Is the cerebellum involved in learning and cognition?

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Current studies are examining whether the cerebellum has a functional role in non-motor tasks using both behavioral and physiological methods with animals, and computer simulations of a classical conditioning task. Cerebellar involvement in cognition has been assessed in studies with healthy and neurologically impaired humans. The results have led to new hypotheses that are providing testable predictions about the role of the cerebellum in perception, attention, and other cognitive functions.

Introduction

The cerebellum has traditionally been considered part of the motor system, associated with the control of balance and fine motor coordination. New results suggest that the computational properties of the cerebellum extend beyond the domain of motor control and may be important in learning and other aspects of cognition. This review is intended to provide a sample of these exciting developments. The recent computational investigations of the role of the cerebellum in motor control are not covered (see [1,2•,3,4]).

Behavioral studies of classical conditioning

Ten years ago, the cerebellum was hypothesized to be the critical site for the formation and storage of learned responses in a classical conditioning task study with mammals [5]. In this preparation, rabbits learned to make a conditioned nictitating membrane response following repeated pairings of a neutral stimulus such as a tone, with an aversive unconditioned stimulus such as an air-puff. Numerous studies have demonstrated that cerebellar lesions produce a deficit in the learned conditioned response (CR), while sparing the unconditioned response (UR) (for reviews, see [6,7••]). That the UR is unimpaired suggests that cerebellar lesions are disrupting learning processes and not motor functions.

Recent studies have sought to identify the essential neuroanatomical components involved in this associative process. One debate has centered on the relative importance of the cerebellar cortex and nuclei. The former is the primary site of integration of inputs from extracerebellar sources; the latter are the source of output from the cerebellum. Yeo [7••] has recently summarized a careful analysis of the effects of different cortical lesions, and provides strong evidence that large cortical lesions are sufficient to massively impair or prevent learning in naive animals as well as result in a selective and near complete abolition of the CR in trained animals.

Another line of research has sought to identify the sources of the conditioned stimulus (CS) and unconditioned stimulus (US). Theoretical models have postulated that the US is conveyed via the olivocerebello pathway whereas the CS is relayed via pontine nuclei [8,9]. These hypotheses have recently received strong experimental support. CRs were obtained by direct electrical stimulation of pontine and olivary fibers [10,11]. There was also training with electrical stimulation of pontine nuclei as the CS transferred to a tone CS [12]. With electrical stimuli, learning was only observed when pontine stimulation preceded olivary stimulation, and was not obtained with the reverse pairing (e.g. backward conditioning). Moreover, activity in inferior olive neurons in response to the US diminished during the course of training [13], a result that is in accord with the hypothesis that olivary input constitutes an error signal [14], (for contradictory evidence, see [15]).

Ito [16] has proposed that the cellular mechanism for cerebellar learning involves a long-term reduction in the responsiveness of Purkinje cells. Long-term depression (LTD) has been induced using both *in vivo* and *in vitro* preparations [16] with stimulation conditions that are unlikely to be generated in a natural environment. Contrary to the LTD hypothesis, an increase in the excitability of Purkinje cells was observed in cerebellar slices extracted from rabbits who had been trained in the nictitating membrane task [17], (but see R Thompson, this issue, pp 203–208). The validity of the LTD hypothesis should become clearer as more laboratories begin to address the cellular basis of classical conditioning.

The hypothesis that the cerebellum plays a critical role in learning has been challenged on a couple of fronts. First, Welsh and Harvey [18] have proposed that cerebellar lesions produce a performance (i.e. motor) deficit

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Abbreviations

CR—conditioned response; CS—conditioned stimulus; CT—computer tomography; LTD—long-term depression; MRI—magnetic resonance imaging; PET—positron emission tomography; UR—unconditioned response; US—unconditioned stimulus.

rather than a learning one. CRs were observed in animals with extensive cerebellar lesions although these responses were irregular, of small amplitude, and frequently began after the time of the US. More importantly, URs were also affected by the lesions, leading the authors to suggest that cerebellar lesions produce changes in the tonic state of brainstem nuclei that are part of the relevant motor pathways. Lesions of the cerebellar cortex, however, yielded a reduction (or elimination) of CRs and an increase in the amplitude of URs. It would seem that a performance hypothesis should predict that any lesion which reduces the CR should have a similar effect on the UR [7••], a prediction that is not supported. In addition, CRs were present on a large percentage of the trials for only a subset of the animals and it is unclear from the histological reports whether the lesions were complete in these animals.

The second challenge comes from Kelly, Zuo, and Bloedel [19] who claim to have obtained classical conditioning of the nictitating membrane response in decerebrate–decerebellate rabbits. They report that the kinematics of the CRs approximate those of intact animals and, in concurrence with Welsh and Harvey [18], argue that the reduction and/or elimination of CRs in previous studies was an artifact of tonic changes created by cerebellar lesions. A performance artifact was not present in the decerebrate animals because the cortical lesions offset the tonic changes imposed by cerebellar lesions.

There are several reasons for questioning whether these provocative results pose a serious challenge to the learning hypothesis. First, Kelly et al. [19] used a scoring procedure which may have mistakenly led to spontaneous eyeblinks being recorded as CRs [20•]. Second, the training procedure used by Kelly et al. was highly atypical. For example, whereas the inter-trial interval during eyeblink conditioning is generally 30 s, Kelly et al. used a 9 s interval. Nordholm, Lavond, and Thompson [20•] have recently shown that intact animals fail to develop CRs with 9 s inter-trial intervals. This null result was consistent across a range of stimulus conditions. Thus, the authors conclude that the responses observed by Kelly et al. [19] in decerebrate-decerebellate animals are not true CRs, but rather represent a different, perhaps simpler, form of learning such as pseudoconditioning or sensitization (see also [7••]).

Computational models of the cerebellar role in learning

Models of the nictitating membrane task must represent the temporal relationship between the CS and US and the topography of the CRs. Learning in this task is not simply a matter of associating two coactive stimuli. Rather, it is only adaptive if the association is made between an US and a preceding CS, and if the CR occurs prior to the onset of the aversive second stimulus.

Three groups of researchers have presented models that can simulate learning in the nictitating membrane task. While there are many similarities between the models, one important difference is how they represent the CS.

In each model, the selected CS representation can be viewed as a potential real-time neural mechanism. Bartha, Thompson, and Gluck [21] represent the CS as a set of low frequency oscillators whose output varies sinusoidally for the duration of the CS. They propose that these oscillatory patterns may be generated by pre-cerebellar structures or between pre-cerebellar and cerebellar structures. The low frequency property of the oscillators effectively increases the extent of the CR, thus enabling it to precede the US (and extend beyond as well).

Grossberg and Schmajuk [22] present a related model in which the CS activates a population of input units. The units are not oscillators, but rather differ from one another in their activation functions. Some become maximally active quickly, while others turn on more slowly. The varying activation rates effectively extend the CS over time and allow learning to be greatest for those units that are most active at the onset of the US.

In the model of Desmond and Moore [23], stimulus events tap into a cascading series of delay lines. Each delay line is active for a fixed amount of time and triggers the onset of the next delay line after a brief period. In this manner, a representation of the CS is prolonged, but the units that are active change over time. Turning on the US bolsters the output from currently active delay units to drive the CR.

In developing these models, the need for a mechanism that could represent the temporal interval between the CS and US was made explicit. Indeed, in the modelling work, the emphasis has shifted from asking where is the critical site of plasticity to what are the essential computations for the formation of this type of memory. Keele and Ivry [24••] have argued that the cerebellum is critical in the acquisition and maintenance of the CR in the nictitating membrane task because this neural system is uniquely capable of performing the temporal computations required for this task.

The modelling work should lead to experimental explorations of the physiological viability of different real-time mechanisms. In addition, it has led to some interesting behavioral predictions. In the Desmond and Moore model [23], delay lines become activated by any stimulus change, be it the onset or offset of an input signal. Given this assumption, the model can also learn in a trace-conditioning paradigm where the CS terminates prior to the onset of the US. Desmond and Moore noted that the model creates two representations of the CS in trace conditioning: one activated by the CS onset and one activated by the CS offset. This led them to predict that, if the CS–US interval was shifted after trace training, the animal should exhibit two distinct CRs, one coupled to each representation of the CS. This is exactly what was observed in trace conditioning of the nictitating membrane response in rabbits [25•].

The cerebellum and cognition

The cerebellum is extensively connected with associative areas of the cerebral cortex. These anatomical re-

sults have fueled speculation that the cerebellum may be involved in non-motor functions [26]. Moreover, it has been argued that there was a parallel expansion of the neocerebellum and cerebral association areas during the course of phylogenetic evolution [27,28]. Leiner et al. [27] assume that the increase in size in both structures was a necessary prerequisite for the advanced information processing capability of primates and other mammalian species.

A different source of intriguing anatomical evidence has come from neuroimaging studies of patients with autism. The deficits in this disease are severe and can be seen in social, language, and cognitive functioning. Courchesne [29•] has reviewed a number of studies in which autistic patients underwent either magnetic resonance imaging (MRI) or computer tomography (CT) testing. The most consistent site of pathology was the neocerebellum and, in most studies, the only abnormalities were found in the cerebellum. Moreover, Purkinje cell loss has been observed in the cerebellar hemispheres in ten out of ten postmortem case studies of autistic individuals [29•].

Other studies do not support the hypothesis that autism is correlated with cerebellar pathology. In a recent study, cerebellar abnormalities were not observed in the MRI scans of 15 autistic children [30]. Normal metabolic functioning was also reported in a positron emission tomography (PET) study of autism [31]. At least two possibilities exist for these negative results: first, there may be very distinct pathologies associated with different forms of autism; and second, poor resolution due to the thickness of the imaged slices may have obscured small regions of pathology [29•].

The preceding evidence is anatomical. What is the functional role of the cerebellum in non-motor tasks? Based on his observations of autistic symptoms, Courchesne [29•] suggests that the cerebellum may play a role in the allocation of attention. Leiner et al. [27,28] provide a less specific hypothesis. They propose that due to its widespread pattern of connectivity, the cerebellum improves the efficiency of communication between different cortical areas. Rigorous tests of these hypotheses have yet to be conducted.

Nonetheless, there are some provocative results that implicate the cerebellum in tasks that have no obvious motor requirements (for an early review of related evidence, see [32]). Three studies have reported that patients with cerebellar lesions are impaired on various neuropsychological assessment batteries [33–35], including tests of verbal IQ, spatial reasoning, and associative (visual-verbal) learning. Interestingly, the patients were generally not impaired on memory subtests.

PET scan studies with healthy adults have revealed activation of cerebellar regions that do not appear to be tied to motor responses. In one study, blood flow was measured during three conditions: rest, silent counting, and mental practice of tennis strokes [36]. Whereas no blood flow differences between conditions were found in focal cortical areas, blood flow increased significantly in the cerebellum during both the silent counting and mental practice tasks. Significant activation of the cerebel-

lum has also been reported during a task in which subjects had to generate a verb associated with a noun (e.g. ball–throw) [37]. The increase in cerebellar metabolism was still evident even when the activation due to speaking was removed.

The studies reviewed in the preceding paragraphs suggest an involvement of the cerebellum in non-motor tasks. There is little discussion as to the specific role of the cerebellum in these tasks, however. Keele and Ivry [24••] offer a specific functional hypothesis in proposing that the cerebellum operates as an internal timing mechanism that is invoked for all tasks which require precise temporal computations. This hypothesis can account for many of the movement disorders observed following cerebellar lesions. For example, hypermetria results from the failure to activate antagonist muscles at the appropriate time [38]. The hypothesis can also account for the role of the cerebellum in conditioning of the nictitating membrane response given the temporal requirements of this task. More importantly, the hypothesis provides some testable predictions about the role of the cerebellum in perceptual tasks that require precise timing. Ivry and Keele [39] report that patients with cerebellar lesions are impaired in judging the duration between two auditory tones. More recently, the timing hypothesis has been supported in experiments showing that cerebellar patients are impaired in judging the velocity of moving stimuli [40] and regulating temporal aspects of speech sounds [41].

Conclusions

The relegation of the cerebellum to the motor system has been challenged in recent years as researchers have investigated the role of this structure in learning and, more recently, in cognitive functions. The impetus for these ideas has been generated in the spirit of an interdisciplinary cognitive neuroscience, embracing behavioral research with normal and neurologically impaired humans, in vivo and in vitro physiological studies, and computer models. These new hypotheses are clearly controversial, and for the most part, a functional role for the cerebellum in non-motor tasks has not been well specified. Nonetheless, the hypotheses should prove useful in generating tests which will lead to a more explicit understanding of the role of the cerebellum.

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