Is the cerebellum relevant in the circuitry of neuropsychiatric disorders?

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A comprehensive neurobiologic model for the major psychiatric disorders is not currently available. Contemporary classification systems remain symptom based, despite the growing body of literature on abnormalities in structural and functional neuroanatomy.1 In the late 19th century, Babinski observed that patients with cerebellar lesions could not properly execute complex motor tasks and named the resulting condition “dysemetria.” Andreasen et al1 have reported that disruption of neural circuits linking the cortex, thalamus and cerebellum (the cortico-thalamic-cerebellar-cortical circuit, or CTCCC) may presage the complex psychopathology of schizophrenia. They hypothesized that the CTCCC monitors and coordinates the fluid execution of mental activity, a process that appears to be aberrant in schizophrenia. Structural and functional cerebellar abnormalities have been described in several disorders other than schizophrenia, including anxiety disorders, depression and mania.2

We conducted a MEDLINE search of all English articles...
published between 1966 and 2004 using the key words “bipolar disorder,” “depression,” “schizophrenia,” “cerebellum” and “cerebellar.” The search was supplemented by a manual review of relevant references. Priority was given to controlled data; where such were unavailable, uncontrolled studies were included if sample size was reasonable (more than 10).

This review summarizes published data describing and characterizing the role of the cerebellum in normal and abnormal mood states, with specific attention to states of psychosis, depression and mania. We propose that the CTCCC model, heretofore applied to the pathophysiology of schizophrenia, may also be applicable to a pathophysiologic understanding of affective states and other psychiatric disorders.

The cerebellum

Neuroanatomy

The cerebellum overlies the posterior aspect of the pons and projects bidirectional fibres to brainstem structures via 3 paired peduncles. The midline (vermis) and lateral hemispheres are demarcated by fissures into smaller lobes and lobules. Inside, 4 pairs of intrinsic nuclei — dentate (most lateral), emboliform, globose and fastigial — can be found under the grey cortical mantle within a medullary core of white matter.

Traditionally, the emphasis of studies on cerebellar function has been on the coordination of somatic motor function, control of muscle tone and equilibrium. The cerebellum, however, receives input directly or indirectly (via projections from cortical association areas and the midbrain) from nearly all sensory receptors; its output systems emanate from the cerebellar nuclei, and their influences upon cortical function are mediated primarily through brainstem nuclei at multiple levels.

Connections between the cerebellum and the nonmotor cortical and subcortical areas have been documented through both electrophysiologic studies and anatomic tracing techniques. The cerebellum shares bidirectional connections with a large portion of the limbic lobe and the associated subcortical nuclei, the amygdaloid complex, the septal nuclei, and various hypothalamic and thalamic nuclei, regions of interest to psychiatry through their association with emotional processing. Furthermore, the cerebellum also communicates with the monoamine-producing brainstem nuclei, which supply the limbic system and the cerebrum with serotonin, norepinephrine and dopamine.

In animal studies, axonal transport mechanisms have been used to document synaptic contact between the fastigial nucleus of the cerebellum and the ventral tegmental area, the periaqueductal gray, the locus ceruleus and the pontine raphe. Conversely, the ventral tegmental area and the mammillary body have been shown to project back to the monkey cerebellum.

Functionally, electrical stimulation of the cerebellum, particularly stimulation of the vermis area 3 (V3) and the fastigial nucleus, modulates the physiology of limbic lobe structures. Evoked responses in the orbitomesial cortex, anterior cingulate gyrus, amygdala, hippocampal and dentate gyri, pyriform and preamygdaloid cortical regions and hypothalamus have been recorded through stimulation of the cerebellum. Thus, the cerebellum earns its Latin name of “miniatu-
bellar modulation of neural circuits that link prefrontal, posterior parietal, superior temporal and limbic cortices with the cerebellum.27

Interestingly, these displays of passivity and flattening or blunting of emotion and a disinhibition of restraint are phenotypically similar to the depressed and manic states in mood disorders. This presentation may also resemble some of the classical symptoms of schizophrenia, although schizophrenia is also associated with more severe cognitive impairments.

Similarly, children with mutism resulting from cerebellar tumours also display altered moods.27 In particular, lesions of the vermis produced behavioural changes that extended beyond the cognitive domain, including a flattening of affect and a silly, disinhibited, regressive quality to the children’s interactions, with some exhibiting a reduced tolerance of others and a general tendency to avoid physical and eye contact.

Disruption of the cerebellar circuitry may thus impair the processing of emotional responses to challenging stimuli. Furthermore, the finding that single lesions of the cerebellum can impart such a marked change in the personality of affected individuals highlights the role of cerebellar interconnectivity in affective and cognitive processing.

Schizophrenia

Rationale

Clinical observations of affective and cognitive changes arising from cerebellar lesions and stimulation permit the hypothesis that the cerebellum may not be irrelevant in some neuropsychiatric states.22 There is evidence that patients with schizophrenia have an altered corticocerebellar connectivity.24 Andreasen et al.21 and Wiser et al.18 proposed that disruption of the CTCCC may underlie the combination of symptoms observed in schizophrenia. Analogous to the cerebellar role in facilitating rapid and smooth execution of motor tasks, they further proposed that the CTCCC performs a similar function in the monitoring and coordination of the fluid execution of mental activity resulting in normal cognitive function. Conversely, disruption in the activity of this circuit leads to the disordered cognition and clinical symptoms characteristic of schizophrenia.29

Structural neuroimaging studies

During the 1980s and early 1990s, with the growing availability of computed tomography (CT), reports of cerebellar vermian atrophy or hypoplasia in patients with schizophrenia began appearing in the literature.21,22,26 although such reports could not be confirmed by others22 (Table 1).

Structural magnetic resonance imaging (MRI) analyses using quantitative anthropometric techniques have yielded more consistent reports of cerebellar atrophy in schizophrenia,23,24,25 with some authors attempting to delineate a subset of patients with reduced or atrophied cerebella. Global reductions in cerebellar volume have been associated specifically with perinatal brain insults,26 schizophrenia in men,27 childhood-onset schizophrenia,28 very-late-onset schizophrenia,29 chronic schizophrenia30 and psychotic symptoms.31 Other authors have noted atrophy delimited to the vermis.32,33,34

As was the case with CT studies, not all investigators using MRI have found reduced cerebellar volumes in schizophrenia. Some have reported a larger vermis in the brains of patients with schizophrenia,35 as well as increased grey matter.36 Other MRI studies have failed to locate any consistent change in the cerebellar structure in schizophrenia.37

Although the structural mapping studies have been equivocal, the weight of evidence supports extending the study of cerebellar activity in schizophrenia. For example, the finding that unaffected first-degree relatives of probands with schizophrenia have reduced cerebellar volumes,38 along with the observation of reduced cerebellar volumes in neuroleptic-naive patients with schizophrenia,39 suggests that cerebellar atrophy may be a hereditary trait rather than a psychotropic-associated epiphenomenon.

Functional imaging studies

Results from memory tasks involving both words and faces in patients with schizophrenia provide further support for the CTCCC model. The CTCCC regions that are activated in healthy control subjects during recall (the prefrontal, thalamic and cerebellar areas) displayed less or no activation in patients with schizophrenia. Recent functional MRI (fMRI) investigations using a variety of additional cognitive tests (Wisconsin Card Sorting Test,40 Working Memory [n-back] Task41 and Periodic Sequence-Learning Task42) have similarly reported decreased activation of the cerebellum (Table 1).

Differences in cerebellar perfusion between patients with schizophrenia and control subjects have been noted even in the absence of cognitive or affective challenges. These results may be reversible, with a decrease in cerebellar blood perfusion43 and activation44 after administration of atypical antipsychotics. Reports of aberrant cerebellar activity, with concomitant medication effects, suggests that disturbances in cerebellar activation, and concomitant changes in blood volume and perfusion, are partly state, partly trait and partly medication mediated. Future investigations should strive to further delineate and characterize the relative influence of each factor.

Cellular abnormalities in the cerebellum

Postmortem studies have also revealed altered cerebellar structure, specifically a smaller anterior vermal lobe,21 which appears to correlate with occipital asymmetry.32 Postmortem analyses of cerebellar cytoarchitecture have revealed a reduction in the density of vermal Purkinje cells in the brains of patients with schizophrenia and, more recently, a reduction in the size of the Purkinje cells, although other investigators have failed to replicate these results.35

At the subcellular level, evidence is accumulating that cerebellar abnormalities in schizophrenia might arise from impaired synaptic architecture.34–36 Synaptophysin, complexin I and complexin II are integral proteins in the construction of
functional synapses; as such, a reduction in their expression has been taken as indicative of impaired synaptic connectivity. Whereas synaptophysin is found in both inhibitory ($\gamma$-aminobutyric acid [GABA]-ergic) and excitatory (glutamatergic) synapses, complexin I prefers the former and complexin II associates preferentially with the latter. On the basis of the finding that mRNA and protein levels of synaptophysin and complexin II, but not complexin I, were reduced, the authors proposed that it was the excitatory neurons in the cerebellum, in particular, that were affected by or responsible for the observed cerebellar phenotypes in schizophrenia. However, there is also evidence that inhibitory neurotransmission is impaired, for example, reports that both reelin, a glycoprotein secreted preferentially by GABAergic interneurons, and glutamic acid decarboxylase, a prerequisite enzyme for GABA synthesis, were reduced in the cerebellum of patients with schizophrenia. The concept of impaired cerebellar synapse formation in schizophrenia is further supported by findings of reduced levels of synaptosomal-associated protein 25 (SNAP-25, a synaptic protein involved in the docking of synaptic vesicles) against a background of unaffected levels of cytoskeletal proteins. Perhaps the underlying source of impaired synaptogenesis is an increase in expression of an axonal chemorepellant, such as semaphorin 3A. Comparing gene expression in the cerebellum of patients with schizophrenia and healthy subjects, Eastwood et al showed that this particular chemorepellant is elevated in expression and is associated with the downregulation of genes involved in synaptic formation and maintenance in the brains of patients with schizophrenia.

**Major depressive disorder**

Using a positron emission tomography analysis of regional blood flow, Reiman et al investigated the neuroanatomic correlates of externally generated emotions. These authors...
imaged the brains of healthy volunteers as they watched film clips designed to evoke a variety of emotional states, including happiness, sadness and disgust. In addition to finding activation of the limbic and paralimbic areas, the group noted activation of the cerebellar hemispheres. Using a similar technique, Lane et al\textsuperscript{62} extended these results by demonstrating that sadness, but not happiness, increased activation of the anterior cerebellar vermis.

In contradistinction to the relevant body of morphometric studies examining cerebellar structure in schizophrenia, there are very few studies examining cerebellar size in unipolar depression. Early MRI studies\textsuperscript{63,64} showed reduced cerebellar size in patients with unipolar depression, whereas a more recent quantitative MRI investigation failed to find any statistically significant differences.\textsuperscript{65} The most recent MRI investigation\textsuperscript{65} did reveal, however, that in patients who did not respond to fluoxetine treatment, total cerebellar tissue volume decreased as baseline depression scores increased (Table 2).

In an effort to discern the differential brain activation pattern that results from evoking sadness in healthy control subjects and patients with unipolar depression, Beauregard et al\textsuperscript{49} performed fMRI scans while both groups viewed an emotionally laden film. Transient sadness produced significant activation of the left medial prefrontal cortices and the middle temporal cortex, but also activation in both groups, not only in the medial and inferior prefrontal cortices and the middle temporal cortex, but also in the cerebellum. Furthermore, the patients with depression displayed greater activation of the left medial prefrontal cortex and the right anterior cingulate gyrus, but less activation of the cerebellum.

In a positron emission tomography investigation, cerebral blood flow was compared in subjects with acute depression and healthy controls, before and after a transient mood challenge. In line with the results obtained with fMRI, the patients with depression displayed less activation of the cerebellum and thalamus.\textsuperscript{75}

To test whether subjects who recover from depression show abnormal brain activity, Smith et al\textsuperscript{46} acquired fMRI data during a conditioning paradigm with a noxious pain stimulus. Although similar patterns of brain activation during painful stimulation were found for both patients and healthy controls, subjects who had recovered from depression displayed less cerebellar activation than the control subjects during anticipation of the noxious stimulus. These findings suggest that depression may impart a permanent and irreversible change in cerebellar function.

These findings of cerebellar hypoactivity in response to an emotional challenge are comparable to reduced cerebellar activation to cognitive challenges in schizophrenia.\textsuperscript{41–43} This apparent reduction in cerebellar dynamic range may result if the cerebellum is tonically hyperactive and thus near the ceiling of maximal activation. Dolan et al\textsuperscript{76} were the first to report an increase in baseline cerebellar vermal blood flow in a subset of patients with depression and cognitive impairment. More recent data suggest that this tonic increase in cerebellar

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<tr>
<td>Videbech et al\textsuperscript{72}</td>
<td>42 MDD, 47 HC</td>
<td>MRI</td>
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<td>Kibbrell et al\textsuperscript{72}</td>
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<td>Ketter et al\textsuperscript{75}</td>
<td>43 BPV, 43 HC</td>
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<td>Osuch et al\textsuperscript{73}</td>
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<td>Davies et al\textsuperscript{74}</td>
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<td>MRI</td>
<td>(\Rightarrow) Tc SPECT</td>
<td>(\Rightarrow) R Cb (MDD v. MDE)</td>
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Note: BPM = bipolar disorder — depressed; BPE = bipolar disorder — euthymic; BPB = bipolar disorder — familial; BPM = bipolar disorder — manic; BPV = bipolar disorder — varied (all phases of illness); CB = cerebellum; CBH = cerebellum hemisphere; CBT = cerebellum total; CBV = cerebellum vermis; FDG = fluoro-deoxyglucose; fMRI = functional MRI; HC = healthy control; L = left; MDD = major depressive disorder — depressed; MDE = major depressive disorder — euthymic; MDV = major depressive disorder, various severities of depression; MRI = magnetic resonance imaging; PET = positron emission tomography; R = right; SZ = schizophrenia; SPECT = single-photon emission computed tomography; V3 = vermis area 3, \(\Rightarrow\) = no differences.

*Patients were scanned twice, before and after treatment of acute depression.
activity is characteristic of major depression, regardless of mood state or medication history.\textsuperscript{7,74}

Similar to the findings in schizophrenia, in which cerebellar blood flow decreases following antipsychotic treatment,\textsuperscript{64} an association between successful treatment of depression and a decrease in cerebellar perfusion has been reported.\textsuperscript{7} Thus, a positive treatment outcome in patients with both mood and psychotic disorders may be associated with a reduction in cerebellar activity and blood flow (Table 2).

Preliminary studies appear to indicate that patients with unipolar depression and schizophrenia may share similar structural (volumetric reductions) and functional (baseline hyperactivity) abnormalities in the cerebellum. However, the available results from investigations in unipolar depression are extremely limited and prevent definitive conclusions. Moreover, the high prevalence of depressive symptoms among people with schizophrenia\textsuperscript{79} may account for some of the observed similarities. Future imaging investigations should strive to clarify the role of cerebellar structural and functional abnormalities in unipolar depression, and their relation to clinical outcomes and changes in metabolism.

**Bipolar disorders**

Because cerebellar atrophy has been documented in depression and schizophrenia, it is important to investigate the structural and functional aspects of the cerebellum in bipolar disorders.\textsuperscript{46} An early report of cerebellar atrophy in mania\textsuperscript{69} was followed by several studies confirming this initial observation.\textsuperscript{26–30} In 2 of the 3 studies,\textsuperscript{77–79} which controlled for alcohol use in both patient and healthy control groups, atrophy of the vermis was reported, whereas Dewan et al\textsuperscript{80} were not able to find any differences in cerebellar atrophy or cerebellar grey and white matter densities.

A subsequent MRI investigation of the cerebellum in patients with bipolar disorder did not reveal any gross morphologic differences between the patient group and healthy controls.\textsuperscript{81} However, when the patients with bipolar disorder were subdivided into first-manic-episode and multiple-manic-episode groups, the researchers found that the V3 region was significantly smaller in the multiple-episode group. Further analysis revealed that among multiple-episode patients it was the number of previous depressive episodes, not substance abuse or duration of lithium exposure, that contributed to the reduction in V3 volume.\textsuperscript{82}

The only other morphometric MRI study examining the cerebellum in bipolar disorder\textsuperscript{83} did not reveal any statistically significant difference in total cerebellar or vermal size between patients with bipolar disorder and healthy controls. However, the authors did find a smaller vermis in patients with at least 1 first-degree relative possessing a history of mood disorders. Furthermore, there was a significant trend for an inverse correlation between number of prior affective episodes and size of the V3 region. These results corroborate the earlier MRI finding,\textsuperscript{16} leading to the possibility that atrophy of this particular region of the vermis may be associated with duration or course of illness.\textsuperscript{85}

Loeber et al\textsuperscript{44} employed dynamic susceptibility contrast MRI and reported that patients with bipolar disorder have lower cerebellar blood volumes than healthy controls and patients with schizophrenia, even after adjustment for anatomic volume differences. The cerebellar region reported most frequently in neuroimaging studies of patients with bipolar disorder, the vermis, showed the largest reduction in blood volume. With atypical antipsychotic medication, however, this relative decrease in blood volume appeared to show a reversal toward age- and sex-matched norms.\textsuperscript{82}

In another study, Kruger et al\textsuperscript{17} investigated blood flow changes in patients with bipolar disorder (both with depression and in remission) and in healthy individuals during a sadness induction protocol. Baseline differences were noted between the 2 groups, with the bipolar cohort displaying less cerebellar blood flow. Interestingly, when challenged with the sadness induction protocol, different, nonoverlapping regions of the cerebellum were activated in the 2 groups; specifically, among the patients with bipolar disorder, a greater fraction of cerebellar tissue was activated.

In contrast to findings of decreases in blood volume and flow, Ketter et al\textsuperscript{75} reported increases in metabolism in the cerebellar and posterior cortical areas, occurring independently of illness phase, in a relatively large study of treatment-resistant patients with bipolar disorder.

Preliminary investigations into cerebellar structure and function in bipolar disorder have consistently noted differences relative to healthy controls; however, definitive conclusions are not yet possible. Provisional studies have reported a smaller cerebellum, with decreased blood volume and increased glucose metabolism. Seemingly discrepant findings of decreased blood volume and increased glucose metabolism may reflect the clinical heterogeneity of the bipolar populations studied. Thus, it may be possible that cerebellar hypermetabolism is a finding particular to treatment-resistant subjects with bipolar disorder.

In summary, preliminary results in patients with unipolar and bipolar depression suggest aberrant cerebellar function and, possibly, size. The studies indicate that both patient populations may have abnormalities in cerebellar function under both baseline and challenge conditions. Given the small number and inadequate replication of these studies, caution should be exercised in interpreting their results.

**Summary and discussion**

Results from a number of neuropsychiatric investigations have documented abnormalities in cerebellar function and structure. Moreover, pharmacologic and psychosocial therapeutic interventions for patients with these disorders have been reported to coincide with changes in cerebellar function. Recent scrutiny of the cerebellum in neuropsychiatric investigations has been facilitated by technologic advances in imaging instruments that were formerly (in the mid to late 1990s) unable to fully capture the cerebellum. A growing awareness of the putative role of the cerebellum in higher cognitive function has promoted the practice of using this brain region for standardizing global brain activity.

The finding of simultaneous alteration in activation of the
cerebellum, the thalamus and parts of the frontal cortex has led some authors to propose the CTCCC model to explain the diverse symptoms of schizophrenia. Thus, reduced “monitoring” of cortical activity by the cerebellum may initiate a dysregulation of certain neural circuits involved in emotional and cognitive function. It remains possible that overlapping aberrations in cerebellar function could contribute to the phenomenology observed in mood disorders. Research into the putative cerebellar role in mood disorders has been conspicuously absent.

The analysis of gene expression in the cerebellum is allowing researchers to look at cellular changes that accompany psychiatric illnesses at the molecular levels. The results of altered cerebellar gene expression in psychiatric illnesses will invite the study of genetic polymorphism in the general population, allowing an endophenotypic classification of psychiatric conditions. Basic research on the cellular pathways at work in the cerebellum also offers additional insight in the search for novel targets for pharmacologic intervention. Putative models of neural networks implicated in the pathophysiology of mood disorders and schizophrenia provide a neu roanatomic framework for such future endeavours.

It is tempting to speculate that atrophy of the cerebellum may be a nonspecific response to psychologic stress. After reporting altered resting blood flow to the vermis in adolescents with prior childhood sexual abuse, Anderson et al proposed that early trauma may interfere with the development of the vermis, producing neuropsychiatric symptoms more commonly observed with drug use. Like the hippocampus, the vermis has a protracted period of postnatal development and may produce granule cells postnatally. Since the vermis has the highest density of glucocorticoid receptors during development, even exceeding that of the hippocampus, it may be particularly vulnerable to the effects of stress hormones, which are frequently elevated in subjects with psychiatric conditions.

To recapitulate, an ideal model for neuropsychiatric disorders does not exist. With minimal equivocation, current models fall short of providing a comprehensive explanation for the diverse phenomenology observed in persistent mental illness such as mood and psychotic disorders. It is possible that cerebellar abnormalities noted in the extant literature are epiphenomena relating to abnormalities elsewhere. The alternative hypothesis, that the cerebellum may be relevant secondarily or play an integral role in aberrant neural network systems, remains to be confirmed or refuted.

Competing interests: None declared for Mr. Konarski and Dr. Grupp. Dr. McIntyre is a consultant and speaker for AstraZeneca, Eli-Lilly, Janssen-Ortho, Organon, Wyeth, Lundbeck, GlaxoSmithKline and ORYX; he has received research funding from Wyeth. Dr. Kennedy is a consultant or speaker for and has received research funding or honoraria from AstraZeneca, Biovail, Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Merck, Organon, Pfizer, Servier and Shire Wyeth.

Contributors: The review was conceived and designed by Mr. Konarski, who was also responsible for data acquisition. Drs. McIntyre, Grupp and Kennedy interpreted the data. All authors participated in drafting the article, and Drs. McIntyre and Kennedy revised the article. All authors gave final approval for the article to be published.

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