

REVIEW

Eric Courchesne^{1,2,4} and
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Fundamental Functions of
the Cerebellum

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Introduction

For well over a century, scientists have continually questioned the role of the cerebellum in the central nervous system (CNS) (for review, see Schmahmann 1997). Traditionally viewed as a structure dedicated to motor control, indications to the contrary have never ceased to emerge in a variety of experimental and clinical contexts. In recent years, the burgeoning use of functional neuroimaging methodology—namely, positron emission tomography (PET) and, more recently, functional magnetic resonance imaging (fMRI)—has led to a substantial increase in findings implicating the cerebellum in various nonmotor as well as motor operations. It now appears quite clear that the cerebellum is involved in a wide range of motor, sensory, and cognitive functions. However, as for the actual role the cerebellum serves, the question remains.

Certain new concepts of the cerebellum have attempted to account for its apparent functional diversity. For instance, one view suggests that the cerebellum guides movements that reposition sensory receptors to optimize the quality of sensory information that the nervous system acquires (Bower and Kassel 1990). Although improving on older notions, this idea still views the ultimate function of the cerebellum as one of motor control; rather than freeing us from the binds of tradition, it is simply a variation on the motor theme. Another view suggests that the cerebellum is a system that tracks the trajectories of sensory information moving through the environment. Such tracking is thought to facilitate the efficiency of movement relative to or in response to moving stimuli (Paulin 1993). Although it is somewhat broader in its ability to account for the functional diversity of the cerebellum, this view is inconsistent with findings indicating that the cerebellum is involved whether the information it is acquiring is moving or not. Thus, although they are improvements on tradition, most recent attempts to reconceptualize the role of the cerebellum are too limited in scope to account for the breadth of existing data.

There is little reason to believe that the actual function of the cerebellum would be as limited as most concepts of cerebellar function

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might suggest. In terms of the number of neurons it contains, the cerebellum is the largest structure in the human brain (Williams and Herrup 1988). This tremendous number of neurons, coupled with the high input-to-output axon ratio (cerebellar afferents to efferents are 40:1; Carpenter 1991) suggests that its function must be massively integrative. It is also one of the most widely connected structures, having physiological connections with all major divisions of the CNS (Moruzzi and Magoun 1949; Snider 1950, 1967; Bava et al. 1966; Sasaki et al. 1972, 1979; Kitano et al. 1976; Watson 1978; Itoh and Mizuno 1979; Newman and Reza 1979; Saint-Cyr and Woodward 1980a,b; Vilensky and Van Hoesen 1981; Crispino and Bullock 1984; Ito 1984; Haines and Dietrichs 1987; King 1987; Nieuwenhuys et al. 1988; Schmähmann and Pandya 1989; Ghez 1991; Ikai et al. 1992; Llinás and Sotelo 1992; Thielert and Thier 1993; Glickstein et al. 1994; Lynch et al. 1994; Middleton and Strick 1994; Schmähmann 1996).

Moreover, experimental data and, in particular, the results of recent fMR imaging and PET studies, indicate that the cerebellum might be involved in a wide range of functions, including attention, associative learning, practice-related learning, procedural learning, declarative memory, working memory, semantic association, conditioned anxiety, mental exploration, and complex reasoning and problem solving as well as sensory, motor and motor skill acquisition (see Table 1). A general theory must be able to encompass and explain the functional role played by the cerebellum in these diverse motor and nonmotor domains.

A More Encompassing Theory

New concepts of cerebellar function are obliged to account for new facts and findings. Such a concept, which has been proposed previously (Courchesne et al. 1994; Akshoomoff et al. 1997; Allen et al. 1997; Courchesne 1997), suggests that the fundamental purpose of the cerebellum is *to predict internal conditions needed* for a particular mental or motor operation and *to set those conditions* in preparation for the operation at hand. This cerebellar preparatory function is neither a sensory nor a motor activity but, rather, a general one that prepares whichever neural systems (e.g., sensory, motor, autonomic, memory, attention, affective, speech, language) may be needed in upcoming moments. In other words, the cerebellum prepares internal conditions (e.g., by repositioning sensory receptors; by altering cerebral blood flow levels; by enhancing neural signal to noise; by enhancing neural responsiveness in hippocampus, thalamus, and superior colliculus; by modulating motor control systems) for imminent information acquisition, analysis, or action. Its preparatory actions thereby facilitate and improve sensory processing and mental and motor performance in response to subsequent sensory events.

To perform this function, the cerebellum must learn the predictive relationships among temporally ordered multidimensional sequences of exogenously derived (e.g., sensory events) and endogenously derived (e.g., signals from prefrontal and posterior parietal cortex, hippocampus, hypothalamus, etc.) neural activities, including those derived from the consequences of its own output—preparatory signaling. Whenever an analogous sequence begins to unfold in real time, the cerebellum predicts—based on such prior learning—what is about to happen and triggers preparatory actions (from neural to cerebrovascular; from motor to mental) that alter neural response thresholds and readiness in systems

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Table 1: *PET and fMRI studies show that the cerebellum is active*

During	References
Attention	Allen et al. (1997); T.H. Le and X. Hu (unpubl.)
Sensory discrimination	Gao et al. (1996)
Semantic association	Petersen et al. (1989); Martin et al. (1995)
Working memory	Awh et al. (1995); Courtney et al. (1996); Fiez et al. (1996); Klingberg et al. (1996); J.E. Desmond, J.D.E. Gabrieli, B.L. Ginier, J.B. Demb, A.D. Wagner, D.R. Enzman, and G.H. Glover (unpubl.)
Associative learning	Molchan et al. (1994); Logan and Grafton (1995); Blaxton et al. (1996)
Practice-related learning	Raichle et al. (1994)
Procedural learning	Grafton, et al. (1994); Jenkins et al. (1994); Flament et al. (1996); S.L. Rao, D.L. Harrington, K.Y. Haaland, J.A. Bobholz, J.R. Binder, T.A. Hameke, J.A. Frost, B.M. Myklebust, R.D. Jacobson, P.A. Bandettini, and J.S. Hyde (unpubl.)
Motor skill acquisition	Friston et al. (1992); Seitz et al. (1994)
Problem solving	Kim et al. (1994)
Concept formation	Berman et al. (1995); Nagahama et al. (1996)
Conditioned anxiety	A.L. Malizia, S.J. Wilson, J.-B. Poline, D.J. Nutt, and P.M. Grasby (unpubl.)
Mental exploration	Mellet et al. (1995)
Spatial memory	Moscovitch et al. (1995)
Object memory	Moscovitch et al. (1995)
Verbal memory	Grasby et al. (1993); Andreasen et al. (1995)
Episodic memory	Andreasen et al. (1995)
Semantic memory	Andreasen et al. (1995)
Speech	E. Artiges, M.J. Giraud, B. Mazoyer, C. Trichard, L. Mallet, H. de la Caffiniere, M. Verdys, A.M. Syrota, and J.L. Martinot (unpubl.)
Motor imagery	Decety et al. (1994); Parsons et al. (1995)
Motor preparation	Deiber et al. (1996)
Motor control	Fox et al. (1985); Ellerman et al. (1994); Allen et al. (1997)

expected to be needed in upcoming moments. Complete knowledge of upcoming events is not necessary to trigger specific preparatory actions. What is important is the probabilistic relevance of a particular sequence or stimulus as a predictor of an upcoming event (Coenen and Sejnowski 1996; their computational model of the cerebellum as a “predictive machine” is discussed below). Simple exposure to aspects of a sequence of activities (even a single exogenous or endogenous event) that are predictive of events that will soon arrive may be sufficient to trigger preparatory responding by the cerebellum. The consequences of this responding are fed back to the cerebellum and modify these temporally

ordered multidimensional predictive sequences and the cerebellar preparatory responses that they engender. In this way, the predictions and preparatory signals of the cerebellum are adjusted to meet changing internal and external conditions. The end result is a dynamically modifiable prediction and preparatory response representation.

Cerebellar learning, then, is not strictly speaking motor learning, declarative learning, or procedural learning. Rather, it is preparatory learning, the purpose of which is to predict and prepare *internal conditions* needed to facilitate the efficient and timely responses of a wide variety of motor and nonmotor systems. Such learned associative responses provide automatic, moment-to-moment signaling. To be maximally efficient and timely, the cerebellum must be able to trigger, via signals to different neural systems (autonomic, sensory, attention, etc.), preparation response enhancement periods of variable duration from tens of milliseconds to minutes, and it must also be able to effect specific local neural changes as well as nonspecific global system-wide changes. An exact knowledge of upcoming sensory and neural sequences can improve the precision of preparatory responses, and experimenters can deliberately or unwittingly supply this sort of information in test situations. However, in the natural world, it is unusual to have such a complete, conscious foreknowledge of upcoming events. To be maximally adaptive to real world variability, then, the cerebellum must be a “pattern extractor,” capable of getting the “gist” of what has been happening, what is likely to happen next, and what internal conditions are needed to prepare for a particular predicted up-coming operation, be it acquisition, analysis, or action. Interestingly, if one were to name a single characteristic of the cognitive style of patients with autism, a developmental disorder involving prenatal loss of Purkinje neurons (Courchesne 1997), it would be that they are literal-minded and unable to get the gist of things [e.g., see the very first description of an autistic child (Kanner 1943)].

Without the specific type of automatic yet modifiable, moment-to-moment preparatory aid provided by the cerebellum, other systems—motor, sensory, attention, language, and so forth—could continue to perform their prescribed specific functions but would do so suboptimally in situations in which prediction and preparation facilitate performance. For instance, observations and experiments show that in situations demanding movement, perception, attention, or association learning, cerebellar damage does not eliminate function, but it does increase suboptimal variability in response thresholds, times, and amplitudes, and it does increase conscious effort when performing motor or mental tasks. Gordon Holmes (1939) quotes a cerebellar-lesioned patient as saying, “The movements of my left (unaffected) arm are done subconsciously, but I have to think out each movement of the right (affected) arm. I come to a dead stop in turning and have to think before I start again.” In short, in this patient, automatic, continuous, and unconscious preparatory facilitation was eliminated, and he had to operate, metaphorically speaking, “in the present tense.” The cerebellar pathology did not eliminate the patient’s voluntary motor action but, instead, made motor action slow, inaccurate, and effortful; the patient had to consciously “think” through each step in preparation for action and during the execution of each action. In a parallel fashion, evidence shows

that cerebellar pathology does not eliminate voluntary shifts of attention but, instead, makes such shifts slow and inaccurate (Akshoomoff and Courchesne 1992, 1994; Courchesne et al. 1994). Similarly, cerebellar pathology apparently does not prevent relatively good perceptual judgments of time intervals between any two stimuli but, instead, makes such judgments more variable. For instance, whereas normal subjects and patients with cerebellar damage differ from each other by as little as 1% in correctly tapping out a 550-msec time interval between two tones, the patients show a significant increase relative to normals in the standard deviations associated with such performance or perceptual judgments (± 45.7 vs. ± 26.1 msec) (Ivry and Keele 1989). Likewise, cerebellar lesions do not necessarily eliminate the classically conditioned nictitating membrane response, but they do produce variability in response onset latency and amplitude (e.g., Fig. 16.13 from Welsh and Harvey 1992). We suggest that in all of the above cases, damage to the cerebellum disrupted the normal preparation of other neural systems, thereby impairing performance.

It should be noted that this is not the first concept of cerebellar function to include the element of prediction. Certain models that have ascribed a predictive role to the cerebellum have done so as a means of explaining the role that the cerebellum plays in motor control (e.g., Darlot 1993; Miall et al. 1993). In their paper describing the cerebellum as a Smith predictor, Miall et al. (1993) suggest “that the cerebellum may be involved in more complex predictions, linking it to more cognitive processes.” Also, in his model of cerebellar function described above, Paulin (1993) proposes that the cerebellum improves the efficiency of motor control through the process of “state estimation,” which might involve prediction. Finally, Coenen and Sejnowski (1996) have begun to consider the physiological foundation for the formation of predictions in the cerebellum. In our theory, and in this paper, we consider how predictions generated in the cerebellum might be implemented in order to prepare diverse neural systems, both motor and nonmotor.

To this date, there have been no experiments that directly test the specific elements of the proposed theory of cerebellar function. However, two contexts in which such a function is predicted to be most evident are studies of attention and studies of learning, two areas in which cerebellar involvement has been investigated extensively.

Cerebellar Involvement in Attention and Preparation

A novel approach to elucidating the role of the cerebellum in human neural functioning is through examination of its role in the coordination of attention and other preparatory functions. Because attention, sensory response modulation, and related preparatory functions can operate independently of motor control, studies of attention offer a new way of looking at the nonmotor functions of the cerebellum. This novel perspective may increase the chances of discovering the fundamental properties of cerebellar function that are common across and underlie its influence on different neurobehavioral domains.

It is common sense that paying attention “after the fact” is too late (you have already run the red light or missed what the teacher said), and that conversely the benefits of attention accrue when it is properly directed and applied before something important occurs. That way, one is properly prepared to sense, analyze, and act. Of course, to direct attention properly, the brain must guess from past experience,

learning, and knowledge of current events what is most likely to happen next.

Attention, then, is an act of preparation, and involves the selective modulation of neural responsiveness in many systems in advance of anticipated sensory information (see Animal Studies, below). So, when sensory information is anticipated that may have signal value to the task at hand or may have imminent, inherent biological significance, attention is normally redirected toward the predicted source of that information to prepare for acquisition, analysis, or action. Thus, attention is a “preprocessing” or “advanced preparation” mechanism that facilitates and improves sensory processing and mental and motor performance in response to subsequent sensory events.

Therefore, if the theorized cerebellar function is indeed a general one that prepares whichever neural systems may be necessary in upcoming moments, then it should be true that the cerebellum plays a role in attention and other preparatory operations independent of motor involvement. In fact, a role for the cerebellum in attention operations was demonstrated by what was arguably one of the first attempts to directly test the role of the cerebellum in a specific cognitive operation, as discussed next (Courchesne et al. 1990, 1994; Akshoomoff and Courchesne 1992, 1994). That series of studies paved the way for functional neuroimaging studies of attention in the normal human cerebellum and also prompted a reexamination and reinterpretation of past studies of the cerebellum in animals and recent hypotheses (Bower and Kassel 1990; Gao et al. 1996) (see below).

EARLY STUDIES OF SHIFTING ATTENTION AND THE CEREBELLUM

Based on its privileged physioanatomical position allowing it to affect known attention systems, it was hypothesized over a decade ago that the cerebellum contributes to attention operations in a manner analogous to its role in motor control (Courchesne 1987 and unpubl.). Thus, it was predicted that the cerebellum allows attention to be shifted rapidly, accurately, smoothly, and effortlessly.

To investigate this new hypothesis, patients with acquired focal neocerebellar lesions were tested in an original paradigm (Fig. 1, top) in which cues presented at unpredictable time intervals directed patients to initiate shifts of their focus of attention between visual and auditory sources of information (Akshoomoff and Courchesne 1992; Courchesne et al. 1994) or between color and form information (Akshoomoff and Courchesne 1994). Also tested were patients with autism, a disorder involving Purkinje neuron loss (Courchesne 1997). Performance on this task was compared to performance on a task that was identical apart from the fact that it did not require subjects to shift their focus of attention. Rather, attention was sustained on a single source of information (e.g., visual) throughout the task. Several lines of neurobehavioral and neurophysiological evidence demonstrated an impaired ability to rapidly and accurately shift the mental focus of attention in neocerebellar patients and autistic patients. Evidence also showed that this impairment was not attributable to motor control deficits.

NEUROBEHAVIORAL EVIDENCE

Within 2.5 sec or less following a cue to shift attention, patients with neocerebellar lesions and autistic patients were significantly worse than normal subjects and patients with focal cerebral lesions in correctly detecting target information in the new focus (Courchesne et al. 1990;

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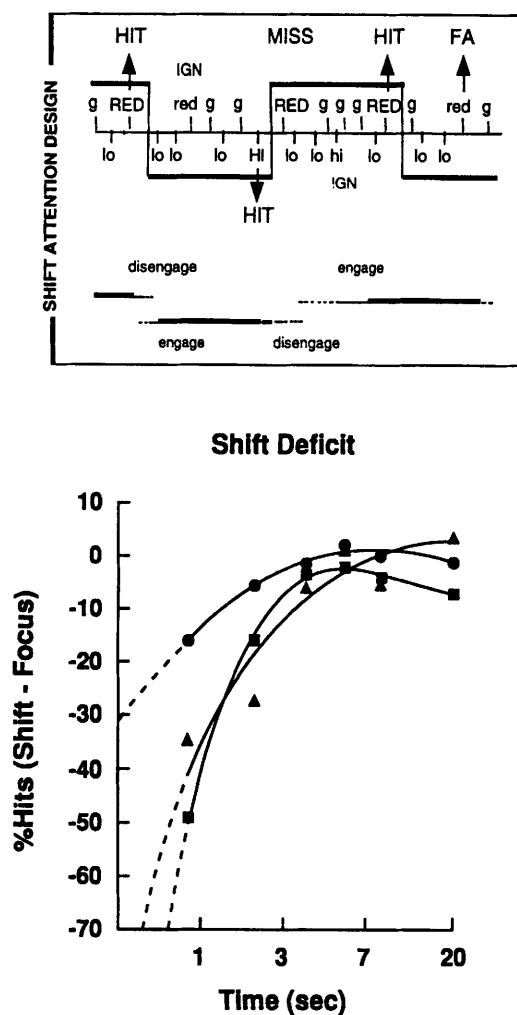


Figure 1: (Top) Schematic of a visual-color/auditory-tone shift attention task. Visual stimuli were red and green flashes; auditory stimuli were 2 kHz (hi) and 1 kHz (lo) tone pips. (HIT) Correctly detected target; (MISS) failure to respond to a target; (FA) an erroneous response to a rare stimulus that was in a modality to be ignored; (ign) a rare stimulus that was correctly ignored. In the example of the shift experiment, the subject pressed a button (arrow) to the first rare visual target stimulus. This served as a cue to shift attention to the auditory stimuli, ignore (IGN) the visual stimuli, and respond to the next auditory target, which in turn served as a cue to shift attention back to the visual stimuli. The subject's attentional field is indicated by the heavy line. (Adapted from Akshoomoff and Courchesne 1992). (Bottom) Time-related shift attention deficits in 6 patients with acquired neocerebellar lesions (\blacktriangle) and 13 patients with autism (\blacksquare), a disorder involving Purkinje neuron loss in early development; performance compared to 25 normal controls (\bullet). Larger negative difference values indicate a larger decrement in performance on the shift task (see top) relative to a baseline control sustained attention task. This difference in the median percent hits is graphed as a function of elapsed time since the immediately preceding target. Natural log time scale in seconds. (Adapted from Courchesne et al. 1994).

Akshoomoff and Courchesne 1992; Courchesne et al. 1994) (Fig. 1). Akshoomoff and Courchesne (1994) demonstrated further that in patients with neocerebellar lesions, this deficit is present even when shifting

occurs within a single visual spatial location between color and form stimuli. All of the reaction times for the neocerebellar and autistic patients were well within a 200- to 1400-msec time window allotted for responses [their median reaction times (RTs) being ~500–600 msec], eliminating the possibility that motor responses were so slow that they were not counted. Also, as long as they were not required to shift attention, that is, while attention was sustained on a single modality, these patients were not significantly impaired when responding to two target stimuli occurring rapidly in succession. That is, as long as the neocerebellar-lesioned patients did not have to change preparatory states, their attention and motor performance were not impaired.

EVENT-RELATED BRAIN RESPONSE
EVIDENCE

To verify that the neocerebellar and autistic patients had not mentally shifted their attention when they missed targets, we recorded the P3b event-related potential (ERP) to all hits and misses. The P3b is a sign of covert attention independent of overt motor action (Courchesne et al. 1977), and it is absent when a target stimulus is ignored or missed (Squires et al. 1973; Ciesielski et al. 1990). Like normal subjects, the neocerebellar and autistic patients exhibited a P3b response to correctly detected targets but not to missed stimuli that occurred 2.5 sec or less following a cue. These findings suggest that when these patients missed targets that rapidly followed a cue, they were not covertly attending and thus had not fully shifted their attention to the new focus. As with the preceding behavioral observations, this neurophysiological observation also reflects a mental rather than motor output error.

To further verify the behavioral evidence showing that neocerebellar patients needed more time to completely reestablish a selective focus of attention following a cue to shift, we analyzed the P3b response to all hits as a function of time since the last target was correctly detected. Figure 2 shows the results from the task requiring shifts between color and form stimuli. In normal subjects, within the shortest time interval (as well as long ones) following a cue to shift attention to the other perceptual domain, targets in that new focus elicited a large P3b amplitude, whereas correctly ignored rare stimuli in the old focus elicited little or no P3b. This large P3b response difference between attended and ignored stimuli is nonmotor evidence that in the shifting attention task, normal subjects were able to very rapidly and selectively turn off active attention to one perceptual domain (e.g., color) and turn it on to the other (e.g., form). However, this was not the case with the neocerebellar patients (Fig. 2). Within the shortest time interval (<2.5 sec) following a cue to shift attention, targets to correctly detected and correctly rejected stimuli elicited similar amplitude P3b responses. However, given more time (2.5–30.0 sec), attentional selectivity did emerge as demonstrated by the clear amplitude difference between P3b responses to correctly detected targets and those to correctly ignored rare stimuli. This is motor-free neurophysiological evidence that neocerebellar damage impairs the ability to rapidly and selectively enhance or reduce attention.

Finally, in normal subjects the cue to execute a mental shift of attention elicits a shift attention difference, ERP, the Sd potential (Courchesne et al. 1995). Its regional distribution may vary according to whether the eliciting cue signals the need to shift attention to auditory or visual information (E. Courchesne, N. Akshoomoff, J. Townsend, and O. Saitoh, unpubl.), and so the Sd may reflect operations involved in setting up a

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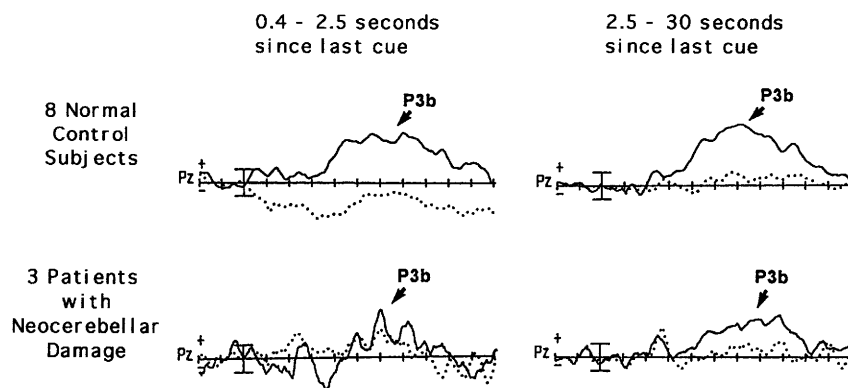


Figure 2: ERP recordings during a visual-color/visual-form shift attention task analogous to the visual-color/auditory-tone shift attention task diagrammed in Fig. 1 (top). Shown are time-related attention effects for three patients with neocerebellar damage (mean age, 9.7 years) and eight normal control subjects (mean age, 9.6 years). Note the minimal difference in the P3b between correctly detected rare stimuli (solid line) and correctly ignored rare stimuli (broken line) when these neocerebellar patients were required to rapidly shift their focus of attention. In contrast, within even the shortest time interval following a cue to shift attention to a different perceptual domain, normal children displayed a large P3b response to targets in that new perceptual focus, but no P3b to correctly ignored rare stimuli in the old perceptual focus. Thus, following cues to shift, normal children were able to very quickly establish a new selective focus of attention and selective P3b enhancement, but children with neocerebellar damage were not. Calibration bars represent $\pm 5 \mu\text{V}$; total epoch = 1310 msec. (Adapted from Akshoomoff and Courchesne 1994).

new focus of selective attention. The Sd potential is absent in neocerebellar-lesioned patients and autistic patients.

NEW STUDIES OF ORIENTING ATTENTION AND THE CEREBELLUM

In addition to studies of shifting attention, a new set of experiments using the Posner paradigm (see Fig. 3, top; Posner et al. 1984) demonstrated neocerebellar involvement in a different domain of attention, the automatic orienting of attention (Townsend et al. 1996a). Although the Posner paradigm has been much studied and is familiar to most cognitive neuroscientists, use of one feature in its design has been overlooked, namely, the initial step of how quickly the spatial cue orients attention. In a typical Posner paradigm, on 80% of the trials, the cue correctly indicates the future location of the target stimulus (i.e., "valid" trial). It is therefore clear that the more quickly attention is oriented to the cue at this location, the more rapid the detection of and reaction time to a target at that location. The converse is also true; the more slowly attention is oriented, the slower the RT. An index of the speed of orienting attention (the Orienting Effect), then, compares the RT to short cue-to-target delays with the RT to long cue-to-target delays on valid trials (Fig. 3). Using this measure, Townsend et al. (1996a) demonstrated that patients with acquired focal neocerebellar lesions and autistic patients were substantially slower to orient attention than patients with focal frontal lesions, patients with parietal lesions, patients with developmental language delay (DLD), patients with attention-deficit/hyperactivity disorder (ADHD), normal children, and normal adults (Fig. 3).

These findings have been confirmed and extended by a new motor-free

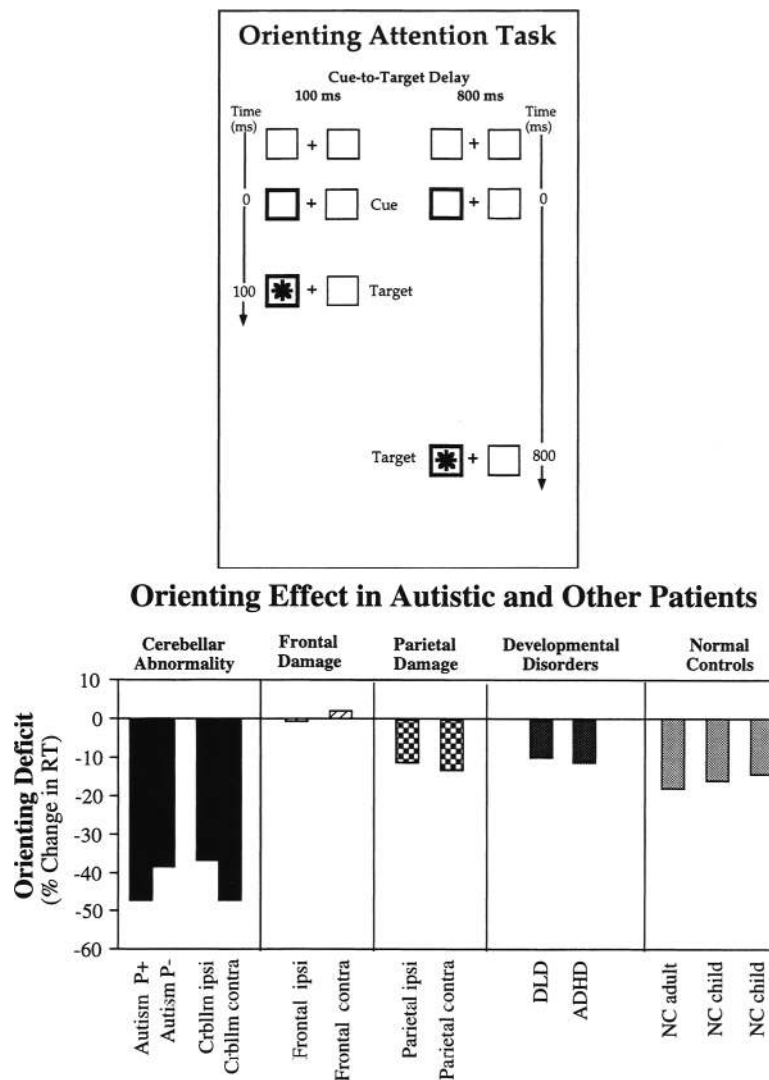


Figure 3: (Top) Diagram of one version of the Posner visual spatial attention task. Trials begin with the basic visual display, followed by the cue onset (box brightening) and 100 or 800 msec later by the target onset (asterisk). Subjects press a button in response to the target stimulus (Adapted from Townsend et al. 1996a). (Bottom) On such Posner tasks, patients with acquired neocerebellar lesions and autistic patients are slower to orient visual attention than patients with cerebral lesions, ADHD, DLD, or three groups of normal control subjects. The Orienting Effect is a measure that compares the RT to the short 100 msec cue-to-target delays with the RT to the long 800 msec cue-to-target delays on correctly cued trials [(RT at 800 msec) minus (RT at 100 msec) divided by (RT at 800 msec) times 100%]. By this measure larger negative scores mean a larger Orienting Deficit with the short 100 msec cue-to-target delay. P+ is data from autistic patients with MRI evidence of parietal volume loss; P- is data from autistic patients with no parietal volume loss. Data from patients with acquired neocerebellar lesions were from Townsend et al. (1996a); data from patients with unilateral parietal damage were from Posner et al. (1984); data from five patients with unilateral frontal lobe damage from pilot studies were adapted from Townsend, Courchesne, and colleagues (Courchesne 1995); adult normal control subjects from Townsend et al. (1996a); children with ADHD and normal control children from Swanson et al. (1991); normal controls and children with DLD from Nichols et al. (1995). (Adapted from Townsend et al. 1996a).

design in which accuracy of the attention-dependent discrimination, and not speed of the motor response, serves as an index of orienting attention effects (Townsend et al. 1996b).

In sum, studies of patients with neocerebellar damage have shown that such damage does slow the initiation or decrease the accuracy of operations that mobilize changes in attention, but it does not eliminate such operations.

NEW NEUROIMAGING EVIDENCE

The relatively recent arrival of fMRI brought with it the possibility of investigating the role of the healthy, normal cerebellum in attention. The first fMRI study to do this (Allen et al. 1997) was aimed at addressing two questions: (1) Is the cerebellum involved in attention operations that do not utilize the motor system; and (2) if there is such cerebellar involvement in attention, is it localized to the same region(s) involved in movement, or is it differentially localized within the cerebellum? This study employed three tasks. During an Attention task, circles, squares, or triangles in red, green, or blue were presented one at a time at a central fixation point. Subjects silently counted target stimuli (squares or red shapes) within a predetermined visual dimension (form or color). Thus, this task required attention in the absence of a motor response. During a Motor task, subjects repeatedly executed a self-paced, right-hand movement in the absence of visual stimulation. This movement was then used in a final, attention-with-motor task, in which subjects responded to each target using the right-hand movement rather than silently counting target stimuli. To control for visual sensory stimulation, activation during both the attention and attention-with-motor tasks was compared with activation during passive visual stimulation, during which subjects observed the same set of visual stimuli but did not selectively attend or respond to targets. The motor task was compared with rest.

Thus, this study was designed to dissociate the involvement of the cerebellum in attention from its involvement in motor output and sensory input. Such a dissociation was essential. The cerebellum has long been considered a motor control structure, and it receives input from a variety of sensory systems. Therefore, 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 activation. The Attention task controlled for motor output by employing a silent counting response involving neither the planning, the preparing, nor the executing of overt movements. As all stimuli were presented at a single spatial location in the center of foveal vision, eye movement activation was not predicted to occur. Moreover, previous work would predict that had eye movements occurred, the resulting activation would have been observed in the cerebellar vermis (Petit et al. 1996), a region not activated during the Attention task. All areas that were active 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 results. Furthermore, when four subjects were instructed to silently count from 1 to 10 repeatedly in the absence of any visual stimuli, no cerebellar activation was observed within the most common and prominent site of attention-related activation. Finally, as visual sensory stimulation was the baseline control condition to which the two attention tasks were compared, this study controlled for sensory input as well.

By employing the above controls, the cerebellum was shown to be

involved in selective attention operations independent of its involvement in motor output and sensory input. This involvement was dissociated neuroanatomically from cerebellar involvement in motor operations, with motor output activating the right anterior cerebellum and attention activating the superior posterior cerebellum, most prominently on the left (Fig. 4). Moreover, there was a sharp distinction between the manner in which motor output and attention activated these separate cerebellar regions. At the onset of the motor task, which was performed without any visual sensory stimulation, there was a transient increase in activation in the Attention hotspot, that is, in each subject, the maximally activated voxel in the left superior posterior cerebellum during the Attention task (Fig. 5A). This pattern of activation suggests that the initiation of the required motor output involved some degree of attention, but sustaining these simple actions did not. In contrast, during the Attention task, which was performed in the absence of motor planning or execution, there was no increase in activation in the Motor hot spot, that is, in each subject, the maximally activated voxel in the right anterior cerebellum during the Motor task (Fig. 5B). This suggests that neither the initiation nor the sustained execution of the Attention task required the use of cerebellar regions most involved in the Motor task. These results emphasize the functional independence of cerebellar involvement in attention; motor activation required attention, but attention activated the cerebellum irrespective of visual sensory input or motor output (Allen et al. 1997).

Recently, a separate group replicated the shifting attention paradigm developed in our laboratory (Akshoomoff and Courchesne 1994) and used

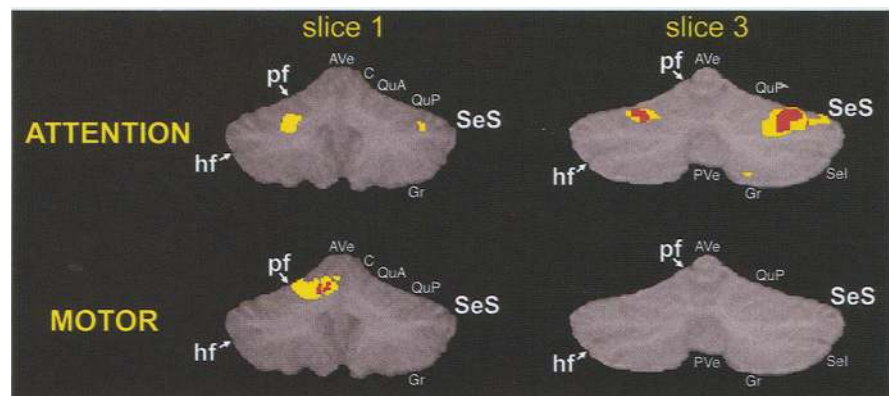


Figure 4: Functional maps demonstrating the most common sites of activation across subjects overlaid on averaged coronal anatomical images of the most anterior slice position (slice 1) and the most posterior slice position (slice 3) of the cerebellum analyzed. (Red) Overlap of three or more subjects; (yellow) any two subjects. 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 ($x = -37$, $y = -63$, $z = -22$)]. 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 ($x = 7$, $y = -51$, $z = -12$)]. (pf) Primary fissure; (hf) horizontal fissure; (PVe) posterior vermis; (Sel) superior portion of the semilunar lobule; (Gr) gracile lobule. (Adapted from Allen et al. 1997).

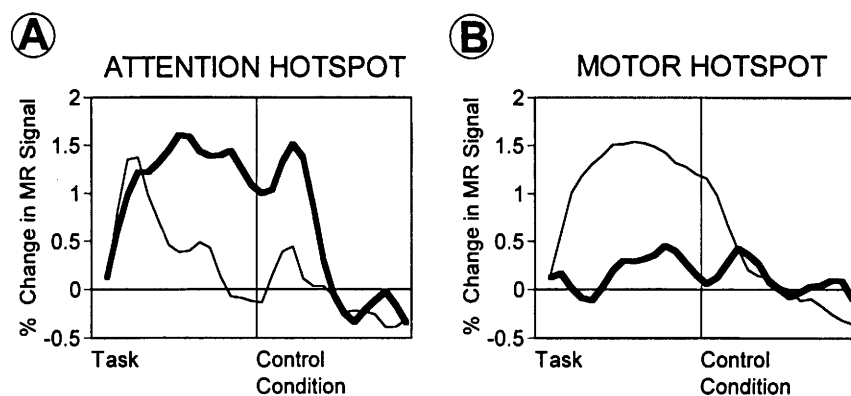


Figure 5: Intertask comparisons within averaged Attention (A) and Motor (B) Hot spots. For each hotspot, the time course signal data for each subject were averaged, collapsed across the four cycles between task and control conditions, and plotted in terms of percent change in MR signal. (Thick line) Attention task activation; (thin line) Motor task activation. (Adapted from Allen et al. 1997).

it to investigate with fMRI the role of the normal cerebellum in shifting attention (T.H. Le and X. Hu, unpubl.). These investigators reported that compared to sustained attention on a single dimension within the visual modality (e.g., color), shifts of attention between different dimensions induced activation in the right lateral cerebellum in all subjects and the ventral dentate nucleus in nearly half of subjects. This demonstration confirmed the predictions of previous neurobehavioral and neurophysiological studies: The healthy, normal cerebellum is involved in the dynamic control of attention.

ANIMAL STUDIES

In the theory of cerebellar preparatory function, the cerebellum predicts what is likely to happen next and what neural network conditions may therefore be needed, and then it signals preparatory changes in neural responsiveness of those networks expected to be needed in upcoming moments. Animal studies show that the cerebellum is in a position to be involved in specific as well as global preparatory processes.

First, animal studies show cerebellar involvement in arousal, alerting, and attention. In the report of the discovery of the reticular activating system (RAS), cerebellar stimulation was found to modulate the RAS response (Moruzzi and Magoun 1949), and subsequent experiments found that cerebellar stimulation triggers behavioral and parietal EEG alerting responses in primates (e.g., Siegel and Wepsic 1974). The size of the cerebellar molecular layer in normal rats is positively correlated with the degree of attention to novelty (Anderson 1994). Also, the cerebellum has connections with brain stem, thalamic, and cerebral systems involved in attention (for review, see Akshoomoff and Courchesne 1992; Courchesne et al. 1994).

Second, when the cerebellum in fish and mammals is activated in advance of sensory information, neural responsiveness to subsequent sensory events is altered in nonmotor brain stem, thalamic, cerebral, and hippocampal sites. Such effects have been documented for visual, auditory, somatosensory, and nociceptive stimuli (e.g., Newman and Reza 1979; Crispino and Bullock 1984; Liu et al. 1993). For example,

stimulation of cerebellar vermal lobules VI and VII in awake but nonbehaving rats modulates superior colliculus (Crispino and Bullock 1984) and hippocampus (Newman and Reza 1979) responses to a sensory stimulus if the vermis stimulation occurs in advance of the sensory stimulus. The effectiveness of cerebellar stimulation varies with time and is described by a response modulation tuning curve with the optimal peak being at 50 msec *in advance of the subsequent sensory stimulus* (Fig. 6). This modulation is independent of motor involvement.

Third, when the cerebellum is activated in advance of sensory information, there is a signal-to-noise enhancement of subsequent sensory responses in brain stem, thalamic, and cerebral sites. This is a crucial property of cerebellar functioning because it allows the optimization of neural conditions for the acquisition of sensory information. For instance, when background luminance is sufficient to reduce to noise levels the colliculus response to a flash stimulus, stimulation of cerebellar vermal lobules VI and VII in rats causes the colliculus response to that flash to emerge above noise levels *if the cerebellar stimulation occurs in*

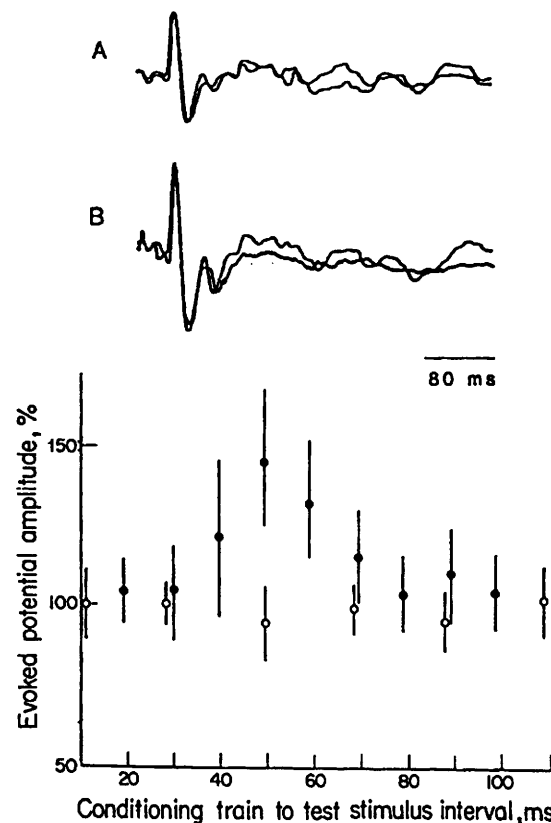


Figure 6: (Top) Effect of cerebellar stimulation on the flash-evoked potential in the superior colliculus in the rat. (A) Control response; (B) after cerebellar stimulation applied 50 msec before flash. Superimposed averages, 64 sweeps each. (Bottom) Relationship between the relative amplitude of the superior colliculus flash-evoked response and the interval between cerebellar stimulus and flash in the rat. (○) Control responses; (●) responses after cerebellar stimulation. Bars represent the whole range of responses. Each point is the average of four experiments of 64 stimulus presentations each. (Adapted, with permission, from Crispino and Bullock 1984).

PREDICTION AND PREPARATION BY THE CEREBELLUM

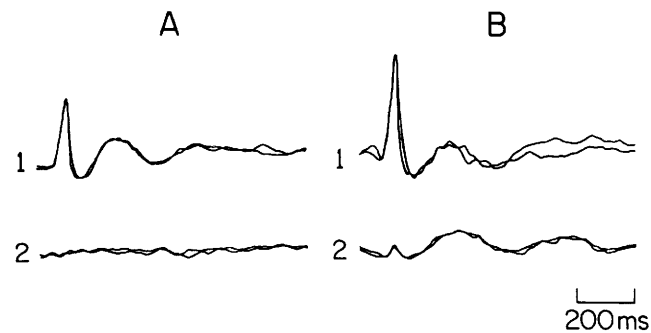


Figure 7: Combined effects of background illumination, flash, and cerebellar stimulation on superior colliculus evoked potentials. (A, 1) Control response to flash; (A, 2) abolition of such response by addition of background light; (B, 1) response to flash after cerebellar stimulation; (B, 2) response to flash, under background illumination, after cerebellar stimulation. Superimposed averages, 64 stimulus presentations. (Adapted, with permission, from Crispino and Bullock 1984).

advance of the visual stimulus (Crispino and Bullock 1984) (Fig. 7). This improvement in signal-to-noise is independent of motor involvement.

This cerebellar property may help explain the poor performance of patients with cerebellar lesions when they must rapidly orient attention to detect a brief flash of light. In the Posner paradigm (Fig. 3, *top*), the box brightening serves as a conditioned stimulus to a subsequent flash of light. We suggest that the normal cerebellum facilitates detection performance by learning this association and using the box brightening as a signal to enhance signal-to-noise conditions (e.g., in the superior colliculus) in preparation for the subsequent flash. As in the Crispino and Bullock experiments, this cerebellar preparatory response enhancement period may be brief. Therefore, lesions of the cerebellum would be expected to impair this preparatory enhancement mechanism and so, impair detection of the subsequent flash. Such impaired detection abilities have been reported in patients with neocerebellar lesions, as discussed above (Townsend et al. 1996a,b) (Fig. 3).

Fourth, the cerebellum appears to be able to effect global preparatory actions, in addition to its ability to effect sensory modality specific changes. Stimulation of the fastigial nucleus in rats, cats, rabbits, and primates increases rCBF throughout the brain, and in the rat, such rCBF increases in cerebral cortex, hippocampus, and amygdala were independent of changes in metabolism (Nakai et al. 1983). The investigators hypothesized that the fastigial nucleus “may elicit preparatory changes in rCBF to increase flow of substrate for cerebral metabolism, in anticipation of the possibility of a more widespread increase in metabolism elicited by the (subsequent) actual performance of behaviors.”

Fifth, the effectiveness of preparatory cerebellar activation lasts for variable lengths of time, perhaps thereby allowing the cerebellum to help smoothly integrate rapid moment-to-moment response demands within a larger and longer-term goal-oriented framework. At one extreme, the cerebellar preparatory response enhancement period lasts on the order of 50 msec (Crispino and Bullock 1984) (Fig. 6). At the other extreme, following the cessation of cerebellar stimulation, the subsequent changes to pain thresholds in primates (Siegel and Wepsic 1974), to neural spike

activity in parafasciulus thalami evoked by noxious stimulation in rats (Liu et al. 1993), and to somatosensory cortex responses in humans (Snider and Mitra 1970) last for many minutes.

The preparatory role of the cerebellum encompasses motor functions as well as nonmotor sensory, attention, or even cerebrovascular functions. For instance, in the monkey, repeated perturbation of a handheld object has been shown to evoke preparatory increases in grip force that occur in anticipation of perturbation. These changes in grip are accompanied by the modulation of simple spike discharges in cerebellar Purkinje cells (Dugas and Smith 1992). Likewise, changes in amplitude of the vestibulo-ocular reflex (VOR) have been shown to occur in anticipation of changes in vergence angle, and transient Purkinje cell discharges in association with such changes in vergence occurred “early enough to drive the changes in VOR amplitude” (Snyder et al. 1992).

Using their own model of cerebellar function, Coenen and Sejnowski (1996) computationally reproduced results similar to those of Snyder et al. (1992). These investigators also view the cerebellum as a structure that learns to predict neural events, and “therefore is particularly successful in anticipating the temporal sequences of events experienced repeatedly” (Coenen and Sejnowski 1996). In this model, the deep cerebellar nuclei are specialized to encode immediate or short-term predictions, whereas the cerebellar cortex, because it receives much more complete neural contextual information, can inhibit these short-term predictions of the cerebellar nuclei and replace them with longer-term, higher-quality predictions. In addition, in this model, the inferior olive integrates inhibitory input from the deep cerebellar nuclei and excitatory sensory inputs to compute a prediction error that is then reported back to the cerebellar cortex. Inhibitory input is also used to modulate the synchronous firing of olivary neurons and thus change the number of climbing fibers reporting the prediction error, which in turn changes the number of Purkinje cells that will be utilized to learn a given prediction. Thus, in this model the cerebellum serves a predictive function that is “under the regulatory control of the inferior olive” (Coenen and Sejnowski 1996).

Another recent hypothesis is that the cerebellum guides movements so as to improve the “quality of sensory information” received (Bower and Kassel 1990; Gao et al. 1996). According to this model, during active tactile exploration of novel objects or environments, or during a search for a known and expected tactile stimulus, the cerebellum uses movement as a tool for repositioning tactile receptors so as to “improve the efficiency of sensory processing (*) by the rest of the nervous system.” If we insert into this quote at the * the phrase “of subsequent stimuli,” then we have a more complete account of the preparatory purpose of cerebellar signals that affect the repositioning of tactile receptors. That is, such motoric repositioning is a *preparatory action* occurring in advance of the next moment of sensory acquisition and serving to set conditions needed for that predicted moment of acquisition. In this way, the cerebellum may use movement to accomplish goals that are comparable as well as complementary to those achieved by the nonmotor repositioning of the focus of attention. Thus, the particular hypothesis that the cerebellum “adjusts” movement to improve acquisition of anticipated tactile information is fully consistent with the general theory of cerebellar function presented herein.

Additionally, because the cerebellum can improve the quality of sensory information *without* any movement (Fig. 7), the common denominator of functional importance is not motor control alone but, rather, preparatory control involving a wide variety of mechanisms (e.g., motor, sensory, attention, cerebrovascular).

Functional Neuroimaging Evidence of Cerebellar Involvement in Learning

CONDITIONAL ASSOCIATIVE LEARNING

For the cerebellum to implement preparatory responses, it must signal activations according to predictions about what is about to happen. This requires prior learning of temporally ordered sequences of endogenously derived and exogenously derived neural activities. A wealth of evidence from PET and fMRI studies as well as animal studies supports a role for the cerebellum in such learning.

The idea that the cerebellum might be involved in associative learning dates back decades (e.g., Brogden and Gantt 1942). In 1971, Asdourian and Preston showed that cerebellar stimulation can serve as a conditioned stimulus. They suggested that “if an animal can utilize activity originating in the cerebellum as a signal for some subsequent event, then the traditional role assigned to the cerebellum as a silent coordinator of sensory-motor functions will need reevaluation.”

Presently, the importance of the cerebellum to associative learning has been well documented (McCormick and Thompson 1984; Krupa, Thompson and Thompson 1993) and confirmed independently with PET by three groups (Molchan et al. 1994; Logan and Grafton 1995; Blaxton et al. 1996). All three examined activation during the acquisition of an association between a tone and an air puff to the right cornea. The first such study measured regional cerebral blood flow (rCBF) during three conditions: (1) unpaired presentations of the tone and air puff; (2) conditioning trials during which the tone preceded and terminated with the air puff; and (3) extinction trials during which the tone was presented in the absence of an air puff (Molchan et al. 1994). This study reported that relative to the unpaired and extinction conditions, conditioning trials resulted in significantly decreased activation in the right cerebellar cortex. In the second study, which measured relative cerebral glucose metabolism, Logan and Grafton (1995) also compared activity during the presentation of random, unpaired tones and air puffs to that during paired conditioning trials. They reported that relative to the unpaired condition, activity increases in the paired condition were seen in several bilateral and midline cerebellar sites. They also showed that activity in these regions correlated positively with increases in subjects’ conditioned responses (i.e., activation correlated positively with the degree of associative learning that occurred). Finally, Blaxton et al. (1996) measured rCBF during visual fixation, uncorrelated presentations of air puffs and tones, and four separate paired conditioning trials. This design allowed a more detailed test of how activation changes over the course of acquisition. Like Logan and Grafton (1995), these investigators showed that activity increased bilaterally in the cerebellum as the number of conditioned responses produced by their subjects increased.

The proposed theory of preparatory learning predicts that the initial stages of learning in the cerebellum will be accompanied by increases in cerebellar activation. In two of the associative learning studies reviewed here (Logan and Grafton 1995; Blaxton et al. 1996), this pattern was observed. However, in one study, no increased cerebellar activation was

observed during learning, the only cerebellar finding being decreased right cerebellar cortex activation during conditioning trials (Molchan et al. 1994). What might account for this inconsistency?

A crucial aspect of any functional neuroimaging study is the careful control for unintended differences between contrasting conditions that may introduce alternate explanations for the observed changes in activation. In the case of a classical conditioning experiment in which the standard comparison is between activation induced by unpaired stimuli versus that induced by learning the association between unconditioned and conditioned stimuli, it is crucial that subjects have an equal amount of experience with both stimulus conditions prior to image acquisition. If not, the study may be more an investigation of the brain response to a novel stimulus situation rather than the response to learning conditional associations. There are indications that the cerebellum is involved in the response to novelty (Anderson 1994). Moreover, the proposed theory of cerebellar function predicts that a novel stimulus situation will elicit cerebellar activation reflecting cerebellar attempts to learn and make sense of the new environment such that it might ultimately prepare neural systems required to respond to the novel stimulus demands. Therefore, control for novelty is essential. In both studies demonstrating an increase in activation with conditioning (Logan and Grafton 1995; Blaxton et al. 1996), subjects received a number of tone and air puff presentations prior to the onset of image acquisition for both the unpaired and the conditioning trials. In contrast, Molchan et al. (1994), who reported an overall decrease in cerebellar activation during the conditioning trials, initiated the unpaired and extinction trials only 30 sec prior to the onset of the PET scan. However, for the conditioning trials, subjects had 18 min of prescan experience with the stimulus pairs for the first scan and 30 min of prescan experience for the second. Thus, prior to the unpaired and extinction conditions, subjects were exposed to far fewer trials than they were prior the learning condition. This discrepancy points to the possibility that the observed cerebellar deactivation during learning was attributable to the novelty of the unpaired and extinction conditions relative to the learning conditions. Increased activation due to such novelty may have obscured any changes due to the factor of interest, associative learning.

SEMANTIC ASSOCIATION LEARNING

In the first PET report of cerebellar activation during a cognitive task, Petersen et al. (1989) described activity increases in the right inferior lateral cerebellum when subjects spoke verbs appropriate to nouns that they saw or heard. That same group later used PET to image the effects of practice on rCBF during this verb generation task (Raichle et al. 1994). These investigators found that ~15 min of practice resulted in a significant reduction in activation in the right cerebellar hemisphere to the point that it was comparable to activation seen during simple noun repetition, whereas generation of verbs to a novel set of nouns caused activation to return to prepractice levels (Fig. 8). The investigators interpreted these results as indicating that two separate neural pathways subserve performance of the verb generation task. One pathway operates when the task is novel, and the other operates when the task is in the learned or automatic state. Raichle et al. (1994) proposed that involvement of the right cerebellar hemisphere in the task when it was novel, but not when it was learned, serves as evidence that the right cerebellar hemisphere is

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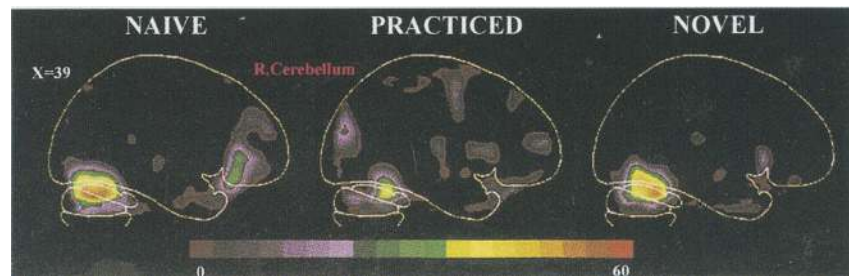


Figure 8: PET difference images show areas of *increased* blood flow in the right cerebellar hemisphere when subjects spoke a verb appropriate to a visually presented noun relative to simply speaking aloud the visually presented noun itself. The color scale is a linear scale of normalized radioactive counts, with maximum and minimum as shown. Brain outlines were traced from the stereotaxic atlas of Talairach and Tournoux (1988) and represent a sagittal slice position 39 mm to the right of midline. The three images represent the three conditions of the experiment (i.e., naive, practiced, and novel). Note the reduced right cerebellar activity in the practiced condition (*center*) that reappeared in the novel condition (*right*). (Adapted, with permission, from Raichle et al. 1994).

“of critical importance in practice-related learning and the detection of errors in a variety of tasks involving complex nonmotor processing.”

The study of Raichle et al. (1994) provides a strong demonstration of cerebellar involvement in learning outside of the pure motor domain. It is important to emphasize here that cerebellar hemisphere activity did not disappear completely when the verb generation task was in the practiced state; it simply reduced. Although the investigators suggest that this represents a shift from the use of one neural pathway to the use of another, the persistent cerebellar activity might also reflect a learning-dependent modulation in the degree to which a single pathway involving the cerebellum is being utilized. We suggest that during the “naive” performance of the verb generation task, increased cerebellar activation reflects the initial attempts at learning semantic associations and preparing neural systems involved in the required response while cerebellar activation that remained after the task had been practiced reflects more refined and efficient cerebellar preparatory learning continuing to aid neural systems required to perform this task.

PROCEDURAL LEARNING

Several investigators have examined cerebellar involvement in procedural learning, that is, learning to perform a motor action in response to a particular sensory input. For instance, the question of which neuroanatomic regions show changes in rCBF during learning of the pursuit rotor task was investigated with PET by Grafton et al. (1994). In this task, subjects are instructed to maintain contact between the tip of a metal stylus held in the right hand and a 2-cm target located on a rotating disc. The key to improving performance on this task is to learn to predict the motion of the target and the necessary location of the hand to maintain contact. Thus, as it requires the learning of predictions, this task should be especially effective in eliciting cerebellar activation. In fact, Grafton et al. (1994) showed that during the early stages of learning this task, significant increases in activation across trials were observed in the anterior cerebellum ipsilateral to the moving right hand. Furthermore, when correlating the actual rate of performance improvement with

changes in activation, the left anterior cerebellum showed a positive correlation. Together, these findings were seen as “strong support for the widely held idea that the cerebellum is critically involved in motor learning” (Grafton et al. 1994).

The structures involved in “cognitive-motor learning” were examined with fMRI (S.L. Rao, D.L. Harrington, K.Y. Haaland, J.A. Bobholz, J.R. Binder, T.A. Hameke, J.A. Frost, B.M. Myklebust, R.D. Jacobson, P.A. Bandettini, and J.S. Hyde, unpubl.). In their task, an adaptation of the serial reaction time (SRT) task, subjects executed one of four possible key presses with the right index finger in response to a visual stimulus appearing in one of four possible spatial locations. Subjects performed multiple blocks of trials consisting of a repeating 12-element sequence, that is, a nonrandom sequence that could be learned. Thus, this study provides a test of one aspect (i.e., sequence learning) of the theory of cerebellar function proposed herein. During the first five blocks of trials, subjects showed evidence of learning the sequence as indexed by decreases in reaction time. This learning was paralleled by significantly increased activation primarily in the left lateral cerebellum as compared to activation during rest. The investigators argued that this pattern of activation demonstrates the importance of the left lateral cerebellum to cognitive-motor sequence learning, and they also pointed out that the left lateralization of the activity modulations suggests that the effect was unrelated to the motor aspects of the task. In fact, this lateralization is consistent with the involvement of the cerebellum in learning sequences to aid performance of the task at hand. In this case, the task at hand has a significant visual spatial attention component, a type of task thought to involve the right cerebral hemisphere more than the left and, hence, the left cerebellar hemisphere more than the right.

In another test of cerebellar involvement in sequence learning, Jenkins et al. (1994) imaged with PET while subjects learned by trial and error a sequence of key presses in response to a pacing tone. Subjects were scanned during rest; during learning of a new, unfamiliar sequence; and during a prelearned, highly practiced sequence. During the unfamiliar sequence, activation foci were seen bilaterally in the cerebellar cortex and the cerebellar nuclei in addition to the vermis, whereas during the prelearned task, only the vermis and nuclei were active. Moreover, in terms of percent signal change, the magnitude of activation during the unfamiliar sequence was greater than that during the prelearned task. So, as in Raichle et al. (1994), this study indicated that the transition from naive to highly practiced task performance is accompanied by reduced activation in the cerebellum. This study also suggests that such reductions are more prominent in cerebellar cortex than they are in the cerebellar nuclei. The investigators interpreted their results as being “compatible with the hypothesis that the cerebellum plays some role in the process by which learned tasks become automatic” (Jenkins et al. 1994).

Finally, Flament et al. (1996) used fMRI to measure cerebellar involvement in three different conditions of a tracking task requiring subjects to use joystick movements to superimpose a cursor on eight targets appearing one at a time at eight different spatial locations. In the “standard” condition, joystick movement corresponded exactly with movement of the cursor. In the “random” condition, there was no predictable relationship between joystick and cursor movement. Finally, in the “reversed” condition, the relationship was constant but reversed

such that joystick movement in one direction caused cursor movement in the opposite direction. During the random condition, performance was initially impaired, it did not improve with practice, and activation in “both intermediate and lateral cerebellar cortex” was sustained at levels exceeding that seen during the standard condition. On the other hand, repeated trials of the reversed condition resulted in improved performance and a related decrease in cerebellar activation such that it approximated that seen in the standard condition (Fig. 9).

Based on the finding that the greatest amount of cerebellar activation was observed when performance was at its worst, these investigators interpreted their results as being consistent with a cerebellar role in “error detection and correction” (Flament et al. 1996). A slightly different, but equally consistent, interpretation suggests that the activation changes reflect the cerebellum learning to predict the relationship between hand and cursor movement to prepare other neural systems involved in the required response. With experience, the quality and precision of the predictions improve, partly through the detection of “errors” of prediction. Such errors are incorporated into continued learning, which in turn recruits less and less neural tissue as prediction and preparation become more precise. The ultimate, observable result is reduced cerebellar activation.

An additional finding in the study of Flament et al. (1996) was that whereas cerebellar cortex activation decreased across trials, activation in the dentate nucleus remained elevated throughout all trials of the “reversed” condition. From this, the investigators suggested that the role of the dentate in learning “may differ from that of the overlying cortex”

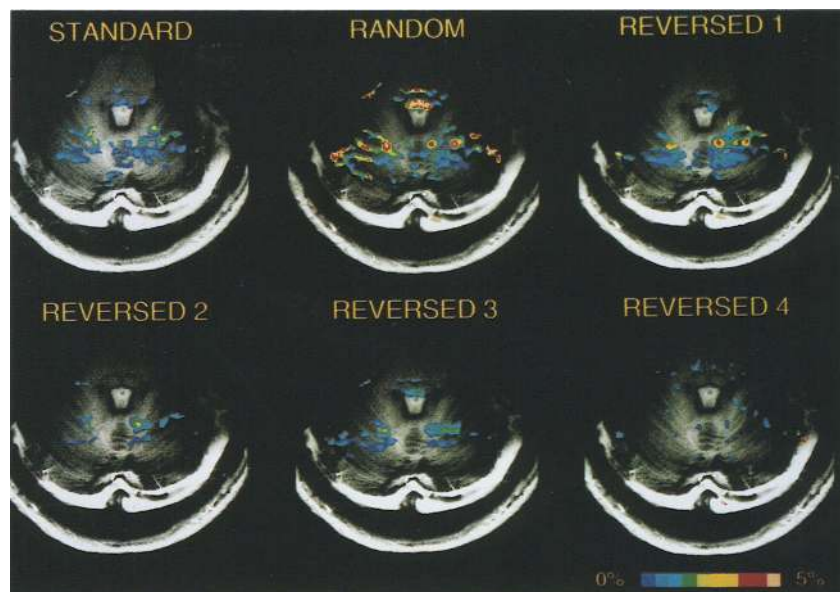


Figure 9: Functional activation maps for a single subject showing the different task activation results on an axial section through the cerebellum at the level of the dentate nuclei. Note that the greatest amount of cerebellar activation occurred during the random task and then decreased as the subject gained experience with the reversed task. (Reprinted from Flament et al. 1996, by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Copyright 1996.).

(Flament et al. 1996). We suggest, in accordance with the proposed theory of cerebellar preparatory learning, that the sustained deep nuclei activation in this study, in addition to that seen in the study of Jenkins et al. (1994), reflects continued cerebellar preparatory output to neural systems required to perform the respective tasks. Although activation in certain regions decreased as learning and prediction improved, preparatory output was continuously required to facilitate task performance, and the related activation was sustained throughout the task.

MOTOR SKILL ACQUISITION

A final approach to investigating cerebellar involvement in learning is simply to examine functional activity changes accompanying the progression of a particular motor action from a novel to a more automatic state. This approach was used by Friston et al. (1992), who employed a factorial PET design intended to examine rCBF changes accompanying practice of a finger-to-thumb opposition task. To avoid obscuring learning-related changes in activation with changes due to increased movement rate, these investigators maintained movement at a constant rate. In doing so, they demonstrated that experience was accompanied by an attenuation of activation in the right lateral cerebellum and the medial cerebellum at the level of the cerebellar nuclei (Friston et al. 1992). Similarly, Seitz et al. (1994) imaged with PET while subjects learned to write novel ideograms with the right hand. Initial performance of the novel writing task resulted in significant increases in activation in the right dentate nucleus and the vermis. However, activation of the dentate was reduced during the execution of more automatic or overlearned writing movements (i.e., rapid writing of r's).

Unlike other functional neuroimaging studies investigating a cerebellar role in learning, these two studies reported reductions in activation in the cerebellar nuclei accompanying skill acquisition. Based on the theory of cerebellar preparatory learning, activation in the cerebellar nuclei is hypothesized to continue throughout performance of the task at hand. However, with experience, the preparatory output should approach a state of optimal quality. As greater precision is achieved, there may be a refinement in the amount of cerebellar activity required to prepare other neural systems, and activation reflecting the preparatory output may in turn decrease. Simpler tasks will allow quicker progress through the learning process. In turn, preparatory responses should be optimized much sooner. The motor skill acquisition tasks employed by Friston et al. (1992) and Seitz et al. (1994) both had a relatively low level of difficulty, as they did not involve the complex stimulus-response associations characteristic of procedural learning tasks. Because these tasks were relatively simple and repetitive, once the initial preparatory signals were generated by the cerebellum, little more adaptation should have been required before subjects reached a stage of optimal performance. Thus, the attenuation in activation of the cerebellar nuclei that was observed during the acquisition of motor skills in the studies of Friston et al. (1992) and Seitz et al. (1994) may in fact have been a reflection of the cerebellar preparatory responses becoming more efficient and precise.

CONCLUSION

The cerebellum shows modulations in functional activity during a variety of learning paradigms. However, there is some variability as to the direction of change; some studies report increases in activation during

learning while others report decreases. Any attempt to reconcile this discrepancy must consider the differences in task difficulty and complexity and the related factor of where subjects were in their respective learning curves when imaging took place. We propose that the onset of learning will be accompanied by an increase in cerebellar activation that will then wane with time as a task becomes learned and ultimately automatic. However, the difficulty of a task can potentially have a profound effect on the amount of time it takes for this pattern to resolve (Fig. 10). For instance, a particularly difficult task, in which the slope of the learning curve is protracted, might be expected to result in steady increases in cerebellar activation that will be observed for an extended period of time before the direction of change turns back toward zero. One example of such a situation may be the results of Blaxton et al. (1996), who showed that cerebellar activation continued to show a steady bilateral increase through their final learning condition. At that point in

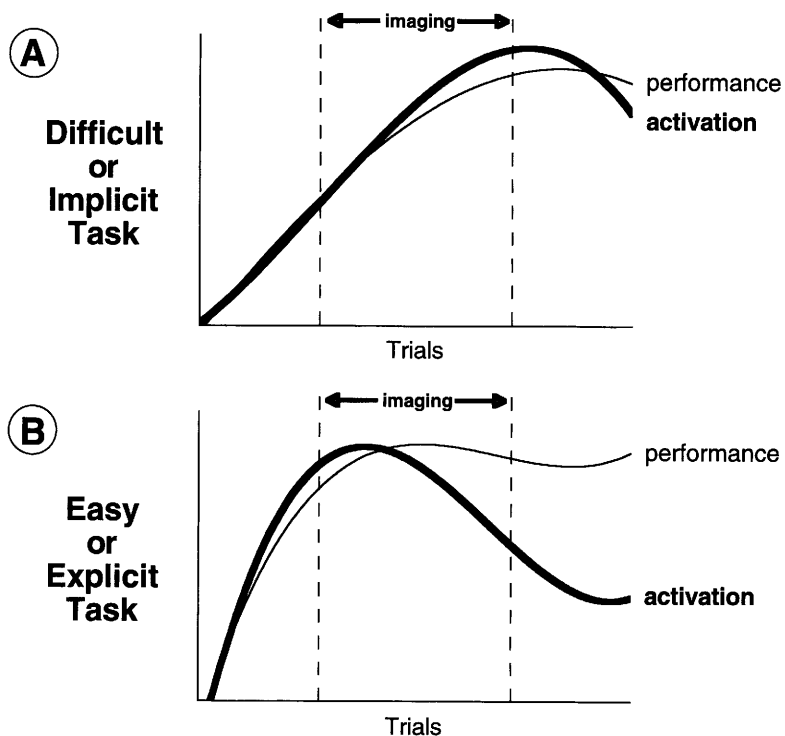


Figure 10: Hypothetical performance and activation data from two learning tasks. The general predicted pattern of learning-related cerebellar activation is that the onset of learning will be accompanied by an increase in activation that will then wane with experience as a task becomes learned. However, the difficulty of a task and the amount of explicit knowledge of the task goal possessed by subjects can profoundly affect the amount of time it takes for this pattern to resolve. (A) For instance, a particularly difficult task with a more protracted learning curve might be expected to result in steady increases in cerebellar activation for some time before the direction of change turns toward zero. (B) On the other hand, the predicted pattern is expected to resolve much sooner in less difficult tasks. The importance of taking these factors into account when designing and interpreting activation results is clearly demonstrated by this hypothetical data, in which imaging at the same relative time during two tasks produces opposite results.

time, however, the percentage of conditioned responses was only 59%. In contrast, when the task to be learned has a relatively low level of difficulty, the pattern of activation change may be expected to resolve much quicker. Here, activation will increase rapidly and then quickly turn back toward baseline levels. So, the easier a task is, the shorter the period of activation increase, and the more likely one is to image during a period of decreasing activation. For example, Friston et al. (1992) imaged subjects during the learning of a relatively simple motor task. During such a task, the duration of the initial learning phase is likely brief, as is the amount of time that transpires before activation has increased to its highest level. Thus, during such tasks, it is more likely that imaging will occur during a period of decreasing cerebellar activation.

The observed pattern of activation may also be a function of whether the ultimate goal of a task is explicitly known to the subject. It may be the case that when the goal is explicit [e.g., in the visuomotor tracking task of Flament et al. (1996)], signals from other systems (e.g., prefrontal cortex) can guide the learning process in the cerebellum and hasten the changes in activation, such that the most likely observed pattern is a reduction. However, when the goal is implicit, [e.g., in the associative learning task of Blaxton et al. (1996)], such prefrontal aid may be unavailable, thus protracting the learning process, and increasing the likelihood that the observed pattern is an increase. An important question for future neuroimaging studies is whether variations in the amount of task difficulty and/or explicit knowledge of the task goal elicit within-subject variation in patterns of cerebellar activation. Figure 10 demonstrates hypothetically how imaging at the same relative time during two different tasks can produce completely opposite results.

In addition to variability in the direction and time course of changes in activation across these studies, there is also some variability in the site of activation. All of the studies reported activation in the cerebellar cortex during learning, whereas a subset also reported activation in the deep cerebellar nuclei. A key difference between the nature of cerebellar cortex and cerebellar nuclei activations seems to be the manner in which they change over the course of learning. As described above, activation in the cerebellar cortex seems to change in parallel with other behavioral indicators of learning (e.g., reaction time). However, activation in the deep cerebellar nuclei (when evident) is more likely to be sustained beyond the point of other learning-related changes. For example, Flament et al. (1996) reported that unlike activation in cerebellar cortex, activation in the cerebellar nuclei did not change over the course of learning a visuomotor dissociation task. Likewise, although learning of an unfamiliar key press sequence led to bilateral activation of the cerebellar cortex and nuclei in addition to the vermis, performance of a prelearned, highly practiced sequence activated only the vermis and nuclei (Jenkins et al. 1994). We suggest that this discrepancy between the patterns of activation in cerebellar cortex and the cerebellar nuclei is accounted for by the differential involvement of these two regions in the different aspects of cerebellar preparatory function. Learning-related activation can wane as the learning of predictions improves, but preparatory output-related activation must be sustained as long as a task is being performed. This sustained output-related activation will be most prominent in the deep cerebellar nuclei, the sites of output to other neural systems.

Functional Neuroimaging of Cerebellar Prediction and Preparatory Learning

The proposed theory of cerebellar function suggests a reinterpretation of a wide variety of PET and fMRI results while also guiding the formulation of hypotheses about how new tasks might be expected to activate the cerebellum. For it to implement its prime preparatory function, the cerebellum must first learn sequences of temporally ordered, multidimensional, exogenously and/or endogenously derived neural activities. This is no small task. The volume of information coming into the cerebellum far exceeds that which ultimately leaves. In fact, the ratio of cerebellar afferents to efferents has been estimated to be ~40:1 (Carpenter 1991). This massive converging input to the cerebellum is hypothesized to be reflected in marked increases in functional activation as attempts at learning and integrating this input commence. Then, as learning progresses, cerebellar activation will decrease, with the rate, degree and regional extent of decrease being a function of both the difficulty and complexity of the task at hand, and the amount of explicit knowledge subjects have of the task goal (Fig. 10).

Although it is decreasing, activation specific to learning will not disappear. Rather, it is hypothesized to continue changing as long as changes in the sequence to be learned occur. What is initially a large region of activation reflecting the initial attempts at learning and generating preparatory output will ultimately become a stable area of activity reflecting the regional extent of neural tissue required to perform a particular motor or mental action whenever it is encountered in the future. At one extreme, if the sequence is random and thus constantly changing, cerebellar activation will be sustained at a relatively constant magnitude for the duration of the task as the cerebellum attempts (yet fails) to discern a meaningful and predictive pattern. In contrast, if the sequence is very repetitive and thus predictive, the cerebellum will learn quickly, and this will be reflected in a rapid decrease in learning-related cerebellar activation with experience. In the Attention task used by Allen et al. (1997), the random relationship between the target stimuli to which subjects were to respond and the nontarget stimuli that preceded them precluded the cerebellum from learning a meaningful, predictive sequence. Despite the lack of any predictive relationship between events, we argue that the cerebellum searched for one, and activation was sustained through the duration of the task as the cerebellum attempted to learn. Figure 5A shows that during the Attention task, activation was sustained at a relatively constant magnitude in the Attention Hot spot. In contrast, activation in this location showed a strikingly different pattern during a task involving simple repetitive finger movements. At the onset of this Motor task, there was a transient increase in activation in the Attention Hot spot, which then quickly returned to baseline long before the end of the task (Fig. 5A). One interpretation of this pattern is that the repetitive nature of the task, in which events occurring in the present (the motor actions) were predicted by those occurring in the past (the same motor actions), enabled the cerebellum to learn quickly. As the nature of the task went unchanged once initiated and no new learning was required, cerebellar activation in this particular region waned. This transient activation may represent the amount of neural activity from this particular cerebellar region necessary to generate a preparatory response for systems involved in performing these simple motor actions each time they are to be encountered.

Interpreting the results from the experiment of Allen et al. (1997) in

light of the proposed theory of preparatory learning also provides an explanation for certain neurobehavioral results from our laboratory (see above, Early Studies of Shifting Attention and the Cerebellum). Although the sustained attention task consistently activates the cerebellum, patients with cerebellar lesions are unimpaired when performing such a task (Akshoomoff and Courchesne 1992, 1994; Courchesne et al. 1994). Although this effect might seem intuitively paradoxical, it makes perfect sense when reconsidered in the context of a cerebellar preparatory function. As the sequence of events in this task is randomly ordered and thus unpredictable, the cerebellum is unable to learn and provide a preparatory service for systems involved in detecting and responding to target stimuli. Although the cerebellum is active in its attempts to learn the sequence, its failure to learn precludes it from providing effective aid to these regions of the CNS. Thus, when a particular sequence to be learned is completely random, the normal cerebellum has less of an advantage over the damaged cerebellum, and successful performance is not significantly impeded by cerebellar lesions. On the other hand, performance of the shifting attention task, a task that also activates the cerebellar cortex in addition to the dentate nucleus (T.H. Le and X. Hu, unpubl.), *is* impeded by cerebellar lesions (Akshoomoff and Courchesne 1992, 1994; Courchesne et al. 1994). In this task, the appearance of target stimuli cues subjects to attend to a new stimulus dimension and prepare for a target, thus entailing a predictive relationship between stimuli that the cerebellum is able to learn. In turn, the cerebellum can provide useful preparatory output to neural systems required to detect and respond to the next target. We suggest that an impairment of learning and implementing such a preparatory output may be the culprit behind impaired performance of the shifting attention task in patients with lesions to the neocerebellum.

Activation specific to learning is hypothesized to occur in the cerebellar cortex, the point of convergence for massive inputs to the cerebellum. Further predictions about within-cortex activation can be made based on the purpose for which the cerebellum is learning a particular sequence. The majority of cerebral input to the human cerebellum comes from the contralateral hemisphere via cerebro-ponto-cerebellar projections innervating the posterior lobe of the cerebellum (Ito 1984). Thus, if learning in the cerebellum is going to aid the efficient performance of a language task or a task typically performed with a verbal strategy, activation will be more prominent in the right posterior cerebellar hemisphere, as shown now by several functional neuroimaging studies employing language tasks (e.g., Petersen et al. 1989; Raichle et al. 1994; Martin et al. 1995; E. Artiges, M.J. Giraud, B. Mazoyer, C. Trichard, L. Mallet, H. de la Caffiniere, M. Verdys, A.M. Syrota, and J.L. Martinot, unpubl.) (Fig. 8). In contrast, if the cerebellum is attempting to learn a sequence to facilitate performance of a sustained, selective attention task, a type of task thought to involve right prefrontal cortex more than left (Stuss et al. 1995), cerebellar activation is expected to be more prominent in the left posterior cerebellum, as demonstrated by Allen et al. (1997) (Fig. 4).

Once the cerebellum has begun to learn a particular sequence, it will begin to predict what is about to happen and prepare other neural systems accordingly. This preparatory output will begin as soon as the cerebellum has learned enough to generate an approximation of the

sequence in an attempt to prepare other neural systems. Initially, this preparation will not be perfect, and the “error,” that is, the discrepancy between the form, degree, and timing of the preparation that is required and that which has been achieved, will be fed back to the cerebellum, aiding further attempts to learn the sequence. Such adaptive adjustments will improve the quality of a particular preparatory response. As greater precision in prediction and preparation is achieved, activation reflecting learning in the cerebellar cortex will decrease. This change may manifest as a shift from widespread activation to more focal sites of activity, as seen, for instance, in Raichle et al. (1994) (Fig. 8).

What would be the functional activation “signature” of prediction and preparation by the cerebellum? With respect to a particular sequence, this form of activation would not be expected to be apparent during the earliest attempts at learning. However, shortly after learning begins, early attempts at a preparatory output will be made, and this will be reflected in an emergence of related activation. Such activation may then decrease as the preparatory response becomes more efficient, but it will continue throughout performance of the task at hand, and it will re-emerge whenever the particular context is encountered in the future. In the functional neuroimaging studies reviewed here, cerebellar activation did not disappear completely once learning had occurred. For instance, Flament et al. (1996) reported that over the course of learning a “visuomotor dissociation task,” activation in “both intermediate and lateral cerebellar cortex” reduced but did not disappear (Fig. 9). We suggest that such cerebellar activity that remains after learning has occurred may in fact reflect a combination of preparatory output from the cerebellum to systems involved in the task, and continued learning of adaptive adjustments to the quality of this output in response to feedback from such systems.

As the cerebellum provides preparatory output to other neural systems, activation is also hypothesized to emerge in the sites of cerebellar output, the deep cerebellar nuclei. In a subset of studies reviewed here, such nuclei activation did occur. For instance, Flament et al. (1996) and Jenkins et al. (1994) both reported that the areas in which activation was sustained after tasks had been learned included the cerebellar nuclei. Overall, however, cerebellar nuclei activations have not been a common occurrence in functional neuroimaging studies of the cerebellum, and the reason for this is not completely clear. One possibility is that to observe activation in the output nuclei by conventional design and analysis methods, a task must require continuous updating in the preparatory output emanating from the cerebellum. A possible example of such a task was employed by Gao et al. (1996), who explored with fMRI the role of the cerebellum in shape and texture discrimination. These investigators reported bilateral activations in the dentate nuclei during shape discrimination involving finger movements and during texture discriminations that involved no explicit finger movements, but not during finger movements alone. The discrimination tasks used a match-to-sample design in which subjects were presented with a sample shape or texture, followed by a new shape or texture, and were then required to determine whether the new item was identical to the sample. Thus, each stimulus presentation served as a predictor for a subsequent required discrimination. This continuous presentation of predictors may have driven the cerebellar output nuclei to remain active as they

continuously prepared relevant efferents for the upcoming discriminative judgements.

Such continuous prediction and preparation may also explain the dentate nucleus activation observed in the fMRI study of shifting attention of T.H. Le and X. Hu (unpubl.). Unlike the sustained attention task employed by Allen et al. (1997), the shifting attention task enables the cerebellum to learn and generate a more precise and informative preparatory response. In this task, target stimuli cue subjects to shift attention to a new stimulus dimension and prepare for a new target. Thus, there is a predictive relationship between stimuli that the cerebellum should be able to learn quite readily. In turn, the learning of this relationship should allow the cerebellum to generate a preparatory output to neural systems required to detect and respond to upcoming target stimuli. We suggest that dentate activation in the Le and Hu study may in fact reflect such cerebellar preparatory output.

Activation in the cerebellar nuclei is hypothesized to continue throughout performance of the task at hand. However, with continued adaptive adjustments, the preparatory output is expected to approach a state of optimal quality, and as greater precision is achieved, activation reflecting such output may decrease. For instance, Friston et al. (1992) and Seitz et al. (1994) both imaged subjects during the learning of motor tasks having a relatively low level of difficulty and not involving the complex stimulus-response associations characteristic of procedural learning paradigms. During such tasks, the duration of the initial learning phase is likely brief, as is the amount of time that transpires prior to the onset of cerebellar preparatory output. Moreover, because such tasks are relatively simple and repetitive, once the initial preparatory responses are generated by the cerebellum, little more adaptation to the preparation is required before subjects reach a stage of optimal performance. Thus, during such tasks, preparatory output-related activation might actually show a decrease as the preparatory response becomes more efficient and precise. We suggest that the attenuation in activation of the cerebellar nuclei that was observed after the acquisition of motor skills in the studies of Friston et al. (1992) and Seitz et al. (1994) may in fact have been a reflection of such an optimization of preparatory output.

Whether the hypothesized patterns of cerebellar activation will be observed in any particular study is largely dependent on both the careful design of tasks and the thoughtful choice of analysis procedures. The proposed preparatory operation of the cerebellum is a dynamic process, constantly adapting to internal and external variation in an attempt to provide other neural systems with the most up-to-date preparatory information possible. Each phase of this dynamic operation is less likely to be detected in the context of the conventional subtraction or “box-car” correlation method of design and analysis, as these approaches are intended to detect simple dichotomous variation between two conditions, not the complex and dynamic patterns of change that are expected in light of the proposed theory.

Although it is dynamic with respect to a particular sequence, the proposed preparatory operation is also an ongoing function that persists as the cerebellum attempts to make sense of, or get the gist of, what is occurring at any given time. This may explain the fact that the cerebellum seems to be active in some way almost regardless of the task employed (see Table 1 for several examples). Up until now, methods of functional

image analysis have almost always involved simple comparisons between conditions. Yet, if nearly every condition activates the cerebellum in some way, then conclusions about how any one task of interest activates the cerebellum are going to be limited by conventional design and analysis procedures. Thus, future tests of cerebellar function will require far more sophisticated design and statistical approaches to investigating functional activation changes in the cerebellum.

Conclusions

A long line of research investigating diverse species and diverse operations supports the theory of a prediction and preparation learning function for the cerebellum. Studies of fish, rats, rabbits, cats, monkeys, and humans using intracerebellar stimulation, focal lesion, neurophysiological, neurobehavioral, or neuroimaging methods show that the cerebellum can and does prepare/set a variety of internal conditions in advance of sensory events and neural operations. There is experimental evidence that cerebellar signal effects can alter neural responses to subsequent sensory stimuli that occur not only milliseconds later, but also seconds or minutes later. So, this cerebellar influence can be local and brief (e.g., signal-to-noise changes in the superior colliculus), global and last for seconds (e.g., rCBF changes), or even local and last for minutes (e.g., neural responsiveness in parafasciulus).

The observations that the cerebellum can trigger changes that can last seconds or minutes stand in contrast to the computational models and traditional experiments (e.g., eye-blink conditioning, VOR) that support cerebellar associative learning and prediction time scales in the millisecond to hundreds of milliseconds range. This contrast highlights the need for new computational models of the cerebellum and new designs for experiments of cerebellar associative learning that will bridge this “temporal gap.” Previous concepts of the cerebellum have tended to be derived from an unnecessarily narrow base of sensory and motor experimental paradigms and data. The explanatory power of such concepts may be correspondingly limited. For instance, how do motor control, motor learning, sensory tracking, error detection and correction, or timing hypotheses of the cerebellum account for the reciprocal cerebellar connections with virtually all hypothalamic nuclei (Haines and Dietrichs 1987), for cerebellar modulation of parafasciular neuron responsiveness to noxious stimuli (Liu et al. 1993), or for cerebellar stimulation affecting rCBF? It is likely that more powerful explanatory concepts will emerge in the future as the paradigm and databases are broadened.

At present, a large body of neuroimaging and neurobehavioral evidence in humans shows cerebellar involvement in a remarkably diverse array of cognitive as well as noncognitive operations (e.g., Table 1). The current preparatory theory of the cerebellum helps to explain the involvement of the cerebellum in this wide array of operations; it helps to explain the functional importance of massive input from cerebral cortical association areas, particularly prefrontal, which may be crucial during initial, conscious-controlled stages in preparatory learning; and it moves us away from the “motor mind-set” that has stood for so long as a roadblock limiting our ability to fully comprehend the function of the cerebellum.

The fact that virtually any sensory, motor, or cognitive task can lead to cerebellar activation is a phenomenon that, like the question of cerebellar function itself, has either perplexed or been ignored by the majority of

neuroscientists for many years. It is our hope that the theory proposed here will provide neuroscientists with a fresh viewpoint from which to reconsider cerebellar involvement in operations ranging from simple motor actions and cerebrovascular control to complex executive functions.

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