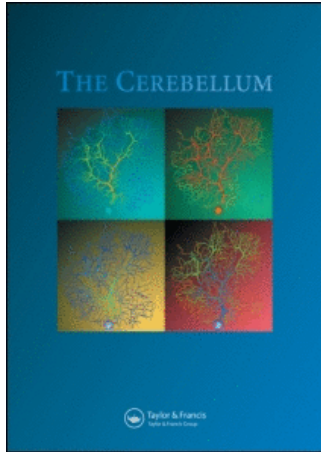


This article was downloaded by:[Schmahmann, Jeremy]
On: 19 September 2007
Access Details: [subscription number 782115788]
Publisher: Informa Healthcare
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



The Cerebellum

Publication details, including instructions for authors and subscription information:
<http://www.informaworld.com/smpp/title~content=t713681311>

The neuropsychiatry of the cerebellum - insights from the clinic

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Online Publication Date: 01 January 2007

To cite this Article: Schmahmann, Jeremy D., Weilburg, Jeffrey B. and Sherman, Janet C. (2007) 'The neuropsychiatry of the cerebellum - insights from the clinic', *The Cerebellum*, 6:3, 254 - 267

To link to this article: DOI: 10.1080/14734220701490995

URL: <http://dx.doi.org/10.1080/14734220701490995>

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ORIGINAL ARTICLE

The neuropsychiatry of the cerebellum – insights from the clinic

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Abstract

A central aspect of the cerebellar cognitive affective syndrome is the dysregulation of affect that occurs when lesions involve the ‘limbic cerebellum’ (vermis and fastigial nucleus). In this case series we describe neuropsychiatric disturbances in adults and children with congenital lesions including cerebellar agenesis, dysplasia, and hypoplasia, and acquired conditions including cerebellar stroke, tumor, cerebellitis, trauma, and neurodegenerative disorders. The behaviors that we witnessed and that were described by patients and families included distractibility and hyperactivity, impulsiveness, disinhibition, anxiety, ritualistic and stereotypical behaviors, illogical thought and lack of empathy, as well as aggression and irritability. Ruminative and obsessive behaviors, dysphoria and depression, tactile defensiveness and sensory overload, apathy, childlike behavior, and inability to appreciate social boundaries and assign ulterior motives were also evident. We grouped these disparate neurobehavioral profiles into five major domains, characterized broadly as disorders of attentional control, emotional control, and social skill set as well as autism spectrum disorders, and psychosis spectrum disorders. Drawing on our dysmetria of thought hypothesis, we conceptualized the symptom complexes within each putative domain as reflecting either exaggeration (overshoot, hypermetria) or diminution (hypotonia, or hypometria) of responses to the internal or external environment. Some patients fluctuated between these two states. We consider the implications of these neurobehavioral observations for the care of patients with ataxia, discuss the broader role of the cerebellum in the pathogenesis of these neuropsychiatric symptoms, and revisit the possibility of using cerebellar stimulation to treat psychiatric disorders by enhancing cerebellar modulation of cognition and emotion.

Key words: *Cognition, emotion, dysmetria, imaging, anatomy*

Introduction

It is perhaps remarkable that fully two centuries after Franz Joseph Gall (1758–1828) first postulated the cerebellum as the seat of ‘amative love’ (1,2) we are beginning to take under serious consideration the question of the role of the cerebellum in the regulation of emotion. In this report we describe our clinical experience with emotional disturbances in children and adults with cerebellar lesions, and highlight the role of the cerebellum in emotional processing in the developing nervous system. We consider the dysregulation of affective control in the light of our dysmetria of thought theory, and conclude with some implications of these ideas for the understanding of the cerebellum and the approach to the treatment of neuropsychiatric disorders.

The cerebellar cognitive affective syndrome – the cognitive deficits

The description of the cerebellar cognitive affective syndrome (CCAS) in adults (3) and children (4)

provided a clinical grounding for the conclusions derived from anatomical tract tracing studies and behavioral investigations in animals, and from functional imaging data in humans indicating a role for the cerebellum beyond motor control. Adults with large unilateral or bilateral cerebellar lesions that involve the posterior lobe manifest a constellation of cognitive, affective and behavioral abnormalities that are clinically relevant and detectable on bedside mental state tests. Deficient executive functions include working memory, motor or ideational set shifting, and perseveration of actions or drawings; and impairment of verbal fluency that manifests as telegraphic speech. In some cases the speech impairment is severe enough to resemble mutism. Visuospatial disintegration may appear as difficulty copying and conceptualizing drawn images. Simultanagnosia; anomia; agrammatism and dysprosodia; deficient mental arithmetic; and mildly abnormal verbal and visual learning and recall may also be found. The constellation of executive, visual spatial and linguistic changes forms the core of the intellectual deficits of the CCAS, and renders

patients impaired on standardized tests of intelligence for a period of four to six months following the injury. Our understanding of the manifestations of the syndrome continues to evolve, as exemplified by patients who report problems with multi-tasking, organizing their thoughts, sustaining their level of concentration and energy, and being somewhat forgetful. One patient who experienced such problems was a businessman with post-infectious cerebellitis who developed impaired judgment, diminished insight, and inability to predict consequences of his actions that would previously have been second nature to him, with major personal and financial consequences. In another instance, an artist with a posterior inferior cerebellar artery territory infarct reported loss of creativity that persisted for almost a year, with an inability to experience the flow of visual images that had characterized his abilities prior to the lesion.

Following cerebellar tumor resection, children may demonstrate executive impairments in planning and sequencing, visual-spatial function, expressive language, and verbal memory, indicating that the CCAS is also relevant in the pediatric population (4) a finding replicated by other investigators (5–9).

The cerebellar cognitive affective syndrome – the emotional deficits

Emotional dysregulation can be a striking aspect of the CCAS. In our original report (3), 15 of 20 patients experienced changes in the modulation of their behavior and personality style. Flattening of affect or disinhibition were manifested as overfamiliarity, flamboyant and impulsive actions, and humorous but inappropriate and flippant comments. Behavior was regressive and childlike in some, whereas others demonstrated obsessive compulsive traits. Further, these behavioral changes had an anatomical signature – they were most notable when the lesions involved the vermis and paravermian regions.

One-third of children in the Levisohn et al. (4) study exhibited affective changes including irritability and impulsivity, difficulty modulating behavior and acting in a silly, giggling and disinhibited manner. Some had marked emotional lability, swinging from withdrawn and apathetic to inconsolable whining, agitation and crying, particularly early in the course, sometimes with the mutism that characterizes the posterior fossa syndrome (10–12). Like the adults, these patients had lesions in the vermis and paravermian structures. Subsequent studies of behavioral aberrations in children following cerebellar tumor resection include descriptions of stereotypies and interpersonal relations that meet criteria for the diagnosis of autism (13), disinhibition, impulsivity and irritability (14), dysphoria, inattention and irritability (6) as well as anxiety and aggression (8).

The range of affective impairments resulting from cerebellar lesions – clinical reports

Since the description of the CCAS we have had the opportunity to examine patients with cerebellar dysfunction whose chief complaints relate to impairments in intellect and emotion. The following cases portray the nature and extent of these deficits, with our focus here on the disturbances of mood and emotion.

Behavioral alterations in the setting of cerebellar tumors in childhood

Delayed psychosis following cerebellar tumor resection

Case 1 had normal birth and development except for enuresis. He developed morning headaches and emesis at age 4, leading to the diagnosis and resection of a cerebellar vermis astrocytoma at age 6. He received neither radiation nor chemotherapy. After surgery he became clumsy, withdrew from sports, and became socially awkward and isolated, although attendance and performance at his religious school remained good. At age 17, in the absence of any discernable situational or known neurological precipitant, he began having difficulty making decisions, his school performance deteriorated because he could not study, and his thinking became 'stuck' and ruminative. He slipped into a state of paranoid ideation, bizarre illogical and at times nearly psychotic thinking, depressed mood, obsessive preoccupation, and personal stereotypical rituals. He became more isolated from family and friends, and was unable to organize his thoughts and plan his life. He came to our attention at age 22 complaining of concentration difficulties, lethargy, and mental and physical rigidity. His elementary medical and neurological examination was normal. On neuropsychiatric evaluation he appeared stiff and tense, with a flat facial expression that did not vary. He was gaze avoidant, and had very limited capacity to engage. His speech was slow and soft, with limited prosodic variation. His thinking was concrete and his responses were idiosyncratic and at times hard to understand, but he did not have loose associations, delusions, or paranoia. There was a ruminative and obsessional aspect to his thinking, but he did not display formal rituals, compulsions, or obsessions. His mood was flat and distant, but he denied symptoms of depression. His insight was very limited, and judgment poor. Neuropsychological studies revealed marked discrepancy between verbal and performance scores, (VIQ 130, PIQ 98), he showed difficulties with perceptual organization, attention and processing speed, and poor performance in complex or unstructured situations. Schizotypal traits were very significantly elevated on the Millon Clinical Multiaxial Inventory (II) evaluation (15), and his score on the Yale-Brown

Obsessive Compulsive Scale (16) was consistent with that observed in individuals with mild obsessive compulsive disorder (OCD). Neuroimaging revealed evidence of remote post-operative change in the vermis (Figure 1A). Following treatment with fluoxetine his family noted he was more active and social, but he denied subjective improvement. Citalopram plus olanzapine produced a subjective sense of improved concentration and reduced fatigue. Although he remained emotionally and intellectually stilted, he was able to return to his studies, and to marry.

At age 19, Case 2 was diagnosed with a fourth ventricle choroid plexus papilloma. The diagnosis was made when hydrocephalus resulted in increasing lethargy, headaches, nausea and emesis. He had experienced problems with sustained attention and concentration since childhood. Progressive school failure was observed from approximately age 13, with increasing inattention, inability to complete assignments, and poor math, along with limited frustration tolerance, and difficulty understanding social cues and controlling his anger. On standardized tests, performance scores were more affected than verbal (VIQ 104, PIQ 80). Surgical excision of the tumor was complicated by post-operative mutism and dysphagia for two weeks. Two years after surgery he had persistent left facial paralysis, and a severe cerebellar motor syndrome with a score of 70/120 on the Modified International Cooperative Ataxia Rating Scale (MICARS) (17,18) affecting gait and equilibrium, extremity coordination,

speech, and eye movements. Cognitive testing revealed relative deficits in complex problem-solving, mental flexibility and working memory. Prominent changes in behavior were reported: he was unable to control his emotions, he would experience irritability, frustration and excessive anger, his thinking would 'go round in circles' and he would behave as though he had a 'one-track mind'. He often expressed sadness or regret subsequent to his inability to control his feelings. Depression and anxiety increased, and his parents described his mood as dark and his behavior as 'atrocious'. His behaviors responded to psychoactive medications including anticonvulsants. Anatomical changes in the cerebellum (Figure 1B) included the vermis and paravermian region, with mild prominence of the cerebellar fissures.

Case 3 underwent resection of a pilocytic astrocytoma at age 7, complicated by intraventricular hemorrhage, subdural hematoma and ventriculoperitoneal shunt. After intensive rehabilitation measures she returned to school at age 8 despite her cerebellar motor syndrome. She spoke in a monotone, required assistance with math and reading, but was behaviorally appropriate and made the honor roll. Tumor recurrence at age 10 necessitated radiation therapy. Shunt revision was required for obtundation at age 12. Behavior problems commenced at age 13. She became increasingly aggressive, impulsive, difficult to manage and, at times, uncontrollable. She developed paranoia and depression with suicidal thoughts. Video EEG monitoring was normal. At

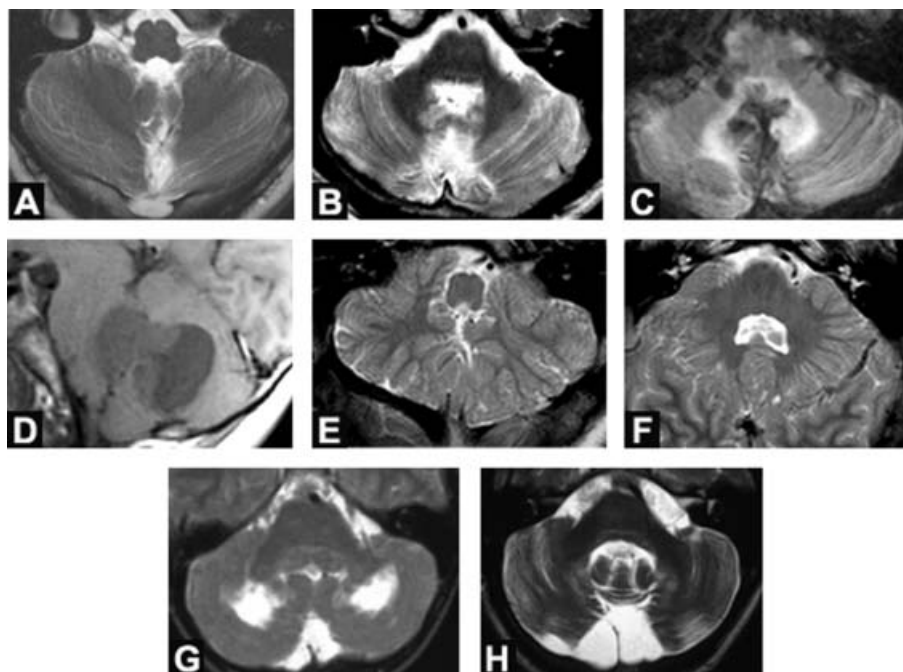


Figure 1. Magnetic resonance imaging (MRI) views of the cerebellum. (A) T2-weighted axial image in Case 1 following resection of a cerebellar vermis astrocytoma. (B) T2-weighted axial view in Case 2 following resection of a choroid plexus papilloma of the fourth ventricle. (C) Axial FLAIR view in Case 3 after resection of a juvenile pilocytic astrocytoma. (D) T1-weighted sagittal image of the cystic astrocytoma in case 6. (E) and (F) T2-weighted axial views of the cerebellar dysplasia in case 7 (E, inferior, F, superior). (G) and (H) T2-weighted axial views in Case 8, showing the evolution of the lesion at age 10 in (G) and age 19 in (H).

age 16, behaviors fluctuated from interactive and engaged; to having conversations with herself, laughing and responding to internal stimuli, and obsessing over delusional ideas; to periods where she would lie awake, responding minimally, apparently 'out of it'. The elementary examination was marked by facial diplegia, absence of horizontal eye movements, and a severe cerebellar motor syndrome. Anatomic imaging (Figure 1C) revealed gliosis and encephalomalacia at the vermis and paravermian regions, and residual tumor at the floor of the fourth ventricle, unchanged over multiple successive scans. Her constellation of delusions, hallucinations, impulsivity, and paranoia, with insomnia and negativism, as well as depression and suicidality has required management with behavioral measures and psychotropic agents.

Persistent behavior changes following cerebellar tumor excision

In Case 4, an astrocytoma affecting the midline cerebellar region declared itself with nausea, vomiting, vertigo, and ataxia at age 12. His mother reported her surprise at witnessing a prominent and persistent behavior change post-operatively. His personality had been characterized by impulsiveness and assertiveness to the point of aggression from the age of 5. His personality changed from the moment that he recovered from anesthesia. He became passive, immature, and child-like and showed no hint of the previous aggressive behavior. He remained unchanged for the 6 years prior to our meeting.

A 2-year-old boy (Case 5) underwent resection of a cerebellar ganglioglioma that declared itself with myoclonic jerks and intermittent ataxia. Excision was complicated by lethargy and slowness in waking. He experienced cerebellar mutism for two weeks, gradually recovering to using single words and prominent dysarthria, with dense left facial and mild left 6th nerve paresis, left sided cerebellar motor syndrome and impaired vestibulo-ocular reflex cancellation (VORC). In the 3 years following surgery, behavior was characterized as labile, hyperactive, difficult to control and often non-responsive to behavioral feedback. He demonstrated obsessive compulsive features. Minor changes in daily routine would 'set him off' rendering him quite inconsolable.

Behavior changes heralding the tumor, in the absence of hydrocephalus

Case 6 was diagnosed with a cystic astrocytoma affecting the midline of the cerebellum (Figure 1D) after she experienced recurrent vomiting spells for 2 years, followed by mild clumsiness that led to neuroimaging. Her teachers reported that she was disorganized in her approach to work, her desk was becoming increasingly cluttered, and she was unable

to learn as she had previously. There was also a personality change in that she became easily irritable, and she would have tantrums over trivial events that previously would not have bothered her in the least. Her preoperative examination showed a mild cerebellar motor syndrome, as well as a flattened affect and reduced spontaneous verbal output.

Aggression and behavioral dyscontrol in the setting of cerebellar disease in childhood

Some pediatric and adolescent patients with psychosis following tumor resection display aggressive behaviors as part of a more encompassing neurobehavioral profile. In the following patients, violent behaviors either self-inflicted or directed towards others were the major challenge.

Case 7 is an 18-year-old man with cerebellar dysplasia (Figures 1E and 1F) and an aggressive personality disorder that has resulted in institutionalization and multiple, minimally successful attempts at behavior modification and improvement. Developmental milestones were delayed, and ocular motor apraxia was identified at age 2. Along with requirement for special education, behavioral dyscontrol was identified in early childhood, including aggression, impulsivity, obsessive compulsive and ruminative behavior, inability to shift behavior, and attention deficit disorder. As an adolescent, he experienced violent outbursts that included incidents in which he threw furniture around, attacked a pregnant caregiver, and thrust his wrist through glass. These episodes were sometimes accompanied by a smile on his face, and escalation could be heralded by willful attempts to produce maximum irritation to authority figures. He claimed he was unable to stop himself, instead requesting medications to prevent these incidents. On examination his affect was bland, although tearfulness and an expression of concern could be coaxed from him. He had alternating esophoria, and head thrusts when attempting to direct gaze horizontally, but no ataxia, dysmetria, or dysarthria. Memory and declarative learning were preserved, but concept formation was deficient.

Case 8 has the rare disorder of central nervous system histiocytosis confined to the cerebellum. Diagnosed at age 3 with skin biopsy, he developed signs of the cerebellar motor syndrome at age 6, with progression through teenage years. Because of cognitive impairment he was placed in special education classes for much of his education. His behavior has proven most difficult to manage, characterized as impetuous, impulsive, self-absorbed, immature, unreliable, demonstrating poor judgment, taking unnecessary risks and engaging in inappropriate interactions. He perseverated over the loss of a job, blamed others for his problems, had no friends, and was intermittently agitated. His family described him as 'his own worst enemy'.

Examination revealed a cerebellar motor syndrome of moderate severity, MICARS score 53/120. He was minimally cooperative during the examination, alternately tearful and sarcastic. Neuroimaging (Figures 1G and 1H) shows the lesion confined to the cerebellum: high T2 signal throughout the cerebellar white matter early in the course, with more recent images demonstrating pancerebellar atrophy and attenuated white matter.

Panic disorder from cerebellar lesions

A proposed vermal-fastigial dysregulation syndrome

Case 9 has a daughter with merosin deficient congenital muscular dystrophy, an autosomal recessive disorder characterized by mutation in the α_2 -chain of laminin-2 (LAMA2) gene on chromosome 6. Our patient has prominence of cerebellar folia with hypoplasia of the cerebellar vermis on MRI (Figure 2A). She presented with a clinical constellation of recurrent and disabling panic disorder with a sense of impending doom, tachycardia with chest pressure, and perspiration. The episodes were exaggerated by vertigo (feeling that she would fall – even if lying down), and during the attacks she was unable to walk or move. The episodes were triggered by watching moving stimuli, turning her head rapidly, or riding an escalator – an activity she learned to avoid. Examination revealed difficulty with tandem gait, inability to stand on one leg for 10 seconds, and mild dysdiadochokinesis. Oculomotor findings included subtle downbeat nystagmus in primary position, intermittent square wave jerks, persistent gaze evoked nystagmus, prominent saccadic intrusions into pursuit eye movements, hypometric saccades, and failure of the VORC. Symptoms improved with beta blockers, meclizine, and a serotonin reuptake inhibitor (SSRI).

Panic following stroke involving the right inferior cerebellum

Case 10 is a 36-year-old woman who suffered infarction in the lateral and medial aspects of the cerebellar posterior lobe including lobule IX (Figure 2B). Her presenting symptoms were vertigo

and emesis, but no motor impairment. She was premorbidly very active physically. Two weeks following the stroke, she was in a car when she developed new onset of extreme anxiety associated with tachycardia, chest pain, tachypnea, and fleeting sensory symptoms in all four extremities. The symptoms lasted for ten minutes before subsiding, but recurred a few times the first day, and repeatedly over the next few months. A diagnosis of new onset panic disorder was made. The symptoms were precipitated and exaggerated by motion, so that she was unable to travel in a car. After approximately 6 months the panic disorder symptom complex subsided.

Emotional blunting

Case 11 was a 19-year-old student involved in a motor vehicle accident, sustaining closed head trauma. She underwent rehabilitation and returned to university 6 months later, traveling internationally on a work-study internship. She was aware of mild dysarthria, incoordination and intermittent tremor of the right arm and numbness of the left hemibody, difficulty with spatial cognition and some forgetfulness. She also described a major change in her emotional state, in that she had a ‘muted affect’, emotions were not available to her, whether angry, happy or sad, and she was unable to cry. Examination revealed paralysis of the right fourth nerve and motor aspect of the left fifth nerve, right sided rubral tremor with hemiataxia, and left spinthalamic sensory loss. Neuroimaging showed encephalomalacia of the superior vermis on the right and hemiatrophy of the right pons (Figure 2C), as well as high T2 signal in the left inferior olivary nucleus. The closed head trauma likely inflicted more widespread damage than was identified on MRI, but corroboration of the clinical examination by the neuroimaging findings speaks to involvement of cerebellar-brainstem pathways.

Obsessive compulsive behaviors, autistic stereotypies, hyperactivity, social skill set

Cerebellar agenesis

Agenesis of the cerebellum is a rare condition that has traditionally been considered to be asymptomatic or

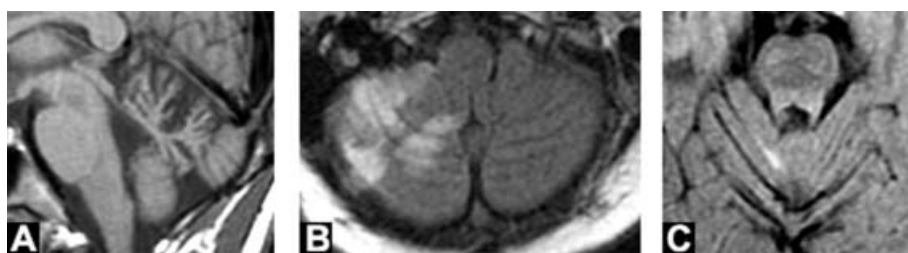


Figure 2. MRI of the cerebellum. (A) T1-weighted sagittal image of case 9 with hypoplasia of the cerebellar vermis. (B) Diffusion weighted image in case 10 with infarction identified in the lateral and medial aspects of the cerebellar posterior lobe including lobule IX. (C) Axial FLAIR image in case 11 showing encephalomalacia of the superior vermis on the right, and mild hemiatrophy of the right pons.

of little clinical significance (19,20). The early literature, however, suggests that rather than being an incidental observation, cerebellar agenesis is indeed clinically relevant (21–23), a conclusion that is consistent with our own observations, a brief synopsis of which is presented here.

Case 12 has near complete agenesis, with a cerebellar remnant at the left anterior superior vermis (Figure 3A). He had delayed speech and motor development, and demonstrated a clumsy and mildly ataxic gait with poor coordination of the extremities, right worse than left. In the decade we have been following him, he has consistently demonstrated lower Performance than Verbal IQs, and his abilities on tasks that tap prefrontal function, visual spatial abilities and linguistic tests have all been deficient, with relative sparing of tests of information and vocabulary. Behavioral features in his preteen years included tactile defensiveness, and a dislike of textured substances. Distractibility and impulsivity led to a diagnosis of attention deficit disorder treated with stimulants. Obsessive compulsive behaviors were evident early in his methods of play, and persisted into early adulthood. Disinhibition and lack of awareness of social boundaries have proved troublesome for him in social situations.

When examined at age 4, Case 13 with near complete cerebellar agenesis (small nubbin in the region of the superior medullary velum, as in case 12) had a history of delayed motor and speech milestones, fine motor skill was delayed, and he was markedly hyperactive.

Case 14 has absence of the left cerebellar hemisphere and the right posterior cerebellum (Figure 3B). He had delayed motor milestones, poor motor planning and execution and language delay (expressive more than receptive). Balance and equilibrium varied according to his attention level. At age 10 he manifested stereotypical behaviors with his hands and feet, trouble with bilateral integration and knowing where his body was in space. He disliked touching messy materials, tended to be gullible and appeared unable to assign ulterior motives to people.

Case 15 has near complete agenesis of the right cerebellum (Figure 3C). At age 6 she had right-sided cerebellar motor findings, unsteady tandem gait, normal eye movements, and prominent behavioral features. Speech was dysfluent and language characterized by echolalia, loose associations and confabulation. She would make up her own language. She displayed hyperactive, obsessive and repetitive behaviors. She demonstrated head banging and disliked cuddling. She walked on tiptoes, stared at television static, rocked in chairs and had temper tantrums. She suffered from night terrors. Emotional stresses elicited shuddering and tremors. She was territorial, aggressive to others, rough with animals, and played alone. She had tactile defensiveness, sought out pressure and displayed a need to touch people or objects but became irritated when touched, disliked wearing clothing and eating textured foods, and would lick her lips until raw. She disliked loud sounds and had difficulty identifying the direction of sound. She would ‘break down’ if she had too much stimulation, becoming overwhelmed and fretful in group settings. Tests of intelligence revealed average verbal scores and weaker non-verbal scores.

Cerebellar hypoplasia (non-progressive cerebellar ataxia)

A 10-year-old boy with a hypoplastic cerebellum (Case 16) had moderate ataxia, stronger verbal comprehension than visual spatial processing, and impaired attentional capacity, working memory, set shifting and ability to organize complex information. He had difficulty establishing long-term interactions with other boys because of their level of physical play, made friends one at a time, latching on to them until the friendships ‘burned out’. He perseverated on thoughts and statements, said things that made no sense, and showed feelings incongruous to the situation.

The parents of Case 17, a 6-year-old boy with a cerebellar motor syndrome but unremarkable MRI, were concerned that he obsessed about watches, was intrigued by his shadow, and engaged in stereotypical rocking behaviors.

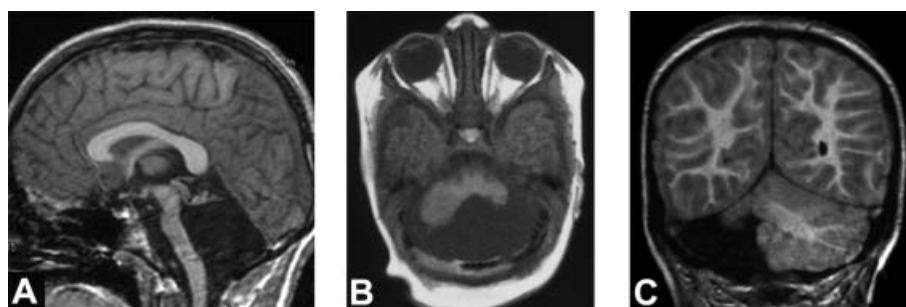


Figure 3. MRI of the cerebellum. (A) T1-weighted sagittal image of near complete cerebellar agenesis in case 12. (B) T1-weighted axial image in case 14 showing absence of the left cerebellar hemisphere and the right posterior cerebellum. (C) SPGR coronal image in case 15, which shows near complete agenesis of the right cerebellum.

Cerebellitis

Three patients who survived post-infectious cerebellitis in childhood demonstrated behavioral impairments including oppositional behavior and attentional deficits (Case 18); emotional difficulties with avoidance behaviors (Case 19); and emotional lability and impaired learning (Case 20). These cognitive and emotional issues persisted in the absence of the cerebellar motor syndrome that characterized the acute presentation.

Friedreich's Ataxia (FA)

The parents of Case 21, a 34-year-old woman with FA expressed concern at her emotional lability (rage, hitting herself and others, threatening suicide), emotional immaturity (emotional dependence, stormy and broken relationships with family and peers), and impaired judgment and planning. She had unpredictable swings from astute and cogent to acting out with infantile and irrational emotional outbursts. They wondered to what extent this was the disease as opposed to the patient's reaction to chronic illness.

Depression

The serotonin hypothesis of ataxia (24) supported by evidence of mild efficacy in small studies (25) led us some years ago to attempt to treat patients with cerebellar degeneration syndromes with SSRIs as an off-label indication. Some did report improvement in dysarthria and gait, however many patients and their families were surprised to see a prominent improvement in range of affect, mood, and irritability. Case 22, a 46-year-old woman with idiopathic late onset cerebellar ataxia reported: 'I did not know I felt so bad until I felt so good'. Case 23, a 43-year-old woman with the rare combination of Behcet's disease and a pure cerebellar degeneration syndrome (Figure 4) has been plagued by unremitting depression in addition to a moderately severe cerebellar motor syndrome.

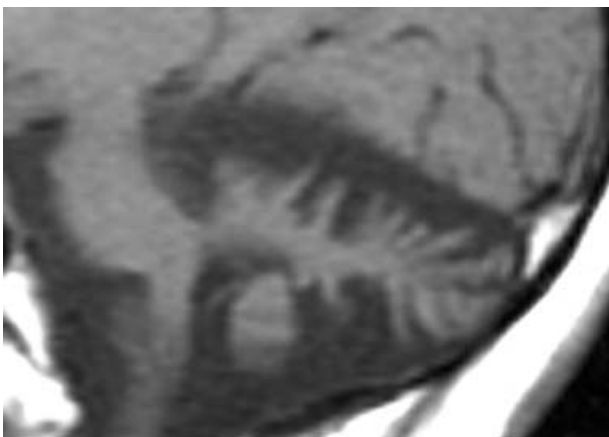


Figure 4. T1-weighted sagittal MRI of the cerebellum in case 23 with Behcet's disease showing cerebellar atrophy.

Disentangling the etiology of depression in patients with chronic illness is challenging, but the prevalence of depression in patients with degenerative cerebellar disorders is unusually high. In a study of 31 patients with cerebellar degeneration (26) depression was present in 68% (35% major depression, 32% dysthymia or a brief depressive episode), a level higher than in patients with Huntington disease (43%) studied by the same group. Further, the cerebellar degeneration group had an overall rate of psychiatric disorder of 78%, including personality change, anxiety and psychotic disorders.

Pathological laughing and crying

A behavioral feature we have identified in patients with multiple system atrophy of the cerebellar type (MSAc; Figure 5) is the clinical phenomenon of pathological laughing and crying (PLC, also known as pseudobulbar affect). In our series of 28 patients with MSAc, 10 patients (36%) reported PLC, witnessed also on routine office visits (27). This disorder is marked by episodes of laughter or crying or both, without motivating stimulus, to a stimulus that would not be expected to elicit such an emotional response, incongruent with or contradictory to the valence of the triggering stimulus and patient's mood, or pathologically exaggerated in intensity or duration.

Summary and synthesis of neurobehavioral/neuropsychiatric features

In this group of patients with cerebellar abnormalities, there was evidence of a range of behavioral and emotional disorders, many of which were diagnosable entities. These included attention deficit hyperactivity disorder, OCD, depression, bipolar disorder, disorders on the autism spectrum, anxiety, and panic disorders. Other features of these patients' behaviors included symptoms that have been observed in those with frontal-subcortical network

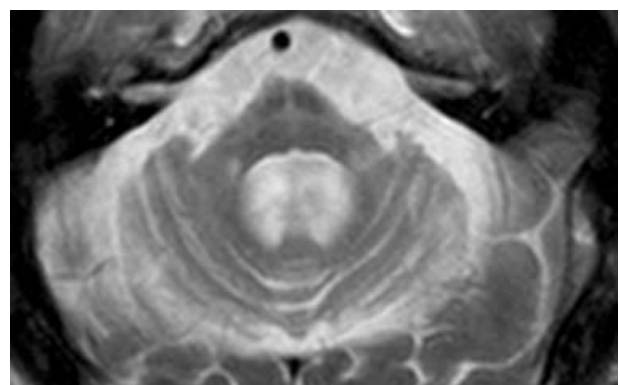


Figure 5. T2-weighted MRI of the cerebellum (axial view) in a patient with multiple system atrophy cerebellar type, showing cerebellar and pontine atrophy and the hot cross bun sign in the pons.

disruption, such as a lack of initiation, apathy and irritability (see Table I).

We conceptualize these behaviors as either excessive or reduced responses to the external or internal environment. The exaggerated, positive, released, or hypermetric responses may be regarded as analogous to the overshoot in the motor domain resulting from cerebellar lesions (akin to 'cognitive overshoot' (28)). The diminished, negative, restricted or hypometric responses may be likened to hypotonia (29), or to hypometric movements (undershoot) in the motor system following cerebellar lesions. The behaviors seem to group in 5 major categories – attentional control, emotional control, autism spectrum, psychosis spectrum, and social skill set. As discussed further below in the elucidation of the dysmetria of thought hypothesis, the loss of cerebellar (predominantly vermal-fastigial) influence on these behaviors may hamper the individual's ability to smoothly and automatically maintain the homeostatic, context-dependent responses that govern behavior.

Whether the current formulation of major domains of behavior and their respective positive-negative symptoms are valid will need to be assessed in prospective studies using more rigorous approaches including factor analysis and structure-function correlations. Some manifestations, such as the social skill set negative symptoms, are reminiscent of observations regarding the cerebellar role in theory of mind studies (30,31), providing a clinical underpinning to this observation from experimental psychology.

With regard to panic arising from cerebellar lesions, we have conceptualized the constellation of panic and vestibulocerebellar disorder with abnormal eye movements as a vermal-fastigial dysregulation syndrome. In this sense, panic disorder may

represent an overshoot of anticipatory fear, and thus fits well into this formulation of cerebellar-induced emotional dyscontrol. Exploration of the mechanisms operating in these unusual cases of panic disorder, like patients with partial seizures who present with panic (32), may help elucidate the neurobiological basis of anxiety. Further, insofar as these patients have aspects of psychiatric syndromes such as depression, panic and OCD, this work may suggest a possible role for the cerebellum in the neuropathology of these disorders.

With respect to our patients with MSAC, two lines of thought suggest that PLC may be ascribed to involvement of the cerebellum. First, the Parkinsonian form of MSA in which the cerebellum and pons are neuropathologically less affected has a low incidence (3%) of PLC (33). Second, PLC has been described in a patient whose lesions were confined to the pontocerebellar circuit (34). These findings provide support for the notion that the cerebellum is engaged in the voluntary control of emotional expression. Whereas PLC may occur in the absence of an accompanying mood disorder, our patients also reported true depression, whether their involuntary emotional expression was characterized by laughing (5 of 10 cases) or both laughing and crying (5 of 10 cases). The question of the cerebellar influence on expression versus experience of emotion remains to be further evaluated, but from most of these patient accounts it appears that the behavior extends deeper than affective display to genuinely influence the feeling state.

Why patients have such heterogeneous manifestations from midline lesions, and why the clinical features vary so widely in different disease states, e.g., post-tumor resection versus neurodegeneration, remains to be established.

Table I. Table of neuropsychiatric symptoms in patients with cerebellar disorders, arranged according to major domains, each with positive and negative symptoms.

	Positive (exaggerated) symptoms	Negative (diminished) symptoms
Attentional Control	Inattentiveness Distractibility Hyperactivity Compulsive and ritualistic behaviors	Ruminativeness Perseveration Difficulty shifting focus of attention Obsessional thoughts
Emotional control	Impulsiveness, disinhibition Lability, unpredictability Incongruous feelings, pathological laughing / crying Anxiety, agitation, panic	Anergy, anhedonia Sadness, hopelessness Dysphoria Depression
Autism spectrum	Stereotypical behaviors Self stimulation behaviors	Avoidant behaviors, tactile defensiveness Easy sensory overload
Psychosis spectrum	Illogical thought Paranoia Hallucinations	Lack of empathy Muted affect, emotional blunting Apathy
Social skill set	Anger, aggression Irritability Overly territorial Oppositional behavior	Passivity, immaturity, childishness Difficulty with social cues and interactions Unawareness of social boundaries Overly gullible and trusting

Overview of the background to the cerebellar role in emotion

Historical evolution

Within a decade of Flourens' (35) determination that the cerebellum is involved in the coordination of movement, clinical reports began to appear linking cerebellar developmental impairments to behavioral aberrations (22,36). Subsequent clinical evidence mounted over the years together with compelling physiological and behavioral studies (22,37–42), implicating the cerebellum in the regulation of cognitive and emotional processing, even though the traditional notion of cerebellum as a motor control device remained well entrenched. Heath (43) reported patients in whom there appeared to be a relationship between the cerebellum and personality, aggression, and emotion, and the linked psychosis, and schizophrenia in particular, with cerebellar structural abnormalities. Cooper and colleagues (44) ameliorated aggression in patients with epilepsy by placing stimulating dural electrodes over the cerebellar cortex. And the patients of Nashold and Slaughter (45) provided subjective reports of emotional experiences following stimulation of the cerebellar nuclei. Stimulation or lesion studies of fastigial nucleus or vermis in animals either provoked or ameliorated autonomic phenomena, grooming, aggression, sham rage, and predatory attack (43,46,47). These findings lent credence to the notion that midline structures of the cerebellum play a role in the modulation of emotion. The demonstration in early infantile autism of cerebellar pathology involving the vermis, nuclei, and cortex of the lateral hemispheres, both on neuroimaging (48) and neuropathology (49–51), appears to have been confirmed in the subsequent literature (52). In schizophrenic patients and those with catatonia, enlargement of the fourth ventricle, smaller cerebellar vermis, and cerebellar atrophy (53–55) have been noted, and magnetic resonance tractography studies cast new light on this relationship. Reports describe abnormal fractional anisotropy in cerebellar afferents (56) and efferents (57) and morphometric MRI studies indicate aberrations in volumetric measures (58,59), including reduced volume of the vermis (60). The correlation that exists in the healthy population between cerebellar size and performance on standardized measures of intelligence (61) also appears to be absent in schizophrenics (62), and there is progressive cerebellar volume loss during adolescence in childhood-onset schizophrenia, a finding thought to occur as part of a more generalized process (63). (Synthetic reviews and analyses of cerebellar neurobiology in schizophrenia may be found in Snider (64); Schmahmann (65); Konarski et al. (66) amongst others).

Neural substrates

Neuroanatomical tract tracing studies show how the cerebellum is an integral node in the distributed neural circuits subserving cognition and emotion. In our elaboration of the concept of a 'limbic cerebellum' residing in the vermis and fastigial nucleus, the anatomical connections that facilitate this role can be categorized into three broad areas: cerebellar connections with reticular nuclei (the arousal system), with the hypothalamus (autonomic functions), and with both the interoceptive (cingulate) and exteroceptive components (other limbic structures) of emotional behavior. There is solid anatomical and physiological evidence linking the fastigial nucleus and vermis with reticular nuclei in the brainstem, intralaminar thalamic nuclei, and the hypothalamus, facilitating its role in autonomic control, arousal and nociception. Earlier physiological and some anatomical studies point to vermal interactions with the anterior thalamic nuclei, hippocampus, septum, amygdala, ventral tegmental area, periaqueductal gray and mammillary bodies relevant for memory and emotion. Anatomical studies show projections into the cerebrocerebellar system from the cingulate gyrus, pregenual, retrosplenial and paralimbic neocortical regions that form the cortical component of Papez' (67) limbic ring. The cerebellar connections with the cerebral association areas that subserve complex behaviors including executive function, linguistic processing, and visuospatial awareness provide the higher order component of the link between cerebellum and those behaviors (arousal, autonomic, limbic, and associative) necessary to support the complex functions inherent in emotion and affect (65,68–76).

Some other contemporary clinical reports

Our case reports are in harmony with an accumulating experience reflecting the relationship between the cerebellum and emotion. The CCAS is reported in adults following cerebellar stroke (77–80), with cerebellar mass lesions (81), and in the uncommon disorder of superficial siderosis (82). It has also been reported in children post-tumor resection, as discussed above. This is exemplified by the study of 24 patients (83) operated upon during childhood for benign cerebellar tumors, 57% of whom showed abnormalities in cognitive testing, with behavioral deficits in 33% of patients particularly when the vermis was involved. Problems included attention deficit disorder, mutism, addiction, anorexia, uncontrolled temper tantrums and phobias. Cognitive and emotional deficits conforming to the description of the CCAS are also described in children born very preterm (84), with cerebellar hypoplasia and non-progressive cerebellar ataxia (85), and in cerebellar agenesis (86). Infants with inferior vermian hypoplasia have motor and language delays and behavior problems (87), and the

vermis has been implicated in neuroimaging studies of attention deficit hyperactivity disorder (88,89), of psychoneurotic symptoms following early childhood trauma, and in addictive behaviors that underlie substance abuse (90,91).

Imaging of cerebellum during pain and autonomic phenomena

Functional imaging studies demonstrate cerebellar activation by multiple domains of cognitive performance (for review, see Desmond (92); Schmahmann (93)). The availability of atlases of the cerebellar cortex and lobules (94) as well as the cerebellar nuclei (95) have made it possible to derive a more accurate picture of the structure-function correlations in cerebellum. Functional imaging data in emotional states point to activation of midline structures in studies of panic (96), sadness (97,98), states of great emotion (99), pain (100,101), and autonomic responses (102). These studies are consistent with the behavioral and clinical conclusions implicating the vermis in the regulation of emotion.

Mechanisms of the cerebellar contribution to emotion and emotion

The foregoing clinical cases and discussion appear to provide support for the assertion that cerebellum is the 'great modulator of neurologic function (39,43). How should we conceptualize this role, and how does cerebellum influence emotion?

Dysmetria of thought hypothesis

We introduced the dysmetria of thought hypothesis (22,65,103) in an attempt to provide a theoretical basis for testable hypotheses. The theory recognizes the equipotential notions of cerebellar function of Flourens (35) and the localizationist approach of Bolk (104) and Snider (39). It views cerebellum within the prevailing notion that brain function is subserved by multiple distributed neural circuits, such that each cerebral cortical area interacts with discrete ensembles of neurons located in a limited set of cortical and subcortical regions, or nodes, which contribute in a unique manner to the specified behavior (105). Our dysmetria of thought hypothesis is central to the exploration of the role of the cerebellum in schizophrenia, for example, an approach that has subsequently been widely adopted by others (106,107).

The cerebellum then is viewed as an integral node in the distributed neural circuits subserving sensorimotor, cognitive, autonomic and affective processing. We have proposed the existence of a Universal Cerebellar Transform (UCT) subserved by the essentially uniform cerebellar histology that modulates behavior, acting as an oscillation dampener

maintaining function around a homeostatic baseline and smoothing out performance in all domains, modifying it according to context. It does so automatically, and does not rise to the level of conscious awareness. Thus, in the same way that cerebellum regulates the rate, force, rhythm, and accuracy of movements, so does it regulate the speed, capacity, consistency, and appropriateness of cognitive and emotional processes (22,65,103).

The specificity of the anatomical connections between cerebellum and spinal cord, brainstem, and cerebral structures facilitates topographic organization of motor, cognitive and emotional functions in the cerebellum. In this proposed schema, the sensorimotor cerebellum is situated in lobules IV and V of the anterior lobe in particular, with a contribution from a second sensorimotor area in lobule VIII, and perhaps from lobule VI acting as the cerebellar equivalent of a premotor region, with the corticonuclear microcomplex (108) extending to the anterior interpositus nucleus. Lobule VIIA (crus I and crus II of the ansiform lobule) and lobule VIIB in the posterior lobe (the hemispheres in particular) are engaged in higher order behaviors, together with the ventral part of the dentate nucleus. The vermis and the fastigial nucleus are the equivalent of the limbic cerebellum. The vestibulocerebellum is in lobules IX and X and the lateral vestibular nuclei.

If the UCT is the essential functional contribution that cerebellum makes to the distributed neural system, then by corollary, there should be a Universal Cerebellar Impairment (UCI). This UCI, the hypothesis holds, is dysmetria. When the motor cerebellum is damaged the dysmetria manifests as ataxia of extremity movements, eye movements, speech and equilibrium. When the lesion is in areas of cerebellum that govern non-motor functions, the result is dysmetria of thought, or cognitive dysmetria, which manifests as the various components of the cerebellar cognitive affective syndrome. When the limbic (midline) cerebellum is damaged, the behaviors manifest predominantly as the kinds of neuropsychiatric impairments that the patients in this report demonstrate.

What remains to be shown, however, is the fundamental mechanism by which the cerebellum modulates these sensorimotor, cognitive, and affective behaviors, and how the regulatory mechanisms governed by the cerebellum interface with operations of other areas involved with these functions.

Implications for therapy

This evolving body of knowledge and clinical experience has relevance for understanding the neural bases of emotion, the role of cerebellum in neuropsychiatric diseases, and the potential for novel strategies for intervention in disorders of emotional modulation.

It provides, first, an opportunity for counseling and medical management of previously unrecognized emotional disturbances in the cerebellar patient population. This meets the 'need to know' imperative in patients with cerebellar disorders whose concerns regarding cognitive and emotional impairments can be addressed by discussion of the non-motor roles of the cerebellum. Active therapeutic intervention is possible once the association is recognized, by using counseling, cognitive rehabilitation, and available pharmacological agents that treat the presenting neuropsychiatric symptoms.

The role of cerebellar-vestibular interactions in higher order deficits such as dyslexia has been proposed previously (109–111), and the utility of cross-model therapies in disorders of higher function has also been postulated (112). Some have claimed success in the management of attention deficit disorder and dyslexia by physical interventions (113) but this remains a matter of controversy. The theoretical underpinning remains plausible, however, i.e., a disturbance in the cerebellar modulation of cognitive and emotional systems may potentially be ameliorated by focusing on cerebellar motor function through putative cross-modal interaction in cerebellum. This approach deserves rigorous experimental challenge.

We referred above to the work of Heath and Cooper who reported successful management of behavioral disorders with electrical stimulation of the cerebellum. The current era of psychosurgery utilizes the safer techniques of focal surgical ablation (114) and deep brain stimulation (115), as well as transcranial magnetic stimulation that has been introduced as a potential therapy for depression (116). The contemporary evidence pointing to emotional dysregulation in patients with lesions of the limbic cerebellum, and the theory that speaks to modulation of emotion by the cerebellum, raises for consideration the experimental investigation of contemporary methods of cerebellar stimulation for the treatment of psychiatric disorders. Enhancing the cerebellar modulation of neural systems that subserves intellect and mood may result in clinical improvements in neuropsychiatric conditions and in the clinical manifestations of psychiatric illness.

Conclusions

The intent of this paper was to relate the case histories of our patients with cerebellar lesions. We focused here on the dysregulation of affect that occurs as part of the CCAS in a manner that portrays the range and the quality of the disordered behaviors. Based on our observations we have been able to define a set of five neuropsychiatric domains in which the cerebellum appears to play a role: attentional control; emotional control; autism spectrum disorders; psychosis spectrum disorders; and

social skill set. Further, we propose that each of these domains includes both positive (hypermetric) and negative (hypotonic, or hypometric) components. We provide brief reference to anatomical studies of cerebellar connections with behaviorally relevant regions of the cerebral association and paralimbic cortices, brainstem and hypothalamus; and animal behavioral and human functional imaging experiments that explore emotional and autonomic functions. Whereas we view our patients' deficits within the framework of the dysmetria of thought hypothesis, the accuracy of these proposed symptom groupings, and the underlying mechanisms of how the loss of cerebellar input into the distributed neural circuits results in these clinical manifestations remain to be determined. This approach has the potential to further elucidate the neurobiological substrates of higher function, to better understand deficits in patients with cerebellar lesions, and to advance the development of novel diagnostic and therapeutic strategies that enhance the cerebellar modulation of behavior in patients with mental health disorders.

Acknowledgements

Supported in part by MH067980 and the Birmingham Foundation. We are grateful to our referring physicians, our patients and their families. The assistance of Jason MacMore, BA, and Marygrace Neal, MEd, is gratefully acknowledged.

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