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The Role of the Cerebellum in Schizophrenia: an Update of Clinical, Cognitive, and Functional Evidences

Hernàn Picard[1,2], Isabelle Amado[2], Sabine Mouchet-Mages[2], Jean-Pierre Olié[2], and Marie-Odile Krebs[2]

[2]INSERM U796, Pathophysiology of psychiatric diseases, University Paris Descartes, Faculty of Medicine Paris Descartes, Sainte-Anne Hospital, Paris F-75014, France

The role of the cerebellum in schizophrenia has been highlighted by Andreasen's hypothesis of "cognitive dysmetria," which suggests a general dyscoordination of sensorimotor and mental processes. Studies in schizophrenic patients have brought observations supporting a cerebellar impairment: high prevalence of neurological soft signs, dyscoordination, abnormal posture and proprioception, impaired eyeblink conditioning, impaired adaptation of the vestibular-ocular reflex or procedural learning tests, and lastly functional neuroimaging studies correlating poor cognitive performances with abnormal cerebellar activations. Despite those compelling evidences, there has been, to our knowledge, no recent review on the clinical, cognitive, and functional literature supporting the role of the cerebellum in schizophrenia. We conducted a Medline research focusing on cerebellar dysfunctions in schizophrenia. Emphasis was given to recent literature (after 1998). The picture arising from this review is heterogeneous. While in some domains, the role of the cerebellum seems clearly defined (ie, neurological soft signs, posture, or equilibrium), in other domains, the cerebellar contribution to schizophrenia seems limited or indirect (ie, cognition) if present at all (ie, affectivity). Functional models of the cerebellum are proposed as a background for interpreting these results.

Key words: neurological/cognition/symptoms/cerebellar dysfunction/models

Introduction

The cerebellum is traditionally regarded as an organ that subserves coordination, balance, gait, and fine motor control. Nevertheless, its involvement in cognition has also been suggested[1] and a cerebellar dysfunction could underlay psychiatric disorders such as schizophrenia[2] or autism.[3] The potential role of the cerebellum in schizophrenia has been highlighted by Andreasen's hypothesis of "cognitive dysmetria," which suggests an impaired sequencing and coordination of sensorimotor and mental processes,[2] resulting in dyscoordinated language and disordered thought, the core feature of the cognitive dysmetria hypothesis. Functional brain imaging studies have suggested the involvement of cortico-cerebellar networks in cognition.[4]

Converging evidence suggests that schizophrenia may be associated with cerebellar anomalies. Neuropathological studies have reported a reduction in size and density of Purkinje cells,[5] and magnetic resonance spectroscopy studies have shown an altered expression of synaptic proteins in the cerebellum of schizophrenic patients.[6] In addition, an atrophy of the cerebellar vermis has been described, though not always found.[7] There is also available evidence that a cerebellar dysfunction could underlay some of the clinical psychiatric and neurological symptoms as well as cognitive dysfunctions observed in schizophrenia. Recent reviews have already focused on the implication of the cerebellum in psychiatric illnesses in general,[8] in emotion[9] or behavior and cognition.[10] Here, we propose an updated and synthetic review of clinical, cognitive, behavioral, and functional neuroimaging studies supporting the involvement of the cerebellum in schizophrenia. We aimed to highlight the domains where convincing evidence is already available. Some functional models of the cerebellum will be briefly discussed, yet the review of all hypothesized functions of the cerebellum itself, is beyond the scope of this review.

Methods

For every specific domain, Medline searches, limited to studies in humans and in English language, were performed in order to be as exhaustive as possible. Preference

[1]To whom correspondence should be addressed; 7, rue Cabanis, Service Hospitalo-Universitaire. Hôpital Sainte Anne 75014 Paris, France, tel: +33-1-45-65-81-79, fax: +33-1-45-65-81-60, e-mail: picard@broca.inserm.fr.

was given to studies later than 1998, except when the search retrieved mainly older studies. All relevant works, either supporting or challenging a cerebellar dysfunction in schizophrenia, were included. In general, the searches included the keywords "cerebellum" + "schizophrenia" and 1 or 2 terms used in the text below as section titles, eg, "affectivity" or "saccades". Variants or related terms were also used, such as "affect," "affective," or even "emotion." In the case of functional imaging studies, special attention was paid to the inclusion of the cerebellum in the analysis because it is often excluded due to technical constraints. When cited studies did not include the cerebellum in the analysis, this is clearly stated.

Cerebellum and Psychiatric Symptoms

Hallucinations

A few brain imaging studies in schizophrenic patients have provided evidence of the involvement of the cerebellum in hallucinations reported (table 1). Significant reductions in gray matter volume in the cerebellum, bilaterally, in the left superior temporal gyrus and the left thalamus were reported correlated with higher scores in the hallucinations item of the Brief Psychiatric Rating Scale.[11] Two studies functional magnetic resonance imaging (fMRI) studies by Shergill et al[12,13] investigated the neural basis of inner speech and auditory verbal imagery in schizophrenic patients with prominent auditory hallucinations. Compared to controls, patients showed an attenuated activation in a cortical-subcortical network involving the posterior cerebellar cortex while imagining external speech. The authors concluded that hallucinated patients may present a dysfunction in areas implicated in verbal self-monitoring. Yet, 2 other studies using semi-automated algorithms to analyze structural MRIs of schizophrenic patients found correlations of structural changes with the severity of hallucinations.[14,15] Shin et al[14] reported greater gray matter in the frontal and temporal cortices of hallucinated patients vs non-hallucinated patients, but not in the cerebellum, while Gaser et al[15] did not examine the cerebellum.

Altogether, despite several reports of cerebellar structural abnormalities in schizophrenia,[7] the evidence supporting a cerebellar involvement in hallucinations, formal thought disorder (FTD), and blunted affect seems, to date, limited and not conclusive. The most direct support comes from fMRI studies[12,13] reporting decreased activation of a networks including the cerebellar cortex in inner speech control, while structural MRI lead to discrepant results,[11,14] possibly because of differences in techniques as well as methods to induce inner speech control. The interpretation of cerebellar hypoactivations or decreased gray matter volume in the pathophysiology of hallucinations has thus to be considered cautiously considering the extension of other cortical areas also concerned. Thus, caution is warranted interpreting the role of the cerebellum.

Formal Thought Disorder

Thought disorder is one of the fundamental features of schizophrenia.[16] It encompasses disorders in the content (delusions and hallucinations) and disorders in the formal aspects of thought (formal thought disorder, FTD). FTD includes a variety of symptoms such as poverty of content of speech, incoherence, or neologisms. FTD has been associated with dysfunctions in the left superior temporal gyrus,[17] but the cerebellum could also be involved. Three studies by Kircher et al[18–20] examined FTD with fMRI (table 1). Though interpretation of the results highlighted fronto-temporal dysfunctions in patients, cerebellar hypoactivations were also found in two of these works. In one of them,[18] FTD was yielded through a 3-minute speech about Rorschach inkblots. The severity of incoherence and neologisms was positively correlated with the activity in the cerebellar vermis, right caudate nucleus and the precentral gyrus and it was negatively correlated with changes in the Wernicke area. Another fMRI controlled study by the same group[20] reported the cerebellum of patients with FTD significantly less activated compared with healthy controls. Non-FTD patients also presented decreased cerebellar activation but difference was less marked. In this latter study contrasts were obtained between 3 conditions: sentence completion, word-choice and a reading condition. Finaly, Levitt et al[21] found greater vermis white matter volume associated positively with the severity of thought disorder, positive symptoms and impairments in verbal logical memory.

In conclusion, though 2 fMRI studies[17,19] associated FTD with dysfunctions in left temporal regions, another 2 fMRI studies[18,20] found correlations between measures of FTD and reduced activity in the cerebellum, among other regions. A structural MRI work[21] also reported correlations between cerebellar white matter volume and the severity of thought disorder, positive symptoms, and verbal memory impairments. These somewhat contradictory results could be explained by the heterogeneity of the patients groups concerning age, medication, and duration of illness, as well as different measures of FTD and different paradigms of speech production used. More homogeneous groups and replication studies are needed before any definite conclusion.

Affectivity

Some studies have reported the presence of psychotic and affective features in patients with lesions of the cerebellum. A "cognitive affective cerebellar syndrome," initially described in patients after surgery for posterior fossa tumors,[22] has also been reported in patients with cerebellar degenerative diseases.[23] Many structural and

functional neuroimaging studies in affective disorders have reported cerebellar abnormalities.[8,9] The induction of sadness has been correlated with increased cerebellar regional blood flow (rCBF) in the vermis,[8] a region particularly sensitive to stress due to its high concentration of glucocorticoids receptors.[8]

In schizophrenia, functional studies have used the presentation of emotionally charged images to elicit an affective response. Emotional recognition tasks assess the capacity to perceive one aspect of visual stimuli (ie, faces) as much as emotional prosody can be perceived in spoken language. In schizophrenic patients under neuroleptic treatment, functional imaging of blunted affect has reported 2 types of pattern of activation: either decreased activation of widespread cortical and subcortical areas[24] or the implication of areas not normally concerned in controls.[25] The cerebellum has been described as both hypoactivated[24] and hyperactivated.[25] Neuroleptic free patients, though correctly recognizing the emotional stimulus, underactivate the networks normally involved including the amygdala, cerebellum, thalamus, or prefrontal cortex (PFC).[26] It has been suggested that emotional blunting is associated with a shift in the relative contribution of brain regions subserving cognitive and emotional processing. The noncompetitive antagonist of the glutamate receptor ketamine (an anesthetic agent) produces emotional blunting in healthy subjects. Ketamine-induced blunted affect has been correlated with a reduced rCBF in cerebellum and cingulate and visual cortex in fMRI, a pattern similar to that reported in schizophrenic patients.[27]

Functional imaging studies in patients with blunted affect reported either increased[24] or decreased[25,26] activation of the cerebellum during emotional recognition tasks (table 1). Medication status does not seem to account for those differences. Indeed, the fMRI study in medicated patients reporting decreased cerebellar activation[25] is in line with the one in medication-free patients.[26] Both these investigations did not distinguish patients presenting, or not, blunted affect. On the contrary, Stip et al[25] divided the patient group in those presenting (BA+) or not presenting (BA-) blunted affect, the latter being those who presented, among other regions, increased cerebellar activation.

Cerebellum and Neurological Dysfunction in Schizophrenia

Neurological disturbances are commonly found in schizophrenia, including both "hard signs" and "soft signs"[28]. However, "hard signs," such as abnormal developmental reflexes, are rather seldom, and their prevalences have not always been found significantly different between patients and controls.[29] In most cases, the neurological dysfunctions are subtle. In line with these arguments, a set of motor coordination, equilibrium, and sensory integration items (eg, graphesthesia or stereogno-

Table 1 Involvement of the cerebellum in schizophrenia – Non-cognitive aspects.

Psychiatric symptoms		
Hallucinations	Shergill et al, 2003 [13]	+++
	Shergill et al, 2000 [12]	+++
	Neckelman et al, 2006 [11]	++
	Gaser et al 2004 [14]	NIA
	Shin et al 2005 [15]	–
Formal Thought Disorder	Kircher et al, 2001 [20]	+++
	Kircher et al, 2001[18]	+++
	Levitt et al, 1999 [21]	++
	Weinstein et al, 2006 [17]	–
	Kircher et al, 2002 [19]	–
Affect	Stip et al, 2005 [25]	+++
	Paradiso et al, 2003 [26]	+++
	Abel et al, 2003 [27]	+++
	Takahashi et al, 2004 [24]	–
Neurological symptoms		
Neurological Soft Signs	Bottmet et al, 2005 [7]	+++
	Mouchet-Mages et al, 2007 [43]	+++
	Keshavan et al, 2003 [44]	–
	Dazzan et al, 2004 [45]	NIA
	Schroder et al, 1995 [46]	NIA
Cerebellar symptoms	Ho et al, 2004 [33]	++
	Varambally et al, 2006 [47]	++
Motricity & propioception	Daskalakis et al, 2005 [50]	+++
	Muller et al, 2002 [53]	+++
	Stephan et al, 2001 [52]	+++
	Ridler et al 2006 [48]	++
	Bays et al, 2006 [55]	+
	Sukhwinder et al, 2005 [54]	+
	Muller et al, 2002 [51]	–
Posture	Marvel et al, 2004 [56]	++
	Sullivan et al, 2004 [58]	++
	Deshmukh et al, 2002 [59]	++
Oculomotricity		
Saccadic movements	Keedy et al, 2006 [68]	–
	Raemaekers et al, 2002 [69]	–
	Schultze et al 2006 [72]	–
	Tu et al 2006 [70]	–
	McDowell et al 2002 [71]	–
Smooth pursuit movements	Pivik, 1991 [74]	+
	Avila et al, 2002 [75]	+
Nondeclarative learning		
Eyeblink	Sears et al, 2000 [77]	+
	Brown et al, 2005 [78]	+
	Stevens et al, 2002 [79]	–
	Hofer et al, 2001 [80]	–
Vestibulo-Ocular-Reflex	Jones et al, 1983 [82]	+
	Pivik et al, 1987 [83]	+
	Warren et al, 1998 [84]	–
Procedural Learning	Kodama et al, 2001 [94]	+
	Bigelow et al, 2006 [95]	+
	Ninomiya et al, 1998 [96]	–

– No cerebellar involvement reported.
+ Results attributed, on theoretical grounds, to the cerebellum.
++ Behavioural or structural imaging studies (correlation studies) supporting a cerebellar dysfunction.
+++ Functional studies reporting a cerebellar involvement (fMRI, PET, TMS).
NIA, (Cerebellum) Not Included in Analysis

sia) have been grouped under the term Neurological Soft Signs (NSS). In schizophrenia, different NSS scales have been used (eg, Neurological Evaluation Scale [NES],[30] NSS scale[31]). It is usually assumed that NSS in schizophrenic patients reflect minimal brain dysfunction, resulting from abnormal neurodevelopment. Despite the common view that these signs are nonlocalizing, there is growing interest in clarifying the precise structural and psychiatric correlates of NSS taking into account the heterogeneity of schizophrenic symptoms.[32] In particular, some neurological soft signs could reflect mild cerebellar dysfunction such as motor dyscoordination or adiadochokinesia.[28] Moreover, some studies have focussed on specific neurological dysfunctions including cerebellar signs, posture, and gait.[28,33]

Neurological Soft Signs

Compared to healthy controls, never-treated, first-episode schizophrenic patients have higher NSS scores,[28,34] while the nonaffected siblings show intermediate NSS scores.[32,35] Furthermore, several studies have significantly correlated NSS with severity of illness,[36] lower social functioning,[33,36] and negative symptoms.[32,35–37] By comparison with affective psychiatric patients, first-episode schizophrenic patients also present higher NSS scores.[38] Interestingly, NSS are prevalent in 2 pathological states also related with cerebellar pathology: chronic alcoholism[39,40] and autism.[41,42]

A few recent studies have investigated the neural substrate of NSS. Bottmer et al[7] reported diminished volume of both cerebellar hemispheres in a group of 37 first-episode schizophrenic patients matched to controls. Furthermore, a significant inverse correlation between NSS scores and the volume of the right cerebellar hemisphere was found. A study by our own group[43] in first-episode schizophrenia patients with no history of substance abuse showed significant white matter reductions in the left posterior cerebellum and the right insula in patients with high NSS scores compared with patients with low scores. The subscore of motor integration was negatively associated with the gray matter volume of the cerebellum, the right inferofrontal, right occipital, and the left postcentral gyri. Noteworthy, the score of sensory integration was negatively correlated with bilateral gray matter volume of the cerebellum. In the same line, Keshavan et al[44] comparing 17 neuroleptic naive schizophrenic patients and 18 controls reported correlations of the cognitive/perceptual factor of the NES scale with smaller volumes of the left heteronodal association cortices. Two other studies[45,46] found correlations between NSS and basal ganglia, but those studies excluded the cerebellum from their analysis.

A drawback of the NSS literature, in general, is the lack of a consensual tool. Though the NES is often used, only a selection of items is generally used[44] varying from one study to another and other studies used different scales,[43] sometimes not standardized,[33] limiting the comparability of the results. Two studies support the involvement of the cerebellum in NSS,[7,43] but the main limitation is the small size of the samples. Unfortunately, the 2 studies associating NSS in patients to basal ganglia dysfunctions[45,46] did not include the cerebellum in their analysis, so to date, it is not possible to weigh the relative importance of these 2 structures.

Cerebellar Symptoms in Schizophrenia

Ho et al[33] in a study considering specifically cerebellar signs, assessed equilibrium, intentional tremor, dysdiadochokinesis, and hypotonia in 155 schizophrenic patients and controls. Twenty-one percent of the patients versus 4.5% of controls presented at least 1 cerebellar sign. The Romberg test and tandem gait test were the most common signs. Patients with cerebellar signs ($n = 32$) had more severe negative symptoms, poorer premorbid social adjustment, and smaller total cerebellar volume than patients with no cerebellar signs. These latter showed equivalent cerebellar volumes to controls. These findings were independent of medication status. Another recent study by Varambally et al,[47] compared 32 schizophrenic patients to matched controls by using 4 scales: the NES (for the NSS), the International Cooperative Ataxia Rating Scale, ICARS (for cerebellar signs), and the SANS and simplified acute physiology score (for psychopathology). Discriminant analysis revealed 2 ICARS subscores, kinetic abnormalities and dysarthria, (but none of the NES scores) to be significant ($P < .0001$) accounting for 78% of discrimination between patients and controls. Furthermore, ICARS total score, posture subscore, and oculomotor subscore had significant positive correlation with negative syndrome score. Altogether, these works support an intrinsic cerebellar dysfunction in schizophrenia.

Hence, cerebellar signs per se may represent an important part of NSS as a whole, as suggested by 2 studies reporting (1) their relative importance in schizophrenic patients[33] and (2) their discriminative power between patients and controls[47] (this latter, altogether with other 2 cerebellar subscores).

Motor Tasks and Propioception

In addition to its well-known role in motor coordination, the cerebellum takes an important part in the processing of sensory inputs. Cerebellar lesions are indeed frequently associated with ataxic movements and sensory dysfunctions.[23]

Frontal cortico-cerebellar systems implicated in adult executive functions are anatomically related to systems undergoing maturation during normal childhood motor development. Disruption of this anatomical system may underlie both the early developmental and adult cognitive abnormalities in schizophrenia, as supported by the

Finnish prospective study,[48] correlating motor function at 1 year of age with structural MRI measures and executive functions at age 33–35 years (table 1).

Connections between the cerebellum and the motor cortex have been explored using transcranial magnetic stimulation.[49,50] Schizophrenic patients, whether medicated or not, showed an increased excitability of the motor cortex.[49] A deficit in corticocortical inhibition has been incriminated, but a decreased cerebellar inhibition to the motor cortex could possibly contribute to this higher excitability.[50] Altered connectivity has also been reported in fMRI studies, both in the basal ganglia[51] and cerebellum.[52] Stephan et al,[52] using simple unilateral self-paced finger-tapping tasks, reported, after 3 weeks of treatment with the antipsychotic olanzapine, a change in the pattern of cerebellar connectivity, thus suggesting that medication is indeed an important confounding variable in studies assessing motor functions. Furthermore, in this study, olanzapine seemed to affect differently the function of the right and the left cerebellar hemispheres. Similar conclusions were reported by another fMRI study in patients and healthy controls performing a finger-tapping task.[53]

Sensory propioceptive consequences of self-generated movements have been reported to be altered in schizophrenia.[54] Propioceptive inputs are normally attenuated by a sensory prediction mechanism differentiating self-generated from externally generated sensory inputs.[55] Sukhwinder et al[54] observed that patients demonstrated less sensory attenuation than controls. Using a force-matching task that dissociates sensory inputs and self-generated movements, they concluded that patients have a dysfunctional predictive mechanism. Sensory prediction has been proposed as one of the basic cerebellar functions (see below).

Behavioral studies usually analyze the motor responses of subject. Yet, as the motor responses are usually interpreted in the context of other sensory or cognitive functions, studies *specifically* focusing on motor performance are surprisingly sparse in schizophrenia. Based on works with 3 different techniques (TMS,[49,50] fMRI,[51–53] sensory decoupling [54,55]), arguments exist to hypothesize dysfunctions in the motor system of schizophrenia patients before frontal executive control regions intervene. But, to date, evidence is limited and diverse.

Posture

Posture and gait specifically involve the cerebellum. First reports of altered postural reflexes in schizophrenia patients date from the 1970s.[56] Measures of body postural sway are a way to assess postural control. In schizophrenia, 1 study (Marvel et al[56]) explored the postural sway of patients and controls with a pressure-sensitive platform. Patients demonstrated more postural sway than controls, independently of medication. Differences remained significant, even after removing from the analysis the patients with tardive dyskinesia. Bloem et al[57] reported altered long-latency postural reflexes in a heterogeneous group of medicated psychotic patients compared with different types of parkinsonism and controls. Stimuli consisted of predictable or unpredictable sequences of movements of a platform where the subjects were standing. Psychiatric patients showed adapted reflex amplitudes to predictable variations of the stimuli. Under unpredictable displacements, psychiatric and early-onset parkinsonian patients failed to present the stereotypic anticipated response, which was present in controls. Impairments in postural control in patients have also been found by Varambally et al[47] (see ''Cerebellar Symptoms in Schizophrenia'') who reported that the posture subscore of the ICARS scale for cerebellar evaluation was significantly higher compared with controls.

Alcohol abuse is highly prevalent among schizophrenia patients (50%–70%).[58] Alcohol can alter cerebellar structure and function. However, its physiopathology on the cerebellum and any possible interaction are unknown. Sullivan et al[58] measured posture and gait in 4 groups: schizophrenic patients, alcoholic patients, comorbid schizophrenic-alcoholic patients, and controls. All 3 clinical groups were impaired compared with controls, but the comorbid group was significantly more impaired than both the alcoholic and schizophrenic groups, especially when tested with open eyes. This suggested 2 distinct and possibly additive physiopathological processes involving the cerebellum in patients comorbid for schizophrenia and alcohol abuse. This argument was also suggested by Deshmuck et al[59] observing a higher prevalence of dysdiadochokinesia in the schizophrenic group after a comparison of schizophrenics, alcoholics, and controls. Reinforcing the argument of an intrinsic cerebellar dysfunction in schizophrenia, the subgroup of schizophrenic patients showed a lesser prevalence of alcohol abuse, thus suggesting an intrinsic cerebellar dysfunction in schizophrenia.

In conclusion, abnormal postural control in schizophrenia is expected to reflect cerebellar dysfunction. However, only one controlled study assessed posture in patients, reporting abnormal swaying. More extended studies are needed to confirm this result, excluding comorbid alcohol abuse.

To summarize, a consistent and growing set of results suggest that the cerebellum is implicated in a significant part of NSS,[7,43] some of the items of NSS scales being well-known procedure classically used to assess the cerebellum.[33,47] Postural impairments are among these signs though evidence is still limited to confirm its presence and physiopathological origin.[56,58,59]

Oculomotricity, Cerebellum, and Schizophrenia

Saccadic Ocular Movements

The oculomotor vermis (lobuli VI–VII) is part of the control network of ocular movements.[60] The activation of

this region is correlated to the amplitude of saccades,[60] its adaptation to constant shifts in amplitude,[61] and the velocity of smooth eye-tracking movements.[62] Schizophrenic patients present abnormalities in a variety of saccadic movement paradigms. While reactive or simple saccades (to look at a target in a reflexive way) are virtually not impaired,[63] performances in other paradigms have been reported abnormal: predictive saccades[64] (a rapid repetitive sequence of targets elicits anticipated saccadic movements), remembered or memory saccades[65] (a saccade produced after a delay toward one or more targets briefly shown), and antisaccades[66] (inhibition of a reactive saccade, with a saccadic movement to the opposite direction). So far, several dysfunctions have been proposed in networks concerned with oculomotor control in schizophrenic patients.[64–67] However, fMRI studies on saccadic movements (reactive saccades and antisaccades) and smooth eye tracking comparing patients and controls have reported decreased activations of the frontal eye field, parietal eye field, supplementary eye field, the cingulate cortex, and the dorsolateral PFC (DLPFC)[68–71] without revealing abnormal activations of the cerebellum. Furthermore, no structural MRI abnormality has been correlated with performance in antisaccades or smooth pursuit in a large population of patients, their relatives, and healthy controls.[72]

The adaptation of the amplitude of visually guided saccades to unaware constant shifts in the target's position is a function usually ascribed to the cerebellum.[73] This can be supported by studies in monkeys[60] and humans.[61] Despite this relative specificity, no studies have been published using adaptative saccade tasks in schizophrenia.

Smooth Pursuit Eye Movements

Abnormalities in smooth pursuit and in fixation paradigms have been consistently reported in schizophrenic patients.[67] Pivik[74] demonstrated that eye-tracking disruptions in schizophrenic patients were "normalized" in dark-adapting conditions. This effect was attributed to the diminished cerebellar influence, inactivated in the dark because optimal visual fixation is precluded.[74] Avila et al[75] reported that ketamine-induced eye-tracking abnormalities were similar to those observed in relatives of schizophrenic patients, involving a network linking the frontal eye field to the cerebellum (affected by ketamine). However, fMRI (Keedy et al[68] cited above) did not report cerebellar activations during smooth eye tracking.

Despite the fact that the cerebellum is included in networks of brain areas controlling oculomotricity[60–62] and that numerous ocular abnormalities have repeatedly been reported in schizophrenia,[63–66] to date, no functional evidence directly supports that those anomalies are related to cerebellar dysfunctions in schizophrenic patients. Saccadic adaptation maybe the most specific ocular movement paradigm involving the cerebellum[61] but has not been yet studied in schizophrenic patients (table 1).[68,69]

Nondeclarative Learning

Learning and memory systems can be classified as declarative (explicit, verbally mediated) and nondeclarative (implicit). Declarative learning is evaluated with verbal tasks (see "Language" and "Memory"). Nondeclarative, implicit learning comprehends different paradigms: (1) conditioning paradigms usually involving the eyeblink reflex or the vestibular-ocular reflex (VOR) and (2) procedural learning paradigms.

Eyeblink-Conditioned Stimulus

Classical eyeblink conditioning is known as a cerebellar associative motor learning task.[76] The role of cerebellum is to adjust in time the blinking response triggered by the conditioning stimuli (usually a puff of air on the eye). So far, results in schizophrenia are conflicting: facilitation (ie, faster) in some studies,[77] impairment (ie, slower),[78] or no patients-controls differences[79] have been reported. Hofer et al,[80] combining an eyeblink conditioning paradigm with reinforcement learning, reported that schizophrenic patients poorly detected reinforced stimuli; in other terms, they failed to increase eyeblink responses on reinforced trials. The authors attributed these results to temporal (septal-hippocampal) dysfunctions. Thus, even if a cerebellar dysfunction is suggested,[77,78] cortical dysfunctions cannot be excluded as an alternative hypothesis.[80]

Vestibular-Ocular-Reflex

VOR is the ocular response that corrects gaze position in accordance with head movements. It includes a long smooth eye movement phase followed by a fast saccadic corrective phase. VOR can be elicited experimentally through caloric stimulation of the tympanic membrane. Because of its relative simplicity, and its well-documented structure and physiology, VOR has been proposed as a model of cerebellar motor learning.[81] The cerebellar flocculus was found to be responsible for VOR adaptation.[81] In schizophrenia, Jones and Pivik[82] reported dysrhythmic saccades and a slower saccadic component of the VOR. Schizophrenic patients failed to suppress VOR with visual fixation, particularly in patients presenting an active symptomatology. Pivik et al[83] confirmed those former results and correlated this impairment in VOR suppression with dysfunctions in smooth eye tracking. Interestingly, patients' tracking performance was decreased solely when the cerebellar contribution is supposed to be stronger, ie, in light-adapting conditions. Abnormal VOR suppression by gaze fixation has also been recently reported with a moving circling chair.[84] Though a cortical inhibitory deficit has been

proposed at the origin of this impaired VOR inhibition,[84] other studies[82–85] have proposed complex and possibly abnormal interactions between the VOR circuitry and the smooth eye-tracking circuitry to account for abnormal VOR adaptation in schizophrenia. Supporting this view, a study in neurological patients has correlated intentional tremor (considered as being of cerebellar origin), impairments in VOR inhibition and smooth eye movement.[85]

Although only 3 studies evaluated VOR suppression in schizophrenia,[82–84] contrasting with the literature concerning eyeblink conditioning, consistent defective inhibition of the VOR was found in patients that was attributed to well-documented cortically based inhibition abnormalities[81] present in schizophrenia. A refutation of this hypothesis in favor of a cerebellar dysfunction remains to be done.

Procedural Learning

Procedural learning is a rule-based learning in which performance facilitation occurs with practice without conscious awareness. Motor skill learning (eg, with the Serial Reaction-Time Task) has been associated with activation in motor cortical areas, cerebellum, basal ganglia, and thalamus.[86] Cognitive habit learning, assessed with executive functions tests involving the frontal lobes (eg, Tower of London test), has been associated with the DLPFC and association cortices.[87] Cortical and subcortical activations seem to evolve inversely as performance improves. Thus, an fMRI study reported that while cortical activations decreased, activity in the cerebellar dentate nucleus, thalamus, and putamen progressively increased.[88] Furthermore, the activation of the cerebellar cortex seems to follow a lateral-to-medial course during procedural learning tasks. A positron emission tomography (PET) study by Matsumura et al[89] in healthy subjects reported that the lateral cerebellum was predominantly activated during the early phases of learning while the parasagittal cerebellum diminished its activity with training, correlating inversely with task performance.

Though not always, schizophrenic patients usually present deficits in cognitive and motor procedural learning (eg, rotary pursuit task), independently from medication or abnormal motricity.[90] Early reports[91] suggested that problem-solving difficulties (rather than a true learning defect) were at the origin of procedural learning defects in schizophrenia. However, the neural substrate of both aspects and their mutual relation are still unclear.[92–94] Procedural learning impairments have been related to the severity of the disorganization syndrome during the acute phase of the illness, ''normalized'' procedural learning performances appearing after stabilization.[92] In addition to the cerebellum, the premotor area, the presupplementary motor area,[93] or the basal ganglia have been related to motor procedural learning impairments in schizophrenia.[94] The relative weight of problem-solving (attributed to the frontal lobes) and of other learning deficits (possibly related to subcortical structures) is not clear. The phase of the illness could be an important confounding factor, as suggested by a study reporting ''normalized'' procedural learning performances after stabilization.[92]

A simple pointing task performed while wearing special distorting goggles was used by Bigelow et al[95] to test procedural learning in schizophrenic patients and controls. Patients were significantly more impaired than controls in the pointing task suggesting an impairment to adapt their motor performance to the visual distortion. After goggles removal, readaptation was similar in both groups, but patients had significantly greater difficulties in reorientation. The authors attributed this impairment to dysfunctions of a network including the frontostriatal cortices, basal ganglia, and the cerebellum. A similar study by Ninomiya et al[96] reported that schizophrenic patients were significantly worse than control in the pointing motor responses. In spite of the convergent findings of those 2 latter studies, it is worth noting that different dependent variables were used: accuracy of responses in the one,[95] velocity of the responses in the other.[96] The former attributed the results, on a theoretical basis, to dysfunctions in a fronto-striatal-cerebellar network, which is rather unspecific concerning the motor system.

In summary, though the cerebellar involvement in procedural learning paradigms is established in healthy humans,[76,81,86,88,89] there is only indirect evidence suggesting a specific cerebellar dysfunction in procedural learning impairments in schizophrenia (table 1).

Cognition and the Cerebellum in Schizophrenia

Global Cognitive Function and the Cerebellum in Schizophrenia

Five studies attempted to correlate cerebellar volumes to measures of global cognitive functioning in schizophrenia: Toulopoulou et al[97] and 4 other studies reviewed by Antonova et al[98] (table 2). Toulopoulou et al[97] reported that though several cerebral measures correlated with IQ, the cerebellar volume correlated with delayed verbal memory but not IQ. Szeszko et al[99] computing the mean of 6 cognitive domains (executive, motor, language, visuospatial, memory, and attention functions) found that the cerebellar volume correlated significantly with better global functioning in healthy subjects but not among patients. Antonova et al[98] reviewed 4 studies correlating cerebellar structure and cognition in schizophrenia and reported no significant changes in total cerebellar volume in patients. Additionally, cerebellar volume was found positively related to global cognitive functioning in healthy people and affected females but not in affected men. Nevertheless, 2 studies cited by Antonova et al[98] report results that have not been reproduced: (a) the

Table 2 Involvement of the cerebellum in schizophrenia – Studies correlating cerebellar volume and global measures of cognitive function.

	Groups			
Study, by author (All MRI studies)	SZ	HC		Correlations reported with cerebellum
Flaum et al 1994 [98]	50 M 22 F		32 M 27 F	Left CB Vol > Righ CB Vol direct ↔ global IQin HC and affected women. Lack of this relation in affected men.
Nopoulos et al 1999 [98]	65 M		65 M	Total CB Vol preserved.↓ anterior vermis in SZ direct ↔ ↓ global IQ and ↓verbal IQ
Levitt et al 1999 [21]	15 M		15 M	Total CB Vol preserved. Greater vermis in SZ Greater left-than-right CB asymmetry in grey matter in SZ. ↑ vermal white matter in SZ direct ↔ ↓ logical memory; ↑positive symp and ↑ FTD
Szesko et al 2003 [99]	48 M 33 F		14 M 9 F	Total CB Vol direct ↔ global cog. score (constructed with 6 sub-scores: attention, memory, executive, visuospatial , motor, language) This relation, found in HC was absent in SZ Total CB Vol ↔ memory, executive, visuospatial scores in HC, not in SZ
Toulopoulou et al 2004 [97]	56 SZ	90 relat.	55 HC	Total CB Vol direct ↔ delayed memory Global IQ and visual IQ direct ↔ with toal brain vol. and right hippocampus. Right hippocampus direct ↔ performance IQ Left hippocampus direct ↔ verbal IQ

Note: CB : cerebellum; ↔ : correlation; SZ : schizophrenic patients; HC: healthy controls.

correlation of diminished anterior vermis volume in patients, with diminished total and verbal IQ and (b) the increased white matter proportion in vermis of patients linked to decreased logic memory.

Hence, evidence exist to suggest a role of the cerebellum in global aspects of cognition, such as measured by the IQ, in healthy people and affected females yet not in affected men. So far, patient groups studied have been heterogeneous regarding duration of illness and medication status. Future studies should take into account these issues as well as gender differences in order to obtain more reproducible results.

Attention

fMRI studies in healthy subjects have implicated the cerebellum in attentional tasks.[100] Behavioral studies in cerebellar patients[101] have raised the question of a role of the cerebellum in attention. It has been proposed that the cerebellum could participate in preparing and reorienting attention.[102] Studies in autistic patients support this view.[103]

Attention impairments are well documented in schizophrenia.[104–108] Abnormalities in processing salient novel stimuli in oddball tasks have been consistently replicated.[104] Schizophrenic patients display poorer discrimination and slower reaction times than controls. Using fMRI in patients and controls while identifying a letter among similar-looking letters, performance of the 2 groups was comparable, but patients showed a diminished activation in the inferior frontal cortex and an abnormally enhanced activation in right postcentral gyrus, right medial temporal lobe, and left cerebellum, possibly reflecting an increased effort.[105] During auditory oddball tasks in patients, decreased rCBF was seen in a large network including cerebellum and thalamus.[106] Honey et al[107] assessed in schizophrenic patients the Continuous Performance Test in degraded and nondegraded conditions, with fMRI focusing on basal ganglia, amygdala, frontal, temporal, and parietal regions. The degraded condition elicited decrements in sensitivity thought to reflect increased demands on the limited capacity of visual attention. In this case, an attenuated activation of the anterior cingulate and cerebellum was found only in patients. Furthermore, patients presented functional disruptions in 2 networks: cerebellum-medial superior frontal gyrus and cerebellum -anterior cingulate.

Drug-free patients also present differences in neural activation. A PET study compared drug-naive patients and controls in 3 conditions: counting regular auditory clicks, counting in silence, and rest.[108] Cerebellar activation was present in both groups in all conditions. Yet, differences were observed only in the frontal and inferior parietal gyrus when mentally counting without auditory stimulation. This led the authors to conclude that the role of cerebellum was predominantly sensory. Interestingly, 1 fMRI study investigating the effects of rivastigmine (a central nervous system-selective cholinesterase inhibitor) on attention, given in cotherapy to schizophrenic patients,

Table 3 Involvement of the cerebellum in schizophrenia – Cognitive aspects.

Cognition		
Attention		
	Eyler et al, 2004 [105]	+++
	Kiehl et al, 2005 [106]	+++
	Honey et al, 2005 [107]	+++
	Aasen et al, 2005 [109]	+++
	Ojeda et al, 2002 [108]	-
Language		
	Shergill et al, 2003 [118]	+++
	Boksman et al 2005 [130]	+++
	Kircher et al 2005 [131]	+++
	Marvel et al, 2004 [132]	+
	McGuire et al, 1996 [129]	-
	Hofer et al, 2003 [119]	NIA
	Ragland et al, 2004 [120]	NIA
	Weiss et al, 2006 [121]	NIA
	Sommer et al, 2001[122]	NIA
	Bonner-Jackson et al 2005 [123]	NIA
	Jessen et al 2003 [124]	NIA
	Koeda et al 2006 [125]	NIA
	Mitchell et al 2004 [126]	NIA
	Kubici et al 2003 [127]	NIA
	Sommer et al 2003 [128]	NIA
Memory (all types)		
	Mendrek et al, 2005 [139]	+++
	Mendrek et al, 2004 [142]	+++
	Meyer-Lindenberg et al 2001 [144]	+++
	Crespo-Facorro et al, 2001 [148]	+++
	Kindermann et al 2004 [140]	+++
	Schlosser et al 2003 [143]	+++
	Whyte et al 2006 [147]	+++
	Toulopoulou et al, 2004 [97]	++
	Antonova et al, 2004 [98]	++
	Szeszko et al, 2003 [99]	++
Timing		
	Volz et al, 2001 [155]	-
	Ortuno et al, 2005 [156]	-
Planning[a]		

Note: The key is the same as for table 1.
[a]No studies in SZ patients reporting or suggesting a cerebellar involvement.

reported that the improvement of behavioral measures with rivastigmine correlated with increased rCBF only in the cerebellum.[109]

In conclusion, fMRI studies in patients have revealed the involvement of the cerebellum in tasks such as visual oddball detection[105] (enhanced cerebellar activation) or auditory oddball detection[106] (diminished cerebellar activation), albeit the cerebellum was included in large and distributed cortico-cerebellar networks (table 3). Increased visual attentional demands yielded attenuated activation and functional disruption of a cingulate-cerebellum network only in the patient group.[107] The involvement of cerebellum in attentional tasks supports the ''attentional-shift'' hypothesis of cerebellar function (see below). The decreased activation of this structure in schizophrenia patients[106,107] could thus be interpreted as a result of increased demands over a dysfunctional attentional network. Yet, this does not explain the work reporting hyperactivation of the cerebellum in patients during a visual oddball detection tasks.[105] A differential involvement of the cerebellum depending on the sensorial modality (as suggested by Pivik[74] in the context of oculomotor studies) could explain these contradictory results, although it does not account for the cerebellar activations in PET scan found during an auditory driven counting condition, which disappeared during a mentally counting condition, both in patients and controls.[108] Differences between groups were reported in frontal and parietal regions when mentally counting without auditory stimulation. The authors interpreted the role of the cerebellum as predominantly sensory (rather than related to attention). This interpretation is in-line with studies in healthy humans proposing the cerebellum as a sensory prediction organ (see below). Yet the absence of differences between patients and controls in the cerebellum challenged the existence of a cerebellar dysfunction in attentional tasks, at least in the auditory modality. Paucity of results and diversity of methods impede any definitive conclusion.

Language

There are some evidences suggestive of the role the cerebellum in speech perception,[110] word production,[111] and syntactic[112] and semantic aspects of oral and written language.[113,114] Nevertheless, until now, no consensus was found. The right posterolateral cerebellum seems particularly involved in speech perception,[110] lexical semantic retrieval deficits,[115] or agrammatism.[116] Cerebellar language functions could be lateralized as much as it is for cerebral cortex areas.[117]

Studies on language in schizophrenia focussed preferentially on: (a) correlations of language measures with clinical or cognitive aspects (ie, with hallucinations,[118] episodic memory deficits[119]); (b) studies on episodic memory (word encoding and recognition,[120] see below); (c) studies on language lateralization[121,122]; and (d) studies on affective prosody.[126] Unfortunately, most functional neuroimaging studies investigating the neural correlates of language in schizophrenia did not take into account the cerebellum in their analysis[119–128] and, in particular, those evaluating language lateralization[121,122,128] and affective prosody.[126] This fact sensibly decreases the weight of results that do take the cerebellum into account and which report a cerebellar involvement.

A predisposition to verbal hallucinations was associated with a failure of inner speech monitoring. In a task of inner speech production, schizophrenic patients showed an attenuated response in the right temporal, parietal, parahippocampal, and cerebellar cortex compared with controls (Shergill et al[118]). Inner monitoring abnormalities were also reported by McGuire et al[129] though cerebellar activations were not seen.

Regarding word production deficits, a 4-T fMRI investigation on word fluency by Boksman et al[130] reported decreased cerebellar activation during speech production in patients compared with healthy controls. These differences remained significant when controlling for medication effects. An original work by Kircher et al[131] compared the structures associated to word production depending on the syntax of sentences. Patients spoke freely about 7 Rorschach inkblots during an fMRI scan. Patients showed activation of the cerebellum during the production of syntactically simple sentences (though not in the "complex sentences" condition). The contrast between patients and healthy controls reinforced this finding.

It has been proposed that whilst the cerebellum could be involved in word search, the PFC could be preferentially involved in word selection. Marvel et al[132] reported that schizophrenic patients showed impairments in both search and selection conditions. The authors concluded that a search deficit underlies word production problems in schizophrenia and that this may involve fronto-cerebellar circuits.

In summary, inner speech monitoring deficits have been associated in patients with attenuated activation of the cerebellar cortex among other regions,[118] but this finding was not reproduced by another study.[129] In addition, decreased cerebellar activation during speech production was found in patients depending on the syntactic complexity of the produced sentences: only the simple sentences condition activated the cerebellum.[131] A word search defect in schizophrenia, related to fronto-cerebellar networks, has been proposed and need confirmation.[132] However, word tasks used in the studies reviewed do not permit to conclusively exclude a pure motor cerebellar function, even in the study that assessed more abstract levels of speech production (simple vs complex syntactic structures). The same concern is raised from inner speech control studies,[118,129] where brain regions implicated are supposed not to produce speech but rather to control its production. Altogether, any conclusion about the role of the cerebellum in language-related functions would be premature (table 3).

Memory

Short-term,[133] long-term,[133] and episodic memory[134] deficits have been reported in schizophrenia with no apparent link to the severity of psychopathology or the duration of illness.[133] In addition to its role in nondeclarative implicit memory systems (see above), some studies also suggested the implication of the cerebellum in declarative systems, ie, verbal working memory,[135] fact retrieval,[136] and autobiographical memory[137] (for a review, see Weiss and Heckers[138])

Verbal and spatial working memories are impaired in schizophrenia and in a lesser extent in their first-degree relatives.[139] Regarding spatial working memory, Kindermann et al[140] reported patterns of activation significantly different between patients and healthy controls. Increased activation of the anterior cerebellum was present only in the patients group. Verbal working memory has been more frequently evaluated in schizophrenia than spatial working memory. In-line with fMRI studies in healthy subjects,[141] verbal working memory tasks in schizophrenic patients activate a fronto-thalamo-cerebellar network of regions.[139,142] Using an n-back working memory task during fMRI in schizophrenic patients, before and after partial remission, Mendrek et al[142] showed that partial remission was associated with a normalized activity in a right network including the right DLPFC-right thalamus-left cerebellum and cingulate gyrus, although the contralateral network remained disturbed. In a similar controlled study with stable patients, these authors reported relative underactivation in the left DLPFC and the right cerebellum, contrasting with an overactivation in the left cerebellum,[139] the latter possibly reflecting a compensatory mechanism or an increased effort. An fMRI study by Schlosser et al[143] also reported altered fronto-cerebellar connectivity in schizophrenia. These authors found that while the fronto-cerebellar and the cerebello-thalamic loops were hypoactivated, the thalamo-frontal loop revealed hyperactivated. This was interpreted as compensatory increments in the presence of decreased cerebellar inputs. Numerous PET studies have linked verbal working memory with corticocerebellar activations in medication-free schizophrenic patients: Meyer-Lindenberg et al[144] using an n-back verbal working memory task explained more than half the variance of activations in patients, by changes in the inferotemporal, parahippocampal, and cerebellar regions.

Some researches used paradigms of word encoding (reading and memorizing) and word recognition (as "seen" or "not seen") to study the neural substrate of episodic verbal memory.[145–148] Two studies by Ragland et al[145,146] used this kind of tasks with PET[145] and 3-T fMRI.[148] In both, cerebellar activations were reported in the patients group during the encoding condition. However, when comparing with the encoding patterns in healthy controls, cerebellar activations were not significant.[145,146] Noteworthy, medication effects may play a major role. When only medication-naive patients were considered, the cerebellum and the primary motor cortex showed greater activation.[145] Greater cerebellar activation was also reported in high-risk groups (ie, patients' relatives) during the recognition phase.[147] These results are in-line with a study by Crespo-Facorro et al[148] also reporting abnormal cerebro-cerebellar activations in patients during a memory task (recall of lists of words, either recently learned, or well known), compared with controls. This hyperactivation possibly reflects the effect of increased effort over a dysfunctional circuit.

In summary, an important body of literature supports the implication of the cerebellum in mnemonic processes

in schizophrenia (table 3). One spatial working memory[140] and 3 verbal working memory (n-back) fMRI studies[139,142,143] report cerebellar underactivations in the context of cortico-cerebellar circuits. Though medicated effects cannot be excluded, all 4 studies had control groups and results were consistent between studies. In episodic verbal memory, 2 studies report greater cerebellar activation in patients during word encoding,[145,146] while other fMRI studies reported greater cerebellar involvement in the recognition (recalling) phase in patients[148] and in high-risk relatives.[147] Different word recognition tasks could partly explain this apparent contradiction.

Timing

Timing has been proposed as a basic function of the cerebellar cortex-climbing fiber system.[149] Transient inhibition of the cerebellar vermis with transcranial magnetic stimulation has yielded more variable finger-tapping responses in healthy subjects, ie, altered timed movements.[150] Studies on duration perception usually report the activation of a network including the cerebellum, frontal and parietal cortices, supplementary motor area, basal ganglia, and thalamus.[151,152] Schizophrenic patients are less accurate in temporal generalization tasks (recognition of a standard duration)[153] and temporal bisection tasks (categorization of durations as short or long),[153] both in auditory and visual modalities.[154] Timing and working memory could be correlated because recognition of an interval implies storing it (in working memory) for deferred comparison.[152] Investigating if the poorer performances of patients in timing tasks were due to a more global impairment of working memory, Elvevag et al[153] reported no correlations between working memory scores and timing performance, suggesting 2 independent processes. Volz et al[155] explored the neural basis of time estimation in schizophrenia comparing patients and controls in an fMRI study in 3 conditions: an auditory time estimation task, a pitch discrimination task, and a rest condition. Compared with controls, patients presented patterns of hypoactivity in a fronto-thalamo-striatal network in the timing vs rest contrast and the pitch vs rest contrast.[155] No differences in the cerebellum were reported in this work. A PET study by Ortuno et al[156] contrasted 2 timing task conditions (counting 1-Hz auditory clicks at 1 Hz and mentally counting at the same frequency of the heard clicks) to a passively hearing condition and a rest condition. They also reported alterations in fronto-striatal networks in patients (greater frontal activation: area BA 6) and no cerebellar involvement.

Altogether, evidence suggests that a timing estimation deficit exist in schizophrenia[153,154] independent of working memory impairments.[153] Whether the cerebellum is involved or not in time estimation impairments in patients is still subject to debate. Two neuroimaging studies[155,156] suggest that the cerebellum is not concerned in timing in schizophrenia (table 3). However, these results challenge studies in healthy subjects showing the opposite[152] and are based on studies in rather small samples (9 and 11 patients). Neuroimaging studies in greater groups are warranted in this topic.

Planning

Planning performances in schizophrenia have been reported altered both in the cognitive domain[157] and in the motor domain,[158] thelatter being correlated to the severity of the disorganized syndrome.[158] Patients may less anticipate their actions, thus impairing their strategy in complex or unfamiliar situations[159] as shown in a study comparing the performance of patients and controls in 3 tasks: a simple line-copying task, a more complex figure-copying task, and a standard psychomotor test, the Digit Symbol Test. Patients appeared about one-third slower in their total performance time in all 3 tasks. Increased figure complexity or decreased familiarity significantly prolonged the initiation time, particularly in patients with higher scores on negative symptoms. A recent behavioral study using the Cambridge Neuropsychological Test Automated Battery[160] reported poor spatial working memory as a significant predictor of planning impairments. However, in the cognitive domain, even if patients take significantly more moves to solve a series of problems in the Tower of London Test,[157] when latencies of movements are adjusted to consider the slower responses overall, the patients planning times are not significantly increased, thus challenging the existence of a true cognitive planning deficit in schizophrenia.

Although the cerebellum has been involved in movement planning both in cerebellar patients[161,162] and controls,[163] studies in healthy subjects dissociating planning phases and control of execution have linked the cerebellum preferentially to control of execution.[164,165] Functional imaging studies on planning functions in schizophrenia are needed to clarify this point.

Hence, though some studies suggest a true planning deficit in schizophrenia,[157,158] when latencies of movements are adjusted to consider the slower responses, the patients' planning times are not significantly increased, thus challenging the existence of a true planning deficit in schizophrenia. So far, functional neuroimaging studies lack in this domain. Hypothesis about a role for the cerebellum in (at least) motor planning still need direct evidence.

Functional Models of the Cerebellum

Functional models permit to interpret and integrate important amounts of data, often issued from diverse methodologies. Some of the concepts reviewed below, particularly the concepts of error detection and learning, have permitted the development of computational models and hence the simulation of the network functions with

variable success.[166] We will briefly summarize the main models proposed and the specific function attributed to the cerebellum.

Attention-Shift

Courchesne and Allen[167] highlighted the role of the cerebellum in orienting attentional resources. According to these authors, the cerebellum rapidly primes task-relevant systems in order to improve neural responsiveness. This anticipatory effect is supposed to affect sensory, motor, cognitive, affective, and autonomic systems.[166,167] Doing so, the cerebellum ensure that attention resources be implemented in a fast and coordinated manner. The cerebellar cortex would detect patterns of inputs, which should shift attention toward the systems implicated in the ongoing action. Afterward, the cerebellar nuclei, through cortico-cerebellar loops, would control performance.[168]

Error Detection and Learning

Reports of modified cerebellar output and increased activation after unexpected sensory perturbations[169] or during the initial phases of skill learning[89] suggest that detection and correction of errors could be elicited as the basic cerebellar function.[170] Formerly proposed for the motor domain,[171] the hypothesis has been generalized to the cognitive domain on the basis of verbal tasks in cerebellar patients.[171]

Prediction and Timing

Anticipatory adjustments have been hypothesized as a cerebellar function.[172] Through experience (ie, learning), a particular predicted sensory context or cognitive state could become associated with a particular motor or cognitive response. Prediction is a recurrent concept in cerebellar theories.[167,170,172] A variant of the prediction hypothesis is that the cerebellum operates as an internal timing system,[173] providing the precise temporal representation across a range of tasks. The timing hypothesis is coherent with proposals of the cerebellum as a structure devoted to sensory prediction.[174] However, recent studies relate timing abilities to distributed networks.[175]

Discussion

The role of the cerebellum in schizophrenia has been highlighted by the hypothesis of the "cognitive dysmetria," which assumes that dysfunctions in the cortico-cerebellar-thalamo-cortical circuits could result in schizophrenic symptoms, via impaired coordination of mental processes.[2] After reviewing recent clinical, cognitive, and functional imaging studies involving the cerebellum in schizophrenia, a heterogeneous picture emerges. While in some domains the cerebellum seems to be incriminated (ie, NSS, posture, equilibrium), in other domains its contribution seems limited or indirect (ie, cognition) if present at all (ie, affectivity). As a whole, the review is congruent with the classical view of the cerebellum as specifically implicated in sensorimotor control. However, some results point to the involvement of the cerebellum in cognitive functions as well, in particular fMRI studies on disordered thought[18,19] or verbal working memory[139,142,143] (independent from motor performance) or structural imaging studies linking cerebellar volume with cognitive parameters.[97–99]

A significant gap persists however between what we know about the cerebellum in motor function and the evidence for the role of a putative cerebellar dysfunction in schizophrenia. Functional models, mostly tested with motor tasks, have been difficult to generalize to cognitive tasks, even more to schizophrenia, where distributed cerebral abnormalities preclude any simple, localizing interpretation. The computational perspective could theoretically bridge the gap between sensorimotor and cognitive functions.[176] This perspective links the cerebellar structural homogeneity and functional unity, it does not restrict a priori the domains of application and it enables modularity, in the sense that the distinct channels could all implement the same unique cerebellar computation[166,172] (hypothesis usually assumed).

Several complementary arguments may explain the heterogeneity of the reviewed results:

1. Methodological issues. The diversity of domains explains the variety of techniques employed. In addition, in the context of each considered area of research, methodological diversity continues to be the rule, thus making comparisons difficult and generalizations risky. Differences between studies concern the following 2 factors. (1) The characteristics of the patients groups. Most studies, maybe due to their exploratory character, assess medicated patients with varied age and duration of illness. Notwithstanding, it has been reported that the age,[177] duration of illness,[178] and medication[51,52] are important (usually confounding) variables to consider when interpreting data in schizophrenia. (2) Diversity of behavioral paradigms employed to test the same function. While this diversity could be useful because it permits complementarity of results, the limited number of works in most domains and the absence of replication studies render it a drawback rather than an advantage.
2. Not all schizophrenic patients present a cerebellar dysfunction. How could we clinically characterize those patients in whom a cerebellar involvement would be highly probable? Could this be related to a specific etiology? This raises the question of defining more homogeneous endophenotypes in schizophrenia research.[2] Schizophrenic patients with cerebellar anatomical or functional abnormalities have been related to negative symptoms,[32] more impaired cognitive profile,[32,98] poorer outcome,[179] and higher NSS scores.[7]

3. Cerebellar dysfunction in schizophrenia could be restricted to specific parts of the cerebellum. Thus, impairments in some tasks could coexist with a normal cerebellar function assessed through other paradigms. Considering the fact that atrophy of the vermis is the most cited structural cerebellar abnormality in schizophrenia,[7] it could be proposed that only vermis-based cerebellar functions (eg, ocular motricity and posture[58–62]) should be dysfunctional, whereas the hemisphere-based cerebellar functions (those specially related to the frontal lobes and cognition[100,101,110,111,113]) should be preserved.
4. The possibility to estimate the influence of the cerebellum depends on the complexity of the considered neural network. The more a neural network is large and complex, the more it can be difficult to disentangle the precise function of one of its components. Cerebellar functions may be more accessible experimentally in the context of relatively small networks such as those responsible of eyeblink conditioning, VOR, or postural reflexive control, than in the context of larger networks such as those involved in cognition. In these latter, putative cerebellar dysfunctions should be interpreted in the context of networks that have not completely been described (eg, executive functions, language). Moreover, cortical dysfunctions present in schizophrenia and the existence of compensation effects warrant caution in interpreting the data. Investigating hypothesized cerebellar dysfunctions in such a context would be not far from speculation. Functional imaging, though not completely solving these difficulties, could be the best method, to date, to associate behavioral and neural networks level.
5. The cerebellum could indirectly influence cognition through abnormal sensory integration. If the role of the cerebellum in the cognitive aspects of schizophrenia seems limited, how can we interpret reports linking cerebellar volumes or activations with cognitive tasks?[33,97–99] Sensory inputs, presumed to be abnormally integrated by the cerebellum, could result secondarily in abnormal cognitive processes. Sensory integration impairments, associated with dysfunctions in the cerebellum[28] and heteromodal cortices,[43,44] could in turn facilitate the emergence of abnormal cortically based cognitive processes as it seems to be the case for hallucinations[118] and arguably for FTD[18,19] and verbal working memory.[139,142,143]

In conclusion, different lines of research converge to suggest that a cerebellar dysfunction could exist, at least in some patients with schizophrenia, and/or could account for some of the psychiatric, neurological, or cognitive symptoms present in this disease although negative reports are also found. Several explanations could explain divergent findings found in the literature including the clinical heterogeneity, the heterogeneity of the cerebellar structure and functions, and the complexity of the involved networks. The relative prominence of the cerebral cortex in cognition as well as a postulated indirect influence of the cerebellum via impaired sensory or sensorimotor integration could hamper the delimitation of a specific role of the cerebellum in schizophrenia. Computational models appear promising to synthesize the role of the cerebellum in motricity and its elusive role in cognition. Further studies in well-characterized and ideally more homogeneous groups of patients are warranted to fully understand the place of the cerebellum in the symptoms and deficits associated with schizophrenia.

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References

1. Schamhmann J. Dysmetria of thought: clinical consequences of cerebellar dysfunction on cognition and affect. *Trends Cogn Sci*. 1998;2:362–371.
2. Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanism. *Biol Psychiatry*. 1999;46:908–920.
3. Penn HE. Neurobiological correlates of autism: a review of recent research. *Child Neuropsychol*. 2006;12:57–79.
4. Desmond JE, Fiez J. Neuroimaging studies of the cerebellum: language, learning and memory. *Trends Cogn Sci*. 1998;2:355–362.
5. Katsetos CD, Hyde MD, Herman MM. Neuropathology of the cerebellum in schizophrenia—an update: 1996 and future directions. *Biol Psychiatry*. 1997;42:213–224.
6. Abbott C, Bustillo J. What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update. *Curr Opin Psychiatry*. 2006;19:135–139.
7. Bottmer C, Bachmann S, Pantel J, et al. Reduced cerebellar volume and neurological soft signs in first-episode schizophrenia. *Psychiatry Res.* 2005;140:239–250.
8. Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH. Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? [review]. *J Psychiatry Neurosci*. 2005;30:178–186.
9. Schutter DJ, van Honk J. The cerebellum on the rise in human emotion [review]. *Cerebellum*. 2005;4:290–294.
10. Rapoport M, van Reekum R, Mayberg H. The role of the cerebellum in cognition and behavior: a selective review [review]. *J Neuropsychiatry Clin Neurosci*. 2000;12:193–198 .
11. Neckelmann G, Specht K, Lund A, et al. Morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. *Int J Neurosci*. 2006;116: 9–23.
12. Shergill SS, Bullmore E, Simmons A, Murray R, McGuire P. Functional anatomy of auditory verbal imagery in schizophrenic patients with auditory hallucinations. *Am J Psychiatry*. 2000;157:1691–1693.
13. Shergill SS, Brammer MJ, Fukuda R, Williams SC, Murray RM, McGuire PK. Engagement of brain areas implicated in

processing inner speech in people with auditory hallucinations. *Br J Psychiatry*. 2003;182:525–531.

14. Shin SE, Lee JS, Kang MH, Kim CE, Bae JN, Jung G. Segmented volumes of cerebrum and cerebellum in first episode schizophrenia with auditory hallucinations. *Psychiatry Res*. 2005;138:33–42.
15. Gaser C, Nenadic I, Volz HP, Buchel C, Sauer H. Neuroanatomy of "hearing voices": a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. *Cereb Cortex*. 2004;14:91–96.
16. Andreasen NC. A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Arch Gen Psychiatry*. 1999;56:781–787.
17. Weinstein S, Werker JF, Vouloumanos A, Woodward TS, Ngan ET. Do you hear what I hear? Neural correlates of thought disorder during listening to speech in schizophrenia. *Schizophr Res*. 2006;86:130–137.
18. Kircher TT, Liddle PF, Brammer MJ, Williams SC, Murray RM, McGuire PK. Neural correlates of formal thought disorder in schizophrenia: preliminary findings from a functional magnetic resonance imaging study. *Arch Gen Psychiatry*. 2001;58:769–774.
19. Kircher TT, Liddle PF, Brammer MJ, Williams SC, Murray RM, McGuire PK. Reversed lateralization of temporal activation during speech production in thought disordered patients with schizophrenia. *Psychol Med*. 2002;32:439–449.
20. Kircher TT, Bulimore ET, Brammer MJ, et al. Differential activation of temporal cortex during sentence completion in schizophrenic patients with and without formal thought disorder. *Schizophr Res*. 2001;50:27–40.
21. Levitt JJ, McCarley RW, Nestor PG, et al. Quantitative volumetric MRI study of the cerebellum and vermis in schizophrenia: clinical and cognitive correlates. *Am J Psychiatry*. 1999;156:1105–1107.
22. Schmahmann J, Sherman JC. The cerebellar cognitive affective syndrome. *Brain*. 1998;121(Pt 4):561–579.
23. Schmahmann J. The role of the cerebellum in affect and psychosis. *J Neurolinguistics*. 2000;13:189–214.
24. Takahashi H, Koeda M, Oda K, et al. An fMRI study of differential neural response to affective pictures in schizophrenia. *Neuroimage*. 2004;22:1247–1254.
25. Stip E, Fahim C, Liddle P, et al. Neural correlates of sad feelings in schizophrenia with and without blunted affect. *Can J Psychiatry*. 2005;50:909–917.
26. Paradiso S, Andreasen NC, Crespo-Facorro B, et al. Emotions in unmedicated patients with schizophrenia during evaluation with positron emission tomography. *Am J Psychiatry*. 2003;160:1775–1783.
27. Abel KM, Allin MP, Kucharska-Pietura K, et al. Ketamine alters neural processing of facial emotion recognition in healthy men: an fMRI study. *Neuroreport*. 2003;14:387–391.
28. Kinney DK, Yurgelun-Todd DA, Woods BT. Neurologic signs of cerebellar and cortical sensory dysfunction in schizophrenics and their relatives. *Schizophr Res*. 1999;35: 99–104.
29. Chen EY, Shapleske J, Luque R, et al. The Cambridge Neurological Inventory: a clinical instrument for assessment of soft neurological signs in psychiatric patients. *Psychiatry Res*. 1995;56:183–204.
30. Buchanan RW, Heinrichs DW. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Res*. 1989;27:335–350.
31. Krebs MO, Gut-Fayand A, Bourdel MC, Dischamp J, Olié JP. Validation and factorial structure of a standardized examination assessing neurological soft signs in schizophrenia. *Schizophr Res*. 2000;45:245–260.
32. Bombin I, Arango C, Buchanan RW. Significance and meaning of neurological signs in schizophrenia: two decades later. *Schizophr Bull*. 2005;31:962–977.
33. Ho BC, Mola C, Andreasen NC. Cerebellar dysfunction in neuroleptic naive schizophrenia patients: clinical, cognitive, and neuroanatomic correlates of cerebellar neurologic signs. *Biol Psychiatry*. 2004;55:1146–1153.
34. Dazzan P, Murray RM. Neurological soft signs in first-episode psychosis: a systematic review. *Br J Psychiatry Suppl*. 2002;43:s50–s57.
35. Yazici AH, Demir B, Yazici KM, Gogus A. Neurological soft signs in schizophrenic patients and their nonpsychotic siblings. *Schizophr Res*. 2002;58:241–246.
36. Jahn T, Hubmann W, Karr M, et al. Motoric neurological soft signs and psychopathological symptoms in schizophrenic psychoses. *Psychiatry Res*. 2006;142:191–199.
37. Tosato S, Dazzan P. The psychopathology of schizophrenia and the presence of neurological soft signs: a review. *Curr Opin Psychiatry*. 2005;18:285–288.
38. Boks MP, Liddle PF, Burgerhof JG, Knegtering R, van den Bosch RJ. Neurological soft signs discriminating mood disorders from first episode schizophrenia. *Acta Psychiatr Scand*. 2004;110:29–35.
39. Keenan E, O'Donnell C, Sinanan K, O'Callaghan E. Severity of alcohol dependence and its relationship to neurological soft signs, neuropsychological impairment and family history. *Acta Psychiatr Scand*. 1997;95:272–276.
40. Sullivan EV, Deshmukh A, Desmond JE, Lim KO, Pfefferbaum A. Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: relation to ataxia. *Neuropsychology*. 2000;14:341–352.
41. Mandelbaum DE, Stevens M, Rosenberg E, et al. Sensorimotor performance in school-age children with autism, developmental language disorder, or low IQ. *Dev Med Child Neurol*. 2006;48:33–39.
42. Allen G, Courchesne E. Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an fMRI study of autism. *Am J Psychiatry*. 2003;160:262–273.
43. Mouchet-Mages S, Cachia A, Canceil O, et al. Sensory dysfunction is correlated to cerebellar volume reduction in early schizophrenia. *Schizophr Res*. 2007. In press.
44. Keshavan MS, Sanders RD, Sweeney JA, et al. Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. *Am J Psychiatry*. 2003;160:1298–1304.
45. Dazzan P, Morgan KD, Orr KG, et al. The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. *Brain*. 2004;127(Pt 1):143–153.
46. Schroder J, Buchsbaum MS, Siegel BV, Geider FJ, Niethammer R. Structural and functional correlates of subsyndromes in chronic schizophrenia. *Psychopathology*. 1995; 28:38–45.
47. Varambally S, Venkatasubramanian G, Thirthalli J, Janakiramaiah N, Gangadhar BN. Cerebellar and other neurological soft signs in antipsychotic-naive schizophrenia. *Acta Psychiatr Scand*. 2006;114:352–356.
48. Ridler K, Veijola JM, Tanskanen P, et al. Fronto-cerebellar systems are associated with infant motor and adult executive

functions in healthy adults but not in schizophrenia. *Proc Natl Acad Sci U S A*. 2006;103:15651–15656.

49. Fitzgerald PB, Brown TL, Daskalakis ZJ, Kulkarni J. A transcranial magnetic stimulation study of inhibitory deficits in the motor cortex in patients with schizophrenia. *Psychiatry Res*. 2002;114:11–22.
50. Daskalakis ZJ, Christensen BK, Chen R, Fitzgerald PB, Fountain SI, Chen R. Reduced cerebellar inhibition in schizophrenia: a preliminary study. *Am J Psychiatry*. 2005;162:1203–1205.
51. Muller JL, Roder C, Schuierer G, Klein HE. Subcortical overactivation in untreated schizophrenic patients: a functional magnetic resonance image finger-tapping study. *Psychiatry Clin Neurosci*. 2002;56:77–84.
52. Stephan KE, Magnotta VA, White T, et al. Effects of olanzapine on cerebellar functional connectivity in schizophrenia measured by fMRI during a simple motor task. *Psychol Med*. 2001;31:1065–1078.
53. Muller JL, Roder CH, Schuierer G, Klein H. Motor-induced brain activation in cortical, subcortical and cerebellar regions in schizophrenic inpatients. A whole brain fMRI fingertapping study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:421–426.
54. Sukhwinder S, Samson G, Bays P, Frith C, Wolpert D. Evidence for sensory prediction deficits in schizophrenia. *Am J Psychiatry*. 2005;162:2384–2386.
55. Bays PM, Flanagan JR, Wolpert DM. Attenuation of self-generated tactile sensations is predictive, not postdictive. *PLoS Biol*. 2006;4:e28.
56. Marvel CL, Schwartz BL, Rosse RB. A quantitative measure of postural sway deficits in schizophrenia. *Schizophr Res*. 2004;68:363–372.
57. Bloem BR, Beckley DJ, van Vugt JP, et al. Long latency postural reflexes are under supraspinal dopaminergic control. *Mov Disord*. 1995;10:580–588.
58. Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Balance and gait deficits in schizophrenia compounded by the comorbidity of alcoholism. *Am J Psychiatry*. 2004;161:751–755.
59. Deshmukh A, Rosenbloom MJ, Pfefferbaum A, Sullivan EV. Clinical signs of cerebellar dysfunction in schizophrenia, alcoholism, and their comorbidity. *Schizophr Res*. 2002;57:281–291.
60. Thier P, Dicke PW, Haas R, Catz N. .The role of the oculomotor vermis in the control of saccadic eye movements. *Ann N Y Acad Sci*. 2002;978:50–62.
61. Desmurget M, Pélisson D, Grethe JS, et al. Functional adaptation of reactive saccades in humans: a PET study. *Exp Brain Res*. 2000;132:243–259.
62. Ohtsuka K, Enoki T. Transcranial magnetic stimulation over the posterior cerebellum during smooth pursuit eye movements in man. *Brain*. 1998;121(Pt 3):429–435.
63. Broerse A, Crawford TJ, den Boer JA. Parsing cognition in schizophrenia using saccadic eye movements: a selective overview. *Neuropsychologia*. 2001;39:742–756.
64. Karoumi B, Ventre-Dominey J, Dalery J. Predictive saccade behaviour is enhanced in schizophrenia. *Cognition*. 1998;68: B81–B91.
65. Camchong J, Dyckman KA, Chapman CE, Yanasak NE, McDowell JE. Basal ganglia-thalamocortical circuitry disruptions in schizophrenia during delayed response tasks. *Biol Psychiatry*. 2006;60(3):235–241.
66. Harris MS, Reilly JL, Keshavan MS, Sweeney JA. Longitudinal studies of antisaccades in antipsychotic-naive first-episode schizophrenia. *Psychol Med*. 2006;36:485–494.
67. Boudet C, Bocca ML, Chabot B, et al. Are eye movement abnormalities indicators of genetic vulnerability to schizophrenia? *Eur Psychiatry*. 2005;20:339–345.
68. Keedy SK, Ebens CL, Keshavan MS, Sweeney JA. Functional magnetic resonance imaging studies of eye movements in first episode schizophrenia: smooth pursuit, visually guided saccades and the oculomotor delayed response task. *Psychiatry Res*. 2006;146:199–211.
69. Raemaekers M, Jansma JM, Cahn W, et al. Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. *Arch Gen Psychiatry*. 2002;59:313–320.
70. Tu PC, Yang TH, Kuo WJ, Hsieh JC, Su TP. Neural correlates of antisaccade deficits in schizophrenia, an fMRI study. *J Psychiatr Res*. 2006;40:606–612.
71. McDowell JE, Brown GG, Paulus M, et al. Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biol Psychiatry*. 2002;51: 216–223.
72. Schulze K, MacCabe JH, Rabe-Hesketh S, et al. The relationship between eye movement and brain structural abnormalities in patients with schizophrenia and their unaffected relatives. *J Psychiatr Res*. 2006;40:589–598.
73. Hopp JJ, Fuchs A. The characteristics and neuronal substrate of saccadic eye movement plasticity. *Prog Neurobiol*. 2004;72:27–53.
74. Pivik RT. Smooth pursuit eye tracking dysfunction in schizophrenia: subcortical implications. *J Psychiatry Neurosci*. 1991;16:123–130.
75. Avila MT, Weiler MA, Lahti AC, Tamminga CA, Thaker GK. Effects of ketamine on leading saccades during smooth-pursuit eye movements may implicate cerebellar dysfunction in schizophrenia. *Am J Psychiatry*. 2002; 159:1490–1496.
76. Villarreal RP, Steinmetz JE. Neuroscience and learning: lessons from studying the involvement of a region of cerebellar cortex in eyeblink classical conditioning. *J Exp Anal Behav*. 2005;84:631–652.
77. Sears LL, Andreasen NC, O'Leary DS. Cerebellar functional abnormalities in schizophrenia are suggested by classical eyeblink conditioning. *Biol Psychiatry*. 2000;48: 204–209.
78. Brown SM, Kieffaber PD, Carroll CA, et al. Eyeblink conditioning deficits indicate timing and cerebellar abnormalities in schizophrenia. *Brain Cogn*. 2005;58:94–108.
79. Stevens A, Schwarz J, Schwarz B, Ruf I, Kolter T, Czekalla J. Implicit and explicit learning in schizophrenics treated with olanzapine and with classic neuroleptics. *Psychopharmacology (Berl)*. 2002;160:299–306.
80. Hofer E, Doby D, Anderer P, Dantendorfer K. Impaired conditional discrimination learning in schizophrenia. *Schizophr Res*. 2001;51:127–136.
81. Blazquez PM, Hirata Y, Highstein SM. The vestibulo-ocular reflex as a model system for motor learning: what is the role of the cerebellum? *Cerebellum*. 2004;3:188–192.
82. Jones AM, Pivik RT. Abnormal visual–vestibular interactions in psychosis. *Biol Psychiatry*. 1983;18:45–61.
83. Pivik RT, Bylsma FW, Cooper PM. The effects of dark adaptation on pursuit tracking dysfunction in psychotics with

impaired vestibular suppression. *Prog Neuropsychopharmacol Biol Psychiatry*. 1987;11:259–265.

84. Warren S, Ross RG. Deficient cancellation of the vestibular ocular reflex in schizophrenia. *Schizophr Res*. 1998;34:187–193.
85. Helmchen C, Hagenow A, Miesner J, et al. Eye movement abnormalities in essential tremor may indicate cerebellar dysfunction. *Brain*. 2003;126:1319–1332.
86. Kumari V, Gray JA, Honey GD, et al. Procedural learning in schizophrenia: a functional magnetic resonance imaging investigation. *Schizophr Res*. 2002;57:97–107.
87. Weickert TW, Terrazas A, Bigelow LB, et al. Habit and skill learning in schizophrenia: evidence of normal striatal processing with abnormal cortical input. *Learn Mem*. 2002;9:430–442.
88. Floyer-Lea A, Matthews PM. Changing brain networks for visuomotor control with increased movement automaticity. *J Neurophysiol*. 2004;92:2405–2412.
89. Matsumura M, Sadato N, Kochiyama T, et al. Role of the cerebellum in implicit motor skill learning: a PET study. *Brain Res Bull*. 2004;63:471–483.
90. Schwartz BL, Rosse RB, Veazey C, Deutsch SI. Impaired motor skill learning in schizophrenia: implications for corticostriatal dysfunction. *Biol Psychiatry*. 1996;39:241–248.
91. Gras-Vincendon A, Danion JM, Grange D, et al. Explicit memory, repetition priming and cognitive skill learning in schizophrenia. *Schizophr Res*. 1994;13:117–126.
92. Exner C, Boucsein K, Degner D, Irle E. State-dependent implicit learning deficit in schizophrenia: evidence from 20-month follow-up. *Psychiatry Res*. 2006;142:39–52.
93. Exner C, Weniger G, Schmidt-Samoa C, Irle E. Reduced size of the pre-supplementary motor cortex and impaired motor sequence learning in first-episode schizophrenia. *Schizophr Res*. 2006;84:386–396.
94. Kodama S, Fukuzako H, Fukuzako T, et al. Aberrant brain activation following motor skill learning in schizophrenic patients as shown by functional magnetic resonance imaging. *Psychol Med*. 2001;31:1079–1088.
95. Bigelow NO, Turner BM, Andreasen NC, et al. Prism adaptation in schizophrenia. *Brain Cogn*. 2006;61(3):235–242.
96. Ninomiya H, Sato E, Onitsuka T, Chen HD. Adaptation of visually guided behaviour during reversed vision in schizophrenia: a preliminary study. *Psychiatry Res*. 1998;78:51–58.
97. Toulopoulou T, Grech A, Morris RG, et al. The relationship between volumetric brain changes and cognitive function: a family study on schizophrenia. *Biol Psychiatry*. 2004;56:447–453.
98. Antonova E, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. *Schizophr Res*. 2004;70:117–145.
99. Szeszko PR, Gunning-Dixon F, Goldman RS, et al. Lack of normal association between cerebellar volume and neuropsychological functions in first-episode schizophrenia. *Am J Psychiatry*. 2003;160:1884–1887.
100. Allen G, Buxton RB, Wong EC, Courchesne E. Attentional activation of the cerebellum independent of motor involvement science. *Science*. 1997;275:1940–1943.
101. Gottwald B, Mihajlovic Z, Wilde B, Mehdorn HM. Does the cerebellum contribute to specific aspects of attention? *Neuropsychologia*. 2003;41:1452–1460.
102. Courchesne E, Allen G. Prediction and preparation. Fundamental functions of the cerebellum. *Learn Mem*. 1997;4:1–35.
103. Harris NS, Courchesne E, Townsend J, Carper RA, Lord C. Neuroanatomic contributions to slowed orienting of attention in children with autism. *Brain Res Cogn Brain Res*. 1999;8:61–71.
104. Laurens KR, Kiehl KA, Ngan ET, Liddle PF. Attention orienting dysfunction during salient novel stimulus processing in schizophrenia. *Schizophr Res*. 2005;75:159–171.
105. Eyler LT, Olsen RK, Jeste DV, Brown GG. Abnormal brain response of chronic schizophrenia patients despite normal performance during a visual vigilance task. *Psychiatry Res*. 2004;130:245–257.
106. Kiehl KA, Stevens MC, Celone K, Kurtz M, Krystal JH. Abnormal hemodynamics in schizophrenia during an auditory oddball task. *Biol Psychiatry*. 2005;57:1029–1040.
107. Honey GD, Pomarol-Clotet E, Corlett PR, et al. Functional dysconnectivity in schizophrenia associated with attentional modulation of motor function. *Brain*. 2005;128(Pt 11):2597–2611.
108. Ojeda N, Ortuno F, Arbizu J, et al. Functional neuroanatomy of sustained attention in schizophrenia: contribution of parietal cortices. *Hum Brain Mapp*. 2002;17:116–130.
109. Aasen I, Kumari V, Sharma T. Effects of rivastigmine on sustained attention in schizophrenia: an FMRI study. *J Clin Psychopharmacol*. 2005;25:311–317.
110. Mathiak K, Hertrich I, Grodd W, Ackermann H. Cerebellum and speech perception: a functional resonance imaging study. *J Cogn Neurosci*. 2002;14:902–912.
111. Jansen A, Floel A, Van Randenborgh J, et al. Crossed cerebro-cerebellar language dominance. *Hum Brain Mapp*. 2005;24:165–172.
112. Stowe LA, Paans AM, Wijers AA, Zwarts F. Activations of ''motor'' and other non-language structures during sentence comprehension. *Brain Lang*. 2004;89:290–299.
113. Xiang H, Lin C, Ma X, et al. Involvement of the cerebellum in semantic discrimination: an fMRI study. *Hum Brain Mapp*. 2003;18:208–214.
114. Fulbright RK, Jenner AR, Mencl WE, et al. The cerebellum's role in reading: a functional MR imaging study. *AJNR Am J Neuroradiol*. 1999;20:1925–1930.
115. Gebhart AL, Petersen SE, Thach WT. Role of the posterolateral cerebellum in language. *Ann N Y Acad Sci*. 2002;978:318–333.
116. Molinari M, Leggio MG, Silveri MC. Verbal fluency and agrammatism [review]. *Int Rev Neurobiol*. 1997;41:325–339.
117. Hubrich-Ungureanu P, Kaemmerer N, Henn FA, Braus DF. Lateralized organization of the cerebellum in a silent verbal fluency task: a functional magnetic resonance imaging study in healthy volunteers. *Neurosci Lett*. 2002;319:91–94.
118. Shergill SS, Brammer MJ, Fukuda R, Williams SC, Murray RM, McGuire PK. Engagement of brain areas implicated in processing inner speech in people with auditory hallucinations. *Br J Psychiatry*. 2003;182:525–531.
119. Hofer A, Weiss EM, Golaszewski SM, et al. An FMRI study of episodic encoding and recognition of words in patients with schizophrenia in remission. *Am J Psychiatry*. 2003;160:911–918.
120. Ragland JD, Gur RC, Valdez J, et al. Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia. *Am J Psychiatry*. 2004;161:1004–1015.

121. Weiss EM, Hofer A, Golaszewski S, Siedentopf C, Felber S, Fleischhacker WW. Language lateralisation in unmedicated patients during acute episode of schizophrenia: a functional MRI study. *Psychiatry Res*. 2006;146:185–190.
122. Sommer IE, Ramsey NF, Kahn RS. Language lateralisation in schizophrenia, an fMRI study. *Schizophr Res*. 2001;52:57–67.
123. Bonner-Jackson A, Haut K, Csernansky JG, Barch DM. The influence of encoding strategy on episodic memory and cortical activity in schizophrenia. *Biol Psychiatry*. 2005;58:47–55.
124. Jessen F, Scheef L, Germeshausen L, et al. Reduced hippocampal activation during encoding and recognition of words in schizophrenia patients. *Am J Psychiatry*. 2003;160:1305–1312.
125. Koeda M, Takahashi H, Yahata N, et al. Language processing and human voice perception in schizophrenia: a functional magnetic resonance imaging study. *Biol Psychiatry*. 2006;59:948–957.
126. Mitchell RL, Elliott R, Barry M, Cruttenden A, Woodruff PW. Neural response to emotional prosody in schizophrenia and in bipolar affective disorder. *Br J Psychiatry*. 2004;184:223–230.
127. Kubicki M, McCarley RW, Nestor PG, et al. An fMRI study of semantic processing in men with schizophrenia. *Neuroimage*. 2003;20:1923–1933.
128. Sommer IE, Ramsey NF, Mandl RC, Kahn RS. Language lateralization in female patients with schizophrenia: an fMRI study. *Schizophr Res*. 2003;60:183–190.
129. McGuire PK, Silbersweig DA, Wright I, Murray RM, Frackowiak RS, Frith CD. The neural correlates of inner speech and auditory verbal imagery in schizophrenia: relationship to auditory verbal hallucinations. *Br J Psychiatry*. 1996;169:148–159.
130. Boksman K, Theberge J, Williamson P, et al. A 4.0-T fMRI study of brain connectivity during word fluency in first-episode schizophrenia. *Schizophr Res*. 2005;75:247–263.
131. Kircher TT, Oh TM, Brammer MJ, McGuire PK. Neural correlates of syntax production in schizophrenia. *Br J Psychiatry*. 2005;186:209–214.
132. Marvel CL, Schwartz BL, Isaacs KL. Word production deficits in schizophrenia. *Brain Lang*. 2004;89:182–191.
133. Aleman A, Hijman R, de Haan EH, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. *Am J Psychiatry*. 1999;156:1358–1366.
134. Achim AM, Lepage M. Episodic memory-related activation in schizophrenia: meta-analysis. *Br J Psychiatry*. 2005;187:500–509.
135. Chen SH, Desmond JE. Cerebrocerebellar networks during articulatory rehearsal and verbal working memory tasks. *Neuroimage*. 2005;24:332–338.
136. Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia*. 2006;44(12):2189–2208.
137. Nyberg L, Forkstam C, Petersson KM, Cabeza R, Ingvar M. Brain imaging of human memory systems: between-systems similarities and within-system differences. *Brain Res Cogn Brain Res*. 2002;13:281–292.
138. Weiss AP, Heckers S. Neuroimaging of declarative memory in schizophrenia [review]. *Scand J Psychol*. 2001;42:239–250.
139. Mendrek A, Kiehl KA, Smith AM, Irwin D, Forster BB, Liddle PF. Dysfunction of a distributed neural circuitry in schizophrenia patients during a working-memory performance. *Psychol Med*. 2005;35:187–196.
140. Kindermann SS, Brown GG, Zorrilla LE, Olsen RK, Jeste DV. Spatial working memory among middle-aged and older patients with schizophrenia and volunteers using fMRI. *Schizophr Res*. 2004;68:203–216.
141. Chen SH, Desmond JE. Temporal dynamics of cerebrocerebellar network recruitment during a cognitive task. *Neuropsychologia*. 2005;43:1227–1237.
142. Mendrek A, Laurens KR, Kiehl KA, Ngan ET, Stip E, Liddle PF. Changes in distributed neural circuitry function in patients with first-episode schizophrenia. *Br J Psychiatry*. 2004;185:205–214.
143. Schlosser R, Gesierich T, Kaufmann B, et al. Altered effective connectivity during working memory performance in schizophrenia: a study with fMRI and structural equation modeling. *Neuroimage*. 2003;19:751–763.
144. Meyer-Lindenberg A, Poline JB, Kohn PD, et al. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *Am J Psychiatry*. 2001;158:1809–1817.
145. Ragland JD, Gur RC, Raz J, et al. Effect of schizophrenia on frontotemporal activity during word encoding and recognition: a PET cerebral blood flow study. *Am J Psychiatry*. 2001;158:1114–1125.
146. Ragland JD, Gur RC, Valdez JN, et al. Levels-of-processing effects on frontotemporal function in schizophrenia during word encoding and recognition. *Am J Psychiatry*. 2005;162:1840–1848.
147. Whyte MC, Whalley HC, Simonotto E, et al. Event-related fMRI of word classification and successful word recognition in subjects at genetically enhanced risk of schizophrenia. *Psychol Med*. 2006;1–13.
148. Crespo-Facorro B, Wiser AK, Andreasen NC, et al. Neural basis of novel and well-learned recognition memory in schizophrenia: a positron emission tomography study. *Hum Brain Mapp*. 2001;12:219–231.
149. Xu D, Liu T, Ashe J, Bushara KO. Role of the olivo-cerebellar system in timing. *J Neurosci*. 2006;26:5990–5995.
150. Theoret H, Haque J, Pascual-Leone A. Increased variability of paced finger tapping accuracy following repetitive magnetic stimulation of the cerebellum in humans. *Neurosci Lett*. 2001;306:29–32.
151. Ferrandez AM, Hugueville L, Lehericy S, Poline JB, Marsault C, Pouthas V. Basal ganglia and supplementary motor area subtend duration perception: an fMRI study. *Neuroimage*. 2003;19:1532–1544.
152. Mathiak K, Hertrich I, Grodd W, Ackermann H. Discrimination of temporal information at the cerebellum: functional magnetic resonance imaging of nonverbal auditory memory. *Neuroimage*. 2004;21:154–162.
153. Elvevag B, McCormack T, Gilbert A, Brown GD, Weinberger DR, Goldberg TE. Duration judgements in patients with schizophrenia. *Psychol Med*. 2003;33:1249–1261.
154. Davalos DB, Kisley MA, Ross RG. Deficits in auditory and visual temporal perception in schizophrenia. *Cognit Neuropsychiatry*. 2002;7:273–282.
155. Volz HP, Nenadic I, Gaser C, Rammsayer T, Hager F, Sauer H. Time estimation in schizophrenia: an fMRI study at adjusted levels of difficulty. *Neuroreport*. 2001;12:313–316.

156. Ortuno FM, Lopez P, Ojeda N, Cervera S. Dysfunctional supplementary motor area implication during attention and time estimation tasks in schizophrenia: a PET-O15 water study. *Neuroimage*. 2005;24:575–579.

157. Badcock JC, Michiel PT, Rock D. Spatial working memory and planning ability: contrasts between schizophrenia and bipolar I disorder. *Cortex*. 2005;41:753–763.

158. Morris RG, Rushe T, Woodruffe PW, Murray RM. Problem solving in schizophrenia: a specific deficit in planning ability. *Schizophr Res*. 1995;14:235–246.

159. Malla AK, Norman RM, Aguilar O, Carnahan H, Cortese L. Relationship between movement planning and psychopathology profiles in schizophrenia. *Br J Psychiatry*. 1995;167: 211–215.

160. Jogems-Kosterman BJ, Zitman FG, Van Hoof JJ, Hulstijn W. Psychomotor slowing and planning deficits in schizophrenia. *Schizophr Res*. 2001;48:317–333.

161. Fisher BE, Boyd L, Winstein CJ. Contralateral cerebellar damage impairs imperative planning but not updating of aimed arm movements in humans. *Exp Brain Res*. 2006;174(3):453–466.

162. Bonnefoi-Kyriacou B, Trouche E, Legallet E, Viallet F. Planning and execution of pointing movements in cerebellar patients. *Mov Disord*. 1995;10:171–178.

163. Rowe JB, Owen AM, Johnsrude IS, Passingham RE. Imaging the mental components of a planning task. *Neuropsychologia*. 2001;39:315–327.

164. Dagher A, Owen AM, Boecker H, Brooks DJ. Mapping the network for planning: a correlational PET activation study with the Tower of London task. *Brain*. 1999;122(Pt 10):1973–1987.

165. Nair DG, Purcott KL, Fuchs A, Steinberg F, Kelso JA. Cortical and cerebellar activity of the human brain during imagined and executed unimanual and bimanual action sequences: a functional MRI study. *Brain Res Cogn Brain Res*. 2003;15:250–260.

166. Medina J, Garcia K, Nores W, Taylor N, Mauk M. Timing mechanisms in the cerebellum: testing predictions of a large-scale computer simulation. *J Neurosci*. 2000;20:5516–5525.

167. Courchesne A, Allen G. Prediction and preparation, fundamental functions of the cerebellum. *Learn Mem*. 1997;4: 1–35.

168. Akshoomoff N, Courchesne E, Townsend J. Attention coordination and anticipatory control. *Int Rev Neurobiol*. 1997;41:575–598.

169. Nitschke M, Stavrou G, Melchert U, et al. Modulation of cerebellar activation by predictive and non-predictive sequential finger movements. *Cerebellum*. 2003;2:233–240.

170. Wolpert DM, Kawato M. Multiple paired forward and inverse models for motor control. *Neural Netw*. 1998;11:1317–1329.

171. Ravizza SM, McCormick CA, Schlerf JE, Justus T, Ivry RB, Fiez JA. Cerebellar damage produces selective deficits in verbal working memory. *Brain*. 2006;129(Pt 2):306–320.

172. Houk JC, Buckingham JT, Barto AG. Models of the cerebellum and motor learning. *Behav Brain Sci*. 1996;19: 368–383.

173. Ivry RB, Keele SW. Timing functions of the cerebellum. *J Cogn Neurosci*. 1989;1:136–152.

174. Nixon PD. The role of the cerebellum in preparing responses to predictable sensory events. *Cerebellum*. 2003;2: 114–122.

175. Lewis PA, Miall RC. Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging. *Curr Opin Neurobiol*. 2003;13:250–255.

176. Aakerlund L, Hemmingsen R. Neural networks as models of psychopathology. *Biol Psychiatry*. 1998;43:471–482.

177. Andreone N, Tansella M, Cerini R, et al. Cerebral atrophy and white matter disruption in chronic schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. September 7, 2006; [Epub ahead of Print].

178. Premkumar P, Kumari V, Corr PJ, Sharma T. Frontal lobe volumes in schizophrenia: effects of stage and duration of illness. *J Psychiatr Res*. 2006;40:627–637.

179. Wassink TH, Andreasen NC, Nopoulos P, Flaum M. Cerebellar morphology as a predictor of symptom and psychosocial outcome in schizophrenia. *Biol Psychiatry*. 1999; 45:41–48.