Exploring the Role of the Cerebellum in Sensory Anticipation and Timing: Commentary on Tesche and Karhu

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Abstract: The past decade has witnessed a paradigm shift concerning the study of the cerebellum. Results from various studies employing a variety of methodologies suggest that the functional role of this structure is not limited to motor control. The article by Tesche and Karhu appearing in this issue, provides strong evidence that the cerebellum in humans is activated in anticipation of somatosensory events, even when these events do not require overt responses. In their study, the sensory response is observed when the stimuli fail to occur at expected points in time, consistent with the hypothesis that the cerebellum is specialized for representing the temporal relationships between events, motoric or otherwise. Timing and sensory expectancy likely reflect nested hypotheses, and it remains to be seen if one provides a more encompassing yet specific view of cerebellar function. *Hum. Brain Mapping 9:115–118, 2000.*
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Our understanding of the cerebellum has been in a state of upheaval for the past 10 years. In the classic sense described by Kuhn (1970), there has been a paradigm shift regarding the functional role of the cerebellum. With a few notable exceptions [e.g., Watson, 1978], the traditional view of cerebellar function was restricted to an analysis of how this structure contributed to motor control and the acquisition of skilled actions. However, the theoretical perspectives and tools of cognitive neuroscience have made apparent the limitations of dividing neural structures along task domains such as perception, memory, or movement. In parallel with these developments, empirical results, both predicted and serendipitous have indicated that a narrow view of cerebellar function will prove insufficient.

The article appearing in this issue, "Anticipatory Cerebellar Responses During Somatosensory Omission in Man" by Tesche and Karhu [2000] at the Low Temperature Laboratory in Helsinki provides further support to the assault on the traditional view. Using magnetoencephalography (MEG), the researchers compare the neural signals generated in the cortex and cerebellum during the presentation of somatosensory stimuli. The critical finding is that, whereas the response in somatosensory cortex is closely linked to the actual presentation of the stimuli, the cerebellar response is modulated as a function of expectancy and attention. The paper makes significant methodological

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and theoretical contributions in our quest to understand cerebellar function. On the methodological front, Tesche and Karhu demonstrate how MEG can provide a powerful tool for studying the temporal dynamics of neural activity in the cerebellum. Metabolic imaging tools such as PET and fMRI are useful for revealing correlations between neural activity and behavior. However, the poor temporal resolution of these methods limits their analytic power for testing functional hypotheses. Conventional electroencephalography has generally been avoided for studying cerebellar function because of the complex folding of the cerebellar cortex. In this paper and in their previous work, the authors have demonstrated that coherent MEG signals can be obtained from the cerebellum, even if source localization makes it difficult to distinguish between signals arising in the cerebellar cortex and deep nuclei. Moreover, the power of these signals is pronounced in the alpha (6–12 Hz) and gamma range (25–40 Hz), perhaps reflecting activity arising from the climbing and mossy fiber inputs, respectively.

On the theoretical front, the results of this study help identify some of the thorny problems that must be addressed as we seek to develop comprehensive computational accounts of cerebellar function. Converging evidence, obtained with diverse methodologies, has pointed to the need for a more general perspective of cerebellar function. Anatomists have identified pathways in primates between the cerebellum and cortical and subcortical regions that fall outside the traditional motor areas [Haines et al., 1997; Middleton and Strick, 1998; Schmahmann and Pandya, 1997], as students of human evolution have emphasized parallel trends in the expansion of the neocerebellum and prefrontal cortex [Leiner et al., 1986]. Various neurological and psychiatric disorders including autism [Bauman et al., 1997; Courchesne et al., 1994], schizophrenia [Katsetos et al., 1997], dyslexia [Fawcett and Nicolson, 1999], and attention-deficit disorder [Berquin et al., 1998; Mostofsky et al., 1998] have been found to correlate with either cerebellar pathology or physiological abnormalities. Patients with acquired cerebellar disorders have been found to perform poorly on cognitive tasks such as problem solving or verbal retrieval [e.g., Appollonio et al., 1993; Drepper et al., 1999]. Perhaps most provocative, neuroimaging studies have consistently observed task-related activation in the cerebellum even when the motor requirements of the experimental and control tasks have been carefully equated [reviewed in Desmond and Fiez, 1998; but see Beauregard et al., 1997].

These results have inspired the development of various hypotheses concerning cerebellar function. Some of these hypotheses are stated in rather general terms and focus on the interactions of the cerebellum and cortex. For example, it has been proposed that the cerebellum is essential for mental coordination in a manner analogous to how it facilitates motor coordination. Courchesne and Allen [1997] have promoted an attentional view of how such mental coordination might arise. The cerebellum primes activity in extracerebellar systems so that the specific functions of these structures are performed in a rapid and efficient manner. Other hypotheses have focused on processing within the cerebellum, addressing the types of representations that this structure is providing. Two of these are at the heart of the Tesche and Karhu paper: (1) The cerebellum operates as an internal timing system, providing the precise representation of temporal information for motor and nonmotor tasks that require this form of representation [see Ivry, 1996, 1997]. (2) The primary function of the cerebellum is for the acquisition, processing, and utilization of sensory information, with the prominent motor signs associated with cerebellar dysfunction reflecting the disturbed representation of the sensory conditions rather than a loss of control of the motor apparatus [Bower, 1997; Gao et al., 1996].

The work of Tesche and Karhu provides an important step in bringing together these two hypotheses. The fact that salient cerebellar signals are generated during passive stimulation of the finger adds to previous demonstrations regarding the important role of this structure in detecting sensory signals [Blakemore et al., 1999; Gao et al., 1996; but see Weeks et al., 1999]. Even more impressive, the temporal resolution of MEG makes clear that the cerebellar response is not strictly sensory in that it does not require the delivery of an actual stimulus. Prominent activity is observed just prior to the delivery of an anticipated stimulus, and is also found when an expected stimulus is omitted. The cerebellar response appears to be best characterized as a detector of change or deviation in the sequence of sensory events. For example, not only is the alpha signal stronger in anticipation of the somatosensory stimuli, but the response is much stronger for the first stimulus following an omission compared to that obtained in response to predictable stimuli. This pattern is strikingly different from that recorded in somatosensory cortex. In S1, the signal is strongest following the stimuli, and there is no difference in the amplitude or timing of these responses between conditions in which the stimuli are expected and regular compared to when the stimulation resumes following

an omission. Tesche and Karhu thus demonstrate that, whereas the signal in S1 is essentially reactive, the cerebellar response seems to be proactive, related to the expectancy of the sensory signal.

Although these results are in accord with the view that cerebellar activity is related to sensory expectancy, even when no movement is produced or required, the results also emphasize the timing capabilities of the cerebellum. The stimuli in this study are presented periodically with the interstimulus interval set to 500 ms in the main set of experiments. The spectral analyses indicate that, under these conditions, the cerebellar activity is not only predictive of a forthcoming event, but the response is closely linked to the time at which these events are expected. As can be seen in Figure 4B and C [Tesche and Karhu, 2000], the cerebellar response in the epoch surrounding an omitted stimulus is similar to that observed to the standard stimuli.

Interestingly, the cerebellar gamma response appears to rise in advance of the time at which the somatosensory signal is expected. It is tempting to infer that this gamma activity is the MEG correlate of an efference copy command, a result that would be consistent with a link of the gamma range signal to mossy fiber activity. The cerebellar gamma response appears to rise in advance of the time at which the somatosensory signal is expected. We might imagine that a similar predictive model of sensory events would arise during motor performance. We anticipate the sensory consequences of our movements, not in a generic manner, but at a specific point in time. When either the sensory signals or their timing are unexpected, an error is detected and corrective actions can be rapidly implemented. Models of efference copy make clear that the boundary between what is sensory and what is motor can be artificial. It is possible that an error signal could be transmitted to other neural structures that generate the corrective action. Nonetheless, the output from the cerebellar nuclei is well suited to be involved in the control of the actions themselves.

Although this study provides compelling evidence for both the timing and sensory expectancy accounts of cerebellar function, the relationship between these two theories remains difficult to untangle. Do these theories form a nested relationship, with one theory providing a more encompassing view? Or are the representations of temporal relations and sensory predictions distinct functions of the cerebellum that overlap in part? One might suppose that prediction provides the more inclusive characterization, with the timing of sensory signals one manifestation of this general capacity. Alternatively, timing might provide a more specific characterization of cerebellar function,

dictating not only the conditions in which the cerebellum should be engaged, but also identifying those conditions in which the cerebellum will not be involved in sensory expectancy.

Sensory prediction is a ubiquitous property of cognition. In all of our activities, we are generating expectancies of forthcoming events. In some of these cases, our expectancies come with precise temporal specification. When walking down a flight of stairs, we expect to come in contact with the next tread at a particular point in time during the leg extension. In other situations, we generate predictions that do not have this temporal specificity. When calling someone on the phone, we expect that someone (or a machine) will answer. Or in stirring a pudding, I expect the mixture to begin to boil. It is not clear that in either of these latter two situations that my prediction would include a precise representation of the moment at which the expected sensory event would occur. The timing hypothesis would predict that the cerebellum would make little contribution to these forms of prediction because they do not demand the precise timing. However, a model emphasizing sensory expectancy in general would not distinguish between these different situations.

The methods of Tesche and Karhu may be limited for developing the strongest tests to compare the sensory prediction and timing hypotheses. One would like an experimental task in which sensory expectation is violated in two different ways: Violations that are predictive in time and violations that lack temporal specificity. The latter could be accomplished by using nonperiodic stimuli. However, it would no longer be possible to precisely identify the point in time at which a stimulus was omitted and thus the time-locking required for measuring evoked responses would be lost. PET or fMRI might be more appropriate for this sort of comparison because, by their nature, they average neural activity over extended epochs. Another possibility, alluded to in this article, is to look at how the response to anticipated responses changes as a function of the time over which the predictions are generated. It is likely that the extent over which the cerebellum can represent the temporal interval between events is limited, and thus one would expect a reduced response from this structure with long interstimulus intervals. A similar constraint may exist for a general predictive system, although this has been ignored in the studies to date.

We have now passed the point of debating whether cerebellar function is restricted to motor control. It is clear that the cerebellum is engaged in the course of nonmotor tasks. As exemplified by the study of Tesche

and Karhu, it is now necessary to develop and test functional and computational hypotheses of how the cerebellum contributes to these tasks. In this manner, we can begin to ask if general theories will prove sufficient to provide a comprehensive account of the broad range of cerebellar function or whether theoretical models will develop as they have for the cerebrum, and we will view the cerebellum as a network of specialized subregions.

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