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Prediction, Psychosis, and the Cerebellum

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Abstract

An increasingly influential hypothesis posits that many of the diverse symptoms of psychosis can be viewed as reflecting dysfunctional predictive mechanisms. Indeed, to perceive something is to take a sensory input and make a prediction of the external source of that signal; thus, prediction is perhaps the most fundamental neural computation. Given the ubiquity of prediction, a more challenging problem is to specify the unique predictive role or capability of a particular brain structure. This question is relevant when considering recent claims that one aspect of the predictive deficits observed in psychotic disorders might be related to cerebellar dysfunction, a subcortical structure known to play a critical role in predictive sensorimotor control and perhaps higher-level cognitive function. Here, we review evidence bearing on this question. We first focus on clinical, behavioral, and neuroimaging findings suggesting cerebellar involvement in psychosis and, specifically, schizophrenia. We then review a relatively novel line of research exploring whether computational models of cerebellar motor function can also account for cerebellar involvement in higher-order human cognition, and in particular, language function. We end the review by highlighting some key gaps in these literatures, limitations that currently preclude strong conclusions regarding cerebellar involvement in psychosis.

Keywords

Cerebellum; Corollary discharge; Internal model; Prediction; Psychosis; Schizophrenia

PREDICTION, PSYCHOSIS, AND THE CEREBELLUM

Prediction

When walking down the stairs in the dark, we anticipate, both in space and time, that our foot is about to strike a tread. Deviations from this expected sensory input will trigger fast

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corrective actions, and should we encounter a missing tread repeatedly, we will in the future generate compensatory responses to anticipate this gap. This example makes clear how prediction is crucial for adaptive behavior, an idea that has a long history in the study of sensorimotor function (1). For example, in the early 19th century, Bell and Purkinje proposed that our percept of the world remains stable during saccades because the brain anticipates the sensory consequences resulting from an eye movement (1). Predictive mechanisms of this sort have since been verified in many model systems (2), with the term efference copy (3) or corollary discharge (4) used to capture the idea that in addition to generating the signals that produce a movement, a copy of the motor commands is used to generate the predicted sensory consequences of that movement. A related concept, originating from control theory in engineering, is that of an internal model, "a system that mimics its next state given the current state and a motor command" (5). An impressive body of empirical studies has provided compelling demonstrations of the neural signatures of predictive mechanisms, or rather, of how these predictions are presumably subtracted from the actual sensory input. For example, neural activity in the auditory cortex is markedly attenuated in response to hearing oneself speak, relative to hearing the same sounds played back in a passive listening condition (6-9). Importantly, online perturbations of feedback from speech reduces this suppression (10,11), indicating that the suppression is due to a detailed prediction of the auditory input, rather than to nonspecific attentional mechanisms.

Psychosis

As evidenced by this special issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, an increasingly influential hypothesis posits that many of the diverse symptoms of psychosis can be viewed as reflecting dysfunctional predictive mechanisms (12-15). To build on the speech example described above, the suboptimal operation of predictive mechanisms involved in suppressing reafferent auditory feedback could make it difficult to distinguish between self- and externally generated stimuli, leading to delusions of control (16). Likewise, if internal speech engages similar processes as external speech, a failure of anticipatory processes might lead to auditory hallucinations (14,16); i.e., the internal thoughts could be attributed to an external source. In line with these ideas, an increasing body of research has documented decreased suppression of self-generated somatosensory (17,18), visual (19-24), and auditory (25-27) stimuli in patients with schizophrenia, the most debilitating of psychotic disorders.

Moving from such relatively low-level sensory phenomena to higher-level cognition, one of the most characteristic clinical features of psychosis is a loss of coherence in speech output, assumed to reflect an underlying thought disorder (28). One hypothesis is that thought disorder arises from an impairment in predictive processes, with the affected individual unable to use predictive mechanisms to generate lucid ideas. When coupled with a second problem associated with an increase in automatic spreading activation across semantic networks (29), one can understand phenomena such as context-inappropriate associative leaps, exemplified in the following passage: "If you think you are being wise to send me a bill for money I have already paid, I am in nowise going to do so unless I get the whys and wherefores from you to me. But where the fours have been, then fives will be, and other numbers and calculations and accounts to your no-account" (30). This sentence shows

several signs of hyperassociation on the level of single-word identity (“wise” – “no-wise”, “accounts” – “no-account”), phonology (“whys and wherefores”), and category membership (“four” – “five”), but simultaneously reveals a near-complete context blindness. The initial parts of the message are minimally predictive of what follows, and the lack of connection from one phrase to the next renders the final output unintelligible. Empirically, many behavioral studies have highlighted a deficient use of predictive context in both language production and comprehension in schizophrenia (28,30-32), and reduced semantic coherence even shows promise as a predictive marker of conversion to psychosis in high-risk groups (33).

Cerebellum

Theories such as Friston’s free-energy principle (27) make clear that prediction is perhaps the most fundamental neural computation; to perceive something is to take a sensory input and make a prediction of the external source of that signal. For this reason, it is not surprising that prediction has been associated with many parts of the brain. Given the ubiquity of prediction, a more challenging problem is to specify the unique predictive role or capability of a particular brain structure. Here, we focus on the cerebellum, highlighting how the concept of prediction has been central to theories of cerebellar function (34,35).

One influential hypothesis is that the cerebellum is a critical node in a system required for the construction and adaptation of internal models for sensorimotor control (34-36). These internal models take as input an efference copy of the motor commands and, via simulation through an internal model, generate the expected sensory consequences of that movement. The mismatch between the predicted and actual feedback constitutes a sensory prediction error, the signal that can be used to retune the internal model so that in future iterations, the prediction is better matched to the actual feedback. This model provides an elegant account of the critical role of the cerebellum as a feedforward system in sensorimotor control and for sensorimotor learning. Indeed, prediction is essential for skillful motor control, given that the inherent delays in feedback control would produce instabilities in control (5). The internal model hypothesis has spawned a rich empirical test bed, showing how people learn to move in different environmental contexts or interact with objects and tools (5,37), as well as accounting for the sensorimotor adaptation impairments observed in individuals with cerebellar pathology (38-44). The prediction deficits cerebellar patients display in motor (41,43), proprioceptive (45), and auditory (46,47) processing are also in line with the internal model hypothesis.

These computational accounts draw their inspiration from detailed studies of the unique anatomy and physiology of the cerebellum [for more detailed accounts, see Ito (48)].The massive cortical and subcortical input onto cerebellar granule cells from the pontine nuclei allows for the encoding of very complex multimodal contexts (49-51), including what might be thought of as an efference copy. The output of the cerebellum, refined via processing in the cerebellar cortex, can be viewed as the sensory prediction (52). At some place or places, this prediction is compared with the actual feedback, with mismatches resulting in the generation of complex spikes, relayed to the cerebellar cortex via the other major input, the inferior olivary nuclei (35). The complex spike has historically been viewed as an error

signal, hypothesized to serve as the teaching signal that modifies Purkinje cell synapses and thus improves the internal model (35). Neurophysiological cerebellar recordings in behaving animals are remarkably consistent with the internal model hypothesis (52,53).

IS THE CEREBELLUM A RELEVANT BRAIN REGION FOR PSYCHOSIS?

As noted above, prediction is a general feature of brain function. Nonetheless, a number of researchers have asked if the predictive deficits observed in psychotic disorders might, at least in part, be related to cerebellar dysfunction. One motivation for this hypothesis comes from work seeking to generalize the relatively well-understood cerebellar mechanisms for predictive sensorimotor control to higher-level cognition; by this reasoning, these more abstract forms of prediction might be disrupted in psychosis.

Here, we review some recent evidence bearing on these two questions. We first focus on clinical, behavioral, and neuroimaging findings suggesting cerebellar involvement in psychosis and, specifically, schizophrenia. Then we review a relatively novel line of research exploring whether computational models of cerebellar motor function can also account for cerebellar involvement in higher-order human cognition (see Figure 1), and in particular, language function. We also highlight some key gaps in these literatures, limitations that currently preclude strong conclusions regarding cerebellar involvement in psychosis.

Is Cerebellar Pathology Associated With Psychosis?

If cerebellar dysfunction is central to the pathophysiology of psychosis, one might expect individuals with cerebellar disturbances to exhibit psychotic symptoms. At present, the evidence in favor of this hypothesis is modest at best. There are a number of case studies reporting the co-occurrence of cerebellar pathology and psychosis (54-56); however, few systematic studies have been conducted. One notable exception involved the assessment of a wide range of psychiatric symptoms in a cohort of 31 patients with cerebellar degeneration (57). Within this group, 3 of the 31 patients met the criteria for a diagnosis of psychosis, a prevalence estimate of ~10%, compared with the ~1% to 2% prevalence in the general population. Although the sample size is small, this estimate is similar to that reported in a retrospective chart review of a larger group of patients with cerebellar degeneration (n = 133). Here, too, the prevalence of psychotic disorders was ~10%, although the presence of psychosis appeared to primarily be related to concurrent basal ganglia involvement; that is, patients with multisystem atrophy (58). A more recent study also found evidence of basal ganglia impairment in patients with cerebellar degeneration who displayed features of psychosis (59). Thus, while the literature suggests an increased (and possibly underdiagnosed) prevalence of psychotic disorders in patients with cerebellar degeneration, it also highlights that concurrent pathology in the basal ganglia may be more central to psychosis than pathology in the cerebellum.

Given that brain pathology in patients with cerebellar degeneration may extend to extracerebellar structures, it is also important to consider patients with more focal pathology of the cerebellum. Unfortunately, the current literature is limited to case reports: psychosis has been associated with cerebellar congenital malformations (54), cerebellar tumors (60), and cerebellar strokes (61,62). Of course one would expect a small number of these

individuals to have psychoses, given the prevalence rate in the general population. However, there are a few reports of rapid-onset psychosis following cerebellar infarcts, including in individuals with no history of psychopathology (61,62). Cases such as these potentially offer the most compelling evidence for an association between the cerebellum and psychosis, although the database here is quite small.

In summary, while the clinical literature offers some intriguing cases of psychosis linked to cerebellar pathology, more extensive studies are clearly needed to assess the magnitude of this association and examine whether the association also involves abnormalities in noncerebellar structures.

Do Motor Disturbances in Psychotic Disorders Indicate Cerebellar Dysfunction?

Despite the accumulating evidence that the functional territory of the cerebellum extends beyond motor control (see Figure 1), the most unequivocal behavioral signs of cerebellar dysfunction are impairments in motor coordination, or ataxia. To what extent are such symptoms seen in psychotic disorders? While not included among the diagnostic criteria, marked disruptions in bodily movements were noted in the earliest clinical descriptions of schizophrenia (63). More systematic studies have now established a high prevalence of motor abnormalities in patients with schizophrenia (59%–80%) (64-66), even before the onset of antipsychotic medication (65,67). In addition, meta-analyses consistently find that individuals at increased familiar risk for psychosis exhibit delayed motor development (68-74) and marked motor abnormalities as early as 7 years of age (75-81). Thus, motor disturbances appear to be a core and relatively consistent feature of schizophrenia (64,68,82,83). While some of these motor symptoms (e.g., involuntary movements) are typically associated with a basal ganglia etiology, some of the most frequently observed motor deficits are associated with cerebellar dysfunction (65,78,84-86); these include disturbances of gait (e.g., tandem walk), balance (e.g., enhanced postural sway), and manual coordination (e.g., finger-nose test) (65). Indeed, when a relatively large cohort of patients (n = 155) with schizophrenia were specifically assessed for cerebellar neurological signs, 21% presented signs of cerebellar dysfunction (87). Even more compelling behavioral evidence comes from studies using experimental tasks known to critically rely on cerebellar circuitry, such as classical conditioning of the defensive eyeblink reflex (88). Impaired eyeblink conditioning has been observed in both chronic (89) and first-episode (90,91) schizophrenia patients, as well as in their first-degree relatives (92).

In summary, cerebellar motor deficits appear to be a relatively frequent, but largely understudied and underemphasized, feature of schizophrenia (93). The recent addition of a motor domain (93) to the Research Domain Criteria framework (94) advocated by the National Institute of Mental Health should result in a stronger focus on these features of the disorder.

Is Cerebellar Structure and Function Affected in Psychotic Disorders?

Reports of cerebellar structural alterations in schizophrenia date back to the late 1970s and early 1980s (95,96); see Table 1 for selected examples.

For example, Weinberger *et al.* (96) reported pronounced atrophy of the cerebellar vermis in 10 of 60 patients with chronic schizophrenia examined using computerized tomography. With the emergence of magnetic resonance imaging (MRI) in the 1990s, results proved more equivocal, and review articles and meta-analyses thus indicate that structural abnormalities are less consistently observed in the cerebellum than in other brain regions such as the hippocampus, frontal lobe, and temporal lobe (97-99). However, it is also important to keep in mind that there is a corticocentric bias in cognitive neuroscience (100); both scanning protocols and structural analysis tools are generally optimized for the cerebral cortex.

Aiming to avoid such methodological biases, we recently employed an analysis pipeline that was optimized for both the cerebellum and cerebral cortex, looking at volumetric measures in a large sample of participants tested over multiple sites. In sum, we were able to obtain data from 983 individuals with schizophrenia, comparing their brain measures with those obtained from age- and sex-matched healthy control subjects (n = 1349) (101). Overall, the schizophrenia group showed small (Cohen's d = 0.35), but highly significant, reductions in cerebellar volume (Figure 2A). Interestingly, the volumetric reductions in the cerebellum were as pronounced in younger as in older patients, suggesting a neurodevelopmental rather than a neurodegenerative etiology.

We also quantified other subcortical and cortical regions, with the final database containing 49 brain features (e.g., volumetric measures of areas such as the cerebellum and hippocampus, and gray matter thickness for regions of the cerebral cortex). Comparing all brain features, cerebellar volume reductions were among the most pronounced, with stronger effects only observed for reduced hippocampal and increased pallidal volume. Moreover, the cerebellar reduction was the most consistent finding across scanning sites. Strongly supporting our findings in adult patients, later we also found gray matter volume in the posterior cerebellum (lobule VI/crus I) to be the most robust brain predictor of (primarily subclinical) psychotic symptom severity in a large community sample of children and young adults (n = 1401; age range = 8–23 years; mean age = 15.1 years) (102) (Figure 2B). Across the majority of studies (101-106), the most prominent changes are seen in areas considered part of the "cognitive" cerebellum (e.g., crus I/II), given their consistent activation during the performance of tasks such as active maintenance of information in working memory, language processing, and autobiographical memory (107-109) and functional connectivity with cognitive networks of the cerebral cortex (110-112). However, it should be noted that reduced volumes of the anterior vermis [lobules IV–V, primarily associated with motor control (113)], have also emerged as a consistent finding across studies (106).

Functional neuroimaging methods have also been brought to bear on the question of cerebellar abnormalities in schizophrenia (114). A frequently reported finding is that this group exhibits altered cerebello-thalamo-cortical functional connectivity (115-126), and similar patterns have been reported in subjects at increased risk for psychosis (85,127-130) (Table 2).

Of particular note, a recent well-powered study (n = 3434) found an association between altered cerebrocerebellar connectivity (patterns of both hyper- and hypoconnectivity) and psychotic-like phenomena in 9- to 11-year-olds, suggesting that these brain phenotypes may

precede the onset of more serious pathology (131). Consistent with this hypothesis, a few studies have shown longitudinal associations between altered cerebello-thalamo-cortical connectivity and symptom progression and/or conversion to psychosis in clinical high-risk groups (115,127,128). However, a recent meta-analysis failed to find consistent thalamocerebellar connectivity changes associated with psychoses, although the author acknowledged that this may be related to methodological limitations (132). Moreover, as can be seen in Table 2, the directionality of these effects (i.e., hypo- or hyperconnectivity in patients relative to control subjects) varies across studies, complicating the interpretation of these findings. Intriguingly, the connectivity abnormalities may be region specific (123). Thus, hypoconnectivity appears to be more prominent in cerebellar areas involved in cognitive functions (e.g., crus I/II), while reports of hyperconnectivity may be associated with cerebral sensorimotor regions (123).

In summary, structural neuroimaging findings provide compelling evidence for cerebellar involvement in schizophrenia, while the evidence from functional MRI (fMRI) studies is more ambiguous. Moreover, the functional implications of these findings remain unclear.

CAN THE INTERNAL MODEL HYPOTHESIS OF CEREBELLAR FUNCTION BE EXTENDED FROM MOTOR CONTROL TO HIGHER-LEVEL COGNITION?

Over the last 3 decades, there has been widespread recognition that the functional domain of the cerebellum encompasses much of cognition (110). For instance, cerebellar activation in fMRI studies is consistently observed during tasks requiring a broad range of cognitive and affective processes, and these activity patterns cannot be accounted for by the motor demands of the tasks (109) (see Figure 1). Moreover, the distribution of activity, observed during either task performance (109) or rest (111,112), indicates that a larger proportion of the human cerebellum is better classified as cognitive rather than motor. However, exactly how the cerebellum contributes to cognition remains an enigma, despite considerable effort on this problem.

Many of the hypotheses concerning the cognitive functions of the cerebellum are extensions of mechanistic ideas developed for understanding how this structure contributes to motor control (34,133,134). This approach has largely been motivated by the relatively homogenous cerebellar microanatomy and physiology (135), features that suggest a corresponding uniformity of function (34,136-139). Of particular relevance to this special issue are efforts to apply the notions of internal models to cognition: might this idea, which has been fruitful in explaining the cerebellar role in predictive motor control (5,37-44), be extended to account for the cerebellar contribution to cognition? We next review some recent studies addressing this question in the language domain [for more extensive reviews, see Argyropoulos (140) and Moberget and Ivry (141)].

During conversation, the interval between turn taking is close to 0 ms (142). This simple observation underscores the importance of predictive mechanisms in language—assuming we are listening to our conversational partner, we must be anticipating the end of their sentence as we initiate our response. Indeed, the concept of internal models has played a prominent role in theories of language processing. For instance, Pickering and Garrod (143)

argued that people use internal models in both language production and language comprehension to predict "what they are about to perceive or to do, in a way that allows them to 'get ahead of the game.'" In speech production, an internal model can support a comparison between the predicted and actual speech, allowing the output to be adjusted when discrepancies are detected (144); in speech perception, an internal model could facilitate language comprehension through the active prediction of the speaker's next utterance. Supporting a role for the cerebellum in predictive language production, patients with cerebellar degeneration show impairments in adjusting their speech output to predictable perturbations (145), similar to that observed in studies of arm movements (38,39).

But the more intriguing question concerns the role of the cerebellum on the perceptual side of language. Evidence of a cerebellar role in language comprehension was provided by an experiment in which participants listened to spoken sentences and were required to look, as quickly as possible, at 1 of 4 pictures that corresponded to the last word (146,147). The sentences either provided a context that strongly predicted the immediately upcoming final word or created a context in which all of the pictures were equally plausible. Crucially, transient disruption of the right cerebellar hemisphere with either repetitive transcranial magnetic stimulation (146) or cathodal transcranial direct current stimulation (147) selectively slowed saccade reaction times in the predictive conditions, indicating a causal role for the cerebellum in anticipating semantic content.

Following up on the extensive neuroimaging literature implicating the cerebellum in semantic processing (123,124), we designed an fMRI study to focus on the relationship between linguistic predictions and the hemodynamic response in the cerebellum (148). Participants in each trial read sequentially presented words that were of 1 of 3 types: confirmed predictions, in which a coherent sentence ended with a highly predictable last word (e.g., "two plus two is four"); violated predictions, in which the last word violated the context established by the preceding words; and nonpredictive sentences, in which the stimulus consisted of a random sequence of words (e.g., "fast in clock plane").

The analyses focused on the blood oxygen level–dependent response, time-locked to the final word in the sentence. When comparing the violated predictions, either to the confirmed predictions or to the nonpredictive sentences, a broad pattern of activation was observed across the cerebellum, including bilateral posterior regions (Figure 3A). This pattern is consistent with that observed in studies of motor control both in humans (149,150) and animals (151,152), with the cerebellum sensitive to the presence of an error, arising here in the linguistic domain. Perhaps more surprising was the finding that cerebellar activation was greater in the confirmed prediction sentences compared with the nonpredictive sentences. The activation here was much more focal, limited to a small cluster in crus I/II in the right cerebellar hemisphere (Figure 3B). We hypothesize that this signal is reflecting the operation of a linguistic internal model, one involved in generating the semantic expectancy (148). This interpretation is further supported by another fMRI study (153) in which the stimuli involved the parametric manipulation of the semantic likelihood of the final target word. Activity in the right posterior cerebellum was positively correlated with contextual

probability, again suggesting that the cerebellum is engaged when a linguistic context can be exploited to generate a semantic prediction [see also (154,155)] (see Figure 3C).

The noninvasive brain stimulation and fMRI work presented above provide examples of how a hypothesis established in studies of sensorimotor control may be extended to consider an expanded view of cerebellar function. However, it is important to keep in mind three caveats when considering whether the internal model idea provides a useful characterization of cerebellar function in a broad context. First, patients with cerebellar pathology, from either focal lesions or degenerative processes, do not show marked impairments on tasks such as those used in the imaging studies (156). It may be that the cerebellum is not essential for generating semantic predictions, but rather, it helps makes these operations more fluid; as such, behavioral studies may require sensitive measures to detect impairments. Second, to repeat a point raised previously, prediction is a general property of brain function. Surely, the generation of semantic predictions is not the sole province of the cerebellum. As with all work on the cerebellum and cognition, future work is needed to understand how this subcortical structure interacts with other regions of the brain in enabling complex cognition. Third, it remains to be seen if cerebellar dysfunction within the linguistic domain is relevant to our understanding of the language and thought impairments observed in psychosis (28,157).

THE CEREBELLUM, PREDICTION, AND PSYCHOSIS: PLEASE MIND THE GAPS

More generally, might the predictive deficits associated with psychotic disorders reflect an impairment in cerebellar-dependent processes required for generating and implementing internal models? As reviewed above, various lines of evidence point to cerebellar involvement in psychosis and a generalized role in internal model mechanisms across motor and cognitive domains. However, to date, these two literatures have not been integrated. Missing from this picture are experiments that more directly evaluate the hypothesized links among disorder, structure, and function [see Bernard *et al.* (158) for a notable exception].

First, larger studies are needed to map the prevalence and nature of psychotic symptoms in cerebellar disease and cerebellar impairments in psychotic disorders. The emerging picture is that these associations have been underestimated or underappreciated. However, it is also clear that there is considerable heterogeneity in both patient groups. This heterogeneity mandates the need that future studies be sufficiently powered to be able to detect and characterize subgroups of patients (e.g., identify areas within cerebellum that if lesioned, increase likelihood of psychotic symptoms).

In terms of structural imaging, multisite studies have been able to achieve impressive sample sizes, revealing abnormalities in cerebellar structure in both patients with schizophrenia (101) and youths reporting elevated levels of psychotic symptoms (102). However, it is also important to keep in mind that these structural changes tend to be small to modest, with effect sizes very rarely exceeding Cohen's *d* values of 0.5. These modest effect sizes also suggest considerable heterogeneity in individuals who receive the same diagnostic label (104). And, of course, structural abnormalities in schizophrenia are not limited to the

cerebellum, but rather are broadly observed in cortical (159) and subcortical (160) structures.

The inconsistencies in the functional connectivity literature—for example, reports of both decreased (116-119,161) and increased (115,162) cerebello-thalamo-cortical connectivity in psychotic disorders—may likewise reflect the heterogeneity of this population. Moreover, as suggested by Table 2, the direction of these connectivity changes may vary for different cerebellar regions. Future meta-analyses evaluating the robustness and regional specificity of cerebellar connectivity abnormalities would be very useful.

Both structural MRI and fMRI methods have clear limitations when it comes to making inferences about the underlying neurobiology (e.g., microcircuits, cell types). For instance, alterations in gray matter volume may reflect a wide range of micro-structural changes (e.g., in neuron density, dendritic arborization, glia), and current MRI methods lack the resolution to differentiate between them. As for fMRI, the blood oxygen level–dependent signal measured in fMRI studies is likely dominated by inputs to the cerebellum from the pontine nuclei, signals carried along the mossy fiber pathway (163). This measure appears to be much less sensitive (or even blind) to the other major input, the climbing fibers originating in the inferior olive, as well as to activity in the Purkinje cells themselves, the output of the cerebellar cortex (163). These limitations point to the need for animal models of cerebellar function [see Person (164) in this special issue], perhaps with an eye on developing tasks that can ask about more generalized applications of internal models.

Finally, while there are emerging literatures examining predictive mechanisms in psychosis as well as cerebellar involvement in (motor and nonmotor) predictive mechanisms, the links between these two literatures are scarce. Figure 4 presents a schematic, highly subjective picture of the current state of knowledge, with the main intent to feature missing and weak links. The boxes and arrows with solid outlines represent well-established phenomena and those with the strongest evidence of an association. In terms of symptoms, delusions of control, auditory hallucinations, and thought disorder are commonly accepted as core clinical features of psychosis; in contrast, motor symptoms have received far less attention (82,93). At the computational level, there is compelling evidence of predictive mechanisms at play in the coordination of movements (5,37), suppression of sensory signals arising from self-generated actions [such as speech (6-11)], and even higher level aspects of language comprehension (143,165). Whether impairment in these mechanisms plays a core causal role in their associated symptoms is an open question, one in which predictions based on an internal model account need to be pitted against alternative mechanistic hypotheses. Similarly, while there is reasonably strong evidence of a cerebellar role in the putative computations depicted in Figure 4, research on how the core symptoms of psychosis relate to cerebellar dysfunction remains in its infancy.

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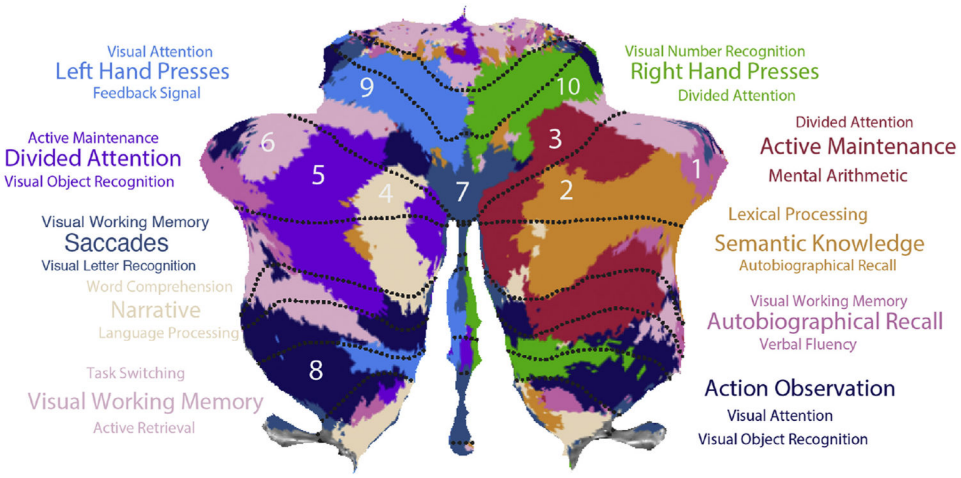

Figure 1.

A flat-map functional representation of the cerebellar cortex, based on functional magnetic resonance imaging data while participants performed a large battery of motor and cognitive tasks (107). The labels refer to the cognitive processes most closely related to the tasks that engaged each region. The study highlights that nonmotor features provide the best descriptors of most of the cerebellar cortex. 1, Autobiographical recall; 2, Semantic knowledge; 3, Active maintenance; 4, Narrative; 5, Divided attention; 6, Visual working memory; 7, Saccades; 8, Action observation; 9, Left hand presses; 10, Right hand presses.

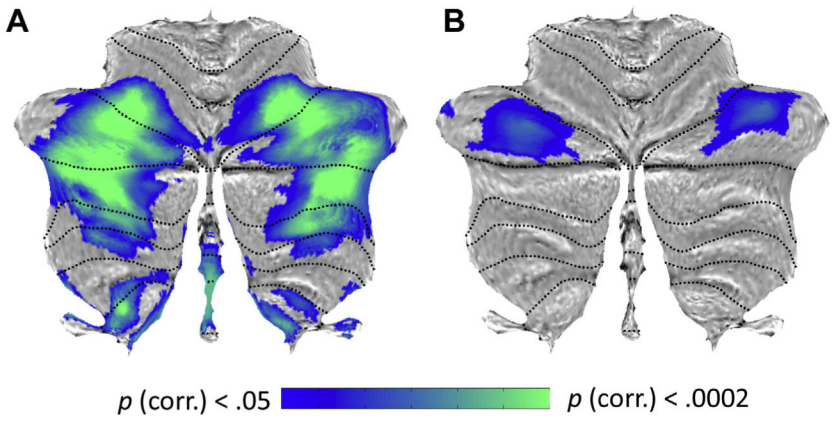

Figure 2.

(A) Significant cerebellar gray matter reductions in a large sample of patients with schizophrenia (n = 983) relative to healthy control subjects (n = 1349) (101). **(B)** Significant negative associations between cerebellar gray matter volume and level of psychotic symptoms in a large community sample (n = 1401) centered on adolescence (102). corr., corrected.

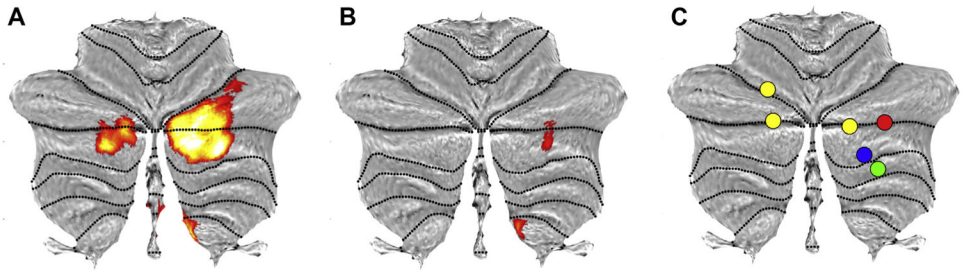

Figure 3.

Cerebellar functional magnetic resonance imaging activations related to **(A)** the violation of semantic expectancies and **(B)** the predictability of an upcoming word (148). Panel **(C)** shows peak cerebellar activations related to linguistic predictability across 4 functional magnetic resonance imaging studies: red (144); blue (153); green (154); yellow (155).

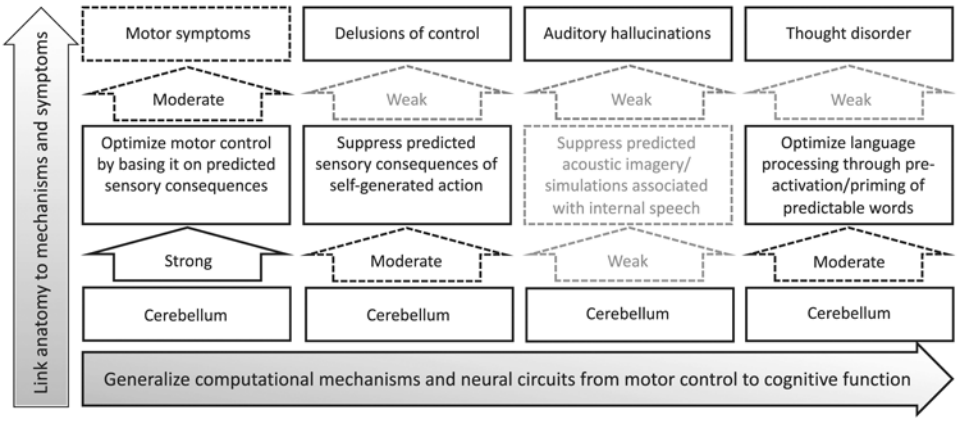

Figure 4.

Schematic summary of existing evidence and knowledge gaps. Symptoms associated with psychosis are represented at the top level, while the middle and bottom levels represent putative computational mechanisms and neural substrates. Arrows denote the links between these levels, solid lines represent relatively well-established phenomena and associations, and dotted and gray lines denote phenomena and associations with a weaker evidence base.

Table 1.

Key Findings From Studies Examining Cerebellar Structural Alterations in Psychotic Disorders

Year, Reference	*n*	Main Cerebellar Finding(s)
1979 (96)	70 patients with SZ	Pronounced atrophy of the cerebellar vermis in ~17% of patients with SZ
1994 (166)	52 patients with SZ, 90 HC subjects	No group differences in total cerebellar volume between patients with SZ and HC subjects
1994 (167)	36 patients with SZ, 52 HC subjects	No group differences in vermal volumes between patients with SZ and HC subjects
2010 (168)	54 patients with SZ, 100 HC subjects	Reduced gray matter volume in bilateral anterior cerebellum
2012 (103)	29 patients with SZ, 45 HC subjects	Reduced volume of left cerebellar crus I and II in patients with SZ
2015 (169)	32 patients with SZ, 52 HC subjects	Reduced total cerebellar volume in patients with SZ
2015 (170)	784 patients with SZ, 936 HC subjects	Patterns of both reduced and increased cerebellar gray matter concentration in patients with SZ
2017 (171)	37 patients with SZ, 62 HC subjects	Reduced volume of bilateral cerebellar crus I and II in patients with SZ
2018 (104)	158 patients with SZ, 88 HC subjects	Reduced volume of bilateral cerebellar lobules VIII and VI/crus I in patients with SZ
2018 (101)	983 patients with SZ, 1349 HC subjects	Reduced total and regional cerebellar volumes in patients with SZ, with most prominent effects in “cognitive” cerebellar regions (e.g., crus I/II)
2018 (105)	218 patients with SZ, 190 patients with BD, 256 HC subjects	Pronounced cerebellar volume reductions in a small subset of patients with SZ and patients with BD, but large within-group variability
2019 (106)	417 patients with SZ, 389 HC subjects	Reduced cerebellar gray matter volume (vermal lobules IV–V and left crus I) in first-episode, drug-naïve patients with SZ (meta-analysis)
2019 (102)	1401 HC subjects	Level of (primarily subclinical) psychotic symptoms were associated with cerebellar volume (VI/crus I) in a community adolescent sample

BD, bipolar disorder; HC, healthy control; SZ, schizophrenia.

Table 2.

Key Findings From Studies Examining Cerebellar Functional Connectivity Alterations in Psychotic Disorders

Year, Reference	*n*	Main Finding(s) in Patients (SZ/PSY/CHR) Relative to HC Subjects
2014 (119)	90 patients with SZ, 90 HC subjects	Reduced functional connectivity between the thalamus and the cerebellum
2014 (119)	90 patients with SZ, 146 HC subjects	Reduced functional connectivity between the mediodorsal (prefrontal-projecting) thalamus and cerebellar regions
2015 (127)	243 individuals at CHR, 154 HC subjects	Reduced cerebellothalamic functional connectivity in youths at CHR for psychosis, with the most pronounced reductions seen in participants who later converted to frank psychosis
2015 (123)	44 patients with SZ, 28 HC subjects	Reduced functional connectivity between associative regions of the cerebral cortex and posterior cerebellum (crus I/II), increased functional connectivity between sensorimotor regions of the cerebral cortex and cerebellar regions
2016 (117)	148 patients with PSY, 105 HC subjects	Reduced functional connectivity between prefrontal-projecting thalamus and posterior cerebellar regions (crus I/II) in patients with PSY
2018 (116)	183 patients with SZ, 178 HC subjects	Reduced functional connectivity between the thalamus and posterior cerebellar regions (crus I/II), associated with delusions and bizarre behavior in SZ
2018 (115)	Sample 1: 182 individuals at CHR, 120 HC subjects Sample 2: 50 patients with SZ, 49 patients with BD, 40 patients with ADHD, 123 HC subjects	Increased cerebello-thalamo-cortical network connectivity in a CHR group, with most pronounced increases seen in those who later converted to psychosis; this hyperconnectivity pattern was also found in patients with SZ, but not in patients with BD or ADHD or in HC subjects
2019 (131)	3434 HC subjects	Both increased and decreased connectivity between the cerebellum (treated as a single region of interest in this study) and various cortical networks were found to be associated with the level of psychotic-like experiences in 9- to 10-year-old children
2019 (132)	1582 patients with PSY, 1272 HC	Failure to observe any consistent changes in thalamocerebellar connectivity in psychotic patients in a meta-analysis of 17 studies

ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; CHR, clinical high risk; HC, healthy control; PSY, psychotic disorder; SZ, schizophrenia.