How Might the Cerebellum Participate in Motor Control, if Life Without One is Possible?

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The cerebellum has long been considered an important motor control structure, but there are reports in the literature of people who have led a relatively normal life without a cerebellum. Such cases of cerebellar agenesis are rare, but it is clear that patients (e.g. HC,[1] & HK[2]) with only a rudimentary cerebellum can lead an independent life and possess the motor skills required to maintain employment (a manual labourer in the case of HC and work within a electronics workshop in the case of HK). These details of adequate motor performance, however, are incompatible with the 'myth' that suggests one can possess normal motor functions without a cerebellum. His early development is uncertain but in later life, HC is said to have exhibited slow/slurred speech, a squint and problems with gait, although as Lemon and Edgley[3] point out, it is difficult to conclude whether these problems were due to cerebellum agenesis or just old age. Like HC, HK is also reported to have problems with speech and gait, together with deficits in motor coordination and learning, and possibly intellect. Nonetheless, cerebellar agenesis appears compatible with leading a relatively 'simple' life.[3] Given these details, what might be the irreplaceable functions that the cerebellum normally contributes to motor control? Over the years, theories of cerebellar function have largely involved its role in motor coordination, motor learning or motor timing.

The cerebellum participates in motor co-ordination

Damage to the adult cerebellum provides strong clues as to its function, unconfounded by the quite dramatic compensation that appears possible if the damage is in early development. For over 200 years it has been known that lesions of the cerebellum impair movement and coordination. In 1891, Luciani published his monograph on the cerebellum and formulated his triad of cerebellar symptoms, which include: atonia (loss of muscle tone), asthenia (loss of muscle strength) and astasia (loss of movement continuity). To account for additional observations he added ataxia, or poor movement coordination.[4] In healthy people, normal movements require the coordination in both time and in strength of contraction of agonist and antagonist muscles at different joints in order for movement to have a smooth trajectory and to smoothly brake at the desired endpoint. In patients with cerebellar lesions, movements have an irregular course, consisting of continuous over-shooting, over-correcting and then over-shooting again around the intended trajectory (as evident in the finger-to-nose test). The cerebellum is therefore thought to be an important structure in coordinating the joints of different limbs, and coordinating between the eye and hand in various manual tasks and during gait. Miall and co-workers[5] provided direct evidence from functional imaging of the brain that the cerebellum supports motor coordination in an eye-hand tracking task when subjects were instructed to follow a moving target with their eyes while simultaneously moving a joystick to control a cursor. Areas in the lateral hemispheres and in the vermis that are concerned with the independent control of hand and eye, respectively, were modulated by the degree of timed coordination between the hand and eye. Additional studies showed learning related changes in these same regions of the cerebellum as participants became familiar with this difficult motor task over a week of practice.[6]

While a person with cerebellar pathology will produce movements slowly and erratically, and with many mid-course corrections, they are still able to initiate movements and decide which movements to execute. Thus, the cerebellum would appear not to initiate movements, or to

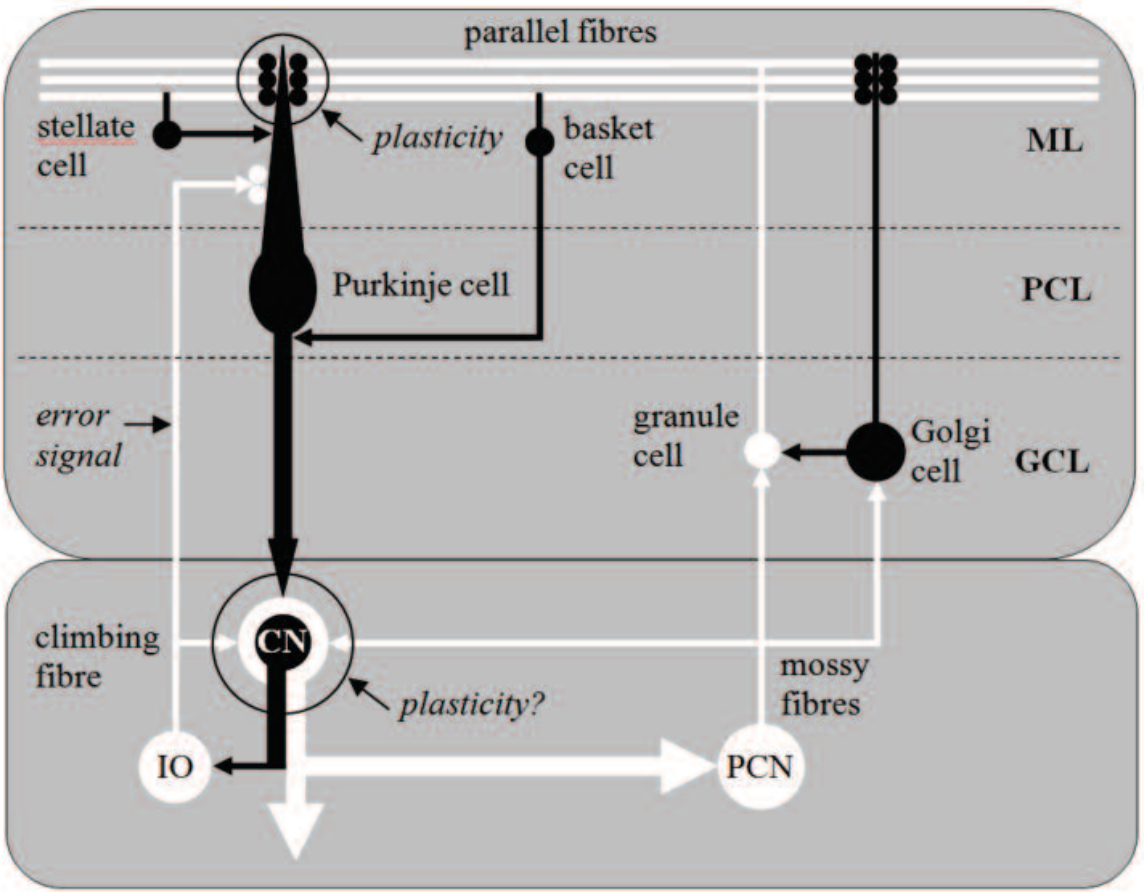

Figure 1: A schematic diagram of the main circuits and interneurones in the cerebellar cortex (after Voogd and Glickstein [1998]. Redrawn by authors). Black cells and arrows make inhibitory connections, white cells and arrows make excitatory connections. ML, molecular layer; PCL, Purkinje cell layer; GCL, granule cell layer; CN, cerebellar nuclei; IO, inferior olive; PCN, precerebellar neurones.

compute which movements to execute, but rather to make on-line adjustments to the form of a movement. Supporting this view is the finding that cerebellar patients exhibit problems making adjustments of eye-hand coordination in throwing while adapting to seeing the world through laterally displacing prisms.[7,8] Studies of cerebellar function that suggest it helps to re-calibrate movement commands are based on the idea of the cerebellum as a 'error-detecting' mechanism. This view is assumed by models of the cerebellum by Marr[9] and Albus,[10] which proposed that the cerebellum is a structure important for motor skill learning, adapting motor commands over repeated experience of an action in order to reduce the performance errors. The details of Marr's theory has been shown to be wrong, but the principles of both models are still thought to be largely correct, and the Marr-Albus-Ito view of the cerebellum dominates all others.[11]

The cerebellum participates in motor learning

The organised structure of the cerebellar cortex has made it a fertile ground for developing theories of cerebellar function. Marr[9] first proposed that the cerebellum is a device for learning to associate information encoded by the two main excitatory inputs to the cerebellar cortex: the mossy fibres and the climbing fibres, which together encode the sensory context of the movement (See Figure 1).

The climbing fibres appear to act as an error-detecting device during the learning of a motor task. This idea was demonstrated in a classic paper by Gilbert and Thach,[12] who recorded activity directly from Purkinje cells in monkeys as they learned an arm movement task, and showed increased complex spike activity during the learning phase. The complex spikes in Purkinje cells are known to reliably indicate activity of climbing fibre inputs which originate in the inferior olive of the brainstem. There are now many studies broadly in agreement with Gilbert & Thach's findings, but it has been difficult to nail down exactly what the climbing fibre activity encodes. The inferior olivary cells that are the source of the climbing fibres fire infrequently, and this infrequent but powerful input to the cerebellar cortex can only record the occurrence of an error, or of an unexpected sensory event,[13] rather than the magnitude of the error. It is also evident that the Marr-Albus-Ito theory that proposed that the site of plasticity was at the synapse between the parallel fibres and Purkinje cells is only part of the story, and plasticity is likely at several other points, especially at the synapse between Purkinje cells and the cerebellar nuclei (See Figure 1). The functional impact of this complexity is still unclear.

Models of motor control also capture the idea that the cerebellum is a learning machine which supports the adaptive plasticity needed for the emergence of automatised motor skills. These models typically contain three basic elements (a) internal models that either predict the sensory consequences of our actions (forward models), or predict the movements necessary to achieve a goal (inverse models), (b) a comparator that detects mismatches between predicted and actual output by comparing internal and external feedback signals, and (c) a learning process that uses error information to modify internal models so that movements become fast and accurate. Evidence that the cerebellum can predicatively update a representation of the current status of the peripheral motor system (i.e. central state estimate) is provided by work with transcranial magnetic stimulation (TMS): a non-invasive method that depolarises neurons in the brain. For example, Miall and colleagues[15] disrupted the cerebellum during a task in which subject's were required to point to a previously observed target. Errors in the initial direction and in the final position were consistent with the reaching movements being planned from an estimated position of the hand, which was about 140 msec out of date. In short, internals models can help to explain the clumsiness observed in cerebellar

patients, and the problems they have in coordinating actions.

The cerebellum participates in motor timing

The hypothesis that the cerebellum computes timing requirements for motor performance has been advocated by Keele and Ivry[16]: a view that is supported by numerous findings. In one particular study,[17] the authors asked cerebellar patients to maintain a simple rhythm in one task, and to discriminate between two different interval durations in another. Compared to normal controls, patients were found to be impaired in both tasks; producing temporal intervals that were more variable, and making temporal judgments that were less accurate. Relating the patients' lesion data with their performance data also revealed that medial cerebellar damage impairs motor execution, while lateral cerebellar damage impairs the internal timing of responses.[18] Interestingly, it is damage to a localised region within lateral portions of the cerebellum (lobule HVI) that disrupt the timing of a conditioned eye-blink response in rabbits[19], and also in humans[20], including patient HK[2]. The eye-blink conditioning paradigm, which is an associative learning task in which the challenge is to learn the predictive cue, and the moment at which to blink, demonstrates that the cerebellum is capable of motor learning, but it also demonstrates the role of this structure in motor timing.

Further support for the hypothesis that the cerebellum is critical for motor timing is revealed by studies of fast single-joint movements with simultaneous electromyographic (EMG) recordings in cerebellar patients. Normally, these movements are characterised by a triphasic pattern of muscle activity, firstly in the agonist muscle providing a launching force, followed by a second burst in the antagonist muscle providing a braking force, followed by a second burst in the agonist muscle providing a clamping force.[21] Manto and others have identified deficits in the timing, duration and amplitude of sequential bursts of EMG activity during rapid movements in cerebellar patients when inertial loading is artificially increased.[22,23]

Despite those patient studies that support a pure timing function for the cerebellum, there is little evidence that it behaves like a timekeeper or 'clock', as suggested by the work of Lamarre and Mercier[24] and Llinas and Yarom[25] on the basis of clock-like periodic cell discharges in the inferior olive. Indeed, Keating and Thatch[26,27] failed to observe a clock-like timing signal in the discharge patterns of cells in the deep cerebellar nuclei or Purkinje cells, which were found to fire aperiodically. Instead, the inferior olive may help to organize movement in time via the synchronized firing of cell ensembles that allow the use of individual muscles.[28]

Conclusion

The cerebellum integrates sensory information from many different parts of the brain to help correct mismatches between predicted and actual movements, and can change its output at the correct time to ensure that movements are smooth and error-free. To ensure these operations are optimised, the cerebellum would have to correctly predict the relationship between sensory stimuli during motor learning performance. There is increasing evidence that predictive control is a major function of the cerebellum. Prediction is critically important in motor control because actions are often required to be performed rapidly, despite relatively slow transmission of sensory and motor signals throughout the CNS. As an example, while typing this manuscript my finger moves to each key on the keyboard within perhaps 400 ms – and much faster than that for a skilled typist who would perform perhaps 8 keystrokes per second (120 ms). And yet, the visual signals reach primary visual cortex with a delay of at least this size, and delays in further visual processing, in conduction delays in the corticospinal tracts and motor nerves, and in neuromuscular coupling means that the fingers cannot be guided by sensory signals but must be predicatively controlled. Short term predictions about the current state of the peripheral motor system can help overcome this difficulty, as corrections and updating of the motor commands can be based on these internal state estimates, rather than on sensory feedback. Failure of these predictions would lead to errors in performance similar to the motor symptoms of cerebellar patients, including hypermetria, intention tremor and loss of coordinated action across the joints. Predictions must be learnt based on past experience, and must be time-sensitive. Hence prediction might be the overall function of the cerebellum. It is perhaps this ability that is dysfunctional in patients with cerebellar damage. It is possible but not yet proven, that the cerebellum might also contribute predictive information to other non-motor processes. For example, there is evidence of disrupted executive function and planning, of linguistic processing, and even of sympathetic functions that might be normally assisted by the cerebellum.[29] ◆

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