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Dysmetria of thought: clinical consequences of cerebellar dysfunction on cognition and affect

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Cognitive and emotional changes might be prominent or even principal manifestations of cerebellar lesions. This realization supports evidence suggesting that the cerebellum is an important part of a set of distributed neural circuits that subserve higher-order processing. Early anecdotal clinical accounts described aberrant mental or intellectual functions in the setting of cerebellar atrophy. Later systematic analyses showed that the cerebellum is able to influence autonomic, vasomotor, and emotional behaviors, and further studies revealed neuropsychological deficits in patients with degenerative diseases. Current descriptions of behavioral changes in adults and children with acquired cerebellar lesions bring the debate about the cerebellar role in neural function within the realm of clinically relevant cognitive neuroscience. The activation of focal cerebellar regions by cognitive tasks on functional neuroimaging studies, and morphologic abnormalities of cerebellum in psychiatric diseases such as autism and schizophrenia further support this view. Anatomical substrates have been elucidated that could support a cerebellar role in cognition and emotion. Our concept of 'dysmetria of thought' draws an analogy with the motor system to describe and explain the impairments of higher-order behavior that result when the distributed neural circuits subserving cognitive operations are deprived of cerebellar modulation.

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The possible role of the cerebellum in sensory, cognitive and affective processing has long been overshadowed by interest in the cerebellar coordination of voluntary movement. Cerebellar motor disturbances are characterized by incoordination of the limbs (dysmetria), wide based, unsteady, and lurching gait (ataxia), speech impairment (dysarthria), and a variety of disturbances of eye movements (such as nystagmus, and overshoot and undershoot with attempted volitionally directed gaze). Midline lesions are characteristically associated with truncal ataxia, and lesions

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of the cerebellar hemispheres produce incoordination of the limbs. In degenerative diseases of the cerebellum, these motor phenomena are the major features of the clinical presentation. From the earliest days of clinical case reporting, however, instances of mental and intellectual dysfunction were described in the setting of cerebellar pathology[1,2]. Investigators in the nineteenth and early part of the twentieth centuries lacked the necessary clinical and pathological techniques to provide a clear understanding of their patients' lesions and psychiatric or cognitive disturbances. Consequently their anecdotal clinical reports have been essentially ignored. Physiologists and anatomists in the first half of the 20th century were not convinced that cerebellar function was confined to motor control. The cerebellum was shown to receive sensory projections from the periphery and from the cerebral hemispheres, as well as vagal, auditory and visual input, and it was demonstrated that the cerebellum exerts some control in the sensory sphere and on autonomic functions. The results of these investigations indicated that the interpretation of cerebellar function suggested by the careful motor analyses of Babinski, Holmes and others was too narrow. Snider[3], for example, believed that if the effects of experimental or clinical lesions of the cerebellum were analyzed by means of adequate physiological and psychological tests, aspects of cerebellar function might be unveiled beyond its role in motor control. He viewed the cerebellum as 'the great modulator of neurologic function' and predicted for it a role not only in the field of neurology, but also in psychiatry.

There is now a sizeable body of evidence that links the cerebellum with nonmotor processing. This is derived from anatomical, physiological, theoretical, and functional neuroimaging studies[4]. Contemporary clinical investigations in patients have further supported this notion. Evidence is derived from the study of patients in whom there is a disorder of cognition and in whom a search has been made for the presence of previously unsuspected cerebellar pathology. In the complementary series of investigations, patients with cerebellar lesions have been studied by neuropsychological tests to determine the presence and nature of any impairment of cognition and emotion. An implicit assumption in most of these studies is that structure and function are tightly interwoven, and that regions of the brain that are anatomically interconnected are functionally related.

Psychiatric disorders and studies of the cerebellum

The earliest reports of abnormal behaviors in association with cerebellar atrophy or agenesis described both emotional and intellectual dysfunction[1,2]. In more recent times, Heath *et al.*[5] observed increased neuronal discharges in the fastigial nucleus of an emotionally disturbed patient that correlated with the patient's experience of fear and anger. Heath later produced amelioration of aggression in patients with severe emotional dyscontrol by chronically stimulating the cerebellar vermis through subdurally implanted electrodes[6]. This technique was also employed by Riklan *et al.*[7] for achieving seizure control but it improved aggression, anxiety and depression as well. Heath *et al.*[8] performed CT scans in schizophrenics, and found abnormalities in the cerebellum in 40% of their 85 patients. The abnormal radiologic features were noted particularly in the cerebellar vermis, and included atrophy in some cases, and mass lesions in others. The cerebral hemispheres in these patients appeared radiographically normal. Vermal abnormalities in patients with schizophrenia were suggested by others as well[9–12]. In 1981 Kutty and Prendes[13] described psychotic behavior in their adult patients who had cerebellar degeneration, and Hamilton *et al.*[14] reported psychotic behavior and cognitive deficits in patients who were found at autopsy to have cerebellar degeneration, infarct, or tumor.

The search for a neurobiological substrate for autism was advanced by the finding of morphologic changes on autopsy in the amygdala, as well as loss of neurons in the deep cerebellar nuclei, depletion of Purkinje cells throughout the cerebellar cortex and particularly in the posterior lobe, and abnormalities in the inferior olivary nucleus[15]. MRI studies have shown hypoplasia of vermal lobules VI and VII (the 'neocerebellar vermis')[16] as well as of the cerebellar hemispheres[17]. Children with attention deficit hyperactivity disorder have also been shown to have statistically smaller vermal lobules VI and VII on MRI (Ref. 18), and a similar observation has been made in fragile-X syndrome[19]. These observations of morphologic changes in the cerebellum in diseases characterized by their psychopathology have been made in concert with the evolution of a new approach to the understanding of psychiatric disease, that is, in terms of the relationships between structure, chemistry, and function in the nervous system. The presence of cerebellar abnormalities in these disorders has been difficult to explain. Previous synthetic analyses[20–23] relied upon the early anatomical, physiological and behavioral literature as well as anecdotal case reports to account for a possible role of the cerebellum in the generation of these psychiatric disorders. The evolution of the many disciplines within the cognitive neurosciences, including neuropsychology, functional neuroimaging and connectional anatomy, has aided the interpretation of these cerebellar findings in psychiatric diseases, and has helped advance hypotheses regarding the nature of the cerebellar contribution to the psychopathology, as discussed later.

Cerebellar lesions and disorders of cognition and emotion

Neuropsychological studies

In the past two decades neuropsychological tests have been performed in patients with degenerative cerebellar disorders. Patients with olivopontocerebellar atrophy (OPCA) were found by Landis *et al.*[24] to have impairments in verbal and nonverbal intelligence, memory and frontal system functions. Difficulties with concept formation, learning of paired associates, visual–spatial abilities (see Box 1), and general intellectual slowing were noted in the patients studied by Kish *et al.*[25], Bracke-Tolkmitt *et al.*[26], and Akshoomoff and Courchesne[27]. Kish *et al.*[28] further observed that the degree of cognitive impairment was correlated with the severity of the ataxia. Botez-Marquard and Botez[29] reported a mild parietal-like syndrome with visual–spatial disturbances in their fifteen OPCA patients, as well as longer visual and auditory reaction times. Cognitive deficits have been

Box 1. Visual–spatial versus visual-object dichotomy in cerebellar function

The corticopontine projections (see Fig.) derived from the association areas reveal a consistent dichotomy in the visual domain. Areas that are concerned with visual motion (the 'where' pathway) and the peripheral visual field have projections to pons (the first stage in the feedforward limb of the cerebrocerebellar circuit), whereas cortical regions concerned with visual feature discrimination (the 'what' pathway) and the central visual field do not. Thus the dorsal visual stream that includes the dorsal part of the prelunate gyrus, the caudal lower bank of the cortex in the superior temporal sulcus, the polymodal convergence zones in the lower bank of the cortex in the intraparietal sulcus, and the paralimbic parts of the caudal inferior parietal lobule all project to pons. Additionally, the dorsolateral and dorsomedial prefrontal cortices concerned with, *inter alia*, the spatial features of working memory, also have projections to the pons. In contrast the ventral visual stream which includes the ventral prelunate gyrus, rostral lower bank of the superior temporal sulcus, and middle and inferior temporal gyri as well as the lateral aspects of the posterior parahippocampal gyrus do not have projections to the pons. Similarly, the ventral prefrontal and orbitofrontal cortices with which these areas are interconnected do not send projections into the basis pontis[a,b].

These anatomical arrangements suggest that the cerebellum plays a role in spatial cognition. The clinical studies performed to date are consistent with this hypothesis. Neuropsychological evaluations in patients with degenerative cerebellar diseases, and the clinical evaluations of patients with the cerebellar cognitive affective syndrome have shown that impairment of visuospatial functions is frequent. This spatial/object dichotomy in the visual domain lends itself to specifically testable predictions that can be examined using functional imaging studies.

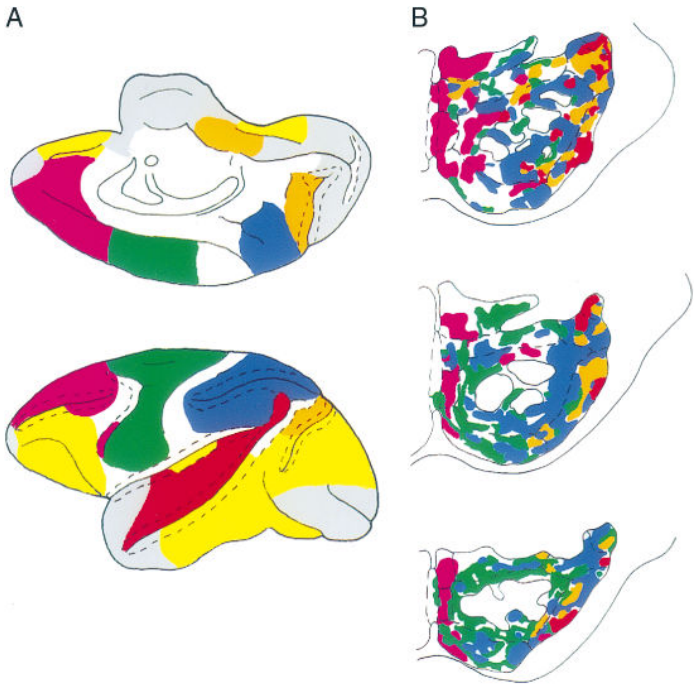

Fig. Composite summary diagram of the corticopontine projections in the rhesus monkey. (A) Anterograde tract tracers were injected into the prefrontal cortex (purple), motor and supplementary motor cortices (green), posterior parietal regions (blue), superior temporal regions (red), and parastriate and posterior parahippocampal gyri (orange) shown on medial (top) and lateral (bottom) views of the rhesus monkey cerebral hemisphere. The corresponding colors in the transverse sections of the basis pontis **(B)** (the rostral level IV of the pons at top, VI in the middle, and VIII below) represent the termination sites of these corticopontine pathways. The yellow and gray areas in (A) represent regions of cortex that received tracer injections but did not have projections to the pons (the ventral temporal, ventral and orbital frontal, and ventral prelunate cortices, and parts of the parahippocampal gyrus). (From Schmahmann[a].)

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described in patients with Friedreich's ataxia[30,31] but this has not been a consistent observation.

Neuropsychological abnormalities in patients with cerebellar cortical atrophy have included impaired executive function demonstrated by increased planning times when performing the Tower of Hanoi test[32] and poor performance on tests of fluency and the initiation/perseveration subtest of the Mattis Dementia Rating Scale[33]. Additionally, a profound deficit was noted in the acquisition of implicit procedural and declarative knowledge in a fixed sequence visuomotor association task[34] .

Wallesch and Horn[35] reported deficits in cognitive operations in three-dimensional space in patients who had tumors excised from the left cerebellar hemisphere. Visual–spatial disturbances were reported by Botez-Marquard *et al.*[36] following infarction in the territory of the left superior cerebellar artery. Botez *et al.*[37] had previously shown a number of cognitive deficits including visual–spatial impairments in a patient with chronic phenytoin intoxication. In single case reports of patients with right cerebellar infarction, linguistic processing was impaired as evidenced by agrammatism[38], decreased verbal fluency[39], and impaired error detection and practice-related learning of a verb-for-noun generation task[40].

Investigators have used patient populations to study specific hypotheses regarding cerebellar function in both motor and nonmotor domains. Cerebellar patients show deficits in their ability to learn motor skills such as rotor pursuit tasks[41] and prism adaptation[42], acquire classically conditioned eye blink reflexes[43–45], and judge the duration of short auditory stimuli or the velocity of moving visual stimuli[46]. Cerebellar patients also have difficulty on tasks that require shifts of attention between different modalities[47], and these results have been consistent with the suggestion that the cerebellum is important for anticipatory planing and prediction in a wide range of different behaviors.

Some observers have reached different conclusions regarding the performance of their patients with cerebellar dysfunction on tests of cognition. In a study of 15 hereditary and 24 sporadic cases of OPCA, Berent *et al.*[48] found that patients had a full-scale IQ on the WAIS-R of 93.46 (+/– 13.19) compared with the control subjects who scored 113.72 (+/– 12.68). The conclusion of the authors of this study was that the 20-point difference between controls and patients could be ascribed to the fact that the controls were a highly educated group and that motor dysfunction and depression accounted for the impaired performance of the patient group. This raises questions concerning the choice

of controls, an important consideration in determining if the patients are impaired or not. In a study of patients with cerebellar stroke, Gomez-Baldarrain *et al.*[49] were unable to document cognitive deficits except for mild impairments of naming. The patients and controls in this study had a mean educational level of 8 years, and the controls were regarded as being normal if their mini-mental state fell at or above a level of 23, regardless of age. These authors subsequently reported[50] that patients with unilateral cerebellar infarction demonstrated impairments of procedural learning on a serial reaction time task independent of the motor incapacity resulting from the cerebellar stroke.

Some cognitive functions appear to be spared in cerebellar lesions. Patients with cerebellar degeneration were studied by Dimitrov *et al.*[51] and tests of selective attention, spatial attention, spatial rotation and memory for temporal order were preserved. As discussed below there are likely to be differences in clinical presentation of patients who have slowly progressive cerebellar degeneration as opposed to those who have acute loss of cerebellar tissue resulting from stroke. These case reports and studies stress the point, however, that ongoing clinical investigation is required to determine specifically what functions are impaired in patients with cerebellar injury, and what is the time course of these deficits.

Clinical investigations

A persistent concern shared by investigators and clinicians is that there are very few descriptions of clinically relevant cases that address the possibility of a cerebellar contribution to nonmotor behaviors. It has been argued that detection of subtle behavioral deficits only by neuropsychological tests in patients with cerebellar lesions might be insufficient grounds to warrant a revision of the understanding of the role of the cerebellum in nervous system function. New evidence regarding the consequences of cerebellar lesions on behavior addresses this issue directly.

Posterior fossa syndrome in children

For some years surgeons have been struck by the development of mutism in approximately 15% of children 1–4 days following resection of tumors of the cerebellar vermis[52–54]. In the study of Pollack *et al.*[53] the mutism was associated with an almost stereotyped response, with the children lying curled up in bed and whining inconsolably without speaking intelligible words. They seemed unable to initiate voluntary eye opening. They were unwilling or unable to eat, had difficulty initiating the chewing or swallowing process, and displayed an impairment of oral motor coordination. Speech returned to normal by four months following the surgery, but during the recovery phase the children spoke in a dysarthric and whispered or high-pitched voice. Neuropsychological studies showed difficulties in initiating and completing age appropriate motor-responses, and impairments in recent memory, attention span, and problem solving abilities. This posterior fossa syndrome occurs almost exclusively with resection of midline cerebellar mass lesions via an inferior vermian incision, but not with resection of large hemispheric lesions. Pollack[55] has suggested that the syndrome could result from edema, inflammation, or focal hypoperfusion around the resection cavity and this might reversibly compromise the functioning of the deep cerebellar nuclei and/or their afferent and efferent connections.

Cerebellar cognitive affective syndrome in adults

We studied 20 patients with lesions confined to the cerebellum prospectively over a seven-year period in order to determine if there are clinically relevant behavioral changes in adults with acquired cerebellar lesions[56]. Thirteen patients had stroke, three post-infectious cerebellitis, three cerebellar cortical atrophy, and one was studied following excision of a midline tumor. All patients received neurological examinations and bedside mental state tests, and most underwent neuropsychological testing. A pattern of clinically relevant behavioral changes was found that could be diagnosed at the bedside and quantified by neuropsychological tests. These deficits conformed to an identifiable syndrome, that we termed the cerebellar cognitive affective syndrome. It is characterized by:

(1) Disturbances of executive function: this includes deficient planning, set-shifting, abstract reasoning, working memory, and decreased verbal fluency.

(2) Impaired spatial cognition, including visual–spatial disorganization and impaired visual–spatial memory.

(3) Personality change characterized by flattening or blunting of affect, and disinhibited or inappropriate behavior.

(4) Linguistic difficulties, including dysprosodia, agrammatism and mild anomia.

The net effect of these disturbances in cognitive functioning is a general lowering of overall intellectual function.

These impairments are present on routine bedside mental state tests, and on standardized neuropsychological tests of cognitive function (see Box 2 for an example). They are not so subtle as to be detected only on high level cognitive tests. Rather, they are clinically relevant and noted by family members and nursing and medical staff. The observed impairments cannot be explained by difficulties with motor control. In many cases motor incoordination was very mild as determined by clinical observation. Moreover, tests that are highly demanding of motor function were not administered to patients with moderate or severe dysmetria. Motor incapacity does not account for abnormalities of Verbal IQ score (where responses are verbal and are untimed); impairment of Picture Arrangement and Picture Completion (where the motor requirement is minimal); and poor performance on the Boston Naming Test. On tests with a significant motor component (Rey Copy, Trail Making, Porteus Mazes) patients do not have difficulty drawing the lines. Rather their errors result from poor planning, and in the Mazes task they would often go into blocked paths and require several attempts to find the correct solution. This suggests that these patients have difficulty with planning and integration of cognitive responses.

The neurobehavioral presentation in our patients was more pronounced and generalized in those with bilateral, or large unilateral infarctions in the territory of the posterior inferior cerebellar arteries, and in those with subacute onset of pancerebellar disorders such as occurs with post-infectious cerebellitis. It was less evident in patients with more

Box 2. Cognitive overshoot from cerebellar dysfunction

Recent descriptions of a cerebellar cognitive affective syndrome[a] provide supportive evidence for clinically relevant cognitive dysfunction resulting from acquired cerebellar lesions. The syndrome is characterized by impairments of executive function, spatial cognition, linguistic processing and affective regulation. The cognitive profile has been conceptualized as dysmetria of thought[b] , analogous to the motor impairment from cerebellar lesions. Dysmetria in the motor system is characterized by undershoot as well as overshoot of intended movements. If disturbances of higher-order function are to be conceptualized as cognitive dysmetria, then it might be expected that cerebellar disorders produce exaggerated cognitive responses as well. The disinhibited and inappropriate behavior sometimes seen in patients with the cerebellar cognitive affective syndrome supports this notion. The following patient demonstrated an unusual response to a standard bedside mental state test that seems to represent cognitive 'overshoot'.

The patient is a 28-year-old architect with a four-year history of progressive cerebellar degeneration. Abnormalities on examination were confined to the cerebellar system, including abnormal eye movements, dysarthria and loss of coordination of extremities and gait. Mental state testing revealed a flattened affect and impaired verbal working memory. He was asked to write a sentence, and he wrote eight lines (see Fig.). He was asked to draw a clock with numbers on it. He proceeded to draw the intricate diagrams shown in the Figure. One was a wrist watch with all the details including the date, second hand, outline of the watch and the pattern on the strap made to look like leather. He then drew a grandfather clock with pendulum, shading, biblical scroll on the wooden paneling and patterns on the base. This was followed by a person drawn next to the grandfather clock. His drawing took over 20 minutes. During this time no instructions were given and the patient was not interrupted.

This unique response to a task requested commonly in the mental state evaluation reveals no motor impairment. Rather, this reflects a misjudging of the situation, a mismatch between stimulus (request) and the response (drawing), and a failure by the patient to appreciate the nature of the response or to correct the error. The overly elaborate planning and misinterpretation of the stimulus seem to provide evidence for the concept of cognitive overshoot. This phenomenon appears to be part of the spectrum of cognitive impairments resulting from cerebellar injury, and might represent a manifestation of dysmetria of thought.

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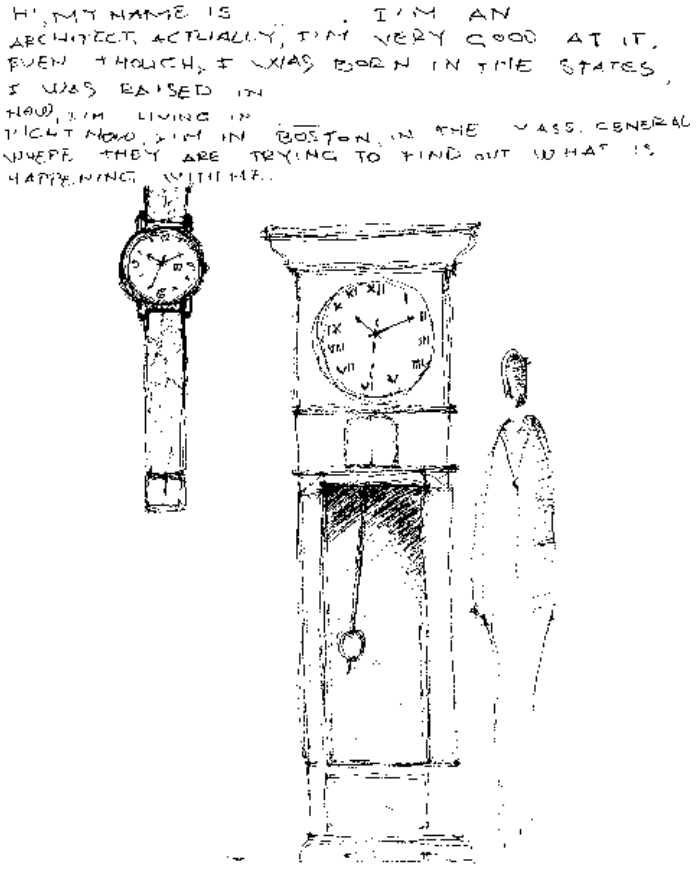

Fig. Responses of a patient with cerebellar degeneration to requests to write a sentence and draw a clock with numbers on it. (See text for details.)

insidious disease (slowly progressive cerebellar degenerations), in the recovery phase (3–4 months) after acute stroke, and in those with restricted cerebellar pathology (small branch occlusions affecting the anterior lobe of the cerebellum or the rostral part of the posterior lobe supplied by the superior cerebellar artery). Lesions of the posterior lobe are particularly important in the generation of the disturbed cognitive behaviors. The vermis is consistently involved in patients with pronounced affective presentations. The anterior lobe seems to be less prominently involved in the generation of these cognitive and behavioral deficits. One patient with an autonomic syndrome had a lesion involving the medial posterior lobe, including the fastigial nucleus.

Cerebellar cognitive affective syndrome in children

Early case studies of agenesis and hypoplasia of the cerebellum reported an association with mental retardation or emotional disability[1,2]. More recent reports include the description of mania in a child with cerebellar degeneration[57], and Joubert *et al.*[58] described mental retardation in children with dysplasia of the cerebellar vermis. We have been impressed particularly by the language delay as well as oculomotor apraxia in patients with Joubert syndrome and

cerebellar agenesis (unpublished data). Apart from the observations of children with the posterior fossa syndrome characterized predominantly by postoperative mutism, little is known regarding the behavioral effects of acquired cerebellar lesions in the pediatric population. Most studies of the neurobehavioral consequences in children treated for posterior fossa tumors have essentially documented the combined effects of tumor, radiation, and chemotherapy. In the reports of children with astrocytomas[59,60] almost one half of the patients who did not receive radiation showed serious behavioral, academic or intellectual deficits, such as memory, language, or visuospatial problems.

The finding of a cerebellar cognitive affective syndrome in adults led Levisohn *et al.*[61] to investigate the behavioral consequences of tumor resections in children. In this study, a retrospective analysis was performed of the clinical evaluations and neuropsychological test results in 19 children (ages 3–14 yrs, mean age 8yrs 2 mths) who had undergone resection of cerebellar tumors. Eleven had medulloblastomas involving the vermis; seven had astrocytomas in the cerebellar hemisphere; and one child had an ependymoma near the midline. The children showed characteristic behavioral deficits. These included difficulties with language initiation, such as reluctance to engage in conversation and long response latencies. Language impairments were seen in children with damage to the right hemisphere and included impaired verbal fluency and word finding difficulties. Digit Span scores were poor in many patients, with deficits notable particularly in sequencing and planning as well as perseveration and difficulty maintaining set. Impairment of initiation was a common feature, and resulted in poor confrontation naming and story retrieval. Visual–spatial deficits were prominent, and verbal memory deficits were accompanied by a failure to organize and encode verbal or visuospatial material. Impaired regulation of affect was seen in children with extensive damage to the vermis. Five patients exhibited the posterior fossa syndrome. Dissociation between fine-motor and cognitive deficits was seen such that four patients without cognitive deficits had fine-motor deficits, and one without fine-motor deficits had visuospatial deficits and mild word-finding problems. These deficits in visuospatial skills, expressive language, initiating and sequencing of responses, verbal memory, and modulation of affect were similar to the observations in the adult population, and suggest that the cerebellar cognitive affective syndrome is valid also in the pediatric population.

Implications of clinical findings

The demonstration of a characteristic behavioral syndrome resulting from acquired lesions of the cerebellum, the cerebellar cognitive affective syndrome, provides documentation of clinically relevant cognitive deficits in patients with pathology restricted to the cerebellum. Furthermore, the defining features of this syndrome are similar to the functional affiliations of the cerebral cortical regions with which the cerebellum has reciprocal interconnections[62]. Specifically, the prefrontal, posterior parietal, superior temporal polymodal, and paralimbic cortices (posterior parahippocampal and cingulate gyri) have topographically organized feedforward projections to the cerebellum[63-66] as well as feedback projections from the cerebellum[65,67]. These connections provide the anatomical substrate that could support the cerebellar participation in higher-order processing. The projections from the associative and paralimbic regions of the cerebral cortex appear to be funneled through the cerebrocerebellar circuit within multiple parallel but partially overlapping loops in the corticopontine pathway. These channels of information converge with topographic ordering within the basilar pontine nuclei, and this precise organization is probably present also in the pontine projections to the cerebellar cortex, although this still remains to be demonstrated for the associative inputs. These streams of information are acted upon by the cerebellar corticonuclear microcomplexes[68], and then transmitted via the deep cerebellar nuclei back to both specific and nonspecific thalamic nuclei, before returning to the cerebral cortex (see Schmahmann[64], Middleton and Strick, this issue). The cerebrocerebellar system in this view then consists of discretely organized parallel anatomical subsystems that serve as the substrates for differentially organized functional subsystems (or loops[36]) within the framework of distributed neural circuits[65]. The cerebellar contribution to these different subsystems might facilitate the production of harmonious motor, cognitive, and affective/autonomic behaviors. The hypothesis derived from this anatomical model is that disruption of the neural circuitry linking the cerebellum with the associative and paralimbic cerebral regions prevents the cerebellar modulation of functions subserved by the affected subsystems, thus producing the observed behavioral deficits.

'Dysmetria of thought' is the concept that we proposed as the fundamental mechanism underlying disorders of intellect and emotion resulting from cerebellar dysfunction[1,64]. When cognitive performance, affect, and autonomic function are considered in the light of the understanding of cerebellar motor deficits, then intact cerebellar function facilitates actions harmonious with the goal, appropriate to context, and judged accurately and reliably according to the strategies mapped out prior to and during the behavior. In this view, the cerebellum detects, prevents, and corrects mismatches between intended outcome and perceived outcome of the organism's interaction with the environment. In the same way as the cerebellum regulates the rate, force, rhythm, and accuracy of movements, so might it regulate the speed, capacity, consistency, and appropriateness of mental or cognitive processes. In this model, the cerebellar contribution to cognition is one of modulation rather than generation. This is in accord with the suggestions of Snider[3] that the cerebellum is the great modulator of neurologic function, of Heath[6] that the cerebellum is an emotional pacemaker for the brain, and of Ito[69] that the cerebellum serves to prevent, detect, and correct errors of thought in the same way as it does so for errors of movement. In agreement with Leiner *et al.*[70,71] that the cerebellum serves as a multi-purpose computer designed to smooth out performance of mental operations, we have suggested that the cerebellum serves as an oscillation dampener, maintaining function steadily around a homeostatic baseline. When the cerebellar component of the distributed neural circuit is lost or disrupted, the oscillation dampener

Box 3. Treatment options: science or science-fiction?

If physicians and caregivers recognize the cerebellar cognitive affective syndrome, and the posterior fossa syndrome of postoperative mutism, counseling and cognitive rehabilitation efforts can be initiated. The knowledge that seemingly bizarre behavior, inappropriate social interactions, disinhibited personality style and limited intellectual flexibility and abilities might be explained by the cerebellar insult itself, can provide the patient and family with an explanation and understanding that has previously been unavailable.

In this era of re-awakened interest in, and clinical acceptance of brain stimulation techniques for Parkinson's disease and epilepsy, it is worth recalling that previous investigators have improved both aggression and depression by cerebellar cortical stimulation[a,b]. Are we at a point now where these avenues can be re-explored? The stigma surrounding psychosurgery that developed in the first half of the 20th century has been replaced by acceptance of routine temporal lobectomy and even hemispherectomy for intractable epilepsy, and cingulotomy for obsessive–compulsive disorder. The amelioration of aggression in monkeys by selective archicerebellar ablations[c] has not yet been replicated. The question of whether it should be attempted, and whether there are clinical applications for this approach should now be addressed.

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is removed. Mental processes are imperfectly conceived, erratically monitored, and poorly performed. There is unpredictability to social and societal interaction, a mismatch between reality and perceived reality, and erratic attempts to correct the errors of thought or behavior. This concept of dysmetria of thought facilitates a new approach to the psychoses, because it focuses on aberrations of the cerebellum[1,67]. Other investigators have adopted this anatomically based model in considering the cognitive and affective deficits that characterize schizophrenia[72].

A number of other hypotheses about the role of the cerebellum in cognitive and emotional behaviors have been proposed, some of which are briefly summarized here. (Readers are referred to Ref. 4 for full discussion of these hypotheses by their principal proponents.) Ivry and colleagues[46] have maintained that the problems of coordination and mental functions that patients with cerebellar lesions experience can be understood as a problem in controlling and regulating the temporal patterns of movement and behavior. Thus, the timing capabilities of the cerebellum are not limited to the motor domain but are utilized in perceptual tasks that require the precise representation of temporal information. In the view of Courchesne and colleagues[73] the cerebellar role in motor and non-motor behaviors is that the cerebellum is a master computational system that is able to anticipate and adjust responsiveness in a variety of brain systems in order to achieve goals determined by cerebral and other subcortical systems. These investigators have supported their view that the cerebellum is important for the coordination of the direction of selective attention by demonstrating impairments in this function in patients with cerebellar strokes and also in autistic individuals. The notions of Bower[74] that the cerebellum is involved in monitoring and adjusting the acquisition of most of the sensory data on which the rest of the nervous system depends has prompted functional imaging studies that have provided support for this view[75]. This concept holds that rather than being responsible for any particular behaviorally related function, the cerebellum instead facilitates the efficiency with which other brain structures perform their own function. In an analogous but slightly different view, Paulin[76] has stated that cerebellar function can be explained by assuming that it is involved in constructing neural representations of moving systems. Thus, the cerebellum could be a neural analog of a dynamical state estimator. The state estimator hypothesis according to Paulin would explain the participation of the cerebellum in controlling, perceiving, and imagining systems that move. Thach[77] has proposed that there is a context response linkage performed by the cerebellum in both motor and non-motor areas of behavior. In this view, through practice, an experiential context automatically evokes a certain mental action plan. This plan could be in the realm of thought but would not necessarily lead to execution. Thus, the specific cerebellar contribution to higher function would be one of context linkage and the shaping of responses to trial and error learning. Ito[69] has conceptualized the cerebellar involvement in thought based on the analogy between movement and thought from the viewpoint of control systems. In this view, the cerebellar corticonuclear microcomplex is connected to neuronal circuits involved in thought and might represent a dynamic or an inverse dynamic model of a mental representation. The cerebellum is designated as a regulatory organ subserving different executive functions and it is defined uniquely by its error driven adaptive control mechanism and the model building capability that is based upon it. Thus, Ito extended the error detection mechanism identified for the vestibulo-ocular reflex to the cerebellar regulation of thought and other aspects of higher function. The anatomically based models have been used in our own conceptualization of the role of cerebellum and higher function as in Schmahmann[1,64] and as described above. Leiner *et al.*[70,71] have also adopted an anatomically based approach, and regarded the cerebrocerebellar system like the circuitry in a versatile computer. Thus, the cerebellum is able to perform a wide repertoire of computations on a wide range of information to which it has access. Each module in the lateral cerebellum is able to communicate with the cerebral cortex by sending out signals over its segregated bundle of nerve fibers, which is a powerful way of communicating

information. The bundling of fibers enables a high level of discourse to take place between the cerebellum and cerebral cortex using internal languages that are capable of conveying complex information about what to do and when to do it.

The cerebellum is also involved in such diverse behaviors as skill learning, classical conditioning, spatial event processing, and autonomic and vasomotor regulation in addition to the clinical manifestations already documented. The anatomically based model in which anatomical loops subserve functional subsystems within the larger framework of the associative, paralimbic, and autonomic cerebrocerebellar communication is compatible with different functional hypotheses. It remains to be determined whether the concept of dysmetria of thought as an overarching functional hypothesis derived from the error detection model can also subsume these other functional hypotheses.

In the clinical studies performed to date, there is a suggestion of dissociation between motor, cognitive and affective consequences of discrete cerebellar lesions, indicating perhaps, that there is topographic organization of behavioral functions within the human cerebellum. Disturbances of affect, for example, have been more pronounced following lesions of the posterior vermis. Executive and visual–spatial abnormalities as well as linguistic difficulties have been more prominent following lesions of the posterior lobe. Motor deficits have been more pronounced in anterior lobe lesions, whereas the cognitive consequences of anterior lobe lesions have been limited. More precise structure–function correlations await the analysis of a larger group of patients with focal cerebellar lesions in order to develop more significant clinical–anatomical correlations than has been possible from the sample sizes studied to date. Such clinical investigations would test the hypothesis that different regions of the cerebellum subserve distinct cognitive functions[1,64]. The results of functional imaging experiments provide support for the notion that different cognitive functions have different anatomical loci within the cerebellum. Linguistic processing, for example, appears to be concentrated in the vermal lobules VI through VII and the hemispheric extensions of these areas, that is, HVI and crus I of the ansiform lobe[40]. This hypothesis has also been supported by functional imaging studies showing separate cerebellar regions of activation for motor and non-motor functions[73,78].

Conclusions

The descriptions of clinically relevant cognitive and affective changes resulting from cerebellar lesions indicate that the discussion concerning the role of the cerebellum in higher-order function has direct relevance for patient care (see Box 3). They also provide an opportunity to study these questions in the patient population. With the new awareness of the cognitive and affective deficits that lesions of the cerebellum can produce, it will be valuable to investigate further the role of the cerebellum in disorders that fall within the psychiatric domain.

Outstanding questions

- What is the topographic organization of the function within the human cerebellum? Are motor, sensory, intellectual, emotional and autonomic functions all discretely arranged, or do they overlap? Are particular cerebellar lobules and folia dedicated to uniquely different functions? Is the cerebellum just like the cerebral cortex in having regions that are mostly motor, mostly sensory, mostly dedicated to expressive language, visuospatial analysis, working memory, and so on?
- How do different elements of the cerebellar cognitive affective syndrome differ from the behavioral consequences of lesions of the cerebral cortical areas with which the cerebellum is linked? Cerebellar patients have deficits in executive functions and they can be either abulic (show poverty of initiation) or socially inappropriate. How does that differ from a patient with a frontal lobe lesion? It seems logical that whereas they might resemble each other, the cerebellar and frontal syndromes should have distinguishing characteristics. How do the impairments in spatial cognition differ between cerebellar patients and parietal patients? The anterior cingulate cortex is also involved in error detection, or at least in the detection of conditions in which errors are likely to occur[79]. How do the cognitive and affective deficits in patients with cingulate lesions compare with those of patients with cerebellar lesions? What is the internal mood state in the cerebellar patients whose affective display is so markedly abnormal: is there a mismatch between experience and display, or does the cerebellar patient show what s/he feels?
- Is there a single unifying mechanism of action that defines the cerebellar contribution to behavior – be it motor or non-motor? Can the different hypotheses regarding the role of the cerebellum in the nervous system be subsumed by one overarching mechanism? We have maintained, as discussed in the text, that this is the case. This remains to be shown.
- What is the role of the cerebellum in psychiatric diseases such as schizophrenia and the related psychoses? We have suggested that in the same way that the cerebellum serves to regulate the rate, rhythm, and force of the movement, so might it play a role in regulating the speech, consistency, and appropriateness of mental and cognitive operations. Failure of cerebellar modulation of normal mental operations might lead, in this model, to illogical thought, mismatch between reality and perceived reality, and inappropriately overactive or restricted behavioral responses (dysmetria of thought). Some of the predictions are borne out by the behavior of patients with the cerebellar cognitive affective syndrome. Further, their behaviors are reminiscent of some of the symptoms of schizophrenia, and so the question of a causative role for as yet undetected cerebellar pathology or pathophysiology in the psychoses is even more relevant now than when first considered some fifty years ago.
- The associative and paralimbic cortices have a highly organized pattern of projections to the basis pontis (the first of two stages of the feedforward limb of the cerebrocerebellar circuit). How does this highly organized arrangement translate to the pontocerebellar projection? Specifically, which parts of the cerebellar cortex receive input from the different cortical association areas?
- The cerebellum receives massive higher-order input via the corticopontocerebellar pathway. It also sends projections back to the associative cerebral cortical areas via the thalamus. How do these two limbs of the cerebrocerebellar circuit differ in their functional contribution to cognition and affect? What are the consequences of disruption of the afferents to the cerebellum versus disruption of the efferents back to the cerebral cortex?

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The Cerebellum: From Structure to Control

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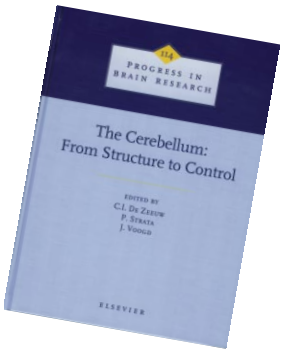

Studies on the cerebellum escalated in the 1960s, and this topic is now established as one of the major fields of neuroscience, where 1700–1900 papers appear each year. The focus of interest in this field has moved rapidly from decade to decade, and one of its features in the present decade seems to be a broadening of interest to diverse subfields of cerebellar research.

This volume is an issue in the series *Progress in Brain Research* and contains the proceedings of a satellite symposium on the European Neuroscience meeting held at the Erasmus University, Rotterdam, in 1995. It contains 35 papers classified into 12 subthemes that deal with a diversity of topics such as molecular, developmental, morphological, physiological and clinical problems. It is a compilation convenient for overviewing the currently ongoing diverse cerebellar studies. In modern neuroscience, interdisciplinary collaboration is of essential importance, and it appears that this meeting was devoted to such interdisciplinary interactions. In that sense, the book successfully provides a good guideline for developing effective interdisciplinary collaborations among cerebellar researchers.

This volume helps its readers to think about the future of cerebellar studies. What sort of discoveries can be expected? Gene regulatory processes governing formation of the fine compartmental, modular structures of the cerebellum? More details of receptors and messengers, and their physiological roles? New types of cellular elements and their functional roles? Further details of neuronal wirings? More details of the mechanisms of developmental and functional plasticity? Further evidence for cerebellar roles in motor learning, motor coordination and cognitive function? Pathogenesis of cerebellar diseases?

A frustrating aspect of the book, which is probably inherent to many proceedings, is that it does not include a description of an emerging new field. On the grounds of the diversified multidisciplinary expansion, certain areas of cerebellar research are now rapidly growing and the recent wealth of new data on developmental and molecular neurobiology of the cerebellum is indeed remarkable. Transgenic technology and cell or tissue transplantation have achieved an epoch-making success. Impressive advances in cognitive studies have recently been documented in *The Cerebellum and Cognition* by J.D. Schmahmann (Academic Press, 1997). The computational approach is also full of new possibilities of uncovering functional principles implied in complex structures of the cerebellum. These moving frontiers of the field are not immediately visible in this volume.

Nevertheless, summarizing the outcome of extensive studies performed in the past four decades on structural–functional–behavioral relationships of the cerebellum, the volume hints at directions to be taken in the coming century. The book will be of interest primarily to cerebellar experts, but also to neuroscientists in other areas who might be interested to see how cerebellar studies have developed, expanded and further diverged to more molecular depth on the one hand and to more computational and cognitive levels on the other. Ways to integrate this divergence, which seems likely to increase in all fields of neuroscience, must be seriously considered.

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