functional networks: A fast fMRI study. *Neuroimage* 224:117375. doi: 10.1016/j.neuroimage.2020.117375
- Scally, B., Burke, M. R., Bunce, D., and Delvenne, J.-F. (2018). Resting-state EEG power and connectivity are associated with alpha peak frequency slowing in healthy aging. *Neurobiol. Aging* 71, 149–155. doi: 10.1016/j.neurobiolaging.2018.07.004
- Siegel, M., Donner, T. H., and Engel, A. K. (2012). Spectral fingerprints of large-scale neuronal interactions. *Nat. Rev. Neurosci.* 13, 121–134. doi: 10.1038/nrn3137
- Solomon, E. A., Sperling, M. R., Sharan, A. D., Wanda, P. A., Levy, D. F., Lyalenko, A., et al. (2021). Theta-burst stimulation entrains frequency-specific oscillatory responses. *Brain Stimul.* 14, 1271–1284. doi: 10.1016/j.brs.2021.08.014
- Soltani, A., Murray, J. D., Seo, H., and Lee, D. (2021). Timescales of cognition in the brain. *Curr. Opin. Behav. Sci.* 41, 30–37. doi: 10.1016/j.cobeha.2021.03.003
- Tatti, E., Rossi, S., Innocenti, I., Rossi, A., and Santarnecchi, E. (2016). Non-invasive brain stimulation of the aging brain: State of the art and future perspectives. *Ageing Res. Rev.* 29, 66–89. doi: 10.1016/j.arr.2016.05.006
- Wang, Y., Dai, G., Liu, F., Long, Z., Yan, J. H., and Chen, H. (2015). Steady-state BOLD response to higher-order cognition modulates low frequency neural oscillations. *J. Cogn. Neurosci.* 27, 2406–2415. doi: 10.1162/jocn_a_00864
- Wang, Y., Huang, X., Yang, X., Yang, Q., Wang, X., Northoff, G., et al. (2019). Low-frequency phase-locking of brain signals contribute to efficient face recognition. *Neuroscience* 422, 172–183. doi: 10.1016/j.neuroscience.2019.10.024
- Wang, Y., Long, Z., Cui, Q., Liu, F., Jing, X., Chen, H., et al. (2016). Low frequency steady-state brain responses modulate large scale functional networks in a frequency-specific means. *Hum. Brain Mapp.* 37, 381–394. doi: 10.1002/hbm.23037
- Wang, Y., Yang, C., Li, G., Ao, Y., Jiang, M., Cui, Q., et al. (2022). Frequency-dependent effective connections between local signals and the global brain signal during resting-state. *Cogn. Neurodyn.* doi: 10.1007/s11571-11022-09831-11570
- Wischniewski, M., Schutter, D. J. L. G., and Nitsche, M. A. (2019). Effects of beta-tACS on corticospinal excitability: A meta-analysis. *Brain Stimul.* 12, 1381–1389. doi: 10.1016/j.brs.2019.07.023
- Wolinski, N., Cooper, N. R., Sauseng, P., and Romei, V. (2018). The speed of parietal theta frequency drives visuospatial working memory capacity. *PLoS Biol.* 16:e2005348. doi: 10.1371/journal.pbio.2005348
- Yang, A. C., Tsai, S. J., Lin, C. P., Peng, C. K., and Huang, N. E. (2018). Frequency and amplitude modulation of resting-state fMRI signals and their functional relevance in normal aging. *Neurobiol. Aging* 70, 59–69. doi: 10.1016/j.neurobiolaging.2018.06.007