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## Cognitive Neuroscience: Functional Specialization in Human Cerebellum

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**A new brain imaging study reveals that the human cerebellum contains a region that represents visual space that is dissociable from a region displaying visual memory-related activity, with both regions exhibiting precise functional coupling with corresponding cerebral cortical areas.**

Although the cerebellum contains more than 50% of the neurons in the human brain, many of its functions remain relatively poorly understood. The classical view of the cerebellum has focused on its roles in the control and coordination of body movements. Research over the past few decades, however, has generated substantial evidence for a variety of non-motor cerebellar functions in domains such as cognition, language, perception, and affective/emotional processing. A study reported in this issue of *Current Biology* by Brissenden *et al.* [1] shows that the human cerebellum contains representations of visual space, revealed by functional magnetic resonance imaging (fMRI). The authors of this study also describe a region in the cerebellum that exhibits responses related to visual memory and is distinct from the one that represents visual space. Finally, they report that the regions encoding visual space and memory signals exhibit very precise patterns of functional coupling with corresponding regions in the cerebral cortex.

The role of the cerebellum in planning and executing movements is well established. Damage to portions of the cerebellum results in motor deficits in both animal models and human patients,

and many cerebellar neurons display patterns of activity that are related to the timing and execution of voluntary body movements. Investigations of patients with cerebellar damage, as well as neuroimaging studies of subjects with intact brains, have demonstrated that the cerebellum also has important roles in cognition and perception (reviewed in [2–4]), and anatomical studies have revealed connections between the cerebellum and many higher-order cerebral cortical areas in the macaque brain (reviewed in [5]). A range of extremely diverse functions have been associated with the human cerebellum in recent years, including visual and auditory perception, pain, attention, memory, emotion, language, executive function, and social cognition. These findings have raised questions about the organization of functional specialization in the cerebellum.

In the cerebral cortex, one foundational principle of functional organization is the topographic map. For example, many cerebral cortical areas contain a continuous map of the visual field on their surface [6,7]. In at least some of these maps, the spatial layout of visual field locations is retinotopic, reflecting the two-dimensional

representation of the visual environment on the retina. There are also continuous tonotopic maps of frequency in auditory cortex and somatotopic maps of the surface of the body in somatosensory cortex.

Cerebral cortical areas that represent the visual field exhibit spatial specificity — a given neuron or local population of neurons encodes information from a particular visual field location. Brissenden *et al.* [1] tested whether fMRI responses in the human cerebellum also have spatial specificity. In their study, subjects were shown groups of line segments in both the left and right sides of the visual field, followed by a blank screen that was displayed for one second (the delay period). Participants were instructed to pay attention to only one side of the visual field and to ignore the line segments on the opposite side, while maintaining their gaze at a central fixation point.

A subset of the line segments were colored red, and subjects attempted to remember the orientations of these segments over the delay period. This type of brief storage of visual information is known as visual working memory. After the delay period, participants indicated whether the orientation of one of the red



bars in a second set of stimuli had changed from the original set or not, thereby revealing how successful they were in remembering the original stimuli.

Brissenden *et al.* [1] recorded fMRI responses during performance of this task and compared trials in which subjects directed their attention towards the left side of the display (ignoring the right side) to trials in which the right side was attended (ignoring the left side). Attention-related responses in the cerebellum displayed an ipsilateral representation of visual space — the left hemisphere primarily represented the left side of visual space, and the right hemisphere represented the right side. Furthermore, within the cerebellum, these spatially-selective responses were localized to lobule VIIb/VIIIa in both sides of the brain.

To further characterize these cerebellar visual field representations, Brissenden *et al.* [1] performed population receptive field mapping [8]. Visual stimuli were systematically presented at a variety of visual field locations while subjects used attention to track the stimuli without moving their eyes. For each voxel — the unit of fMRI analysis, here a cube of tissue approximately 2 x 2 x 2 mm — the visual field location that evoked the maximum response was determined. These results confirmed the previous finding of ipsilateral visual field representations and also demonstrated that a large number of visual field locations are represented in lobule VIIb/VIIIa of the cerebellum.

In addition to characterizing coding of visual spatial locations in the cerebellum, Brissenden *et al.* [1] compared easier trials of the memory task in which subjects were required to memorize the orientation of only one line segment (low memory load) to trials in which subjects were instructed to remember the orientations of four line segments (high memory load). This comparison revealed larger responses for high-load relative to low-load trials (replicating [9]) in a region of the cerebellum that partially overlapped the region that exhibited spatially-selective responses but was also spatially offset within lobule VIIb/VIIIa. Specifically, in both cerebellar hemispheres, the location of the spatial coding region was dorsal and medial to the region that showed

dependence on visual working memory load.

A similar pattern of overlapping yet dissociable regions of representation of visual space and working memory load-dependent responses had previously been described in posterior parietal cortex [10], a finding that was also replicated in the present study. Brissenden *et al.* [1] further measured functional coupling during ‘resting state’ fMRI scans, in which subjects had no specific task to perform, by computing correlations between time series from the cerebellar regions they had identified and those from all cerebral cortical locations. They observed extremely precise patterns of coupling between each of the cerebellar seed regions — the one with visual field representations and the one showing working memory load dependence — and the cerebral cortical regions that functionally corresponded to each of these seed regions.

The findings of Brissenden *et al.* [1] advance our knowledge of cerebellar function and organization by demonstrating a dissociation of regions that encode spatial locations in the visual field and those that represent visual working memory load, and they raise a number of important questions for future research. First, are the visual field representations in the cerebellum organized in the form of continuous topographic maps, as they are in the cerebral cortex, and if so, how many cerebellar maps are there? It is known that the human cerebellum has at least two somatotopic/motor maps of the body [11,12], and the ability to objectively identify visual field maps in individual participants and their spatial relationships with one another would greatly facilitate investigation of the functional specialization of these cerebellar visual field representations.

Second, given that both the cerebellum and multiple cerebral cortical areas contain visual field representations as well as load-dependent working memory signals, what are the unique functional contributions made by the cerebellum and each of the various cerebral cortical areas to spatial attention and working memory?

Third, more research is needed to characterize the load-dependent memory signals described by Brissenden *et al.* [1].

Working memory involves selection of the stimuli to be remembered, encoding of these stimuli into memory, maintenance of the memory, and retrieval. Which of these component processes contribute to the observed load-dependent cerebellar responses? Also, verbal working memory signals have been reported in lobule VIIb of the right side of the cerebellum [13] — is the region with load-dependent responses described by Brissenden *et al.* [1] unique to visual working memory, or do these responses generalize to other forms of memory?

Finally, the surprising finding of dissociable visual field representations and load-dependent memory signals in cerebellum serves as a cautionary tale to ‘corticocentric’ neuroscientists (see [14]). In some cases, investigators sacrifice coverage of the cerebellum in fMRI experiments in order to increase spatial and/or temporal resolution of recordings from the cerebral cortex. Similarly, scientists who primarily visualize fMRI data superimposed on cortical flat maps often ignore the cerebellum in their analyses.

In conclusion, the experiments of Brissenden *et al.* [1] demonstrate previously unknown visual field representations in the cerebellum that are distinct from the region that exhibits load-dependent working memory responses. In addition, there is precise functional coupling between these portions of the cerebellum and corresponding cerebral cortical regions. Together, these findings suggest that the cerebellum should be routinely incorporated in future studies of the neural bases of attention, working memory, and other cognitive functions.

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## Neuroenergetics: Astrocytes Have a Sweet Spot for Glucose

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**Astrocytes are polarized cells that are known to take up glucose while delivering lactate, not glucose, for neuronal use. A new study suggests how astrocytes could facilitate glucose uptake, storage and funneling at energy-requiring sites through a privileged intracellular route.**

Several decades of investigation *in vitro* and *in vivo* have provided strong evidence that astrocytes represent a privileged site of glucose uptake in the central nervous system [1,2]. Furthermore, it was recently shown that astrocytes might be the main source of signal in functional brain imaging techniques that are based on the measurement of glucose utilization using the glucose analog deoxyglucose [3,4]. Astrocytes possess specialized structures called end-feet that are in close contact with cerebral blood vessels. Indeed, most of the surface of cerebral blood vessels is covered by these particular processes [5]. Moreover, the glucose transporter GLUT1 is highly expressed on end-feet-facing blood vessels [6]. Thus, astrocytes are morphologically tuned and ideally positioned to take up glucose as it enters

the brain parenchyma. However, the functional regulation of glucose uptake and its specific intracellular handling within the astrocyte remain partially unknown. A new study by Müller *et al.* [7] in this issue of *Current Biology* sheds light on this question and reveals a surprising feature: astrocytes may have a secret storage site and a specific intracellular distribution network for free glucose.

Like hepatocytes, astrocytes have been known for a long time to have a (small) glucose-containing energy reserve in the form of glycogen [8]. The exact purpose of this limited energy reserve in astrocytes is still debated, but it seems clear that it is mobilized during periods of high neuronal activity through the action of various neuroactive substances and that an energy substrate arising from glycogenolysis is released

by astrocytes, most likely to be used by neurons. Unlike the situation in hepatocytes, however, this released energy substrate is not glucose but lactate. One key biochemical element that determines the capacity of a cell to release glucose is the combined expression of the enzyme glucose-6-phosphatase (G6Pase) and a glucose-6-phosphate translocase (G6PT). In the hepatocyte (Figure 1), the formation of glucose-6-phosphate (G6P) coupled to its translocation and dephosphorylation in the endoplasmic reticulum (ER) by G6PT and G6Pase, respectively, leads to the release of glucose in the bloodstream during periods of fasting by an as yet unknown vesicular mechanism. Up to now, both the translocase and phosphatase, abundantly present in the liver, were not considered of significant importance in the brain. Indeed, the

