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Why Does the Neocortex Need the Cerebellum for Working Memory?

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Review of [Brissenden et al.](#)

The cerebellum has long been regarded as synonymous with motor function, while cognitive neuroscientists have often ignored this brain area. However, over the last 30 years, clinical observations ([Schmahmann et al., 2019](#)) and human neuroimaging ([Diedrichsen et al., 2019](#)) have identified cerebellar contributions in a broad range of cognitive functions, and recent optogenetic studies in rodents have demonstrated that cerebellar contributions to decision-making ([Deverett et al., 2018](#)) and working memory ([Gao et al., 2018](#)) are necessary for correct task performance. These findings are supported by extensive functional cerebello-cortical connectivity ([Diedrichsen et al., 2019](#)), and closed-loop, multisynaptic pathways with prefrontal cortex ([Kelly and Strick, 2003](#)). Yet, a detailed understanding of how the cerebellum contributes to cognitive functions is still missing, given the relatively young interest of cognitive and systems neuroscience in this area.

Importantly, neurophysiological recordings in mice have recently identified stimulus-specific, persistent delay activity in cerebellum during a motor preparation task ([Gao et al., 2018](#)), much like persistent activity in neocortex that is commonly

thought to underlie working memory maintenance ([Funahashi et al., 1989](#)). However, the stimulus identity in [Gao et al. \(2018\)](#) was correlated with the correct motor response; as a result, it is still unclear whether motor-independent working memory is maintained in the cerebellum. In a recent study published in the *Journal of Neuroscience*, [Brissenden et al. \(2021\)](#) conducted an fMRI study in healthy human subjects to answer this question.

Their main finding was a sustained representation of the remembered stimulus throughout the whole memory delay in a combined cerebellar region, lobule VIIb/VIIIa, that cannot be trivially explained through motor preparation. This result extends previous findings of activity changes during working memory in lobule VIIb/VIIIa ([Brissenden et al., 2018](#); [Diedrichsen et al., 2019](#)) by highlighting the role of this cerebellar region in stimulus-specific, motor-independent working memory maintenance.

To study maintenance-related brain activity, [Brissenden et al. \(2021\)](#) asked subjects to remember the motion directions of briefly presented clouds of moving dots (random-dot kinematograms). Motion directions held in memory were then reconstructed using multivariate analyses of BOLD activity in prefrontal, parietal, and visual cortices, as well as in several regions of interest across the entire cerebellar cortex. Along with the expected stimulus-specific decoding in prefrontal, parietal, and visual cortices ([Christophel et al., 2017](#)), [Brissenden et al. \(2021\)](#) could read out remembered motion directions

from activity patterns in cerebellar lobules VIIb and VIIIa throughout the entire delay (Fig. 3 in [Brissenden et al., 2021](#)). At the same time, other cerebellar regions, including oculomotor vermis, did not represent the memorized stimuli (Figs. 4, 5 in [Brissenden et al., 2021](#)). Importantly, a carefully designed task allowed [Brissenden et al. \(2021\)](#) to rule out alternative hypotheses about the motor or perceptual origins of working memory representations: two kinematograms were encoded into working memory, but after the stimuli disappeared, a retro-cue instructed subjects to remember only one of them, allowing the authors to compare encoded versus maintained stimulus representations. Moreover, subjects were asked to report the stimulus by rotating a line segment from a random orientation to the remembered one through repeated button presses, rather than motorically reproducing the motion direction of the point cloud itself. This decoupling of stimulus and response modalities discards a motor interpretation of cerebellar delay activity.

A series of further results in the study by [Brissenden et al. \(2021\)](#) supports the idea that lobule VIIb/VIIIa forms part of a distributed cerebello-frontoparietal working memory network. First, they report trialwise correlations between the decoding strength in lobule VIIb/VIIIa and in frontal, parietal, and visual cortices. Critically, brain-wide fluctuations in signal-to-noise ratio might confound these analyses, given that correlations were found between all areas with significant stimulus decoding. To understand

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cortico-cerebellar interactions during working memory processing on a more fine-grained level, temporally precise neural recordings like MEG or invasive electrophysiology will be necessary in future experiments. Moreover, future work should assess trial-by-trial (rather than between-subjects) correlations of stimulus representations with behavioral reports (Barbosa et al., 2020; Wolff et al., 2020) to identify behaviorally relevant neural variability in cerebellar and neocortical areas. The second main finding in support of a cerebello-frontoparietal working memory network is based on resting-state functional connectivity between the regions of interest: only those subdivisions of lobule VIIb/VIIIa that were functionally connected to frontal and parietal cortices held robust working memory representations; those functionally connected to visual cortex did not (Figs. 6, 7 in Brissenden et al., 2021). Together, these network-level analyses suggest a joint participation of cerebellar, prefrontal, and parietal cortices in working memory maintenance.

In sum, Brissenden et al. (2021) make an important contribution to cerebellar and working memory research by demonstrating that sustained, stimulus-specific, and motor-independent representations of working memory items are found in cerebellar activity. Together with earlier results from mouse electrophysiology (Gao et al., 2018), this study obliges working memory researchers to start considering the contributions of cerebello-cortical interactions to working memory and cortical persistent activity. Most notably, optogenetic experiments in the study by Gao et al. (2018) underscore this conclusion by showing the dependence of persistent activity in ALM (a motor preparation- and working memory-related region of mouse neocortex) and correct behavioral performance on sustained cerebellar input during memory delays. While a full picture is currently limited by the comparison of brain mechanisms across species, the temporal and spatial resolution of human neuroimaging, and the difficulty of studying cognition in rodents, accumulating evidence highlights the importance of cerebellar contributions to working memory maintenance and to persistent activity in neocortex.

The most intriguing outstanding question concerns the functional role of cerebellum in working memory. Specifically, it is not clear what the advantage is of a recurrent cerebello-cortical loop in working

memory maintenance, compared with a single, recurrent neocortical circuit. Simple working memory tasks with continuous stimuli, such as the task used by Brissenden et al. (2021), are parsimoniously solved by attractor models implemented in a single, strongly recurrent cortical circuit, such as the prefrontal cortex (Compte et al., 2000). In these models, recurrent connectivity between similarly tuned neurons assures the localized maintenance of memories within a persistently active subgroup of neurons. In contrast, because of its feedforward architecture that mostly lacks strong recurrent connections, it is unlikely that cerebellum autonomously maintains persistent activity, and probably inherits tuned persistent firing. Therefore, two possibilities are conceivable for the functional role of cerebellar stimulus-specific activity: first, neocortical recurrent connectivity might be insufficient to maintain stable mnemonic attractor states throughout the delay. If this is the case, subcortical activity might support prefrontal or parietal activity by delivering additional recurrent, stimulus-specific input (Wang, 2001). Inherited persistent activity would then be fed back to the neocortex with a temporal delay, but without further processing. However, this mere “outsourcing” of recurrent connectivity seems inefficient, considering the large spatial distances between higher neocortical areas and cerebellum.

A second possibility is that the cerebellum complements neocortical delay activity with additional processing that cannot be performed by cortical regions. In this scheme, the cerebellum would inherit neural representations of memory items, process them, and feed altered signals back to adjust or instruct neocortical activity. This hypothesis seems plausible considering the fundamental architectural differences between association cortices and cerebellum: while neocortical circuits are highly recurrently interconnected, the cerebellar circuit is characterized by a divergent-convergent feedforward architecture, together with error signal-driven plasticity within the circuit on intermediate time-scales (Raymond and Medina, 2018). From these anatomic considerations and from analogies with its role in motor control, theories of cerebellar function postulate a role in pattern separation supporting supervised learning of input-output relations (Cayco-Gajic and Silver, 2019), but also in learning and providing “internal”, predictive models of explicit behavior or mental operations (Wolpert et al., 1998; Ito, 2008). It is currently

unclear how these theories relate to the findings in the studies by Brissenden et al. (2021) and Gao et al. (2018). Experiments that more directly test specific hypotheses will be necessary to establish the importance of cerebellar involvement in working memory, beyond delivering recurrent input to neocortical areas. In the following, I will discuss how the concepts of pattern separation and predictive models could translate to the context of working memory and inform future experiments and modeling.

The cerebellum is thought to perform pattern separation through the divergent processing and decorrelation of overlapping input patterns, so that behaviorally relevant neural representations can be easily identified and selected (Cayco-Gajic et al., 2017). Pattern separation could benefit memory performance by enhancing the separability and increasing the precision of similar memory items in contexts that require stimulus discrimination, rather than generalization. This function might be particularly important over the course of long delays, where continuous attractor dynamics in cortical circuits can lead to the merging of similar, simultaneously held memories (Almeida et al., 2015) or to a “collapse” of memories onto a few categorical classes (Panichello et al., 2019). It has been shown previously that learned or instructed task relevance can selectively increase recall precision (Klyszejko et al., 2014), as well as the resolution and separability of representations of specific memory items in prefrontal and parietal cortices (Panichello and Buschman, 2021). In this sense, cerebellar pattern separation and the enhancement of task-relevant memories could prevent prioritized items from merging or from collapsing onto a categorical representation, a hypothesis supported by the cerebellar participation in visual attention networks (Brissenden and Somers, 2019).

In cognitive tasks, which stimulus features or items are relevant and should therefore be prioritized can be explicitly instructed through external cues (Panichello and Buschman, 2021) or, alternatively, it can be learned over the course of several trials (Klyszejko et al., 2014). The latter option indicates another potential function of cerebellum in working memory and cognition more broadly: the learning of predictive models for a task. Specifically, cerebellar plasticity might underlie error-based learning of task statistics, such as probability distributions of different memory items, blockwise stimulus–response mappings, or the probability of cueing different memories for recall. Predictive models of such task

statistics or priors could then be used to adaptively improve working memory performance by biasing memories toward likely values. In support of this idea, computational work by Narain et al. (2018) demonstrates that the cerebellar circuit can learn to represent and use prior distributions in time-interval estimation tasks. Experimentally, Deverett et al. (2019) have shown that cerebellar disruptions during evidence accumulation decreased the weighting of early information, and Sendhilnathan et al. (2020) found that previous decisions were represented in cerebellar activity during the relearning of novel stimulus–response associations. Inactivation experiments with transcranial magnetic stimulation or optogenetic perturbations could test the cerebellar dependence of adaptive behavior in working memory tasks where performance is contingent on the learning of statistical regularities.

To conclude, mechanistic knowledge about the functional role of cerebellum in working memory is currently limited by the difficulty of translating specific hypotheses to cognitive domains, but also by the difficulty of assessing motor-independent working memory in rodents, or cerebellar activity on a single-neuron level in human or nonhuman primates. Brissenden et al. (2021) contribute to understanding cognition in cerebellum by demonstrating that its involvement in visual working memory goes beyond delivering nonspecific background input, opening the door toward novel hypotheses that explore the role of cerebellum in cognition.

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