Letters to the Editor

Evaluating the role of the cerebellum in temporal processing: beware of the null hypothesis

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The cerebellum has been characterized as an internal timing system, providing representations of the timing of salient events spanning hundreds of milliseconds. Harrington and colleagues (2004) challenge this idea, reporting that patients with focal cerebellar lesions from stroke perform similarly to control participants on time production and perception tasks. We note three problems with their conclusion. First, it rests on the acceptance of the null hypothesis. Secondly, a subgroup of their patients, i.e. those with lesions of more superior regions of the cerebellum, were impaired on both tasks, although the deficit on the perception task was only marginally significant. Thirdly, the failure to find a marked time perception deficit is actually consistent with previous results (Ivry and Keele, 1989) and may reflect reliance on the intact half of the cerebellum or the integration of timing signals from the two halves of the cerebellum.

The neural regions involved in temporal processing for tasks spanning hundreds of milliseconds have been the subject of considerable debate in the neuropsychological literature. This debate stems from the fact that, across a number of papers, similar patterns of deficits have been reported in disparate patient groups. For example, poor acuity on a time discrimination task has been reported in patients with lesions of the cerebellum (Ivry and Keele, 1989; Nichelli *et al*., 1996; Mangels *et al*., 1998), right cerebral cortex (Harrington *et al*., 1998*b*) and Parkinson's disease (Ivry and Keele, 1989; Pastor *et al*., 1992; Harrington *et al*., 1998*a*). Moreover, at least for the studies in which cerebellar (Ivry and Keele, 1989; Spencer *et al*., 2003) and Parkinson's disease (Ivry and Keele, 1989; O'Boyle *et al*., 1996; Harrington *et al*., 1998*a*) patients were tested, a corresponding increase in temporal variability is observed on a time production task.

Observation of similar deficits across different patient groups could indicate that temporal information is represented by dynamic interactions across a neural network. Alternatively, these tasks involve various component operations and the common pattern of impairments may reflect the inadequacy of our analytical tools for isolating a particular function. For example, judging if a stimulus is short or long requires an accurate representation of stimulus duration, sustained attention, and decision processes that compare the temporal representation with an internalized reference memory of what constitutes 'short' and 'long'.

The interpretation of impaired performance on a single task is ambiguous, given the engagement of various component operations. A functional characterization of a neural system requires the integration of evidence from a wide range of tasks. This approach has been fundamental to the hypothesis that the cerebellum can be characterized as an internal timing system. In brief, this hypothesis states that the cerebellum provides representations of the precise timing of salient events, the onset and offset of movements or the duration of a stimulus. This hypothesis provides a parsimonious account of the functional contribution of the cerebellum to disparate tasks, such as throwing, eyeblink conditioning, vestibulo-ocular adaptation, rhythmic anticipation and speech production and perception (reviewed in Ivry *et al*., 2002).

Harrington and colleagues (2004) report a new neuropsychological study that would appear to challenge the cerebellar timing hypothesis. Twenty-one patients with focal cerebellar lesions due to stroke were tested on time production and perception tasks. As a group, the patients' performance did not differ statistically from that of matched control participants. These results would appear to constitute a failure to replicate, given that previous studies have reported that patients with cerebellar lesions are impaired on essentially identical tasks (Ivry *et al*., 1988; Ivry and Keele, 1989; Spencer *et al*., 2003). To account for this, the authors suggest that results from previous studies were exaggerated by the inclusion of patients with cerebellar degeneration, and functional deficits in such patients may reflect the abnormal operation of extracerebellar structures.

We believe that the dismissal of the cerebellar timing hypothesis is not warranted; on the contrary, the results of Harrington and colleagues help identify subregions within the cerebellum that are essential for these particular tasks. The authors divide their patients into two subgroups. In one group, the lesions were restricted to inferior aspects of the

cerebellum, a region encompassing the inferior semilunar, gracile and biventer lobules and the tonsils. In the other, the lesions were more superior and extended into the superior semilunar, posterior and anterior quadrangular lobules, and/or the central lobule. Thus, the inferior/superior division is between crus I and crus II (Schmahmann *et al*., 2000).

Notably, the patients in the superior group were impaired on both the temporal perception and production tasks. On the tapping task, these patients were more variable than their control group. This increase in variability was associated with greater noise in central planning processes, or what has been called the 'clock' component, rather than with added noise in processes associated with motor implementation. This result is consistent with previous reports of patients with focal lesions, although previous work had suggested that increased clock variability was restricted to patients with lesions of lateral neocerebellum (Ivry *et al*., 1988). On the perception task, the mean difference threshold for the patients with superior lesions was elevated, although the comparison with the control group only approached significance ($P = 0.07$).

As outlined in their Introduction, one of the goals of the study of Harrington and colleagues was to determine if 'different regions within the cerebellum were more crucial for temporal processing than others' (p. 562). Their results would suggest that this is true. Lesions restricted to inferior aspects of the cerebellum had no effect on either task. In contrast, lesions of the superior aspects led to the dual pattern of impairment that the authors take as the signature of a neural system associated with temporal processing. Of course, this interpretation is based on viewing the marginally significant effect ($P = 0.07$) as indicative of a deficit. This view seems reasonable when coupled with previous reports of elevated perceptual thresholds on similar time perception tasks in patients with cerebellar lesions, and with the consistent finding of increased timing variability on the production task. At the very least, it is premature to accept the null hypothesis (no impairment) on the basis of a marginally significant result that is not in accord with previous findings (see note at end of letter).

Even if we accept the null hypothesis, the results of Harrington and colleagues are actually in agreement with the initial study of perceptual timing in patients with focal cerebellar lesions (Ivry and Keele, 1989). Deficits on the time perception task were most pronounced in patients with cerebellar atrophy or in patients with acute unilateral lesions (i.e. within 8 months of their neurological incident). Patients with chronic focal lesions tend to perform similar to control participants (discussed in Ivry *et al*., 1988). The mean number of years after stroke for the patients in the study of Harrington and colleagues study was 3.6, indicating that most of these patients were tested in a chronic state.

There are a number of reasons why patients with chronic lesions might perform within the normal range. First, recovery from cerebellar lesions is striking, suggesting that spared tissue might serve a compensatory function. Secondly, assuming that sensory inputs are projected bilaterally to the cerebellum, the unaffected cerebellar hemisphere in patients with unilateral lesions might be sufficient to provide the requisite temporal representation. Four patients in the study of Harrington and colleagues did have bilateral damage. However, these lesions primarily affected the inferior cerebellum.

A more subtle hypothesis is based on the idea that the cerebellum is best conceptualized as forming a system of multiple timing elements rather than a single amodal 'clock' (Ivry, 1996). This hypothesis assumes that specific timing elements within the cerebellum are recruited in a task-specific manner. For example, during unimanual finger tapping, ipsilateral regions of the cerebellar cortex generate the requisite timing signals. In this way, patients with unilateral lesions are selectively impaired when tapping with their ipsilesional hand. Interestingly, the movements become less variable during bimanual tapping (Franz *et al*., 1996). While this might reflect reliance on spared tissue, an alternative is that each half of the cerebellum generates the timing signals for the ipsilateral hand and that these signals are integrated to maintain temporal coupling. A statistical consequence of a simple integration process is reduced temporal variability (Ivry and Richardson, 2002). This idea can also account for the normal performance of patients with unilateral cerebellar lesion on the time perception task: the noisy temporal representation generated within the damaged half of the cerebellum is combined with the normal representation generated by the spared half. Quantitatively, the integration model predicts that the increase in overall variability would be minimal even if the representation from the damaged side is twice as variable as that from the intact side. Thus, this model predicts that increases in temporal acuity will be minimal in patients with unilateral lesions.

Harrington and colleagues provide the most thorough analysis to date of how different regions of the cerebellum are associated with performance on time production and perception tasks.

Rather than accept the null hypothesis because one result only approached a conventional statistical threshold, we believe their results suggest that, for these tasks, impaired performance is associated with lesions of the more superior aspects of the cerebellum. Impaired eyeblink conditioning is also selectively associated with superior cerebellar damage (Yeo and Hesslow, 1998; Gerwig *et al*., 2003), while lesions of the cerebellar cortex abolish the adaptive timing for this form of sensorimotor learning (Perrett *et al*., 1993; Koekkoek *et al*., 2003). It is possible that timing functions of the cerebellum are restricted to superior subregions, such as lobule VI and crus I. However, other regions of the cerebellum may also be important for temporal processing, but in different task domains.

Note

The tasks used by Harrington and colleagues are identical to that used in previous duration discrimination studies involving patients with cerebellar lesions, the one difference being the duration of the standard interval. Given that the standard deviation is proportional to duration, it is necessary to use the

coefficient of variation (CV = SD/mean) to compare absolute performance across studies. Interestingly, the patients with superior lesions in the study of Harrington and colleagues perform much worse than the patients tested in previous work. The CV for in the study of Harrington and colleagues is 0.17 when the standard duration was 300 ms and 0.13 when the standard was 600 ms. In the studies of Ivry and colleagues (Ivry and Keele, 1989; Ivry *et al*., 1988; Spencer *et al*., 2003), the CV has consistently been around 0.10. However, the controls in the study of Harrington and colleagues also performed worse than the controls in previous work (average of 0.11 compared with 0.7).

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