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COMMENTARY

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Longitudinal indices of human cognition and brain structure

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Changes in human cognition, brain structure, and function occur with development and throughout aging. This change occurs across timescales of years, and scientific inquiry into these changes has inspired the neuroscientific fields of development, life span, and aging. Likewise, interventions that remediate or enhance cognitive performance can thwart or truncate the temporal progression by which change might naturally occur, and are drawing increasing interest from basic science, clinical, and commercial audiences alike. Understanding the neural basis of cognitive change is a primary goal of human neuroscience. Although cross-sectional studies inform questions related to life span and intervention *differences*, only longitudinal studies which compare the same participants across multiple time points can mechanistically explain *change*. This In Focus issue brings together longitudinal research from developmental neuroscience and cognitive training in effort to gain insights into how changes occur in cognition and brain structure over timescales of weeks to years.

There are unique challenges associated with longitudinal research. Logistical challenges include planning, sometimes years in advance, for potential problems related to participant retention and research implementation. Furthermore, longitudinal studies are resource consuming in terms of finances and manpower, often preventing early- and mid-career researchers from pursuing ambitious, potentially paradigm-shifting lines of research. Here, research involving human participants was brought to a standstill in March 2020 due to the unforeseen global COVID-19 pandemic. Scientific researchers had to adjust plans for data collection and dissemination, rework project aims, reconsider what is feasible, and strive to balance professional and personal while working from home. Perhaps the least devastating outcome of the pandemic was the 50% dropout of planned contributions to this In Focus issue. With that in mind, below we showcase the three articles of this issue. We then conclude with a call for future research that takes a longitudinal approach across multiple intersecting fields of inquiry to bring us closer to understanding the neural basis of cognitive change.

A core challenge in longitudinal research is the development and use of measures with robust test–retest reliability (Ofen et al., 2019). If a measure does not show stable outcomes in the same participant across multiple points close in time, without intervention, then it cannot reliably measure stability or change. Homayouni et al. (2021) tackled this core challenge by validating a measure of brain structure, specifically, hippocampal subfield volumes using structural MRI. The hippocampus is critical to declarative memory, and cross-sectional life span differences in hippocampal subfields have been linked to life span differences in declarative memory performance (Daugherty et al., 2017). In this study, hippocampal subfields were measured in the same pediatric participants, aged 7–20 years, at baseline and both 1-month and 2-year delays (Figure 1a). The reliability of the measure was demonstrated by means of structural stability over 1 month and change over 2 years, replicated in two independent samples. These results further demonstrate the utility of the measure as sensitive enough to detect longitudinal changes in brain structure over an expected maturational timescale of 2 years.

Interventions that aim to remediate or enhance cognitive performance, if successful, can thwart or truncate life span timescales of change, or simply enhance performance. The other studies in this issue tackled questions related to cognitive training-based intervention, a field that is plagued with unreliable outcomes (Boot & Kramer, 2014; Hampshire et al., 2019; Kable et al., 2017; Owen et al., 2010; Sala &

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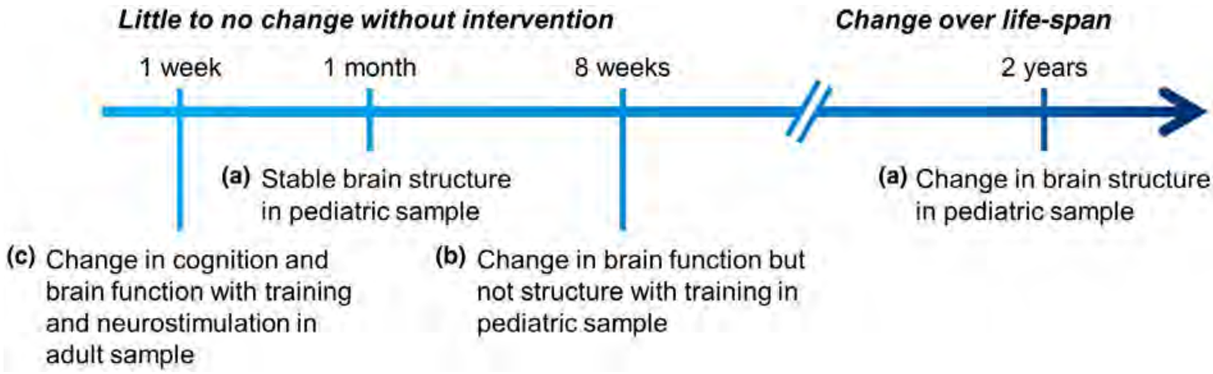

FIGURE 1 Timeline summary of articles in this In Focus issue. (a) Test–retest reliability demonstrated in a measure of hippocampal subfield volumes in two samples aged 7–20 years. Stability is shown at a 1-month delay and change is shown at a 2-year delay. (b) No structural brain network indices of cognitive enhancement following adaptive working memory training compared to task control identified in 7-year-olds at risk of working memory impairment. Indices were investigated 2 weeks after a 5- to 7-week training regimen. (c) Training impairment identified with DLPFC tDCS compared to sham control applied immediately after working memory training in young adults. Training effects were assessed daily over 1 week [Correction added on August 13, 2021, after first online publication: The figure 1 label was changed from 'd' to 'a'.] [Correction added on August 13, 2021, after first online publication: The figure 1 label was changed from 'd' to 'a'.]

Gobet, 2019; Simons et al., 2016). Compounding this unreliability are subtle effects and improvements limited to the trained cognitive task, without any transfer of benefit to untrained tasks and therefore no benefit to daily living (Melby-Lervåg et al., 2016; Richmond et al., 2011). Attempts to improve outcomes by augmenting cognitive training with noninvasive neurostimulation have been met with similarly unreliable results (Berryhill et al., 2019; Horvath et al., 2015; Polanía et al., 2018). This problem of unreliability is further compounded by differential methods utilized between research laboratories and the *file drawer problem*, where only statistically significant results are rewarded with publications and further grants (Medina & Cason, 2017; Melby-Lervåg et al., 2016). Successful intervention requires mechanistic explanations of what works and for whom, as a "one-size-fits-all" approach is not sustainable for reliable, beneficial interventions.

Kelly et al. (2021) sought to identify structural brain indices of cognitive enhancement following a working memory training program in children at risk of working memory impairment. Specifically, they compared 5–7 weeks of working memory training that was either adaptive ("Cogmed") or consistently low in difficulty (control) in 7-year-olds who had been born extremely preterm or with low weight. Cognitive assessment and both functional and structural MRI data were collected at baseline and 2 weeks post-training for investigation of changes related to adaptive training that taxed working memory. Increased functional connectivity in the precuneus network was previously identified as a functional network index of cognitive enhancement following Cogmed training (Tseng et al., 2019). In this study, despite identification of a whole-brain structural change following Cogmed training, no structural network indices were identified that correlated with cognitive enhancement (Figure 1b). Structure–function links in brain networks are complex (Suárez et al., 2020), and these results highlight the importance of examining both functional and structural brain measures to achieve a mechanistic understanding of cognitive change.

Au et al. (2021) sought to identify optimal stimulation parameters for pairing noninvasive neurostimulation, here, transcranial direct current stimulation (tDCS), with working memory training in young adults. Specifically, they combined 5 days of working memory training with active or sham (control) tDCS to the right dorsolateral prefrontal cortex (DLPFC) that was applied before, during, or after each training session. The effects of tDCS on neuronal resting-state polarization are believed to outlast the stimulation period (Reinhart et al., 2017), so, probing the benefit of tDCS applied before, during, or after cognitive training leads to greater mechanistic understanding of how to elicit cognitive benefits through paired training and neurostimulation. Working memory was assessed at baseline and 1 day post-training for investigation of changes related to the timing of tDCS. The DLPFC is known to support working memory, and DLPFC tDCS applied online during training has been shown to enhance young adults' working memory compared to training alone (Au et al., 2016; Katz et al., 2017). In this study, working memory improved across all training conditions and was not further enhanced with online tDCS; however, benefits were impaired with tDCS applied immediately after training (Figure 1c). These results reveal an interaction between the right DLPFC and post-training processes, and underscore the importance of directly examining the neural mechanisms by which training and tDCS change the brain to elicit changes in working memory performance (Jones et al., 2017, 2020).

Collectively, the articles in this In Focus issue illuminate the need for studies which aim to determine not only what changes in human cognition and the brain over different timescales, but also how changes in the brain underpin changes in behavior. To do this, it is necessary to determine measures with test–retest reliability (Homayouni et al., 2021), extend previous findings from interventions (Au et al., 2021; Kelly et al., 2021), and engage in longitudinal research despite the challenges. With this knowledge, we may not need to speculate about why certain findings do not replicate. Moreover, we may be able to predict how people's brains and behaviors change over their lives, and how different interventions should target different people for maximum efficacy. Future research should take an interdisciplinary approach to derive indices of longitudinal change, tackling issues from different angles to bring us closer to understanding the neural basis of cognitive change.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

E.L.J. and K.T.J. *Conceptualization*, *Writing – original draft*, *Writing – review & editing*.

PEER REVIEW

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REFERENCES

Au, J., Katz, B., Buschkueh, M., Bunarjo, K., Senger, T., Zabel, C., Jaeggi, S. M., & Jonides, J. (2016). Enhancing working memory training with transcranial direct current stimulation. *Journal of Cognitive Neuroscience*, *26*(3), 194–198. https://doi.org/10.1162/jocn

Au, J., Katz, B., Moon, A., Talati, S., Abagis, T. R., Jonides, J., & Jaeggi, S. M. (2021). Post-training stimulation of the right dorsolateral prefrontal cortex impairs working memory training performance. *Journal of Neuroscience Research*, *2020*, 1–13. https://doi.org/10.1002/jnr.24784

Berryhill, M., Arciniega, H., Jones, K., Stephens, J., & Gozenman, F. (2019). Who, what, where and how much: tDCS and training effects on working memory. *Brain Stimulation*, *12*(2), 460. https://doi.org/10.1016/j.brs.2018.12.496

Boot, W. R., & Kramer, A. F. (2014). The brain-games conundrum: Does cognitive training really sharpen the mind? *Cerebrum*, *2014*, 15. https://pubmed.ncbi.nlm.nih.gov/26034522

Daugherty, A. M., Flinn, R., & Ofen, N. (2017). Hippocampal CA3-dentate gyrus volume uniquely linked to improvement in associative memory from childhood to adulthood. *Neuroimage*, *153*, 75–85. https://doi.org/10.1016/j.neuroimage.2017.03.047

Hampshire, A., Sandrone, S., & Hellyer, P. J. (2019). A large-scale, cross-sectional investigation into the efficacy of brain training. *Frontiers in Human Neuroscience*, *13*, 221. https://doi.org/10.3389/fnhum.2019.00221

Homayouni, R., Yu, Q., Ramesh, S., Tang, L., Daugherty, A. M., & Ofen, N. (2021). Test–retest reliability of hippocampal subfield volumes in a developmental sample: Implications for longitudinal developmental studies. *Journal of Neuroscience Research*. https://doi.org/10.1002/jnr.24831, https://onlinelibrary.wiley.com/action/showCitFormats?doi=10.1002%2Fjnr.24831

Horvath, J. C., Forte, J. D., & Carter, O. (2015). Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). *Brain Stimulation*, *8*(3), 535–550. https://doi.org/10.1016/j.brs.2015.01.400

Jones, K. T., Johnson, E. L., & Berryhill, M. E. (2020). Frontoparietal theta-gamma interactions track working memory enhancement with training and tDCS. *Neuroimage*, *211*, 116615. https://doi.org/10.1016/j.neuroimage.2020.116615

Jones, K. T., Peterson, D. J., Blacker, K. J., & Berryhill, M. E. (2017). Frontoparietal neurostimulation modulates working memory training benefits and oscillatory synchronization. *Brain Research*, *1667*, 28–40. https://doi.org/10.1016/j.brainres.2017.05.005

Kable, J. W., Caulfield, M. K., Falcone, M., McConnell, M., Bernardo, L., Parthasarathi, T., Cooper, N., Ashare, R., Audrain-McGovern, J., Hornik, R., Diefenbach, P., Lee, F. J., & Lerman, C. (2017). No effect of commercial cognitive training on brain activity, choice behavior, or cognitive performance. *Journal of Neuroscience*, *37*(31), 7390–7402. https://doi.org/10.1523/JNEUROSCI.2832-16.2017

Katz, B., Au, J., Buschkuehl, M., Tessa, A., Zabel, C., Jaeggi, S. M., & Jonides, J. (2017). Individual differences and long-term consequences of tDCS-augmented cognitive training. *Journal of Cognitive Neuroscience*, *29*(9), 1498–1508. https://doi.org/10.1162/jocn_a_01115

Kelly, C. E., Harding, R., Lee, K. J., Pascoe, L., Josev, E. K., Spencer-Smith, M. M., Adamson, C., Beare, R., Nosarti, C., Roberts, G., Doyle, L. W., Seal, M. L., Thompson, D. K., & Anderson, P. J. (2021). Investigating the brain structural connectome following working memory training in children born extremely preterm or extremely low birth weight. *Journal of Neuroscience Research*, 1–11. https://doi.org/10.1002/jnr.24818, https://onlinelibrary.wiley.com/action/showCitFormats?doi=10.1002%2Fjnr.24818

Medina, J., & Cason, S. (2017). No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations. *Cortex*, *94*, 131–141. https://doi.org/10.1016/j.cortex.2017.06.021

Melby-Lervåg, M., Redick, T. S., & Hulme, C. (2016). Working memory training does not improve performance on measures of intelligence or other measures of "far transfer": Evidence from a meta-analytic review. *Perspectives on Psychological Science*, *11*(4), 512–534. https://doi.org/10.1177/1745691616635612

Ofen, N., Tang, L., Yu, Q., & Johnson, E. L. (2019). Memory and the developing brain: From description to explanation with innovation in methods. *Developmental Cognitive Neuroscience*, *36*, 100613. https://doi.org/10.1016/j.dcn.2018.12.011

Owen, A. M., Hampshire, A., Grahn, J. A., Stenton, R., Dajani, S., Burns, A. S., Howard, R. J., & Ballard, C. G. (2010). Putting brain training to the test. *Nature*, *465*(7299), 775–778. https://doi.org/10.1038/nature09042

Polanía, R., Nitsche, M. A., & Ruff, C. C. (2018). Studying and modifying brain function with non-invasive brain stimulation. *Nature Neuroscience*, *21*(2), 174–187. https://doi.org/10.1038/s41593-017-0054-4

Reinhart, R. M. G., Cosman, J. D., Fukuda, K., & Woodman, G. F. (2017). Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. *Attention, Perception & Psychophysics*, *79*(1), 3–23. https://doi.org/10.3758/s13414-016-1224-2

Richmond, L. L., Morrison, A. B., Chein, J. M., & Olson, I. R. (2011). Working memory training and transfer in older adults. *Psychology and Aging*, *26*(4), 813–822. https://doi.org/10.1037/a0023631

Sala, G., & Gobet, F. (2019). Cognitive training does not enhance general cognition. *Trends in Cognitive Sciences*, *23*(1), 9–20. https://doi.org/10.1016/j.tics.2018.10.004

Simons, D. J., Boot, W. R., Charness, N., Gathercole, S. E., Chabris, C. F., Hambrick, D. Z., & Stine-Morrow, E. A. L. (2016). Do "brain-training" programs work? *Psychological Science in the Public Interest*, *17*(3), 103–186. https://doi.org/10.1177/1529100616661983

Suárez, L. E., Markello, R. D., Betzel, R. F., & Misic, B. (2020). Linking structure and function in macroscale brain networks. *Trends in Cognitive Sciences*, *24*(4), 302–315. https://doi.org/10.1016/j.tics.2020.01.008

Tseng, C.-E.- J., Pascoe, L., Roberts, G., Doyle, L. W., Lee, K. J., Thompson, D. K., Seal, M., Josev, E. K., Chen, J., Nosarti, C., & Anderson, P. J. (2019). Working memory training is associated with changes in resting state functional connectivity in children who were born extremely preterm: A randomized controlled trial. *Journal of Cognitive Enhancement*, *3*(4), 376–387. https://doi.org/10.1007/s41465-019-00150-7

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