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NEWS & VIEWS

The cerebellum and non-motor function: clinical implications

The recent demonstration that the human cerebellum is involved in attention operations independent of sensory input or motor output highlights the inadequacy of traditional concepts of cerebellar function, and calls for psychiatrists, neurologists, and neuropsychologists to reconsider the possible contribution of cerebellar abnormalities to disorders characterized by non-motor symptoms.

Since the earliest attempts to explain neurobiologically the nature of mental disorders, the cerebellum has been largely ignored as a possible site of abnormality. This is because the cerebellum has been viewed for nearly 200 years as a structure involved exclusively in motor control. Why would such a structure be involved in the social, emotional, or cognitive features of any disorder?

In fact, there is little reason to believe that the actual function of the cerebellum is as limited as tradition suggests. For instance, in terms of sheer number of neurons, the cerebellum is the largest structure in the human brain.[1] It has an extremely high input-to-output axon ratio (cerebellar afferents-to-efferents: 40-to-1),[2] and it is one of the most widely connected structures in the human brain, having physiological connections with all major divisions of the central nervous system (CNS).[3] These factors suggest that rather than being limited to the motor domain, the cerebellum must serve a function that is both general and highly integrative. Furthermore, experimental data, and in particular the results of recent functional neuroimaging studies, indicate that the cerebellum might be involved in a wide range of functions including attention, associative learning, practice-related learning, procedural learning, motor skill acquisition, declarative memory, working memory, semantic association, conditioned anxiety, mental exploration, complex reasoning and problem solving as well as motor control and sensory operations.[3] Why, then, have clinicians and researchers by and large remained bound to the motor tradition?

One possible explanation for the durability of the traditional view is that despite many indications that the cerebellum is involved in various non-motor as well as motor operations, few studies of cerebellar involvement in such operations have employed all of the proper controls. As the cerebellum is clearly involved in motor operations, and as it receives input from a variety of sensory systems, a crucial component of experiments attempting to demonstrate that its role extends beyond the motor and sensory domains is the careful control for motor and sensory aspects of the experimental tasks. One recent functional magnetic resonance imaging (fMRI) study[4] which included such controls addressed two questions: (1) Is the cerebellum involved in attention operations that do not require use of the motor system; and (2) if there is such involvement in attention, is it localized to the same cerebellar region(s) involved in movement, or is it differentially localized within the cerebellum? This study included three tasks. During the Attention task, circles, squares, or triangles in red, green, or blue were presented one at a time at fixation. Subjects silently counted target stimuli (eg, squares) within a predetermined visual dimension (eg, form). Thus, attention was required, but use of the motor system was not. During the Motor task, subjects repeatedly executed a self-paced, right-hand movement in the absence of visual stimulation. Then, this movement was used in the final, Attention-with-Motor task, in which, rather than silently counting, subjects responded to each target using the right-hand movement.

In order to overcome the aforementioned obstacles of previous studies, this one employed a number of crucial behavioral controls. First, in order to control for visual sensory stimulation, functional activation during both the Attention and Attention-with-Motor tasks was compared with activation during a passive visual stimulation condition, during which subjects observed the same visual stimuli, but did not selectively attend or respond. Second, to control for activation due to eye movement, all stimuli were presented at fixation. (Work from other laboratories would predict that had eye movements occurred, they would have activated the cerebellar vermis,[5] a region not activated during the Attention task.) Third, the Attention task controlled for motor involvement by employing a silent counting response requiring subjects to neither plan, prepare, nor execute overt movements. All cerebellar regions

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showing functional activation during the Attention task were also active during the Attention-with-Motor task, which did not employ silent counting, indicating that silent counting did not add to the activation results. Furthermore, when four of the subjects were instructed to count silently in the absence of any visual sensory stimulation, no cerebellar activation was observed within the most common and prominent site of attention-related activation.

By employing the above controls, the cerebellum was shown to be involved in selective attention operations independent of motor output and sensory input. This involvement was dissociated neuroanatomically from cerebellar involvement in motor operations, with the Attention task activating the superior posterior cerebellum, most prominently on the left, and the Motor task activating the right anterior cerebellum (Figure 1). In addition, there was a sharp distinction between the nature of attention *vs* motor-related activation in these separate cerebellar regions. This distinction was identified by first determining the locations of the Attention Hotspot (ie, in each subject, the maximally activated voxel in the left superior posterior cerebellum during the Attention task) and the Motor Hotspot (ie, in each subject, the maximally activated voxel in the right anterior cerebellum during the Motor task). At the onset of the Motor task, there was a transient increase in activation in the Attention Hotspot (Figure 2a), suggesting that initiating, but not sustaining, the simple motor actions required some degree of attention. By contrast, during the Attention task, there was no increase in activation in the Motor Hotspot (Figure 2b), suggesting that neither the initiation nor the sustained execution of the Attention task required the use of cerebellar regions most involved in the Motor task. Together, these findings emphasize the functional independence of cerebellar involvement in attention and highlight the need for a new and broader concept of cerebellar function.

One such concept, which has been proposed previously,[3,4,6–8] suggests that the fundamental function of the cerebellum is to predict the neural conditions needed for a particular motor or non-motor operation and to set those conditions in preparation for the operation at hand. To perform this preparatory function, the cerebellum must first learn multidimensional sequences of exogenous (eg, sensory events) and endogenous (eg, signals from frontal cortex, hippocampus, hypothalamus, etc) neural activities. Then, whenever an analogous sequence begins to unfold, the cerebellum predicts—based on prior learning—what is about to happen, reads out the remainder of the sequence, and initiates preparatory actions that alter response thresholds and readiness in neural systems expected to be needed in upcoming moments. The product of such preparatory signaling is also fed back to the cerebellum and incorporated into continued learning, allowing the cerebellum to adjust its predictions and preparatory signals to meet changing internal and external conditions. In this manner, the cerebellum

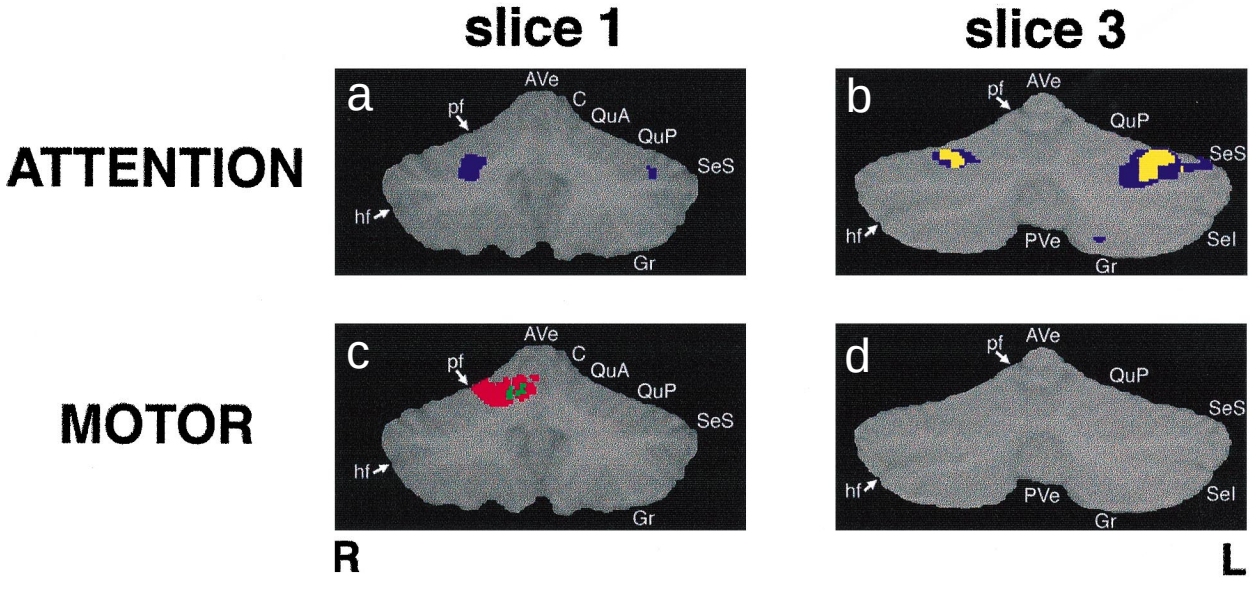

Figure 1 Functional maps demonstrating the most common sites of activation across subjects overlaid on averaged coronal anatomical images of the most anterior slice position (slice 1) and the most posterior slice position (slice 3) of the cerebellum analyzed. (a and b) during the Attention task, the most common site of activation was in the left superior posterior cerebellum (the posterior portion of the quadrangular lobule (QuP) and the superior portion of the semilunar lobule (SeS); approximate Talairach coordinates of center of mass ($x = -37$, $y = -63$, $z = -22$)). YELLOW = overlap of three or more subjects; BLUE = any two subjects. (c and d) During the Motor task, the most common site was in the right anterior cerebellum (the anterior portion of the quadrangular lobule (QuA), the central lobule (C), and the anterior vermis (AVe); approximate Talairach coordinates of center of mass ($x = 7$, $y = -51$, $z = -12$)). GREEN = overlap of three or more subjects; RED = any two subjects. pf = primary fissure; hf = horizontal fissure; PVe = posterior vermis; Sel = inferior portion of the semilunar lobule; Gr = gracile lobule (adapted from Ref 4).

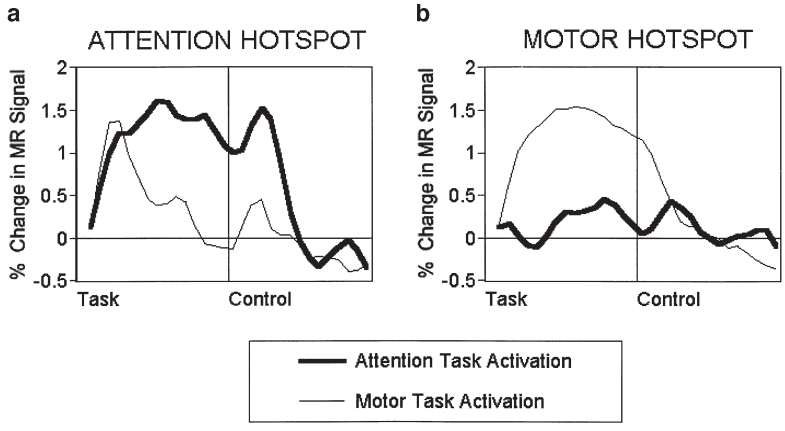

Figure 2 Inter-task comparisons within averaged attention (a) and motor (b) hotspots. For each hotspot, the time course signal data for each subject were averaged, collapsed across the four cycles between task and control conditions, and plotted in terms of percent change in MR signal (adapted from Ref 4).

learns to predict and implement the most adaptive preparatory response to the sequences that it has learned, the end result being a dynamically modifiable preparatory response representation.

Thus, according to the proposed theory, the cerebellum is not a motor device, a sensory device, or a cognitive device, but rather a general purpose device that prepares whichever neural systems (eg, sensory, motor, autonomic, memory, attention, affect, language) may be needed in upcoming moments. Unlike traditional motor theories of the cerebellum, this theory *does* suggest that cerebellar pathology will lead to significant impairments in a variety of neurobehavioral domains. Without the preparatory aid provided by the cerebellum, other systems can continue to perform their prescribed functions. However, they will do so suboptimally in situations where prediction and preparation might aid performance. For instance, previous work from our laboratory has shown that cerebellar pathology does not eliminate the ability to shift attention, but instead makes attention shifts slow and inaccurate.[6,9,10] In the shifting attention task, the appearance of a target stimulus (eg. a red shape) cues subjects to attend to a new stimulus dimension (eg, form) and prepare for a new target (eg, a square of any color). Thus, this task entails a predictive relationship between events that the cerebellum is able to learn. In turn, the cerebellum can provide preparatory signals to neural systems required to detect and respond to the next target. When given adequate time to shift the mental focus of attention, patients with neocerebellar lesions and patients with autism (a disorder involving widespread Purkinje cell loss)[8] show no impairments on this task. However, within 2.5 seconds or less following a cue to shift attention, neocerebellar lesion patients and autistic patients are significantly worse than normal subjects and patients with focal cerebral lesions in detecting target stimuli in the new dimension.[6,9,10] In other words, in the absence of normal preparatory output from the cerebellum, other neural systems involved in detecting target stimuli are not prepared to respond during the shortest of time intervals.

In contrast to the shifting attention task, performance of a sustained attention task analogous to that used by Allen *et al*,[4] is unimpaired in neocerebellar lesion patients and autistic patients regardless of the time interval between successive stimuli.[6,9,10] The fact that cerebellar pathology does not impair performance on a task that consistently activates the cerebellum might at first seem paradoxical. However, it makes perfect sense when considered in light of the proposed theory of cerebellar function. The sequence of events in this task is randomly ordered and thus cannot be learned by the cerebellum. As the sequence cannot be learned, the cerebellum is incapable of providing useful preparatory output to neural systems involved in detecting and responding to target stimuli. Although the normal cerebellum is active in its attempts to learn,[4] it is not effectively aiding the rest of the CNS and thus does not have a noticeable advantage over the damaged cerebellum. If there were a predictive relationship to be learned, as in the shifting attention task, and thus useful preparatory output from the cerebellum, then additional activation reflecting such output would have been expected in the cerebellar output nuclei. And, in fact, a recent fMRI study examining activation in normal subjects during the shifting attention task reported activity in the dentate nucleus,[11] the major source of output from the neocerebellum.

The attention context is but one example of an impairment of the proposed cerebellar preparatory function. The cerebellum shares physiological connections not just with motor and attention systems, but with all major functional divisions of the CNS.[3] Therefore, cerebellar pathology might manifest in a number of ways. The effects of cerebellar damage are no longer limited to the obvious motor signs and symptoms of medical yore, but instead might encompass the various socioemotional, language, and cognitive abnormalities that are used as diagnostic signs and symptoms for a variety of mental disorders. This is not to suggest that damage to the cerebellum is at the 'core' of all of these disorders. However, the possible contribution of cerebellar abnormalities to disorders characterized by

non-motor symptoms can no longer be dismissed. Autism can serve as a model.

Autism is a pervasive developmental disorder characterized by a variety of social, language, and cognitive impairments. Theories about its biological basis have included abnormalities in a wide range of neuroanatomical and neurochemical systems. However, experiments have demonstrated that the most consistent site of neural abnormality in patients with autism is the cerebellum (for review, see Ref 8). This abnormality involves the early developmental, and possibly even prenatal, loss of Purkinje neurons.[8] Despite evidence of cerebellar abnormality continually emerging from both autopsy and neuroimaging studies of autism, researchers who investigate autism have been greatly resistant to theories that incorporate this evidence, no doubt due to their adherence to traditional motor views of the cerebellum. The majority of autism researchers instead have remained loyal to older notions of autism that focus on traditionally non-motor systems (eg limbic, prefrontal, serotonergic). Ironically, these various notions are neither inconsistent nor incompatible with the evidence of cerebellar pathology. On the contrary, through mechanisms of activity-dependent development, prenatal damage to the cerebellum might in fact contribute to abnormal development in the wide range of neural systems with which it is physiologically connected (eg, limbic, prefrontal, serotonergic).[12] Furthermore, in the developed brain, cerebellar pathology may continue to contribute to functional abnormalities in these diverse systems in situations where those systems might normally benefit from the proposed preparatory function of the cerebellum. Thus, cerebellar pathology is not only strongly evident in autism, it is consistent with the wide range of functional and other structural abnormalities which have been reported.

Although it is arguably the most thoroughly investigated, autism is not the only mental disorder of which cerebellar pathology is a feature. In fact, autopsy and neuroimaging reports have indicated the possibility of cerebellar abnormalities in a variety of conditions including attention-deficit hyperactivity disorder,[13] unipolar depression and bipolar disorder,[14] obsessive-compulsive disorder,[15] and schizophrenia.[16] In light of such findings, it is our hope that the proposed theory will provide researchers and clinicians with a fresh viewpoint from which to reconsider cerebellar involvement in a wide range of neurobehavioral functions. In turn, this should encourage a more open-minded consideration of the cerebellum as a possible site of abnormality in hypotheses and models of the neuropathology underlying various mental disorders.

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