Thinking about the cerebellum

The cerebellum – motor control or more?
Prompted by functional imaging studies, there have been a number of recent suggestions that the cerebellum may be involved in functions other than motor control. Lesions or abnormalities of the cerebellum have been claimed to be associated with cognitive deficits and autism; and the cerebellum is said to control shifting attention and be active both during the performance of cognitive tasks and in short-term memory. Many of these reports are summarized in Schmahmann and Sherman (1998). The paper by Susan Ravizza and colleagues in this issue of *Brain* reports the results of a series of studies comparing the performance of cerebellar patients with that of normal control subjects on short-term memory tasks.

It is difficult to evaluate suggestions about affective or cognitive functions for several reasons. Lesions of the cerebellum may not occur in isolation. Traumatic, vascular, developmental anomalies and tumours typically cause damage to brain structures outside of the cerebellum and treatments associated with cerebellar resection, such as chemotherapy and radiation, may themselves produce cognitive deficits (Drepper et al., 1999; Konczak et al., 2005). Additionally, there is a one-way valve in the literature whereby negative results are harder to publish than positive results; failures to replicate published findings pose a challenge to the acceptance of claims for a role for the cerebellum in cognition or mental illness.

Suggestions for a cognitive role of the cerebellar hemispheres are not new. Although nineteenth century neurologists recognized that lesions of the midline cerebellum produce deficits in eye movements and equilibrium, they found that cerebellar hemispheres often seemed to be unrelated to those functions. Thus, Gowers (1888) suggested that there might be some validity to the idea of a cognitive function for the cerebellum, whilst André-Thomas (1912) disagreed.

Participation in short-term memory has been suggested to be one non-motor function of the cerebellum, but as Fig. 2 of the present paper shows, the association is weak. Cerebellar lesions were associated on average with only a single digit difference in the ability to recall a list of verbally presented digits. There was no difference between the patients and control subjects in backward recall and, contrary to the authors’ expectation, there were no differences in this task between patients with damage to the right or left side of the cerebellum. The authors suggest that one reason for the failure of other authors to find differences between patients and controls might be due to small sample sizes, but even in cases in which differences are statistically significant, they may be rather weak and associated with chemo- or radiotherapy rather than cerebellar loss (Drepper et al., 1999). The strongest association in the present study is the correlation between motor deficit and the short-term memory tasks.

Verb generation is an aspect of language function in which the cerebellum has been implicated. For example, Fiez et al. (1992) reported a detailed neuropsychological study of a single patient who had sustained a massive lesion of the right cerebellar hemisphere caused by a stroke. The most distinctive feature of this man’s difficulty was revealed in a word generation task. Presented with a noun, he was asked for an appropriate verb. Compared with a healthy control group, the patient produced a number of atypical or inappropriate responses. Fiez et al. (1992) suggested that with the right half of the cerebellum damaged, the left cerebral cortex and its language areas would be deprived of their normal input, hence the inappropriate choice of verbs. Two groups failed to replicate this finding. Richter et al. (2004) tested 10 subjects with degenerative cerebellar disorders associated with reduced cerebellar volume, and compared their responses to those of ten healthy age-matched control subjects. Although the patients had slower response times both in control naming tasks and in verb generation, their ability to learn to reduce verbal response times across blocks of trials was preserved.

**Anatomical evidence: cerebellum and pre-frontal cortex—the ‘re-entrant circuit’**

Anatomical studies have been put forward in support of a possible role for the cerebellum in cognition. The cerebellar hemispheres in humans as well as in the old world primates and great apes are very large (Matano et al., 1985). The hemispheres project to the dentate nucleus, which is the largest of the cerebellar nuclei in man and the higher primates. Peter Strick and his colleagues (Kelly and Strick, 2003) injected the prefrontal cortex of a monkey with a trans-neuronal retrograde tracer and found that injections into prefrontal cortex labelled cells in the ventral dentate nucleus. They suggested that this link to the prefrontal cortex is part of a pathway whereby the cerebellum influences cognitive functions. They put forward a comprehensive characterization of the relationship between cerebral cortex and cerebellum. In analogy to the connections of the basal ganglia, they proposed that the connections are reciprocal. A region of cerebral cortex would project via the pontine nuclei to the cerebellar cortex; the output from this area of the cerebellum would project back to that same region of the cerebral cortex. Strick’s anatomical study is sufficient to show there is
a link from dentate to prefrontal cortex. But since the same prefrontal injections also labelled lobules VII, the oculomotor vermis, it seems premature to assume that this pathway serves solely cognitive and not motor functions.

**Autism**
The cerebellum has also been implicated in mental disorders. Courchesne et al. (1988) studied mid-sagittal images of the cerebellum in autistic children and age-matched controls. In their first report (Courchesne et al., 1988), they noted that lobule VI of the vermis of the cerebellum was smaller in children with autism. In a later report (1991), they found that in some cases lobule VI was actually larger in a sub-group of autistic children. The claim that lobule VI is either smaller or bigger than normal in autistic children does not prove that a deficit in cerebellar development is the cause. If there is a deficit that affects normal brain development including the cerebellum, and autism is related to deficits in structures other than the cerebellum, the easiest place to quantify differences would be to study the relative size of cerebellar lobules in a mid-sagittal section of the cerebellum.

**What might the hemispheres do?**
The Dutch anatomist Bolk (1906) suggested that the cerebellum is arranged in a medio-lateral organization. The midline vermis he proposed, controls proximal muscles, hemispheres, distal muscles. Bolk erred in assuming only a single representation of the body on the cerebellar cortex (Glickstein and Voogd, 1995), but his medio-lateral organization principle remains an intriguing one. Consistent with Bolk’s view, one important function of the hemispheres is control of the fingers (Glickstein et al., 2005). The deficit caused by lesions of the cerebellar hemispheres is similar to that caused by lesions of the pyramidal tract. Lesions of the pyramidal tract result in an inability to appose the thumb with the other fingers. The same deficit is present in monkeys with cerebellar lesions. Babinski (1902) called attention to the inability of his cerebellar patients to execute rapidly alternating movements, a deficit which he labelled disdiadochokinesis. There is anatomical evidence (Ugolini and Kuipers, 1986) that every pyramidal tract fibre gives off a collateral to the pontine nuclei as it traverses the pons. The deficit that Babinski described may be due in part to the lack of this corollary discharge to the cerebellum.

One reason for my scepticism about alleged cognitive functions of the cerebellum derives from the pattern of input that the cerebellum receives from the cerebral cortex. While in rats the entire cerebral cortex projects to the cerebellum via the pontine nuclei (Legg et al., 1989), in monkeys only about half of the input arises from those areas of the cerebral cortex that are involved in the planning of a movement or the corollary discharge from an intended movement. Thus, for example, in the case of the visual input, it arises almost entirely from the dorsal stream of extrastriate visual areas. There are no inputs to the pontine nuclei from inferotemporal cortex. Although there is a modest input from medial prefrontal cortex, there is very little or none from the more lateral prefrontal areas. Both are dwarfed by a massive projection from the frontal eye fields.

**Cerebellum and functions beyond direct control of ongoing movement**
The cerebellum is involved in several forms of motor learning: smooth-pursuit eye movements (Westheimer and Blair, 1974), adaptation of the vestibulo-ocular reflex (Robinson, 1976), saccadic adaptation (Takagi et al., 1998; Barash et al., 1999) and classical conditioning of the nictitating membrane response (Thompson et al., 1983; Yeo et al., 1985). All of these deficits appear in every case with the appropriate cerebellar lesion. The best evidence in my view for a cerebellar input to non-motor cortical targets is to the visual areas of the parietal lobe. Richard Andersen and his colleagues studied the changes in receptive field properties of parietal lobe visual cells dependent on eye and head position. I propose that it is the cerebellar input, first described by Shinoda et al. (1993) in the cat, which provides the necessary signal. A cerebellar pathway might also be involved in the visual perception of motion (Dietrichs et al., 2003).

Evidence for a critical role for the cerebellum in cognition or emotion remains unconvincing. The anatomical evidence is of interest but is incomplete. There are often failures to replicate published findings, and there seems to be a lower threshold for proof.

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Cognition, emotion and the cerebellum

The traditional teaching that the cerebellum is purely a motor control device no longer appears valid, if, indeed, ever it was. There is increasing recognition that the cerebellum contributes to cognitive processing and emotional control in addition to its role in motor coordination. Anatomical and physiological studies reveal that there is a primary sensorimotor region of the cerebellum in the anterior lobe, and a secondary sensorimotor region in the medial aspect of the posterior lobe. In contrast, cerebral association areas that subserve higher order behaviour are linked preferentially with the lateral hemispheres of the cerebellar posterior lobe—in feedforward loops via the nuclei of the basis pontis, and in feedback loops from deep cerebellar nuclei via the thalamus. There are also reciprocal connections between the cerebellum and hypothalamus. These pathways facilitate cerebellar incorporation into the distributed neural circuits governing intellect, emotion and autonomic function in addition to sensorimotor control.

The clinical relevance of these observations is found in anecdotal observations of cognitive and psychiatric manifestations of cerebellar lesions, and in the description of the cerebellar cognitive affective syndrome (CCAS) in patients with lesions confined to the cerebellum (Schmahmann and Sherman, 1998). The CCAS has subsequently been observed in adults and children with stroke, tumour, cerebellar degeneration, superficial siderosis, cerebellar hypoplasia and agenesis, and children born very preterm who have disproportionately small cerebella. These neurobehavioural deficits may occur in the absence of the cerebellar motor syndrome. They are characterized by impairments in executive function (planning, set shifting, verbal fluency, abstract reasoning, working memory), spatial cognition (visual spatial organization and memory) and linguistic processing (agrammatism and dysprosodia) when the lesions involve the hemispheric regions of the cerebellar posterior lobes. Patients with the CCAS experience dysregulation of affect when their lesions encroach upon the vermis.

Cerebellar activation by language tasks in functional imaging experiments was initially regarded as surprising, but subsequent PET and functional MRI studies show that multiple cognitive domains are associated with cerebellar activation. Further, these studies are in agreement with anatomical and clinical observations. Sensorimotor tasks activate primary (anterior lobe) and secondary sensorimotor regions. Cognitive paradigms preferentially activate different and, sometimes, discretely localized regions of the cerebellar posterior lobes.