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REVIEW

Cerebellar Sequencing: a Trick for Predicting the Future

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Abstract "Looking into the future" well depicts one of the most significant concepts in cognitive neuroscience: the brain is constantly predicting future events. Such directedness toward the future has been recognized to be relevant to and beneficial for many aspects of information processing in humans, such as perception, motor and cognitive control, decision-making, theory of mind, and other cognitive processes. Because one of the most adaptive characteristics of the brain is to correct errors, the ability to look into the future represents the best chance to avoid repeating errors. Within the structures that constitute the "predictive brain," the cerebellum has been proposed to have a central function, based on its ability to generate internal models. We suggested that "sequence detection" is the operational mode of the cerebellum in predictive processing. According to this hypothesis, the cerebellum detects and simulates repetitive patterns of temporally or spatially structured events and generates internal models that can be used to make predictions. Consequently, we demonstrate that the cerebellum recognizes serial events as a sequence, detects a sequence violation, and successfully reconstructs the correct sequence of events. Thus, we hypothesize that pattern detection and prediction and processing of anticipation are cerebellum-specific functions within the brain and that the sequence detection hypothesis links the multifarious impairments that are reported in patients with cerebellar damage. We propose that this cerebellar operational mode can advance our understanding of the pathophysiological mechanisms in various clinical conditions, such as schizophrenia and autism.

Keywords Cerebellum · Sequence processing · Internal model · Anticipation · Corticocerebellar connectivity · Autism

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Introduction

Predictive processing is one of the fundamental principles of neural computations because it is crucial for driving motor, cognitive, and behavioral functions. Prediction refers to the representation of an event that is going to occur in the future. The prediction of an incoming behavior effects anticipation—that is, "the process of formulating and communicating this expectation to the cortical areas which become activated prior to the realized event" [1].

Because correcting errors is one of the most adaptive characteristics of the brain, the ability to "look into the future" represents the best opportunity to avoid repeating errors. If this is true, the brain is constantly predicting future events and comparing these predictions to actual outcomes.

Of the structures that constitute the "predictive brain," the cerebellum has been proposed to have a central function [2–5]. The prediction of future states has been suggested to require the generation of internal models. The cerebellum, at least in the motor domain, mediates implementation of forward internal models, integrating predictions about the consequences of a motor action with sensory feedback to fine-tune motor behavior [6, 7].

In the past decade, the cerebellum has been reported to encode internal models "that reproduce the essential properties of mental representation in the cerebral cortex" [7]. Thus, in motor and nonmotor domains, functional state patterns are recorded by cerebellar processing and compared with stored templates. If a match is obtained, then it is assumed that the next incoming event can be predicted from the stored template. Accordingly, the cerebral cortex can be activated in advance, alerting the correct modules. This forward-looking function of the cerebellum enables the central nervous system to plan ahead [5], and the cerebellum can perform the two crucial processes of foresight: prediction and anticipation.

Despite the agreement that the cerebellum is part of the predictive brain network, however, what it processes to implement such predictions remains debated.

For a long time, the Marr-Albus-Ito theory of cerebellar function has been quite influential. In the last decade, different model-based theories have been advanced to provide a theoretical framework in which a unitary mode of operation could be proposed for all the many cerebellar functional domains. The cerebellum has been linked to the representation of temporal information [8]. It has been proposed as a "universal cerebellar transform" that allows to maintain any type of behavior, motor or cognitive, around a homeostatic baseline [9]. It has been hypothesized as a sensory coordination of data acquisition [10]. For a broader overview of the theories on the cerebellar functioning, see Koziol et al. [11]. However, in spite of the large body of literature, the question is still open.

The "Sequence Detection" Hypothesis

We advanced the idea that sequence detection could be the operational mode of the cerebellum in predictive processing [12, 13].

According to this hypothesis, the cerebellum detects and simulates repetitive patterns of temporally or spatially structured events, regardless of whether they constitute sensory consequences of one's actions in motor planning, expected sensory stimuli in perceptual prediction, or inferences of higher-order processes (e.g., cognitive elaboration or social cognition). The simulation allows internal models to be created [7] that can be used to make predictions about future events that involve any component, such as the body, other persons, and the environment.

In the late 1990s, sequence processing was proposed to be the basic cerebellar functional mechanism of the motor [14] and cognitive [15] domains. But, it is only recently that neurophysiological and neuroimaging data have supported this hypothesis.

Magnetoencephalographic (MEG) records during repetitive somatosensory stimulations that contain various patterns of omission have demonstrated separate time courses of MEG responses in the cerebellum and somatosensory cortex. The somatosensory cortex does not react to the omission, whereas its activity increased during the first stimulus after the omission. The reverse pattern was observed in the cerebellum, the activity of which was enhanced by the unattended omission. The reaction to the absence of a signal can be understood only as an indication that something that is expected does not appear [16], supporting the hypothesis that the cerebellum's ability to categorize patterns of sensory inputs allows it to predict the sequence of events and consequently anticipate each of them [3].

By functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), Bubic et al. [17] compared functional activation during a serial prediction task with that during a target detection task. In both tasks, participants were occasionally presented with events that deviated from the standard context of the trial—in one case, the violation regarded a sequential order ("sequential deviant"), and in the other case, the violation regarded a stimulus that was distinct from standard events in the trial ("nonsequential deviant"). The authors found that "processing sequentially embedded and nonembedded stimuli is, even when these are comparable in their perceptual characteristics, supported by distinct functional networks." Specifically, presenting sequential violations triggered an increase in activation in the lateral and medial premotor cortex and cerebellum.

According to our sequence detection theory the cerebellum detects and memorizes a pattern, creating an internal model of it. Thus, it expects specific incoming stimuli that are clearly defined by the underlying internal model. The correctness of the predictions is evaluated by comparing the incoming bottom-up information with top-down expectations. If the prediction holds, a signal is sent to alert select cortical areas, allowing the predicted stimulus to be perceived more efficiently. Conversely, presentation of an event that violates expectations effects more widespread brain activation that accelerates the processing of salient sensory information by the changing events and attunes the behavioral response to the new event.

If our assumption is true, damage to the cerebellum should affect the ability to recognize serial events as a sequence, detect a sequence violation, and successfully reconstruct a correct sequence of events.

Cerebellar Damage Affects the Ability to Recognize Serial Events as a Sequence

We administered a serial reaction time task (SRTT) to patients who developed cerebellar lesions [18]. SRTT is based on the generation of a motor response to stimuli, usually visual, that are organized in fixed or random sequences and tests procedural learning. This test is the benchmark method of analyzing sequence detection and acquisition. Subjects can improve their motor response only if they recognize, implicitly or explicitly, the sequential presentation of different spatial positions. Patients who are affected by cerebellar lesion fail to improve their performance with regard to presentation of a repetitive fixed sequence, due to the inability to recognize the sequence, as demonstrated by their normal performance when the sequence information is provided explicitly before the SRTT.

Thus, the hypothesis that cerebellar damage affects the ability to recognize serial events as a sequence is confirmed.

Cerebellar Damage Affects the Ability to Detect a Sequence Violation

We performed a somatosensory mismatch negativity (s-MMN) study in patients with unilateral cerebellar lesions [12]. s-MMN is generated by an automatic cortical change detection process that is activated by differences in current input from the mental representation of the standard input. In our experimental protocol, the deviant stimulus was the electrical stimulation of the fifth finger on the left hand, interspersed among frequent electrical stimulation of the left thumb.

Administering this task to subjects with unilateral cerebellar lesions allows us to test s-MMN in the same patient in the presence of cerebellar processing (the hemisphere contralateral to the spared hemicerebellum) or in its absence (the hemisphere contralateral to the damaged hemicerebellum). s-MMN responses to stimuli that were applied in an unexpected area (from the first to fifth finger) were recorded easily in the cortical hemisphere with the cerebellar input but were absent in the cortical hemisphere that was not reached by the cerebellar input.

Thus, the hypothesis that cerebellar damage affects the ability to detect a sequence violation is fulfilled.

Cerebellar Damage Affects the Ability to Reconstruct a Correct Sequence of Events Successfully

We developed a card-sequencing test to analyze the ability of patients who were affected by cerebellar lesions to reconstruct the correct sequence of a set of cards, specifically differentiated with regard to the material (verbal, spatial, or behavioral) that was to be sequenced [19]. The patients presented with clear cognitive sequencing impairments independently of the material that was to be processed. Further, there were notable findings when performances were grouped by lesion type (focal vs degenerative) and lesion side (right vs left). Whereas degenerative pathologies uniformly impaired performance throughout all modalities, focal cerebellar damage preferentially affected sequence reconstruction, with material-related specificity based on cerebellar lesion side, indicating that each cerebellar hemisphere is dominant in processing sequences for various domains.

Thus, the hypothesis that cerebellar damage affects the ability to reconstruct a correct sequence of events successfully is demonstrated.

Conclusion

The sequence detection hypothesis is proposed to represent the cerebellar specificity in the predictive brain and link the multifarious impairments that are reported in patients with cerebellar damage. This theoretical model has relevance to our understanding of the pathophysiological mechanisms in many clinical conditions, such as schizophrenia and autism, in which impairments in patterns of information processing and disruptions in error signal prediction have been advanced. In this framework, we are examining cerebellar function in the social cognition of patients with autism spectrum disorders (ASDs). Preliminary data indicate altered functional connectivity between the dentate nucleus and the “default mode network,” which mediates cognitive processes that are related to social deficits in ASDs. We hypothesize that corticocerebellar connectivity has a crucial role in determining the social behavior features in ASDs.

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Conflict of Interest The authors have no conflict of interest to declare.

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