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Motor aging results from cerebellar neuron death

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As we age, movements become slower and inconsistent and require more attention. These hallmarks of aging suggest a switch from predictive to reactive motor control. Here I examine evidence supporting the hypothesis that motor aging is primarily determined by the early death of neurons in the cerebellum, a critical structure for predictive motor control.

In our rapidly aging society, functional independence is a critical challenge for the health and well-being of individuals and has considerable socioeconomic consequences. In this regard, the ability to control movement is crucial. Therefore, to succeed in promoting longer functional independence we need to understand the normal aging process of movement control. Such motor aging is obviously multifactorial and complex. However, specific structures may have a prevailing role. If this is the case, targeting these structures may allow more efficient interventions. Here I examine evidence supporting the hypothesis that motor aging is primarily determined by early death of cerebellar neurons.

Populations of neurons in the cerebrum and cerebellum are not equally affected by normal aging. The number of neurons is stable in numerous cerebral areas including the primary motor cortex, primary visual cortex, prefrontal cortex, hippocampus, and entorhinal cortex [1]. Conversely, the cerebellum displays a significant loss of neurons. The anterior lobe is especially affected, with a 40% loss of both Purkinje and granule cells [2]. This difference in neuron loss between the cerebrum and cerebellum may be explained by the vulnerability of cerebellar neurons. Specifically, Purkinje cells show high and premature susceptibility to mitochondrial and proteostasis defects [3] and cerebellar granule cells are particularly vulnerable to oxidative stress [4].

What makes the cerebellum critical for motor control is its ability to estimate both extrinsic and intrinsic forces acting on the body. Based on these estimates, movement is controlled before the availability of sensory reafferences. While such predictive motor control supported by the cerebellum was suggested long ago [5], neurophysiological evidence started to appear only recently. Specifically, Purkinje cells output an estimate of physical principles acting on the body such as gravity [6]. Granule cells potentially integrate a copy of a motor command and sensory inputs from the spinocerebellar tract to estimate the sensory consequence of the motor command [7]. This predictive control has consistently been shown to be impaired after cerebellar damage [8]. It follows that the death of cerebellar neurons observed in normal aging impairs the predictive control of movement.

Here I propose that, in older adults, early cell loss prevents the cerebellum from outputting accurate estimates of intrinsic and extrinsic forces acting on the body, thereby increasing the computational load required to perform a motor task at the same level as in young adults. As age-related neuron death appears to prominently affect the cerebellum, the resulting impairment of predictive motor control is likely to have a major role in motor aging. The high percentage of neuron loss in the anterior lobe, a cerebellar region critical for motor control, further supports this hypothesis.

At the brain level, this additional load is indicated by age-related overactivation, which has been consistently observed in regions involved in skilled movement such as the prefrontal cortex, presupplementary motor area, premotor cortex, parietal cortex, and supplementary motor area [9]. Furthermore, cerebellar overactivation [9] suggests that the remaining neurons operate less efficiently. At the behavioral level, the additional computational load is indicated by a declining ability to perform a motor task concurrently with another task [10].

If cerebellar neuron death primarily determines motor aging as hypothesized, the behavior of older adults should reflect impaired predictive motor control. In fact, slowness and inconsistency, the hallmarks of movement in older adults, perfectly match the behavior expected in the context of impaired predictive control. The direct consequence of impaired predictive control would be increased reliance on reactive control, which is based on time-delayed sensory feedback. Due to such delays, movement corrections are always late with regard to the portion of movement they intend to correct. Accordingly, individuals with impaired predictive motor control are expected to reach their goal through a series of corrective movements. Such behavior has consistently been found in older adults [11]. Furthermore, direct consequences of time-delayed feedback and corrective movements are slowness and inconsistency.

In summary, there is consistent evidence supporting the hypothesis that motor aging is primarily determined by early death of cerebellar neurons. To delay motor aging and promote longer functional independence, future work investigating the cerebellum and means to compensate for this cellular death is warranted. In this regard, a recent study demonstrating enhanced motor adaptation in older adults following transcranial direct current stimulation over the cerebellum is encouraging [12]. Finally, the critical

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role of the cerebellum in motor aging does not exclude the involvement of other brain structures.

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