Journal Club

Editor's Note: These short reviews of recent *JNeurosci* articles, written exclusively by students or postdoctoral fellows, summarize the important findings of the paper and provide additional insight and commentary. If the authors of the highlighted article have written a response to the Journal Club, the response can be found by viewing the Journal Club at www.jneurosci.org. For more information on the format, review process, and purpose of Journal Club articles, please see http://jneurosci.org/content/jneurosci-journal-club.

Cognitive Control and Neural Activity during Human Development: Evidence for Synaptic Pruning

Leland L. Fleming[1] and Timothy J. McDermott[2]

[1]Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, Massachusetts 02478 and [2]Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, Georgia 30322

Review of Liuzzi et al.

The modern world is full of distractions that steal our attention from important tasks. As a result, the world places ever-growing demands on cognitive control: the ability to coordinate mental resources to achieve our goals (Koechlin et al., 2003). A key mediator of cognitive control is the prefrontal cortex (PFC), which is heavily involved in processes like learning and memory, attention, and inhibition of improper responses (Koechlin et al., 2003). Yet the PFC, with its sophisticated circuitry that enables these roles, is one of the last brain regions to develop (Hill et al., 2010; Kolk and Rakic, 2022). Indeed, the maturation of the PFC is an important component of adolescent development (Larsen and Luna, 2018), as is the development of cognitive control. This delayed development of the PFC may lead to undesired outcomes, such as risky behaviors in teenagers (Larsen and Luna, 2018), which may be linked specifically to deficits in response inhibition or the suppression of competing responses during a given task or everyday situation (Luna and Sweeney, 2004). Therefore, understanding the developmental changes in the circuitry that underlies cognitive control, particularly response inhibition, is an important area of investigation.

A major component of PFC maturation is the removal of excess connections via synaptic pruning (Kolk and Rakic, 2022). During early childhood, the PFC undergoes rapid expansion, with dorsolateral and medial PFC expanding to nearly double the surface area of other cortical regions such as occipital and insular cortices (Hill et al., 2010). Underlying this rapid expansion is a period of extensive synaptic growth (synaptogenesis), which begins prenatally but peaks postnatally (Teffer and Semendeferi, 2012), at ~3.5 years of age in humans (Kolk and Rakic, 2022). PFC cortical thickness, which can serve as a measure of synaptic density, also shows rapid growth early in life. However, this is followed by a decline in adolescence and then slight increases and stabilization during adulthood (Teffer and Semendeferi, 2012). Consequently, dendritic spine density in the PFC in early childhood is up to 2–3 times greater than in adulthood. The developmental decline in synaptic density, which results from synaptic pruning, is thought to enhance the efficiency of information transfer between local circuits (Fig. 1), thus improving the PFC's ability to modulate behavioral responses (Luna and Sweeney, 2004; Averbeck, 2022). Consistent with this hypothesis, changes in the cortical structure of the PFC seem to match the developmental timelines of its known functions, such as working memory and cognitive control (Teffer and Semendeferi, 2012), at least in animal models. Evidence in humans remains limited, however.

Previous research using EEG has demonstrated that event-related potentials related to cognitive control behavior, such as conflict monitoring and error processing, increase in amplitude during human adolescence (Segalowitz et al., 2010), likely related to synaptic pruning. Computational modeling work has sought to link such changes in electrophysiological responses to developmental changes in behavior and brain structure. For example, this relationship has been explored previously using artificial neural networks (ANNs), a type of computational model designed to simulate the activity of real-world neurons. A previous study (Averbeck, 2022) showed that removing or "pruning" artificial synapses from an ANN model increased its performance on cognitive control-like tasks (i.e., working memory and reinforcement learning). Additionally, it was observed that this "pruning" led to faster neural activity decay or the return of activity back to its unperturbed state. This led to the proposition that neural activity decay provides an indicator of synaptic pruning and subsequent improvement in cognitive control (Averbeck, 2022).

While computational models like ANNs are useful simulations of the brain, they often face limitations, specifically in risking the oversimplification of more complex neurobiological mechanisms. As a result, simulation-based hypotheses

Received Feb. 23, 2024; revised April 25, 2024; accepted April 29, 2024.

We thank the authors for carrying out their thoughtful and careful analyses; our postdoctoral research advisors, Dr. Kerry Ressler and Dr. Negar Fani; our writing mentor for this document, Dr. Daniela Schiller, for her constructive feedback; and our funders, National Institutes of Health–National Institute of Child Health and Human Development Grant No. K00HD111352 (L.L.F.) and National Institute of Mental Health (NIMH) Grant No. F32MH134631 (T.J.M.).

The authors declare no competing financial interests.

Correspondence should be addressed to Leland L. Fleming at llfleming@mclean.harvard.edu.

https://doi.org/10.1523/JNEUROSCI.0373-24.2024

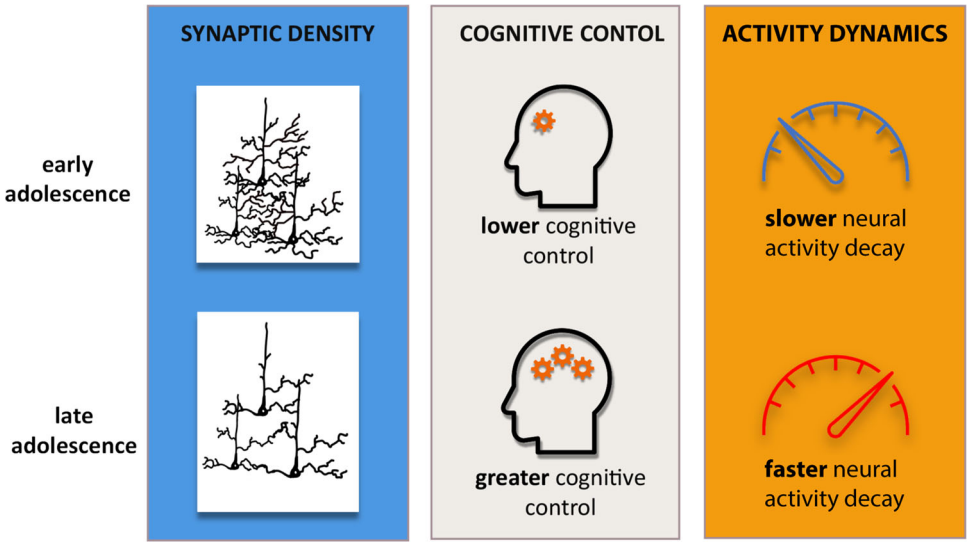

Figure 1. Conceptual schematic. A diagram depicting the conceptual hypothesis of the relationship between synaptic pruning and neural activity decay. Between early and late adolescence (left panel), the overall number of synapses is reduced through synaptic pruning. The time course of these neural structural changes follows timelines of increased cognitive control in late adolescence compared with early adolescence (middle panel). As described in Liuzzi et al. (2023), dynamic neural activity during a response inhibition task shows slower neural activity decay during early adolescence compared with late adolescence. This work is consistent with the hypothesis that the refinement of synaptic connectivity during adolescence enables the enhancement of cognitive control by increasing the efficiency of neural activity in the PFC.

need to be tested with real brain data to ensure their accuracy and relevance to understanding brain function. To address this need, Liuzzi et al. (2023) investigated whether simulation-based models of synaptic pruning and cognitive control apply to PFC development and changes in behavior during human adolescence.

Liuzzi et al. (2023) recorded brain activity with EEG from 179 adolescents as they completed a response inhibition task (Eriksen flanker) at ages 12, 15, and 18. The task provided adaptive feedback based on participant performance to obtain between 75 and 90% accuracy. The 331 recordings from 104 electrodes were filtered and then grand-averaged (across all participants) into event-related potentials. To reduce data dimensionality, that is, to make the data simpler to work with and understand, the investigators conducted a principal component (PC) analysis—a mathematical way of summarizing information contained in large datasets. From this analysis, they identified two PCs (groups of electrodes across the brain) that collectively explained 79 and 14% of signal variance, respectively. The first PC consisted of electrodes covering the frontal/occipital cortex and reflected early visual processing of stimuli. The second PC consisted of central/parietal and temporal regions and distinguished between correct and error trials. The investigators then used a technique called linear dynamical system modeling to characterize how neural activity decay (the rate at which evoked activity returns to the baseline) from the two groups of electrodes changed over time. The authors hypothesized that older adolescents would exhibit faster neural activity decay, likely related to greater synaptic pruning, while younger adolescents would exhibit slower neural activity decay, indicating more unpruned, redundant synapses. This was rooted in the idea that a more well-pruned system is a more efficient system and thus takes less time to return to its baseline state following activation.

Using EEG-derived neural activity in early-to-late adolescence during a response inhibition task, the investigators showed that rates of neural activity decay were significantly associated with both age and behavioral performance. Specifically, age during adolescence was positively associated with faster neural activity decay around the time of stimulus presentation and during subjects' responses, but not during stimulus cueing. Similarly, behavioral performance (faster reaction time) was also associated with faster neural activity decay during stimulus presentation and subjects' responses, consistent with results showing faster reaction times with increasing age during adolescence. Together with previous work, these results support the hypothesis that a key component of cognitive control in adolescence involves the altering of brain activity through the removal of recurrent processes (Fig. 1). The study builds upon prior work using network computational models that support the hypothesis that changes in behavior, due to synaptic pruning, are related to changes in neural activity decay. This in turn is based on the premise that the main function of synaptic pruning is to enhance the efficiency of information transfer (Averbeck, 2022). In the study by Liuzzi et al. (2023), this is reflected in faster neural activity decay at age 18 compared with ages 12 and 15. The study also builds upon previous work in animals, in addition to human studies of structural MRI and postmortem tissue examining cortical structure and synaptic density during development (Koechlin et al., 2003; Luna and Sweeney, 2004; Teffer and Semendeferi, 2012).

The findings by Liuzzi and colleagues serve as a missing link in human neurodevelopmental studies that associate brain changes with behavioral changes in adolescence. The authors connect neural activity to behavior and development in a way that is consistent with a potential biological mechanism that has long been hypothesized: synaptic pruning. Given the limitation of current neuroscience methods, directly measuring synaptic pruning in living humans cannot be ethically conducted. Therefore, the results of Liuzzi and colleagues represent an important advance in our understanding of the potential function of synaptic pruning in the developing human brain. These results not only provide insights for the field of developmental neuroscience, but also may lead to a better understanding of the underlying mechanisms of healthy aging at other points during the lifespan, in addition to mechanisms of neuropsychiatric disease processes.

Despite the valuable contributions of the study, a few limitations point to several possible future directions. First, Liuzzi and colleagues did not include a direct measure of synaptic pruning, which is not possible to obtain with noninvasive approaches. To increase the validity of the conclusions, future work should include gray matter volume (extracted from structural MRI) as an indirect measure of synaptic pruning. While it may have been beyond the scope of this present study, linking neural activity decay (extracted from EEG data) to brain structure would also help further strengthen the argument that these functional changes relate to synaptic pruning.

In addition to linking neural activity decay back to brain structure, another potentially useful direction may be to examine how adolescent neural activity decay relates to more global measures of development using EEG. Within this area, recent work using machine learning on large magnetoencephalography (MEG) and EEG datasets has begun characterizing resting-state brain activity as a measure of "brain age" (Engemann et al., 2022). While this work has linked neural activity to developmental timelines, it has not yet associated EEG-/MEG-based "brain age" with specific neural responses, like those evoked during response inhibition tasks. Examining this link, in addition to generalizing the findings to other samples, would be an important future direction. Still, the results presented by Liuzzi et al. (2023) provide insightful evidence in support of the idea that synaptic pruning during adolescence leads to more efficient neural activity that underpins developmental improvements in cognitive control.

References

Averbeck BB (2022) Pruning recurrent neural networks replicates adolescent changes in working memory and reinforcement learning. Proc Natl Acad Sci U S A 119:e2121331119.

Engemann DA, Mellot A, Höchenberger R, Banville H, Sabbagh D, Gemein L, Ball T, Gramfort A (2022) A reusable benchmark of brain-age prediction from M/EEG resting-state signals. Neuroimage 262:119521.

Hill J, Inder T, Neil J, Dierker D, Harwell J, Van Essen D (2010) Similar patterns of cortical expansion during human development and evolution. Proc Natl Acad Sci U S A 107: 13135–13140.

Koechlin E, Ody C, Kouneiher F (2003) The architecture of cognitive control in the human prefrontal cortex. Science 302:1181–1185.

Kolk SM, Rakic P (2022) Development of prefrontal cortex. Neuropsychopharmacology 47:41–57.

Larsen B, Luna B (2018) Adolescence as a neurobiological critical period for the development of higher-order cognition. Neurosci Biobehav Rev 94:179–195.

Liuzzi L, Pine DS, Fox NA, Averbeck BB (2023) Changes in behavior and neural dynamics across adolescent development. J Neurosci 43:8723–8732.

Luna B, Sweeney JA (2004) The emergence of collaborative brain function: FMRI studies of the development of response inhibition. Ann N Y Acad Sci 1021:296–309.

Segalowitz SJ, Santesso DL, Jetha MK (2010) Electrophysiological changes during adolescence: a review. Brain Cogn 72:86–100.

Teffer K, Semendeferi K (2012) Human prefrontal cortex: evolution, development, and pathology. Prog Brain Res 195:191–218.