PREDICTIVE MECHANISMS OF THE CEREBELLO-CEREBRAL NETWORKS

EDITED BY: Mario U. Manto and Aasef G. Shaikh
PUBLISHED IN: Frontiers in Cellular Neuroscience, Frontiers in Human Neuroscience and Frontiers in Integrative Neuroscience

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88963-405-7
DOI 10.3389/978-2-88963-405-7

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

PREDICTIVE MECHANISMS OF THE CEREBELLO-CEREBRAL NETWORKS

Topic Editors:
Mario U. Manto, CHU de Charleroi, University of Mons, Belgium
Aasef G. Shaikh, Case Western Reserve University, United States

Citation: Manto, M. U., Shaikh, A. G., eds. (2020). Predictive Mechanisms of the Cerebello-Cerebral Networks. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88963-405-7

Table of Contents

frontiers in Cellular Neuroscience

EDITORIAL
published: 10 December 2019
doi: 10.3389/fncel.2019.00549

Editorial: Predictive Mechanisms of the Cerebello-Cerebral Networks

Mario U. Manto[1] *and Aasef G. Shaikh*[2,3,4]*

[1] Department of Neurology, CHU-Charleroi, University of Mons, Mons, Belgium, [2] Movement Disorders Division, Neurological Institute, University Hospitals Cleveland, Cleveland, OH, United States, [3] Departments of Neurology and Biomedical Engineering, Case Western Reserve University, Cleveland, OH, United States, [4] Neurology Service and Daroff-Dell'Osso Ocular Motility Laboratory, Louis Stokes Cleveland Medical Center, Cleveland, OH, United States

Keywords: cerebellum, behavior, model, cognition, memory

Editorial on the Research Topic

Predictive Mechanisms of the Cerebello-Cerebral Networks

Two apparently distinct tasks, action and perception, are closely interlinked from the physiological and philosophical standpoints. In general terms, the action is comprised of interpreting, in motor context, what had been perceived, modulating the future motor commands to make the consequence (i.e., perception) favorable, and program the movement for seamless performance. Given their interdependence, nature has provisioned many strategies to facilitate flawless interaction between the action and perception.

One of the fundamental needs for the smooth action is precise movement and its online correction. The crystalline architecture of the cerebellum, its huge number of neurons and its multimodal connectivity had historically fascinated the neuroscience community by its highly responsive ability to adapt movements and correct errors. The cerebellum is famously known as the brain's learning machine. The advent of the concept of internal model in the 1970s by Franscis and Wonham promoted the idea that the cerebellum is not only the learning machine, but it also excels in machine learning (Francis and Wonham, 1976). The principle of internal model emphasizes that the motor system is controlled by the constant communication between the conveyer of action (i.e., the motor plant—the muscles and joints) and the executor of action (i.e., the controller—the cerebral cortex). The interaction between the conveyer and executer through multiple cerebello-cerebral running in parallel is facilitated and modulated by the intervening process, the internal models, that rely on the internal and external information. The motor command from the executor, when it reaches the conveyer, also provides a "carbon copy" to cerebellar cortex and nuclei, also known as the efference copy. Latter is utilized by the conceptual mechanism called the forward model that subsequently predicts the consequence (i.e., the predicted outcome). The predicted consequence is then utilized by the brain to refine the future commands. The fundamental question that remains is—how does the brain predict the future? Contemporary literature has suggested the fundamental role of the cerebellum in prediction and facilitating the forward model. In this facilitation the cerebellum utilizes the prior experiences and runs inbuilt algorithms, just like machine learning, to predict consequences that are then linked to the action. After three centuries of experimental and clinical experiments, cerebellar research has jumped from motor control to cognition, behavior, and evolution of homo sapiens. The frontiers topic "Predictive Mechanisms of the Cerebello-Cerebral Networks" highlights a unique collection of papers offering a succinct understanding of cerebellar predictive mechanisms of forward model utilizing various contexts and neurological systems.

In a comprehensive review Molinari and Masciullo summarizes how predictions utilizing the forward model are implemented in an important cerebellar function of determining right sequence

OPEN ACCESS

Edited and reviewed by:
Enrico Cherubini,
European Brain Research Institute, Italy

***Correspondence:**
Aasef G. Shaikh
aasefshaikh@gmail.com

Specialty section:
This article was submitted to Cellular Neurophysiology, a section of the journal Frontiers in Cellular Neuroscience

Received: *10 November 2019*
Accepted: *27 November 2019*
Published: *10 December 2019*

Citation:
Manto MU and Shaikh AG (2019) Editorial: Predictive Mechanisms of the Cerebello-Cerebral Networks. Front. Cell. Neurosci. 13:549. doi: 10.3389/fncel.2019.00549

of desired task. Complementing review by Popa and Ebner further emphasizes the mutually beneficial dependence of cognitive and motor tasks that are necessary for effective prediction.

Four original research papers describe the concept of forward model in mutually exclusive experiment models and neurological systems. In non-human primate ocular motor system Kim et al. discovered the neural correlate of the forward model vs. those of the motor commands by examining the neural responses during smooth pursuit eye movements. The authors conclude that predictive information is constructed from the motor command information and the construction of such predictive signal happens at the level of cerebellar cortex. The studies in ocular motor system in non-human primate was accompanied by the paper by Kakei et al. where physiological analysis of limb movements was performed in the ataxia victims. By utilizing a non-invasive computational method of analyzing the movement kinematics the authors identified two components of the arm movements—one encoding the velocity and position of the moving object while another the position control. The cerebellar patients had abnormal measure of the first component suggesting impaired accuracy of the predictive control.

The subsequent study by Sheu et al. switched gears, examining the role of cerebellar prediction and forward model in verbal working memory. The authors demonstrated a predictive process that provides the supervision for the cerebellar non-motor function, particularly predictive role in phonological loop in verbal working memory.

Clausi et al. focused on the role of cerebellum in the social cognition, on the "theory of mind"—the process involving the emotions, intentions, and beliefs. The authors found that the cerebellum may implicitly match the external information with the internal presentation, for example linking the facial expression and corresponding mental state. It was suggested that cerebellum constructs the internal models of the mental processes during social interaction where the prediction of sequential events helps anticipate the other person's behavior.

Finally, in a hypothesis paper, Vandervert extended the cerebellar role of prediction-based sequence detection on human evolution and relentless advancement of the culture. This is a particularly challenging concept with social and cultural implications for humans. Cerebellum appears as a highly modifiable hard disk refining behavior (motor and social) to adapt to a constantly changing world. Physiology and philosophy are intimately linked again. Cerebellar sequencing detection participates in the evolution of culture, language and stone-tool technology, landmarks of Homo sapiens.

Ultimately this Research Topic heightened our understanding of the well-rounded application of the cerebro-cerebellar predictive mechanism featuring the forward model. The consequences of malfunctioning forward model can be grave, and they can affect a wide range of systems from motor functioning to perception, cognition, and behavior. Specific targeted approaches to rehabilitate the predictive mechanisms in the diseased states, either by means of drugs, non-invasive neuromodulation or combinations are needed. The contribution of the cerebellum in numerous brain functions is growingly recognized, with implications in numerous prevalent neurological and neuropsychiatric conditions including essential tremor, Parkinson's disease, multiple sclerosis, autism spectrum disorders and schizophrenia (Miterko et al., 2019). We predict that the future of cerebellar research will just keep spreading.

AUTHOR CONTRIBUTIONS

MM and AS interacted and validated the final version of the manuscript.

ACKNOWLEDGMENTS

We would like to thank our friendly and collaborative community of cerebellar scientists for all they do to move the field forward.

REFERENCES

Francis, B. A., and Wonham, W. M. (1976). The internal model principle of control theory. *Automatica* 12, 457–465.

Miterko, L. N., Baker, K. B., Beckinghausen, J., Bradnam, L. V., Cheng, M. Y., Cooperrider, J, et al. (2019). Consensus paper: experimental neurostimulation of the cerebellum. *Cerebellum* 18, 1064–1097. doi: 10.1007/s12311-019-01041-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cellular Neuroscience

HYPOTHESIS AND THEORY
published: 13 November 2018
doi: 10.3389/fncel.2018.00408

How Prediction Based on Sequence Detection in the Cerebellum Led to the Origins of Stone Tools, Language, and Culture and, Thereby, to the Rise of Homo *sapiens*

*Larry Vandervert**

American Nonlinear Systems, Spokane, WA, United States

This article extends Leiner et al.'s watershed position that cerebellar mechanisms played prominent roles in the evolution of the manipulation and refinement of ideas and language. First it is shown how cerebellar mechanism of sequence-detection may lead to the foundational learning of a predictive working memory in the infant. Second, it is argued how this same cerebellar mechanism may have led to the adaptive selection toward the progressively predictive phonological loop in the evolution of working memory of pre-humans. Within these contexts, cerebellar sequence detection is then applied to an analysis of leading anthropologists Stout and Hecht's cerebral cortex-based explanation of the evolution of culture and language through the repetitious rigors of stone-tool knapping. It is argued that Stout and Hecht's focus on the roles of areas of the brain's cerebral cortex is seriously lacking, because it can be readily shown that cerebellar sequence detection importantly (perhaps predominantly) provides more fundamental explanations for the origins of culture and language. It is shown that the cerebellum does this in the following ways: (1) through prediction-enhancing silent speech in working memory, (2) through prediction in observational learning, and (3) through prediction leading to accuracy in stone-tool knapping. It is concluded, in agreement with Leiner et al. that the more recently proposed mechanism of cerebellar sequence-detection has played a prominent role in the evolution of culture, language, and stone-tool technology, the earmarks of Homo sapiens. It is further concluded that through these same mechanisms the cerebellum continues to play a prominent role in the relentless advancement of culture.

Keywords: acheulean artifacts, cerebellum, cerebellar internal models, cerebellar sequence detection, language evolution, phonological loop, working memory

OPEN ACCESS

Edited by:
Mario U. Manto,
University of Mons, Belgium

Reviewed by:
Frank Van Overwalle,
Vrije Universiteit Brussel, Belgium
Maria Leggio,
Università degli Studi di Roma La Sapienza, Italy

***Correspondence:**
Larry Vandervert
lvandervert@aol.com

Received: *09 September 2018*
Accepted: *22 October 2018*
Published: *13 November 2018*

Citation:
Vandervert L (2018) How Prediction Based on Sequence Detection in the Cerebellum Led to the Origins of Stone Tools, Language, and Culture and, Thereby, to the Rise of Homo sapiens. Front. Cell. Neurosci. 12:408. doi: 10.3389/fncel.2018.00408

INTRODUCTION

A Monumental Neuroscience Breakthrough

Some three decades ago, Leiner et al. (1986, 1989, 1991) proposed that just as the cerebellum contributes to the refinement and automaticity of motor skills, the cerebellum's connections to the prefrontal cortex and Broca's language areas (areas 44 and 45) contribute to planning and language.

In essence, they proposed that, operating below the level of conscious awareness, the cerebellum contributed to increased levels of thought in the following way:

> Cerebellar connections to Broca's area may not only increase the speed and skill of speaking but also confer other benefits on humans. Because Broca's area communicates with other association areas in the cerebral cortex, the cerebellar signals to Broca's area could increase the speed and skill of such intracortical communication. These communications between cortical association areas are said to comprise the language of thought (Luria, 1980). Therefore, the processes of rationale thought may be performed with increased speed and skill in the human brain as a consequence of its enlarged cerebro-cerebellar connections [notably during the last million years of human evolution] (1989, p. 1006).

In line with Leiner et al.'s foregoing proposal on the mechanism of thought, Ito (1997, 2008) described how through repetition not only does the cerebellum automate skills at their high levels but is behind both the phylogenetic and ontogenetic origins of thought in working memory.

The evidence that Leiner et al. (1986, 1989, 1991) provided for their foregoing breakthrough hypothesis that cerebellum assisted the association cortex in the skillful manipulation of thought was massive and solid. Accordingly, their watershed proposal spurred a huge amount of brain imaging research on the cerebellum's contributions to the motor, cognitive, and affective functions, and, specifically, the cerebellum's contributions to what they referred to as the "skillful manipulation of ideas" (1986, p. 444). Over the last three decades, Leiner et al.'s above—quoted proposal has been broadly confirmed and further extended (Ito, 1993, 1997; Akshoomoff et al., 1997; Desmond and Fiez, 1998; Dum and Strick, 2003; Strick et al., 2009; Balsters et al., 2010, 2013; Imamizu and Kawato, 2012; Marvel and Desmond, 2012; Stoodley et al., 2012; Bostan et al., 2013; Schmahmann, 2013; Leggio and Molinari, 2015; Moberget and Ivry, 2016; Vandervert, 2016, 2017a,b; Adamaszek et al., 2017).

Balsters et al. (2010, 2013) and Bostan et al. (2013) are of particularly strong support of Leiner et al. (1986, 1989, 1991) in finding that (1) cerebro-cerebellar connections between the prefrontal cortex and the lateral cerebellum have grown more in volume in recent evolution than the rest of the cerebro-cerebellar connections, and (2) that, in these two-way connections, the cerebellum contributes skill routines and strategies for both first—and second-order rule-governed information processing, the highest levels of idea manipulation.

Nearly a decade after (Leiner et al.'s, 1989) proposal that the cerebellum contributed to the process of rational thought, Akshoomoff et al. (1997) convincingly argued that the cerebellum contributes to the manipulation of such mental skills through the control of *attention*. The cerebellum's role in the control of attention in both motor and cognitive processes has been widely confirmed (e.g., Kellermann et al., 2012; Stoodley et al., 2012; Brissenden et al., 2015, 2017). Akshoomoff et al. proposed that attentional control (among other processes) is learned in the cerebellum in the following manner:

> The cerebellum is a master computational system that adjusts responsiveness [toward optimization] in a variety of networks to obtain a prescribed goal [this would include the optimization of *attentional control* in the central executive in Baddeley (1992) working memory model] (Courchesne et al., 1994; Courchesne, 1995). These networks include those thought to be involved in declarative memory, working memory, attention, arousal, affect, language, speech, homeostasis, and sensory modulation as well as motor control. This may require the cerebellum to implement a succession of precisely timed and selected changes in the pattern or level of neural activity in these diverse networks. We hypothesized that the cerebellum does this by *encoding ("learning") temporally ordered sequences* [italics added] of multi-dimensional information about external and internal events (effector, sensory, affective, mental, autonomic), and, as similar sequences of external and internal events unfold, they elicit a readout of the full sequence in advance of the real-time events [this readout is a *prediction*]. *This readout is sent to and alters, in advance [italics added], the state of each motor, sensory, autonomic, attentional, memory, or affective system which, according to the previous "learning" of this sequence, will soon be actively involved in the current real-time events* [italics added]. So, in contrast to conscious, longer time-scale anticipatory processes mediated by cerebral systems, output of the cerebellum provides moment-to-moment, unconscious, very short time-scale, anticipatory information (p. 592–593).

In cerebellum studies, of the above-described "encoding *("learning") temporally ordered sequences* [italics added] of multi-dimensional information about external and internal events" is referred to as the learning of cerebellar *internal models*[1].

Akshoomoff et al. (1997) found the cerebellum to be important in *shifting* and *orienting* attention in patients with cerebellar damage and, in normal adults, they found the cerebellum to be important in *focusing* and *shifting* attention. Overall they concluded that, the cerebellum is important in optimizing the quality of sensory information necessary to the coordination of the direction of selective attention (shifting, distribution, orienting) leading to prediction and anticipation of future states of affairs.

In the March Toward *Homo sapiens*, the Cerebellum Fine-Tuned the Brain to a Cause-and-Effect World

Since, according the Akshoomoff et al. (1997), the cerebellum predicts sequences of future events which are then sent to ("alters in advance"), for example, working memory, by definition cerebellar internal models mirror *cause-and-effect relationships* pertaining to the brain's modeling of internal and external

[1] Ito (2008, Glossary) defines internal models as follows: "Internal model: a dummy [in the cerebellum] of a body part or a mental representation in the cerebral cortex. It is encoded in the neuronal circuitry of the cerebellum and mimics essential properties of a body part or a mental representation for control [of movement or thought]." In other words, cerebellar internal models are models of the *internal* world going on in the cerebral cortex. The cerebral cortex on the other hand forms models of the relationships of the body to the *external* world and mental models of those relationships in, for example, working memory. Ito (2008) provides an excellent discussion of the roles of cerebellar internal models in a variety of contexts.

events. That is, our knowledge of cause-and-effect relationships is ultimately based not primarily on functions of the cerebral cortex, but on *simulations in the cerebellum* of those events as to how they fit progressively more refined states of goal attainment as conceived in working memory in the cerebral cortex.

It may seem that the brain's cerebral cortex would have its own, perhaps innate, knowledge of cause-and-effect relationships. However, Vandervert (2015, 2016, 2017a) has combined extensive cerebellum research with infant studies that, together, describe how beginning in infancy the cerebellum likely played the predominant role in establishing the foundation of cause-and-effect relationships via its computation of *sequence detection* (Akshoomoff et al., 1997; Leggio and Molinari, 2015) of objects and the body moving in space. He argued that this process provided the foundational cause-and-effect basis for the infant's visual-spatial working memory. As will be shown later in this article, this model of the cerebellar origin of cause-and-effect will become critically important to a new way to understand how the predictive and anticipatory roles of the cerebellum were predominant in the origins of stone-tool technology, language and culture and, thereby, the origins of *Homo sapiens*.

Strongly substantiating (Akshoomoff et al., 1997) foregoing cerebellar mechanism of sequence detection, Leggio and Molinari (2015) independently proposed that the "operational mode" of the cerebellum is sequence detection leading to prediction. It is well worth quoting Leggio and Molinari's sequence detection position, as it strongly reinforces the role of cerebellar *internal models* to specifically include the prediction of future events via higher-order cognitive processes (working memory):

> According to this hypothesis, the cerebellum detects and *simulates* [italics added] 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* [italics added] or social cognition]. The simulation allows internal models [in the cerebellum] to be created that can be used to make predictions about *future events* (italics added) that involve any component, such as the *body, other persons, and the environment* [italics added] (p. 36).

Working Memory

Working memory has been described by Baddeley (1992) as a multi-component "brain system that provides temporary storage and manipulation for complex cognitive tasks such as language comprehension, learning, and reasoning" [abstract]. Baddeley divided working memory into the following three subcomponents: (1) an attention-controlling system which serves as a "central executive," (2) a visual-spatial sketchpad which manipulates visual images within an ongoing flow of visual-spatial experience, and (3) a phonological loop which both *stores* and *rehearses* speech-based information. In addition, Cowan (2014) defined working memory as, "the small amount of information that can be held in mind and used in the execution of cognitive tasks" (p. 197). In that same article Cowan also described working memory as *the cauldron of concept formation* and further argued that concepts are bound together through executive attention in working memory.

Within this overall framework of the components and conceptual formation in working memory, Leggio and Molinari (2015) cerebellar internal model simulations of the "cognitive elaboration" of higher-order cognitive processes indicates that the cerebellum refines working memory through sequence detection. This strongly supports Leiner et al. (1986) earlier proposal that the cerebellum contributes to the "skillful manipulation of ideas," which itself is a reasonable definition of working memory. Vandervert (2015, 2016) suggested that Akshoomoff et al. (1997) and Leggio and Molinari (2015) complementary models of sequence detection place the cerebellum as the unconscious basis of prediction and anticipation in the origin and advancement of human socialization, language, and thought in working memory.

Purpose

Within the foregoing framework of cerebellar sequence detection leading to prediction and anticipation of future states of affairs, it is the purpose of this article to make the case that the last million years of natural selection toward the three- to fourfold increase in the size of the cerebellum, especially its cognitive areas, was the key to the rise of *Homo sapiens*. It will be argued that the cerebellum played the *predominant* role in the rise of *Homo sapiens* via the following two homologically[2] linked research traditions. *First*, the cerebellum-driven development of attentional control of cause-and-effect relationships and thus prediction in the working memory of the infant will be described. *Second*, it will be argued that increases in this same cerebellum-driven development of attentional control in working memory increased early human capacities for the mental and dexterous manipulation of these cause-and-effect relationships which undergirded the evolution of the advanced stone-tool technology and language of *Homo sapiens* (Vandervert, 2011, 2015, 2016, 2017b).

The Prominent Role of the Cerebellum in the Foundational Establishment of Attentional Control in the Working Memory of the Infant

The most detailed behavioral research in which the infant's initial foundations of the central executive (attentional control) and conceptual processes of working memory can be clearly revealed is that of Mandler (1992a,b, 2008, 2010, 2012). Mandler's model of infant mental development is presented in this article's context of cerebellar prediction and anticipation, because to an astonishing degree it can be directly mapped onto (1) the

[2]The definition of *homology* here follows that of Greenfield (1991):
In developmental psychology homology refers to common structural origins in the ontogeny of individual members of the species.… Whereas phylogenetic homology is defined as *descent from a common antecedent structure* [italics added] within an ancestral species, ontogenetic homology can be defined as descent from a common antecedent structure within the same organism (p. 533).

unconscious learning of internal models in the cerebellum, and (2) the foundational development of attention-driven visual-spatial working memory that jibes with Baddeley (1992) model.

Mandler proposed that the infant repeatedly "notices" (pays attention to) specific aspects of its own bodily movement in relation to objects moving in the environment (the relationships among objects, space, and time), and that these movement parameters are "*distilled*" or "*condensed*" (1992a) into *conceptual primitives*. The infant uses these conceptual primitives to begin to understand and negotiate its environment (see **Figure 1**). (By "primitive" Mandler meant foundational, and did not mean unstructured, but structured).

Mandler (2012) proposed that this "distillation" process in the infant is the result of the infant's unconscious, *innately-initiated* and highly repetitive *perceptual meaning analysis* (PMA): "PMA is an attentional mechanism dedicated to simplifying spatiotemporal information. This innately driven "watching" on the part of the infant is activated by attention to objects, especially when they move, thus emphasizing the paths that objects take through space," (p. 426). The infant's PMA doesn't simply "look" at the passing stimulus array, but repetitively "notices" and encodes aspects related to movement (Mandler, 1992b). Through this repetitive process of the noticing of movement and the distillation of the parameters of those movements, the infant derives the conceptual primitives consisting of animacy, causality, and agency (**Figure 1**). These conceptual primitives represent cause-and-effect relationships and thus permit the infant to predict and anticipate the effects of its own bodily movement in relation to objects moving in space.

Since the cerebellum encodes attentional (executive) patterns related to all repetitive motor, perceptual and working memory processes Ito (1997, 2008), Vandervert (2015, 2017a,b) proposed that these highly repetitive mechanisms of attention and distillation in Mandler's (1992b); Mandler (2012) perceptual meaning analysis in fact describe the process of cerebellar sequence detection toward *predictive* attentional control proposed earlier in this article by Akshoomoff et al. (1997) and Leggio and Molinari (2015). Since, within Vandervert's proposal, Mandler's conceptual primitives (**Figure 1**) are the result of cerebellar internal models of the attentional control of visual-spatial (spatiotemporal) information, they, within Baddeley's (1992) scheme, constitute the foundations of a *predictive* visual-spatial working memory. Accordingly, this means the infant's foundational visual-spatial working memory is adaptive because, as Akshoomoff et al. argue, *it is able to predict future states of affairs before they happen.* Indeed, in agreement with this position, Baddeley and Andrade (2000) argued that the key evolutionary advantage of bringing increasingly detailed memory into the current cognition in the form of working memory was/is prediction:

> Baddeley (1993, 1998, chap. 18) has proposed that working memory plays a central role in the processes underlying consciousness, and that it has evolved as a means of allowing the organism to consider simultaneously a range of sources of information about the world, and uses these processes to set up mental models that facilitate the *prediction* [italics added] of events and the planning of action. Consider, for example, the task of a hunter-gatherer who recollects that as this time of year a tree bears fruit near a waterfall in potentially hostile territory. In order to reach the tree safely, he may need to use remembered spatial cues, together with the sound of the waterfall and the shape of the tree, while listening and looking for signs of potential enemies. A dynamic image that is capable of representing these varied sensory features simultaneously is likely to provide a planning aid of considerable evolutionary value (p. 128).

Prediction Intensifies With the Evolution of Working Memory Toward Acquisition of the Phonological Loop

Within a pre-human scenario of stone-tool evolution, Vandervert (2011) offered a somewhat detailed explanation of how, as in the infant, cerebellar *sequence detection* in early Homo might have led to the *decomposition and re-organization* (Imamizu et al., 2007) of visual-spatial working memory *with* accompanying vocalizations and, thereby, more refined levels of prediction. He argued that this cerebellar decomposition and re-organization within working memory provided early Homo the powerful selective advantage of increased detail in observable cause-and-effect relationships pertaining not only to stone tools themselves but to social interactions related to stone-tool making and use. Thus, executive control (attentional control) in working memory gained the capacity to focus on more detailed cause-and-effect aspects of the physical and social environments. Vandervert argued that this cerebellar decomposition and re-organization of existing visual-spatial working memory with vocalizations provided the adaptive selection basis for the phonological loop of working memory, the second slave component of working memory proposed by Baddeley (1992). Vandervert further argued that this adaptive selection of the phonological loop parallels Mandler's (1992b, 2008) position that the infant's conceptual primitives (**Figure 1**) provide the bases for both simple inferential and analogical thought and the conceptual basis for the acquisition of the relational aspects of language. Via the acquisition of the adaptive phonological loop in working memory, then, more detailed cause-and-effect relationships could be mentally held and manipulated in working memory toward more refined predictions of future states, future states that became the framework for the adaptive origins of culture and, then, the relentless advance of culture (Vandervert, 2011, 2016). We will return to Vandervert (2011) pre-human stone-tool scenario below.

Broader Supportive Evidence for the Development of a Visual-Spatial Working Memory in the Infant and a Transition to Phonological Working Memory in Early Childhood

In overall support of Vandervert's (2015, 2016, 2017a,b) interpretation of Mandler (1992b, 2008, 2012) infant studies, it

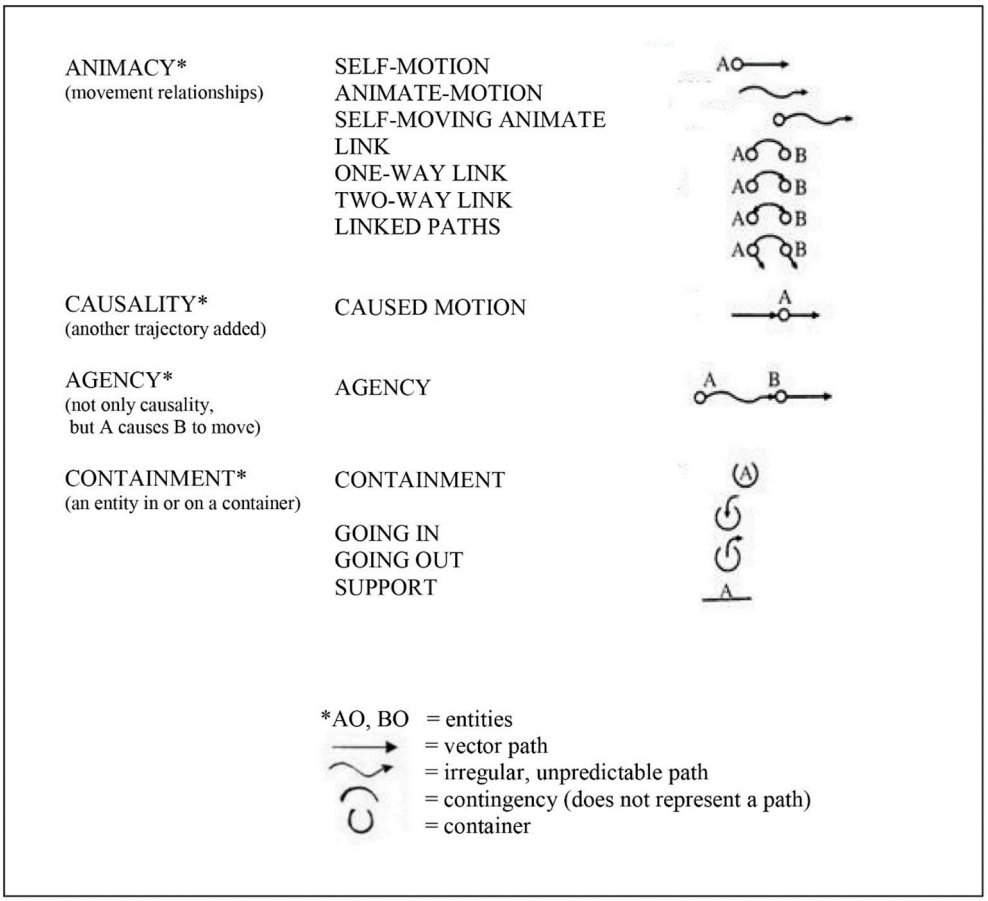

FIGURE 1 | Mandler (1992a); Mandler's (1992b, 2008); Mandler (2012)) conceptual primitives—collectively, the infant's unconscious "primitive physics." That is, the conceptual primitives represent the meaning of images and thereby establish the foundations of cause-and-effect relationships in the infant's visual-spatial working memory, notably the depicted categories of animacy, causality, and agency. It is argued that these conceptual primitives depict optimized predictive/anticipatory cerebellar internal models. It is not suggested that the conceptual primitives are constructed in the brain in this graphic form, but rather in the form of cerebellar microcomplexes as described by Ito (1997, 2008). Figure prepared by Kimberly Weathers-Moe Illustrations (kweathers10@mywhitworth.edu).

is well established that the infant acquires appreciable visual-spatial working memory, especially between ages 6–12 months (Pelphrey et al., 2004; Reznick et al., 2004; Diamond et al., 2005). Moreover, there is strong evidence that, as Vandervert (2011) proposed, the cerebellum continues to play a predominant role in working memory development as the infant transitions from visual-spatial working memory to an added phonological component as the child develops. For example, Knickmeyer et al. (2008) argued that the 240% increase in the size of the cerebellum in the first year suggested that the cerebellum provides precisely the basis for such later development in the cerebral cortex:

> Because the cerebellum is critically involved in motor coordination and balance (Bastian and Thach, 2002) the striking cerebellar growth may underpin the rapid motor developments of infancy. The cerebellum has also been implicated in a plethora of other cognitive abilities including planning, set-shifting, language abilities, abstract reasoning, *working memory* [italics added], and *visual-spatial organization* [italics added] (Schmahmann and Sherman, 1998). Given that "cognitive" regions of the cerebellum have reciprocal projections with non-primary frontal, parietal, and occipital association cortex (Thach, 1996), *the extremely rapid growth of the cerebellum in the first year may be a prerequisite for specific aspects of later cortical development* [italics added] (p. 12180).

Short et al. (2013) found significant associations between infants' (12 months of age) visual-spatial working memory and white matter tracts that connect brain regions known to support working memory in older children and adults. Within the context of Knickmeyer et al.'s (2008) above proposal that "the extremely rapid growth of the cerebellum in the first year may be a prerequisite for specific aspects of later cortical development," Short et al. can be seen as strongly supporting the idea that the cerebellum may be a prerequisite for specific later cortical development [and thereby supported Vandervert (2011) proposal that the cerebellum continues to play a role in the transition to phonological working memory].

The Evolution of the Cerebellum's Dentate Nucleus, a Powerful Clue to the Cerebellum's Important Predictive Role in Working Memory

Directly in this regard, it has been suggested that the evolutionary division of the cerebellum's dentate nucleus into motor and cognitive portions played a key role in the phylogenetic evolution of silent speech in within working memory (Marvel and Desmond, 2010a). The dentate nucleus of the cerebellum transmits learned movement and cognitive control models to the cerebral cortex (Leiner et al., 1986; Bostan et al., 2013). The dentate is divided into an older dorsal (motor) portion and a more newly evolved ventral portion (cognitive). Leiner et al. (1986) and Marvel and Desmond (2010a,b) provided strong evidence that the newer ventral dentate (cognitive output) was naturally selected *from* the evolutionarily older dorsal dentate (motor loop) as the cerebellar cortex and frontal areas of cerebral cortex expanded over the last million years. In humans, the cerebellum's ventral dentate is twice as large as the dorsal dentate and is proportionately larger than that of the great apes (Leiner et al., 1986; Bostan et al., 2013). The ventral dentate of the cerebellum outputs to the prefrontal, parietal and temporal areas of the cerebral cortex (Sokolov et al., 2017), and Marvel and Desmond (2010a) found that the dentate output served prefrontal and parietal language and executive working memory functions.

The cerebellum's dentate nucleus, then, appears to have evolved within the natural selection context of the adaptive advantage of a working memory able to quickly manipulate complex movement and mental skills in highly coordinated ways (Marvel and Desmond, 2010a). Based on extensive research studies, Bostan et al. (2013) argued that the "signal from the dentate to the prefrontal and posterior parietal areas of the cortex is as important to their function as the signal the nucleus sends to motor areas of the cerebral cortex" (p. 3). Thus, within the coordinated evolution of the cerebellum's dentate nucleus (from dorsal to dorsal-ventral) along with the parallel evolution of the prefrontal and parietal association areas of the cerebral cortex, the evidence strongly supports the idea that the rapid manipulation of mental skills evolved seamlessly within the context of the rapid manipulation of motor skills. It is suggested with Marvel and Desmond (2010a) that this certainly included the transition from the strongly motor-driven visual-spatial working memory (mostly dorsal dentate) toward the more cognitively driven phonological (silent speech-related) component of working memory (mostly ventral dentate) which would guide those motor systems in increasingly adaptive ways.

Thus Mandler's (1992b, 2008) idea that later, consciously accessible language concepts are built from the infant's visual-spatial conceptual primitives (**Figure 1**) and Vandervert's (2015, 2016, 2017a,b) interpretation that this sequence actually represents the foundations of working memory squares well with Knickmeyer et al. (2008) suggestion that the unparalleled growth of the cerebellum in infancy is a prerequisite for the later cognitive development of specific regions of the cerebral cortex. Likewise, in the next section of this article it will be argued that the unparalleled expansion of the cerebellum over the last million years was an undergirding requisite for cognitive developments of specific regions of the cerebral cortex related to a co-evolution of stone tool technologies and language.

How Language Might Have Evolved From Predictive Decompositions and Blends of Visual-Spatial Working Memory With Vocalizations Within the Co-evolving Context of Tool Use

Vandervert (2011, 2016) followed directly in the path of Mandler's (1992b, 2004; 2008) proposal that language develops/evolved from the foundational spatiotemporal primitive concepts shown in **Figure 1**. Vandervert argued that language was selected from vocalizations that were adaptively *blended* (Imamizu et al., 2007) with progressively more intricate visual-spatial image sequences required in the repetitive, structured sequences of tool use. Vandervert (2011) argued that in pre-humans and early humans, new environmental challenges set in motion the decomposition and re-organization of cerebellar internal models (Flanagan et al., 1999; Nakano et al., 2002; Imamizu et al., 2007; Imamizu and Kawato, 2009) of patterns of attentional focus on visual-spatial images and linked vocalization patterns related to stone-tool manipulation. These newly decomposed visual-spatial images and their linked sound patterns were re-organized or *blended* in the cerebral cortex (Imamizu et al., 2007) and error-corrected toward optimization in the cerebellum to meet the requirements of the new, challenging situation (Ito, 1997, 2008; Imamizu and Kawato, 2009).

A simple illustration of the cerebellar mechanisms of sequence detection, decomposition and blending that shows a movement-by-movement breakdown of the classic stone-tool sequences used by the pre-human example of capuchin monkeys was provided in Vandervert (2011). See **Figure 2**. This scenario draws directly from the findings of the extensive capuchin field research of Dorothy Fragaszy et al. (e.g., Fragaszy et al., 2013, 2017; Visalberghi et al., 2013; Mangalam et al., 2018). While the capuchin monkey is not in direct line with early Homo, several who have extensively studied, for example, the capuchin's (1) spontaneous stone tool selection, (2) bipedal stone transport, (3) highly refined manipulation of stone tools in nut-cracking, and (4) attention to the dynamics of stone hammer throw impact (Liu et al., 2011 have argued that the capuchin is an ideal model that can provide insights into the anthropological study of stone-tool use (Haslam et al., 2017. This is precisely the vein in which a cerebellum-focused analysis of the capuchin's use of stone tools is presented here.

In **Figure 2**, the capuchin's sequence of actions (A) begins with the internal mental representation (I) or goal involving stone-tool use on the left. The sequence of actions then progresses in a series of "if no—repeat" decisions in the capuchin's working memory. The resulting orderly action and decision-making defines a *syntax* of actions, as does syntax in speech. This syntax in

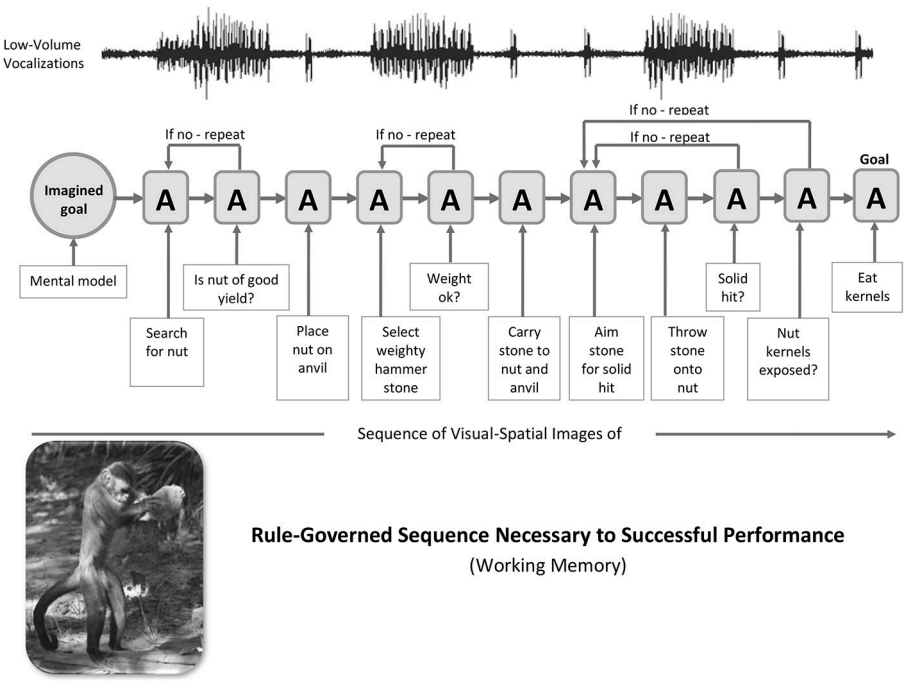

FIGURE 2 | Capuchin Stone-Tool Use: A generalized sequence of stone-tool nut-cracking actions (A) driven by an imagined goal in visual-spatial working memory in capuchins. The stone-tool actions of the capuchin serve as a pre-human model for hand axe manufacture and use by early hominins between a million and a half and 150,000 years ago. Following the internal representation (imagined goal) of a prospective goal (I), the orderly series of actions (A) is mediated by cerebro-cerebellar loops. It is argued that the cerebro-cerebellar decomposition and blending of visual and vocal components of skill routines and strategies across the series of "If no—repeat" sub-routines of actions led to syntax (including the force component, i.e., verb forms) in working memory's phonological loop during language evolution. Photo of capuchin engaged in nut-cracking (lower left) obtained through Dr. Dorothy Fragaszy, Professor and Chair, Behavioral and Brain Sciences Program, University of Georgia and printed with permission of Barth W. Wright, EthoCebus Project (http://www.ip.usp.br/site/ethocebus). Figure prepared by Kimberly Weathers-Moe Illustrations (kweathers10@mywhitworth.edu).

capuchins is suggested to be the precise equivalent of the "abstract sequential operations" found to involve the collaboration of the cerebellum and the frontal and parietal areas of the cerebral cortex in monkeys (Obayashi et al., 2007). In Baddeley's (1992) model this mental processing in the capuchin would be that of visual-spatial working memory.

Vocalizations Paralleling the Nut-Cracking Sequence: The Earliest Sub-vocal Moments of the Phonological Loop

Dorothy Fragaszy, whose extensive research on capuchins is cited above, has indicated that capuchins in general "comment" on their manipulative activities with low-volume vocalizations (personal communication, 2011). Running across the top of the action sequence in **Figure 2** is a line representing those ongoing low-volume vocalizations.

It is suggested that the vocalizations seen in **Figure 2** accompany stone-tool use, because they serve a similar enhancing purpose for capuchins as does sub-vocal speech (silently talking to one's self) during intensive human tasks, especially those task intensively involving the hands. That is, it is hypothesized that sub-vocalization in capuchins helps to maintain cognitive focus on the immediate task at hand. This idea is supported by Marvel and Desmond (2010a) studies on how sub-vocal speech mechanisms enhance working memory in humans; they concluded as follows:

> …the cerebellum enhances working memory by supporting inner speech mechanisms. This capability emerged from overt speech and motor systems as an evolutionarily adaptive way to boost cognitive processes that rely on working memory, such as language acquisition (p. 277).

In accordance with Akshoomoff et al. (1997) and Leggio and Molinari (2015) cerebellar sequence detection, the evolutionary adaptive advantage of low volume vocalization among capuchins would be that it enhanced attentional control in visual-spatial working memory that improved the prediction of successful goal attainment.

In summary here it is suggested that the cerebellar mechanisms discussed (decomposition and blending) are predominant in the processes shown in **Figure 2**. This predominant role of the cerebellum is supported by the foregoing evidence that the decomposition of vocalizations toward more articulated attention-sustaining sub-vocalization, and thereby enhanced prediction (Leggio and Molinari, 2015) would occur only through the learning of cerebellar internal models. These internal models would only then be sent to the cerebral cortex for possible blending with internal models of

likewise decomposed visual-spatial images and thus the earliest evolutionary development of the phonological loop (Vandervert, 2011).

The foregoing scenario represents an emerging primitive physics as it may have occurred across generations of pre- and early humans. That is, the cerebro-cerebellar decomposition and blending processes would have resulted in the gradual emergence of a working memory where composites of images and vocalizations representing new cause-and-effect relationships could be quickly logged into long-term memory using sub-vocal or vocal tags. These phonological tags could subsequently be used to rapidly access the cognitive representations of cause-and-effect relationships from long-term memory to meet a variety of fast-moving environmental situations. The foregoing scenario provides an explanation for Baddeley et al.'s (1998) conclusion that the phonological loop selectively evolved due to its adaptive advantage of temporarily storing unfamiliar sound patterns while more permanent pathways were being constructed in long-term memory in the acquisition of language. The evolution of the phonological loop within the pre-existing visual-spatial working memory (and long-term memory) enabled the social sharing of detailed cause-and-effect relationships as well as the silent sub-vocal manipulation of ideas in planning, including the envisioning and manufacture of progressively advanced stone-tool technology.

From Capuchins to Homo *sapiens*

To illustrate this cerebellar decomposition and blending process in the evolution of greater prediction capacity of the phonological loop among Homo *sapiens*, I refer to leading anthropologists (Stout and Hecht, 2017) extensive research on how the cognitive, procedural and social complexities of stone-tool knapping, notably beginning with the complex, skill-intensive Late Acheulean period beginning 700 thousand years ago, might have led to the rise of cumulative culture. Stout and Hecht's robust research offers an ideal backdrop within which to illustrate many details of Leiner et al.'s (1986, 1989) last one million years of cerebellum evolution, including the cerebellum's prominent role in the accumulation of culture (Vandervert, 2016). Stout and Hecht's account of cultural evolution within stone-tool technology will be discussed in some detail, including the cerebellar mechanisms of both cultural origin and advancement as proposed by Vandervert (2016).

Repetitive Complex Skill-Intensive Stone-Tool Knapping: The Last 700 Thousand Years

The central basis for Stout and Hecht's (2017) Acheulean procedural and social complexities argument for cumulative culture is seen is their following account of the rigorous technical and social requirements of stone-tool knapping:

> Knapping is a "reductive" technology involving the sequential detachment of flakes from a stone core using precise ballistic strikes with a handheld hammer (typically stone, bone, or antler) to initiate *controlled and predictable* [italics added] fracture. This means that small errors in strike execution can have catastrophic, irreversible effects. Experiments by Bril et al. have shown that fracture prediction and control is a demanding perceptual-motor skill reliably expressed only in expert knappers (Greenfield, 1991; Haslam et al., 2017). Building on this work, Stout and et al. (Ito, 1993; Higuchi, 2007; Imamizu and Kawato, 2012) found that even 22 mo ($\bar{x} = 167$ h) of knapping training produced relatively little evidence of perceptual-motor improvement, in contrast to clear gains in conceptual understanding (p. 7862).

In accordance with Akshoomoff et al. (1997) and Leggio and Molinari (2015) cited earlier, this highly precise, long-term, repetitive knapping would be mediated first and foremost through cerebellar sequence detection and error-correction toward attentional control and prediction, toward "controlled and predictable fracture." Stout and Hecht (2017) continue directly on:

> The key bottleneck in the social reproduction of knapping is thus the extended practice required to achieve perceptual-motor competence. This requires mastery of relationships, for example between the force and location of the strike and the morphology, positioning, and support of the core (Ito, 1997, 2007; Haslam et al., 2017), that are not perceptually available to naïve observers and cannot be directly communicated as semantic knowledge. Attempts to implement semantic knowledge of knapping strategies before perceptual motor skill development are ineffective at best (Ito, 2008, 2011), and such knowledge decays rapidly along knapping transmission chains when practice time is limited, even if explicit verbal teaching is allowed (Gallese, 2005). For *observational learning* [italics added], the challenge is to translate visual and auditory information of another's actions to appropriate motor commands for one's own body. This may be accomplished by linking the observed behavior with preexisting internal models [authors are here referring to models in the cerebral cortex, not in the cerebellum] of one's own body and actions through associative learning and stimulus generalization (Knickmeyer et al., 2008; Leggio and Molinari, 2015)….These learning challenges call for an interactive approach that alternates social-learning opportunities (observation, instruction) with motivated individual practice (Leiner et al., 1991), as commonly seen in coaching and apprenticeship practice (p. 7862–7863).

The first paragraph in the above quote describes the *repetitive*, fine *sequential* motor, and perceptual-cognitive requirements of stone-tool knapping, along with the integrally-related absolutely critical strike *prediction*/strike *error-correction* cycle. The second above quoted paragraph makes the key points of (1) "the challenge is to translate visual and auditory information of another's actions to appropriate motor commands for one's own body knapping mastery," and (2) the therefore necessity of *social apprenticing* requirements for what the authors argue is necessary to the extreme rigors of complex knapping. Both of these points are well-reasoned and well-summarized, and it is agreed they are largely behind the evolutionary origin of culture and the subsequent ongoing evolution of culture. However, what brain mechanisms are actually involved in these processes, and how do they actually come about?

The More Complete Story Behind the Last Million to 700,000 Years of Stone-Tool Evolution

Stout and Hecht (2017) placed the foregoing highly skilled stone-tool knapping processes exclusively in areas of the cerebral cortex, predominantly in the parietal, temporal and prefrontal areas. There is no doubt that these brain areas are importantly involved in the skilled tool knapping and manipulation description they provided. However, and this is a game-changing however, it is quite straight-forward to show that Stout and Hecht's account is seriously lacking as to the prominent contributions of mechanisms of the cerebellum in the following highly salient ways: (1) the cerebellum is involved in all complex movement and mental skill learning (Ito, 1997, 2008), (2) the cerebellum orchestrates the decomposition of and participates in the re-organization (blending) of these skills toward new skills (Baddeley, 1992; Nakano et al., 2002; Imamizu et al., 2007) (3) the cerebellum has been found to be involved in both the imagined and actual use of a variety of tools, with modular organization of internal models for imagined use of the various tools more lateral and posterior (Higuchi, 2007; Imamizu and Kawato, 2012). (4) the cerebellum automates imitative social learning of complex procedural spatial skills (Petrosini, 2007; Van Overwalle and Mariën, 2016), and (5) all of these cerebellar contributions occur below the level of conscious awareness. The addition of these five contributions of the cerebellum offer entirely new understandings of the predominately *unconscious* origin and accumulation of culture (Vandervert, 2016; Van Overwalle and Mariën, 2016).

Moreover, in a review of the cerebellum and non-motor functions, Strick et al. (2009) strongly supported this facilitative (and elaborative) role of cerebellar inner speech in working memory. In a fashion similar to that of vocalizations in the capuchin monkeys discussed earlier in this article (**Figure 2**), they suggested that the cerebellum is recruited whenever people engage in inner speech "to represent, maintain and organize task-relevant information and conscious thoughts" (p. 426), including in, for example, verbal working memory. It is proposed that as stone-tool knapping apprentices, in their early forms of language, overtly and silently "talked" themselves through the actual knapping process, this same inner speech process was adaptively selected across countless generations of cerebellar decomposition and the complex prediction requirements of "using precise ballistic strikes with a handheld hammer (typically stone, bone or antler) to initiate controlled and predictable fracture" (Stout and Hecht, 2017, p. 7862).

Overall, what Stout and Hecht have actually described in their above quoted social knapping arguments is an astonishingly congruent (and well-established) fit to (Adamaszek et al., 2017) the functions of the cerebellum (e.g., Bostan et al., 2013), and (Akshoomoff et al., 1997) it's evolutionarily concomitant volumetric anatomical and physiological changes which have occurred with stone-tool making over the last 700 thousand to one million years (Leiner et al., 1986, 1989). Thus, it can quite reasonably be shown that the actual brain mechanisms behind learning proficiency in stone-tool knapping would be dependent upon the procedural, cognitive and *socially contexted learning* of internal models in the cerebellum and their cerebellar error-correction toward proficiency optimization and innovation (Vandervert, 2016; Van Overwalle and Mariën, 2016).

Before moving on, it is important to emphasize that the foregoing cerebro-cerebellar approach does *not* necessarily conflict with (Stout and Hecht, 2017) proposed roles of the cerebral cortex in stone-tool manufacture. Rather, the cerebro-cerebellar approach brings to bear the functions of additional necessary brain mechanisms of the cerebellum that provide more detailed and more comprehensive explanations for how stone tool technology may have led to language and the origin of cumulative culture. The cerebro-cerebellar approach allows culture to be seen as a phenomenon that it was not in any way "thought out" by exceptional early humans or even as the product of the evolving "intelligence" of the cerebral cortex, but rather as the product of the silent, predictive role of the cerebellum constantly error-correcting toward optimization of complex motor, mental and social skills.

Predictive Social Learning Contributions of the Cerebellum

In their earlier quote in this article, Stout and Hecht (2017) made the strong point that for new learners, adequate stone-tool techniques "are not perceptually available to naïve observers and cannot be directly communicated as semantic knowledge" (p. 7862), and must be acquired through observational learning. Stout and Hecht further argued that therefore, "For *observational learning* [italics added], the challenge is to translate visual and auditory information of another's actions to appropriate motor commands for one's own body" (p. 7862).

In solid, preliminary support of such social learning contributions of the cerebellum, Van Overwalle and Mariën (2016) concluded that the cerebellum learns internal models for "social cognition" that are constantly error-corrected and sent to the cerebral cortex for the moment-to-moment, predictive "fluent and automatic social interaction" (p. 254). Van Overwalle and Mariën defined social cognition within the following context of observational learning: "Social cognition is the capacity to infer the social purpose of the behaviors of other persons or the self (i.e., "body" reading) and their state of mind (i.e., "mind" reading or mentalizing)," (2016, p. 248). This body- and mind-reading notion is in strong general agreement with the idea that the unique evolutionary expansion of human cognitive capacities was due to the demands of complex social interactions, as proposed in the *social brain hypothesis* (Dunbar, 1998, 2016), In this regard, Vandervert (2013, 2016) argued that, operating below the level of conscious awareness, the cerebellum learns and manipulates internal model *simulations* (Leggio and Molinari, 2015) of the actions and perceived thoughts of others, and thereby directly supported the social brain hypothesis as a product of the cognitive, emotional, and social functions of the cerebellum. Moreover, this cerebello-cerebral approach shows how social interactions became adaptively faster, more appropriate, and automatized, thus bonding social groups together and leading to cultural advances. The cerebello-cerebral approach strongly supports the *embodied simulation*

explanations of the social brain hypothesis as espoused by Barrett and Henzi (2005) and Gallese (2005). At the same time, it is suggested that Vandervert's (2007) cerebellum approach is essential in clarifying the neural mechanism(s) behind this embodied simulation, and that it does this via internal models based on the sequence detection process articulated earlier in this article by Akshoomoff et al. (1997) and Leggio and Molinari (2015).

Due to the strong fit between Van Overwalle and Mariën's account of cerebellar social modeling, prediction, and error-correction and (Stout and Hecht, 2017) earlier quoted account of the rigors and social learning requirements of complex stone-tool knapping, Van Overwalle and Mariën's findings are presented in some detail as follows:

> What is the function of the cerebellum in the service of social cognitive processes? The general assumption seems to be that an evolutionary older function of the cerebellum is to construct internal models of motor processes involving sequencing and planning of action, in order to automate and fine-tune voluntary motor processes. Scaffolding on this earlier function, a more recent function is to construct internal models [in the cerebellum] of purely mental processes during cognitive and social reasoning in which event sequences play a role (Ito, 2008; Pisotta and Molinari, 2014). This internal model is a copy [in the cerebellum] from the social event implications generated in mentalizing areas in the cerebrum (e.g., mPFC or TPJ), and allows humans to anticipate better action sequences during social interaction in an *automatic and intuitive way* [italics added] and to fine-tune these anticipations (p. 254).

Van Overwalle and Mariën's above cerebellum-driven capacity which "allows humans to anticipate [and predict] better action sequences during social interaction in an automatic and intuitive way" provides precisely the requirement for the social learning of stone-tool knapping outlined earlier by Stout and Hecht (2017). This strongly suggests that in the apprentice's observational learning in stone-tool knapping as described earlier by Stout and Hecht (2017), it is the cerebellum that provides the key neural mechanisms for sequence-detecting (e.g., Leggio and Molinari, 2015), error-correcting (e.g., Ito, 2008) and the automating (e.g., Hayter et al., 2007) of knapping toward optimal levels.

A Brief Digression on Working Memory's Relationship to Automaticity

It may seem that automaticity learned in the cerebellum might lessen a person's online attention to or interfere with tasks at hand. However, along with automated sequences learned in the cerebellum, it has been shown that the learner maintains a complete online working memory focused on goals at hand (e.g., Hayter et al., 2007). In their above-quoted article, Van Overwalle and Mariën (2016) noted this necessity and indicated that their overall data provided evidence that the cerebellum was alerted whenever the automatic sequences it had learned were inappropriate to the situation at hand. Online working memory would then attend the specifics of such inappropriate matches and the cerebellum would respond accordingly.

Thus, the prominent role of the cerebellum in developing automaticity does not detract from or interfere with the ongoing, online conscious role of working memory. Rather, the cerebral cortex and the cerebellum constantly operate together to both consciously (in working memory) deal with immediate problems at hand while at the same time learning cerebellar internal models which, as Ito (1997, 2008) convincingly argued, unconsciously regulate the speed, consistency and appropriateness of these working memory operations. This allows automaticity to be both learned unconsciously and then to operate automatically below the level of conscious awareness (Leiner et al., 1986; Ito, 2011). This same back-and-forth between the cerebellum and working memory areas of the cerebral cortex would of course apply to an ongoing apprenticeship in the repetitive, skill-demanding stone-tool knapping described earlier by Stout and Hecht (2017).

CONCLUSIONS AND DISCUSSION

Some three decades ago Leiner et al. (1986, 1989, 1991) proposed that the cerebellum's 3–4-fold increase in the size and its projections to the parietal and prefrontal areas of the cerebral cortex in the last million years is an indication of its involvement in cognitive functions including language and the manipulation of thought. In this article it is concluded that while Leiner et al.'s proposal has been greatly extended by subsequent imaging research, it can now be even further extended to new levels of analysis via the mechanism of sequence detection (Akshoomoff et al., 1997; Leggio and Molinari, 2015). Understanding how cerebellar sequence detection further extends the cognitive functions of cerebellum provides more detailed explanations of the evolution of the interrelationships among stone-tool making, language and culture among Homo *sapiens*.

Cerebellar Sequence Detection Led to More Detailed Prediction of the Outcomes of Cause-and-Effect Relationships

Thus within the context of cerebellar sequence detection, further conclusions can be reached in at least three areas. *First*, as a result of its basic operation of sequence detection (Leggio and Molinari, 2015), the cerebellum can be seen to be the predominant player in the infant's foundational development of visual-spatial working memory. This cerebellum-driven working memory allows the infant's working memory to predict the movement of objects in relation to those of its body. *Second*, within the context of its sequence detection, the cerebellum can be argued to decompose and re-organize visual-spatial working memory and vocalizations in the adaptive selection of the phonological loop of working memory (Vandervert, 2011). This cerebellar decomposition and re-organization was adaptive because during long evolution of the phonological loop they predicted more detailed cause-and-effect outcomes related of food procurement in pre-humans through Homo *sapiens*. *Third*, it is further concluded within this cerebellar sequence detection context, that even though leading anthropologists Stout and Hecht (2017) provided a robust evolutionary neuroscience analysis of the origins of culture and language, their exclusive

focus on functions of areas of the cerebral cortex can be seen as seriously lacking due to its omission of neuroscience detail that can be provided by newer imaging research on cognitive and language contributions of the cerebellum. Specifically, it can readily be shown that prediction necessary to complex, detailed visual-spatial stone-tool knapping and its socially contexted observational learning can best be explained not by functions of cerebral cortex alone, but by cerebro-cerebellar mechanism, with highly refined prediction predominately cerebellum driven.

These prominent cerebellum-driven contributions to the evolution of the cognitive functions behind stone tool making, language and culture include at least the following: (1) the cerebellum is involved in all complex movement and mental skill learning (Ito, 1997, 2008), (2) the cerebellum orchestrates the decomposition (Nakano et al., 2002) and participates in the re-organization (blending) of these skills toward new, more refined skills (Imamizu et al., 2007), (3) the cerebellum has been found to be involved in both the imagined and actual use of a variety of tools, with modular organization of internal models for imagined use of the various tools more lateral and posterior, thus producing a brain-based proclivity toward not only language learning but also tool use. (Higuchi, 2007; Imamizu and Kawato, 2012), (4) the cerebellum automates imitative social learning of complex procedural spatial skills (Petrosini, 2007; Van Overwalle and Mariën, 2016), and (5) all of these cerebellar contributions are learned and implemented below the level of conscious awareness (Leiner et al., 1986; Hayter et al., 2007; Ito, 2011).

In collaboration with the cerebral cortex the foregoing decomposition and blending in cerebellar internal models may be thought of as an "unconscious mode of thought" that leads to constant innovation and creativity, the earmarks of Homo *sapiens* (Vandervert, 2007, 2015; Ito, 2008). The cerebello-cerebral system apparently does this through the refinement of cause-and-effect relationships which opens new manipulative and thought horizons in language and tool configurations that can, through resulting refined cerebello-cerebral-driven prediction, further adapt Homo *sapiens* to its environment. At the same time, by so doing, it could suggest ways to alter that environment in new ways that were not previously found in nature. It is suggested that these adaptive cerebello-cerebral processes in the genus Homo and particularly Homo *sapiens* were/are the source of what leading anthropologist Holloway (1981, 2008) refers to uniquely human *arbitrary* forms. Within at least the last 700 thousand years it is suggested, in agreement with Holloway (1981), that these arbitrary forms included, for example, the evolution of language and of Acheulean stone tools.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

Adamaszek, M., D'Agata, F., Ferrucci, R., Habas, C., Keulen, S., Kirkby, K. C., et al. (2017). Consensus paper: cerebellum and emotion. *Cerebellum* 16, 552–576. doi: 10.1007/s12311-016-0815-8

Akshoomoff, N., Courchesne, E., and Townsend, J. (1997). "Attention coordination and anticipatory control," in *The Cerebellum and Cognition,* ed J. D. Schmahmann (New York, NY: Academic Press), 575–598.

Baddeley, A. (1992). Working memory. *Science* 255, 556–559. doi: 10.1126/science.1736359

Baddeley, A. (1998). *Human Memory: Theory and Practice*. Needham Heights, MA: Allyn & Bacon.

Baddeley, A., and Andrade, J. (2000). Working memory and the vividness of imagery. *J. Exp. Psychol. Gen.* 129, 126–145. doi: 10.1037/0096-3445.129.1.126

Baddeley, A., Gathercole, S., and Papagno, C. (1998). The phonological loop as a language learning device. *Psychol. Rev.* 105, 158–173. doi: 10.1037/0033-295X.105.1.158

Baddeley, A. D. (1993)."Working memory and conscious awareness," in *Theories of Memory*, eds A. F. Collins, S. E. Gathercole, M. A. Conway, and P. E. Morris (Hove: Erlbaum), 11–28.

Balsters, J., Whelan, C., Robertson, I., and Ramnani, N. (2013). Cerebellum and cognition: evidence for the encoding of higher order rules. *Cerebral Cortex* 23, 1433–1443. doi: 10.1093/cercor/bhs127

Balsters, J. H., Cussans, E., Diedrichsen, J., Phillips, K., Preuss, T. M., Rilling, J. K., et al. (2010). Evolution of the cerebellar cortex: selective expansion of prefrontal-projecting lobules. *Neuroimage* 49, 2045–2052. doi: 10.1016/j.neuroimage.2009.10.045

Barrett, L., and Henzi, P. (2005). The social nature of primate cognition. *Proc. R. Soc. B Biol. Sci.* 272, 1865–1875. doi: 10.1098/rspb.2005.3200

Bastian, A., and Thach, W. T. (2002). "Structure and function of the cerebellum," in *The Cerebellum and Its Disorders,* eds M. Manto and M. Pandolfo (Cambridge: Cambridge University Press), 49–66.

Bostan, A. C., Dum, R. P., and Strick, P. L. (2013). Cerebellar networks with the cerebral cortex and basal ganglia. *Trends Cogn. Sci.* 17, 241–254. doi: 10.1016/j.tics.2013.03.003

Brissenden, J., Levin, E., Osher, D., Rosen, M., Halko, M., and Somers, D. (2015). Cerebellar contributions to visual attention and visual working memory revealed by functional MRI and intrinsic functional connectivity. *J. Vis.* 15:232. doi: 10.1167/15.12.232

Brissenden, J., Osher, D., Levin, E., Halko, M., and Somers, D. (2017). Visuospatial attentional selectivity within the cerebellum. *J. Vis.* 17:524. doi: 10.1167/17.10.524

Courchesne, E. (1995). Infantile autism. 2. A new neurodevelopmental model. *Int. Pediatr.* 10, 86–96.

Courchesne, E., Townsend, J., Akshoomoff, N., Saitoh, O., Young-Chouchesne, R., Lincoln, A., et al. (1994). Impairment in shifting attention in autistic and cerebellar patients. *Behav. Neruosci.* 108, 848–865.

Cowan, N. (2014). Working memory underpinns cognitive development, learning, and education. *Educ. Pyschol. Rev.* 26, 197–233. doi: 10.1007/s10648-013-9246-y

Desmond, J., and Fiez, J. (1998). Neuroimaging studies of the cerebellum: language, learning and memory. *Trends Cogn. Sci.* 2, 355–362. doi: 10.1016/S1364-6613(98)01211-X

Diamond, A., Carlson, S. M., and Beck, D. M. (2005). Preschool children's performance in task switching on the dimensional change card sort task: separating the dimensions aids the ability to switch. *Dev. Neuropsychol.* 28, 689–729. doi: 10.1207/s15326942dn2802_7

Dum, R. P., and Strick, P. L. (2003). An unfolded map of the cerebellar dentate nucleus and its projections to the cerebral cortex. *J. Neurophysiol.* 89, 634–639. doi: 10.1152/jn.00626.2002

Dunbar, R. (2016). "The social brain hypothesis and human evolution," in *Oxford Research Encyclopedia of Psychology*. Available online at: http://psychology.oxfordre.com/view/10.1093/acrefore/9780190236557.001.0001/acrefore-9780190236557-e-44.

Dunbar, R. I. (1998). The social brain hypothesis. *Evol. Anthropol.* 6, 178–190.

Flanagan, R., Nakano, E., Imamizu, H., Osu, R., Yoshioka, T., and Kawato, M. (1999). Composition and decomposition of internal models in learning under altered kinematic and dynamic environments. *J. Neurosci.* 19, 1–5. doi: 10.1523/JNEUROSCI.19-20-j0005.1999

Fragaszy, D. M., Eshchar, Y., Visalberghi, E., Resende, B., Laity, K., and Izar, P. (2017). Synchronized practice helps bearded capuchin monkeys learn to extend attention while learning a tradition. *Proc. Natl. Acad. Sci. U. S. A.* 114, 7798–7805. doi: 10.1073/pnas.1621071114

Fragaszy, D. M., Liu, Q., Wright, B. W., Allen, A., Brown, C. W., and Visalberghi, E. (2013). Wild bearded capuchin monkeys (*Sapajus libidinosus*) strategically place nuts in a stable position during nut-cracking. *PLoS ONE* 8:e56182. doi: 10.1371/journal.pone.0056182

Gallese, V. (2005). Embodied simulation: from neurons to phenomenal experience. *Phenom. Cogn. Sci.* 4, 22–48. doi: 10.1007/s11097-005-4737-z

Greenfield, P. (1991). Language, tools and brain: the ontogeny and phylogeny of hierarchically organized sequential behavior. *Behav. Brain Sci.* 14, 531–595. doi: 10.1017/S0140525X00071235

Haslam, M., Hernandez-Aguilar, A., Proffitt, T., Aroyyo, A., Falotico, T., Fragaszy, D., et al. (2017). Primate archaeology evolves. *Nat. Ecol. Evol.* 1, 1431–1437. doi: 10.1038/s41559-017-0286-4

Hayter, A. L., Langdon, D. W., and Ramnani, N. (2007). Cerebellar contributions to working memory. *Neuroimage* 36, 943–954. doi: 10.1016/j.neuroimage.2007.03.011

Higuchi, S, Imamizu, H, and Kawato, M (2007). Cerebellar activity evoked by common tool-use execution and imagery tasks: an fMRI study. *Cortex* 43, 350–358. doi: 10.1016/S0010-9452(08)70460-X

Holloway, R. (2008). The human brain evolving: a personal retrospective. *Ann. Rev. Anthro.* 37, 1–19. doi: 10.1146/annurev.anthro.37.081407.085211

Holloway, R. L. (1981). Culture, symbols, and human brain evolution: a synthesis. *Dialect. Anthropol.* 5, 287–303.

Imamizu, H., Higuchi, S., Toda, A., and Kawato, M. (2007). Reorganization of brain activity for multiple internal models after short but intensive training. *Cortex* 43, 338–349. doi: 10.1016/S0010-9452(08)70459-3

Imamizu, H., and Kawato, M. (2009). Brain mechanisms for predictive control by switching internal models: implications for higher-order cognitive functions. *Psychol. Res.* 73, 527–544. doi: 10.1007/s00426-009-0235-1

Imamizu, H., and Kawato, M. (2012). Cerebellar internal models: Implications for dexterous use of tools. *Cerebellum* 11, 325–335. doi: 10.1007/s12311-010-0241-2

Ito, M. (1993). Movement and thought: identical control mechanisms by the cerebellum. *Trends Neurosci.* 16, 448–450. doi: 10.1016/0166-2236(93)90073-U

Ito, M. (1997). "Cerebellar microcomplexes," in *The Cerebellum and Cognition,* ed J. D. Schmahmann (New York, NY: Academic Press), 475–487.

Ito, M. (2007). How working memory and the cerebellum collaborate to produce creativity and innovation *Creativity Res. J.* 19, 35–38.

Ito, M. (2008). Control of mental activities by internal models in the cerebellum. *Nat. Rev. Neurosci* 9, 304–313. doi: 10.1038/nrn2332

Ito, M. (2011). *The Cerebellum: Brain for an Implicit Self*. Upper Saddle River: FT Press.

Kellermann, T., Regenbogen, C., De Vos, M., Mößnang, C., Finkelmeyer, A., and Habel, U. (2012). Effective connectivity of the human cerebellum during visual attention. *J. Neurosci.* 32, 11453–11460. doi: 10.1523/JNEUROSCI.0678-12.2012

Knickmeyer, R., Gouttard, S., Kang, C., Evans, D., Wilber, K, Smith, J., et al. (2008). A structural MRI study of human brain development from birth to 2 years. *J. Neurosci.* 28, 12176–11182. doi: 10.1523/JNEUROSCI.3479-08.2008

Leggio, M., and Molinari, M. (2015). Cerebellar sequencing: a trick for predicting the future. *Cerebellum* 14, 35–38. doi: 10.1007/s12311-014-0616-x

Leiner, H., Leiner, A., and Dow, R (1986). Does the cerebellum contribute to mental skills? *Behav. Neurosci.* 100, 443–454.

Leiner, H., Leiner, A., and Dow, R. (1989). Reappraising the cerebellum: What does the hindbrain contribute to the forebrain? *Behav. Neurosci.* 103, 998–1008. doi: 10.1037/0735-7044.103.5.998

Leiner, H., Leiner, A., and Dow, R. (1991). The human cerebro-cerebellar system: its computing, cognitive, and language skills. *Behav. Brain Res.* 44, 113–128. doi: 10.1016/S0166-4328(05)80016-6

Liu, Q., Fragaszy, D., Wright, B., Wright, K., Izar, P., and Visalberghi, E. (2011). Wild bearded capuchin monkeys (*Cebus libidinosus*) place nuts in anvils selectively. *Anim. Behav.* 81, 297–305. doi: 10.1016/j.anbehav.2010.10.021

Luria, A. R. (1980). *Higher Cortical Functions in Man, 2nd Edn*. New York, NY: Basic Books.

Mandler, J. (1992b). The foundations of conceptual thought in infancy. *Cogn. Dev.* 7, 273–282.

Mandler, J. (2004). *The Foundations of Mind: Origins of Conceptual Thought*. Oxford: Oxford University Press.

Mandler, J. M. (1992a). How to build a baby II: conceptual primitives. *Psychol. Rev.* 99, 587–604.

Mandler, J. M. (2008). On the birth and growth of concepts. *Philos. Psychol.* 21, 207–230. doi: 10.1080/09515080801980179

Mandler, J. M. (2010). The spatial foundations of the conceptual system. *Lang. Cogn.* 2, 21–44. doi: 10.1515/langcog.2010.002

Mandler, J. M. (2012). On the spatial foundations of the conceptual system and its enrichment. *Cogn. Sci.* 36, 421–451. doi: 10.1111/j.1551-6709.2012.01241.x

Mangalam, M., Pacheco, M.M., Izar, P., Visalberghi, E., and Fragaszy, D.M. (2018). Unique perceptuomotor control of stone hammers in wild monkeys. *Biol. Lett.* 14:20170587. doi: 10.1098/rsbl.2017.0587

Marvel, C., and Desmond, J. (2012). From storage to manipulation: how the neural correlates of verbal working memory reflect varying demands on inner speech. *Brain Lang.* 120, 42–51. doi: 10.1016/j.bandl.2011.08.005

Marvel, C. L., and Desmond, J. E. (2010a). Functional topography of the cerebellum in verbal working memory. *Neuropsychol. Rev.* 20, 271–279. doi: 10.1007/s11065-010-9137-7

Marvel, C. L., and Desmond, J. E. (2010b). The contributions of cerebro-cerebellar circuitry to executive verbal working memory. *Cortex* 46, 880–895. doi: 10.1016/j.cortex.2009.08.017

Moberget, T., and Ivry, R. B. (2016). Cerebellar contributions to motor control and language comprehension: searching for common computational principles. *Ann. N. Y. Acad. Sci.* 1369, 154–171. doi: 10.1111/nyas.13094

Nakano, E., Flanagan, J., Imamizu, H., Rieko, O., Yoshioka, T., and Kawato, M. (2002). Composition and decomposition learning of reaching movements under altered environments: an examination of the multiplicity of internal models. *Syst. Comp. Jap.* 33, 80–94. doi: 10.1002/scj.1166

Obayashi, S., Matsumoto, R., Suhara, T., Nagai, Y., Iriki, A., and Maeda, J. (2007). Functional organization of the monkey brain for abstract operation. *Cortex* 43, 389–396. doi: 10.1016/S0010-9452(08)70464-7

Pelphrey, K.A., Reznick, J.S., Goldman, B., Sasson, N., Morrow, J., Donahoe, A., and Hodgson, K., (2004). Development of visuospatial short-term memory in the second half of the 1st year. *Dev. Psychol.* 40, 836–851. doi: 10.1037/0012-1649.40.5.836

Petrosini, L. (2007). "Do what I do" and "do how I do": different components of imitative learning are mediated by different neural structures. *Neuroscientist* 13, 335–348. doi: 10.1177/1073858407013004070l

Pisotta, I., and Molinari, M. (2014). Cerebellar contribution to feedforward control of locomotion. *Front. Hum. Neurosci.* 8:475. doi: 10.3389/fnhum.2014.00475

Reznick, J. S., Morrow, J. D., Goldman, B. D., and Snyder, J. (2004). The onset of working memory in infants. *Infancy* 6, 145–154. doi: 10.1207/s15327078in0601_7

Schmahmann, J. (2013). Dysmetria of thought: a unifying hypothesis for cerebellar role in sensorimotor function, cognition and emotion. *Cerebellum* 13, 151–171.

Schmahmann, J. D., and Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain* 121, 561–579. doi: 10.1093/brain/121.4.561

Short, S. J., Elison, J. T., Goldman, B. D., Styner, M., Gu, H., Connelly, M., et al. (2013). Associations between white matter microstructure and infants' working memory. *Neuroimage* 64, 156–166. doi: 10.1016/j.neuroimage.2012.09.021

Sokolov, A.A., Miall, R.C., and Ivry, R.B. (2017). The cerebellum: adaptive prediction for movement and cognition. *Trends Cogn. Sci.* 21, 313–332. doi: 10.1016/j.tics.2017.02.005

Stoodley, C., Valera, E., and Schmahmann, J. (2012). Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *Neuroimage* 59, 1560–1570. doi: 10.1016/j.neuroimage.2011.08.065

Stout, D., and Hecht, E. (2017). The evolutionary neuroscience of cumulative culture. *PNAS* 114, 7861–7868. doi: 10.1073/pnas.1620738114

Strick, R., Dum, R., and Fiez, J. (2009). Cerebellum and nonmotor function. *Annu. Rev. Neurosci.* 32, 423–434. doi: 10.1146/annurev.neuro.31.060407.125606

Thach, WT. (1996). On the specific role of the cerebellum in motor learning and cognition: clues from PET activation and lesion studies in humans. *Behav. Brain Sci.* 19, 411–431. doi: 10.1017/S0140525X00081504

Van Overwalle, F., and Mariën, P. (2016). Functional connectivity between the cerebrum and cerebellum in social cognition: a multi-study analysis. *Neuroimage* 124A, 248–255. doi: 10.1016/j.neuroimage.2015.09.001

Vandervert, L, Schimpf, P, and Liu, H. (2007). How working memory and the cognitive functions of the cerebellum collaborate to produce creativity and innovation. *Creativity Res. J.* 19, 1–18. doi: 10.1080/10400410709336873

Vandervert, L. (2011). The evolution of language: the cerebro-cerebellar blending of visual-spatial working memory with vocalizations. *J. Mind Behav.* 32, 317–331.

Vandervert, L. (2013). How the cerebro-cerebellar blending of visual-spatial working memory with vocalizations supports Leiner, Leiner and Dow's explanation of the evolution of thought and language. *Cerebellum*. 13, 151–71.

Vandervert, L. (2015). How music training enhances working memory: a cerebrocerebellar blending mechanism that can lead equally to scientific discovery and therapeutic efficacy in neurological disorders. *Cerebellum Ataxias* 2:11. doi: 10.1186/s40673-015-0030-2

Vandervert, L. (2016). The prominent role of the cerebellum in the origin, advancement and individual learning of culture. *Cerebellum Ataxias* 3:10. doi: 10.1186/s40673-016-0049-z

Vandervert, L. (2017a). Vygotsky meets neuroscience: the cerebellum and the rise of culture through play. *Am. J. Play* 9, 202–227. Available online at: http://www.journalofplay.org/issues/9/2/article/3-vygotsky-meets-neuroscience-cerebellum-and-rise-culture-through-play

Vandervert, L. (2017b). The origin of mathematics and number sense in the cerebellum: with implications for finger counting and dyscalculia. *Cerebellum Ataxis* 4:12. doi: 10.1186/s40673-017-0070-x

Visalberghi, E., Haslam, M., Spagnoletti, N., and Fragaszy, D. (2013). Use of stone hammer tools and anvils by bearded capuchin monkeys over time and space: construction of an archeological record of tool use. *J. Archeol. Sci.* 40, 3222–3232. doi: 10.1016/j.jas.2013.03.021

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cellular Neuroscience

ORIGINAL RESEARCH
published: 08 January 2019
doi: 10.3389/fncel.2018.00510

The Cerebellar Predictions for Social Interactions: Theory of Mind Abilities in Patients With Degenerative Cerebellar Atrophy

Silvia Clausi[1,2], *Giusy Olivito*[1,2,3], *Michela Lupo*[1], *Libera Siciliano*[4], *Marco Bozzali*[3] and *Maria Leggio*[1,2]*

[1] Ataxia Laboratory, IRCCS Fondazione Santa Lucia, Rome, Italy, [2] Department of Psychology, Sapienza University of Rome, Rome, Italy, [3] Neuroimage Laboratory, IRCCS Fondazione Santa Lucia, Rome, Italy, [4] PhD Program in Behavioral Neuroscience, Sapienza University of Rome, Rome, Italy

Recent studies have focused on the role of the cerebellum in the social domain, including in Theory of Mind (ToM). ToM, or the "mentalizing" process, is the ability to attribute mental states, such as emotion, intentions and beliefs, to others to explain and predict their behavior. It is a fundamental aspect of social cognition and crucial for social interactions, together with more automatic mechanisms, such as emotion contagion. Social cognition requires complex interactions between limbic, associative areas and subcortical structures, including the cerebellum. It has been hypothesized that the typical cerebellar role in adaptive control and predictive coding could also be extended to social behavior. The present study aimed to investigate the social cognition abilities of patients with degenerative cerebellar atrophy to understand whether the cerebellum acts in specific ToM components playing a role as predictive structure. To this aim, an *ad hoc* social cognition battery was administered to 27 patients with degenerative cerebellar pathology and 27 healthy controls. In addition, 3D T1-weighted and resting-state fMRI scans were collected to characterize the structural and functional changes in cerebello-cortical loops. The results evidenced that the patients were impaired in lower-level processes of immediate perception as well as in the more complex conceptual level of mentalization. Furthermore, they presented a pattern of GM reduction in cerebellar portions that are involved in the social domain such as crus I-II, lobule IX and lobule VIIIa. These areas showed decreased functional connectivity with projection cerebral areas involved in specific aspects of social cognition. These findings boost the idea that the cerebellar modulatory function on the cortical projection areas subtends the social cognition process at different levels. Particularly, regarding the lower-level processes, the cerebellum may act by implicitly matching the external information (i.e., expression of the eyes) with the respective internal representation to guarantee an immediate judgment about the mental state of others. Otherwise, at a more complex conceptual level, the cerebellum seems to be involved in the construction of internal models of mental processes during social interactions in which the prediction of sequential events plays a role, allowing us to anticipate the other person's behavior.

Keywords: cerebellum, cerebro-cerebellar networks, VBM, SBA, theory of mind, prediction, social interaction

OPEN ACCESS

Edited by:
Aasef G. Shaikh,
Case Western Reserve University,
United States

Reviewed by:
Laurens Bosman,
Erasmus University Rotterdam,
Netherlands
Mohamed Jaber,
University of Poitiers, France

***Correspondence:**
Maria Leggio
maria.leggio@uniroma1.it

Received: *05 October 2018*
Accepted: *10 December 2018*
Published: *08 January 2019*

Citation:
Clausi S, Olivito G, Lupo M, Siciliano L, Bozzali M and Leggio M (2019) The Cerebellar Predictions for Social Interactions: Theory of Mind Abilities in Patients With Degenerative Cerebellar Atrophy. Front. Cell. Neurosci. 12:510. doi: 10.3389/fncel.2018.00510

INTRODUCTION

Estimation of mental states of others is a key aspect for human communication and social interactions. This capacity is a fundamental component of the social cognition and involves both lower-level processes of immediate perception and higher-level inferences (Coricelli, 2005; Van Overwalle et al., 2014). The lower-level processes are automatic, refer to a primitive understanding of another person's mind and are based on action and emotion recognition and "emotional contagion" (Meltzoff and Moore, 1989). The higher-level inferences imply the capacity to attribute mental states to others (such as emotion, intentions and beliefs) and adopting the perspective of the other person to understand and predict the behavior (Van Overwalle et al., 2014). This ability is known as Theory of Mind (ToM) (Premack and Woodruff, 1978; Brothers and Ring, 1990) or the "mentalizing" process and is based on intentionality, empathy, and higher depths of reasoning, requiring more conceptual and voluntary processes (Coricelli, 2005).

Such complex functions require a correspondent sophisticated neural mechanism. Indeed, complex interactions between limbic, associative areas and subcortical structures are crucial to these processes (Van Overwalle et al., 2014; Van Overwalle and Mariën, 2016; Heleven and Van Overwalle, 2018). Within the social cognition domain, ToM abilities seem to mainly depend on a group of brain regions, called the "mentalizing network," which includes regions in the superior temporal sulcus (STS), temporoparietal junction, medial precuneus, and medial prefrontal cortex (Saxe and Kanwisher, 2003; Aichhorn et al., 2009). The neural circuitry underlying social cognition also involves fronto-limbic connections (Beer et al., 2006), mirror neurons in the ventral premotor and rostral posterior parietal cortices (Rizzolatti et al., 2006), the amygdala (Adolphs, 2004), the insula (Kipps et al., 2007; Gu et al., 2012), and the middle temporal gyrus (Johnstone et al., 2006).

Most neuroanatomical models of social behavior/mentalizing emphasize the putative role of the cortical regions (Abu-Akel and Shamay-Tsoory, 2011) and fail to acknowledge the contribution of the cerebellum. However, recent studies have focused on the role of the cerebellum in the social domain, including some aspects of ToM (Sokolov, 2018).

Abbreviations: AC-PC, anterior-posterior commissure; BA, Brodmann area; BADA, Batteria per l'Analisi dei Deficit Afasici (Battery for the analysis of the aphasic deficits); BOLD, blood oxygenation level dependent imaging; CB, cerebellar patients; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; DMN, Default Mode Network; EA, Emotion Attribution test; EPI, echo planar imaging; FC, functional connectivity; FLAIR, fluid attenuated inversion recovery; FOV, field of view; FP, Faux Pas test; FWE, familywise error; FWHM, full width at half maximum; GM, gray matter; HS, healthy subjects; ICARS, International Cooperative Ataxia Rating Scale; MDEFT, Modified Driven Equilibrium Fourier Transform; MNI, Montreal Neurologic Institute; RME, Reading the Mind in the Eyes test; ROIs, regions of interest; RS-fMRI, resting-state functional magnetic resonance imaging; SMA, supplementary motor area; SN, Salience Network; SPM-8, Statistical Parametric Mapping version 8; STS, superior temporal sulcus; SUIT, Spatially Unbiased Infratentorial Template; TE, echo time; TI, inversion time; TR, repetition time; ToM, theory of mind; TSE, turbo spin echo; VAS, Visual Analogue Scale; VBM, voxel-based morphometry.

The revolutionary view of a "social cerebellum" is supported by observations of cerebellar activation in many functional imaging studies involving social emotions and mental state inference tasks (Brunet et al., 2000; Calarge et al., 2003) as well as by findings showing that the performance of patients with cerebellar damage is impaired in a range of perceptual (Ivry and Keele, 1989; Ackermann et al., 1997), cognitive (Schmahmann and Sherman, 1998; Tedesco et al., 2011), and ToM tasks (Sokolov, 2018) that are essential in social interactions. In particular, alterations in social cognition tasks are reported in patients with complex cerebello-cerebral degeneration, such as spino-cerebellar ataxia (SCA) type 1, SCA type 2, and SCA type 7 as well as in patients with isolated cerebellar degeneration, such as SCA type 6, SCA type 8 and episodic ataxia type 2 (Sokolovsky et al., 2010; D'Agata et al., 2011; Hoche et al., 2016).

Moreover, cerebellar abnormalities and dysfunctions of cerebellar-cortical networks have been described in several psychiatric disorders characterized by mentalizing impairments (i.e., schizophrenia and autism spectrum disorders) (Andreasen and Pierson, 2008; Fatemi et al., 2012).

The cerebellar function in social behavior is anatomically supported by the fact that the cerebellum is incorporated into associative and paralimbic circuits involved in social cognition processes by way of feedforward connections from these cerebral cortical areas to the cerebellum via the pons (corticopontocerebellar projections) and by feedback connections from the cerebellum through the thalamus back to the cerebral cortex (cerebellothalamocerebral projections) (Schmahmann and Pandya, 1997; Ramnani, 2012).

Although there is widespread agreement about the neural substrate of social cognition, much less is known about the neural representations and computations that are implemented in cerebello-cerebral circuitries. In particular, the specific role of the cerebellum in the social domain remains to be elucidated.

As it is well acknowledged, cerebellar operations in the sensorimotor domain are believed to involve outcome prediction based on forward models and signaling deviations from these outcomes (prediction errors) to the cerebral cortex (Ito, 2006). In particular, the cerebellum receives and combines the motor commands with exteroceptive and proprioceptive sensory inputs, generating a representation of the expected sensory consequences of those commands (internal models) (Miall and Reckess, 2002). Therefore, the sensory predictions generated by a forward model can be used to coordinate motor output, providing a means to anticipate the consequences of a motor command and to update a state estimate of the motor system. These predictions are constantly compared with afferent input, and in the presence of deviations from prediction, the cerebellum emits corrective signals. These error signals allow us to refine future sensory predictions and reduce the prediction error signal on subsequent movements (Wolpert and Kawato, 1998).

In the present work, we followed the hypothesis that the typical cerebellar role in adaptive control and predictive coding in the sensorimotor domain could be extended to the

social cognition domain (Ito, 2008; Sokolov, 2018). Indeed, anticipation, adaptation and learning appear indispensable for successful social interactions. Particularly, prediction is a central component of socioemotional processing (Brown and Brüne, 2012; Koster-Hale and Saxe, 2013) in the sense that the understanding and inference of another individual's state of mind requires not only the creation of a mental model of that mental state but also the ability to simulate how it might influence the others' behavior. Recognizing deviations from our expectation in the outcome of a social interaction and using that information to calibrate future social predictions guarantee adaptive social behavior (Sokolov et al., 2017).

In the complex mentalizing process, the predictions are allowed by stored internal models of human behaviors based on expectations that actions will be rational and efficient and consistent with individual beliefs, personality traits, or social norms (Koster-Hale and Saxe, 2013). Thus, in analogy with the information processing in the sensorimotor domain, the cerebellum might modulate the high-order cortical activity (Middleton and Strick, 2000) by detecting predictable sequences (i.e., internal model of a social action) and allowing optimized feedforward control that is necessary to accomplish these functions in a fluid and automated manner (Leggio et al., 2011; Leggio and Molinari, 2015). If this is the case, a cerebellar malfunction that interferes with using the internal model would prevent the prediction function and the correct inferences about the others' mental state or the recognition of a deviance from the expected social behavior.

In the present work, we investigated the social cognition abilities of patients with degenerative cerebellar atrophy to understand whether the cerebellum plays a role in particular components of social cognition and to elucidate its role as a predictor in social interactions. To this aim, the participants were tested using an *ad hoc* social cognition battery to examine the unconscious and automatic process and the more complex and conscious aspects of ToM by using tasks in which the stimuli implied different levels of prediction. Considering the etiological heterogeneity of the cerebellar disease in the present population, a morpho-volumetric analyses was also performed to characterize the common cerebellar structural changes and their neuroanatomical localization. Moreover, considering that meta-analytic connectivity data in healthy subjects and studies in patients affected by SCA2 indicated interactions between the cerebellum and cerebral areas that are crucial in social cognition (Habas et al., 2009; Van Overwalle et al., 2015; Olivito et al., 2017), functional connectivity (FC) between the common cerebellar areas affected in our sample and the cerebral cortex was analyzed by means of resting-state functional magnetic resonance imaging (RS-fMRI) (Friston et al., 1993; Biswal et al., 1997; van de Ven et al., 2004).

We expected that the cerebellar structural alterations that occurred in patients affected by cerebellar degeneration would interfere with the modulatory function of the cerebellum on the cortical projection areas involved in the mentalizing process. This interference could account for specific impaired ToM outcomes, particularly when the stimuli processing requires a high level of prediction.

MATERIALS AND METHODS

Participants

Twenty-seven patients affected by degenerative cerebellar atrophy (CB) [mean age/SD: 46.4/10.8 (years); mean education/SD: 13.1/3.3 (years); M/F: 6/21] were recruited at the Ataxia Lab of the Santa Lucia Foundation Hospital. They were selected from among those in-patients and out-patients admitted between the 2014 and 2017 (n. 38) for rehabilitation or clinical follow up. Only the patients presented with diffuse cerebellar atrophy and no other brain macroscopic abnormalities, as detected by visual inspection of clinical MRI scans, were enrolled in the study.

At the time of the assessment, all the 27 patients had more than 6 months of illness from the diagnosis and showed a pure cerebellar motor syndrome, with no extra-cerebellar symptoms, as evidenced by a comprehensive neurological examination. The International Cooperative Ataxia Rating Scale (ICARS, Trouillas et al., 1997) was used to quantify the cerebellar motor signs. The demographic and clinical characteristics of the patients are reported in **Table 1**.

Additionally, 27 well-matched healthy subjects (HS) [mean age/SD: 45.9/9.7 (years); mean education/SD: 13.1/2.6 (years); M/F: 6/21] with no history of neurological or psychiatric illness were enrolled in the study. *T*-test analyses showed no significant difference in the mean age ($t = 0.17$; $p = 0.62$) and educational level ($t = -0.05$; $p = 0.20$) between the two groups. Raven's 47 Progressive Matrices test (Raven, 1949) was administered to assess intellectual level and used as inclusion criterion.

The Ethics Committee of Fondazione Santa Lucia (IRCCS) approved the present study, according to the principles expressed in the Declaration of Helsinki, and written informed consent was obtained from all the participants.

Neuropsychological Screening

A neuropsychological battery was administered to the CB patients to assess the following domains: current intellectual functioning [Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981; Orsini and Laicardi, 1997)]; verbal comprehension [Token test (De Renzi and Vignolo, 1962)]; verbal production [Denomination of words subtest of the BADA–Batteria per l'Analisi dei Deficit Afasici–(Miceli et al., 1994); Phrase Construction subtest of the Italian-language Mental Deterioration Battery (Caltagirone et al., 1995)]; verbal memory [Immediate and Delayed recall of Rey's 15 words (Rey, 1958); forward and backward digit span (Wechsler, 1945; Orsini et al., 1987)]; episodic memory [Short-Story Recall task (Carlesimo et al., 2002)]; visuospatial memory [Rey-Osterrieth Complex Figure Test (recall) (Caffarra et al., 2002); Corsi Test Corsi, 1972]; visuospatial ability [Rey-Osterrieth Complex Figure (copy) (Caffarra et al., 2002)]; attention [Multiple features targets cancellation task (Marra et al., 2013); Lines cancellation task (Albert, 1973); Trail Making Test (Giovagnoli et al., 1996)]; and executive functions [Phonological fluency (Borbowsky et al., 1967); Wisconsin Card Sorting Test (Heaton, 1981)].

Social Cognition Tasks

To investigate social cognition abilities, the following tests were administered.

The Reading the Mind in the Eyes test (RME) (Baron-Cohen et al., 2001; Serafin and Surian, 2004) was used to assess the automatic lower-level processes of emotion and mental state attribution based on immediate perceptions of the eye-region expression and regardless of the context. Indeed, within the face, the eyes are the most important contact between agents (Hainline, 1978; Maurer, 1985). This test was made up of 36 photos of actors' eyes, and for each, the participants had to choose from four alternative words the one that best described what the person in the photograph is thinking or feeling. This process is assumed to involve an unconscious, automatic and rapid matching of past memories/categorization concerning similar expressions with a lexicon of mental state terms to arrive at a judgment of which word the eyes most closely match (Baron-Cohen et al., 2001). Responses were scored 1 or 0 for correctness.

The Emotion Attribution test (EA) (Blair and Cipolotti, 2000; Prior et al., 2003) was used to assess the ability to attribute emotions to others in a social context. Fifty-eight short stories describing an emotional situation were presented to the subject and required providing a one-word description of how the main character might feel in that situation. The sentences were designed to elicit sadness, fear, embarrassment, disgust, happiness, anger or envy. The sequential events of the story were explicit and univocal, requiring a low level of prediction about the emotional consequences of the event (see **Appendix** in Supplementary Material for example of the story). The correct answer was based on the coherent expectation about the social interaction.

The Faux Pas test (FP) (Stone et al., 1998; Liverta Sempio et al., 2005) was used to assess a more advanced capacity to make inferences regarding another person's state of mind. This test included 10 stories in which a social "faux pas" occurred ("faux pas" stories) and 10 control stories in which no social "faux pas" occurred ("no-faux pas" stories) (see **Appendix** in Supplementary Material for examples of the stories).

A social "faux pas" occurs when a speaker says something without considering that the listener might not want to hear it or might be hurt by what has been said, implying false or mistaken belief. To recognize the "faux pas," the subject had to understand that the person committing the faux pas does not know that they should not say it and that the person hearing it would be upset by the faux pas. Moreover, the subject had to identify a wrong behavior or action with respect to the predicted social norms or a more likely behavior in the social interaction. In the "faux pas" stories, the sequential events are unexpected and not univocal and a constant comparison between the event and the social expectation are necessary, thus requiring a high level of prediction. Conversely, in the "no-faux pas" stories, the sequential events are explicit and univocal, requiring a low level of prediction about the consequences of the event.

All the stories were read to participants, while they had a copy of the story to read along and check back over (to reduce the memory requirement). When a "faux pas" was identified, five clarifying questions were proposed to evaluate the understanding of the mental states and emotions of the agents involved in the stories. Each "faux pas" story question correctly answered was scored as 1, resulting in a maximum score of 6 for each story.

The "no-faux pas" stories were given a score of 2 if they were correctly identified as not containing a faux pas. Two more control questions were asked for all 20 stories to confirm that the participant had a factual understanding of the stories.

The Advanced ToM task (Happè, 1994; Blair and Cipolotti, 2000; Prior et al., 2003; Van Harskamp et al., 2005) was used to assess the more advanced concepts of ToM, such as double bluff, white lies, and persuasion. The participant was presented with 13 stories describing naturalistic social situations and was asked to interpret and justify the behavior of the main character. The subject had to accurately identify the underlying intention behind a character's utterance that was not literally true and to explain why the main character acted in a particular manner. Successful performance required the attribution of mental states, such as desires, beliefs or intentions, and higher-order mental states, such as one character's belief about what another character knows. The sequential events of the story were not univocal as in the FP stories, requiring a high level of prediction about the consequence of the events. The correct answer was based on the capacity to make a choice taking into account different expectations about the social interaction (see **Appendix** in Supplementary Material for examples of the stories).

Visual Analog Scales for Mood and Anxiety

The possible anxiety and mood effects on emotional evaluation have been controlled by using the self-evaluation 'Visual Analogue Scale' (VAS) (Hayes and Paterson, 1921). The VAS consists of a horizontal line, 100 mm in length, anchored at each end by a word descriptor and the subject is required to mark on the line the point they felt best represented how they perceived their current state. The VAS score is calculated by measuring the distance from the left-hand end of the line to the point that the subject marked in millimeters.

Two VAS were used to assess the two different domains: anxiety (0 mm, no anxiety and 100 mm, the worst anxiety ever) and mood (0 mm, the worst mood and 100 mm, the best mood ever).

Data Analyses

Non-parametric Mann- Whitney U test for independent samples was used to detect differences in accuracy row score of each test between CB patients and HS. Spearman rank-order correlation coefficient was used to correlate each test score with the VAS, the ICARS total score, the disease duration and executive function scores to exclude the possible effect of mood, motor impairment and executive function on social cognition performance. The statistical analyses were performed using Statistica software 12 (http://www.statsoft.com).

MRI Data Acquisition Protocol

All participants underwent an MRI examination at 3T (Magnetom Allegra, Siemens, Erlangen, Germany). MRI image acquisition included the following: (1) dual-echo turbo

spin echo (TSE) [repetition time (TR) = 6190 ms, echo time (TE) = 12/109 ms] and (2) T2 fluid attenuated inversion recovery (FLAIR) [TR = 8170 ms, TE = 96 ms, inversion time (TI) = 2100 ms] for conventional MRI visualization of the brain; (3) anatomical 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan [TR = 1338 ms, TE = 2.4 ms, matrix = 256 × 224 × 176, in-plane field of view (FOV) = 250 × 250 mm^2, slice thickness = 1 mm] for structural T1-weighted imaging of the brain; (4) T2* weighted echo planar imaging (EPI) sensitized to blood oxygenation level dependent imaging (BOLD) contrast [TR: 2080 ms, TE: 30 ms, 32 axial slices parallel to anterior-posterior commissure (AC-PC) line, matrix: 64 × 64, pixel size: 3 × 3 mm^2, slice thickness: 2.5 mm, flip angle: 70°] for resting-state functional MRI (RS-fMRI).

BOLD echo planar images were collected during rest for a 7 min and 20 s period, resulting in a total of 220 volumes. During this acquisition, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. The absence of macroscopic extra cerebellar abnormalities was excluded by the visual inspection of the TSE and FLAIR scans of patients, acquired as part of this research study, by an expert neuroradiologist. According to the inclusion criteria, conventional MRI scans of HS were also reviewed and any pathological conditions affecting the brain was excluded.

Image Processing

T1-Weighted Scans

Anatomical T1-weighted images were used to quantify the cerebellar gray matter (GM) patterns. The cerebellum was preprocessed individually using the Spatially Unbiased Infratentorial Template (SUIT) toolbox (Diedrichsen et al., 2009) implemented in Statistical Parametric Mapping version 8 [Wellcome Department of Imaging Neuroscience; SPM-8 (http://www.fil.ion.ucl.ac.uk/spm/)]. The procedure involved cropping and isolating the cerebellum from the T1 anatomical images, normalizing each cropped image into SUIT space, reslicing the probabilistic cerebellar atlas into individual subjects' space using the deformation parameters obtained by normalization, and smoothing the images using 8-mm full width at half maximum (FWHM) Gaussian kernel. Additionally, every participant's MDEFT was also segmented in SPM to estimate the total GM volume and a two sample *t*-test was performed to compared the GM total volume between groups to exclude the presence of cerebral atrophy in patients.

Resting-State fMRI Data

FMRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and in-house software implemented in MATLAB (The Mathworks Inc., Natick, Massachussetts, USA). For each subject, the first four volumes of the fMRI series were discarded to allow for T1 equilibration effects. The preprocessing steps included correcting for head motion, compensating for slice-dependent time shifts, normalizing to the EPI template in Montreal Neurologic Institute (MNI) coordinates provided with SPM8, and smoothing with a 3D Gaussian Kernel with 8 mm^3 full-width at half maximum. For each data set, motion correction was checked to ensure that the maximum absolute shift did not exceed 2 mm and the maximum absolute rotation did not exceed 1.5°. The global temporal drift was removed using a 3rd order polynomial fit, and the signal was regressed against the realignment parameters and the signal averaged over whole brain voxels to remove other potential sources of bias. Then, all images were filtered by a phase-insensitive band-pass filter (passband 0.01–0.08 Hz) to reduce the effect of low frequency drift and high frequency physiological noise.

Neuroimaging Data Analysis

Since 5 CB (CB3, CB13, CB23, CB32, CB34) patients did not complete the MRI protocol due to claustrophobic concerns and 2 HS were excluded from the MRI data analyses due to motion exceeding the set thresholds (2 mm translation and 1.5° rotation) during their MRI scans, only 22 CB patients (mean age/SD: 46.2/11.7; M/F: 4/18) and 25 HS (mean age/SD: 53.8/5.9; M/F: 6/19) were included in the final MRI data analyses.

Voxel-Based Morphometry

The individual GM maps obtained were used to perform statistical analysis and to assess differences in regional cerebellar volume between CB patients and HS by performing voxel-based morphometry (VBM) and a voxelwise two-sample *t*-test in SPM-8 to compare the GM maps. Age and sex were set as variables of no interest. The results were considered significant at *p*-values < 0.05 after familywise error (FWE) cluster-level correction.

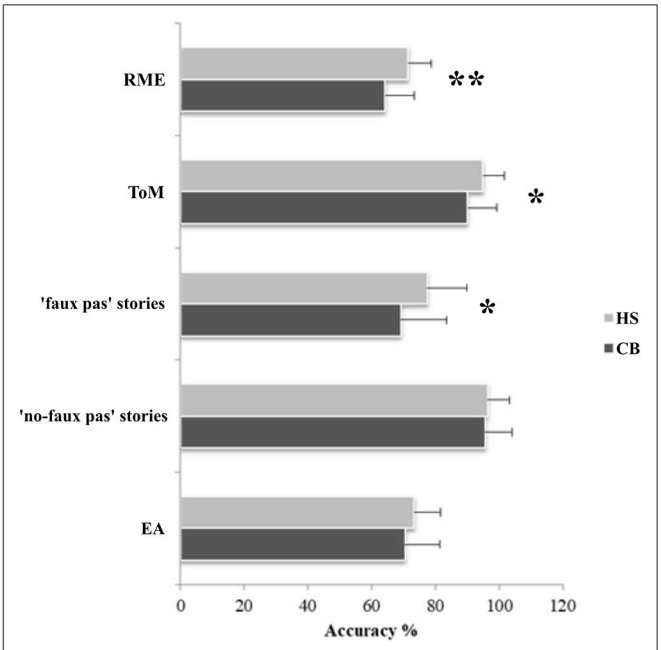

FIGURE 1 | Results of the social cognition battery. Data are presented as the percentage of the total number of correct responses for the RME (max = 36), for the Advanced ToM test (max = 13), faux pas stories (max = 60) and no-faux pas stories (max = 20), and for the EA test (max = 58). Mean and standard deviation of the accuracy percentage, where 0% is totally wrong and 100% is totally correct, are reported for both patients and healthy subjects; $^{*}p < 0.05$; $^{**}p < 0.005$.

Definition of Regions of Interest (ROIs) and Seed-Based fMRI Analyses

Based on the VBM results, specific cerebellar regions were identified and used as regions of interest (ROIs) in the seed-based analysis. Each cerebellar region of significantly reduced GM volume was extracted according to the SUIT atlas template of the cerebellum (Diedrichsen et al., 2009) using the FSL command line from the FMRIB software library (FSL, www.fmrib.ox.ac.uk/fsl/) and resliced into EPI standard space. The mean time course of the voxels within the affected ROI was calculated for every participant and used as a regressor in a 1st level SPM analysis, thus extracting the voxels in the whole brain showing a significant correlation with it. At the second level, a two-sample *t*-test model was used to explore differences in connectivity between CB patients and HS in the ROI. To remove the effect of confounding variables, the quantity of total brain GM volume, age and sex were entered in the analysis as covariates of no interest. The results were considered significant at p-values < 0.05 after FWE cluster-level correction.

RESULTS

Neuropsychological Results

The performances obtained by the CB patients in the neuropsychological evaluation are reported in **Table 2**. The neuropsychological assessment revealed the presence of selective and very slight impairments in some patients but did not show clear evidence of general cognitive impairment. Indeed, only some patients displayed impaired performance in specific tasks, as shown in **Table 2**.

Social Cognition Profile

In the RME test, the CB patients showed an impaired performance compared to HS (MWU $= 163$; $Z = -2.89$; $p = 0.004$). Moreover, the patients failed in the Advanced ToM test, with a significantly lower score than HS (MWU $= 255$; $Z = -2.02$; $p = 0.041$). In the Faux Pas test, the patients obtained significantly lower scores than HS selectively in the "faux pas" stories (MWU $= 228.5$; $Z = -2.36$; $p = 0.018$), while no significant difference was observed in the "no-faux pas" stories (MWU $= 347.5$; $Z = -0.23$; $p = 0.82$). Normal performance

TABLE 1 | Clinical and demographic characteristics of the cerebellar patients.

	ID	Diagnosis	Gender	Age (years)	Education (years)	Duration (months)	ICARS*	Triplet expansions
1	CB1	FRDA	F	47	13	24	59	–
2	CB3	SCA2	F	38	12	12	33	CAG 22/41
3	CB4	SCA2	F	42	13	12	47	CAG 22/39
4	CB5	ICA	F	53	11	7	21	–
5	CB7	Cerebellitis	F	59	13	-	12	–
6	CB9	SCA2	F	44	18	13	26	CAG/CTG 14/47
7	CB12	ICA	F	59	13	8	16	–
8	CB13	ICA	F	56	13	17	29	–
9	CB14	ICA	F	52	13	44	28	–
10	CB15	SCA1	F	24	16	12	33	CAG 27/57
11	CB16	SCA2	F	36	13	8	37	CAG 22/42
12	CB17	ICA	F	24	13	10	8	–
13	CB18	ICA	F	46	13	24	9	–
14	CB20	SCA15	F	51	14	48	44	ITPR1 gene Heterozygous deletions
15	CB21	SCA2	F	54	18	12	27	CAG 22/37
16	CB22	SCA28	F	42	18	–	21	–
17	CB23	SCA15	F	56	13	–	35	ITPR1 gene Heterozygous deletions
18	CB24	SCA2	F	60	8	48	31	CAG 22/37
19	CB26	FRDA	M	29	13	48	25	–
20	CB27	SCA2	M	40	8	36	18	CAG 22/38
21	CB29	SCA2	M	64	17	36	27	CAG 22/35
22	CB30	SCA2	F	43	13	12	28	CAG
23	CB31	ICA	F	62	18	–	17	–
24	CB32	SCA1	M	45	8	48	33	CAG/CTG 18/58
25	CB33	SCA2	M	42	8	12	24	CAG 22/39
26	CB34	SCA2	M	42	18	12	17	CAG 22/39
27	CB35	ICA	F	44	8	–	33	–

*The table reports for each patient diagnosis, gender, age, education, disease duration, the total motor scores as assessed by the International Cooperative Ataxia Rating Scale (ICARS) (Trouillas et al., 1997) and the CGA repeats. *ICARS: minimum score 0 (absence of motor deficits), maximum score 100 (maximum presence of motor deficits); FRDA, Friedreich's ataxia; SCA1, spinocerebellar ataxia type 1; SCA2, spinocerebellar ataxia type 2; SCA15, spinocerebellar ataxia type 15; SCA28, spinocerebellar ataxia type 28; ICA, Idiopathic Cerebellar Atrophy; F, Female; M, Male.*

was detected in the EA test total score (MWU = 310; $Z = -0.94$; $p = 0.34$). Boxplots of the row scores obtained by CB and HS in each social cognition task are reported in **Supplementary Figure 1**.

The percentage of accuracy, calculated as the percentage of the correct responses for each test, is shown in **Figure 1**.

No correlations were evidenced between each task score and the ICARS total score, the disease duration and executive function scores. Regarding the VAS scores, an inverse correlation was detected only between VAS-Mood and EA score. The results of Spearman correlation analyses are reported in **Table 3**.

MRI Results

Voxel-Based Morphometry

The between-group voxel wise comparison of the GM maps revealed a statistically significant GM loss in the cerebellar cortex of CB patients compared to HS. More specifically, a large cluster of significantly decreased GM volume (cluster size: 34334; FWE $p = 0.05$) was found. Peak voxels were centered in the left and right lobules I-IV of the anterior cerebellum and right lobule VI with extension in the left side and vermis portion and in the left and right crus I-II. A second large cluster of significantly decreased GM volume (cluster size: 11568; FWE $p = 0.05$) was also found. Peak voxels were centered in the bilateral hemispheric

TABLE 2 | Neuropsychological results for the CB patients.

Neuropsychological Tests	Mean (sd)	Range	Cut-off	Number impaired	Not tested
INTELLECTUAL FUNCTIONING					
WAIS-R	88.30 (13.11)	61–115	<70	1 (CB35)	–
Ravens' 47	29.44 (3.20)	22–34	<18.96	–	–
VERBAL COMPREHENSION					
Token test	32.50 (1.53)	29–35	<32	1 (CB21)	1 (CB27)
VERBAL PRODUCTION					
Denomination of words described by the examiner	1.22 (1.51)	0–5	>2	2 (CB3, CB33)	4 (CB1, CB27, CB9, CB35)
Phrase Construction	10.64 (2.61)	3–15	<8.72	3 (CB5, CB14, CB21)	5 (CB1, CB3, CB7, CB9, CB12)
VERBAL MEMORY					
Rey's 15 mots short term	44.24 (6.47)	34–61	<28.53	–	1 (CB7)
Rey's 15 mots long term	9.92 (2.36)	5–14	<4.69	–	1 (CB7)
Forward digit span	5.72 (0.89)	4–8	<5	2 (CB5, CB24)	1 (CB7)
Backward digit span	4.32 (1.07)	3–7	<3	–	1 (CB7)
EPISODIC MEMORY					
Short-Story recall	10.75 (3.57)	2–15	<4.75	2 (CB4, CB33)	1 (CB7)
VISUOSPATIAL MEMORY					
Rey-Osterrieth figure (recall)	12.57 (6.76)	1–27	<9.47	7 (CB3, CB4, CB14, CB21, CB29, CB30, CB32)	1 (CB7)
Forward Corsi	5.36 (1.19)	3–9	<5	5 (CB5, CB12, CB15, CB16, CB35)	2 (CB7, CB4)
Backward Corsi	4.64 (1.11)	3–8	<3	–	2 (CB7, CB4)
VISUOSPATIAL ABILITY					
Rey-Osterrieth figure (copy)	30.97 (3.60)	18–36	<28.88	2 (CB3, CB32)	1 (CB7)
ATTENTION					
Multiple features targets cancellation task	0.93 (0.07)	0–1	<0.869	2 (CB14, CB30)	1 (CB7)
Lines cancellation task	0.28 (0.74)	0–3	–	–	1 (CB7)
Trail making test: A	65.13 (28.26)	29–153	≥94	1 (CB33)	3 (CB7, CB9, CB35)
B	127.54 (37.14)	60–211	≥283	–	3 (CB7, CB9, CB35)
A-B	59.71 (37.01)	−8 to 178	≥187	–	3 (CB7, CB9, CB35)
EXECUTIVE FUNCTIONS					
Phonological fluency (FAS)	30.38 (9.04)	17–54	<17.35	1 (CB9)	1 (CB7)
WCST:					
Total Errors	107.62 (10.48)	81–119	<85-91	1 (CB9)	1 (CB7)
Perseverative Responses	110.58 (24.38)	81–138	<85-91	–	1 (CB7)
Perseverative Errors	114.54 (13.71)	81–138	<85-91	1 (CB9)	1 (CB7)

The patients' performance to each test was considered impaired when the score was below the cut-off value, with exception of the "Denomination of words described by the examiner" and the "Trial making test" in which the performance resulted impaired when the score was higher than the cut-off value.

TABLE 3 | Correlations between each social cognition tasks score and the VAS, the ICARS total score, the disease duration and executive functions scores (WCST, FAS).

	RME	ToM	"FP" Stories	"no-FP" Stories	EA
VAS-Mood	$R = -0.27$	$R = 0.11$	$R = -0.20$	$R = 0.09$	$R = -0.60$
	$P = 0.25$	$P = 0.61$	$P = 0.34$	$P = 0.68$	$P = 0.00$
VAS-Anxiety	$R = 0.02$	$R = 0.01$	$R = 0.26$	$R = -0.17$	$R = -0.22$
	$P = 0.93$	$P = 0.98$	$P = 0.22$	$P = 0.43$	$P = 0.30$
ICARS Total Score	$R = -0.07$	$R = -0.41$	$R = 0.12$	$R = -0.13$	$R = 0.11$
	$P = 0.74$	$P = 0.06$	$P = 0.54$	$P = 0.53$	$P = 0.58$
Disease Duration	$R = -0.16$	$R = -0.20$	$R = -0.02$	$R = 0.05$	$R = -0.15$
	$P = 0.50$	$P = 0.38$	$P = 0.94$	$P = 0.83$	$P = 0.50$
WCST (Total Errors)	$R = -0.08$	$R = -0.02$	$R = -0.24$	$R = 0.00$	$R = -0.03$
	$P = 0.72$	$P = 0.93$	$P = 0.25$	$P = 0.99$	$P = 0.88$
WCST (Perseverative Errors)	$R = -0.07$	$R = -0.10$	$R = -0.22$	$R = 0.01$	$R = -0.11$
	$P = 0.76$	$P = 0.64$	$P = 0.27$	$P = 0.95$	$P = 0.60$
FAS	$R = 0.02$	$R = -0.31$	$R = 0.22$	$R = 0.09$	$R = 0.05$
	$P = 0.94$	$P = 0.12$	$P = 0.29$	$P = 0.69$	$P = 0.79$

VAS, Visual Analogue Scale; ICARS, International Cooperative Ataxia Rating Scale; WCST, Wisconsin Card Sorting Test; FAS, Phonological fluency.

lobule VIIIa as well as vermis VIIIa with extension in vermis IX (**Figure 2**). Detailed results with peak voxel coordinates of voxel wise analyses are reported in **Table 4**.

No significant differences were found between total GM volumes of CB patients (mean = 645.91 mm^3; $SD = 68.05$) and HS (mean = 656 mm^3; $SD = 49.93$) as assessed by the t-test analysis (t-value 0.8567; $p = 0.39$).

Seed-Based fMRI Analysis

Taking into account the VBM results, specific cerebellar regions of reduced GM were chosen as ROIs for the seed-based analysis (see section Materials and Methods). A total of 13 different voxel wise analyses were performed. When comparing CB patients and HS, selectively in the CB patients, distinct patterns of significantly decreased FC were found between cerebellar ROIs and the cerebral cortex (**Figure 3**; **Table 5**).

In the anterior cerebellum, lobules I-IV showed decreased FC with cortical regions related to motor and somatosensory control, such as the precentral gyrus (BA 4, 6), postcentral gyrus (BA 3, 43), rolandic operculum, and inferior frontal gyrus (BA 44, 45). Moreover, decreased FC was also evidenced with cerebral areas involved in mentalizing processes, such as the supramarginal gyrus, anterior cingulate cortex (BA 24, 32), posterior cingulate cortex (BA 23) (right lobule I-IV), left orbitofrontal cortex (BA 47) and middle frontal gyrus (dorsolateral prefrontal cortex - dlPFC - BA 46) (**Figure 3A**).

In the intermediate cerebellum, lobule VI showed a decreased FC with the middle frontal gyrus (dlPFC - BA 46), left premotor cortex (BA 6), inferior frontal gyrus (BA 44) and temporal pole area (BA 38) (**Figure 3B**).

In the posterior cerebellum, crus I-II showed decreased FC with cortical regions implicated in more complex and abstract aspects of social cognition. In particular, decreased FC was found between the left crus I-II and the middle frontal gyrus, the dorsomedial prefrontal cortex (dmPFC) (BA 8, 9), the superior frontal gyrus (BA 10) and the orbitofrontal cortex (BA 11). Reduced FC was also present between the right crus I and left inferior frontal gyrus (BA 45) and precentral gyrus (in the supplementary motor area - SMA - BA 6) (**Figure 3C**).

No significant functional alterations were found between the right crus II, the right and left lobule VIIIa and the cerebral cortex.

Finally, decreased FC was evidenced between specific portions of the vermis and cerebral areas involved in emotional processing or belonging to mirroring and mentalizing networks, such as the middle frontal gyrus (dmPFC - BA 9), anterior cingulate cortex (BA 32, 24), premotor cortex and supplementary motor areas (BA 6, 8), orbitofrontal cortex (BA 11, 47), inferior frontal gyrus (BA 44), middle frontal gyrus (dlPFC - BA 46), angular gyrus, and superior temporal sulcus (STS) (BA 21/22) (**Figure 3D**).

A detailed report of the seed-based analyses with MNI coordinates, and peak Z scores is summarized in **Table 5**, where the numbers of voxels in each cluster express the extension and magnitude of significant FC modifications and the peak z-scores express the highest significance in a voxel.

DISCUSSION

In recent decades, the cerebellum has been acknowledged as a central area in the context of adaptive control and predictive coding, including the prediction and organization of sensorimotor and cognitive behavior (Ito, 2008; Molinari et al., 2009; D'Angelo and Casali, 2013; Sokolov et al., 2017).

In the present study, we used well-known social cognitive tasks focusing on different anticipation/prediction requirements to clarify the possible role of the cerebellum as a predictor in social interactions. As previously stated, in social interactions, at least two distinct processes are fundamental: lower-level processes of immediate perception that include an immediate affective response (i.e., the visceral feelings perceived when we look at another fearful, smiling or crying person) and a more reflective and conscious representation based on the role and

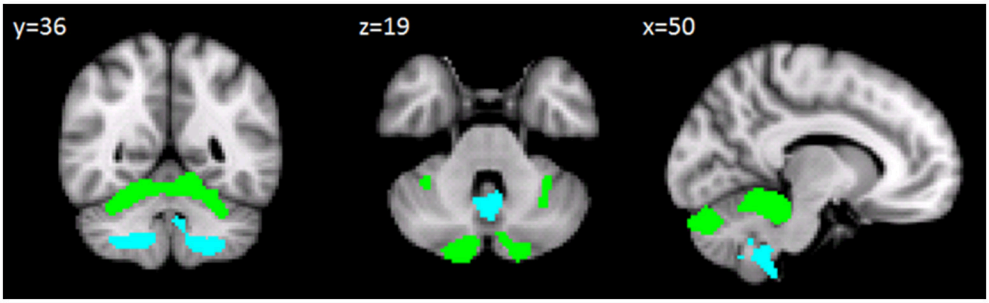

FIGURE 2 | Between-group voxel-based comparison of cerebellar GM density. Cerebellar regions showing patterns of significantly reduced GM in CB compared to HS are reported and superimposed on the Spatially Unbiased Infratentorial Template (SUIT) (Diedrichsen et al., 2009) in coronal ($y = 36$), axial ($z = 19$) and sagittal ($x = 50$) slices. Clusters of significantly decreased GM in the cerebellum are shown in green (cluster size: 343334) and light blue (cluster size: 11568). The results significant at p-values < 0.05 after family wise error (FWE) cluster-level correction. Images are shown in radiological convention.

TABLE 4 | Statistics of voxel wise comparisons of cerebellar GM density (CB < HS).

Cluster Size (NoV)	Coordinates			Cluster Peak *Z*-score	Brain region
	x	*y*	*z*		
34334	−10	−38	−19	5.23	L-Hem I-IV
	13	−38	−22	5.12	R-Hem I-IV
	22	−63	−25	4.66	R-Hem VI
11568	−23	−57	−50	4.65	L-Hem VIIIa
	0	−59	−34	4.51	R-Hem VIIIa
	23	−58	−49	4.50	Vermal-VIIIa

perspective taking (i.e., the capacity to suppose and understand why a person is scared, happy, or sad) to make predictions about imminent or future social behavior (Coricelli, 2005; Shamay-Tsoory et al., 2009).

Interestingly, we found that our cohort of patients presented with alterations both in the immediate and automatic perception of emotion and mental state and in the more complex conceptual level of ToM process. Specifically, the CB patients showed an impaired performance in the RME test, which involves the automatic attribution of relevant mental states regardless of the context. The RME test requires the subjects to "tune in" to the mental state of the actor's eye-region expression at an unconscious, rapid, and automatic level (Baron-Cohen et al., 2001). In this case, automaticity and categorization are crucial to determine the meaning of expression (Knutson et al., 2007) and to infer the other's mental state (Hoche et al., 2016).

Looking at the more complex level of the mentalizing process, the CB patients showed impairments in the Advanced ToM task and in the social "faux pas" stories (Stone et al., 1998; Blair and Cipolotti, 2000). In these conditions, the sequential events are unexpected and not univocal, requiring a constant comparison between the event and the social expectation and a high level of prediction. For example, the detection of a "faux pas" (i.e., when someone says something they should not and not realizing they should not say it) requires not only the cognitive understanding that a person has said something inappropriate with respect to the expected behavioral patterns but also the prediction of the consequences of the actor's behavior. The subject is required to predict the actor's behavior based on previous experiences to recognize the upcoming error.

When the patterns of the stories required a minor level of prediction and of error monitoring, such as in the "no-faux pas" stories and in the Emotion Attribution test, the CB patients showed good performance. Indeed, in these conditions, the social situation was univocal and well described in the story text.

Our results are in line with earlier reports of patients affected by cerebellar pathology that revealed specific deficits in the RME test (Hoche et al., 2016) and in social emotion identification from faces (D'Agata et al., 2011; Adamaszek et al., 2014). Moreover, an impairment in the Advanced ToM task was found in patients with superficial siderosis (a pathological condition predominantly involving the cerebellum), despite normal performance on the Emotion Attribution test and social judgment tasks (Van Harskamp et al., 2005).

In our cohort of CB patients, the alterations in specific aspects of ToM are not explained by a generalized intellectual and/or a verbal comprehension impairment. Indeed, the neuropsychological assessment revealed the presence of selective and very slight impairments in some patients but did not show clear evidence of general cognitive impairment. This result is consistent with findings that patients who are affected by cerebellar damage do not present with intellectual deterioration

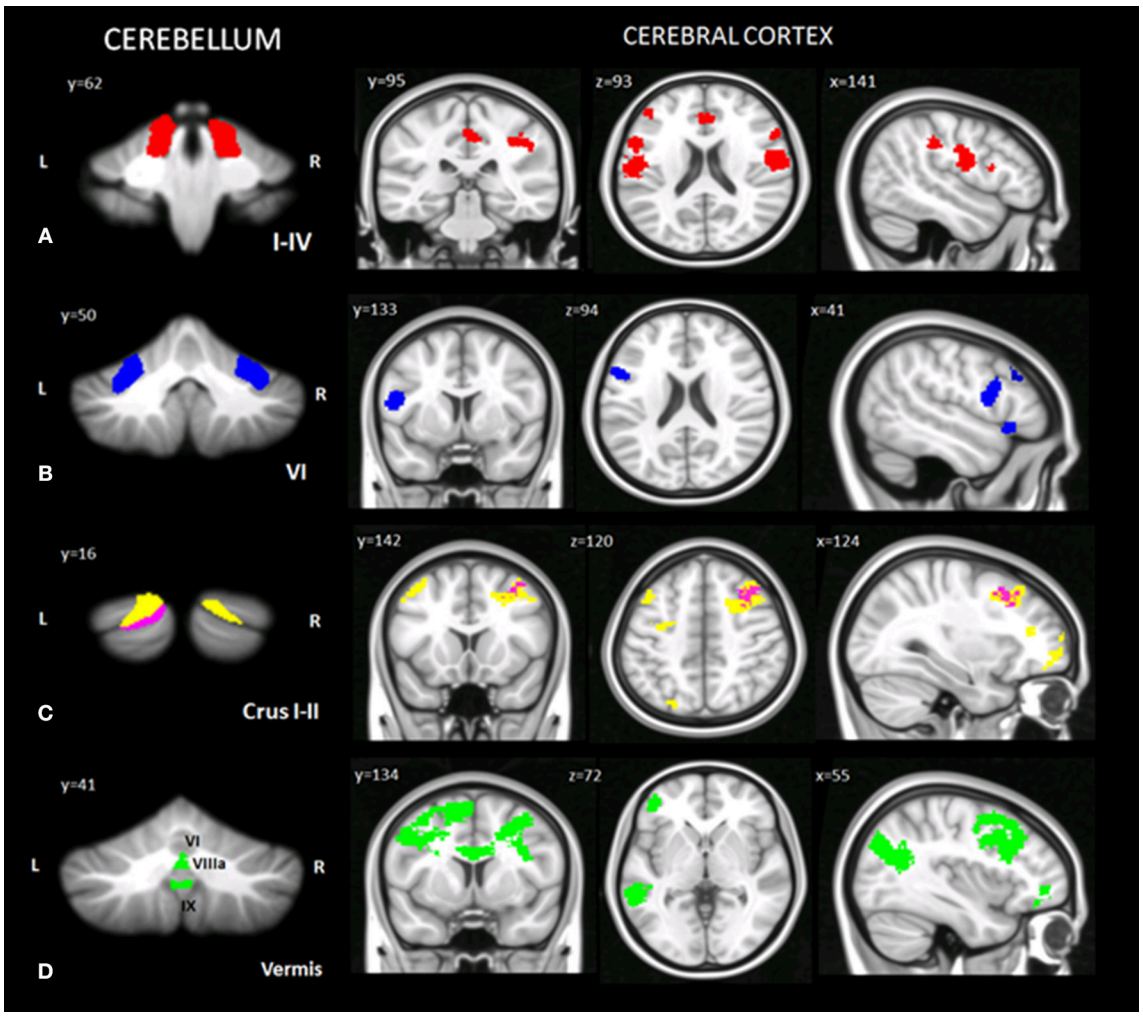

FIGURE 3 | Cerebello-cerebral functional connectivity. Cerebellar regions of interest and corresponding cluster of decreased functional connectivity in the cerebral cortex. **(A)** Anterior cerebellar ROIs (I-IV, in red); **(B)** intermediate cerebellar ROIs (VI, in blue); **(C)** posterior cerebellar ROIs (crus I, in yellow; crus II, in magenta); **(D)** vermal cerebellar ROIs (VI, VIIIa, IX, in green). Cluster of significantly decreased functional connectivity in the cerebral cortex of patients, shown in coronal (y), axial (z), and sagittal (x) slices. Cluster-level FWE correction ($p < 0.05$). Detailed statistics and coordinates of the peak voxels showing statistical significance in the cluster are reported in **Table 5**. R = right, L = left.

(Tedesco et al., 2011). It is worth noting that in cerebellar patients' cohorts, mostly standard norms of testing do not detect cognitive impairments characterizing the "cerebellar cognitive affective syndrome" (CCAS) (Schmahmann and Sherman, 1998), and very often they can be detected only when the patients are compared to matched healthy controls. In this respect, a scale was recently published to diagnose the CCAS (Hoche et al., 2018), but we unfortunately collected our data before its publication. Moreover, our sample had no difficulties in understanding other story-type stimuli, such as "no-faux pas" stories or emotion attribution tasks. Additionally, it is also unlikely that a generalized executive impairment accounts for our patients' mentalizing deficit, considering the absence of correlation between the ToM scores and the executive test scores in our cohort. This claim is in line with the increasing literature suggesting that executive functioning and ToM abilities are dissociable (Blair and Cipolotti, 2000; Fine et al., 2001; Bird et al., 2004). Moreover, the correlation analysis excluded any relationship between mood and motor impairment on task performance. It has to be noted that the correlation between the EA score and the VAS-Mood score was inverse; thus, it does not explain CB performance in EA test.

Altogether, these findings indicated that in the presence of cerebellar damage, the performances subtending the social interaction become less accurate mainly when the stimuli require automatic processing or a high level of prediction.

Particularly, regarding the automatic processing and the well-known cerebellar role in implicit elaboration (Molinari et al., 2002; Schmahmann, 2018), the cerebellum may act at the implicit

TABLE 5 | Statistics of cerebellar ROI functional connectivity results (CB < HS).

		Cluster Size (NoV)	Coordinates			Cluster Peak *Z*-score	Brain region	Brodmann areas
			x	*y*	*z*			
Anterior	Left I-IV	1024	−48	−20	28	4.97	L- Postcentral Gyrus	3
			−54	12	8	4.58	L- Inferior Frontal Gyrus	44
			−52	10	18	4.18		
		493	−38	50	0	4.66	L- Middle Frontal Gyrus	46
			−40	46	10	4.41		
			−36	42	2	4.23	L- Orbitofrontal cortex	47
		335	50	−30	36	4.39	R- Postcentral Gyrus	2
			38	−32	40	3.98	R- Supramarginal Gyrus	40
			40	−40	46	3.95		40
		240	58	24	22	4.35	R- Inferior Frontal Gyrus	45
			60	2	10	4.08	R- Rolandic Operculus	–
			50	−6	14	3.23		
		302	−6	36	14	4.03	L- Anterior Cingulate	24
			6	36	8	3.53	R- Anterior Cingulate	25
			6	36	24	3.52		32
	Right I-IV	1189	−42	44	10	4.73	L- Inferior Frontal Gyrus	45
			−38	42	0	4.57	L- Orbitofrontal Cortex	47
			−38	50	2	4.33	L- Middle Frontal Gyrus	46
		906	52	−4	20	4.61	R- Rolandic Operculum	–
			58	20	16	4.45	R- Inferior Frontal Gyrus	44
			66	−12	24	3.99	R- Postcentral Gyrus	43
		1411	−54	14	8	4.38	L- Inferior Frontal Gyrus	44
			−48	−8	24	4.28	L- Precentral Gyrus	4
			−46	−18	28	4.26	L- Postcentral gyrus	3
		182	6	−28	44	3.90	R- Posterior Cingulate	23
			14	−22	46	3.62		
			18	−28	42	3.35		
Intermediate	Left VI	192	−44	26	28	4.24	L- Middle Frontal Gyrus	46
			−48	26	36	4.17		
			−42	32	38	3.47		
	Right VI	447	−50	6	18	4.28	L- Precentral gyrus	6
			−52	20	−8	3.70	L- Temporal Pole	38
			−54	12	24	3.60	L- Inferior Frontal Gyrus	44
Posterior	Left Crus I	295	−34	6	56	4.85	L- Middle Frontal Gyrus	8
			−44	20	46	4.04	L- Middle Frontal Gyrus	9
		1006	36	26	42	4.80	R- Middle Frontal Gyrus	9
			28	22	40	4.77		
			28	8	42	4.40		
		406	26	54	0	4.71	R- Orbitofrontal Cortex	11
			30	50	−10	3.56		
			28	28	12	4.21	R- Superior Frontal Cortex	10
		246	48	36	16	3.71	R- Inferior Frontal Gyrus	45
			30	34	16	3.68		
			36	40	16	3.67		
	L-Crus II	366	30	22	44	4.58	R- Middle Frontal Gyrus	8/9
			46	24	40	4.18		
			36	18	48	3.96		
	R-Crus I	239	−46	28	14	4.50	L- Inferior Frontal Gyrus	45

(Continued)

TABLE 5 | Continued

		Cluster Size (NoV)	Coordinates			Cluster Peak *Z*-score	Brain region	Brodmann areas
			x	*y*	*z*			
		210	−30	−14	56	3.96	L- Precentral Gyrus	6
			−34	−8	42	3.89		
			−34	4	62	3.77		
Vermis	VIIIA	7964	−44	20	28	4.43	L - Inferior Frontal Gyrus	44
			36	14	30	3.77	R - Inferior Frontal Gyrus	44
			−16	10	60	3.60	L - Superior Frontal Gyrus	6
		2783	−40	58	16	3.79	L- Frontal Pole	46
			−34	−56	32	3.77	L - Angular Gyrus	19
			−58	−42	−6	3.66	L- Middle Temporal Cortex (STS)	21/22
	VI	228	−42	48	−4	4.36	L- Frontal Pole	47
			−40	40	−16	3.89	L- Frontal Pole	47
			−30	50	−10	3.68	L- Frontal Pole	11/47
		202	26	8	44	4.27	R- Middle Frontal Gyrus	6/8
			34	8	52	4.02	R- Middle Frontal Gyrus	9
			16	2	40	3.55	R- Anterior Cingulate	24
		387	−12	8	50	4.11	L- Supplementaly Motor Area	6
			−16	12	64	4.01		
			−10	8	58	3.79		
	IX	635	−30	20	56	3.78	L- Middle Frontal Gyrus	8
			−40	12	54	3.77	L- Middle Frontal Gyrus	9
			−16	16	46	3.56	L- Anterior Cingulate	32

MNI coordinates (x, y, z) in the Montreal Neurological Institute space and peak Z score of the peak voxels showing the greatest statistical differences in a cluster are reported. Only regions that survived after correction for multiple comparisons (FWE corrected $p < 0.05$) were considered. NoV = number of voxels; L: left; R: right.

level by matching the external information (i.e., expression of the eyes) with the internal model of eye-region expression linked to previous emotional experiences, contributing to guarantee an immediate judgment about the mental state of others. When cerebellar damage is present, the required fast and continuous exchange of information between the external stimuli and the internal model might be affected, thus interfering with the automatic processes.

At a more complex level, to obtain a sense of another individual's state of mind, we need to predict the social consequences of how we act or what we say across various contexts, and we have to understand what caused a specific behavior and how it may impact the social situation (Mahon and Caramazza, 2008; Koster-Hale and Saxe, 2013). In this context, the capacity to recognize deviations/errors in the outcome of a social interaction and to use this information to regulate and adjust future social expectations becomes useful for adaptive social behavior.

To study error processing in the ToM domain, Berthoz et al. (2002) used a contrast between scenarios in which a social prediction was confirmed or violated. They found that violations of social norms elicited higher activation not only in a frontotemporal network associated with social cognition but also in the cerebellum. According to the forward model theory (Ito, 2008), signals from the cerebellum might continuously check whether an anticipated event based on social information fits with current behavior, contributing to the more complex and abstract forms of prediction and guaranteeing fluid control in social interactions. In the presence of cerebellar dysfunction, the error signal is missed, and the performance becomes less accurate when the level of predictive load is high.

The present data are in line with the idea that the cerebellum plays a role both in implicit processes and in prediction mechanisms (Doyon et al., 2003) and reinforce the idea that the cerebellum can be conceptualized as a unique predictive structure in different domains and that its functional role in social cognition is similar to that for sensorimotor control (Wolpert and Kawato, 1998; Ito, 2008; Sokolov et al., 2017).

In the social domain, the processing mechanisms are supported by the bidirectional anatomical connections of the cerebellum with limbic areas and specific portions of the frontal and temporo-parietal lobes that are involved in emotional regulation and in the perception of socially salient material (Schmahmann, 1991; Schmahmann and Pandya, 1997; Middleton and Strick, 2001; Kelly and Strick, 2003). Coherently, in the present study, CB patients showed structural and functional alterations within cerebello-cortical networks that are involved in different aspects of social interactions. Specifically, in our patients, cerebellar atrophy, in terms of GM reduction, was localized in specific portions of the vermis (VI, IX, VIIIa) and in lobule VI.

fMRI studies demonstrated that these cerebellar areas are activated during classic mirror tasks (Van Overwalle et al., 2014) and belong to the Salience Network (SN) as well as to the

Default Mode Network (DMN) (Habas et al., 2009; Buckner et al., 2011). Moreover, the posterior vermis is recruited during emotional processing (Baumann and Mattingley, 2012), and indeed, it is considered the "limbic cerebellum" (Schmahmann, 2007; Stoodley and Schmahmann, 2010).

In our cerebellar patients, these regions of reduced GM also showed decreased FC with cerebral areas involved in mirroring, emotional and mentalizing processing, such as the middle frontal gyrus, precentral gyrus, premotor cortex, orbitofrontal cortex, anterior cingulate, inferior frontal gyrus, angular gyrus, STS and temporal pole (Abu-Akel and Shamay-Tsoory, 2011). Indeed, it has been evidenced that higher-order cortices in the temporal pole, orbitofrontal cortex and inferior frontal gyrus subserve the processing of emotions from facial expression and in emotional contagion (Adolphs, 2004; Chakrabarti et al., 2006; Dapretto et al., 2006; Gazzola et al., 2006; Jabbi et al., 2007; Ross and Monnot, 2008; Shamay-Tsoory, 2011). The superior temporal sulcus and premotor cortex belong to the mirror network (Bickart et al., 2014). The medial prefrontal cortex, medial temporal lobe and angular gyrus belong to the DMN, which is thought to be involved in mental simulation for planning, self-evaluation, and social interaction (Habas et al., 2009).

We also found a pattern of GM reduction in the anterior cerebellum (bilateral lobule I-IV). These cerebellar regions are more involved in somatosensory and motor control aspects (Schmahmann, 2010; Stoodley and Schmahmann, 2010). As expected, these lobules showed reduced FC with the precentral gyrus, postcentral gyrus, and rolandic operculum. However, we also observed a pattern of decreased FC between the anterior cerebellum and cerebral areas involved in the mirror network and mentalizing processes, such as the inferior frontal gyrus, supramarginal gyrus (Reed and Caselli, 1994; Carlson, 2012), anterior and posterior cingulate cortex, orbitofrontal cortex and middle frontal gyrus (in the dlPFC).

Finally, the posterior cerebellum showed a specific pattern of GM reduction mainly localized in the bilateral crus I/II. The posterior lateral cerebellum has been described as involved in more reflective, cognitive components of the mentalizing tasks (Sokolov et al., 2017). Interestingly, our CB patients showed a pattern of decreased FC between these posterior regions of the cerebellum and areas of the cerebral cortex involved in high-order social behavior and executive control, such as the dmPFC and the superior frontal gyrus and orbitofrontal cortex (Habas et al., 2009; Abu-Akel and Shamay-Tsoory, 2011; Shamay-Tsoory, 2011; Bickart et al., 2014).

Overall, in our patients, the structural alterations in the specific lobule of the cerebellum interfered with the modulatory function that the cerebellum exerts on the cortical projection areas, thus accounting for altered functional connectivity in the cerebellar-cortical networks involved in different aspects of social cognition and, in particular, in the mentalizing process. Indeed, the disrupted cerebellar modulatory function resulted in impaired ToM outcomes, particularly when the stimuli processing requires a high level of prediction.

In light of the present observations, the cerebellum could be conceptualized as a part of the social brain by virtue of the role that it plays in supporting other more classically social regions (Jack and Morris, 2014). Particularly, the cerebellar-cerebral networks could have a role in the predictive aspects of social behavior by guaranteeing the continuous communication between cerebellar modules and projection cerebral areas. Therefore, important theoretical breakthroughs can be made by studying cerebellar function in social behavior from the prediction perspective.

LIMITATIONS

The present study is correlative at descriptive level and does not bring evidence of a direct link between the observed atrophies in the cerebellum and the reported performances in social and cognitive tasks. This is a limitation due to the heterogeneity of the study population and needs to be addressed in patients affected by homogeneous cerebellar pathologies.

Another important issue that needs to be discussed is that, even if in the present study the macroscopic damage of cerebral cortex was excluded by the visual inspection of the clinical MRI scans by an expert neuroradiologist and there was not a significant difference in the total GM volume between CB patients and HS, the possibility of local and microscopic GM loss, as reported in previous studies (Brenneis et al., 2003; Della Nave et al., 2008; Selvadurai et al., 2016) cannot be ruled out.

However, it has to be noted that the aim of the present study was to investigate the cerebello-cerebral functional connectivity that it is particularly suitable for the study of the cerebellum, in which the function of each sub-region is defined by its connections with specific brain areas (Schmahmann and Pandya, 1997; Middleton and Strick, 2001).

CONCLUSION

In conclusion, in the presence of cerebellar damage, patients fail in both automatic lower-level and conceptual/abstract components of social cognition, and the idea can be advanced that the cerebellar modulatory function on the cortical projection areas subtends these processes. These findings can be explained considering different aspects of the prediction mechanisms needed for the social interactions (Brown and Brüne, 2012) and taking into account the connections that the cerebellum has with limbic areas and specific portions of the frontal and temporo-parietal lobes involved in metalizing processes (Schmahmann and Pandya, 1997; Middleton and Strick, 2001). According to the "sequence detection theory" (Braitenberg et al., 1997; Leggio et al., 2011; Leggio and Molinari, 2015), during social interactions in which event sequences play a role, the cerebellum allows the prediction of the other person's behaviors in an intuitive way to optimize the social behavior.

AUTHOR CONTRIBUTIONS

SC and MAL contributed to conception and design of the study. SC, MIL, and LS, contributed to the data acquisition and data

analysis. GO acquired the MRI protocol, processed and analyzed the MRI data. MB supervised MRI data processing. SC wrote the first draft of the manuscript. MAL supervised development of the work. All co-authors contributed to final editing and critical revision of the original manuscript.

FUNDING

The present study was supported by grants from the Italian Ministry of Instruction, University and Research (MIUR) (Grant Number RM11715C7E67E525) to MAL and from the Italian Ministry of Health to SC (Grant Number GR-2013-02354888).

ACKNOWLEDGMENTS

The editing support of American Journal Experts is acknowledged.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fncel.2018.00510/full#supplementary-material

Supplementary Figure 1 | Boxplots of the row scores obtained by the cerebellar patients and healthy subject in each social cognition task. CB, cerebellar patients; HS, healthy subjects; SE, standard error; SD, standard deviation.

REFERENCES

Abu-Akel, A., and Shamay-Tsoory, S. (2011). Neuroanatomical and neurochemical bases of theory of mind. *Neuropsychologia* 49, 2971–2984. doi: 10.1016/j.neuropsychologia.2011.07.012

Ackermann, H., Gräber, S., Hertrich, I., and Daum, I. (1997). Categorical speech perception in cerebellar disorders. *Brain. Lang.* 60, 323–331. doi: 10.1006/brln.1997.1826

Adamaszek, M., D'Agata, F., Kirkby, K. C., Trenner, M. U., Sehm, B., Steele, C. J., et al. (2014). Impairment of emotional facial expression and prosody discrimination due to ischemic cerebellar lesions. *Cerebellum* 13, 338–345. doi: 10.1007/s12311-013-0537-0

Adolphs, R. (2004). "Processings of emotional and social information by the human amygdala," in *The New Cognitive Neurosciences III*, ed M. S. Gazzaniga (Cambridge, MA: MIT Press), 1005–1016.

Aichhorn, M., Perner, J., Weiss, B., Kronbichler, M., Staffen, W., and Ladurner, G. (2009). Temporo-parietal junction activity in theory-of-mind tasks: falseness, beliefs, or attention. *J. Cogn. Neurosci*. 21, 1179–1192. doi: 10.1162/jocn.2009.21082

Albert, M. L. (1973). A simple test of visual neglect. *Neurology* 23, 658–664. doi: 10.1212/WNL.23.6.658

Andreasen, N. C., and Pierson, R. (2008). The role of the cerebellum in schizophrenia. *Biol. Psychiatry* 64, 81–88. doi: 10.1016/j.biopsych.2008.01.003

Baron-Cohen, S., Wheekwright, S., Hill, J., Raste, Y., and Plumb, I. (2001). The "Reading the mind in the eyes" test revised version: a study with normal adults, and adults with asperger syndrome or high-functioning autism. *J. Child. Psychol. Psych.* 42, 241–251. doi: 10.1111/1469-7610.00715

Baumann, O., and Mattingley, J. B. (2012). Functional topography of primary emotion processing in the human cerebellum. *Neuroimage* 61, 805–811. doi: 10.1016/j.neuroimage.2012.03.044

Beer, J. S., Mitchell, J. P., and Ochsner, K. N. (2006). Special issue: multiple perspectives on the psychological and neural bases of social cognition. *Brain Res.* 1079, 1–3. doi: 10.1016/j.brainres.2006.02.001

Berthoz, S., Armony, J. L., Blair, R. J., and Dolan, R. J. (2002). An fMRI study of intentional and unintentional (embarrassing) violations of social norms. *Brain* 125, 1696–1708. doi: 10.1093/brain/awf190

Bickart, K. C., Dickerson, B. C., and Barrett, L. F. (2014). The amygdala as a hub in brain networks that support social life. *Neuropsychologia* 63, 235–248. doi: 10.1016/j.neuropsychologia.2014.08.013

Bird, C. M., Castelli, F., Malik, O., Frith, U., and Husain, M. (2004). The impact of extensive medial frontal lobe damage on 'theory of mind' and cognition. *Brain* 127, 914–928. doi: 10.1093/brain/awh108

Biswal, B. B., Van Kylen, J., and Hyde, J. S. (1997). Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. *NMR Biomed.* 10,165–170. doi: 10.1002/(SICI)1099-1492(199706/08)10:4/5<165::AID-NBM454>3.0.CO;2-7

Blair, R. J., and Cipolotti, L. (2000). Impaired social response reversal. a case of 'acquired sociopathy'. *Brain* 123, 1122–1141. doi: 10.1093/brain/123.6.1122

Borbowsky, J. G., Benton, A. L., and Spreen, O. (1967). Word fluency and brain-damage. *Neuropsychologia* 5, 135–140. doi: 10.1016/0028-3932(67)90015-2

Braitenberg, V., Heck, D., and Sultan, F. (1997). The detection and generation of sequences as a key to cerebellar function: experiments and theory. *Behav. Brain. Sci.* 20, 229–245. doi: 10.1017/S0140525X9700143X

Brenneis, C., Bösch, S. M., Schocke, M., Wenning, G. K., and Poewe, W. (2003). Atrophy patternin SCA2 determined by voxel-based morphometry. *Neuroreport* 14, 1799–1802. doi: 10.1097/01.wnr.0000094105.16607.18

Brothers, L., and Ring, B. (1990). A neuroethological framework for the representation of mind. *J. Cogn. Neurosci.* 4, 107–118. doi: 10.1162/jocn.1992.4.2.107

Brown, E. C., and Brüne, M. (2012). The role of prediction in social neuroscience. *Front. Hum. Neurosci.* 6:147. doi: 10.3389/fnhum.2012.00147

Brunet, W., Sarfati, Y., Hardy-Baylé, M. C., and Decety, J. (2000). A PET investigation of the attribution of intentions with a nonverbal task *Neuroimage* 11, 157–166. doi: 10.1006/nimg.1999.0525

Buckner, R. L., Krienen, F. M., Castellanos, A., Diaz, J. C., and Yeo, B. T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. *J Neurophysiol.* 106, 2322–2345. doi: 10.1152/jn.00339.2011

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., and Venneri, A. (2002). Rey-Osterrieth complex figure: normative values in an Italian population sample. *Neurol. Sci.* 22, 443–447. doi: 10.1007/s100720200003

Calarge, C., Andreasen, N. C., and O'Leary, D. S. (2003). Visualizing how one brain understands another: a PET study of theory of mind. *Am. J. Psychiatry*.160, 1954–1964.doi: 10.1176/appi.ajp.160.11.1954

Caltagirone, C., Gainotti, G., Carlesimo, G. A., and Parnetti, L. (1995). Batteria per la valutazione del deterioramento mentale: i. descrizione di uno strumento di diagnosi neuropsicologica [The Mental Deterioration Battery: I. Description of a neuropsychological diagnostic instrument]. *Arch. Psicol. Neurol. Psichiatr*. 56, 461–470.

Carlesimo, G. A., Buccione, I., Fadda, L., Graceffa, A., Mauri, M., Lorusso, S., et al. (2002). Standardizzazione di due test di memoria per uso clinico: breve racconto e figura di rey. *Nuova Rivista Neurol.* 1, 1–13.

Carlson, N. R. (2012). *Physiology of Behavior, 11th Edn*. Amherst, MA: Pearson.

Chakrabarti, B., Bullmore, E., and Baron-Cohen, S. (2006). Empathizing with basic emotions: common and discrete neural substrates. *Soc. Neurosci.* 1, 364–384. doi: 10.1080/17470910601041317

Coricelli, G. (2005). Two-levels of mental states attribution: from automaticity to voluntariness. *Neuropsychologia* 43, 294–300. doi: 10.1016/j.neuropsychologia.2004.11.015

Corsi, P. M. (1972). Human memory and the medial temporal regions of the brain. *Diss. Abstr. Int.* 34:891B.

D'Agata, F., Caroppo, P., Baudino, B., Caglio, M., Croce, M., Bergui, M., et al. (2011). The recognition of facial emotions in spinocerebellar ataxia patients. *Cerebellum* 10, 600–610. doi: 10.1007/s12311-011-0276-z

D'Angelo, E., and Casali, S. (2013). Seeking a unified framework for cerebellar function and dysfunction: from circuit operations to cognition. *Front. Neural Circuits* 6:116. doi: 10.3389/fncir.2012.00116

Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., et al. (2006). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nat. Neurosci.* 9, 28–30. doi: 10.1038/nn1611

De Renzi, E., and Vignolo, L. A. (1962). The token test: a sensitive test to detect receptive disturbances in aphasics. *Brain* 85, 665–678. doi: 10.1093/brain/85.4.665

Della Nave, R., Ginestroni, A., Tessa, C., Giannelli, M., De Grandis, D., Plasmati, R., et al. (2008). Brain structural damage in spinocerebellar ataxia type 2, a voxel-based morphometry study. *Mov. Disord.* 23, 899–903. doi: 10.1002/mds.21982

Diedrichsen, J., Balsters, J. H., Flavell, J., Cussans, E., and Ramnani, N. (2009). A probabilistic MR atlas of the human cerebellum. *Neuroimage* 46, 39–46. doi: 10.1016/j.neuroimage.2009.01.045

Doyon, J., Penhune, V., and Ungerleider, L. G. (2003). Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. *Neuropsychologia* 41, 252–262. doi: 10.1016/S0028-3932(02)00158-6

Fatemi, S. H., Aldinger, K. A., Ashwood, P., Bauman, M. L., Blaha, C. D., Blatt, G. J., et al. (2012). Consensus Paper: pathological role of the cerebellum in autism. *Cerebellum* 11, 777–807. doi: 10.1007/s12311-012-0355-9

Fine, C., Lumsden, J., and Blair, R. J. (2001). Dissociation between 'theory of mind' and executive functions in a patient with early left amygdala damage. *Brain* 124, 287–298. doi: 10.1093/brain/124.2.287

Friston, K. J., Frith, C. D., Liddle, P. F., and Frackowiak, R. S. (1993). Functional connectivity: the principal-component analysis of large (PET) data sets. *J. Cereb. Blood. Flow. Metab.* 13, 5–14. doi: 10.1038/jcbfm.1993.4

Gazzola, V., Aziz-Zadeh, L., and Keysers, C. (2006). Empathy and the somatotopic auditory mirror system in humans. *Curr Biol.* 16, 1824–1829. doi: 10.1016/j.cub.2006.07.072

Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., and Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. *Ital. J. Neuro. Sci.* 17:305. doi: 10.1007/BF01997792

Gu, X., Gao, Z., Wang, X., Liu, X., Knight, R. T., Hof, P. R., et al. (2012). Anterior insular cortex is necessary for empathetic pain perception. *Brain*. 135, 2726–2735. doi: 10.1093/brain/aws199

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C. F., Menon, V., et al. (2009). Distinct cerebellar contributions to intrinsic connectivity networks. *J. Neurosci.* 29, 8586–8594. doi: 10.1523/JNEUROSCI.1868-09.2009

Hainline, L. (1978). Developmental changes in visual scanning of face and non-face patterns by infants. *J. Exp. Child. Psychol.* 25, 90–115. doi: 10.1016/0022-0965(78)90041-3

Happè, F. G. E. (1994). An advanced text of theory of mind: understanding of story characters' thoughts and feelings by able autistic, mentally handicapped and normal children and adults. *J. Autism Dev. Disord.* 24, 129–154.

Hayes, M. H. S., and Paterson, D. G. (1921). Experimental development of the graphic rating method. *Psychol. Bull.* 18, 98–99.

Heaton, R. K. (1981). *A Manual for the Wisconsin Card Sorting Test*. Odessa: Western Psycological Services.

Heleven, E., and Van Overwalle, F. (2018). The neural basis of representing others' inner states. *Curr Opin. Psychol.* 23, 98–103. doi: 10.1016/j.copsyc.2018.02.003

Hoche, F., Guell, X., Sherman, J. C., Vangel, M. G., and Schmahmann, J. D. (2016). Cerebellar contribution to social cognition. *Cerebellum* 15, 732–743. doi: 10.1007/s12311-015-0746-9

Hoche, F., Guell, X., Vangel, M. G., Sherman, J. C., and Schmahmann, J. D. (2018). The cerebellar cognitive affective/Schmahmann syndrome scale. *Brain* 141, 248–270. doi: 10.1093/brain/awx317

Ito, M. (2006). Cerebellar circuitry as a neuronal machine. *Prog. Neurobiol.* 78, 272–303. doi: 10.1016/j.pneurobio.2006.02.006

Ito, M. (2008). Control of mental activities by internal models in the cerebellum. *Nat. Rev. Neurosci.* 9, 304–313. doi: 10.1038/nrn2332

Ivry, R. B., and Keele, S. W. (1989). Timing functions of the cerebellum. *J. Cogn. Neurosci.* 1, 136–152. doi: 10.1162/jocn.1989.1.2.136

Jabbi, M., Swart, M., and Keysers, C. (2007). Empathy for positive and negative emotions in the gustatory cortex. *Neuroimage* 34, 1744–1753. doi: 10.1016/j.neuroimage.2006.10.032

Jack, A., and Morris, J. P. (2014). Neocerebellar contributions to social perception in adolescents with autism spectrum disorder. *Dev. Cogn. Neurosci.* 10, 77–92. doi: 10.1016/j.dcn.2014.08.001

Johnstone, T., van Reekum, C. M., Oakes, T. R., and Davidson, R. J. (2006). The voice of emotion: an FMRI study of neural responses to angry and happy vocal expressions. *Soc. Cogn. Affect. Neurosci.* 1, 242–249. doi: 10.1093/scan/nsl027

Kelly, R. M., and Strick, P. L. (2003). Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *J. Neurosci.* 23, 8432–8444. doi: 10.1523/JNEUROSCI.23-23-08432.2003

Kipps, C. M., Duggins, A. J., McCusker, E. A., and Calder, A. J. (2007). Disgust and happiness recognition correlate with anteroventral insula and amygdala volume respectively in preclinical huntington's disease. *J. Cogn. Neurosci.* 19, 1206–1217. doi: 10.1162/jocn.2007.19.7.1206

Knutson, K. M., Mah, L., Manly, C. F., and Grafman, J. (2007). Neural correlates of automatic beliefs about gender and race. *Hum. Brain. Mapp.* 28, 915–930. doi: 10.1002/hbm.20320

Koster-Hale, J., and Saxe, R. (2013). Theory of mind: a neural prediction problem. *Neuron* 79, 836–848. doi: 10.1016/j.neuron.2013.08.020

Leggio, M., and Molinari, M. (2015). Cerebellar sequencing: a trick for predicting the future. *Cerebellum*. 14, 35–38. doi: 10.1007/s12311-014-0616-x

Leggio, M. G., Chiricozzi, F. R., Clausi, S., Tedesco, A. M., and Molinari, M. (2011). The neuropsychological profile of cerebellar damage: the sequencing hypothesis. *Cortex* 47, 137–144. doi: 10.1016/j.cortex.2009.08.011

Liverta Sempio, O., Marchetti, A., and Lecciso, F. (2005). *Faux Pas: Traduzione Italiana*. Milan: Theory of Mind Research Unit; Department of Psychology; Catholic University of the Sacred Heart.

Mahon, B. Z., and Caramazza, A. (2008). A critical look at the embodied cognition hypothesis and a new proposal for grounding conceptual content. *J. Physiol. Paris* 102, 59–70. doi: 10.1016/j.jphysparis.2008.03.004

Marra, C., Gainotti, G., Scaricamazza, E., Piccininni, C., Ferraccioli, M., and Quaranta, D. (2013). The Multiple Features Target Cancellation (MFTC): an attentional visual conjunction search test. normative values for the italian population. *Neurol. Sci.* 34, 173–180. doi: 10.1007/s10072-012-0975-3

Maurer, D. (1985). "Infants' perception of facedness," in *Social perception in infants,* eds T. Field and N. Fox (Norwood, NJ: Ablex), 73–100.

Meltzoff, A. N., and Moore, M. K. (1989). Imitation in newborn infants: exploring the range of gestures imitated and the underlying mechanisms. *Dev. Psychol.* 25, 954–962. doi: 10.1037/0012-1649.25.6.954

Miall, R. C., and Reckess, G. Z. (2002). The cerebellum and the timing of coordinated eye and hand tracking. *Brain Cogn.* 48, 212–226. doi: 10.1006/brcg.2001.1314

Miceli, G., Laudanna, A., Burani, C., and Capasso, R. (1994). *Batteria per l'Analisi dei Deficit Afasici (BADA)*. Rome: CEPSAG.

Middleton, F. A., and Strick, P. L. (2000). Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. *Brain. Cogn.* 42, 183–200. doi: 10.1006/brcg.1999.1099

Middleton, F. A., and Strick, P. L. (2001). Cerebellar projections to the prefrontal cortex of the primate. *J. Neurosci.* 21, 700–712. doi: 10.1523/JNEUROSCI.21-02-00700.2001

Molinari, M., Filippini, V., and Leggio, M. (2002). Neuronal plasticity of interrelated cerebellar and cortical networks. *Neuroscience*. 111, 863–870. doi: 10.1016/S0306-4522(02)00024-6

Molinari, M., Restuccia, D., and Leggio, M. (2009). State estimation, response prediction, and cerebellar sensory processing for behavioral control. *Cerebellum* 8, 399–402. doi: 10.1007/s12311-009-0112-x

Olivito, G., Cercignani, M., Lupo, M., Iacobacci, C., Clausi, S., Romano, S., et al. (2017). Neural substrates of motor and cognitive dysfunctions in SCA2 patients: a network based statistics analysis. *Neuroimage Clin.* 14, 719–725. doi: 10.1016/j.nicl.2017.03.009

Orsini, A., Grossi, D., Capitani, E., Laiacona, M., Papagno, C., and Vallar, G. (1987). Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. *Ital. J. Neurol. Sci.* 8, 539–548. doi: 10.1007/BF02333660

Orsini, A., and Laicardi, C. (1997). *Wais-r. Contributo alla taratura italiana*. Firenze: Organizzazioni Speciali.

Premack, D., and Woodruff, G. (1978). Does the chimpanzee have a 'theory of mind'? *Behav. Brain. Sci.* 4, 515–526.

Prior, M., Marchi, S., and Sartori, G. (2003). *Cognizione Sociale e Comportamento*. Vol. 1, *Uno Strumento Per la Misurazione*. Padova: Upsel Domenghini Editore.

Ramnani, N. (2012). Frontal lobe and posterior parietal contributions to the cortico-cerebellar system. *Cerebellum* 11, 366–383. doi: 10.1007/s12311-011-0272-3

Raven, J. C. (1949). *Progressive Matrices. Sets A, Ab, B: Board and Book Forms*. London: Lewis.

Reed, C. L., and Caselli, R. J. (1994). The nature of tactile agnosia: a case study. *Neuropsychologia* 32, 527–539. doi: 10.1016/0028-3932(94)90142-2

Rey, A. (1958). "Memorisation d'une sèrie de 15 mots en 5 rèpètions," in *L'examen Clinique en Psychologie*, ed A. Rey (Paris: Paris Presses), 141–193.

Rizzolatti, G., Fogassi, L., and Gallese, V. (2006). Mirrors of the mind. *Sci. Am*. 295, 54–61. doi: 10.1038/scientificamerican1106-54

Ross, E. D., and Monnot, M. (2008). Neurology of affective prosody and its functional-anatomic organization in right hemisphere. *Brain. Lang*. 104, 51–74. doi: 10.1016/j.bandl.2007.04.007

Saxe, R., and Kanwisher, N. (2003). People thinking about thinking people. The role of the temporo-parietal junction in "theory of mind". *Neuroimage* 19, 1835–1842. doi: 10.1016/S1053-8119(03)00230-1

Schmahmann, J. D. (1991). An emerging concept: the cerebellar contribution to higher function. *Arch. Neurol*. 48, 1178–1187. doi: 10.1001/archneur.1991.00530230086029

Schmahmann, J. D. (2007). The neuropsychiatry of the cerebellum – insights from the clinic. *Cerebellum* 6, 254–267. doi: 10.1080/14734220701490995

Schmahmann, J. D. (2010). The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. *Neuropsychol. Rev*. 20, 236–260. doi: 10.1007/s11065-010-9142-x

Schmahmann, J. D. (2018). The cerebellum and cognition. *Neurosci. Lett*. 688, 62–75. doi: 10.1016/j.neulet.2018.07.005

Schmahmann, J. D., and Pandya, D. N. (1997). The cerebrocerebellar system. *Int. Rev. Neurobiol*. 41, 31–60. doi: 10.1016/S0074-7742(08)60346-3

Schmahmann, J. D., and Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain* 121, 561–579. doi: 10.1093/brain/121.4.561

Selvadurai, L. P., Harding, I. H., Corben, L. A., Stagnitti, M. R., Storey, E., Egan, G. F., et al. (2016). Cerebral and cerebellar grey matter atrophy in Friedreich ataxia: the IMAGE-FRDA study. *J. Neurol*. 263, 2215–2223. doi: 10.1007/s00415-016-8252-7

Serafin, M., and Surian, L. (2004). Il test degli Occhi: uno strumento per valutare la 'teoria della mente'. *Giornale Italiano di Psicol*. 31, 213–236.

Shamay-Tsoory, S. G. (2011). The neural bases for empathy. *Neuroscientist* 17, 18–24. doi: 10.1177/1073858410379268

Shamay-Tsoory, S. G., Aharon-Peretz, J., and Perry, D. (2009). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain* 132, 617–627. doi: 10.1093/brain/awn279

Sokolov, A. A. (2018). The cerebellum in social cognition. *Front. Cell. Neurosci*. 12:145. doi: 10.3389/fncel.2018.00145

Sokolov, A. A., Miall, R. C., and Ivry, R. B. (2017). The Cerebellum: Adaptive Prediction for Movement and Cognition. *Trends. Cogn. Sci*. 21, 313–332. doi: 10.1016/j.tics.2017.02.005

Sokolovsky, N., Cook, A., Hunt, H., Giunti, P., and Cipolotti, L. (2010). A preliminary characterization of cognition and social cognition in spinocerebellar ataxia types 2, 1, and 7. *Behav. Neurol*. 23, 17–29. doi: 10.1155/2010/395045

Stone, V. E., Baron-Cohen, S., and Knight, R. T. (1998). Frontal lobe contributions to theory of mind. *J. Cogn. Neurosci*. 10, 640–656. doi: 10.1162/089892998562942

Stoodley, C. J., and Schmahmann, J. D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex* 46, 831–844. doi: 10.1016/j.cortex.2009.11.008

Tedesco, A. M., Chiricozzi, F. R., Clausi, S., Lupo, M., Molinari, M., and Leggio, M. G. (2011). The cerebellar cognitive profile. *Brain* 134, 3672–3686. doi: 10.1093/brain/awr266

Trouillas, P., Takayanagi, T., Hallett, M., Currier, R. D., Subramony, S. H., Wessel, K., et al. (1997). International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. the ataxia neuropharmacology committee of the world federation of neurology. *J. Neurol. Sci.* 145, 205–211. doi: 10.1016/S0022-510X(96)00231-6

van de Ven, V. G., Formisano, E., Prvulovic, D., Roeder, C. H., and Linden, D. E. (2004). Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. *Hum. Brain. Mapp*. 22, 165–178. doi: 10.1002/hbm.20022

Van Harskamp, N. J., Rudge, P., and Cipolotti, L. (2005). Cognitive and social impairments in patients with superficial siderosis, *Brain* 128, 1082–1092. doi: 10.1093/brain/awh487

Van Overwalle, F., Baetens, K., Mariën, P., and Vandekerckhove, M. (2014). Social cognition and the cerebellum: a meta-analysis of over 350 fMRI studies. *Neuroimage* 1, 554–572. doi: 10.1016/j.neuroimage.2013.09.033

Van Overwalle, F., D'aes, T., and Mariën, P. (2015). Social cognition and the cerebellum: a meta analytic connectivity analysis. *Hum. Brain. Mapp*. 36, 5137–5154. doi: 10.1002/hbm.23002

Van Overwalle, F., and Mariën, P. (2016). Functional connectivity between the cerebrum and cerebellum in social cognition: a multi-study analysis. *Neuroimage* 124, 248–255. doi: 10.1016/j.neuroimage.2015.09.001

Wechsler, D. (1945). A standardized memory scale for clinical use. *J. Psychol*. 87–95. doi: 10.1080/00223980.1945.9917223

Wechsler, D. (1981). *Wais-r. Wechsler Adult Intelligence Scale Revised*. Firenze: Organizzazioni Speciali.

Wolpert, D. M., and Kawato, M. (1998). Multiple paired forward and inverse models for motor control. *Neural. Netw*. 11, 1317–1329. doi: 10.1016/S0893-6080(98)00066-5

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cellular Neuroscience

REVIEW
published: 15 January 2019
doi: 10.3389/fncel.2018.00524

Cerebellum, Predictions and Errors

*Laurentiu S. Popa and Timothy J. Ebner**

Department of Neuroscience, University of Minnesota, Minneapolis, MN, United States

Making predictions and validating the predictions against actual sensory information is thought to be one of the most fundamental functions of the nervous system. A growing body of evidence shows that the neural mechanisms controlling behavior, both in motor and non-motor domains, rely on prediction errors, the discrepancy between predicted and actual information. The cerebellum has been viewed as a key component of the motor system providing predictions about upcoming movements and receiving feedback about motor errors. Consequentially, studies of cerebellar function have focused on the motor domain with less consideration for the wider context in which movements are generated. However, motor learning experiments show that cognition makes important contributions to motor adaptation that involves the cerebellum. One of the more successful theoretical frameworks for understanding motor control and cerebellar function is the forward internal model which states that the cerebellum predicts the sensory consequences of the motor commands and is involved in computing sensory prediction errors by comparing the predictions to the sensory feedback. The forward internal model was applied and tested mainly for effector movements, raising the question whether cerebellar encoding of behavior reflects task performance measures associated with cognitive involvement. Electrophysiological studies based on pseudo-random tracking in monkeys show that the discharge of Purkinje cell, the sole output neurons of the cerebellar cortex, encodes predictive and feedback signals not only of the effector kinematics but also of task performance. The implications are that the cerebellum implements both effector and task performance forward models and the latter are consistent with the cognitive contributions observed during motor learning. The implications of these findings include insights into recent psychophysical observations on moving with reduced feedback and motor learning. The findings also support the cerebellum's place in hierarchical generative models that work in concert to refine predictions about behavior and the world. Therefore, cerebellar representations bridge motor and non-motor domains and provide a better understanding of cerebellar function within the functional architecture of the brain.

Keywords: Purkinje cell, simple spike, complex spike, kinematics, performance error, sensory prediction error, forward internal model, generative model

OPEN ACCESS

Edited by:
Mario U. Manto,
University of Mons, Belgium

Reviewed by:
Marco Molinari,
Fondazione Santa Lucia (IRCCS), Italy
Eric J. Lang,
New York University, United States
Chris I. De Zeeuw,
Sophia Children's Hospital, Netherlands

***Correspondence:**
Timothy J. Ebner
ebner001@umn.edu

Received: *15 October 2018*
Accepted: *17 December 2018*
Published: *15 January 2019*

Citation:
Popa LS and Ebner TJ (2019) Cerebellum, Predictions and Errors. Front. Cell. Neurosci. 12:524. doi: 10.3389/fncel.2018.00524

INTRODUCTION

Yogi Berra and Niels Bohr agreed: "Predictions are very hard, especially when they are about the future" (Stanislaw, 1976; Wilford, 1991). It turns out they could be ubiquitous throughout the brain too.

It has been hypothesized that central to brain function is learning to make predictions about behavior and the world. The use of predictions to control behavior relies on computing

prediction errors, the differences between predictions and reality. Early on, motor control research strongly embraced the importance of generating predictions about upcoming movements using the framework of forward internal models of effectors. Recent work has emphasized that controlling and learning self-directed motor behaviors involves both an implicit forward model of the effector and an explicit model of the task (Taylor and Ivry, 2011; Streng et al., 2018b; see **Figure 1F**). Multiple forward models require a more nuanced view on the error sources. Further, self-directed motor behavior cannot be cleanly separated from the underlying cognitive context.

The cerebellum is an integral part of the motor control system and is thought to be geared to predicting aspects of upcoming motor behavior and involved in processing prediction errors. This review focuses on the cerebellum's role in implementing forward internal models and examines whether the discharge of cerebellar neurons have the requisite predictive and feedback signals essential for generating prediction errors. Importantly, the review examines whether the signals encoded are restricted to information only about effectors or whether the signals include task-related information.

PREDICTIVE PROWESS OF THE MOTOR SYSTEM AND FORWARD INTERNAL MODELS

Motor behavior, being amenable to precise measurement and manipulation of well-defined parameters of movement, showcases the nervous system's ability to anticipate motor outcomes over a wide range of behaviors and experimental conditions. For example, during a saccade there is neither visual nor proprioceptive sensory feedback (Keller and Robinson, 1971; Guthrie et al., 1983; Thiele et al., 2002). Yet, the variability in the motor command, as reflected in eye movement velocity, is corrected to maintain saccade accuracy (Golla et al., 2008; Xu-Wilson et al., 2009). Similarly, the neural machinery generating saccades compensates for perturbations due to blinking (Rottach et al., 1998). Therefore, in the absence of sensory feedback, the control of saccadic eye movements relies on predicting the consequences of motor commands rather than sensory feedback. The anticipatory grip forces on an object when predictable loads are applied to the arm (Johansson and Cole, 1992; Flanagan and Wing, 1997) are also consistent with making predictions about arm movements and the associated inertial forces (Kawato, 1999). Adaptation to perturbations, such as force fields or visuomotor transformations, provides compelling evidence that the brain learns to anticipate the consequences of motor commands (Shadmehr and Mussa-Ivaldi, 1994; Thoroughman and Shadmehr, 1999). Similarly, a persuasive framework for hand-eye coordination requires the anticipation of effector kinematics (Scarchilli et al., 1999). In addition, the CNS predicts the effects of common environmental constraints, for example gravitation (Zago et al., 2004; Lacquaniti et al., 2013).

The ubiquitous predictions observed during motor psychophysical experiments have to be integrated into a wider range of control processes including compensating for the inherent delays in sensory feedback, countering sensory reafferent signals, state estimation, and motor learning. Internal models offer a widely accepted computational framework for these control requirements by providing neural representations of the input-output relationships or their inverses for specific elements of the motor plant or properties of the environment to be controlled (Kawato, 1999). With the motor command and current sensory information as its inputs, a forward internal model predicts the consequences of motor actions (Jordan and Rumelhart, 1992; Miall et al., 1993; Miall and Wolpert, 1996). Forward model predictions can be compared to the actual sensory feedback to compute the difference between the intended and achieved action. This difference is termed a sensory prediction error. In turn, sensory prediction errors are used to control movements online, cancel sensory reafference due to self-generated movement, perform state estimation, guide motor learning, and update the forward model (Jordan and Rumelhart, 1992; Miall et al., 1993; Wolpert et al., 1995; Doya, 1999; Shadmehr et al., 2010). In support of this concept, sensory prediction errors have been shown to be used in motor adaptation across different effectors and behaviors (Wallman and Fuchs, 1998; Noto and Robinson, 2001; Morton and Bastian, 2006; Tseng et al., 2007; Xu-Wilson et al., 2009).

CEREBELLUM AS A FORWARD INTERNAL MODEL

Many investigators have hypothesized that internal models of the motor system, in general, and forward models, specifically, are acquired and maintained in the cerebellum (Miall et al., 1993; Shidara et al., 1993; Shadmehr and Holcomb, 1997; Wolpert et al., 1998; Kawato, 1999; Imamizu et al., 2000; Pasalar et al., 2006; Taylor et al., 2010; Popa et al., 2013). As a large body of literature supports this hypothesis, we summarize only a few key findings. The motor deficits in patients with cerebellar disorders are consistent with corrupted forward models, including loss of saccade accuracy due to motor command variability (Golla et al., 2008; Xu-Wilson et al., 2009), inability to adapt reaching movements to motor perturbations such as force fields or visuomotor rotations (Maschke et al., 2004; Tseng et al., 2007; Taylor et al., 2010) and selective disruptions of predictive adjustments during split belt locomotion (Bastian, 2006; Morton and Bastian, 2006).

In healthy subjects, functional imaging reveals changes in cerebellar activation following motor learning, further supporting the postulate that the cerebellum is the locus for the acquisition and storage of internal models of the musculoskeletal system (Shadmehr and Holcomb, 1997; Imamizu et al., 2000; Diedrichsen et al., 2005; Bursztyn et al., 2006; Tseng et al., 2007). To illustrate with a specific study, one experiment required participants to perform a ballistic hand movement and use their thumb to press a button at a fixed time interval relative to movement onset. The results reveal that control of the thumb was based on an internal representation of relative time if the time interval was longer than the movement period. Conversely, thumb control was based on

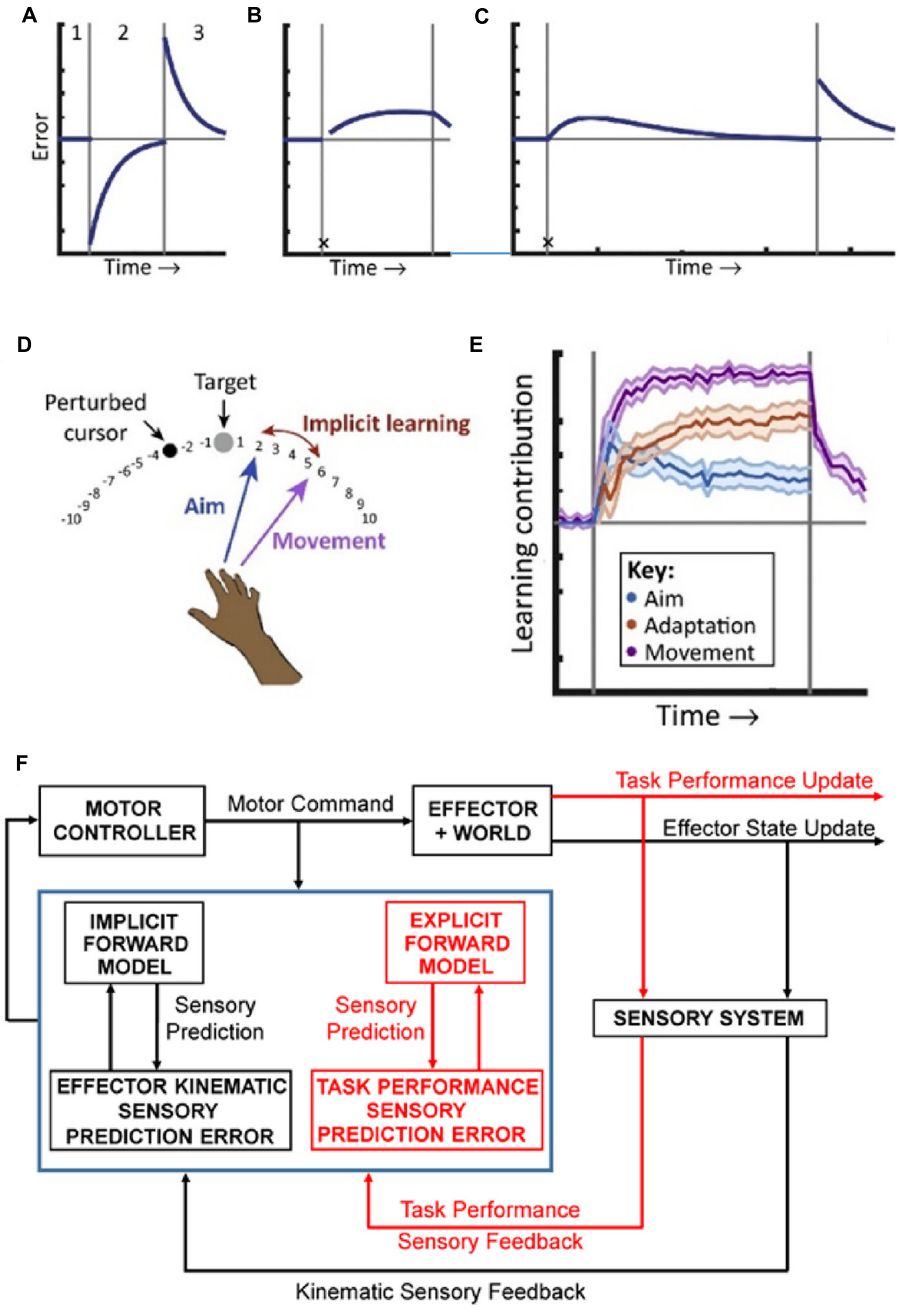

FIGURE 1 | Implicit and explicit mechanisms of motor adaptation. **(A)** The canonical motor-learning curve, including baseline (period 1), adaptation to a sensorimotor perturbation (period 2), and return to baseline (period 3). **(B)** Following the first trial after introducing the perturbation (denoted by the black X), subjects are taught to compensate for the rotation by aiming away from the target, towards an additional marker, resulting in immediate task success. In subsequent trials, performance deteriorates due to implicit learning. **(C)** In an extended training period, task performance is eventually restored by strategy adjustments. An after-effect, indicative of implicit learning is revealed when the participants aim directly to the target and the perturbation is turned off. **(D)** Measuring strategy use during adaptation to a visuomotor rotation task. Before movement, participants explicitly report their aim. The implicit learning magnitude is the difference between aiming angle and actual end-point angle. **(E)** The explicit strategy (Aim) is responsible for a large immediate contribution following the perturbation that declines with time. Implicit learning (Adaptation) is slower and monotonic and matches the magnitude of the initial aftereffect. Adapted with permission from McDougle et al. (2016). **(F)** Schematics of the forward internal model hypothesis. Based on inputs from the motor cortex (Motor Command) and sensory system (Sensory Feedback), the cerebellar cortex (symbolized by the blue box) implements two independent forward models, an implicit one for the effector (coded in black) and an explicit one for the task strategy (coded in red). These models provide sensory predictions in two different spaces: one effector-related (kinematic predictions) and one task-related (task performance predictions). These sensory predictions are compared with the correspondent sensory feedback to compute sensory prediction errors in both spaces. Sensory prediction errors are used to independently update each internal model. The cerebellar output, integrating all sensory prediction errors, is used to update the Motor Controller.

a state estimation of the arm if the time interval overlapped with the arm movement. Consistent with the forward model hypothesis, the cerebellum was selectively activated when state estimation was required by the task (Diedrichsen et al., 2007). Imaging studies also demonstrate strong cerebellar activation by motor errors, both task performance errors (Flament et al., 1996; Imamizu et al., 2000; Diedrichsen et al., 2005; Grafton et al., 2008) and sensory prediction errors (Schlerf et al., 2012). These are essential signals for the formation and modification of internal models. Finally, transient cerebellar disruption using transcranial magnetic stimulation induces movement perturbations that can be accounted for by the cerebellum making a prediction of the kinematic state of the arm at a lead time of 130 ms (Miall et al., 2007), as expected if the cerebellum implements a forward internal model.

IMPLICIT AND EXPLICIT CONTRIBUTIONS TO MOTOR LEARNING

Explicit or declarative information processing occurs under conscious control, for example following a verbal instruction on how to execute a motor task. Implicit or procedural information processing is automatic and manifest in skill performance, such as experience driven improvement in motor output (Haith and Krakauer, 2018). Historically, motor learning was considered as purely an implicit process, solely based on updating an effector forward internal model (**Figure 1A**). However, during motor adaptation, there are both explicit and implicit contributions with different effects and implications for cerebellar forward internal models.

An elegant experiment successfully decoupled the contributions of implicit and explicit processes on motor learning. In a reaching task the visual feedback was perturbed by introducing a constant angular rotation between the hand and cursor positions. In the second trial after introducing this visuomotor rotation, the subjects were instructed to change the aim of the movement to compensate for the visual perturbation. This explicit strategy immediately restored task performance by minimizing the end-point errors, defined as the angular distance between target and cursor. However, in subsequent trials end-point errors gradually increased, reflecting the normal motor adaptation that occurs during visuomotor rotation (Mazzoni and Krakauer, 2006; **Figure 1B**).

This unexpected result challenged the canonical view of motor learning and required a closer look at motor errors. Implicit sensory prediction errors, defined as the difference between the forward model predictions of the kinematics of the arm and the corresponding sensory feedback and, measured in this experiment as the difference between direction of arm movement and direction of cursor movement, are maximal in early perturbed trials. In contrast, end-point error is minimal because the explicit strategy counteracts the perturbation. The findings demonstrate that sensory prediction errors computed in effector-related space drive implicit motor adaptation, as predicted by the forward internal model hypothesis and that implicit learning occurs relatively independently from task performance, as defined by the end-point errors. Conversely, a task performance measure is computed in a task-related space and reflects both the kinematic sensory prediction errors and the explicit strategy. The results establish a functional segregation between an effector-related domain involved in implicit processes and a task-related domain related to explicit strategies. However, when adaptation is allowed to progress over a large number of trials, task performance errors plateau and then decrease (Taylor and Ivry, 2011; **Figure 1C**). This non-monotonic distribution of task performance allows for several possible explanations. One would be that subjects decide to disregard the instructions received. This would result in abrupt changes in task performance unlike the gradual recovery of the end-point errors observed. A model that fits the data adds to the implicit learning driven by kinematic error prediction, an explicit learning strategy driven by task performance. In this scenario, the implicit and explicit adaptation processes compensate each other to restore task accuracy.

To further elucidate the contribution of explicit strategies, in a series of newer studies of adaptation to visuomotor rotation, subjects were required to report their reach aim before movement in the absence of prior knowledge about the perturbation (Taylor et al., 2014; Bond and Taylor, 2015). In contrast with previous studies (Taylor and Ivry, 2011), the declarative contribution was measured by the verbally reported aim direction. The difference between aim and end point directions served as a measure of implicit adaptation, as the subjects endeavored to reach the target (**Figure 1D**). In these conditions an explicit strategy emerges, counteracting the imposed rotation and contributing in parallel with the implicit adaptation to the motor learning, consistent with the observations of the previous experiment. The implicit adaptation is a slow monotonic process and context independent as it is driven by sensory prediction errors computed in an effector centered domain. The explicit learning is faster, driven by task performance errors, exploratory, responsive to changing task demands, accounts for a large fraction of the improvement throughout the learning process (**Figure 1E**) and involves the cerebral cortex as diminished prefrontal function increases task error drift (Taylor and Ivry, 2014; Taylor et al., 2014; Bond and Taylor, 2015). The implicit process is thought to reflect the updating of a cerebellar forward model of the arm while the explicit strategy is thought to be under frontal control, at least in the early phase of learning, and reflects strategic planning and action selection (McDougle et al., 2016). Patients with cerebellar pathology when given a declarative strategy that accounts for the visuomotor rotation lack the after effects associated with motor adaptation and lack the gradual degrading in task performance present in the healthy subjects, confirming that intact cerebellar function is required for implicit motor adaptation (Taylor et al., 2010). One surprising observation is that the emergence of the explicit strategy depends on the cerebellar function (Butcher et al., 2017). As motor adaptation unfolds in both implicit and explicit domains, this raises the question whether are there representations of both of these processes in the discharge of cerebellar neurons?

INFORMATION PROCESSING IN CEREBELLAR NEURONS FOR IMPLICIT AND EXPLICIT FORWARD INTERNAL MODELS

Strong support for cerebellar involvement in forward models and in computing sensory prediction errors is emerging from studying the activity of cerebellar neurons. The output of a well-tuned forward model should be relatively insensitive to sensory reafferents due to self-generated movements, as the predictions should closely match the sensory feedback. Conversely, the output should be highly sensitive to passive movements or unexpected perturbations. During passive movement sensory feedback dominates in the absence of motor commands and during perturbations the model predictions predicted will be poorly matched with the actual feedback. These expectations for a forward internal model were successfully tested in the rostral fastigial nucleus. The discharge of these neurons have higher sensitivity to passive movements compared to comparable self-generated movements (Brooks and Cullen, 2013). Moreover, when the head movement is perturbed by external forces, the initially high sensitivity of fastigial neurons gradually decreases, mirroring the adaptation that occurs in head movement (Brooks et al., 2015). Together these results are consistent with the output of an effector forward model that adapts its predictions to minimize sensory prediction errors.

What about the discharge of Purkinje neurons, the final stage in the information processing of the cerebellar cortex and the only output? Within the framework of the forward internal model hypothesis, we proposed that Purkinje cell firing represents both the predictions of the motor command consequences and the corresponding sensory feedback (Popa et al., 2013, 2016a). For an effector forward model, both the prediction and the sensory feedback are thought to be expressed in the effector kinematics space (Wolpert et al., 1995; Miall and Wolpert, 1996).

Purkinje cell simple spike (SS) discharge modulates with and is correlated to upcoming eye and arm kinematics in a variety of motor behaviors (for reviews, see Ebner and Pasalar, 2008; Ebner et al., 2011). Conversely, SSs modulate with limb kinematics during passive movements, arguing for sensory feedback encoding. The wide timing distribution of SS firing relative to movement, spanning both feedforward and feedback timing with a mean hovering around 100 ms prior to movement, suggests a bias in favor of predictive kinematic representations (Hewitt et al., 2011). More compelling evidence for a forward model is the observation that SS activity is strongly linked to the kinematic consequences of the motor commands and not to the dynamic output of the motor plant (Pasalar et al., 2006). Also, kinematic representations in the SS firing are conserved across different behaviors (Roitman et al., 2005; Hewitt et al., 2011). These findings offer support, but not proof, of the concept that the cerebellar cortex realizes a forward model of the arm.

A better understanding of the nature and temporal aspects of Purkinje cell representations requires a task that imposes robust and sustained online error processing and allows a decoupling of past and future states. These requirements were fulfilled by using a pseudo-random, manual tracking task (Hewitt et al., 2011; Popa et al., 2012, 2017). Purkinje cell recordings during pseudo-random tracking confirm that SS firing encodes arm movement kinematics including position, velocity, and acceleration (Hewitt et al., 2011; Popa et al., 2012, 2017; Streng et al., 2017). The use of linear regression analyses in which we first removed the contribution of all motor parameters from the SS firing except the parameter of interest and then evaluated the relation between the parameter of interest and the residual SS firing show that these kinematic signals are independently represented, and that individual Purkinje cells simultaneously encode several kinematic parameters (Popa et al., 2012, 2017).

The utility of the pseudo-random tracking paradigm is best revealed by establishing the predictive and feedback encoding of kinematics by Purkinje cells (Popa et al., 2012, 2017). The predictive and feedback modulation is illustrated in the sequence of firing maps of SS modulation with velocity across a range of time shifts (i.e., τ-values) as shown in **Figure 2A**. In this example, SS firing relative to the mean firing precedes hand velocity, with higher firing in the lower left quadrant that reaches a maximum at a feedforward timing of −120 ms. At feedback lag, a reciprocal SS modulation pattern emerges, with peak firing in the upper right quadrant at approximately 200 ms. Temporal linear regressions of the SS discharge with each behavioral parameter provide quantitative measures of the temporal relationship (τ-value) and the correlation strength (R^2 and regression coefficient-β; Hewitt et al., 2011; Popa et al., 2012). For this Purkinje cell, the velocity R^2 and β profiles (**Figures 2B,C**, respectively) characterize the feedforward and feedback SS encoding, with local maxima at the leads and lags corresponding to the timing of the maximal modulations in the firing maps (**Figure 2A**). The lead and lag correlations are well above chance, as determined by regressions of the trial randomized data. Approximately, 70% of Purkinje cells exhibit this bi-modal profile with kinematics. We interpret these SS modulation profiles as the predictive and feedback constituents of the sensory prediction error computed by an implicit forward internal model of the arm.

Importantly, pseudo-random tracking provides additional insights into Purkinje cell representations. As the monkeys track the moving target, they attempt to maintain the cursor in the target center. The task also requires that the monkeys correct cursor excursions outside the target within 500 ms. This provides for several natural and continuous measures of performance errors including position error (components of the position error vector defined by the cursor and target center positions), radial error (magnitude of the position error vector) and direction error (angle between the current cursor position and the target center; Popa et al., 2012, 2017). The SS firing encodes these error parameters using bimodal, predictive-feedback representations. The firing maps of a Purkinje cell (**Figure 2D**) shows that the SS discharge leads position error from −300 ms to −100 ms, as the highest firing occurs in the lower left quadrant. The SS firing also lags position error from 300 ms to 500 ms when the highest firing occurs in the

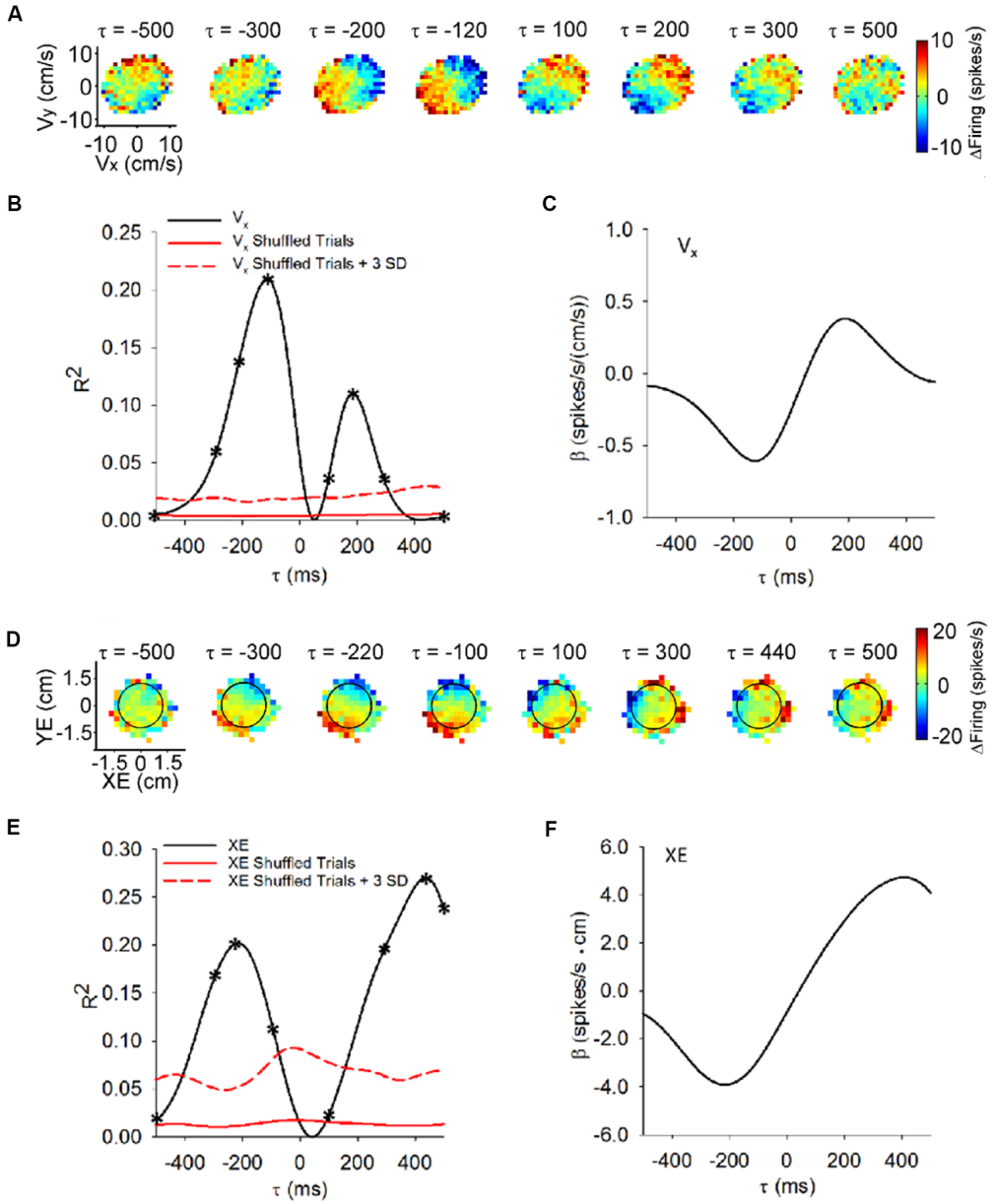

FIGURE 2 | Time course of the simple spike (SS) modulation with behavioral parameters during pseudo-random tracking. **(A)** Color coded maps of the SS firing, relative to the overall mean, for an example Purkinje cell in the velocity space (V_x, V_y) at different lead/lags (τ). Negative τ represents the firing leading velocity. **(B)** For the cell in **(A)**, the R^2 for V_x as a function of lead/lag (τ) reveals modulation at both feedforward and feedback timing. The red trace shows the mean of the control regressions computed on trial shuffled data (100 repetitions). The dashed red trace is the mean +3 SD of the control regressions. On the R^2 temporal profiles asterisks (*) indicate the leads/lags of the corresponding SS firing maps in **(A)**. **(C)** For the same neuron, the regression coefficients for V_x (β_{Vx}) are plotted as a function of τ. The sign change in β_{Vx} represents the reversal in the firing sensitivity at feedforward lead compared to feedback lag. **(D)** SS firing maps of another example Purkinje cell with position error (XE, YE) at different leads/lags (τ). Target depicted by black circles. Same conventions as in **(A)**. **(E,F)** For the cell in **(D)**, the temporal profiles for the R^2 **(E)** and regression coefficients (β_{XE}) for XE **(F)** exhibit predictive and feedback local maxima. β_{XE} shows the reversal in the SS firing sensitivity at lead compared to lag timings **(F)**. Conventions for red lines as in **(B)**. Adapted with permission from Popa et al. (2016a).

upper right quadrant. The R^2 and β profiles (**Figures 2E,F**, respectively) for the x-component (XE) of position error have local maxima at −220 and 440 ms (**Figures 2E,F**, respectively). For a large majority of the Purkinje cells, the SS discharge signals at least one of these performance error parameters.

At the population level, the strength of performance error encoding is robust and comparable to the encoding of kinematics. Also, there is no segregation of Purkinje cells into error or kinematic subpopulations, showing that the integration of the task errors and kinematics occurs at the individual cell level (Popa et al., 2012). As mentioned before,

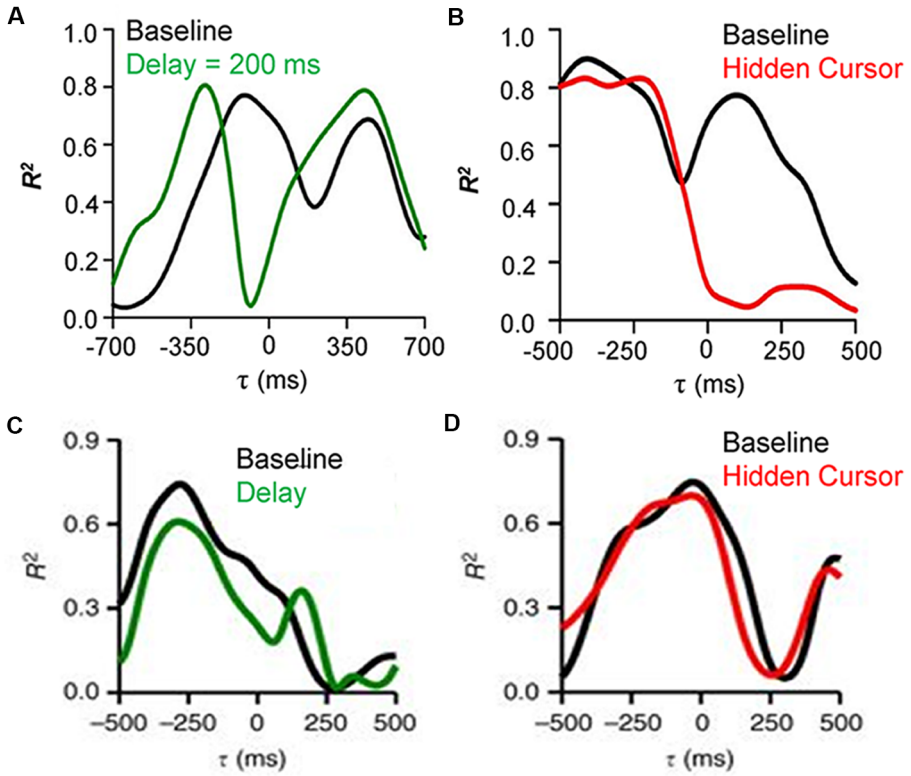

FIGURE 3 | Effects of feedback manipulations on behavioral parameters encoding by SS discharge. **(A)** R^2 temporal profiles for an example Purkinje cell SS firing regressed with position error during delay cursor delay (baseline—black trace, 200 ms delay—green trace). The predictive encoding shifts to more negative τ-values while the timing of the feedback modulation does not change. **(B)** R^2 temporal profiles for an example Purkinje cell SS firing regressed with position error during the hidden cursor condition (baseline—black trace, hidden cursor—red trace). The reduction in visual feedback decreases the strength of the feedback encoding of position error but not the predictive encoding. **(C)** R^2 temporal profiles for an example Purkinje cell SS firing regressed with velocity during cursor delay (baseline—black trace, 100 ms delay—green trace). **(D)** R^2 temporal profiles for an example Purkinje cell SS firing regressed with velocity during the hidden cursor condition (baseline—black trace, hidden cursor—red trace). The kinematic representations are not changed by either manipulation of the visual feedback. Adapted with permission from Streng et al. (2018b).

the pseudo-random tracking task uncouples the past and future behavioral states, thus unveiling that the SS dual representations of individual error parameters, including a pair of predictive and feedback signals with opposing modulations, are ubiquitous in the Purkinje cells population (Popa et al., 2012). As these performance error signals are task-related and independent of kinematics, we interpret these modulation profiles as the feedforward and feedback elements computed by a forward internal model of a task specific, explicit strategy (Popa et al., 2013, 2014).

To establish that Purkinje cells provide the output of a forward internal model of performance errors it needs to be shown that the feedforward signals are the predicted consequences of the motor commands while the feedback signals reflect the sensory input. To test these requirements, Purkinje cell recordings during a modified pseudo-random tracking involving two perturbations of the visual feedback (Streng et al., 2018b). The first manipulation introduced delays between hand and cursor movements. If the feedforward modulation of position error is driven by the motor commands, the prediction will occur earlier relative to the cursor and the temporal shift should match the imposed delay. However, the feedback signal timing, being based on visual sensory input, will not be affected. The results confirmed these expectations, as shown for an example Purkinje cell in which the cursor delay shifts the predictive timing of the position error modulation, as determined by the local maxima in the R^2 temporal profile, to more negative τ-values while the timing of the feedback modulation does not change (**Figure 3A**). The second manipulation hid the cursor while inside the target, thus reducing the visual feedback during task execution (Hidden cursor condition). The expectations were that the SS feedback modulation inside the target will be reduced as a result of reduced visual input, while the predictive modulation, driven by efferent copies of the motor command will not be affected. Again, the experimental findings confirmed the expectations based on a forward internal model of performance errors, with a decrease in the strength of the feedback encoding of position error but not the predictive encoding (**Figure 3B**). Moreover, the kinematic representations were not affected by either manipulation (**Figures 3C,D**), confirming the independence of the error and kinematic representations in the SS firing.

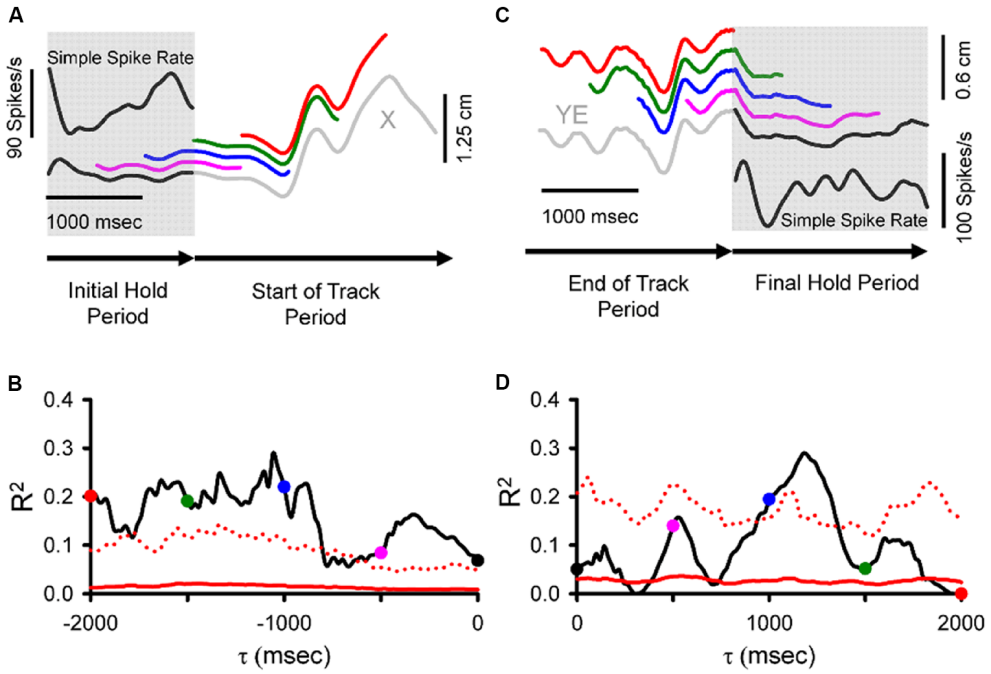

FIGURE 4 | During hold periods SS firing correlates with movement parameters during track period. **(A)** SS firing (inset) during the initial hold period prior to tracking (gray shadow) from an example trial matched to position (specifically X-position) at τ values spanning 0 to −2,000 ms illustrated by the sliding window. Note that the window length is equal in duration to the initial hold period. Colored traces illustrate the X sliding window at different times: black (0 ms), pink (−500 ms), blue (−1,000 ms), green (−1,500 ms), and red (−2,000 ms). **(B)** For the SS discharge of this neuron, the R^2 obtained from correlating firing rate with X-position across all trials is shown as a function of time (τ). The key observation is that the SS firing in the hold period encodes information about the upcoming position. **(C)** SS discharge rate (inset) during the final hold period (gray shadow) matched to position error (specifically YE) recorded in both track (gray) and final hold (black) periods using a sliding window of the same duration as the final hold period spanning from 0 to 2,000 ms. Colored traces illustrate the YE sliding window at different times: black (0 ms), pink (500 ms), blue (1,000 ms), green (1,500 ms), and red (2,000 ms). **(D)** For this Purkinje cell, plot of the R^2 as a function of time (τ) from regressing SS with YE across all trials. Here the critical observation is that the firing in the hold period contains position error information about the just completed track period. Direction of recording time is indicated by bottom arrows in **(A,C)**. For **(B,D)**, conventions for the colored dots conventions are as in **(A,C)**, respectively. Chance encoding (red traces) and conventions for τ values, as in **Figure 2**. Adapted with permission from Popa et al. (2017).

The results described above focused on the SS activity centered on current movement (±500 ms). However, the pseudo-random tracking task also allowed a determination of the relation between Purkinje cell firing and the behavior over longer time intervals (Popa et al., 2017). Both kinematic and task performance parameters were found to be represented in the SS firing at leads and lags spanning 2,000 ms before to 2,000 ms after the movement. We refer to these extended predictive and feedback modulations as "long-range signals." During tracking, these long-range signals allowed decoding of the individual behavioral parameters, kinematic and task performance, with remarkable accuracy, well above the random level. Moreover, during the periods preceding (**Figures 4A,B**) and following tracking (**Figures 4C,D**), when the monkeys were required to hold the cursor within a stationary target, the SS activity encoded expectations or memories of both kinematics and performance errors (Popa et al., 2017).

The long-range signals of effector states and task performance following a movement are consistent with a form of working memory that can bridge the inter-trial intervals as expected by the cerebellar involvement in generating the explicit strategy. The long-range predictive signals are consistent with planning and action expectations that could be used to seed the forward model acquisition. Long-range preparatory Purkinje cells activity could be used for evidence accumulation prior to movement, as observed in a task requiring mice to make a left-right decision (Deverett et al., 2018). Support for these long-range signals likely involves the cerebellum's closed-loops connections with numerous regions in the cerebral cortex (for reviews, see Schmahmann and Pandya, 1997; Strick et al., 2009; Bostan et al., 2013; Lena, 2016). Further, a network relying on hippocampal-cerebellar interactions is involved in learning sequence-based navigation in mice (Babayan et al., 2017). These findings argue for the cerebellar involvement in persistent activity loops with the cerebral cortex related to higher functions.

ROLE FOR COMPLEX SPIKES IN PREDICTIONS, ERROR PROCESSING AND FORWARD MODELS

One of the more prominent hypotheses of cerebellar function is that complex spikes (CSs) are the sole conduits of error information and those error signals drive motor learning

(Marr, 1969; Albus, 1971; Oscarsson, 1980; Ito and Kano, 1982). While supported by several studies (for reviews, see Ito, 2002; Gao et al., 2012), the hypothesis that CS discharge primarily provides error information critical for motor learning does not cover accurately the spectrum of experimental observations. Many studies failed to find error signals in the firing of inferior olivary neurons or in the CS discharge (for reviews, see Catz et al., 2005; Llinás, 2014; Popa et al., 2016b; Streng et al., 2018a). In addition there are multiple demonstrations of cerebellar learning that is independent of climbing fiber input (Boyden et al., 2004; Ke et al., 2009; Nguyen-Vu et al., 2013; Shin et al., 2014; Hewitt et al., 2015).

CSs also convey parametric information related to movements contrasting with the error signaling hypothesis. For example, climbing fiber input modulates with eye and head movements induced by vestibulo-ocular rotation in the dark, when the retinal slip is absent (Winkelman et al., 2014), with movement kinematics during ocular pursuit (Kobayashi et al., 1998) and with reach kinematics (Fu et al., 1997; Kitazawa et al., 1998). Moreover, during pseudo-random tracking CS firing modulates strongly with arm kinematics including position, velocity, and acceleration, showing that climbing fiber input signals movement information beyond motor errors (Streng et al., 2017).

Although typically thought to be primarily driven by feedback errors, during pseudo-random tracking, climbing fiber modulation leads both kinematics and performance errors (Streng et al., 2017). Furthermore, at the population level feedforward CS activity is more frequent than feedback modulation. Others have observed this predictive property, as CSs modulate with eye performance inferred errors (Frens et al., 2001; Winkelman and Frens, 2006; Winkelman et al., 2014), anticipatory errors in eye blink conditioning (Ohmae and Medina, 2015) and with learned sensorimotor predictions of reward (Heffley et al., 2018). Together these observations demonstrate the need to reconsider the view that CSs only convey information about feedback errors and acknowledge the robust kinematic information carried by the climbing fiber input. Therefore, the dominant view that SS and CS discharge carry functionally unique signals cannot withstand a detailed examination.

The roles played by climbing fiber input in motor learning and error signaling are under reconsideration (Catz et al., 2005; Streng et al., 2018a). Taking into account that spontaneous CS firing is essential for cerebellar function and climbing fiber input results in a global depolarization that is likely to alter how Purkinje cells process parallel fiber input (for review, see Kitamura and Kano, 2013; Streng et al., 2018a), we hypothesized that climbing fiber input to Purkinje cells modulates the information present in the SS firing (Streng et al., 2017). An examination of the SS firing encoding uncovered that CSs trigger robust, step-like changes in the kinematic and position error signals present in the SS discharge. This control over a Purkinje cell's encoding state is hypothesized to optimize motor performance and/or compensate for drifts in the SS representations and is consistent with climbing fiber input providing both error and non-error information as well as predictive encoding (Streng et al., 2018a). These findings also account for spontaneous CSs firing as a mechanism to provide SS encoding homeostasis. Consistent with the CSs playing a homeostatic role in spontaneous SS firing, earlier studies showed that removal or stimulation of climbing fiber input produces dramatic and long-term changes in the SS firing (Colin et al., 1980; Montarolo et al., 1982; Cerminara and Rawson, 2004). Moreover, the rapid changes in SS encoding suggest that CS discharge directs an internal model selection process, allowing cerebellar cortical output to accommodate to changes in behavioral conditions.

IMPLICATIONS FOR CEREBELLUM PROVIDING BOTH IMPLICIT AND EXPLICIT MODELS

The encoding of kinematic and performance errors in the discharge of Purkinje cells supports the simultaneous presence of cerebellar effector and task-specific forward models. When visual feedback was disrupted, the predictive and feedback SS modulations are mismatched (Streng et al., 2018b). However, the animals can still perform the task and previous psychophysical studies found that the motor system continues to generate accurate predictions during altered visual feedback (Kumar and Mutha, 2016). The invariance in the SS kinematic signals as well as the constancy of the task error predictions (**Figure 3**) argue that the internal models are making precise estimates of the consequences of the motor command based on the present states of the effector and target, allowing the animals to perform skilled behaviors even with sub-optimal visual feedback.

The independence of arm kinematics and task performance forward models is consistent with recent psychophysical results. When subjects were asked to intercept their moving index finger with the index of the other hand in the absence of visual feedback, there was no difference in performance whether the target finger was moving voluntarily or passively (Darling et al., 2018). This result was interpreted as evidence that forward internal models are not necessary for state estimation. However, the task in this psychophysical study is similar to the hidden condition during pseudo-random tracking by primarily providing sensory feedback about target kinematics. Under these conditions, the effector and task performance forward internal models work in concert to preserve the task performance in noisy conditions.

The presence of arm and task performance forward models integrated at the Purkinje cell level could provide insights into motor learning as presented in **Figure 1**. The effector forward model operates in the kinematics domain and is consistent with the classical view of implicit motor learning (**Figure 1A**). The task model operates in the task performance domain and is consistent with a forward model of the explicit strategy (see **Figure 1E**). In this view, in the initial phase of adaptation only the effector model is updated to exclusively minimize the sensory prediction errors related to kinematic parameters, while the explicit strategy, under cerebral cortical control (McDougle et al., 2016), is conserved. As a result, the implicit learning progresses to the detriment of task performance (**Figure 1B**).

In the late stages of adaptation, the cerebellum acquires and updates forward models of the explicit strategy. Based on the motor command, both forward models provide predictions and compute sensory prediction errors, simultaneously optimizing the effector response and the action outcome (see **Figure 1C**). This two stage hypothesis for the explicit strategy is also consistent with the observation that working memory load interferes with motor learning in the early phase but not in latter phase of motor learning (Keisler and Shadmehr, 2010).

An important aspect of brain function is skilled performance. Skilled behavior requires fast execution, decreased sensitivity to perturbations and reduced cognitive effort (Ramnani, 2014; Haith and Krakauer, 2018). Skilled behavior is thought to involve the acquisition of task-specific cerebellar forward models (Ramnani, 2014), consistent with the task performance forward model observed during pseudo-random tracking. These models, once established and refined by over-training, could be conserved over long period of time without reconsolidation.

IMPLICATIONS FOR GENERATIVE MODELS

Recent attempts at a unifying framework of brain function hypothesize that the CNS acts as a predictive machine (Friston, 2010; Picard and Friston, 2014). The brain improves its belief and hypotheses about the world by continuously generating predictions about inputs, comparing those predictions with results and acting to minimize prediction errors. The theory posits that the brain is organized hierarchically into generative models in which higher levels provide predictions to lower level models and the higher levels use sensory prediction errors from the lower level as inputs to update the predictions (Picard and Friston, 2014). In this framework, perception is understood as inferring causes to sensations by minimizing sensory prediction errors, and action is understood as minimizing sensory prediction errors between expected consequences of action and sensations (Friston, 2010; Aggelopoulos, 2015; Barrett and Simmons, 2015; O'Callaghan et al., 2017). The prediction hypothesis and generative model architecture are being applied to a multitude of brain functions including representation of self (Moutoussis et al., 2014; Picard and Friston, 2014), theory of the mind (Picard and Friston, 2014), and mental disorders (Sterzer et al., 2018a,b).

Cerebellar forward internal models have been proposed as an example of generative models (Pickering and Clark, 2014). The connectivity between the cerebellum and cerebral cortex noted above provides the substrate for recursive network interactions between the two structures, and suggest possible candidates for such hierarchical levels. One of the open issues in this framework is the integration of the cerebellar forward models in the larger cognitive architecture, hinging on whether and how cerebellar models integrate context dependent outputs. The observation that the cerebellar cortex encodes simultaneously forward models of arm kinematics and task performance errors supports the hypothesis that the behavioral context is reflected in the cerebellar activity (see **Figure 1F**). The independence of the kinematic and task specific models suggests that the cerebellum can engage and update combinations of different forward internal models depending on the behavioral context. This could provide a "complete" control mechanism, integrating execution accuracy and outcome, allowing fast execution of complex behaviors in variable contexts.

AUTHOR CONTRIBUTIONS

LP and TE jointly wrote the review.

FUNDING

This work was supported in part by National Institutes of Health (NIH) grant R01 NS18338.

ACKNOWLEDGMENTS

We would like to thank Kathleen Beterams for her help with the manuscript.

REFERENCES

Aggelopoulos, N. C. (2015). Perceptual inference. *Neurosci. Biobehav. Rev.* 55, 375–392. doi: 10.1016/j.neubiorev.2015.05.001

Albus, J. S. (1971). A theory of cerebellar function. *Math. Biosci.* 10, 25–61. doi: 10.1016/0025-5564(71)90051-4

Babayan, B. M., Watilliaux, A., Viejo, G., Paradis, A. L., Girard, B., and Rondi-Reig, L. (2017). A hippocampo-cerebellar centred network for the learning and execution of sequence-based navigation. *Sci. Rep.* 7:17812. doi: 10.1038/s41598-017-18004-7

Barrett, L. F., and Simmons, W. K. (2015). Interoceptive predictions in the brain. *Nat. Rev. Neurosci.* 16, 419–429. doi: 10.1038/nrn3950

Bastian, A. J. (2006). Learning to predict the future: the cerebellum adapts feedforward movement control. *Curr. Opin. Neurobiol.* 16, 645–649. doi: 10.1016/j.conb.2006.08.016

Bond, K. M., and Taylor, J. A. (2015). Flexible explicit but rigid implicit learning in a visuomotor adaptation task. *J. Neurophysiol.* 113, 3836–3849. doi: 10.1152/jn.00009.2015

Bostan, A. C., Dum, R. P., and Strick, P. L. (2013). Cerebellar networks with the cerebral cortex and basal ganglia. *Trends Cogn. Sci.* 17, 241–254. doi: 10.1016/j.tics.2013.03.003

Boyden, E. S., Katoh, A., and Raymond, J. L. (2004). Cerebellum-dependent learning: the role of multiple plasticity mechanisms. *Annu. Rev. Neurosci.* 27, 581–609. doi: 10.1146/annurev.neuro.27.070203.144238

Brooks, J. X., Carriot, J., and Cullen, K. E. (2015). Learning to expect the unexpected: rapid updating in primate cerebellum during voluntary self-motion. *Nat. Neurosci.* 18, 1310–1317. doi: 10.1038/nn.4077

Brooks, J. X., and Cullen, K. E. (2013). The primate cerebellum selectively encodes unexpected self-motion. *Curr. Biol.* 23, 947–955. doi: 10.1016/j.cub.2013.04.029

Bursztyn, L. L., Ganesh, G., Imamizu, H., Kawato, M., and Flanagan, J. R. (2006). Neural correlates of internal-model loading. *Curr. Biol.* 16, 2440–2445. doi: 10.1016/j.cub.2006.10.051

Butcher, P. A., Ivry, R. B., Kuo, S. H., Rydz, D., Krakauer, J. W., and Taylor, J. A. (2017). The cerebellum does more than sensory prediction error-based learning in sensorimotor adaptation tasks. *J. Neurophysiol.* 118, 1622–1636. doi: 10.1152/jn.00451.2017

Catz, N., Dicke, P. W., and Thier, P. (2005). Cerebellar complex spike firing is suitable to induce as well as to stabilize motor learning. *Curr. Biol.* 15, 2179–2189. doi: 10.1016/j.cub.2005.11.037

Cerminara, N. L., and Rawson, J. A. (2004). Evidence that climbing fibers control an intrinsic spike generator in cerebellar Purkinje cells. *J. Neurosci.* 24, 4510–4517. doi: 10.1523/JNEUROSCI.4530-03.2004

Colin, F., Manil, J., and Desclin, J. C. (1980). The olivocerebellar system. I. Delayed and slow inhibitory effects: an overlooked salient feature of cerebellar climbing fibers. *Brain Res.* 187, 3–27. doi: 10.1016/0006-8993(80)90491-6

Darling, W. G., Wall, B. M., Coffman, C. R., and Capaday, C. (2018). Pointing to one's moving hand: putative internal models do not contribute to proprioceptive acuity. *Front. Hum. Neurosci.* 12:177. doi: 10.3389/fnhum.2018.00177

Deverett, B., Koay, S. A., Oostland, M., and Wang, S. S. (2018). Cerebellar involvement in an evidence-accumulation decision-making task. *Elife* 7:e36781. doi: 10.7554/eLife.36781

Diedrichsen, J., Criscimagna-Hemminger, S. E., and Shadmehr, R. (2007). Dissociating timing and coordination as functions of the cerebellum. *J. Neurosci.* 27, 6291–6301. doi: 10.1523/JNEUROSCI.0061-07.2007

Diedrichsen, J., Hashambhoy, Y., Rane, T., and Shadmehr, R. (2005). Neural correlates of reach errors. *J. Neurosci.* 25, 9919–9931. doi: 10.1523/JNEUROSCI.1874-05.2005

Doya, K. (1999). What are the computations of the cerebellum, the basal ganglia and the cerebral cortex? *Neural Netw.* 12, 961–974. doi: 10.1016/s0893-6080(99)00046-5

Ebner, T. J., Hewitt, A. L., and Popa, L. S. (2011). What features of limb movements are encoded in the discharge of cerebellar neurons? *Cerebellum* 10, 683–693. doi: 10.1007/s12311-010-0243-0

Ebner, T. J., and Pasalar, S. (2008). Cerebellum predicts the future motor state. *Cerebellum* 7, 583–588. doi: 10.1007/s12311-008-0059-3

Flament, D., Ellermann, J. M., Kim, S.-G., Ugurbil, K., and Ebner, T. J. (1996). Functional magnetic resonance imaging of cerebellar activation during the learning of a visuomotor dissociation task. *Hum. Brain Map.* 4, 210–226. doi: 10.1002/hbm.460040302

Flanagan, J. R., and Wing, A. M. (1997). The role of internal models in motion planning and control: evidence from grip force adjustments during movements of hand-held loads. *J. Neurosci.* 17, 1519–1528. doi: 10.1523/jneurosci.17-04-01519.1997

Frens, M. A., Mathoera, A. L., and van der, S. J. (2001). Floccular complex spike response to transparent retinal slip. *Neuron* 30, 795–801. doi: 10.1016/s0896-6273(01)00321-x

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nat. Rev. Neurosci.* 11, 127–138. doi: 10.1038/nrn2787

Fu, Q. G., Mason, C. R., Flament, D., Coltz, J. D., and Ebner, T. J. (1997). Movement kinematics encoded in complex spike discharge of primate cerebellar Purkinje cells. *Neuroreport* 8, 523–529. doi: 10.1097/00001756-199701200-00029

Gao, Z., van Beugen, B. J., and De Zeeuw, C. I. (2012). Distributed synergistic plasticity and cerebellar learning. *Nat. Rev. Neurosci.* 13, 619–635. doi: 10.1038/nrn3312

Golla, H., Tziridis, K., Haarmeier, T., Catz, N., Barash, S., and Thier, P. (2008). Reduced saccadic resilience and impaired saccadic adaptation due to cerebellar disease. *Eur. J. Neurosci.* 27, 132–144. doi: 10.1111/j.1460-9568.2007.05996.x

Grafton, S. T., Schmitt, P., Van, H. J., and Diedrichsen, J. (2008). Neural substrates of visuomotor learning based on improved feedback control and prediction. *Neuroimage* 39, 1383–1395. doi: 10.1016/j.neuroimage.2007.09.062

Guthrie, B. L., Porter, J. D., and Sparks, D. L. (1983). Corollary discharge provides accurate eye position information to the oculomotor system. *Science* 221, 1193–1195. doi: 10.1126/science.6612334

Haith, A. M., and Krakauer, J. W. (2018). The multiple effects of practice: skill, habit and reduced cognitive load. *Curr. Opin. Behav. Sci.* 20, 196–201. doi: 10.1016/j.cobeha.2018.01.015

Heffley, W., Song, E. Y., Xu, Z., Taylor, B. N., Hughes, M. A., McKinney, A., et al. (2018). Coordinated cerebellar climbing fiber activity signals learned sensorimotor predictions. *Nat. Neurosci.* 21, 1431–1441. doi: 10.1038/s41593-018-0228-8

Hewitt, A. L., Popa, L. S., and Ebner, T. J. (2015). Changes in Purkinje cell simple spike encoding of reach kinematics during adaptation to a mechanical perturbation. *J. Neurosci.* 35, 1106–1124. doi: 10.1523/JNEUROSCI.2579-14.2015

Hewitt, A., Popa, L. S., Pasalar, S., Hendrix, C. M., and Ebner, T. J. (2011). Representation of limb kinematics in Purkinje cell simple spike discharge is conserved across multiple tasks. *J. Neurophysiol.* 106, 2232–2247. doi: 10.1152/jn.00886.2010

Imamizu, H., Miyauchi, S., Tamada, T., Sasaki, Y., Takino, R., Putz, B., et al. (2000). Human cerebellar activity reflecting an acquired internal model of a new tool. *Nature* 403, 192–195. doi: 10.1038/35003194

Ito, M. (2002). Historical review of the significance of the cerebellum and the role of Purkinje cells in motor learning. *Ann. N Y Acad. Sci.* 978, 273–288. doi: 10.1111/j.1749-6632.2002.tb07574.x

Ito, M., and Kano, M. (1982). Long-lasting depression of parallel fiber-Purkinje cell transmission induced by conjunctive stimulation of parallel fibers and climbing fibers in the cerebellar cortex. *Neurosci. Lett.* 33, 253–258. doi: 10.1016/0304-3940(82)90380-9

Johansson, R. S., and Cole, K. J. (1992). Sensory-motor coordination during grasping and manipulative actions. *Curr. Opin. Neurobiol.* 2, 815–823. doi: 10.1016/0959-4388(92)90139-c

Jordan, M. I., and Rumelhart, D. E. (1992). Forward models: supervised learning with a distal teacher. *Cogn. Sci.* 16, 307–354. doi: 10.1207/s15516709cog1603_1

Kawato, M. (1999). Internal models for motor control and trajectory planning. *Curr. Opin. Neurobiol.* 9, 718–727. doi: 10.1016/s0959-4388(99)00028-8

Ke, M. C., Guo, C. C., and Raymond, J. L. (2009). Elimination of climbing fiber instructive signals during motor learning. *Nat. Neurosci.* 12, 1171–1179. doi: 10.1038/nn.2366

Keisler, A., and Shadmehr, R. (2010). A shared resource between declarative memory and motor memory. *J. Neurosci.* 30, 14817–14823. doi: 10.1523/JNEUROSCI.4160-10.2010

Keller, E. L., and Robinson, D. A. (1971). Absence of a stretch reflex in extraocular muscles of the monkey. *J. Neurophysiol.* 34, 908–919. doi: 10.1152/jn.1971.34.5.908

Kitamura, K., and Kano, M. (2013). Dendritic calcium signaling in cerebellar Purkinje cell. *Neural Netw.* 47, 11–17. doi: 10.1016/j.neunet.2012.08.001

Kitazawa, S., Kimura, T., and Yin, P. B. (1998). Cerebellar complex spikes encode both destinations and errors in arm movements. *Nature* 392, 494–497. doi: 10.1038/33141

Kobayashi, Y., Kawano, K., Takemura, A., Inoue, Y., Kitama, T., Gomi, H., et al. (1998). Temporal firing patterns of Purkinje cells in the cerebellar ventral paraflocculus during ocular following responses in monkeys II. Complex spikes. *J. Neurophysiol.* 80, 832–848. doi: 10.1152/jn.1998.80.2.832

Kumar, N., and Mutha, P. K. (2016). Adaptive reliance on the most stable sensory predictions enhances perceptual feature extraction of moving stimuli. *J. Neurophysiol.* 115, 1654–1663. doi: 10.1152/jn.00850.2015

Lacquaniti, F., Bosco, G., Indovina, I., La, S. B., Maffei, V., Moscatelli, A., et al. (2013). Visual gravitational motion and the vestibular system in humans. *Front. Integr. Neurosci.* 7:101. doi: 10.3389/fnint.2013.00101

Lena, C. (2016). "Cerebrocerebellar loops in the rodent brain," in *The Neuronal Codes of the Cerebellum*, ed. D. H. Heck (New York, NY: Elsevier), 135–153.

Llinás, R. R. (2014). The olivo-cerebellar system: a key to understanding the functional significance of intrinsic oscillatory brain properties. *Front. Neural Circuits* 7:96. doi: 10.3389/fncir.2013.00096

Marr, D. (1969). A theory of cerebellar cortex. *J. Physiol.* 202, 437–470. doi: 10.1113/jphysiol.1969.sp008820

Maschke, M., Gomez, C. M., Ebner, T. J., and Konczak, J. (2004). Hereditary cerebellar ataxia progressively impairs force adaptation during goal-directed arm movements. *J. Neurophysiol.* 91, 230–238. doi: 10.1152/jn.00557.2003

Mazzoni, P., and Krakauer, J. W. (2006). An implicit plan overrides an explicit strategy during visuomotor adaptation. *J. Neurosci.* 26, 3642–3645. doi: 10.1523/JNEUROSCI.5317-05.2006

McDougle, S. D., Ivry, R. B., and Taylor, J. A. (2016). Taking aim at the cognitive side of learning in sensorimotor adaptation tasks. *Trends Cogn. Sci.* 20, 535–544. doi: 10.1016/j.tics.2016.05.002

Miall, R. C., Christensen, L. O., Cain, O., and Stanley, J. (2007). Disruption of state estimation in the human lateral cerebellum. *PLoS Biol.* 5:e316. doi: 10.1371/journal.pbio.0050316

Miall, R. C., Weir, D. J., Wolpert, D. M., and Stein, J. F. (1993). Is the cerebellum a Smith predictor? *J. Mot. Behav.* 25, 203–216. doi: 10.1080/00222895.1993.9942050

Miall, R. C., and Wolpert, D. M. (1996). Forward models for physiological motor control. *Neural Netw.* 9, 1265–1279. doi: 10.1016/s0893-6080(96)00035-4

Montarolo, P. G., Palestini, M., and Strata, P. (1982). The inhibitory effect of the olivocerebellar input on the cerebellar Purkinje cells in the rat. *J. Physiol.* 332, 187–202. doi: 10.1113/jphysiol.1982.sp014409

Morton, S. M., and Bastian, A. J. (2006). Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. *J. Neurosci.* 26, 9107–9116. doi: 10.1523/JNEUROSCI.2622-06.2006

Moutoussis, M., Fearon, P., El-Deredy, W., Dolan, R. J., and Friston, K. J. (2014). Bayesian inferences about the self (and others): a review. *Conscious. Cogn.* 25, 67–76. doi: 10.1016/j.concog.2014.01.009

Nguyen-Vu, T. D., Kimpo, R. R., Rinaldi, J. M., Kohli, A., Zeng, H., Deisseroth, K., et al. (2013). Cerebellar Purkinje cell activity drives motor learning. *Nat. Neurosci.* 16, 1734–1736. doi: 10.1038/nn.3576

Noto, C. T., and Robinson, F. R. (2001). Visual error is the stimulus for saccade gain adaptation. *Cogn. Brain Res.* 12, 301–305. doi: 10.1016/s0926-6410(01)00062-3

O'Callaghan, C., Kveraga, K., Shine, J. M., Adams, R. B. Jr., and Bar, M. (2017). Predictions penetrate perception: converging insights from brain, behaviour and disorder. *Conscious. Cogn.* 47, 63–74. doi: 10.1016/j.concog.2016.05.003

Ohmae, S., and Medina, J. F. (2015). Climbing fibers encode a temporal-difference prediction error during cerebellar learning in mice. *Nat. Neurosci.* 18, 1798–1803. doi: 10.1038/nn.4167

Oscarsson, O. (1980). "Functional organization of olivary projection to the cerebellar anterior lobe," in *The Inferior Olivary Nucleus: Anatomy and Physiology*, ed. J. Courville (New York, NY: Raven), 279–290.

Pasalar, S., Roitman, A. V., Durfee, W. K., and Ebner, T. J. (2006). Force field effects on cerebellar Purkinje cell discharge with implications for internal models. *Nat. Neurosci.* 9, 1404–1411. doi: 10.1038/nn1783

Picard, F., and Friston, K. (2014). Predictions, perception, and a sense of self. *Neurology* 83, 1112–1118. doi: 10.1212/WNL.0000000000000798

Pickering, M. J., and Clark, A. (2014). Getting ahead: forward models and their place in cognitive architecture. *Trends Cogn. Sci.* 18, 451–456. doi: 10.1016/j.tics.2014.05.006

Popa, L. S., Hewitt, A. L., and Ebner, T. J. (2014). The cerebellum for jocks and nerds alike. *Front. Syst. Neurosci.* 8:113. doi: 10.3389/fnsys.2014.00113

Popa, L. S., Hewitt, A. L., and Ebner, T. J. (2012). Predictive and feedback performance errors are signaled in the simple spike discharge of individual Purkinje cells. *J. Neurosci.* 32, 15345–15358. doi: 10.1523/JNEUROSCI.2151-12.2012

Popa, L. S., Hewitt, A. L., and Ebner, T. J. (2013). Purkinje cell simple spike discharge encodes error signals consistent with a forward internal model. *Cerebellum* 12, 331–333. doi: 10.1007/s12311-013-0452-4

Popa, L. S., Streng, M. L., and Ebner, T. J. (2017). Long-term predictive and feedback encoding of motor signals in the simple spike discharge of Purkinje cells. *eNeuro* 4:ENEURO.0036-17.2017. doi: 10.1523/ENEURO.0036-17.2017

Popa, L. S., Streng, M. L., and Ebner, T. J. (2016a). "Signaling of predictive and feedback information in Purkinje cell simple spike activity," in *Neuronal Codes of the Cerebellum*, ed. D. H. Heck (New York, NY: Elsevier), 1–25.

Popa, L. S., Streng, M. L., Hewitt, A. L., and Ebner, T. J. (2016b). The errors of our ways: understanding error representations in cerebellar-dependent motor learning. *Cerebellum* 15, 93–103. doi: 10.1007/s12311-015-0685-5

Ramnani, N. (2014). Automatic and controlled processing in the corticocerebellar system. *Prog. Brain Res.* 210, 255–285. doi: 10.1016/B978-0-444-63356-9.00010-8

Roitman, A. V., Pasalar, S., Johnson, M. T., and Ebner, T. J. (2005). Position, direction of movement, and speed tuning of cerebellar Purkinje cells during circular manual tracking in monkey. *J. Neurosci.* 25, 9244–9257. doi: 10.1523/JNEUROSCI.1886-05.2005

Rottach, K. G., Das, V. E., Wohlgemuth, W., Zivotofsky, A. Z., and Leigh, R. J. (1998). Properties of horizontal saccades accompanied by blinks. *J. Neurophysiol.* 79, 2895–2902. doi: 10.1152/jn.1998.79.6.2895

Scarchilli, K., Vercher, J. L., Gauthier, G. M., and Cole, J. (1999). Does the oculo-manual co-ordination control system use an internal model of the arm dynamics? *Neurosci. Lett.* 265, 139–142. doi: 10.1016/s0304-3940(99)00224-4

Schlerf, J. E., Ivry, R. B., and Diedrichsen, J. (2012). Encoding of sensory prediction errors in the human cerebellum. *J. Neurosci.* 32, 4913–4922. doi: 10.1523/JNEUROSCI.4504-11.2012

Schmahmann, J. D., and Pandya, D. N. (1997). The cerebrocerebellar system. *Int. Rev. Neurobiol.* 41, 31–60. doi: 10.1016/s0074-7742(08)60346-3

Shadmehr, R., and Holcomb, H. H. (1997). Neural correlates of motor memory consolidation. *Science* 277, 821–825. doi: 10.1126/science.277.5327.821

Shadmehr, R., and Mussa-Ivaldi, F. A. (1994). Adaptive representation of dynamics during learning of a motor task. *J. Neurosci.* 14, 3208–3224. doi: 10.1523/JNEUROSCI.14-05-03208.1994

Shadmehr, R., Smith, M. A., and Krakauer, J. W. (2010). Error correction, sensory prediction, and adaptation in motor control. *Annu. Rev. Neurosci.* 33, 89–108. doi: 10.1146/annurev-neuro-060909-153135

Shidara, M., Kawano, K., Gomi, H., and Kawato, M. (1993). Inverse-dynamics model eye movement control by Purkinje cells in the cerebellum. *Nature* 365, 50–52. doi: 10.1038/365050a0

Shin, S. L., Zhao, G. Q., and Raymond, J. L. (2014). Signals and learning rules guiding oculomotor plasticity. *J. Neurosci.* 34, 10635–10644. doi: 10.1523/JNEUROSCI.4510-12.2014

Stanislaw, M. U. (1976). *Adventures of a Mathematician.* New York, NY: Charles Scribner's Sons.

Sterzer, P., Adams, R. A., Fletcher, P., Frith, C., Lawrie, S. M., Muckli, L., et al. (2018a). The predictive coding account of psychosis. *Biol. Psychiatry* 84, 634–643. doi: 10.1016/j.biopsych.2018.05.015

Sterzer, P., Voss, M., Schlagenhauf, F., and Heinz, A. (2018b). Decision-making in schizophrenia: a predictive-coding perspective. *Neuroimage* doi: 10.1016/j.neuroimage.2018.05.074 [Epub ahead of print].

Streng, M. L., Popa, L. S., and Ebner, T. J. (2017). Climbing fibers predict movement kinematics and performance errors. *J. Neurophysiol.* 118, 1888–1902. doi: 10.1152/jn.00266.2017

Streng, M. L., Popa, L. S., and Ebner, T. J. (2018a). Complex spike wars: a new hope. *Cerebellum* 17, 735–746. doi: 10.1007/s12311-018-0960-3

Streng, M. L., Popa, L. S., and Ebner, T. J. (2018b). Modulation of sensory prediction error in Purkinje cells during visual feedback manipulations. *Nat. Commun.* 9:1099. doi: 10.1038/s41467-018-03541-0

Strick, P. L., Dum, R. P., and Fiez, J. A. (2009). Cerebellum and nonmotor function. *Annu. Rev. Neurosci.* 32, 413–434. doi: 10.1146/annurev.neuro.31.060407.125606

Taylor, J. A., and Ivry, R. B. (2011). Flexible cognitive strategies during motor learning. *PLoS Comput. Biol.* 7:e1001096. doi: 10.1371/journal.pcbi.1001096

Taylor, J. A., and Ivry, R. B. (2014). Cerebellar and prefrontal cortex contributions to adaptation, strategies, and reinforcement learning. *Prog. Brain Res.* 210, 217–253. doi: 10.1016/B978-0-444-63356-9.00009-1

Taylor, J. A., Klemfuss, N. M., and Ivry, R. B. (2010). An explicit strategy prevails when the cerebellum fails to compute movement errors. *Cerebellum* 9, 580–586. doi: 10.1007/s12311-010-0201-x

Taylor, J. A., Krakauer, J. W., and Ivry, R. B. (2014). Explicit and implicit contributions to learning in a sensorimotor adaptation task. *J. Neurosci.* 34, 3023–3032. doi: 10.1523/JNEUROSCI.3619-13.2014

Thiele, A., Henning, P., Kubischik, M., and Hoffmann, K. P. (2002). Neural mechanisms of saccadic suppression. *Science* 295, 2460–2462. doi: 10.1126/science.1068788

Thoroughman, K. A., and Shadmehr, R. (1999). Electromyographic correlates of learning an internal model of reaching movements. *J. Neurosci.* 19, 8573–8588. doi: 10.1523/JNEUROSCI.19-19-08573.1999

Tseng, Y. W., Diedrichsen, J., Krakauer, J. W., Shadmehr, R., and Bastian, A. J. (2007). Sensory prediction errors drive cerebellum-dependent adaptation of reaching. *J. Neurophysiol.* 98, 54–62. doi: 10.1152/jn.00266.2007

Wallman, J., and Fuchs, A. F. (1998). Saccadic gain modification: visual error drives motor adaptation. *J. Neurophysiol.* 80, 2405–2416. doi: 10.1152/jn.1998.80.5.2405

Wilford, K. (1991). "Tourist visits to state sites up 0.1% IN '90—blue ridge highlands region has biggest gain, 6.1 percent," in *Richmond Times-Dispatch* (Richmond, VA: NewsBank Access World News).

Winkelman, B. H., Belton, T., Suh, M., Coesmans, M., Morpurgo, M. M., and Simpson, J. I. (2014). Nonvisual complex spike signals in the rabbit cerebellar flocculus. *J. Neurosci.* 34, 3218–3230. doi: 10.1523/JNEUROSCI.3080-13.2014

Winkelman, B., and Frens, M. (2006). Motor coding in floccular climbing fibers. *J. Neurophysiol.* 95, 2342–2351. doi: 10.1152/jn.01191.2005

Wolpert, D. M., Ghahramani, Z., and Jordan, M. I. (1995). An internal model for sensorimotor integration. *Science* 269, 1880–1882. doi: 10.1126/science.7569931

Wolpert, D. M., Miall, R. C., and Kawato, M. (1998). Internal models in the cerebellum. *Trends Cogn. Sci.* 2, 338–347. doi: 10.1016/S1364-6613(98)01221-2

Xu-Wilson, M., Chen-Harris, H., Zee, D. S., and Shadmehr, R. (2009). Cerebellar contributions to adaptive control of saccades in humans. *J. Neurosci.* 29, 12930–12939. doi: 10.1523/JNEUROSCI.3115-09.2009

Zago, M., Bosco, G., Maffei, V., Iosa, M., Ivanenko, Y. P., and Lacquaniti, F. (2004). Internal models of target motion: expected dynamics overrides measured kinematics in timing manual interceptions. *J. Neurophysiol.* 91, 1620–1634. doi: 10.1152/jn.00862.2003

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer EL declared a past co-authorship with the authors to the handling editor.

frontiers in Human Neuroscience

ORIGINAL RESEARCH
published: 21 February 2019
doi: 10.3389/fnhum.2019.00061

Disruption of Cerebellar Prediction in Verbal Working Memory

Yi-Shin Sheu, Yu Liang and John E. Desmond**

Department of Neurology, Division of Cognitive Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Mounting evidence suggests that the right cerebellum contributes to verbal working memory, but the functional role of this contribution remains unclear. In an established theory of motor control, the cerebellum is thought to predict sensory consequences of movements through an internal "forward model." Here, we hypothesize a similar predictive process can generalize to cerebellar non-motor function, and that the right cerebellum plays a predictive role that is beneficial for rapidly engaging the phonological loop in verbal working memory. To test this hypothesis, double-pulse transcranial magnetic stimulation (TMS) was administered over either the right cerebellum or right occipital lobe (control site), on half the trials, to interrupt the rehearsal of a 6-letter sequence. We found that cerebellar stimulation resulted in greater errors in participants' report of the letter in the current position. Additional analyses revealed that immediately after cerebellar TMS, participants were more likely to use out of date information to predict the next letter in the sequence. This pattern of errors is consistent with TMS causing a temporary disruption of state estimation and cerebellar forward model function, leading to prediction errors in the phonological loop.

Keywords: cerebellum, TMS, verbal working memory, forward models, prediction

OPEN ACCESS

Edited by:
Mario U. Manto,
University of Mons, Belgium

Reviewed by:
Elise Lesage,
Ghent University, Belgium
De-Lai Qiu,
Yanbian University, China

****Correspondence:***
Yi-Shin Sheu
yishin.sheu@gmail.com
John E. Desmond
dr.jdesmond@gmail.com

Received: *30 October 2018*
Accepted: *04 February 2019*
Published: *21 February 2019*

Citation:
Sheu Y-S, Liang Y and Desmond JE (2019) Disruption of Cerebellar Prediction in Verbal Working Memory. Front. Hum. Neurosci. 13:61. doi: 10.3389/fnhum.2019.00061

INTRODUCTION

It has become widely accepted in recent years that the human cerebellum contributes not only to motor function, but also to a wide range of non-motor cognitive functions (for reviews, see Stoodley, 2012; Buckner, 2013; Schmahmann, 2019), such as verbal working memory (Chein and Fiez, 2001; Chen and Desmond, 2005; Justus et al., 2005; Ravizza et al., 2006; Hayter et al., 2007; Durisko and Fiez, 2010; Marvel and Desmond, 2010; Peterburs et al., 2010, 2016; Stoodley et al., 2012), executive function (Grafman et al., 1992; Rao et al., 1997; Schmahmann and Sherman, 1998; Karatekin et al., 2000; Neau et al., 2000; Bellebaum and Daum, 2007; Balsters et al., 2013; Wu et al., 2013; Rentiya et al., 2017), and language (Petersen et al., 1989; Desmond et al., 1998; Fulbright et al., 1999; Leggio et al., 2000; Lurito et al., 2000; Seger et al., 2000; Moretti et al., 2002; Xiang et al., 2003; Grönholm et al., 2005; Frings et al., 2006; Ben-Yehudah and Fiez, 2008; Rauschecker et al., 2008; Mariën et al., 2009, 2014; Stoodley and Schmahmann, 2009; Highnam and Bleile, 2011; Argyropoulos and Muggleton, 2013; Keren-Happuch et al., 2014). However, the nature of cerebellar contributions to these cognitive functions remains unclear.

Working memory, the ability to temporarily store and manipulate information for complex cognitive activities (Baddeley, 1998), is perhaps one of the most studied cognitive function that engages cerebellum. Based on the theoretical framework of working memory by Baddeley and Hitch (1974), a central executive system with limited attentional capacity is served by two subsidiary storage systems: the phonological loop for verbal information and the visuospatial sketchpad for visual information. The phonological loop comprises a phonological store, which can hold memory traces for a few seconds before they fade, and an articulatory rehearsal process that can refresh the memory trace through active rehearsal, which is analogous to sub-vocal speech (Baddeley, 1992). Previous neuroimaging studies of verbal working memory suggest that regions in left inferior temporal/parietal regions are associated with the phonological store, and the left inferior frontal regions are associated with articulatory control process (Paulesu et al., 1993; Awh et al., 1996; Fiez et al., 1996). Based on the known neuroanatomy of cerebro-cerebellar pathways (Middleton and Strick, 1994, 1997, 2001) and the use of a phase-specific Sternberg task (Sternberg, 1966), Desmond et al. (1997) proposed a neuroanatomical model of two cerebro-cerebellar circuits participating in the phonological loop: one connecting the frontal cortex to the superior cerebellum, providing the articulatory rehearsal process for phonological encoding, and the other connecting the temporal/parietal cortex to the inferior cerebellum, providing temporary maintenance of phonological information. This model was supported by subsequent functional neuroimaging studies (Chen and Desmond, 2005; Kirschen et al., 2010), cerebellar patient studies (Silveri et al., 1998; Ravizza et al., 2006; Chiricozzi et al., 2008; Kirschen et al., 2008; Peterburs et al., 2010), cerebellar transcranial magnetic stimulation (TMS; Desmond et al., 2005) and transcranial direct current stimulation (tDCS; Boehringer et al., 2013) investigations.

In the literature of motor control, forward models have been postulated as the basic computation provided by the cerebellum in order to control the musculoskeletal system, especially for rapid movements when sensory feedback delay is unavoidable (Wolpert and Miall, 1996; Wolpert et al., 1998). Forward models are essentially internal "neural" models that mimic the motor apparatus, which provide predictions of the sensory consequences of movements before feedback is available. Given the homogeneous cytoarchitecture of the cerebellar cortex, some investigators have argued that there is a common computational operation performed throughout the structure, with difference in function derived from the local input-output connections with the cerebral cortex (Ramnani, 2006; Ito, 2008; Strick et al., 2009; Bellebaum et al., 2012; Ishikawa et al., 2016). If the computational principles are indeed similar across the cerebellum, then our understanding of cerebellar function in sensorimotor control might be relevant to cerebellar involvement in verbal working memory. Therefore, in the current study, we propose the right cerebellum plays a predictive role, similar to forward models in motor control, that is beneficial for rapidly engaging the phonological loop in verbal working memory.

Given our cerebro-cerebellar model of phonological loop described earlier, we hypothesize that the cerebellum contributes to verbal working memory by generating two distinct predictions: (1) predictions of the articulatory trajectory based on the encoded verbal items, which may involve planning of movements of our jaw, tongue, lips, and larynx; and (2) predictions of the content in the phonological store, which may involve streaming a sequence of phonemes for sub-vocal rehearsal process. In a typical verbal working memory task, the success of correct verbal recall depends both on setting up an articulatory trajectory of the encoded verbal items as well as active rehearsal. Thus, we hypothesize that increased error rates in verbal working memory performance would occur if either the frontal/superior cerebellum articulatory prediction, or the parietal/inferior cerebellum phonological prediction, or both, were disrupted.

Direct evidence of disruption of cerebellar prediction in motor control has been observed using TMS, a brain stimulation technique that can temporarily interrupt function of the targeted area with high temporal specificity. Miall et al. (2007) tested the cerebellar forward model in a hand movement trajectory task by applying TMS to the cerebellum while participants made a rapid reaching movement toward a remembered target. This resulted in trajectory errors that could be explained by movements that were planned based on the hand position 138 ms ago. They suggested that the observed directional deviation was a result of a temporary loss of cerebellar predictive function, which caused the planning of reaching movement to be based on the previous (out of date) state of the arm.

Inspired by the Miall et al. (2007) results, we designed an analogous experiment to test our hypothesis that right cerebellum plays a predictive role in verbal working memory. We used TMS to briefly interfere with right cerebellar function as the participants covertly rehearsed a sequence of encoded letters. In order to generate articulatory trajectories with a known state over time, we used guided rehearsal, where a series of # signs, each representing a letter of the encoded sequence, was presented on the screen one at a time to pace the subject's rehearsal of the letter sequence. This rehearsal process was interrupted by TMS, at which time the subject was immediately asked to report if a probe letter was the correct next-letter in the sequence. On half the trials the probe was the correct next letter, and on the other half the probe was either one letter earlier (early probe) or later (late probe) in the sequence. We predicted that, like the Miall et al. (2007) investigation, TMS would make the state estimation of the articulatory trajectory out of date (i.e., the forward models would be predicting a letter that was earlier in the trajectory instead of the correct next letter). Consequently, we predicted that cerebellar TMS would cause the participant to more likely judge an early probe as being in the correct position (more errors in early probe condition), a correct probe as being too late in the sequence (more errors in correct probe condition), and a late probe as (definitely) too late in the sequence (no or fewer errors). We used a control site in right occipital lobe to assess the specificity of cerebellar TMS effects.

MATERIALS AND METHODS

Participants

A total of 23 (seven males, 16 females) healthy young adults, age 19–30 (mean = 22.26 years, SD = 2.649 years), with educational attainment of at least 8 years, participated in the study. All participants were native English speakers with normal or corrected-to-normal vision, had no history of head trauma, seizure or a family history of epilepsy, stroke, neurological or psychiatric disorders, and were not taking anxiolytic, antidepressant, neuroleptic, or sedative medication at the time of the study. This study was carried out in accordance with the recommendations of Institutional Review Board of the Johns Hopkins School of Medicine with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the Johns Hopkins School of Medicine.

Tasks

Participants were asked to covertly encode an array of six letters presented on a screen in uppercase, which was then removed from the screen after 2 s. Participants were instructed to read the letters in the order that they appeared (read from left to right, first row then second row). After a short delay (500 ms), 2–4 # signs then appeared on the screen one at a time (400 ms for each # sign with a 150 ms blank screen between # signs), each representing a placeholder of a letter in the encoding array. On half of the trials, participants received paired 20 Hz TMS pulses 150 ms prior to the last # sign, followed by a probe letter (3 s, presented in lowercase with a question mark. Participants were instructed to press button 1 for "yes" with their right index finger to indicate that the probe letter matches the next letter in the sequence, and to press 2 for "no" with their right middle finger if the probe letter does not match the next letter in the sequence (**Figure 1**). In addition, they were instructed to respond as fast as possible without sacrificing accuracy. The next trial began after a fixed interval of 1,800 ms. Participants were given a short practice at the beginning of the experiment so that they could familiarize themselves with the task. During the task practice, feedback was given to indicate whether the participant's response was "Correct" or "Incorrect, " and the accumulated percent accuracy was displayed. Feedback was not given during the actual TMS experiment.

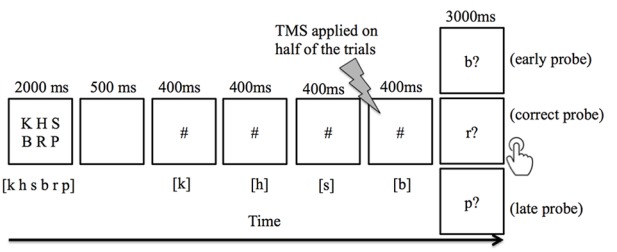

FIGURE 1 | An example of trial events progression in the verbal working memory task. Subjects were instructed to keep in mind six visually-presented letters, and to covertly rehearse the letters in sync with the appearance of # symbols. Between each # presentation, a 150 ms blank screen was included to visually separate the adjacent # presentation. The letter(s) listed in [ ] indicates the correct content for rehearsal. When a probe letter appeared, the subject pressed button 1 to indicate that it matched the next letter in the sequence, or button 2 indicate that it did not match. The correct response for early probe and late probe conditions was the "non-match" button, whereas the "match" button was appropriate for the correct probe condition. Double-pulse transcranial magnetic stimulation (TMS) was applied 150 ms prior to the last # sign in half of the trials.

A total of 80 trials were given for each session (cerebellum vs. occipital lobe stimulation, order counterbalanced). Eighty percent of these trials (n = 64) were longer trials with the probe letter appearing after the fourth # sign (i.e., probe at the fifth position = P5). The remaining 20% (n = 16) containing either 2 or 3 # signs (i.e., probe at the third or fourth position = P3 and P4) were discarded from analysis because a previous pilot study in our lab (unpublished) showed these shorter trials had a ceiling effect due to its short duration and thus lower working memory demands. However, the shorter trials were included to ensure that the timing of the probe letter was unpredictable. For both the longer trials (P5) and shorter trials (P3 and P4), there were an equal number of TMS and non-TMS trials as well as an equal number of match (i.e., correct probe) and non-match (i.e., early and late probe) trials.

TMS Protocol

Biphasic TMS paired-pulses were triggered at 20 Hz (i.e., 50 ms interpulse-interval) by E-Prime 2.0 standard software (Psychological Software Tool, Pittsburg, PA, USA) using a Magstim Rapid^2 stimulator (Magstim Co., Whitland Dyfed, UK) that was connected to a 110-mm diameter double cone coil. Motor threshold (MT) was determined for each participant as the minimal TMS intensity needed to evoke a visible muscle twitch in the right hand in 5 out of 10 trials upon stimulation of the left motor cortex. The coil was placed on the scalp with the handle held backward and with the coil current flowing in an upward direction at the juncture of the two loops of the coil. The optimal stimulation location and the orientation of the coil were marked on a fitting lycra swimming cap placed over participant's head to ensure consistent coil positioning.

For cerebellum stimulation, the double cone coil was centered at 1 cm below and 3 cm to the right of the inion. This coil geometry and position were found to be ideal for stimulating lateral cerebellar gray matter with low probability of passing through occipital cortex (Hardwick et al., 2014). However, in this position, we found that individual variations in skull shape created a gap between the scalp surface and the double cone coil to a varying degree in our participants. Previous studies have found that the scalp-coil distance directly influences the magnitude of stimulator output needed to reach MT (Kozel et al., 2000; McConnell et al., 2001; Stokes et al., 2007). Specifically, using a 70 mm figure-eight coil, Stokes et al. (2007) found for every 1 mm distance, an additional ∼2.8% of stimulator output was required to reach the same level of MT. However, to our knowledge, no studies have systematically manipulated the scalp-coil distance using a double-cone coil, which was designed for stimulating the deeper cortical areas typically at the depth

of 3–4 cm from the scalp, as comparison to figure-eight coil at the depth of 2–2.5 cm (Lu and Ueno, 2017). Therefore, before TMS stimulation of the cerebellum, we measured the MT for each participant at varying scalp-coil distances by placing custom-made moldable plastic separators[1], measuring 3 mm, 7 mm, and 10 mm in thickness between the scalp surface and the coil. This resulted in four scalp-coil measurements: 0 mm (base level), 3 mm, 7 mm, and 10 mm. We then entered our measurements (X = separator thickness in mm, Y = stimulator output needed to reach MT) into a linear regression equation to derive the slope and the constant. In order to measure the actual distance between the participant's scalp and the double cone coil for cerebellar TMS, we measured the scalp-coil distance using seven cylindrical wooden sticks in different diameters (4.75 mm, 6.43 mm, 8.2 mm, 9.75 mm, 11.25 mm, 12.5 mm, 15.04 mm), after we positioned the participant in the TMS chair and placed the coil as close as possible to the scalp. The cylindrical stick that was the best fit between the scalp and coil was used to calculate the adjusted stimulator output using each individual's linear regression equation. The adjusted output number for scalp-coil distance was then multiplied by 110% to ensure excitability of the right cerebellum.

For the right occipital (control) region, the coil was centered at 7 cm above and 3 cm to the right of the inion. In this position, we did not experience any scalp-coil distance issues in all of our participants. Therefore, the stimulator output was directly set to 110% of MT. At this intensity, no participants reported phosphenes during the experiment. Finally, we note that the distance between the scalp and the targeted cortex is greater for cerebellum than for the occipital lobe, and consequently, the occipital lobe overall likely received more stimulation than the cerebellum.

Data Analysis

Error rate and reaction time (RT) were analyzed using SPSS version 24 (IBM Corp, Armonk, NY, USA). Differences in the percentage of error rate between TMS and non-TMS trials were calculated for each participant, separately for each cerebellar and occipital stimulation session. The same subtraction was performed for mean RT. Repeated-measures analysis of variances (ANOVAs) were then conducted on these differences to test for an interaction between stimulation sites (cerebellum vs. occipital lobe) and probe position (early, correct, late). Based on our hypothesis described in the "Introduction" section that cerebellar TMS would make the state estimation of the predicted sequence out of date, we predicted significantly higher error rates for early and correct probe, but not for the late probe. To test this *a priori* hypothesis, we conducted a planned comparison based on the predicted interaction between stimulation site (cerebellum = +1, control site = −1) and probe position (early probe = +1, correct probe = +1, late probe = −2), followed by three planned comparisons using paired *t*-tests to determine whether mean difference in error rate was significantly different between these two stimulation sites for each probe condition.

[1]http://InstaMorph.com

RESULTS

TMS Coil-Scalp Distance and MT

The mean MT (gap = 0 mm) was 36.39% (SD = 5.813%). The mean slope for the linear regression was 0.709%/mm (SD = 0.23%/mm), which means an additional 0.709% of absolute simulator output was required for each 1 mm distance between the scalp and coil to reach the same level of MT excitability. For cerebellar stimulation, the average distance between coil and scalp was 9.464 mm (SD = 2.726 mm). The average absolute stimulator output applied at the stimulation site was 46.91% (SD = 7.096%) for right cerebellum, and was 40.17% (SD = 6.415%) for right occipital lobe. Additionally, no significant gender differences in TMS coil-scalp distance ($t_{(21)} = -0.769$, $p = 0.450$), slope ($t_{(21)} = 1.068$, $p = 0.298$), and MT ($t_{(21)} = 1.158$, $p = 0.26$) were found.

Accuracy Data

Overall, participants made significantly more errors in TMS trials compared to non-TMS trials. For stimulation of the right cerebellum, the mean error rate for non-TMS trials was 13.5% (SD = 8.6%), and increased to 23.9% (SD = 15.4%) for TMS trials. For stimulation of the right occipital lobe, the mean error rate for non-TMS trials was 12.8% (SD = 7.9%), and increased to 16.2% (SD = 12.2%) for TMS trials.

To examine whether the TMS effect on error rate is different between the two stimulation sites, we performed a repeated measure ANOVA with factors of *stimulation site* (cerebellum, occipital lobe) and *trial type* (TMS trial, non-TMS trial). This analysis yielded significant main effects of stimulation site ($F_{(1,22)} = 5.719$, $p = 0.026$), trial type ($F_{(1,22)} = 10.845$, $p = 0.003$), and a significant interaction effect ($F_{(1,22)} = 6.333$, $p = 0.020$), with cerebellar stimulation resulting in higher error rate than occipital lobe on TMS trials (**Figure 2**).

To test our main *a priori* hypothesis that the early and correct probe would be more affected than the late probe by cerebellar TMS, we examined the error rate difference using a repeated measure ANOVA with factors of *probe position*

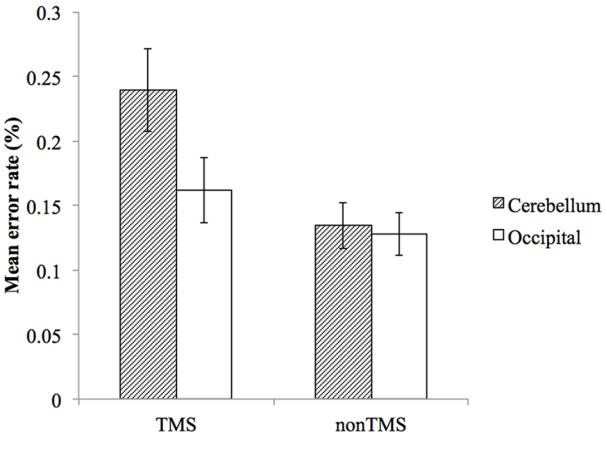

FIGURE 2 | The effect of TMS on mean error rates for cerebellum and occipital lobe. Error bars represent SEM.

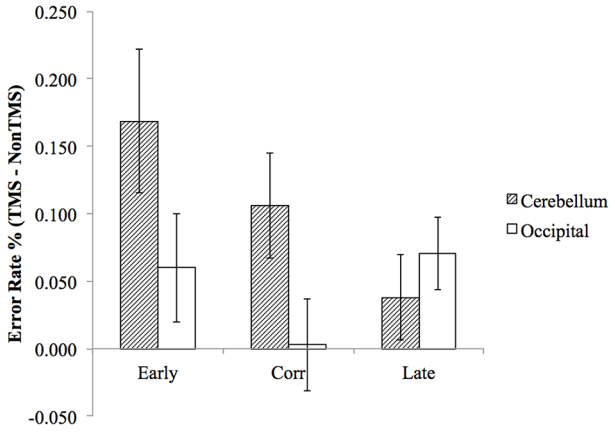

FIGURE 3 | The difference in (TMS minus non-TMS) error rates between cerebellum stimulation and occipital lobe stimulation was significantly greater for "early probe" and "correct probe" condition, but not for the "late probe" condition. Error bars represent SEM.

(early probe, correct probe, late probe) and *stimulation site* (cerebellum, occipital lobe). To perform this analysis, we first calculated the mean error rate difference by subtracting the error rate of non-TMS trial from TMS trials, and then entered them into the repeated measure ANOVA described above. Consistent with our hypothesis, the planned comparison of the interaction between probe positions and stimulation site confirmed that the cerebellar TMS relative to occipital TMS resulted in significantly higher error rate for early probe and correct probe, compared to late probe condition ($F_{(1,22)} = 4.78$, $p = 0.04$). Direct paired *t*-tests were then conducted to assess the difference in error rate between cerebellar TMS vs. occipital TMS for early probe condition ($t_{(22)} = 1.877$, $p = 0.074$), correct probe condition ($t_{(22)} = 2.466$, $p = 0.022$), and late probe condition ($t_{(22)} = 0.435$, $p = 0.795$), as illustrated in **Figure 3**. The ANOVA also revealed a main effect for stimulation sites ($F_{(1,22)} = 5.393$, $p = 0.03$), with higher error rate in cerebellar stimulation condition, a non-significant main effect for probe position ($F_{(2,44)} = 1.645$, $p = 0.205$), and an interaction effect that approached significance ($F_{(2,44)} = 2.670$, $p = 0.08$).

Reaction Time Data

For the RT data, participants were slower on TMS trials (Mean = 750.888 ms, SD = 40.219 ms) compared to non-TMS trials (Mean = 712.993 ms, SD = 30.647 ms). For stimulation of the right cerebellum, the mean RT for non-TMS trials was 706.322 ms (SD = 130.218 ms), and increased to 762.302 ms (SD = 191.992 ms) for TMS trials. For stimulation of the right occipital lobe, the mean RT for non-TMS trials was 719.664 ms (SD = 192.461 ms), and increased to 739.474 ms (SD = 218.334 ms) for TMS trials.

To examine whether the TMS effect on mean RT was different with respect to stimulation site, we performed a repeated measure ANOVA with factors of *stimulation site* (cerebellum, occipital lobe) and *trial type* (TMS trial, non-TMS trial). This analysis yielded a significant main effect of trial type ($F_{(1,22)} = 5.805$, $p = 0.025$) but not *stimulation site* ($F_{(1,22)} = 0.029$, $p = 0.867$), and there was no significant interaction ($F_{(1,22)} = 2.569$, $p = 0.123$). Thus, participants were significantly slower on TMS trials, but there was no difference in RT between TMS applied over cerebellum vs. occipital lobe.

We also examined whether the mean RT difference between TMS vs. non-TMS trials differed by *probe position* (early probe, correct probe, late probe) and *stimulation site* (cerebellum, occipital lobe). To perform this analysis, we first calculated the mean RT difference by subtracting the RT of non-TMS trials from TMS trials, and then entered them into a repeated measure ANOVA. This analysis yielded a significant main effect of probe position ($F_{(2,44)} = 3.431$, $p = 0.042$), but not stimulation site ($F_{(1,22)} = 0.879$, $p = 0.359$), and there was no significant interaction ($F_{(2,44)} = 0.305$, $p = 0.687$). Upon examination of the mean RT difference (TMS RT—nonTMS RT), the correct probe has the greatest RT difference (Mean = 59.338 ms, SE = 17.673 ms), followed by late (Mean = 37.122 ms, SE = 30.257 ms), and finally the early probe (Mean = −9.314 ms, SD = 20.223 ms).

DISCUSSION

We found that TMS administration to the right cerebellum, applied during covert rehearsal of a remembered sequence of letters, resulted in an interference with participants' ability to identify whether a probe letter is in the correct position. Importantly, the pattern of results suggested that the response to the probe was based on out of date information regarding the next letter in the sequence. As a concrete example, in **Figure 1**, if TMS briefly causes the sequence prediction to be "frozen" at the letter B, then this letter b prediction will still be active when the probe letter is presented, and a probe letter of "b" will seem to be correct, whereas the actual correct probe of "r" will not, leading to errors on both the "early probe" and "correct probe" conditions. In contrast, "late probe" letters should still seem to be incorrect after TMS, and thus judgment of these letters should not be affected. The pattern of results depicted in **Figure 3** supports this explanation and is consistent with our hypothesis that TMS pulses temporarily disrupt the function of the right cerebellum, resulting in prediction errors in the phonological loop. Our results therefore provide further evidence for cerebellar forward models in cognitive domains, in particular with respect to verbal working memory.

Our findings support the idea that cerebellar forward models contribute to verbal working memory by predicting upcoming verbal items in the phonological loop. In the motor control domain, the cerebellum is critical for predicting the outcome of an action before sensory feedback is available. These predictions can be compared with reafferent input. When they mismatch, an error signal is generated which allows rapid adjustments to the motor output as well as an update of the predictive model to refine future sensory predictions (Wolpert and Miall, 1996; Wolpert et al., 1998). Here, we presented evidence that the predictive capability of the cerebellum can be extended to verbal working memory.

We proposed a cerebellar forward model that rapidly engages the phonological loop by computing an articulatory trajectory of the phonemes during the encoding phase. During the maintenance phase, the predicted output of the rehearsal process needs to be constantly compared to the content in the phonological store, which holds the correct sequence of phonemes kept in working memory. In previous studies, the encoding-related articulatory control process has been linked to right superior cerebellum *via* connection with Broca's area and premotor cortex, while the maintenance-related phonological loop has been linked to right inferior cerebellum *via* connection with left inferior parietal lobule (Chen and Desmond, 2005). In the current study, TMS was administered to the right cerebellum during the guided rehearsal process. Since cerebellar sub-regions cannot be clearly delineated with TMS techniques, the significantly higher error rate could be a result of a compromised predictive process in the phonological store, the articulatory control system, or both. Interestingly, a recent functional magnetic resonance imaging (fMRI) study found activity in the right posterolateral cerebellum correlated with the predictability of upcoming sentence content, and the same cerebellar cluster that is sensitive to linguistic predictability was recruited in a phonological task, but not in semantic or orthographic tasks (Lesage et al., 2017). These results are consistent with our current findings and are in line with the idea that cerebellum plays a predictive role in verbal working memory and in language comprehension through prediction of phonological information.

Although our results provide further evidence for a forward model account of the cerebellar role in verbal working memory, there is no consensus regarding the basic function that the cerebellum provides for cognition, and other accounts such as the timing hypothesis (Keele and Ivry, 1990; Tesche and Karhu, 2000; Ivry et al., 2002; Leggio et al., 2011), and the sequencing hypothesis (Tesche and Karhu, 2000; Leggio et al., 2011), have also been proposed. According to the timing hypothesis, the cerebellum is essential for the representation of temporal relationships. In our experiment, the probe occurs at the fifth position in a six-letter sequence on 80% of the trials. Therefore, it is possible that participants developed a temporal prediction of the occurrence of the probe stimulus, and that application of TMS disrupted the internal timing component, resulting in an increased error rate. However, under a timing hypothesis, we would expect all probe types to be equally affected by cerebellar TMS. Our data clearly showed that the error rate significantly increased in the early and correct probe conditions, but not in the late probe condition. Hence, the pattern of results may be better understood in the context of forward models. Another putative cerebellar function is sequence detection, which emphasizes the cerebellum's ability to detect and simulate repetitive sequence. It has been suggested that sequence detection is closely related to the predictive function characterized by forward models: the cerebellum creates internal models based on the sequence of events it detects (Leggio and Molinari, 2015). In verbal working memory, the "sequence" simulated by the internal model can be the content in the phonological store or the intended articulatory trajectory for rehearsal, which are respectively compared with the actual output of sub-vocal articulation or the actual trajectory of rehearsal. Therefore, the sequencing hypothesis is compatible with forward model explanations, and complements our findings of the functional role of cerebellum in verbal working memory.

Our data revealed a significant increase of RT in TMS trials compared to non-TMS trials. However, the RT difference was not significantly different between the stimulation sites (cerebellum vs. occipital lobe). In addition, the TMS effect on RT was not modulated by probe types (early, correct, late probes) between the two stimulation sites. This pattern of RT results, together with the significant TMS effects on accuracy, indicate that TMS interferes with the content in verbal working memory, rather than the speed of processing. These results are seemingly in conflict with a previous study showing cerebellar TMS resulted in an increase in RT during verbal working memory performance, but had no effect on accuracy (Desmond et al., 2005). However, a closer look of the task design in the previous study revealed that the TMS was administered immediately after encoding when the demand for preparation of articulatory trajectory is highest. On the other hand, in the current task, the TMS was administered closer to the end of the guided rehearsal phase when phonological store demand is highest. Given the known frontal/superior cerebellum circuit for articulatory preparation, and parietal/inferior cerebellum circuit for phonological store (Desmond et al., 1997, 2003, 2005), the TMS RT effect may likely reflect a compromised frontal/superior cerebellar articulatory control system, and the TMS accuracy effect may likely reflect a compromised parietal/inferior cerebellar phonological storage system. Taken together, the fact that we observed a TMS effect on accuracy (i.e., the content in working memory was affected), but not RT (i.e., processing speed was not affected), provide additional support that the right cerebellum plays a role in non-motor aspects of verbal working memory, and that a cerebellar forward model could explain the contribution of the cerebellum to non-motor cognitive functions, such as phonological storage.

In conclusion, our results are consistent with the idea that the right cerebellum supports verbal working memory by predicting upcoming verbal items in the phonological loop. It is assumed that a predictive process similar to forward models in motor control can be extended to non-motor cognitive functions such as verbal working memory, and the present study is consistent with other recent neuromodulation investigations supporting forward models in predicting verbal content (Lesage et al., 2012; Miall et al., 2016; D'Mello et al., 2017). Given the converging evidence from neuroimaging and anatomical studies, we speculate that: (1) the right superior cerebellum receives an "efference copy" of the articulatory command from Broca's area, from which it generates a predicted articulatory trajectory of the encoded phonemes; and (2) the right inferior cerebellum receives an "efference copy" of the refresh phonological store command from the temporal/inferior parietal lobe, from which it generates a phonological trajectory of phonemes for active rehearsal. These predictions would then feedback to their respective cortical areas

for speedy and accurate processing of phonological information in verbal working memory.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

JD conceived the presented idea and supervised the project. JD and Y-SS designed the experiment, analyzed the data and wrote the manuscript. Y-SS and YL carried out the experiment. Y-SS took the lead in writing the manuscript with support from JD.

FUNDING

This work was funded by the National Institutes of Health (NIH/NIMH; grant number R01MH104588 to JD) and was also supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under Award Number U54HD079123. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

Argyropoulos, G. P., and Muggleton, N. G. (2013). Effects of cerebellar stimulation on processing semantic associations. *Cerebellum* 12, 83–96. doi: 10.1007/s12311-012-0398-y

Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppe, R. A., and Katz, S. (1996). Dissociation of storage and rehearsal in verbal working memory: evidence from positron emission tomography. *Psychol. Sci.* 7, 25–31. doi: 10.1111/j.1467-9280.1996.tb00662.x

Baddeley, A. (1992). Working memory. *Science* 255, 556–559. doi: 10.1126/science.1736359

Baddeley, A. (1998). Working memory. *C. R. Acad. Sci. III* 321, 167–173. doi: 10.1016/S0764-4469(97)89817-4

Baddeley, A. D., and Hitch, G. (1974). *Working Memory*. New York, NY: Academic Press.

Balsters, J. H., Whelan, C. D., Robertson, I. H., and Ramnani, N. (2013). Cerebellum and cognition: evidence for the encoding of higher order rules. *Cereb. Cortex* 23, 1433–1443. doi: 10.1093/cercor/bhs127

Bellebaum, C., and Daum, I. (2007). Cerebellar involvement in executive control. *Cerebellum* 6, 184–192. doi: 10.1080/14734220601169707

Bellebaum, C., Daum, I., and Suchan, B. (2012). Mechanisms of cerebellar contributions to cognition in humans. *Wiley Interdiscip. Rev. Cogn. Sci.* 3, 171–184. doi: 10.1002/wcs.1161

Ben-Yehudah, G., and Fiez, J. A. (2008). Impact of cerebellar lesions on reading and phonological processing. *Ann. N Y Acad. Sci.* 1145, 260–274. doi: 10.1196/annals.1416.015

Boehringer, A., Macher, K., Dukart, J., Villringer, A., and Pleger, B. (2013). Cerebellar transcranial direct current stimulation modulates verbal working memory. *Brain Stimul.* 6, 649–653. doi: 10.1016/j.brs.2012.10.001

Buckner, R. L. (2013). The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron* 80, 807–815. doi: 10.1016/j.neuron.2013.10.044

Chein, J. M., and Fiez, J. A. (2001). Dissociation of verbal working memory system components using a delayed serial recall task. *Cereb. Cortex* 11, 1003–1014. doi: 10.1093/cercor/11.11.1003

Chen, S. H., and Desmond, J. E. (2005). Temporal dynamics of cerebro-cerebellar network recruitment during a cognitive task. *Neuropsychologia* 43, 1227–1237. doi: 10.1016/j.neuropsychologia.2004.12.015

Chiricozzi, F. R., Clausi, S., Molinari, M., and Leggio, M. G. (2008). Phonological short-term store impairment after cerebellar lesion: a single case study. *Neuropsychologia* 46, 1940–1953. doi: 10.1016/j.neuropsychologia.2008.01.024

Desmond, J. E., Chen, S. H., DeRosa, E., Pryor, M. R., Pfefferbaum, A., and Sullivan, E. V. (2003). Increased frontocerebellar activation in alcoholics during verbal working memory: an fMRI study. *Neuroimage* 19, 1510–1520. doi: 10.1016/s1053-8119(03)00102-2

Desmond, J. E., Chen, S. H., and Shieh, P. B. (2005). Cerebellar transcranial magnetic stimulation impairs verbal working memory. *Ann. Neurol.* 58, 553–560. doi: 10.1002/ana.20604

Desmond, J. E., Gabrieli, J. D. E., and Glover, G. H. (1998). Dissociation of frontal and cerebellar activity in a cognitive task: evidence for a distinction between selection and search. *Neuroimage* 7, 368–376. doi: 10.1006/nimg.1998.0340

Desmond, J. E., Gabrieli, J. D., Wagner, A. D., Ginier, B. L., and Glover, G. H. (1997). Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functional MRI. *J. Neurosci.* 17, 9675–9685. doi: 10.1523/jneurosci.17-24-09675.1997

D'Mello, A. M., Turkeltaub, P. E., and Stoodley, C. J. (2017). Cerebellar tDCS modulates neural circuits during semantic prediction: a combined tDCS-fMRI study. *J. Neurosci.* 37, 1604–1613. doi: 10.1523/jneurosci.2818-16.2017

Durisko, C., and Fiez, J. A. (2010). Functional activation in the cerebellum during working memory and simple speech tasks. *Cortex* 46, 896–906. doi: 10.1016/j.cortex.2009.09.009

Fiez, J. A., Raife, E. A., Balota, D. A., Schwarz, J. P., Raichle, M. E., and Petersen, S. E. (1996). A positron emission tomography study of the short-term maintenance of verbal information. *J. Neurosci.* 16, 808–822. doi: 10.1523/jneurosci.16-02-00808.1996

Frings, M., Dimitrova, A., Schorn, C. F., Elles, H.-G., Hein-Kropp, C., Gizewski, E. R., et al. (2006). Cerebellar involvement in verb generation: an fMRI study. *Neurosci. Lett.* 409, 19–23. doi: 10.1016/j.neulet.2006.08.058

Fulbright, R. K., Jenner, A. R., Mencl, W. E., Pugh, K. R., Shaywitz, B. A., Shaywitz, S. E., et al. (1999). The cerebellum's role in reading: a functional MR imaging study. *AJNR Am. J. Neuroradiol.* 20, 1925–1930.

Grafman, J., Litvan, I., Massaquoi, S., Stewart, M., Sirigu, A., and Hallett, M. (1992). Cognitive planning deficit in patients with cerebellar atrophy. *Neurology* 42, 1493–1496. doi: 10.1212/wnl.42.8.1493

Grönholm, P., Rinne, J. O., Vorobyev, V., and Laine, M. (2005). Naming of newly learned objects: a PET activation study. *Cogn. Brain Res.* 25, 359–371. doi: 10.1016/j.cogbrainres.2005.06.010

Hardwick, R. M., Lesage, E., and Miall, R. C. (2014). Cerebellar transcranial magnetic stimulation: the role of coil geometry and tissue depth. *Brain Stimul.* 7, 643–649. doi: 10.1016/j.brs.2014.04.009

Hayter, A. L., Langdon, D. W., and Ramnani, N. (2007). Cerebellar contributions to working memory. *Neuroimage* 36, 943–954. doi: 10.1016/j.neuroimage.2007.03.011

Highnam, C. L., and Bleile, K. M. (2011). Language in the cerebellum. *Am. J. Speech Lang. Pathol.* 20, 337–347. doi: 10.1044/1058-0360(2011/10-0096)

Ishikawa, T., Tomatsu, S., Izawa, J., and Kakei, S. (2016). The cerebro-cerebellum: could it be loci of forward models? *Neurosci. Res.* 104, 72–79. doi: 10.1016/j.neures.2015.12.003

Ito, M. (2008). Control of mental activities by internal models in the cerebellum. *Nat. Rev. Neurosci.* 9, 304–313. doi: 10.1038/nrn2332

Ivry, R. B., Spencer, R. M., Zelaznik, H. N., and Diedrichsen, J. (2002). The cerebellum and event timing. *Ann. N Y Acad. Sci.* 978, 302–317. doi: 10.1111/j.1749-6632.2002.tb07576.x

Justus, T., Ravizza, S. M., Fiez, J. A., and Ivry, R. B. (2005). Reduced phonological similarity effects in patients with damage to the cerebellum. *Brain Lang.* 95, 304–318. doi: 10.1016/j.bandl.2005.02.001

Karatekin, C., Lazareff, J. A., and Asarnow, R. F. (2000). Relevance of the cerebellar hemispheres for executive functions. *Pediatr. Neurol.* 22, 106–112. doi: 10.1016/s0887-8994(99)00128-9

Keele, S. W., and Ivry, R. (1990). Does the cerebellum provide a common computation for diverse tasks? A timing hypothesis. *Ann. N Y Acad. Sci.* 608, 179–207; discussion 207–211. doi: 10.1111/j.1749-6632.1990.tb48897.x

Keren-Happuch, E., Chen, S. H. A., Ho, M. H. R., and Desmond, J. E. (2014). A meta-analysis of cerebellar contributions to higher cognition from PET and fMRI studies. *Hum. Brain Mapp.* 35, 593–615. doi: 10.1002/hbm.22194

Kirschen, M. P., Chen, S. H., and Desmond, J. E. (2010). Modality specific cerebro-cerebellar activations in verbal working memory: an fMRI study. *Behav. Neurol.* 23, 51–63. doi: 10.3233/BEN-2010-0266

Kirschen, M. P., Davis-Ratner, M. S., Milner, M. W., Chen, S. H. A., Schraedley-Desmond, P., Fisher, P. G., et al. (2008). Verbal memory impairments in children after cerebellar tumor resection. *Behav. Neurol.* 20, 39–53. doi: 10.3233/BEN-2008-0216

Kozel, F. A., Nahas, Z., deBrux, C., Molloy, M., Lorberbaum, J. P., Bohning, D., et al. (2000). How coil-cortex distance relates to age, motor threshold and antidepressant response to repetitive transcranial magnetic stimulation. *J. Neuropsychiatry Clin. Neurosci.* 12, 376–384. doi: 10.1176/appi.neuropsych.12.3.376

Leggio, M. G., Chiricozzi, F. R., Clausi, S., Tedesco, A. M., and Molinari, M. (2011). The neuropsychological profile of cerebellar damage: the sequencing hypothesis. *Cortex* 47, 137–144. doi: 10.1016/j.cortex.2009.08.011

Leggio, M., and Molinari, M. (2015). Cerebellar sequencing: a trick for predicting the future. *Cerebellum* 14, 35–38. doi: 10.1007/s12311-014-0616-x

Leggio, M. G., Silveri, M. C., Petrosini, L., and Molinari, M. (2000). Phonological grouping is specifically affected in cerebellar patients: a verbal fluency study. *J. Neurol. Neurosurg. Psychiatry* 69, 102–106. doi: 10.1136/jnnp.69.1.102

Lesage, E., Hansen, P. C., and Miall, R. C. (2017). Right lateral cerebellum represents linguistic predictability. *J. Neurosci.* 37, 6231–6241. doi: 10.1523/jneurosci.3203-16.2017

Lesage, E., Morgan, B. E., Olson, A. C., Meyer, A. S., and Miall, R. C. (2012). Cerebellar rTMS disrupts predictive language processing. *Curr. Biol.* 22, R794–R795. doi: 10.1016/j.cub.2012.07.006

Lu, M., and Ueno, S. (2017). Comparison of the induced fields using different coil configurations during deep transcranial magnetic stimulation. *PLoS One* 12:e0178422. doi: 10.1371/journal.pone.0178422

Lurito, J. T., Kareken, D. A., Lowe, M. J., Chen, S. H., and Mathews, V. P. (2000). Comparison of rhyming and word generation with FMRI. *Hum. Brain Mapp.* 10, 99–106. doi: 10.1002/1097-0193(200007)10:3<99::aid-hbm10>3.0.co;2-q

Mariën, P., Ackermann, H., Adamaszek, M., Barwood, C. H., Beaton, A., Desmond, J., et al. (2014). Consensus paper: language and the cerebellum: an ongoing enigma. *Cerebellum* 13, 386–410. doi: 10.1007/s12311-013-0540-5

Mariën, P., Baillieux, H., De Smet, H. J., Engelborghs, S., Wilssens, I., Paquier, P., et al. (2009). Cognitive, linguistic and affective disturbances following a right superior cerebellar artery infarction: a case study. *Cortex* 45, 527–536. doi: 10.1016/j.cortex.2007.12.010

Marvel, C. L., and Desmond, J. E. (2010). The contributions of cerebro-cerebellar circuitry to executive verbal working memory. *Cortex* 46, 880–895. doi: 10.1016/j.cortex.2009.08.017

McConnell, K. A., Nahas, Z., Shastri, A., Lorberbaum, J. P., Kozel, F. A., Bohning, D. E., et al. (2001). The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. *Biol. Psychiatry* 49, 454–459. doi: 10.1016/s0006-3223(00)01039-8

Miall, R. C., Antony, J., Goldsmith-Sumner, A., Harding, S. R., McGovern, C., and Winter, J. L. (2016). Modulation of linguistic prediction by TDCS of the right lateral cerebellum. *Neuropsychologia* 86, 103–109. doi: 10.1016/j.neuropsychologia.2016.04.022

Miall, R. C., Christensen, L. O., Cain, O., and Stanley, J. (2007). Disruption of state estimation in the human lateral cerebellum. *PLoS Biol.* 5:e316. doi: 10.1371/journal.pbio.0050316

Middleton, F. A., and Strick, P. L. (1994). Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science* 266, 458–461. doi: 10.1126/science.7939688

Middleton, F. A., and Strick, P. L. (1997). Dentate output channels: motor and cognitive components. *Prog. Brain Res.* 114, 553–566. doi: 10.1016/s0079-6123(08)63386-5

Middleton, F. A., and Strick, P. L. (2001). Cerebellar projections to the prefrontal cortex of the primate. *J. Neurosci.* 21, 700–712. doi: 10.1523/jneurosci.21-02-00700.2001

Moretti, R., Bava, A., Torre, P., Antonello, R. M., and Cazzato, G. (2002). Reading errors in patients with cerebellar vermis lesions. *J. Neurol.* 249, 461–468. doi: 10.1007/s004150200040

Neau, J. P., Arroyo-Anllo, E., Bonnaud, V., Ingrand, P., and Gil, R. (2000). Neuropsychological disturbances in cerebellar infarcts. *Acta Neurol. Scand.* 102, 363–370. doi: 10.1034/j.1600-0404.2000.102006363.x

Paulesu, E., Frith, C. D., and Frackowiak, R. S. (1993). The neural correlates of the verbal component of working memory. *Nature* 362, 342–345. doi: 10.1038/362342a0

Peterburs, J., Bellebaum, C., Koch, B., Schwarz, M., and Daum, I. (2010). Working memory and verbal fluency deficits following cerebellar lesions: relation to interindividual differences in patient variables. *Cerebellum* 9, 375–383. doi: 10.1007/s12311-010-0171-z

Peterburs, J., Cheng, D. T., and Desmond, J. E. (2016). The association between eye movements and cerebellar activation in a verbal working memory task. *Cereb. Cortex* 26, 3802–3813. doi: 10.1093/cercor/bhv187

Petersen, S. E., Fox, P. T., Posner, M. I., and Mintun, M. (1989). Positron emission tomographic studies of the processing of single words. *J. Cogn. Neurosci.* 1, 153–170. doi: 10.1162/jocn.1989.1.2.153

Ramnani, N. (2006). The primate cortico-cerebellar system: anatomy and function. *Nat. Rev. Neurosci.* 7, 511–522. doi: 10.1038/nrn1953

Rao, S. M., Bobholz, J. A., Hammeke, T. A., Rosen, A. C., Woodley, S. J., Cunningham, J. M., et al. (1997). Functional MRI evidence for subcortical participation in conceptual reasoning skills. *Neuroreport* 8, 1987–1993. doi: 10.1097/00001756-199705260-00038

Rauschecker, A. M., Pringle, A., and Watkins, K. E. (2008). Changes in neural activity associated with learning to articulate novel auditory pseudowords by covert repetition. *Hum. Brain Mapp.* 29, 1231–1242. doi: 10.1002/hbm.20460

Ravizza, S. M., McCormick, C. A., Schlerf, J. E., Justus, T., Ivry, R. B., and Fiez, J. A. (2006). Cerebellar damage produces selective deficits in verbal working memory. *Brain* 129, 306–320. doi: 10.1093/brain/awh685

Rentiya, Z., Khan, N. S., Ergun, E., Ying, S. H., and Desmond, J. E. (2017). Distinct cerebellar regions related to motor and cognitive performance in SCA6 patients. *Neuropsychologia* 107, 25–30. doi: 10.1016/j.neuropsychologia.2017.10.036

Schmahmann, J. D. (2019). The cerebellum and cognition. *Neurosci. Lett.* 688, 62–75. doi: 10.1016/j.neulet.2018.07.005

Schmahmann, J. D., and Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain* 121, 561–579. doi: 10.1093/brain/121.4.561

Seger, C. A., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. (2000). Functional magnetic resonance imaging evidence for right-hemisphere involvement in processing unusual semantic relationships. *Neuropsychology* 14, 361–369. doi: 10.1037/0894-4105.14.3.361

Silveri, M. C., Di Betta, A. M., Filippini, V., Leggio, M. G., and Molinari, M. (1998). Verbal short-term store-rehearsal system and the cerebellum. Evidence from a patient with a right cerebellar lesion. *Brain* 121, 2175–2187. doi: 10.1093/brain/121.11.2175

Sternberg, S. (1966). High-speed scanning in human memory. *Science* 153, 652–654. doi: 10.1126/science.153.3736.652

Stokes, M. G., Chambers, C. D., Gould, I. C., English, T., McNaught, E., McDonald, O., et al. (2007). Distance-adjusted motor threshold for transcranial magnetic stimulation. *Clin. Neurophysiol.* 118, 1617–1625. doi: 10.1016/j.clinph.2007.04.004

Stoodley, C. J. (2012). The cerebellum and cognition: evidence from functional imaging studies. *Cerebellum* 11, 352–365. doi: 10.1007/s12311-011-0260-7

Stoodley, C. J., Desmond, J. E., and Schmahmann, J. D. (2012). "Functional topography of human cerebellum revealed by functional neuroimaging studies," in *Handbook of the Cerebellum and Cerebellar Disorders*, eds M. Manto, D. L. Gruol, J. D. Schmahmann, N. Koibuchi and F. Rossi (New York, NY: Springer), 735–764.

Stoodley, C. J., and Schmahmann, J. D. (2009). The cerebellum and language: evidence from patients with cerebellar degeneration. *Brain Lang.* 110, 149–153. doi: 10.1016/j.bandl.2009.07.006

Strick, P. L., Dum, R. P., and Fiez, J. A. (2009). Cerebellum and nonmotor function. *Annu. Rev. Neurosci.* 32, 413–434. doi: 10.1146/annurev.neuro.31.060407.125606

Tesche, C. D., and Karhu, J. J. (2000). Anticipatory cerebellar responses during somatosensory omission in man. *Hum. Brain Mapp.* 9, 119–142. doi: 10.1002/(sici)1097-0193(200003)9:3<119::aid-hbm2>3.3.co;2-i

Wolpert, D. M., and Miall, R. C. (1996). Forward models for physiological motor control. *Neural Netw.* 9, 1265–1279. doi: 10.1016/s0893-6080(96)00035-4

Wolpert, D. M., Miall, R. C., and Kawato, M. (1998). Internal models in the cerebellum. *Trends Cogn. Sci.* 2, 338–347. doi: 10.1016/S1364-6613(98)01221-2

Wu, T., Liu, J., Hallett, M., Zheng, Z., and Chan, P. (2013). Cerebellum and integration of neural networks in dual-task processing. *Neuroimage* 65, 466–475. doi: 10.1016/j.neuroimage.2012.10.004

Xiang, H., Lin, C., Ma, X., Zhang, Z., Bower, J. M., Weng, X., et al. (2003). Involvement of the cerebellum in semantic discrimination: an fMRI study. *Hum. Brain Mapp.* 18, 208–214. doi: 10.1002/hbm.10095

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 05 April 2019
doi: 10.3389/fnint.2019.00012

The Macaque Cerebellar Flocculus Outputs a Forward Model of Eye Movement

Gyutae Kim[1], *Jean Laurens*[2], *Tatyana A. Yakusheva*[1] *and Pablo M. Blazquez*[1]*

[1]Department of Otolaryngology, Washington University School of Medicine, St. Louis, MO, United States, [2]Department of Neuroscience, Baylor College of Medicine, Houston, TX, United States

The central nervous system (CNS) achieves fine motor control by generating predictions of the consequences of the motor command, often called forward models of the movement. These predictions are used centrally to detect not-self generated sensations, to modify ongoing movements, and to induce motor learning. However, finding a neuronal correlate of forward models has proven difficult. In the oculomotor system, we can identify neuronal correlates of forward models vs. neuronal correlates of motor commands by examining neuronal responses during smooth pursuit at eccentric eye positions. During pursuit, torsional eye movement information is not present in the motor command, but it is generated by the mechanic of the orbit. Importantly, the directionality and approximate magnitude of torsional eye movement follow the half angle rule. We use this rule to investigate the role of the cerebellar flocculus complex (FL, flocculus and ventral paraflocculus) in the generation of forward models of the eye. We found that mossy fibers (input elements to the FL) did not change their response to pursuit with eccentricity. Thus, they do not carry torsional eye movement information. However, vertical Purkinje cells (PCs; output elements of the FL) showed a preference for counter-clockwise (CCW) eye velocity [corresponding to extorsion (outward rotation) of the ipsilateral eye]. We hypothesize that FL computes an estimate of torsional eye movement since torsion is present in PCs but not in mossy fibers. Overall, our results add to those of other laboratories in supporting the existence in the CNS of a predictive signal constructed from motor command information.

Keywords: forward models, cerebellum, motor control, oculomotor, Purkinje cell, cerebellar interneurons, mossy fibers

OPEN ACCESS

Edited by:
Aasef G. Shaikh,
Case Western Reserve University, United States

Reviewed by:
Yong Gu,
Institute of Neuroscience, Shanghai Institutes for Biological Sciences (CAS), China
Osvaldo Enrique Agamennoni,
Universidad Nacional del Sur, Argentina

***Correspondence:**
Pablo M. Blazquez
pablo@wustl.edu

Received: *15 January 2019*
Accepted: *14 March 2019*
Published: *05 April 2019*

Citation:
Kim G, Laurens J, Yakusheva TA and Blazquez PM (2019) The Macaque Cerebellar Flocculus Outputs a Forward Model of Eye Movement. Front. Integr. Neurosci. 13:12. doi: 10.3389/fnint.2019.00012

INTRODUCTION

An important theoretical concept in motor control is that, for optimal motor performance, a control system must includes two internal models. One model converts the desired movement into forces (inverse model), while a second model works as a predictor that decodes the output of the inverse model (forces) into its consequences (forward or predictive model; **Figure 1**). These two internal models allow the control system to bypass the long delays associated with sensory feedback and adapt to variations in the environment (Wolpert et al., 1998). The forward model plays a pivotal role in maintaining accurate motor control because when its output is compared with the actual movement/sensory feedback, the result can be used to extract not-self generated sensation and to drive motor learning (Wolpert et al., 1998; Sawtell and Williams, 2008).

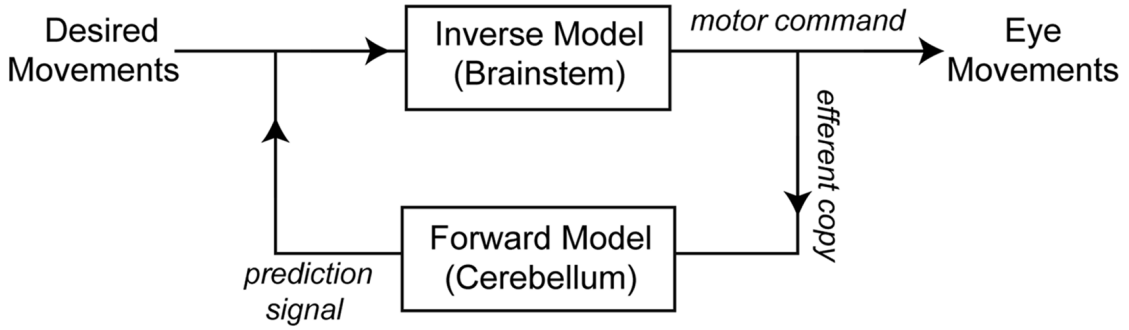

FIGURE 1 | Schematic of the conceptual framework used for eye movement control (as in Green et al., 2007; Ghasia et al., 2008). An inverse model transforms desired movements into appropriate motor commands to move the eyes. A copy of the motor command is sent to a forward model that predicts the consequences of the motor command. The output of the forward model is sent back to the system where it is compared with the desired movement. A candidate structure for implementing the forward model of the eye movement is the flocculus complex (FL), and a candidate structure for the inverse model of the eye is the brainstem.

Neuroscientists have tried to apply this motor control theory to biological systems but finding the neuronal correlate of these internal models has proven difficult (Wolpert et al., 1995; Shadmehr et al., 2010). The existence of inverse models in biological systems is widely accepted because the brain must, somehow, convert desired movements into actual motor commands. However, the existence of biological correlates of forward models is still controversial. Accumulating evidence suggest that the brain uses forward models for motor control and point to a major role of the cerebellum in the construction of these forward models (Shadmehr and Mussa-Ivaldi, 1994; Wolpert and Kawato, 1998; Pasalar et al., 2006; Sawtell and Williams, 2008; Shadmehr et al., 2010; Brooks and Cullen, 2013). For example, cerebellar patients have impairments in perception during active movements suggesting a role of the cerebellum in the construction of sensory predictions of the consequences of motor command (Bhanpuri et al., 2012). Moreover, Purkinje cells (PCs) in cerebellar cortex lobules IV–VI of the non-human primate carry information related to both movement kinematics and error feedback, but not to motor command (Popa et al., 2012).

Eye movements are an ideal motor system to study motor control because of their simplicity when compared to other motor systems like arm movements. Eye movements are controlled by the action of three pairs of muscles and consist of rotations of the eye around three axes (horizontal, vertical and torsional). Interestingly, torsional eye movements during pursuit, saccades and ocular following are implemented by the mechanics of the orbit, not the motor command (Kono et al., 2002; Ghasia and Angelaki, 2005; Klier et al., 2011). Hence, torsion is present in the kinematics (actual movement) of the eye but not in the muscle dynamics (forces). This fact can be used as a powerful tool to search for neuronal correlates of forward and inverse models of the eye movement.

Ghasia et al. (2008) recorded the response of brainstem neurons during pursuit and found that putative flocculus-complex (FL) target neurons [eye head neurons (EH)], but not burst tonic neurons, carry torsional eye movement information during pursuit. They proposed that burst tonic neurons carry the output of the inverse model and FL target neurons carry the output of the forward model of the eye movement. Here, we test the hypothesis that the torsional eye movement signal detectable at the level of EH neurons originates in the FL. Furthermore, we test the hypothesis that this torsional signal is ultimately constructed in the FL. To test these hypotheses, we recorded the activity of PCs (output neurons) and mossy fibers (input elements) during similar pursuit tasks to those used by Ghasia et al. (2008). We present evidence suggesting that PCs carry torsional eye velocity information, but mossy fibers do not. These findings suggest that the torsional eye movement information found in FL target neurons in the vestibular nuclei arrives from the FL. Moreover, because torsional information is found at the output but not the input of the FL, we suggest that the FL plays an important role in the construction of forward models of the eye movement.

MATERIALS AND METHODS

Animal Preparation and Experimental Setup

Two adult male rhesus macaques underwent two surgical operations to implant a scleral search coil, a titanium head-post, and a recording chamber. Recording chambers were implanted stereotaxically to record in the left FL, using zero tilt and pitch angles and with their centers aimed to 13 mm lateral and 1 mm posterior (Paxinos et al., 2000). Following a 3–4 weeks recovery period, we began training animals in oculomotor tasks using a standard water restriction protocol. All procedures conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee.

Animals were comfortably seated in a primate chair and on top of a rotating table (Kollmorgen, Radford, VA, USA) during our recording sessions. Animals were head fixed to the chair by their head posts to allow stable neuronal recordings. Our visual stimulus consisted of a red laser back-projected on a translucent screen located 50 cm in front of the animal. Vertical

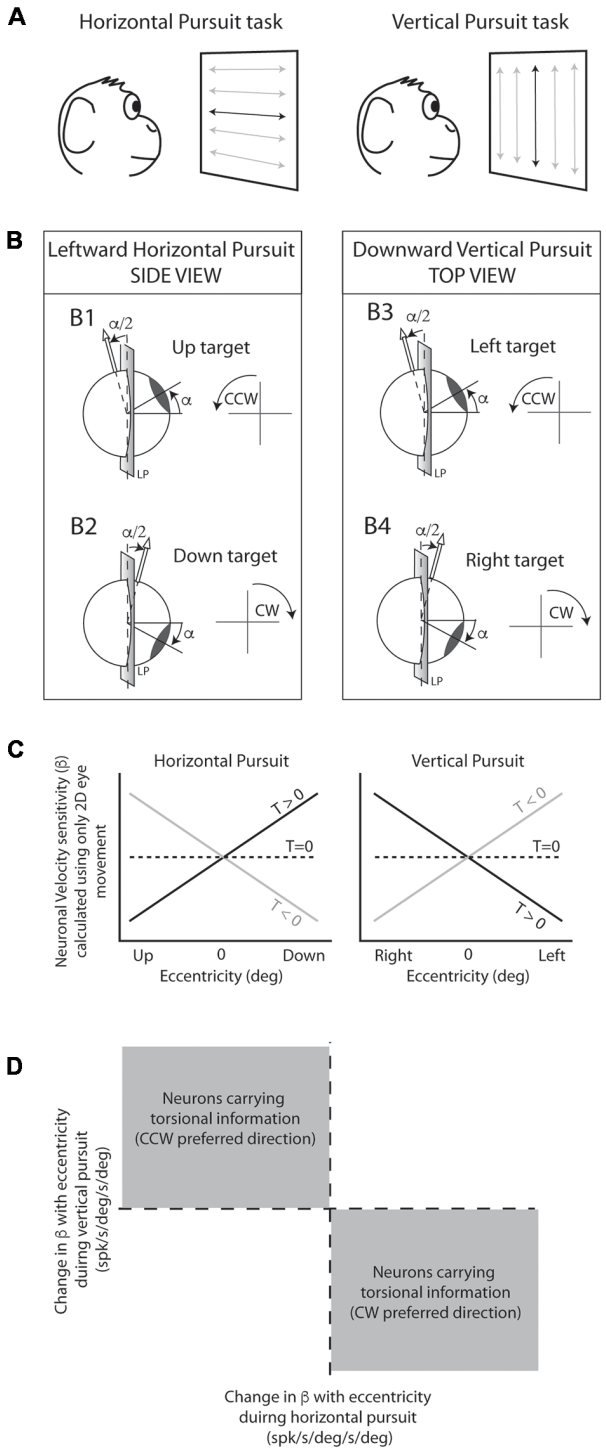

FIGURE 2 | Experimental design and rationale. **(A)** Animals were seated in front of a projecting screen where a back-projected laser moved along specific paths. The main behavioral task consisted of sinusoidal horizontal (left) and vertical (right) pursuit, indicated by horizontal and vertical lines with arrow endings, respectively. Horizontal and vertical centered pursuit (indicated by the dark lines in the center of the projecting screen) consisted of pursuit eye movements around the center fixation point. Horizontal and vertical eccentric pursuit (indicated by the gray lines) consisted of horizontal and

(*Continued*)

FIGURE 2 | Continued

vertical pursuit eye movements that did not cross the center fixation point. **(B)** Schematic cartoon representing the torsional component of the eye movement during pursuit as predicted by the half angle rule. Leftward pursuit eye movements at up-gaze position generate counter-clockwise (CCW) torsional eye movements (B1) while leftward eye movements at down-gaze position generate clockwise (CW) eye movements (B2). Similarly, downward pursuit at left-gaze position generates CCW eye movements (B3) and downward pursuit at right-gaze position generates CW eye movements (B4). **(C)** Predicted changes in neuronal eye velocity sensitivity calculated using only 2D eye movements during the pursuit tasks shown in **(A)**. Neurons carrying 2D eye movement information would not change their eye velocity sensitivity with eccentricity (dashed line). Neurons carrying 3D eye movement information would change their eye velocity sensitivity with eccentricity as shown by the black and gray lines. Importantly, the change in eye velocity sensitivity with eccentricity (slope of the lines) provides information on the preferred torsional direction of the neuron (CW [$T > 0$] or CCW [$T < 0$]). **(D)** If we plot the slopes obtained in **(C)** (horizontal pursuit [left] vs. vertical pursuit [right]), neurons with CCW preferred directions would fall in the top left quadrant, while neurons with CW would fall in the bottom right quadrant.

and horizontal laser positions were controlled using two mirror galvanometers that provided near linear displacement of the laser within the range used in this experiment: maximum deviation from linearity in +/− 20° range was 11.34% and 11.49% for horizontal and vertical directions, respectively. Horizontal and vertical eye positions were continuously measured using a three earth-fixed field coil system (CNC Engineering, Enfield, CT, USA). A reference coil was placed near the animals' temporal bone and attached to the chair. The signal from the reference coil was subtracted from the eye coil signal to obtain the eye in head position. Neuronal data was filtered (bandpass 0.3–8 kHz) and amplified using an AC differential amplifier and headstage system (Model MDA-41 from BAK electronics, Umatilla, FL, USA). Eye, laser, and rotating table positions were recorded at a sampling rate of 0.5 KHz, and neuronal data at a sampling rate of 40 KHz using a power 1401 and spike2 software (Cambridge Electronic Design, Cambridge, UK).

Behavioral Protocol

All behavioral tasks were controlled by custom made software written in spike2 language. The eye coil was calibrated daily using 10–15° horizontal and vertical saccades. The main task used in this study consisted of sinusoidal smooth pursuit eye movements at different eccentricities similar to that used by Ghasia and Angelaki (2005). The laser was moved sinusoidally at 0.4 Hz and ±10° either in the horizontal or the vertical plane. This generated a laser peak velocity of about 25 deg/s. Horizontal pursuit tasks consisted of horizontal eye movements around the horizontal straight-ahead position at different vertical eccentricities (from +20 to −20°). Vertical pursuit tasks consisted of vertical eye movements around the vertical straight-ahead position at different horizontal eccentricities (from +20 to −20°; **Figure 2A**). We used the terms "centered horizontal pursuit" and "centered vertical pursuit" to refer to horizontal and vertical pursuit that pass through the center fixation point (straight-ahead position; black traces over the projecting screen in **Figure 2A**), and "eccentric horizontal" and "eccentric vertical" pursuit to refer to pursuit eye movements that do not

pass through the straight-ahead position (gray traces over the projecting screen in **Figure 2A**). Animals were rewarded every 1–1.5 s with a small drop of water if they kept their eyes within a 3° distance from the moving target.

Neuronal Recording

We recorded single units from FL, mostly ventral paraflocculus, using epoxy-coated tungsten microelectrodes (FHC Inc., Bowdoin, ME, USA, 8–10 MΩ impedance). The FL was identified by its characteristic eye-related activity. We identified the three layers of the cerebellar cortex using a standard procedure. The molecular layer was identified by the presence of complex spikes and the absence of simple spikes. The PC layer was identified by the presence of complex and simple spikes. When complex and simple spikes were recorded simultaneously, we further verified the identity of the recorded neuron (PC) and layer (PC layer) by detecting the complex spike-induced pause in simple spikes (>10 ms; Blazquez et al., 2003). The granular layer was identified by the absence of complex spikes and its characteristic saccade-related hashing activity. We commonly recorded two types of spikes in the granular layer: wide and narrow spikes. Wide spikes had similar width than simple spikes (>0.3 ms width) and typically showed a low firing rate. Narrow spikes (<0.25 ms width) typically showed clear saccade and eye position-related activity that matched the background hashing activity. The first type of spike is thought to be generated by granular layer interneurons, and the second by mossy fibers (Miles et al., 1980; Heine et al., 2010).

Data Analysis

We followed the right-hand rule to define the positive and negative directions for horizontal, vertical and torsional eye movements (Ghasia and Angelaki, 2005; Klier et al., 2006): leftward, downward, and clockwise (CW) eye movements were considered positive, and rightward, upward, and counter-clockwise (CCW) eye movements were considered negative. The directionality of the movement (left/right; down/up; CW/CCW) was defined from the experimental subject point of view.

Spike sorting was performed off-line using analysis tools included in the Spike2 software (Cambridge Electronic Design, Cambridge, UK). Specifically, PC complex and simple spikes were sorted using a waveform template-match algorithm or a voltage threshold. Mossy fibers were first high-pass filtered (>400 Hz) and then sorted using a waveform template-match algorithm or a voltage threshold. Following this, data were exported to Matlab (MathWorks, Natick, MA, USA) for further analysis. In this study, we focused exclusively on the behavioral and neuronal responses to sinusoidal pursuit (0.4 Hz). The times corresponding to saccadic eye movements were detected using a 50 deg/s velocity threshold and removed from the behavioral and neuronal data. Following this, we computed the average behavioral (eye position and velocity) and neuronal response to several cycles of sinusoidal stimulation (at least five cycles). This average data was used for all subsequent analysis.

We fit the average response using a sinusoidal fitting function (0.4 Hz) in order to classify units as vertical or horizontal. Units were classified as horizontal if they showed a larger amplitude of modulation during centered horizontal pursuit than during centered vertical pursuit, and they were classified as vertical in the opposite case. Two horizontal mossy fibers, four horizontal PCs and two vertical PCs could not be recorded during centered pursuit. For these units, we characterized the neuronal directional preference and phase using the eccentric vertical and horizontal pursuit closest to the straight-ahead position. Neuronal response phase was defined with respect to peak eye velocity. We normalized the phases to the range of −90 to 90°, such that units that carry only eye position information would modulate their responses with a phase lag of 90 or −90°, while units that carry only eye velocity would modulate with a response phase of 0°.

Once a neuron was classified as horizontal or vertical unit, we extracted the neuronal sensitivities to eye position and eye velocity from the average neuronal responses using a standard linear fit procedure (Eq. 1, Model_{PV}; Lisberger et al., 1994; Ghasia et al., 2008). Note that sinusoidal pursuit, the paradigm used in this study, is designed to extract the velocity information encoded in PC responses, which is the relevant signal for the question posed in this manuscript. Sinusoidal motion, however, cannot extract acceleration (as well as deceleration) and position signals independently because of cross-correlation effects (acceleration and position signals are 180° out of phase).

$$FR = \beta * \dot{E} + \gamma * E + \delta + \varepsilon \quad (1)$$

where $\dot{E}$ and E correspond to the average eye velocity and position, respectively, β and γ to neuronal sensitivities to eye velocity and eye position, respectively, δ to the baseline (DC) firing rate, and ε the estimation error. These sensitivity values were calculated using horizontal eye movement information during horizontal pursuit and vertical eye movement information during vertical pursuit. Data where there was a change in eye movement in the orthogonal direction to the pursuit task direction (i.e., vertical eye movements during horizontal pursuit, or viceversa) of more than 1 deg/s within +20 and −20° eccentricity were excluded from further analysis. We selected this value arbitrarily, but such that it is much smaller (4–5 times) than the torsional eye velocity generated for the same change in viewing eccentricity (i.e., estimated torsional amplitude of +/−4.4 deg/s amplitude for a peak velocity of 25 deg/s, and +/− 20° eccentricity, see below half angle rule and Ghasia and Angelaki, 2005).

For each neuron, we estimated whether the eye velocity component contributed significantly to the neuronal response using a sequential *F*-test. First, we conducted a multiple linear regression using the $Model_{PV}$ (eq. 1) and computed the sum of square of the regression, SSR_{PV}, and the sum of squared errors, SSE_{PV}, as follows:

$$SSR_{PV} = \sum_{i=1}^{n} \left(Model_{PV}(i) - mean\left(Model_{PV}\right)\right)^2$$

$$SSE_{PV} = \sum_{i=1}^{n} \left(FR(i) - Model_{PV}(i)\right)^2$$

where FR, $Model_{PV}$ and n are the neuronal responses, the reconstructed responses based on the regression, and the number of data points. Second, we conducted a multiple linear regression which contains only position component (i.e., we forced $\beta = 0$) and calculated the sum of square of the regression, SSR_P:

$$SSR_P = \sum_{i=1}^{n} (Model_P(i) - mean(Model_P))^2$$

where $Model_P$ is the regression model with only eye position component, and n is its total number. Lastly, a sequential test was performed by computing the following F-statistics:

$$F = \frac{(SSR_{PV} - SSR_P)/m}{SSE_{PV}/(n-(k+1))}$$

where k and m are the number of regression coefficients for $Model_{PV}$ and $Model_P$ (2 and 1, respectively). This value was compared with a Fisher distribution with m and $n - (k+1)$ degrees of freedom.

Experimental Design and Rationale

Our experimental rationale is identical to that used by Ghasia and Angelaki (2005); Ghasia et al. (2008) and is based on two findings. First, horizontal pursuit above and below primary position, and vertical pursuit to the right and left of primary position generate torsional eye movements. The direction of the torsional eye velocity component can be predicted based on the eccentricity of the eye and the pursuit direction. Second, the torsional component of eye movements during pursuit is not represented in the motor command but implemented by the mechanics of the orbit (Demer, 2006; Klier et al., 2011). Thus, neurons that carry torsional eye velocity signal alone or in combination with horizontal and vertical eye velocity would modify their response depending on pursuit direction and eccentricity.

The rationale is explained graphically in **Figure 2**: the Listing law makes clear predictions about the magnitude and direction of torsional eye movements during pursuit. This is mathematically expressed by the half angle rule:

$$\dot{E}t = \dot{E} * tan(\alpha/2)$$

where $\dot{E}t$ is the torsional eye velocity, $\dot{E}$ is the eye velocity in 2D (horizontal and vertical) and α the eccentricity. During leftward pursuit, while the eyes are holding an upward gaze position the eyes move CCW (**Figure 2B1**), but the same leftward eye movement generates CW eye movements if the eyes are holding a gaze down eye position (**Figure 2B2**). Similarly, the half angle rule predicts CCW eye movements during downward pursuit while holding a leftward eye position, and CW eye movements during downward pursuit while holding a rightward eye position (**Figures 2B3,4**).

Next, let's consider that the overall eye velocity sensitivity of a neuron can be represented by the following equation:

$$f(\dot{E}) = \beta v * (\dot{E}v) + \beta h * (\dot{E}h) + \beta t * (\dot{E}t)$$

where βv, βh, and βt represent the neuronal sensitivities to vertical, horizontal and torsional eye velocity (spk/s/deg/s), respectively. $\dot{E}v$, $\dot{E}h$ and $\dot{E}t$ the vertical, horizontal, and torsional eye velocities (deg/s), respectively. If we calculate the neuronal eye velocity sensitivity ignoring the torsional component of the equation $[\beta t^*(\dot{E}t)]$, a neuron with no torsional information would have the same $f(\dot{E})$ value during our pursuit tasks regardless of eccentricity (dotted lines in **Figure 2C**). However, a neuron with torsional eye velocity information (e.g., CW preferred direction [$\beta t > 0$]) would change $f(\dot{E})$ during horizontal and vertical pursuit at different eccentricities (e.g., black lines in **Figure 2C** left and right panels).

Three important points are worth mentioning.

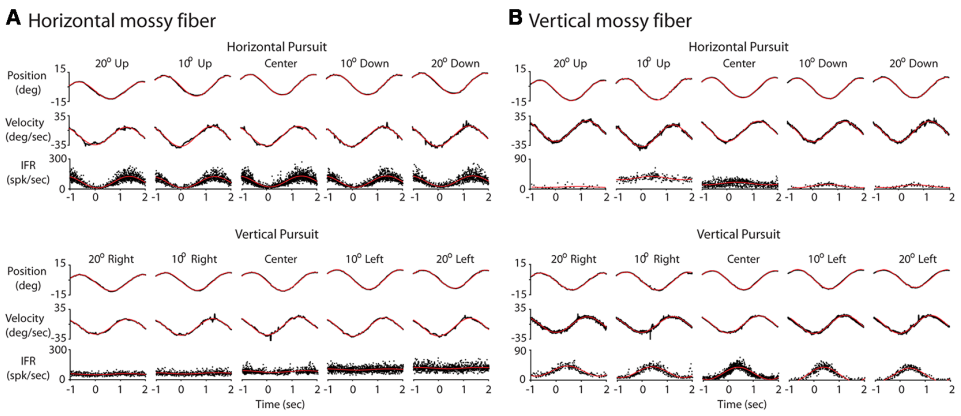

FIGURE 3 | Response of two example mossy fibers during eccentric pursuit. **(A)** Response of a representative horizontal mossy fiber over several cycles of sinusoidal pursuit. The top three rows represent the average eye position (top, deg), average eye velocity (middle, deg/s) and mossy fiber response (bottom, spk/s) during horizontal pursuit at different vertical eccentricities. Neuronal response is shown by folding data (instantaneous firing rate) from multiple cycles into a single cycle. Each column represents one vertical eccentricity, in deg, from straight ahead-gaze (20 up, 10 up, 0, 10 down and 20 down). The bottom three rows show the same cell recorded during vertical pursuit at different horizontal eccentricities from straight ahead-gaze (20 right, 10 right, 0, 10 left and 20 left). The eye position and velocity data showed corresponds to either horizontal (top panels) or vertical (bottom panels) eye data. **(B)** The same as in **(A)** but for a representative example of a vertical mossy fiber. Red lines show the profile of the best fitting sinusoidal functions.

1. It could be difficult to determine whether a single neuron codes torsion because neuronal responses can be noisy, and the actual torsional eye movements during pursuit are small (Ghasia and Angelaki, 2005). However, at the population level, with a sufficiently large "*n*", the presence of torsional information in the neuronal responses would be evident by having a significantly larger number of neurons falling in the gray areas shown in **Figure 2D**. We evaluate this statistically by performing a binomial test, which provides the likelihood of obtaining a particular number of successful draws (torsional coding neurons) given a total number of draws (total number of neurons) and assuming equal probability of getting successful and unsuccessful results in each draw (**Figures 6**, **10**).
2. The sensitivity of our measurements is ultimately limited by the sample size (number of neurons) and the noise in the signal. We used computer simulations to determine the minimum torsional eye velocity sensitivity that can be detected using our analytical methods given our sample size and the noise in the signal (see **Supplementary Figures S1**, **S2**). The noise of the signal was calculated as the variation in firing rate within every single neuron for all tested eccentricities (−20, −10, 0, 10 and 20°); the noise was calculated separately for mossy fibers and PCs. Using the standard deviation of the noise, we created a normal distribution from which we randomly selected values representing gain change due to the noise of simulated neurons. The overall change in gain (eye velocity sensitivity) with eccentricity of a simulated neuron is equal to the gain change due to noise, plus the gain change due to the torsional eye velocity component. This idea can be represented mathematically as:

$$^{\wedge}Gain \;=\; n + \beta t * \left(\dot{E}t\right)$$

where ^Gain represents the gain change, n the gain change due to noise, βt the neuronal sensitivity to torsional eye velocity, and $\dot{E}t$ the torsional eye velocity. Torsional eye velocity is calculated directly from the half angle rule stated previously. A slope representing gain changes with eccentricity is calculated for horizontal and vertical pursuit (see **Supplementary Figures S1A**, **S2A**; same concept as in **Figures 5**, **9**) and a binomial cumulative distribution function is used to look for whether the simulated population significantly represent torsion (located in second and fourth quadrant, **Supplementary Figures S1B**, **S2B**). We generate 100 iterations (simulated populations) with equal signal noise, sample size, and torsional eye velocity sensitivity, and obtain the percentage of iterations that significantly represent torsion (**Supplementary Figures S1C**, **S2C**). This process is repeated for different values of neuronal sensitivity to torsion generating a curve that represents, for a particular sample size and noise, how likely would it for our analytical methods to detect significant torsional signals (**Supplementary Figures S1D**, **S2D**). In the case of our mossy fiber population (n = 10), we could detect significantly torsional eye velocity sensitivities of 0.046 spk/s/deg/s in 95% of iterations. In the case of our horizontal and vertical PC populations (n = >18), we could detect significantly torsional eye velocity sensitivities of 0.035 spk/s/deg/s in 95% of iterations.
3. Although we do not record torsional eye movements, nor we calculate the true primary eye position (this would require knowledge of the actual torsion), because of the rules of ocular motility, we can be confident about how the torsional signal changes with eccentricity. That is, for horizontal pursuit, the more upward is the eccentricity, the more CCW is the torsion for leftward eye movements (viceversa for rightward eye movements). Similarly, for vertical pursuit, the more leftward is the eccentricity, the more CCW is the torsion for downward eye movements (viceversa for upward eye

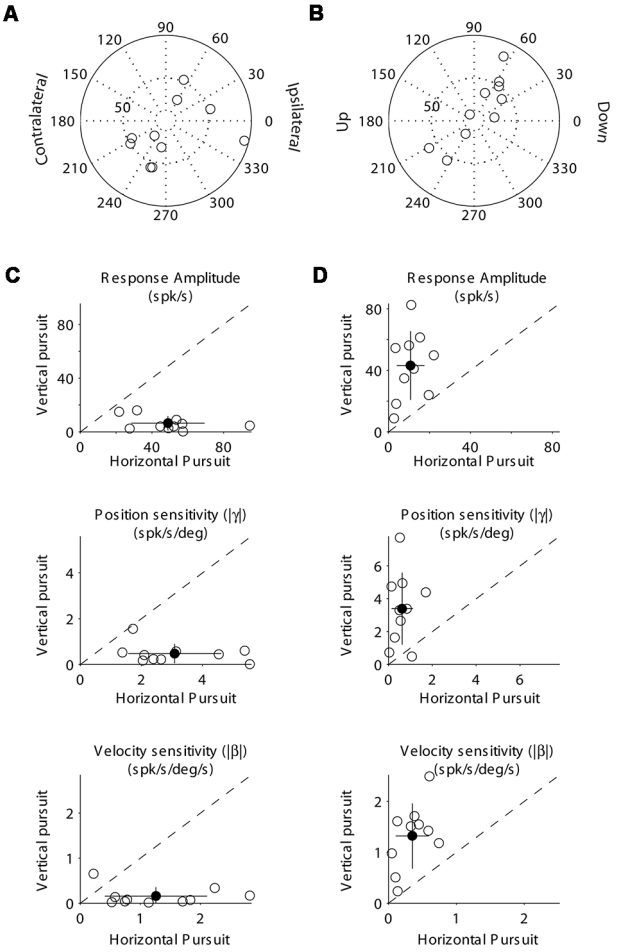

FIGURE 4 | Population data showing the response modulation and neuronal sensitivity to eye movements of horizontal **(A,C)** and vertical **(B,D)** mossy fibers. **(A)** Polar plot showing the gain and phase of individual horizontal mossy fiber with respect to eye velocity during sinusoidal horizontal pursuit. Panel **(B)** same as **(A)** but for vertical mossy fibers during vertical sinusoidal pursuit. Panel **(C)** top, amplitude of neuronal modulation during horizontal vs. vertical sinusoidal pursuit. Middle, neuronal eye position sensitivity (absolute values) calculated during horizontal vs. vertical sinusoidal pursuit. Bottom, neuronal eye velocity sensitivity (absolute values) calculated during horizontal vs. vertical sinusoidal pursuit. Panel **(D)** same as **(C)** but for vertical mossy fibers. Filled symbols in **(C)** and **(D)** show the average values and the lines segments on top of them plus/minus one standard deviation from the mean.

movements; **Figure 2**). Therefore, we can reliably tell the directionality of the changes in torsional eye velocity with pursuit direction and eccentricity. This information is a direct consequence of the Listing law and is sufficient to test our hypothesis.

RESULTS

We recorded the neuronal responses of 60 eye movement-related units (mossy fibers and PCs) in the FL of two macaque monkeys during horizontal and vertical smooth pursuit eye movements. Twenty units were classified as mossy fibers and 40 as PCs. Mossy fibers were identified based on their recording location (granular cell layer) and their characteristically narrow spike width (median of 0.25 ms for mossy fibers vs. 0.43 ms for PCs, respectively; $p < 0.01$, two-tailed t-test; Heine et al., 2010).

General Mossy Fiber Responses During Pursuit

We recorded 10 horizontal and 10 vertical mossy fibers during the horizontal and vertical sinusoidal pursuit at different eccentricities. The mossy fiber shown in **Figure 3A** was classified as horizontal mossy fiber because it showed stronger modulation during horizontal centered sinusoidal pursuit (53.8 spk/s) than during vertical centered sinusoidal pursuit (9 spk/s). Its response phase during the horizontal centered sinusoidal pursuit was 15° (leftward preferred direction), indicating that this neuron carried eye velocity and eye position information. Indeed, the eye position and eye velocity sensitivity of this neuron during horizontal centered sinusoidal pursuit were 1.4 spk/s/deg and 2.2 spk/s/deg/s, respectively. The example mossy fiber shown in **Figure 3B** had an amplitude of modulation of 3.8 spk/s and 18.3 spk/s during the horizontal and vertical centered sinusoidal pursuit, respectively. Hence, it was classified as a vertical mossy fiber. Its modulation phase during the vertical centered sinusoidal pursuit was 57° (upward mossy fiber). Its eye position sensitivity (1.6 spk/s/deg/s) was more than three times larger than its eye velocity sensitivity (0.5 spk/s/deg/s). However, the eye velocity component played a significant role in shaping the neuronal response of this example mossy fiber ($p < 0.01$, partial F test).

At the population level, we found that horizontal mossy fibers could have either ipsilateral ($n = 4$) or contralateral ($n = 6$) directional preference with responses lagging their eye velocity (normalized values with respect to the preferred direction [−90 to 90°] of median 57.3°; mean 46.7°; STD 30.7°; **Figure 4A**). Similarly, vertical mossy fibers could have upward ($n = 4$) or downward ($n = 6$) directional preferences with responses lagging eye velocity (normalized values with respect to the preferred direction of median 55°; mean 38.2°; STD 37.2°; **Figure 4B**). Importantly, mossy fibers with a larger amplitude of modulation along a particular axis (e.g., horizontal) also have larger eye position and eye velocity sensitivity for movements along the same axes (**Figures 4C,D**). This further validates the method

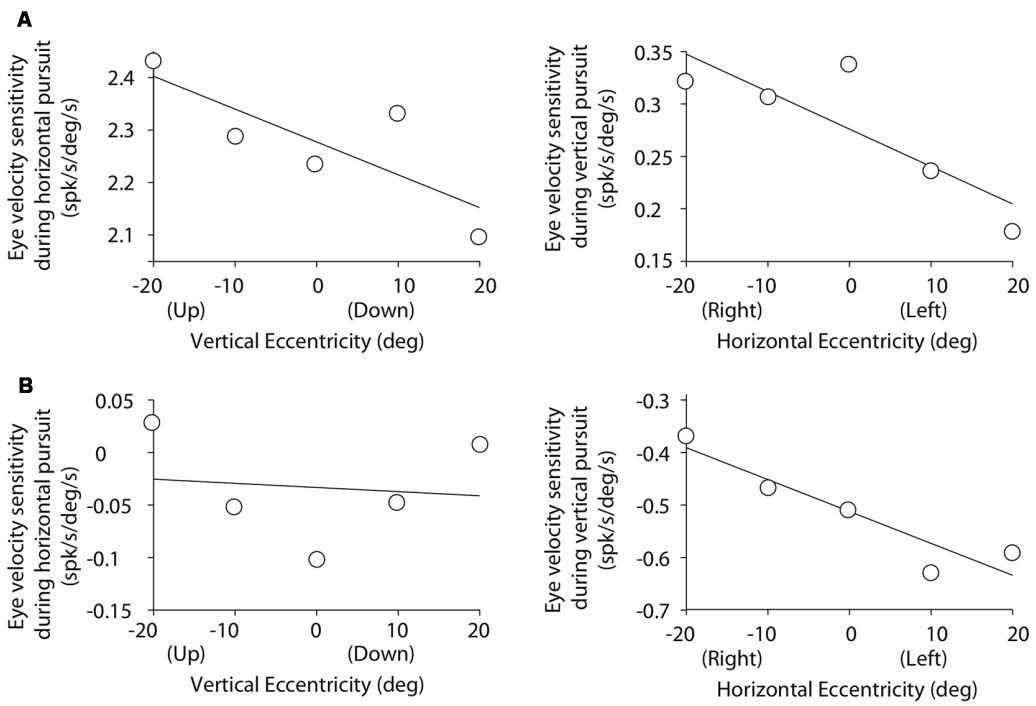

FIGURE 5 | Cartesian plots showing the changes in mossy fiber eye velocity sensitivity with viewing eccentricity for the two example mossy fibers shown in **Figure 3**. **(A)** Data obtained from the example horizontal mossy fiber. Left plot shows the changes in eye velocity sensitivity during horizontal pursuit as we modified vertical viewing eccentricity (−20, −10, 0, 10, and 20°). Right plot shows changes in eye velocity sensitivity during vertical pursuit as we modified horizontal viewing eccentricity (−20, −10, 0, 10, and 20°). Panel **(B)** same for the example vertical mossy fiber.

used to classify mossy fibers as horizontal and vertical units. The average sensitivity to eye position was 3.1 (STD 1.5) and 3.4 (STD 2.2) spk/s/deg for horizontal and vertical mossy fibers, respectively, which was more than twice the average sensitivity to horizontal and vertical eye velocity (1.25 [STD 0.9] and 1.3 [STD 0.6] spk/s/deg/s, respectively). This result agrees with previous work showing that mossy fibers carry both eye position and eye velocity information, but that their response is generally dominated by their eye position component (Miles et al., 1980). Nonetheless, the eye velocity component contributed significantly to the neuronal response of all recorded mossy fibers ($p < 0.01$, partial F-test).

Mossy Fiber Responses During Pursuit at Different Viewing Eccentricities

Figure 5 illustrates the changes in eye velocity sensitivity with eccentricity for the example mossy fibers shown in **Figure 3**. The example horizontal mossy fiber (**Figure 3A**) had larger eye velocity sensitivities during the horizontal pursuit at upward eccentricities than at downward eccentricities (left panel of **Figure 5A**), and during the vertical pursuit at rightward eccentricities than at leftward eccentricities (right panel of **Figure 5**). Similar slope directions were found for the example vertical mossy fiber (**Figure 5B**). Following the rationale explained in our experimental methods (**Figure 2**), our example mossy fibers would not carry torsional eye movement information.

The changes in eye velocity sensitivity calculated for a single mossy fiber could be the result of the inherent noise in the neuronal response. To evaluate this possibility, we looked at the population data (**Figure 6**). Only about one-third of our mossy fiber units (35%, 7/20) showed changes in eye velocity sensitivity with viewing eccentricity that agree with the presence of a torsional component in their pursuit response. This number was not significantly different from chance ($p = 0.13$, binomial cumulative distribution function). Moreover, if we analyze separately horizontal (**Figure 6A**) and vertical mossy fibers (**Figure 6B**), we found that for both cases the numbers of torsional coding and non-torsional coding units were not significantly different from chance ($p = 0.17$ for horizontal mossy fibers and $p = 0.37$ for vertical mossy fibers, binomial cumulative distribution function). Based on our mossy fiber sample size ($n = 10$) and inherent noise of the neuronal response, our analytical method could detect torsional eye velocity sensitivities as small as 0.046 deg/s (see "Materials and Methods" section), which is more than one order of magnitude smaller than the eye velocity sensitivity of mossy fibers to horizontal and vertical eye velocity. Thus, our results suggest that eye movement-related mossy fibers in the FL do not carry significant torsional eye velocity information during pursuit.

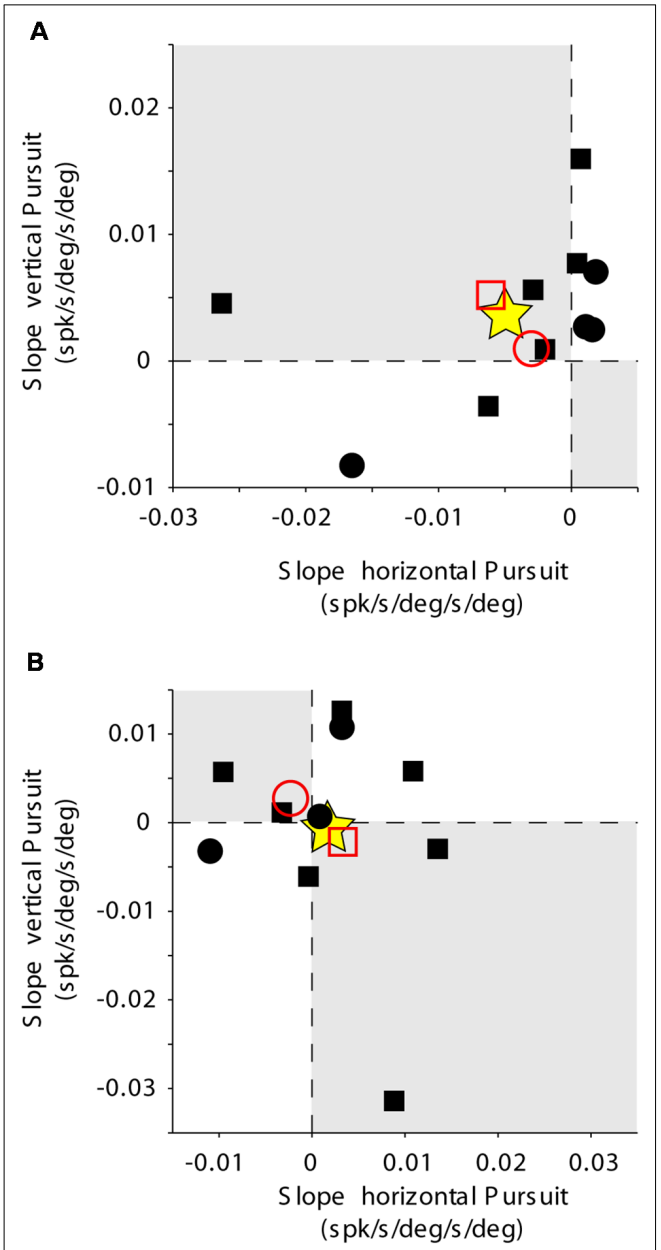

FIGURE 6 | Mossy fiber population data. Rate of change of eye velocity sensitivity with eccentricity during horizontal pursuit (abscissa) vs. vertical pursuit (ordinate). The layout is identical to that shown for **Figure 2D**. **(A)** Data obtained for the population of horizontal mossy fibers. **(B)** Data obtained for the population of vertical mossy fibers. Each data point corresponds to a single mossy fiber. Empty red symbols represent the average value for each animal (animal 1 = circle, animal 2 = square) and stars the total average data.

General Purkinje Cell Responses During Pursuit

We recorded 18 horizontal and 22 vertical PCs during horizontal and vertical sinusoidal pursuit at different eccentricities. **Figure 7** shows the response of one representative horizontal (A) and one representative vertical (B) PC. Both example PCs showed responses dominated by eye velocity information, with amplitudes of modulation of 40.4 spk/s (A) and 66 spk/s (B), and phases of 28.9° (A) and −23.9° (B). Their eye position and eye velocity sensitivities were 1.7 spk/deg and 1.5 spk/deg/s, respectively, for the example horizontal PC (A), and −2.5 spk/s/deg and 2.4 spk/s/deg/s, respectively, for the example vertical PC (B).

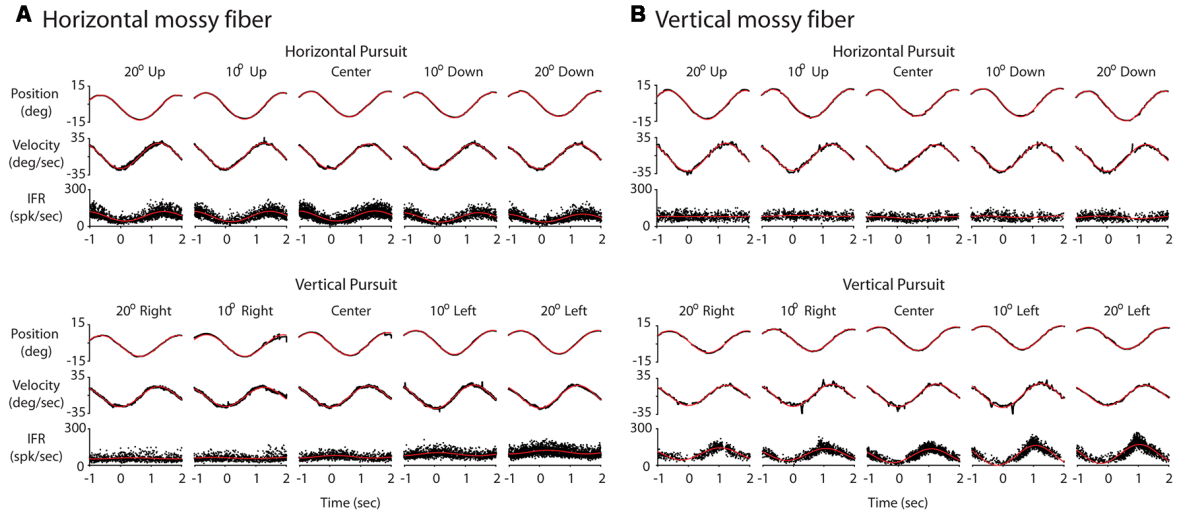

FIGURE 7 | Response of two example Purkinje cells (PCs) during eccentric pursuit. The layout of the figure is identical to that of **Figure 3**. **(A)** Response of a representative horizontal PC averaged over several cycles of sinusoidal pursuit. **(B)** Response of a representative vertical PC averaged over several cycles of sinusoidal pursuit.

At the population level, both horizontal and vertical PCs showed responses dominated by their eye velocity component as indicated by their response phases (median 18.1°, mean 9.6, STD 40° for horizontal PCs; and median −13.7°, mean −12, STD 10.9° for vertical PCs [normalized in −90 to 90°]; **Figures 8A,B**). Most PCs have ipsilateral or downward preferred direction (17 ipsilateral, 0 contralateral, 19 down and 3 up). Alike mossy fibers, the classification of PCs as horizontal or vertical was practically independent of the parameter used [amplitude of modulation (the parameter we used for classification), eye position sensitivity, or the eye velocity sensitivity]. Thus, horizontal PCs tend to have larger eye position and eye velocity sensitivity to horizontal eye movements than to vertical eye movements, while vertical PCs tend to have larger eye position and eye velocity sensitivity to vertical eye movements than to horizontal eye movements (**Figures 8C,D**).

The large influence of eye velocity information and preference for ipsi and downward directions in PCs contrasts with the large influence of eye position information and balance distribution of preferred directions in mossy fibers. This supports the hypothesis that the efferent copy information arriving at the FL undergoes spatial and temporal signal transformations within the cerebellar cortex (Miles and Braitman, 1980; Miles et al., 1980; Blazquez and Yakusheva, 2015).

Purkinje Cell Responses During Pursuit at Different Viewing Eccentricities

The eye velocity sensitivity of horizontal and vertical PCs was differentially affected by viewing eccentricity. The example horizontal PC presented in **Figure 7A** showed, on average, lower values of eye velocity sensitivity during horizontal pursuit at downward eccentricities than during horizontal pursuit at upward eccentricities (slope: −0.0043; **Figure 9A**, left). Similarly, the eye velocity sensitivity is lower during vertical pursuit at leftward eccentricities than during vertical pursuit at rightward eccentricities (slope: −0.012; **Figure 9A**, right). At the population level, the rate of changes in eye velocity sensitivity with gaze eccentricity for horizontal PCs were in disagreement with the torsional coding hypothesis; eight neurons located in torsional coding areas and 10 neurons in not-torsional coding areas, which is not significantly different from chance (p = 0.4, binomial test; **Figure 10A**).

The example vertical PC shown in **Figure 7B** showed, on average, lower values of eye velocity sensitivity during horizontal pursuit at downward eccentricities (slope: −0.006), and during vertical pursuit at rightward eccentricities (slope: 0.04; **Figure 9B**). These slopes indicate that this PC could carry torsional eye velocity information (**Figure 2**). This finding was consistent at the population level. Vertical PCs were found in greater numbers in the torsional coding areas than in the non-torsional coding areas (81% [18/22] in torsional coding areas, which is significantly different from chance $p < 0.0004$, binomial cumulative distribution function). Moreover, most putative torsional cells had CCW preferred direction (15/18, **Figure 10B**).

Two additional findings support the presence of torsional coding information in the response of vertical PCs during pursuit. First, the average change in eye velocity sensitivity with eccentricity is similar in both animals (see empty red symbols in **Figure 10B**). Second, the average change in eye velocity sensitivity during horizontal pursuit along different vertical eccentricities was −0.01, and the average change in eye velocity sensitivity during vertical pursuit along different vertical eccentricities was 0.0072 (see star symbol in **Figure 10**), with a confidence interval for a 95% margin of error of 0.0052 and 0.0065, respectively. This confidently places the population results within the second quarter in **Figure 10B**,

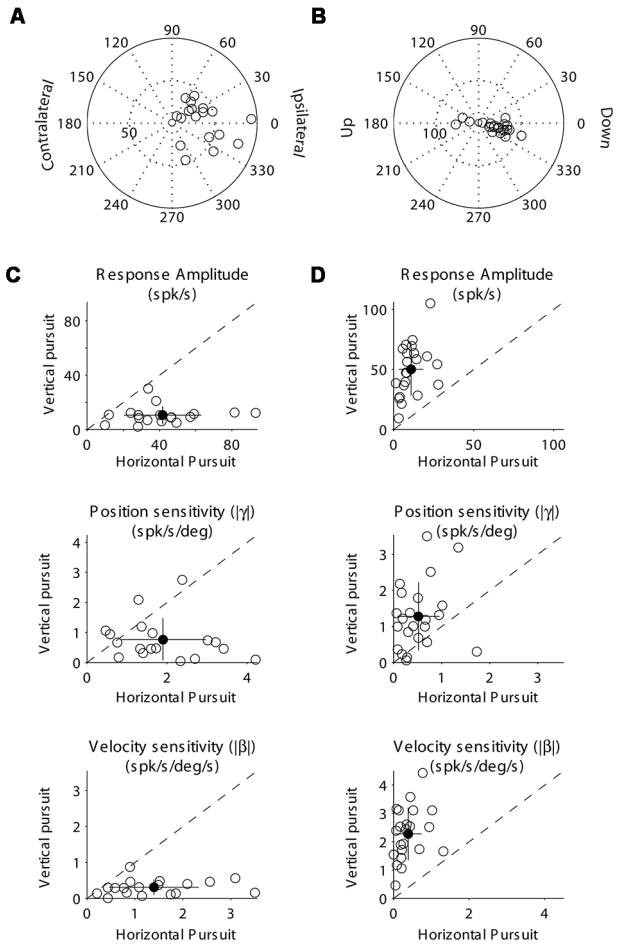

FIGURE 8 | Population data showing the response modulation and neuronal sensitivity to eye movements of horizontal **(A,C)** and vertical **(B,C)** PCs. The layout is identical to that shown for **Figure 4**. **(A)** Polar plot showing the gain and phase of individual horizontal PCs with respect to eye velocity during sinusoidal horizontal pursuit. Panel **(B)** same as **(A)** but for vertical PCs during vertical sinusoidal pursuit. Panel **(C)** top, amplitude of neuronal modulation during horizontal vs. vertical sinusoidal pursuit. Middle, neuronal eye position sensitivity (absolute values) calculated during horizontal vs. vertical sinusoidal pursuit. Bottom, neuronal eye velocity sensitivity (absolute values) calculated during horizontal vs. vertical sinusoidal pursuit. Panel **(D)** same as **(C)** but for vertical PCs. Filled symbols in **(C)** and **(D)** show the average values, and the lines segments on top of them plus/minus one standard deviation from the mean.

which corresponds to the CCW torsional direction. Based on our smallest PC sample size (n = 18) and inherent noise of the neuronal response, our analytical method could detect torsional eye velocity sensitivities as small as 0.035 deg/s (see "Materials and Methods" section), which is almost two order of magnitude smaller than the eye velocity sensitivity of PCs to horizontal and vertical eye velocity.

DISCUSSION

Current theories propose that in order to achieve fine motor control, the central nervous system (CNS) must construct a forward model of the movement (see **Figure 1**; Wolpert et al., 1998; Popa et al., 2012). Neuronal recordings and clinical studies have pointed to the cerebellar cortex as one candidate site where forward models are constructed (Ghasia et al., 2008; Bhanpuri et al., 2012). In this study, we evaluated this hypothesis by recording the activity of mossy fibers and PCs in the FL during sinusoidal smooth pursuit eye movements at different viewing eccentricities. We found that mossy fibers do not carry information related to torsional eye velocity, however PCs do. Our results agree with the hypothesis that mossy fibers carry the efferent copy of the motor command signal and PCs carry a processed signal that resembles the output of the forward model of the eye movement during pursuit (see **Figure 1**). Interestingly, only vertical PCs carry the torsional component of the eye movement. We hypothesize that the FL transforms oculomotor command signals into a prediction of the current state of the eye kinematics.

In these experiments, we did not record torsional eye movements, instead, we estimated the qualitative change in torsion using the half angle rule (see **Figure 2**; Demer, 2006). This is sufficient to evaluate whether the changes observed in PC and mossy fiber responses are indicative of them having 3D eye movement information. Moreover, although we did not calculate primary eye position (this would require knowledge of the actual 3D eye moment), the torsional component of eye movement does change in a predetermined qualitative way when comparing vertical pursuit with leftward and rightward eye position eccentricity, and horizontal pursuit with upward a downward eye position eccentricity (see **Figure 2** and Kono et al., 2002; Klier et al., 2006). Because of all the above, the experimental approach of this study is a valid methodology to evaluate the presence of forward models of the eye movement in the cerebellar cortex.

Mossy Fibers Do Not Carry Torsional Eye Movement Information During Pursuit

The majority of eye-related mossy fibers arrive at the FL from the prepositus hypoglossi nuclei (horizontal mossy fibers) and the paramedian track nuclei (vertical mossy fibers; Langer et al., 1985b; Büttner-Ennever and Horn, 1996; Escudero et al., 1996). Neurons in these nuclei carry eye position and eye velocity information (Escudero et al., 1996), and have dynamical response properties identical to those of motoneurons (Green et al., 2007). Hence, these mossy fibers carry an efferent copy signal to the FL. Our population of horizontal mossy fibers has an average response phase of about 47°, which is within the values reported for prepositus hypoglossi and medial vestibular neurons projecting to the FL (42°, Escudero et al., 1996; and 53°, Green et al., 2007; assuming that eye movement is perfectly out of phase with head during VOR). The directional preference of our eye-related mossy fibers was independent of the parameter used for their characterization (amplitude of response, eye velocity, or eye position sensitivity). Thus, indicating that they carry information related to a specific type of eye movement, like motoneurons or prepositus hypoglossi nuclei neurons do. Also, supporting that our population of mossy fibers represent the efferent copy pathway, we found a similar number of mossy

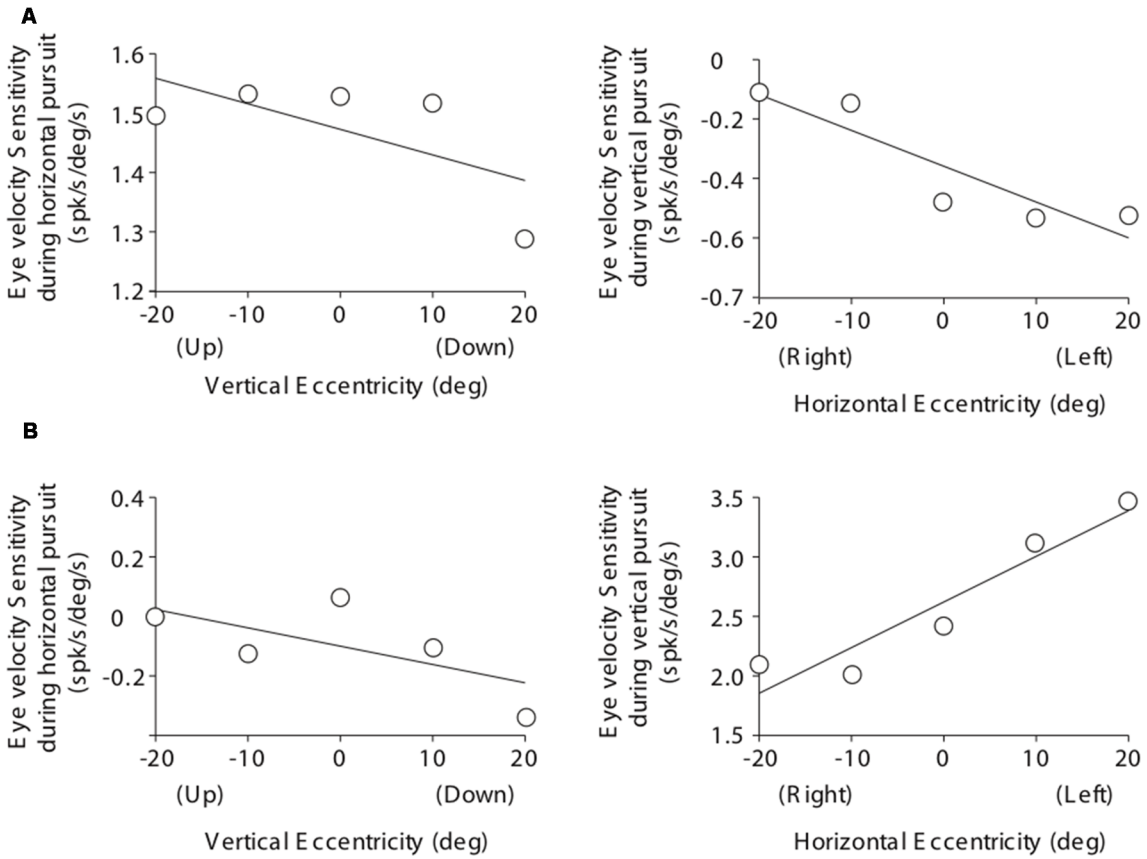

FIGURE 9 | Cartesian plots showing the changes in PC eye velocity sensitivity with viewing eccentricity for the two example PCs shown in **Figure 7**. **(A)** Data obtained from the example horizontal PC. Left plot shows changes in eye velocity sensitivity during horizontal pursuit as we modified vertical viewing eccentricity (−20, −10, 0, 10, and 20°). Right plot shows changes in eye velocity sensitivity during vertical pursuit as we modified horizontal viewing eccentricity (−20, −10, 0, 10, and 20°). Panel **(B)** same as **(A)** but for the example vertical PC.

fibers with ipsilateral preferred direction than mossy fibers with contralateral preferred direction, which is in perfect agreement with the known bilateral projection of the vestibular and prepositus hypoglossi nuclei to FL. In addition to the brainstem nuclei cited above, the pontine nuclei could also send efferent copy information to the FL (Ono et al., 2004).

Our results are in perfect agreement with the interpretation shown in **Figure 1**. Specifically, we found no evidence for a torsional eye velocity component in the response of eye-related mossy fibers. This was true even when we separated our population of mossy fibers between those with horizontal and vertical preferred directions. Our results add to the evidence from MRI and electrophysiological studies suggesting that the torsional component generated during pursuit and saccades eye movements is entirely generated by the mechanics of the orbit, not the motor command (Ghasia and Angelaki, 2005; Demer, 2006; Klier et al., 2011).

Purkinje Cell Carry Torsional Eye Movement Information During Pursuit

To our knowledge, the response of PCs to torsional eye movements have not been investigated to date, however it has been reported that electrical stimulation of the FL generates extorsion of the ipsilateral eye (outward rotation of the eyes about an axis that coincides with the direction of gaze in primary position, Sato et al., 1991). It has also been reported that injection of muscimol generates intorsion of the ipsilateral eye (Chin et al., 2002). These results suggest that PCs play an important role in the control of torsional eye movements and are in perfect agreement with our findings. The majority of our putative torsion coding vertical PCs had CCW (16/18) preferred directions, which correspond to extorsion-preferred direction because they were recorded in the left FL. Anatomical data also support our results (Fukushima and Kaneko, 1995). Vertical PCs inhibit ipsilateral secondary vestibular neurons that receive inputs from ipsilateral anterior semicircular canal afferents and that are responsible for generating compensatory eye movements to ipsilateral head roll turns; therefore, for generating intorsion of the eye. Increased activity in vertical FL PCs would increase inhibition of their target neurons in the vestibular nucleus, therefore, generating extorsion. In the other hand, inactivation of the FL would remove tonic inhibition and would generate intorsion.

Our results also suggest that horizontal PCs do not carry a signal related to torsional eye movement. This result is also

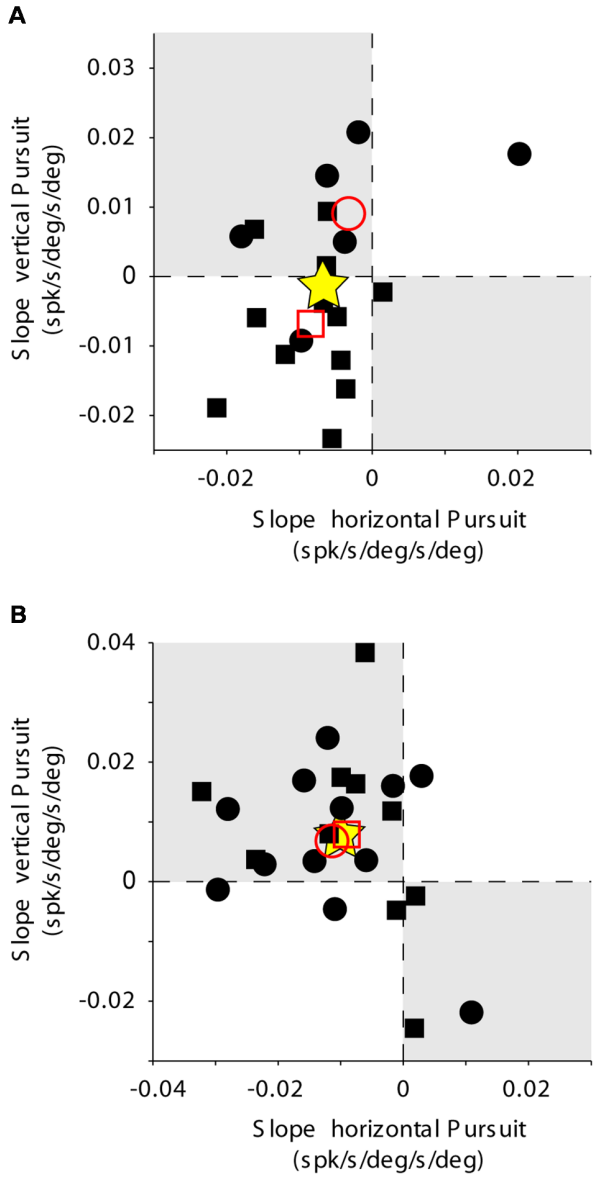

FIGURE 10 | PC population data. The layout is identical to that shown for **Figures 2D**, **6**. Rate of change of eye velocity sensitivity with eccentricity during horizontal pursuit (abscissa) vs. vertical pursuit (ordinate). **(A)** Data obtained for the population of horizontal PCs. **(B)** Data obtained for the population of vertical PCs. Each data point corresponds to a single PC. Empty red symbols represent the average value for each animal (animal 1 = circle, animal 2 = square) and stars the total average data.

expected based on anatomy. Horizontal eye movements are controlled almost exclusively by the lateral and medial rectus muscles, which are eye muscles that do not participate in the active generation of torsional eye movements.

How can the Cerebellar Cortex Compute Torsion?

Because torsional eye movements during pursuit are not neuronally driven, but implemented by the mechanics of the orbit alone (Demer, 2006; Klier et al., 2011), the brain must reverse engineer the mechanics of the orbit neuronally in order to generate an estimation of torsion. What possible mechanism can do this? One possibility is that the input/output gain of the cerebellum is modulated by a context-dependent signal corresponding to the position of the eyes in the orbit. The more eccentric the eyes are in the orbit, the larger the effect on the input/output gain. Interestingly, the cerebellar cortex has the necessary elements to support the above-mentioned reverse engineering of torsion during pursuit.

Our hypothesis is that torsional information would be generated by a context-dependent regulation of FL output *via* granular layer interneurons. We have shown that large interneurons in the FL granular layer with low and high CV2 values (likely, unipolar brush cells [UBCs] and Golgi cells, respectively) show primarily eye-position-related responses (Heine et al., 2010; Laurens et al., 2013). Others have shown that changes in the tonic inhibition of granule cells can modify the gain (input/output) of the granular layer (Mitchell and Silver, 2003). We argue that changes in the level of tonic inhibition of granule cells by Golgi cells in an eye position dependent matter could ultimately modulate PC gain in a matter similar to the half angle rule. In support, we have shown that blockage of GABA-A receptors in the FL results in PC gain increases (Blazquez and Yakusheva, 2015). An alternative mechanism involves UBCs. UBCs are abundant glutamatergic interneurons in the vestibulo-cerebellum (Ruigrok et al., 2011) that receive direct input from mossy fibers and synapse into neighboring granule cells (Mugnaini et al., 2011). Tonic excitation of granule cells by UBCs in an eye position dependent matter could change the gain of the output of the granular layer by mechanisms like firing rate potentiation (Nelson et al., 2003). Lastly, cerebellar motor learning, perhaps using torsional retinal slip signal as the teaching signal, could help tune the added gains to properly implement the half angle rule in the response of vertical PCs.

Implications of our Results for Current Theories of Motor Control

It is still unclear whether internal models operate in the CNS as shown in **Figure 1**, or whether the CNS uses other strategies to control movements. However, accumulating evidence suggests that the CNS builds a forward or predictive signal and that this signal plays a fundamental role in fine motor control (Wolpert et al., 1998; Shadmehr et al., 2010). Our results support the hypothesis that the cerebellar cortex is one place where the CNS generates predictions of the actual state of the motor system (kinematics) based on motor commands.

The cerebellum does not control movement directly, but it plays a modulatory role of the motor output. In support, movement onset usually precedes PC responses (Hirata and Highstein, 2001; Sánchez-Campusano et al., 2007). Moreover, the relation between cerebellar output and motor behavior varies depending on the behavioral state and the behavioral task. For example, during classical conditioning, interpositus neurons do not reliably encode the kinematics of the eyelid through the course of learning. Instead, their response gain is variable, and

their response phase reverses (Sánchez-Campusano et al., 2007, 2009). Similarly, FL PCs do not show the same unique relation to eye movements during pursuit, VOR and cancellation of the VOR (Lisberger and Fuchs, 1978; Blazquez et al., 2003). Hence, it is not surprising to find differences in the relation between PC discharge and motoneuron response during two pursuit conditions: one engaging torsional eye movements and one not engaging torsional eye movements (pursuit along primary eye position and pursuit at eccentric positions, respectively).

A role of the cerebellum in predicting stimulus kinematics has also been proposed, but strong evidence is still lacking. Thus, Kettner and collaborators show that FL PCs may carry a signal related to predicted changes in target trajectory (Suh et al., 2000; Kettner et al., 2002), and Miles and colleagues show that Crus I PC responses correlate with the motion of a tracking moving target (Miles et al., 2006; Cerminara et al., 2009). The interpretation of these previous studies could, however, be confounded by eye movements. We have recently used a task where the stimulus tracking phase is free from contamination of eye movement-related signal. We showed that FL PCs do not respond to the motion of relevant visual stimuli (Blazquez et al., 2017). Hence, it is possible that the cerebellum, at least the motor cerebellum, mainly builds forward models of our movements, while cortical areas or non-motor areas of the cerebellum form forward models of relevant environmental variables (Maus et al., 2010; Cheong et al., 2012; Atmaca et al., 2013; Schmahmann, 2019).

Our results cannot inform on whether PC responses represent the output of the forward model (Green et al., 2007) or a signal indicative of unexpected events; e.g., motion and sensory information not directly generated by the motor command (Sawtell and Williams, 2008; Brooks and Cullen, 2013). Indeed, it is possible that during torsional VOR, when torsional eye movements are generated actively, the predictive signal found in this study would be canceled by torsional efferent copy signal arriving through mossy fibers. Thus, resulting in no appreciable response of PCs to torsional eye movements. One possibility is that the final forward model is formed at the level of FL target neurons (FTNs) in the brainstem by averaging their PC drive (Langer et al., 1985a). In fact, torsional information seems less scattered at the level of individual FTNs than that we found in the FL PCs (Ghasia et al., 2008). But, regardless of whether PCs carry the final output of the forward model or are one step upstream to it, our data strongly suggest that at least part of the computations necessary to construct the forward model of the eye is carried out by the FL.

One important concept in cerebellar physiology is that the cerebellum can function as an adaptable filter that generates forward models (predictions of the consequence of motor command) that will be used for rapid control of motor behavior (Miall et al., 1993). Forward models could play a role in noise cancellation as well as a role in detecting unexpected events (Porrill et al., 2013). But, because the mechanical properties of the motor system change over time due to growth, injury and disease, an ideal forward model must be adaptable and follow specific learning rules. Thus, the circuit implementing the model can learn to generate a new prediction guided by a teaching or error signal (Porrill and Dean, 2007). In the case of the cerebellum, this error and teaching signal corresponds to the climbing fibbers. The construction of a forward model of torsional eye movements must be thus learned and be adaptable. Our experiments were not designed to test this adaptability, however evidence of it can be found in 2D pursuit eye movements (Medina and Lisberger, 2008). The fact that we found torsional signals in vertical PCs, but not in horizontal PCs, is in agreement with current models of cerebellar cortex function that propose that the cerebellar cortex is organized in microzones that perform separate computations (Porrill et al., 2013).

According to Marr and Albus' theory of cerebellar function, the cerebellar cortex is an ideal structure to generate context-specific computations (Marr, 1969; Albus, 1971). They proposed that the input layer of the cerebellar cortex samples the state of the motor system at any given time and generates a pattern of activity that contains contextual information. We believe that this general principle of Marr and Albus' theory of cerebellar function is still valid today and can be readily applied to explain how the cerebellar cortex reverse engineer torsional eye movement information from 2D efferent copy information. According to our view, granular layer interneurons like Golgi cells would provide context-specific information that can modulate granule cell output, hence, PC responses (Heine et al., 2010; D'Angelo et al., 2013). This process, directed by cerebellar plasticity, could generate a signal that implements the half angle rule neuronally.

ETHICS STATEMENT

All procedures conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Washington University Institutional Animal Care and Use Committee.

AUTHOR CONTRIBUTIONS

PB designed the experiments. GK, JL and PB carried out the data acquisition. GK and PB carried out the data analysis. PB, TY and JL carried out the manuscript preparation.

FUNDING

This work supported by NIH grant R01-NS065099, R01-DC016231 and R01-DC014276.

ACKNOWLEDGMENTS

We thank Fanetta Hampton for technical support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2019.00012/full#supplementary-material

FIGURE S1 | Simulation results for mossy fibers with a sample size of 10. **(A)** Example of a simulated neuron during horizontal (top) and vertical (bottom) pursuit, plotting difference in gain over the different eccentricities when torsional eye velocity sensitivity is 0.04 spk/s/deg/s. **(B)** Example of one of the populations simulated using torsional eye velocity sensitivity is 0.04 spk/s/deg/s. **(C)** Percentage of iterations (populations of 10 neurons) over 100 iterations that show significant torsional coding. **(D)** Changes in the percentage of iterations that show significant coding with changes in the torsional eye velocity sensitivity. Note that the larger the torsional eye velocity sensitivity, the most likely we could detect the torsional signal in the population.

FIGURE S2 | Same as in **Supplementary Figure S1** but for Purkinje cells with a sample size of 18.

REFERENCES

Albus, J. S. (1971). A theory of cerebellar function. *Math. Biosci.* 10, 25–61. doi: 10.1016/0025-5564(71)90051-4

Atmaca, S., Stadler, W., Keitel, A., Ott, D. V. M., Lepsien, J., and Prinz, W. (2013). Prediction processes during multiple object tracking (MOT): involvement of dorsal and ventral premotor cortices. *Brain Behav.* 3, 683–700. doi: 10.1002/brb3.180

Bhanpuri, N. H., Okamura, A. M., and Bastian, A. J. (2012). Active force perception depends on cerebellar function. *J. Neurophysiol.* 107, 1612–1620. doi: 10.1152/jn.00983.2011

Blazquez, P. M., Hirata, Y., Heiney, S. A., Green, A. M., and Highstein, S. M. (2003). Cerebellar signatures of vestibulo-ocular reflex motor learning. *J. Neurosci.* 23, 9742–9751. doi: 10.1523/jneurosci.23-30-09742.2003

Blazquez, P. M., Kim, G., and Yakusheva, T. A. (2017). Searching for an internal representation of stimulus kinematics in the response of ventral paraflocculus purkinje cells. *Cerebellum* 16, 817–826. doi: 10.1007/s12311-017-0861-x

Blazquez, P. M., and Yakusheva, T. A. (2015). GABA-A inhibition shapes the spatial and temporal response properties of purkinje cells in the macaque cerebellum. *Cell Rep.* 11, 1043–1053. doi: 10.1016/j.celrep.2015.04.020

Brooks, J. X., and Cullen, K. E. (2013). The primate cerebellum selectively encodes unexpected self-motion. *Curr. Biol.* 23, 947–955. doi: 10.1016/j.cub.2013.04.029

Büttner-Ennever, J. A., and Horn, A. K. (1996). Pathways from cell groups of the paramedian tracts to the floccular region. *Ann. N Y Acad. Sci.* 781, 532–540. doi: 10.1111/j.1749-6632.1996.tb15726.x

Cerminara, N. L., Apps, R., and Marple-Horvat, D. E. (2009). An internal model of a moving visual target in the lateral cerebellum. *J. Physiol.* 587, 429–442. doi: 10.1113/jphysiol.2008.163337

Cheong, D., Zubieta, J. K., and Liu, J. (2012). Neural correlates of visual motion prediction. *PLoS One* 7:e39854. doi: 10.1371/journal.pone.0039854

Chin, S., Fukushima, K., Fukushima, J., Kase, M., and Ohno, S. (2002). Ocular torsion produced by unilateral chemical inactivation of the cerebellar flocculus in alert cats. *Curr. Eye Res.* 25, 133–138. doi: 10.1076/ceyr.25.3.133.13476

D'Angelo, E., Solinas, S., Mapelli, J., Gandolfi, D., Mapelli, L., and Prestori, F. (2013). The cerebellar golgi cell and spatiotemporal organization of granular layer activity. *Front. Neural Circuits* 7:93. doi: 10.3389/fncir.2013.00093

Demer, J. L. (2006). Current concepts of mechanical and neural factors in ocular motility. *Curr. Opin. Neurol.* 19, 4–13. doi: 10.1097/01.wco.0000198100.87670.37

Escudero, M., Cheron, G., and Godaux, E. (1996). Discharge properties of brain stem neurons projecting to the flocculus in the alert cat. II. Prepositus hypoglossal nucleus. *J. Neurophysiol.* 76, 1775–1785. doi: 10.1152/jn.1996.76.3.1775

Fukushima, K., and Kaneko, C. R. (1995). Vestibular integrators in the oculomotor system. *Neurosci. Res.* 22, 249–258. doi: 10.1016/0168-0102(95)00904-8

Ghasia, F. F., and Angelaki, D. E. (2005). Do motoneurons encode the noncommutativity of ocular rotations? *Neuron* 47, 281–293. doi: 10.1016/j.neuron.2005.05.031

Ghasia, F. F., Meng, H., and Angelaki, D. E. (2008). Neural correlates of forward and inverse models for eye movements: evidence from three-dimensional kinematics. *J. Neurosci.* 28, 5082–5087. doi: 10.1523/JNEUROSCI.0513-08.2008

Green, A. M., Meng, H., and Angelaki, D. E. (2007). A reevaluation of the inverse dynamic model for eye movements. *J. Neurosci.* 27, 1346–1355. doi: 10.1523/JNEUROSCI.3822-06.2007

Heine, S. A., Highstein, S. M., and Blazquez, P. M. (2010). Golgi cells operate as state-specific temporal filters at the input stage of the cerebellar cortex. *J. Neurosci.* 30, 17004–17014. doi: 10.1523/JNEUROSCI.3513-10.2010

Hirata, Y., and Highstein, S. M. (2001). Acute adaptation of the vestibuloocular reflex: signal processing by floccular and ventral paraflocular Purkinje cells. *J. Neurophysiol.* 85, 2267–2288. doi: 10.1152/jn.2001.85.5.2267

Kettner, R. E., Suh, M., Davis, D., and Leung, H. C. (2002). Complex predictive eye pursuit in monkey: a model system for cerebellar studies of skilled movement. *Arch. Ital. Biol.* 140, 331–340. doi: 10.4449/aib.v140i4.492

Klier, E. M., Meng, H., and Angelaki, D. E. (2006). Three-dimensional kinematics at the level of the oculomotor plant. *J. Neurosci.* 26, 2732–2737. doi: 10.1523/JNEUROSCI.3610-05.2006

Klier, E. M., Meng, H., and Angelaki, D. E. (2011). Revealing the kinematics of the oculomotor plant with tertiary eye positions and ocular counterroll. *J. Neurophysiol.* 105, 640–649. doi: 10.1152/jn.00737.2010

Kono, R., Clark, R. A., and Demer, J. L. (2002). Active pulleys: magnetic resonance imaging of rectus muscle paths in tertiary gazes. *Invest. Ophthalmol. Vis. Sci.* 43, 2179–2188.

Langer, T., Fuchs, A. F., Chubb, M. C., Scudder, C. A., and Lisberger, S. G. (1985a). Floccular efferents in the rhesus macaque as revealed by autoradiography and horseradish peroxidase. *J. Comp. Neurol.* 235, 26–37. doi: 10.1002/cne.902350103

Langer, T., Fuchs, A. F., Scudder, C. A., and Chubb, M. C. (1985b). Afferents to the flocculus of the cerebellum in the rhesus macaque as revealed by retrograde transport of horseradish peroxidase. *J. Comp. Neurol.* 235, 1–25. doi: 10.1002/cne.902350102

Laurens, J., Heiney, S. A., Kim, G., and Blazquez, P. M. (2013). Cerebellar cortex granular layer interneurons in the macaque monkey are functionally driven by mossy fiber pathways through net excitation or inhibition. *PLoS One* 8:e82239. doi: 10.1371/journal.pone.0082239

Lisberger, S. G., and Fuchs, A. F. (1978). Role of primate flocculus during rapid behavioral modification of vestibuloocular reflex. II. Mossy fiber firing patterns during horizontal head rotation and eye movement. *J. Neurophysiol.* 41, 764–777. doi: 10.1152/jn.1978.41.3.764

Lisberger, S. G., Pavelko, T. A., Bronte-Stewart, H. M., and Stone, L. S. (1994). Neural basis for motor learning in the vestibuloocular reflex of primates. II. Changes in the responses of horizontal gaze velocity Purkinje cells in the cerebellar flocculus and ventral paraflocculus. *J. Neurophysiol.* 72, 954–973. doi: 10.1152/jn.1994.72.2.954

Marr, D. (1969). A theory of cerebellar cortex. *J. Physiol.* 202, 437–470. doi: 10.1113/jphysiol.1969.sp008820

Maus, G. W., Weigelt, S., Nijhawan, R., and Muckli, L. (2010). Does area V3A predict positions of moving objects? *Front. Psychol.* 1:186. doi: 10.3389/fpsyg.2010.00186

Medina, J. F., and Lisberger, S. G. (2008). Links from complex spikes to local plasticity and motor learning in the cerebellum of awake-behaving monkeys. *Nat. Neurosci.* 11, 1185–1192. doi: 10.1038/nn.2197

Miall, R. C., Weir, D. J., Wolpert, D. M., and Stein, J. F. (1993). Is the cerebellum a smith predictor? *J. Mot. Behav.* 25, 203–216. doi: 10.1080/00222895.1993.9942050

Miles, F. A., and Braitman, D. J. (1980). Long-term adaptive changes in primate vestibuloocular reflex. II. Electrophysiological observations on semicircular canal primary afferents. *J. Neurophysiol.* 43, 1426–1436. doi: 10.1152/jn.1980.43.5.1426

Miles, O. B., Cerminara, N. L., and Marple-Horvat, D. E. (2006). Purkinje cells in the lateral cerebellum of the cat encode visual events and target motion during visually guided reaching. *J. Physiol.* 571, 619–637. doi: 10.1113/jphysiol.2005.099382

Miles, F. A., Fuller, J. H., Braitman, D. J., and Dow, B. M. (1980). Long-term adaptive changes in primate vestibuloocular reflex. III. Electrophysiological observations in flocculus of normal monkeys. *J. Neurophysiol.* 43, 1437–1476. doi: 10.1152/jn.1980.43.5.1437

Mitchell, S. J., and Silver, R. A. (2003). Shunting inhibition modulates neuronal gain during synaptic excitation. *Neuron* 38, 433–445. doi: 10.1016/s0896-6273(03)00200-9

Mugnaini, E., Sekerková, G., and Martina, M. (2011). The unipolar brush cell: a remarkable neuron finally receiving deserved attention. *Brain Res. Rev.* 66, 220–245. doi: 10.1016/j.brainresrev.2010.10.001

Nelson, A. B., Krispel, C. M., Sekirnjak, C., and Du Lac, S. (2003). Long-lasting increases in intrinsic excitability triggered by inhibition. *Neuron* 40, 609–620. doi: 10.1016/s0896-6273(03)00641-x

Ono, S., Das, V. E., and Mustari, M. J. (2004). Gaze-related response properties of DLPN and NRTP neurons in the rhesus macaque. *J. Neurophysiol.* 91, 2484–2500. doi: 10.1152/jn.01005.2003

Pasalar, S., Roitman, A. V., Durfee, W. K., and Ebner, T. J. (2006). Force field effects on cerebellar Purkinje cell discharge with implications for internal models. *Nat. Neurosci.* 9, 1404–1411. doi: 10.1038/nn1783

Paxinos, G., Huang, X. F., and Toga, A. W. (2000). *The Rhesus Monkey Brain in Stereotaxic Coordinates*. San Diego, CA: Academic Press.

Popa, L. S., Hewitt, A. L., and Ebner, T. J. (2012). Predictive and feedback performance errors are signaled in the simple spike discharge of individual purkinje cells. *J. Neurosci.* 32, 15345–15358. doi: 10.1523/JNEUROSCI.2151-12.2012

Porrill, J., and Dean, P. (2007). Cerebellar motor learning: when is cortical plasticity not enough? *PLoS Comput. Biol.* 3, 1935–1950. doi: 10.1371/journal.pcbi.0030197

Porrill, J., Dean, P., and Anderson, S. R. (2013). Adaptive filters and internal models: multilevel description of cerebellar function. *Neural Netw.* 47, 134–149. doi: 10.1016/j.neunet.2012.12.005

Ruigrok, T. J. H., Hensbroek, R. A., and Simpson, J. I. (2011). Spontaneous activity signatures of morphologically identified interneurons in the vestibulocerebellum. *J. Neurosci.* 31, 712–724. doi: 10.1523/JNEUROSCI.1959-10.2011

Sánchez-Campusano, R., Gruart, A., and Delgado-Garcia, J. M. (2007). The cerebellar interpositus nucleus and the dynamic control of learned motor responses. *J. Neurosci.* 27, 6620–6632. doi: 10.1523/JNEUROSCI.0488-07.2007

Sánchez-Campusano, R., Gruart, A., and Delgado-Garcia, J. M. (2009). Dynamic associations in the cerebellar-motoneuron network during motor learning. *J. Neurosci.* 29, 10750–10763. doi: 10.1523/JNEUROSCI.2178-09.2009

Sato, Y., Kawasaki, T., and Mizukoshi, K. (1991). Eye movement control by Purkinje cell/climbing fiber zones of cerebellar flocculus in cat. *Acta Otolaryngol. Suppl.* 481, 237–241. doi: 10.3109/00016489109131390

Sawtell, N. B., and Williams, A. (2008). Transformations of electrosensory encoding associated with an adaptive filter. *J. Neurosci.* 28, 1598–1612. doi: 10.1523/JNEUROSCI.4946-07.2008

Schmahmann, J. D. (2019). The cerebellum and cognition. *Neurosci. Lett.* 688, 62–75. doi: 10.1016/j.neulet.2018.07.005

Shadmehr, R., and Mussa-Ivaldi, F. A. (1994). Adaptive representation of dynamics during learning of a motor task. *J. Neurosci.* 14, 3208–3224. doi: 10.1523/jneurosci.14-05-03208.1994

Shadmehr, R., Smith, M. A., and Krakauer, J. W. (2010). Error correction, sensory prediction and adaptation in motor control. *Annu. Rev. Neurosci.* 33, 89–108. doi: 10.1146/annurev-neuro-060909-153135

Suh, M., Leung, H. C., and Kettner, R. E. (2000). Cerebellar flocculus and ventral paraflocculus Purkinje cell activity during predictive and visually driven pursuit in monkey. *J. Neurophysiol.* 84, 1835–1850. doi: 10.1152/jn.2000.84.4.1835

Wolpert, D. M., Ghahramani, Z., and Jordan, M. I. (1995). An internal model for sensorimotor integration. *Science* 269, 1880–1882. doi: 10.1126/science.7569931

Wolpert, D. M., and Kawato, M. (1998). Multiple paired forward and inverse models for motor control. *Neural Netw.* 11, 1317–1329. doi: 10.1016/s0893-6080(98)00066-5

Wolpert, D. M., Miall, R. C., and Kawato, M. (1998). Internal models in the cerebellum. *Trends Cogn. Sci.* 2, 338–347. doi: 10.1016/S1364-6613(98)01221-2

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Human Neuroscience

ORIGINAL RESEARCH
published: 26 June 2019
doi: 10.3389/fnhum.2019.00216

Contribution of the Cerebellum to Predictive Motor Control and Its Evaluation in Ataxic Patients

Shinji Kakei[1], Jongho Lee[2], Hiroshi Mitoma[3], Hirokazu Tanaka[4], Mario Manto[5,6] and Christiane S. Hampe[7]*

[1] Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan, [2] Komatsu University, Komatsu, Japan, [3] Medical Education Promotion Center, Tokyo Medical University, Tokyo, Japan, [4] Japan Advanced Institute of Science and Technology, Nomi, Japan, [5] Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium, [6] Department of Neurosciences, University of Mons, Mons, Belgium, [7] School of Medicine, University of Washington, Seattle, WA, United States

Goal-directed movements are predictive and multimodal in nature, especially for moving targets. For instance, during a reaching movement for a moving target, humans need to predict both motion of the target and movement of the limb. Recent computational studies show that the cerebellum predicts current and future states of the body and its environment using internal forward models. Sensory feedback signals from the periphery have delays in reaching the central nervous system, ranging between tens to hundreds of milliseconds. It is well known in engineering that feedback control based on time-delayed inputs can result in oscillatory and often unstable movements. In contrast, the brain predicts a current state from a previous state using forward models. This predictive mechanism most likely underpins stable and dexterous control of reaching movements. Although the *cerebro-cerebellum* has long been suggested as loci of various forward models, few methods are available to evaluate accuracy of the forward models in patients with cerebellar ataxia. Recently, we developed a non-invasive method to analyze receipt of motor commands in terms of movement kinematics for the wrist joint (B_r/K_r ratio). In the present study, we have identified two components (F1 and F2) of the smooth pursuit movement. We found that the two components were in different control modes with different B_r/K_r ratios. The major F1 component in a lower frequency range encodes both velocity and position of the moving target (*higher* B_r/K_r ratio) to synchronize movement of the wrist joint with motion of the target in a *predictive* manner. The minor F2 component in a higher frequency range is biased to position control in order to generate intermittent small step-wise movements. In cerebellar patients, the F1 component shows a selective decrease in the B_r/K_r ratio, which is correlated with decrease in accuracy of the pursuit movement. We conclude that the B_r/K_r ratio of the F1 component provides a unique parameter to evaluate accuracy of the predictive control. We also discuss the pathophysiological and clinical implications for clinical ataxiology.

Keywords: cerebrocerebellar loop, electromyography (EMG), movement kinematics, cerebellar ataxia, viscosity, elasticity

OPEN ACCESS

Edited by:
Praveen Pilly,
HRL Laboratories, LLC, United States

Reviewed by:
Dai Yanagihara,
The University of Tokyo, Japan
Leanne Chukoskie,
University of California, San Diego, United States

****Correspondence:***
Shinji Kakei
kakei-sj@igakuken.or.jp

Received: *29 November 2018*
Accepted: *12 June 2019*
Published: *26 June 2019*

Citation:
Kakei S, Lee J, Mitoma H, Tanaka H, Manto M and Hampe CS (2019) Contribution of the Cerebellum to Predictive Motor Control and Its Evaluation in Ataxic Patients. Front. Hum. Neurosci. 13:216. doi: 10.3389/fnhum.2019.00216

INTRODUCTION

Goal-directed movements are predictive in nature, especially for moving targets in the environment of daily life. The prediction is in essence multimodal. For instance, during a reaching task for a moving target, humans need to predict both motion of the target and movement of the limb to match them optimally. Making predictions and validating the predictions against actual sensory information is a fundamental function of the nervous system. Prediction errors and assessment of the discrepancy between predicted and actual information are critical parameters (Popa and Ebner, 2019).

Recent computational studies posit a mechanism that predicts current and future states of the body and its environments by integrating an estimate of previous state and efference copies of motor signals, the computation known as an internal forward model (Wolpert et al., 1995; Miall and Wolpert, 1996; Davidson and Wolpert, 2005). Sensory feedback signals through sensory organs have inevitable delays to reach the central nervous system, between tens to hundreds of milliseconds. It is well known in engineering that feedback control based on time-delayed inputs can result in oscillatory and often unstable movements (Miall et al., 1993b; Kawato, 1999). It is most likely that the brain predicts a current state from a previous state with forward models (Wolpert et al., 1995; Miall and Wolpert, 1996). The cerebellum has been suggested as the locus of the forward-model computation of state prediction from psychophysical (Nowak et al., 2007; Tseng et al., 2007; Synofzik et al., 2008), neuroimaging (Blakemore et al., 2001; Kawato et al., 2003; Schlerf et al., 2012), and non-invasive stimulation (Miall et al., 2007; Lesage et al., 2012) studies in humans and electrophysiological studies (Pasalar et al., 2006; Ebner and Pasalar, 2008) in monkeys (for review, see Shadmehr et al., 2010; Ishikawa et al., 2016). Recently, our group demonstrated that current outputs from the cerebellum (firing rates of dentate cells) contained predictive information about future inputs to the cerebellum (firing rates of mossy fibers), thereby providing a strong support to the forward-model hypothesis of the cerebellum (Tanaka et al., 2019). The computation of a forward model contributes to predictive control in the presence of considerable delays in sensory feedback (Desmurget and Grafton, 2000).

The predictive control (also known as internal feedback) and corrective control (known as sensory feedback) (Lacquaniti et al., 1982; Soechting and Lacquaniti, 1988) together play an integral role in the optimal feedback control (OFC) model (Todorov and Jordan, 2002). The OFC model predicts that the gain in sensory feedback is not prefixed but rather adaptive as reported in psychophysical experiments in response to direction-dependent visual perturbations (Franklin et al., 2014), difference in feedback delays across multiple modalities (Crevecoeur et al., 2016), or imposed external force fields (Franklin et al., 2017; see Crevecoeur and Kurtzer, 2018 for review). The task-dependent modulation of feedback gain is likely processed within transcortical feedback loops between cortical sensorimotor areas, particularly the primary motor cortex, and spinal motor circuits (Pruszynski et al., 2011, 2014; for review, see Scott et al., 2015). In summary, the existing studies indicate a dissociation between the two computational elements in the OFC model: the forward-model computation in the cerebellum, and the sensory-feedback computation in cortical sensorimotor areas (Shadmehr and Krakauer, 2008). We therefore hypothesize that cerebellar patients maintain corrective control based on sensory feedback but suffer from impaired predictive control based on forward-model prediction (Popa and Ebner, 2019).

Although the cerebellum, especially its hemispheric part, has long been suggested as containing loci of various forward models (Wolpert et al., 1998; Bastian, 2006; Miall et al., 2007), there is no reliable method to evaluate accuracy of the forward models in patients with cerebellar ataxia to the best of our knowledge. Our previous studies developed a novel method to analyze relationship between muscle activities and movement kinematics of the wrist joint (Lee et al., 2012, 2013, 2015; Mitoma et al., 2016). We found that the muscle activities for a smooth pursuit movement of the normal control subjects encode both velocity and position of the target, resulting in a precise tracking movement. In contrast, the muscle activities of patients with cerebellar ataxia were characterized by a marked decrease in encoding of velocity and a compensatory increase in encoding of position, resulting in a series of irregular stepwise movements with poor accuracy. In these analyses (Lee et al., 2015), we treated the smooth pursuit movement as a whole (i.e., the entire frequency range) assuming a single controller. In the present study, however, we *reanalyzed* the same data to find that the smooth pursuit movement actually contained *two* distinct components, corresponding to separate frequency bands. We further identified that the two components were in different control modes that corresponded to predictive and corrective control reviewed above, respectively. The *major component* in a lower frequency range (referred to as F1) encodes velocity and position of the moving target in a predictive manner, whereas the *minor component* in a higher frequency range (F2) generates intermittent small step-wise movements to correct positional errors. In cerebellar patients, however, the predictive component is associated with a selective decrease in the velocity component, which results in poorer accuracy of the pursuit movement. The impairment in cerebellar patients was succinctly characterized by a ratio of viscosity to elasticity coefficients (B_r/K_r ratio defined below) in the F1 component, thereby providing a reliable metric to assess the performance of forward-model prediction. We propose that our new method provides a unique tool to evaluate accuracy of the predictive control in patients with cerebellar ataxia.

MATERIALS AND METHODS

Subjects

Thirteen healthy control subjects with no history of neurological disorders (6 women and 7 men, 44–71 years old, mean = 56.0 years old, all right-handed; see **Table 1**) and age-matched 19 patients with cerebellar ataxia (12 women and 7 men, 29–77 years old, mean = 60.5 years old, all right-handed; see **Table 1**) took part in the study. For the patients' clinical data including Modified Rankin Scale (MRS), see **Table 2**. All of the

subjects were informed of the purpose and procedures of this study in advance and provided written informed consents prior to their participation. The protocol was approved by the ethics committees of the Tokyo Metropolitan Institute of Medical Science and the Tokyo Metropolitan Neurological Hospital. It was conducted in accordance with the ethical standards of the Declaration of Helsinki.

TABLE 1 | Characteristics of the control subjects.

Case	#ID	Age
1	Se1	46–50
2	Se2	46–50
3	Se4	61–65
4	Se5	41–45
5	Se6	51–55
6	Se8	51–55
7	Se11	51–55
8	Se12	61–65
9	Se15	56–60
10	Se16	41–45
11	Se19	66–70
12	Se22	66–70
13	Se23	71–75

TABLE 2 | Characteristics of the patients with cerebellar ataxia.

Case	#ID	Age	Disease	MRS
1	Ce2	61–65	MSA-C	2
2	Ce3	76–80	CCA	2
3	Ce4	61–65	SCA6	2
4	Ce6	71–75	MSA-C	2
5	Ce8	66–70	CCA	2
6	Ce12	61–65	MSA-C	2
7	Ce16	56–60	SCD	2
8	Ce22	31–35	SCA3	2
9	Ce25	66–70	SCA6	2
10	Ce35	66–70	SCA31	2
11	Ce37	36–40	SCA3	2
12	Ce10	61–65	MSA-C	3
13	Ce11	26–30	SCA3	3
14	Ce15	76–80	CCA	3
15	Ce19	56–60	CCA	3
16	Ce20	56–60	MSA-C	3
17	Ce28	56–60	MSA-C	4
18	Ce1	71–75	MSA-C	4
19	Ce7	56–60	MSA-C	4

MSA-C, multiple system atrophy (MSA) with cerebellar features; SCD, spinocerebellar degeneration; MRS, Modified Rankin Scale. MRS score – 0: No symptoms at all; 1: No significant disability despite symptoms; able to carry out all usual duties and activities, 2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance, 3: Moderate disability; requiring some help, but able to walk without assistance, 4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance, 5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention.

Experimental Setup and Movement Task

The apparatus and experimental setup were the same as those described in our previous study (see Lee et al., 2008, 2015 in detail). Briefly, the subject sat on a chair approximately 60 cm in front of a monitor that displayed a cursor and a target, and grasped a Strick–Hoffman type manipulandum (Hoffman and Strick, 1999; Lee et al., 2015, Hoyo Elemec Co., Ltd., Sendai, Japan) with his/her right hand. The forearm was supported with an armrest. The cursor was a black dot that moved in proportion to movement of the subject's wrist. The central position of the manipulandum corresponded to the center of the monitor, and the cursor moved left for flexion, right for extension, up for radial deviation, and down for ulnar deviation. The target was displayed as an open circle whose inside diameter corresponded to 4.5° of wrist movement.

The subjects were asked to perform the smooth pursuit task of the wrist joint (**Figure 1A**) employed in our previous study (Lee et al., 2012, 2015). Each subject was asked to perform a smooth pursuit movement of the wrist joint for a target moving at a constant speed (**Figure 1A**). To start a trial, the subject placed the cursor within the target, which was stationary at the upper left ($X = -10°$, $Y = 8°$) of the monitor. After a fixed hold period (4 s), the target started moving along the path of the **Figure 2** at a constant speed (6.2°/s). The subject was requested to maintain the position of the cursor inside of the moving target as much as possible. After repeating practice three times, each subject performed the task five times. The path of the target was not visible to the subject during the task, however, he/she had some knowledge about the movement of the target thanks to the practice trials.

Data Acquisition

During the task, we recorded the wrist position (X and Y) and muscle activities [electromyography (EMG) signals] from four wrist prime movers [*flexor carpi radialis* (FCR), *flexor carpi*

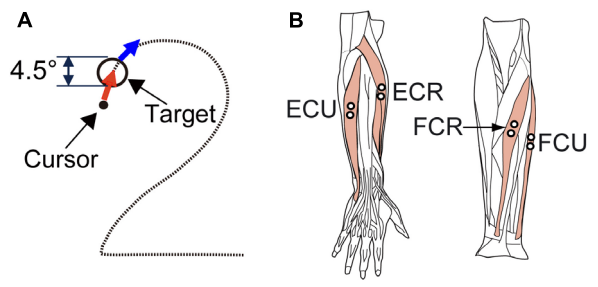

FIGURE 1 | Experimental design. **(A)** Arrangement of the target (circle) and required movement (red arrows) of the cursor (black dot) for the smooth pursuit tasks. The diameter of the targets was equivalent to 4.5 degrees of wrist movement. For the smooth pursuit task, the subjects were required to maintain the cursor within the target. **(B)** The four wrist prime movers from which EMG activity was recorded. ECR, *extensor carpi radialis*; ECU, *extensor carpi ulnaris*; FCU, *flexor carpi ulnaris*; FCR, *flexor carpi radialis*. We recorded the activity of the *extensor carpi radialis longus* (ECRL) and *extensor carpi radialis brevis* (ECRB) together as ECR because these two muscles are indistinguishable with surface electrodes.

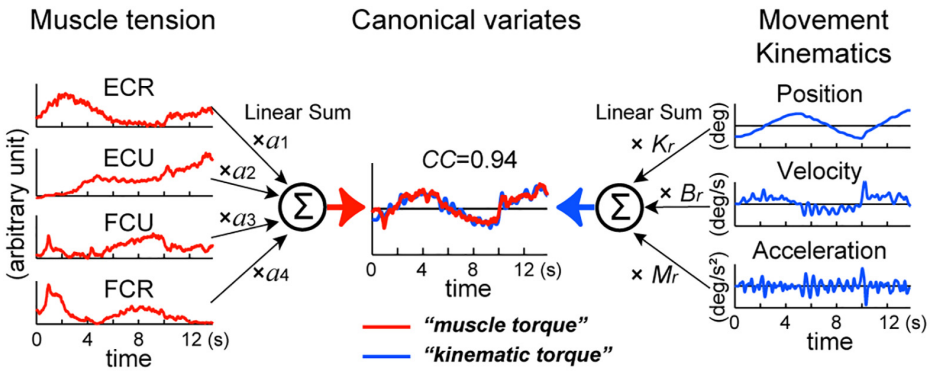

FIGURE 2 | Identification of the relationship between muscle tension and movement kinematics modeled in equation (1). The left panel represents the middle of equation (1). EMG activities of the four muscles (ECR, ECU, FCU, FCR) converted into *muscle tension* (*red lines*) are linearly summed (Σ) after multiplying parameter a_1–a_4, respectively to obtain *muscle torque* in the center (*red line*) (see section "Materials and Methods"). The right panel represents the right side of equation (1). Acceleration (Ax), velocity (Vx), and position (X) of the wrist joint (*blue lines*) are summed (Σ) after multiplying the inertia parameter (M), the viscous coefficient (B_r) and the elastic coefficient (K_r), respectively to obtain *kinematic torque* in the center (*blue line*) (see section "Materials and Methods"). We used a canonical correlation analysis (CCA) to obtain values of these parameters. The two canonical variates, *muscle torque* and *kinematic torque*, were calculated by substituting the values for the fitting parameters in equation (1). Note the high canonical correlation (CC = 0.94) between the two canonical variates (in *Estimated torque*). This figure explains calculation of torque around the x-axis, but the same method applies to calculation of torque around the y-axis. Modified from Lee et al. (2015).

ulnaris (FCU), *extensor carpi ulnaris* (ECU), and *extensor carpi radialis* (ECR)] (**Figure 1B**).

We recorded the EMG signals with Ag-AgCl electrode pairs spaced 10 mm apart. EMG signals were amplified (×100,000) and band-pass filtered (150–30,000 Hz) using an amplifier (AB-611J, Nihon Kohden, Tokyo, Japan), and sampled at 2 kHz. The typical locations of the recording electrodes are shown in **Figure 1B**. The position of each electrode pair was adjusted to maximize the activities of the wrist movements and to minimize those of the finger muscles.

The EMG signals were rectified and filtered with a second-order low-pass filter (cut-off frequency, 3.0 Hz; Mannard and Stein, 1973; Koike and Kawato, 1995) to estimate the muscle tensions from the surface EMG signals (Mannard and Stein, 1973; Koike and Kawato, 1995; Shin et al., 2009; Standenmann et al., 2010). Muscle tension was normalized using a simple normalization technique that sets the amplitude of the muscle tension for 0.78 Nm of isometric wrist joint torque as one (Shin et al., 2009). Finally, we subtracted the normalized muscle tension at the center from the normalized tension to set the tension at the central position to zero. We used the processed muscle tension of the four muscles to estimate wrist joint torque.

Wrist Joint Model and Identification of the Relationship Between Muscle Activities and Movement Kinematics

We assumed that, if the activity of the wrist muscles determines movement of the wrist joint, it is possible to estimate the wrist joint torque that is calculated from the equation of motion with the activities of the four muscles [equation (1)].

$$\tau(t) = \sum_{i=1}^{4} a_i T_i(t) = M\ddot{\theta}(t) + B\dot{\theta}(t) + K\theta(t) \qquad (1)$$

where $\tau(t)$ represents the wrist joint torque. T_i represents muscle tension processed as explained above (see **Figure 2**: muscle tension: ECR, ECU, FCU, and FCR) and a_i represents the coefficients that convert muscle tension into wrist joint torque (see left side of **Figure 2**). a_i's are the moment arm with plus or minus sign according to the pulling direction (i.e., direction of the mechanical action) of each muscle (Lee et al., 2015). The variables $\theta(t)$, $\dot{\theta}(t)$, and $\ddot{\theta}(t)$ represent the angle, angular velocity, and angular acceleration of the wrist joint, respectively. M, B, and K are the inertia parameter (kgm^2), the viscous coefficient (Nms/rad) and the elastic coefficient (Nm/rad).

Equation (1) is justified if there is a high correlation between the wrist joint torque that is calculated from the movement kinematics [*kinematic torque*: right-hand side of equation (1)] and the wrist joint torque that is calculated from the muscle activities [*muscle torque*: middle of equation (1)]. To identify the relationships between the muscle activities and the movement kinematics for the pursuit task, it is necessary to find the two sets of parameters a_1, a_2, a_3, a_4, and M, B, K that optimize the match between the kinematic torque and the muscle torque. We used canonical correlation analysis (CCA) (Härdle and Simar, 2003) for the muscle activities, i.e., [T_1(t), T_2(t), T_3(t), T_4(t)], and the movement kinematics, i.e., [$\ddot{\theta}(t)$, $\dot{\theta}(t)$, $\theta(t)$] in each subject with SAS (University Edition, Release: 3.1, SAS Institute Inc., Cary, NC, United States). The program yielded two parameter vectors (a_1, a_2, a_3, a_4), and (M, B, K) such that the pair of canonical variates (a_1, a_2, a_3, a_4) $[T_1(t), T_2(t), T_3(t), T_4(t)]^T$ $[= \sum_{i=1}^{4} a_i T_i(t)]$ and (M, B, K) $[\ddot{\theta}(t), \dot{\theta}(t), \theta(t)]^T$ $[= M\ddot{\theta}(t) + B\theta(t) + K\theta(t)]$ maximize their correlation [i.e., canonical correlation (CC)] (see **Figure 2**). In the analysis, we used the "NOINT" option that omits subtraction of means from the data, because the muscle activities are always positive or zero. It should be noted that, using CCA, it is not possible to determine absolute values of M, B, or K. Instead, we can obtain their ratios. Therefore, in the following part of this

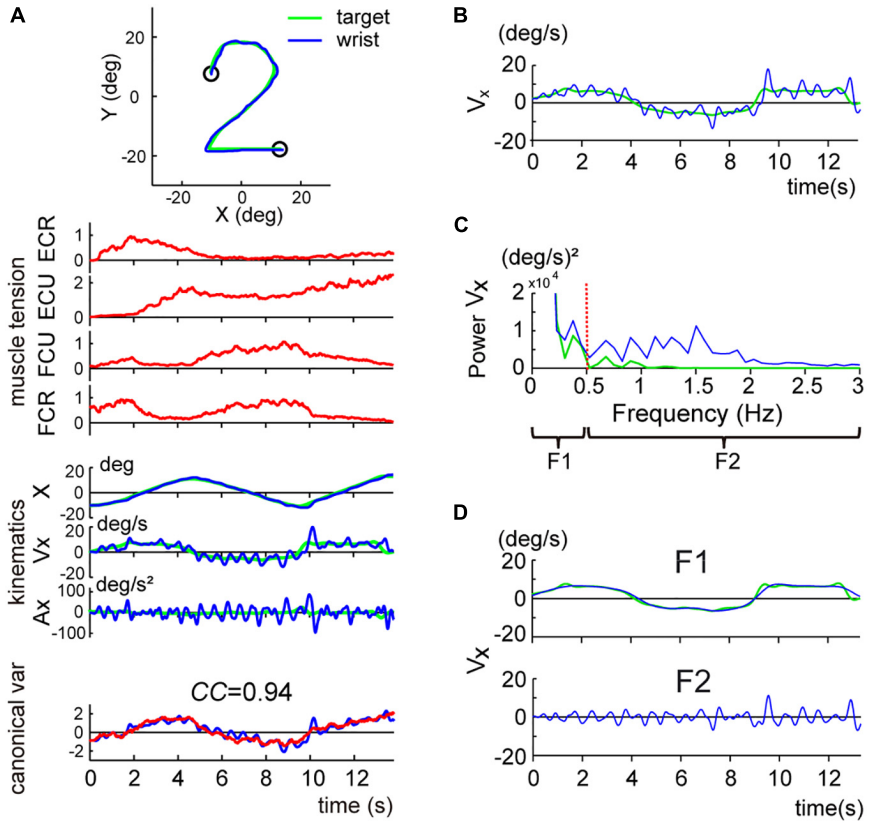

FIGURE 3 | Two components of the smooth pursuit movement. The color convention is the same as in **Figure 2**. **(A)** Identification of the relationship between muscle activities and movement kinematics in a control subject for the pursuit task. The *blue line* and the *green line* in the *top inset* indicate the *wrist* movement and the *target* motion in a single trial, respectively. *Muscle tension* traces [the top four traces (*red lines*)] show the normalized muscle tension of the four wrist prime movers: ECR, ECU, FCU, and FCR. *Kinematics* traces [the middle three traces (*blue lines*)] show the horizontal (i.e., *x*-axis) components of the movement kinematics: angle (X), angular velocity (Vx), and angular acceleration (Ax), respectively. The *green lines* indicate the kinematics of the target motion. *Canonical var.* traces (the bottom traces) depict the two canonical variates [i.e., *muscle torque* (*red line*)] and *kinematic torque* (*blue line*). The high canonical correlation *CC's* for the two canonical variates indicate the similarities of the two estimates. The B_r/K_r ratio for the CCA was 1.35. The same color convention applies to **Figures 4**, **6**. This panel used the same data as Figure 4B in Lee et al. (2015). **(B)** X component of the angular velocity (V_x) of the smooth pursuit wrist movement (*blue line*) and the target (*green line*). **(C)** Frequency analysis of angular velocity. Note that the target motion (*green line*) has little power above 0.5 Hz (*red vertical dotted line*), while the wrist movement (*blue line*) has components below and above 0.5 Hz. Wrist movement was, therefore, separated into two frequency ranges: F1 (0–0.5 Hz) (*top*) and F2 (0.5–3 Hz) (*bottom*). **(D)** Separation of the angular velocity of the smooth pursuit wrist movement into the two frequency domains, F1 and F2 (*blue lines*). The *green line* indicates the motion of the target. Note that the F1 domain of the wrist movement nearly matches the target motion.

paper, we use M_r, B_r, K_r instead of M, B, and K to emphasize that we focus only on their ratios (see Lee et al., 2015 for discussion).

Furthermore, in our previous study (Lee et al., 2015), we demonstrated a negligible contribution of the acceleration term in equation (1). Therefore, we can simplify the wrist joint model of equation (1) to get equation (2) by removing the acceleration term, at least for the present experimental setup, without sacrificing accuracy of analysis.

$$\sum_{i=1}^{4} a_i T_i(t) \approx B_r\dot{\theta}(t) + K_r\theta(t) \qquad (2)$$

Data Analysis

Calculation of B_r/K_r Ratio

In the pursuit task in which the subjects tracked a smooth motion of the target, the joint torque was characterized by the velocity-dependent term and the position-dependent term in Eq. (2). Therefore, we introduce a metric to characterize the contributions of velocity and position as a ratio of the viscous coefficient (B_r) to the elastic (K_r) coefficient: B_r/K_r. To obtain B_r and K_r, we used the equation (2) and CCA as mentioned above, and calculated B_r/K_r *ratio*. See section "Different *B/K* Ratios for the Two Components of the Pursuit Movements" in the results for more detail.

Frequency Analysis of the Wrist Movement

To analyze components of the wrist movement (see section "Two Components of Motor Commands for the Pursuit Movements" and "Different *B/K* Ratios for the Two Components of the Pursuit Movements" in the results for more detail), we performed a frequency analysis (*Fast Fourier Transformation, FFT*) for the velocity of the movement. The wrist movement was decomposed into a low-frequency (≤0.5 Hz) component and a high-frequency

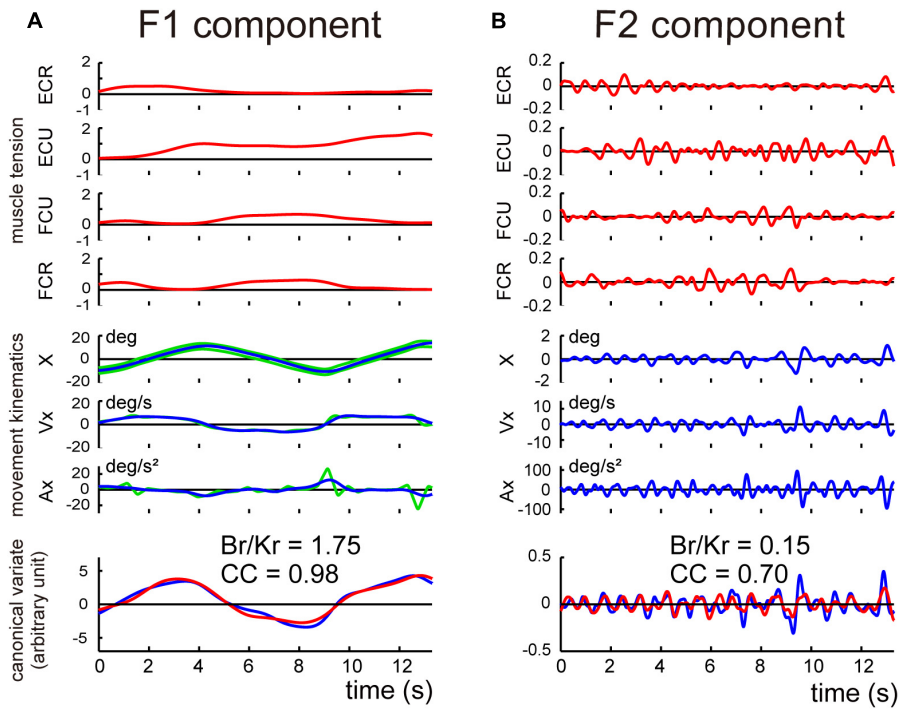

FIGURE 4 | Identification of the relationship between muscle activities and movement kinematics for F1 component **(A)** and F2 component **(B)** of the movement of the control subject shown in **Figure 3A**. The same convention as in **Figure 3A**. The high canonical correlation *CC's* for the two estimated torques in both **(A,B)** indicate the similarities of the two estimates.

(>0.5 Hz) component, referred to as the F1 and F2 components, respectively. The B_r/K_r ratio, defined above, was computed for the F1 and F2 components separately.

Calculation of Delay of the Wrist Movement From the Target Motion

To determine the delay of the wrist movement from the target motion, we searched for the optimal delay that provided the best match between the target motion and the wrist movement. The best match was identified when a delay provided the highest R^2-value for the cross-correlation analysis. See section "Functional Characterization of the F1 Component of the Pursuit Movements" in the results for more detail.

Calculation of Errors in Pursuit of the Target

We evaluated the accuracy of the pursuit movement (i.e., motor error) as a sum of instantaneous difference (i.e., distance in degree) between target position and cursor position of the F1 component throughout the trial. We name it an F1 error.

Statistical Tests

Statistical tests were made using two-sample *t*-test [*t-test2* function in the statistics toolbox of Matlab, Ver. 7.11.0.584 (R2010b), Mathworks, Natick, MA, United States] or Mann–Whitney *U* test [*ranksum* function in the statistics toolbox of Matlab, Ver. 7.11.0.584 (R2010b), Mathworks, Natick, MA, United States].

RESULTS

Identification of the Relationship Between Movement Kinematics and Muscle Activity With CCA

We used CCA to analyze the causality relationship between the muscle activities and the movement kinematics of the wrist joint in 13 control subjects using the wrist joint model (2). With CCA (**Figure 2**), we obtain the two sets of parameters a_1, a_2, a_3, a_4, and B_r, K_r that maximize the CC between the two canonical variates (i.e., *muscle torque* and *kinematic torque*) (**Figure 2** *middle*). **Figure 3A** shows a typical example of the relationships during the task, for a control subject. We obtained a precise match between *muscle torque* {i.e., (B_r, K_r) $[\dot{\theta}(t), \theta(t)]^T$} (**Figure 3A**, red lines in *canonical variate*) and *kinematic torque* {i.e., (B_r, K_r) $[\ddot{\theta}(t), \theta(t)]^T$} (**Figure 3A**, blue lines in *canonical variate*) with high values of canonical correlation (*CCs*) (*CC* = 0.94). For all control subjects, the average *CC* was 0.93 ± 0.01 (range: 0.91–0.95, n = 13) for the pursuit task.

Two Components of Motor Commands for the Pursuit Movements

When we examined the kinematics of the pursuit movement more closely, we noticed that the velocity profile of the wrist (**Figure 3B**, blue line) was largely correlated with the smooth velocity profile of the target (**Figure 3B**, green line), with additional smaller and somewhat vibratory movement of the

wrist. This dual pattern was common for all control subjects. To analyze the components of the wrist movement in more detail, we performed a frequency analysis for the velocity of the movement (**Figure 3C**). The velocity of the pursuit movement was clearly separated into two components: a major component with lower frequency (≤0.5 Hz) and a minor component with higher frequency (>0.5 Hz). The lower frequency component was apparently related to the target motion *per se* (**Figure 3D**, *F1*) [i.e., most of the power for the target motion (green solid line) was left of the red dotted line (0.5 Hz) in **Figure 3C**]. Indeed, the wrist movement in the lower frequency range (F1 domain, 0–0.5 Hz; blue line in **Figure 3D**, *F1*) almost perfectly matched with the target motion (green line in **Figure 3D**, *F1*). In contrast, the higher frequency component (F2 domain, 0.5–3 Hz, blue line in **Figure 3D**, *F2*) corresponded to the vibratory wrist movement, which was not correlated with the target motion (green line in **Figure 3D**).

Different *B/K* Ratios for the Two Components of the Pursuit Movements

Next, we separated the movement kinematics and activity of each of the four muscles into F1 and F2 components (**Figures 4A,B**). We then identified the relationship between the muscle activities and movement kinematics for the F1 and F2 components separately with CCA. **Figures 4A,B** provide examples of the relationship for F1 and F2 of the same trial shown in **Figure 3A**. Movement kinematics and muscle activity were fairly well correlated for F1 and F2, respectively (*CC* for F1 = 0.98, *CC* for F2 = 0.70). Surprisingly, the B_r/K_r ratios were different for the two components. In this example, the muscle activity for the lower frequency range (F1) demonstrated a higher B_r/K_r ratio (1.75), while the muscle activity for the higher frequency range (F2) demonstrated a much lower B_r/K_r ratio (0.15). The clear dissociation of B_r/K_r ratios for F1 and F2 components were common for the other trials and for the other control subjects. As illustrated in **Figure 5A**, muscle activity of the F1 domain (0–0.5 Hz) demonstrated higher B_r/K_r ratios (1.4–2.5, mean ± SD = 1.84 ± 0.28, n = 13) than the pursuit wrist movement as a whole [see Figure 9, in Lee et al. (2015), 0.86–1.91, mean ± SD = 1.30 ± 0.27, n = 10]. Thus, the major muscle activity in the F1 domain encoded both velocity and position of the wrist to reproduce the motion of the target. In contrast, muscle activity of the F2 domain (0.5–3 Hz) demonstrated low B_r/K_r ratios (0.1–1.0, mean ± SD = 0.51 ± 0.32, n = 130) (**Figure 5A**, *F2*), like muscle activity for the step-tracking movement [see Figure 9, in Lee et al. (2015), 0.03–0.28, mean ± SD = 0.17 ± 0.06, n = 10]. In other words, the minor muscle activity of the F2 domain appeared to be concerned with frequent small adjustments of wrist position.

Functional Characterization of the F1 Component of the Pursuit Movements

Muscle activity for the pursuit wrist movement consisted of two components with different B_r/K_r ratios, and the two components appeared to play distinct roles in the pursuit movement. The F1 component appeared to play the primary role to synchronize the movements of the wrist and the motion of the target. To test this hypothesis, we calculated the cross-correlation of the target motion and the F1 component of the wrist movement. As demonstrated by one control subject (**Figure 6A**), the target position led the wrist movement, but the lead time was very short (56 ms). The average lead time was 47.5 ms for 13

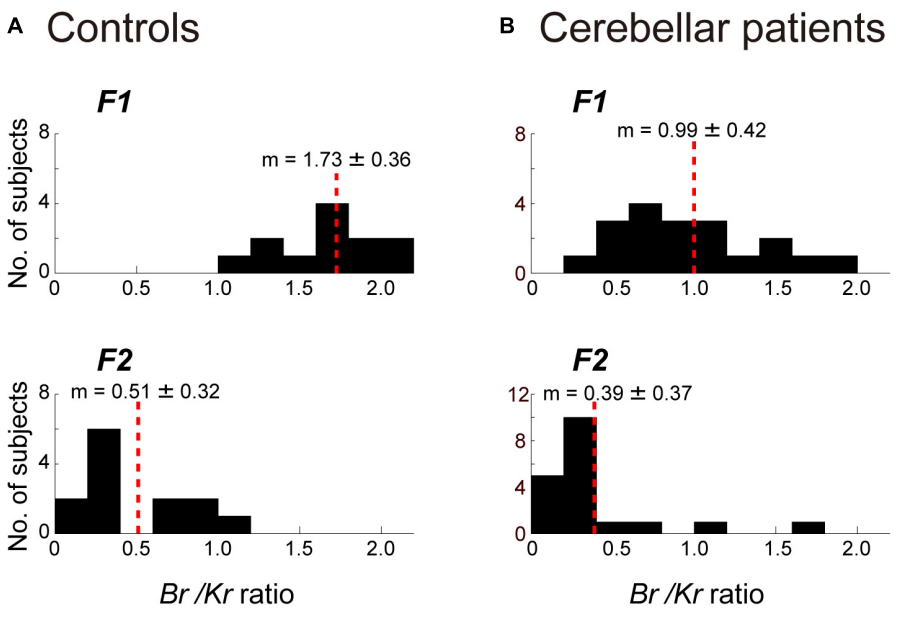

FIGURE 5 | Comparison of the B_r/K_r ratios for the F1 and F2 components between the controls **(A)** and the cerebellar patients **(B)**. **(A)** B_r/K_r ratios of the control subjects for the F1 component (top) and the F2 component (bottom) (n = 13). Note the highly significant difference for the two components. **(B)** B_r/K_r ratios of the patients (**Table 2**, n = 19) for the F1 (top) and the F2 (bottom) components (n = 19). Note the selective decrease of B_r/K_r ratios for the F1 component in the patients.

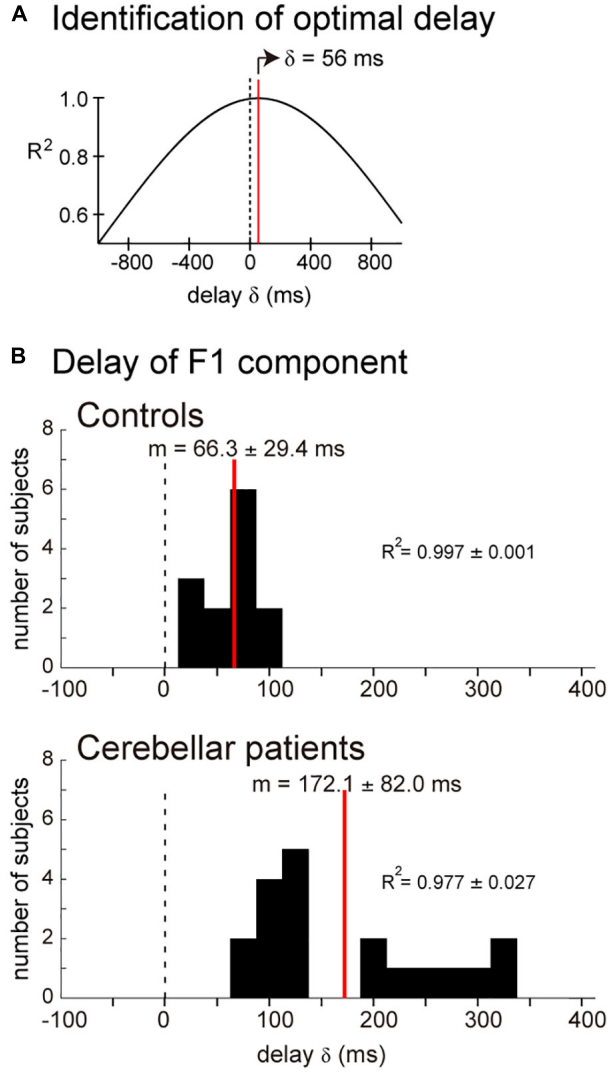

FIGURE 6 | Similarity of the target motion and the F1 domain of the wrist movement. Cross-correlation was calculated by changing delay δ of the target motion relative to the wrist movement. **(A)** Relationship between δ and R^2 for the cross-correlation. The optimal δ (59 ms) was determined as the δ for the highest R_2. **(B)** *Controls*: Histogram of the optimal delay δ for the control subjects (n = 13). *Cerebellar patients*: Histogram of the optimal delay δ for the cerebellar patients (n = 19).

control subjects (mean ± SD = 66.3 ± 29.4 ms, n = 13) (**Figure 6B**, *Controls*). This short lead time means that the F1 component of the wrist movement cannot be generated with a visuomotor feedback control of the target motion, because the conduction time of the peripheral motor nerve (∼10 ms) and electromechanical delay (∼50 ms) alone would take that long. Thus, the delay was too short to be a visuomotor feedback delay. Rather, generation of the motor command in the CNS *must have preceded* the corresponding motion of the target, if we take the average lead time of neuron activity in the motor cortex of the monkey for the wrist movement (∼100 ms) into account (Kakei et al., 1999, 2003).

Decrease in B_r/K_r Ratio of the F1 Component in Cerebellar Patients

Next, we determined the B_r/K_r ratios separately for F1 and F2 components for the cerebellar patients. **Figure 7** demonstrates the relationship between movement kinematics and activity of the four muscles for the whole wrist movement (A) and F1 (B) and F2 (C) components in a cerebellar patient. Movement kinematics and muscle activities demonstrated considerably strong canonical correlation for both F1 and F2 components (*CC* for F1 = 0.98, *CC* for F2 = 0.82). Nevertheless, the dissociation of B_r/K_r ratios for the two components observed in the control subject (**Figure 4**) was significantly different due to the selective decrease in B_r/K_r ratios for the F1 component (**Figure 7B**). The B_r/K_r ratio for F1 (**Figure 7B**) was no more than 0.35 and therefore much lower than that observed in the control subject (**Figure 4A**, B_r/K_r = 1.75), while the B_r/K_r ratio for F2 (**Figure 7C**, B_r/K_r = 0.15) was the same as that of the control subject (**Figure 4B**, B_r/K_r = 0.15).

The marked decrease in B_r/K_r ratios for the F1 component and relative preservation of low B_r/K_r ratios for the F2 component were shared by all cerebellar patients (**Figure 5B**). B_r/K_r ratios of the F1 component for the cerebellar patients (0.3–1.9, mean ± SD = 0.99 ± 0.42) (**Figure 5B**, *F1*) were significantly lower than those of the control subjects (1.4–2.5, mean ± SD = 1.84 ± 0.28) (**Figure 5A**, *F1*) ($p < 0.001$). In contrast, B_r/K_r ratios of the F2 component were comparable for both groups (compare **Figure 5B**, *F2* and **Figure 5A**, *F2*). To summarize, the poor performance of target tracking in the cerebellar patients was attributed to the selective decrease in *Br/Kr* ratios for the F1 component (**Figure 5B**).

It should be noted that the decrease in B_r/K_r ratios is not the only anomaly of the F1 component in the cerebellar patients. When we calculated the delay of the F1 component relative to the target motion for the cerebellar patients (**Figure 6B**, *Cerebellar patients*), we found that the F1 component of the patients was delayed on average by about 100 ms (79.5–322.4 ms, mean ± SD = 172.1 ± 82.0 ms) than that of the controls (15.0–107.4 ms, mean ± SD = 66.3 ± 29.4 ms) ($p < 0.0001$).

Relationship Between B_r/K_r Ratio of the F1 Component and Accuracy of Predictive Control

Next we examined the relationship between B_r/K_r ratios of the F1 component and performance of pursuit movement in the cerebellar patients and the control subjects (**Figure 8**). As shown in **Figures 4**, **6**, **7**, the F1 component of the pursuit movement is closely related to the predictive component of the movement. Therefore, the characteristic decrease in B_r/K_r ratio of the F1 component in the cerebellar patients may be an outcome of deterioration of predictive motor control. To test this hypothesis, we examined the relationship between the B_r/K_r ratio of the F1 component and accuracy of the pursuit movement (i.e., F1 error, see section "Data Analysis"). As shown in **Figure 8A**, B_r/K_r ratio of the F1 component and the F1 error demonstrated a clear negative correlation, although the F1 error showed little decrease for higher B_r/K_r ratio (>1.5). In

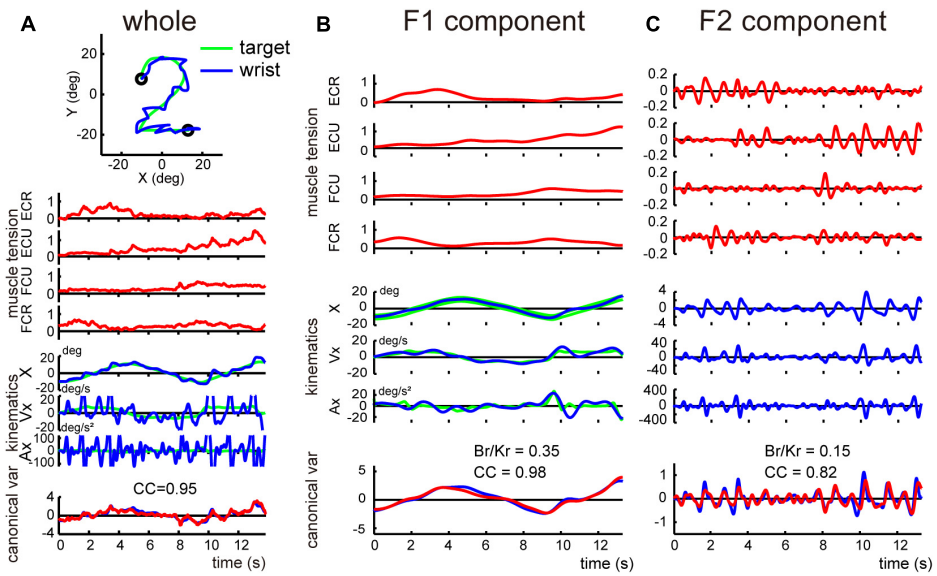

FIGURE 7 | Analysis of the F1 and the F2 components in a cerebellar patient. **(A)** Identification of the relationship between muscle activities and movement kinematics for the *whole* wrist movement. Note a highly ataxic wrist movement shown in the top inset. The same convention as in **Figure 3A**. This panel used the same data as Figure 5B in Lee et al. (2015). **(B,C)** Identification of the relationship between muscle activities and movement kinematics for the F1 component **(B)** and the F2 component **(C)** of the movement shown in **(A)**. The same convention as in **Figure 4**. The high canonical correlation *CC's* for the two estimated torques in both **(B,C)** indicate the similarities of the two estimates.

other words, relative decrease of muscle activity proportional to velocity resulted in poorer accuracy of tracking. However, there remains a possibility that an increase in F1 error (i.e., prediction error) may be compensated by a feedback control and does not affect the overall performance of the pursuit movement. In order to test this possibility, we examined the relationship between the B_r/K_r ratio of the F1 component and the tracking score. The tracking score is defined as a percentage of time when the cursor was kept within the target in a single trial (**Figure 8B**). The B_r/K_r ratio of the F1 component and the tracking score demonstrated a clear positive correlation, although the tracking score showed little increase for higher B_r/K_r ratios (>1.5). Furthermore, the F1 error and the tracking score demonstrated a strikingly linear (negative) correlation (**Figure 8C**). In summary, the F1 error is the primary determinant of the overall accuracy of the pursuit movement and a parameter to measure accuracy of the F1 component alone. Overall, B_r/K_r ratio of the F1 component is a parameter that represent overall accuracy of the pursuit movement.

Finally, we have examined a possibility that the F2 component could be related to an error-correction mechanism. The power (i.e., amount) of F2 component (see **Figure 3C**, F2) and the F1 error demonstrated a clear positive correlation (**Figure 8D**, $R^2 = 0.53$), suggesting that the F2 component is recruited to compensate for increase in F1 error.

DISCUSSION

We demonstrate that the smooth pursuit movement of the wrist joint consists of two components with distinct B_r/K_r ratios in control subjects. The major F1 component with higher B_r/K_r ratio appears to play the primary role to reproduce both velocity and position of the target motion in a *predictive* manner. In contrast, the minor F2 component with lower B_r/K_r ratio encodes mostly position of small step-wise movements. Therefore, the two control modes, predictive control based on the forward-model prediction and corrective control based on sensory feedback, were identified as the F1 and F2 components, respectively. In cerebellar patients, the predictive F1 component demonstrates a selective decrease in the B_r/K_r ratio. Notably, the B_r/K_r ratios of the F1 component has a strong correlation with accuracy of the pursuit movement. In contrast, there was no significant difference between the B_r/K_r ratios of the F2 component for control and patient groups. Taken together, our results support the hypothesis that cerebellar patients have an impairment in the forward-model prediction while maintaining corrective control in response to sensory feedback. In the following sections, we will focus on five points: (1) dissociation of two components of pursuit movement; (2) functional interpretation of the B_r/K_r ratio; (3) the B_r/K_r ratios for F1 and F2 components in patients with cerebellar ataxia and the role of the cerebellum in predictive control; (4) the F1 (*predictive*) component of the pursuit movement and precision of motor control; (5) quantitative evaluation of motor function of patients with cerebellar ataxia based on the B_r/K_r ratio.

Dissociation of Two Components of Pursuit Movement

The basic design of this study owes to Beppu et al. (1987) and Miall et al. (1993a). They have examined a specific

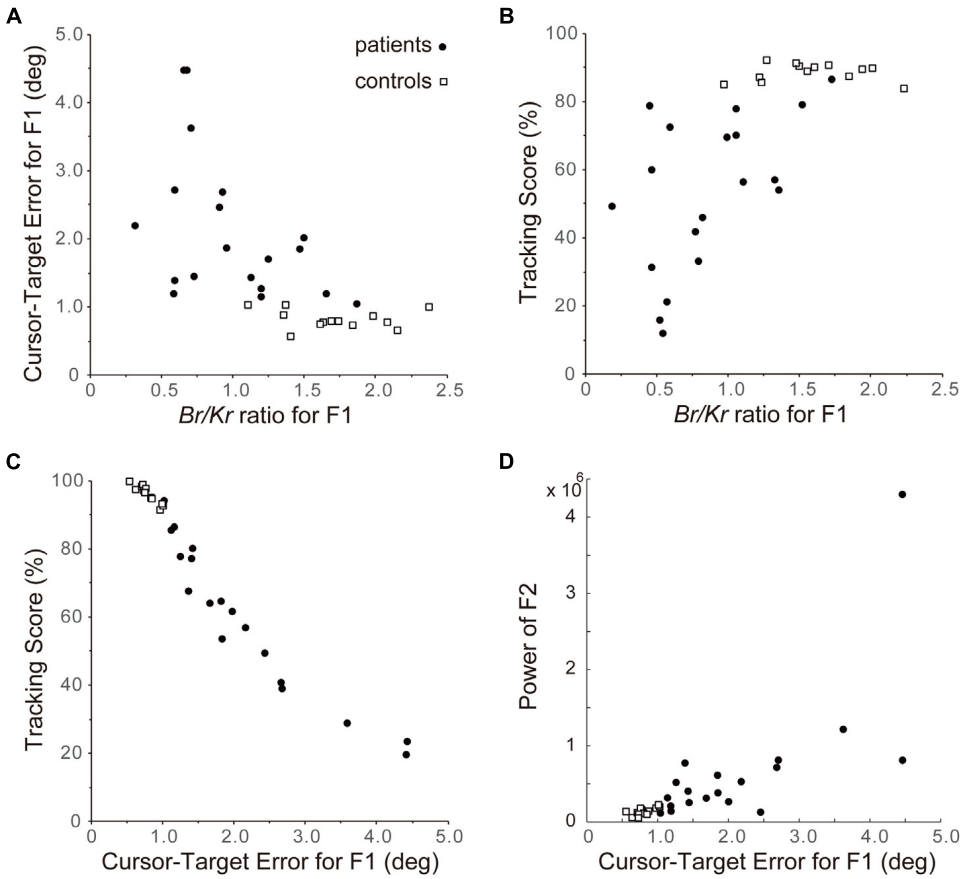

FIGURE 8 | Importance of F1 component of the pursuit movement to determine accuracy of control. **(A)** Relationship between the B_r/K_r ratios for F1 component and Cursor-Target error for F1 (*F1 error*, in short). The Cursor-Target error for F1 (F1 error) is defined as an average error between the target motion and the F1 component of the movement during a trial. Note the negative correlation. **(B)** Relationship between the B_r/K_r ratios for F1 component and Tracking Score. Tracking Score is defined as percentage of time when the cursor is kept within the target during a trial. Note the positive correlation. **(C)** Relationship between Cursor-Target Error for F1 (F1 error) and Tracking Score. Note the linear relationship. Overall, B_r/K_r ratio for F1 component has a strong positive correlation with accuracy of pursuit movement. In other words, poor performance of the cerebellar patients is ascribed to their lower B_r/K_r ratio for F1 component. **(D)** Relationship between Cursor-Target Error for F1 (F1 error) and power of F2 component. Note the positive correlation.

type of tracking movement in which a visual target moves slowly and smoothly in a predictive manner. They recognized two components of movement during the smooth-tracking movement. The primary component is in lower frequency and the secondary component is in higher frequency and intermittent. They concluded that the lower frequency component reproduces the smooth target motion and the higher frequency/intermittent component represents feedback control. We reasoned that the outputs from the two controllers could be separated with a Fourier transformation due to the differences in the frequency ranges of the two components. In the present study, we established a new method to separate the outputs from the two controllers and to evaluate the accuracy of the predictive controller (**Figures 3**, **4**). We further applied the method to evaluate the predictive controllers in patients with cerebellar ataxia (**Figures 7**, **8**). Our novel finding was that the F1 component was predictive of the target motion and was selectively impaired in the cerebellar patients (**Figures 5B**, **6B**).

Functional Interpretation of the B_r/K_r Ratio

In our previous study (Lee et al., 2015), we established a simple linear model for the wrist joint to analyze the causal relationship between muscle activities and movement kinematics. With this model, we compared the characteristics of muscle activities for two movement tasks, a step-tracking task and a smooth pursuit task. In control subjects, the CNS adjusted two components of motor command (i.e., muscle activities) to meet the requirements of the tasks. For example, for the step-tracking task to stationary targets without any reference velocity, patterns of the muscle activities were correlated primarily with the position, with very low correlation with velocity (low B_r/K_r ratio). In contrast, for the smooth pursuit task in which the target moves with known velocity and position, the muscle activities were correlated comparably with the velocity and position of the target motion (higher B_r/K_r ratio). In contrast, the ability of cerebellar patients to select a proper B_r/K_r ratio depending on the task requirement was markedly deteriorated (Lee et al., 2015). Overall, B_r/K_r ratio

provides a novel parameter to characterize the motor function of cerebellar patients.

When we analyzed the smooth pursuit movement in the previous study, we treated the movement of all frequencies as a whole, based on an assumption that there is a single controller operating at all frequencies. In the present study, however, we *reanalyzed* the same data to find that it actually contained *two* distinct components in different frequency ranges, i.e., F1 and F2 (**Figures 3C,D**). Therefore, we further employed the same method to evaluate each component separately, with the B_r/K_r ratio. The major F1 component belonged to the same lower frequency range as the target motion (**Figure 3C**, <0.5 Hz, F1 component) and encoded both velocity and position (i.e., higher B_r/K_r ratio) of the smooth target motion (**Figure 4A**). This composition of the F1 component appeared suitable to synchronize the wrist movement with the target motion in a *predictive* manner (**Figure 6**). In contrast, the minor F2 component belonged to a higher frequency range (**Figure 3C**, 0.5 Hz<, F2 component) and mostly encoded position (i.e., low B_r/K_r ratio) of small step-wise movements (**Figure 4B**). So far, we do not fully understand the functional roles of the F2 component. Nevertheless, the low B_r/K_r ratio of the F2 component suggests that the F2 component may provide small and intermittent positional corrections (i.e., feedback) during the pursuit movement. Indeed, the F2 component appeared to provide quick corrective (i.e., feedback) mechanism (Beppu et al., 1987; Miall et al., 1993a) and is recruited more when the precision of the F1 component is deteriorated (**Figure 8D**). In other words, the F1 and the F2 components appear to function cooperatively. We will focus on the nature of the F2 component and its cooperation with the F1 component in a separate paper. Overall, the B_r/K_r ratio again provides a unique tool to characterize functional significance of motor commands for goal directed movements.

The B_r/K_r Ratios for F1 and F2 Components in Patients With Cerebellar Ataxia and the Role of the Cerebellum in Predictive Control

In contrast to the distinct B_r/K_r ratios for F1 and F2 components in control subjects mentioned above, the component-specific differences in the B_r/K_r ratio were much smaller in the cerebellar patients (**Figure 5B**). Indeed, the patients relied on position-dominant control even for the predictive F1 component (**Figures 5B**, **7B**). In other words, they were not able to recruit the velocity-dominant control. These findings suggest that the cerebellum makes an important contribution to the predictive control of the pursuit movement, which is impaired in cerebellar ataxia. Our observations also explain why movements in cerebellar ataxia are characterized by a lack of smoothness. In contrast to control subjects, who achieve smooth movement with continuous velocity control (**Figure 3A**, *top inset*), cerebellar patients must rely on position-dominant step-wise movements (**Figure 7A**, *top inset*), which are probably manageable only with position control. The step-wise position-dominant movement appears to be a *default* mode of motor control that utilized by patients with cerebellar ataxia as a compensation method. Indeed, the low B_r/K_r ratio for the F2 component in cerebellar patients was similar to that in control subjects (**Figure 5B**, *F2*). On the other hand, velocity control is continuous and predictive in nature. Therefore, the impaired velocity control and decrease in tracking accuracy (**Figure 8C**) in these patients may suggest a deficit in prediction in cerebellar ataxia. It should be noted that the poor precision is not the only problem with the predictive control of the cerebellar patients. The prediction is delayed significantly more (∼100 ms) than in controls (**Figure 6B**). The delay itself may be simply explained as poor recruitment of output from the cerebellar nuclei due to decrease in *disinhibition* of output neurons (Ishikawa et al., 2014, 2015, 2016). The prediction that is delayed by this amount is no longer a prediction and may force the patients to depend on the *pure* feedback control *further destabilizing* the wrist movement ataxic as typically seen in **Figure 7A**.

The Predictive (F1) Component of the Pursuit Movement and Precision of Motor Control

The B_r/K_r ratio reflects the composition of the motor command from the controller in the CNS. Considering the redundancy between muscle activities and movement kinematics, it is possible that different patterns of muscle activities could generate exactly the same movement kinematics. In other words, it is possible, at least theoretically, that accurate pursuit movement observed in the control subjects (**Figure 3A**, *top inset*) could be generated with muscle activities with even lower B_r/K_r ratios compared to those observed in cerebellar patients. Nevertheless, the B_r/K_r ratio of the F1 (*predictive*) component demonstrated a strong negative correlation with the error of the predictive movement (**Figure 8A**) and a strong positive correlation with the accuracy of the overall pursuit movement (**Figure 8B**). Therefore, the B_r/K_r ratio of the predictive (F1) component provides a unique parameter that represents accuracy of the predictive control for the pursuit movement in patients with ataxia.

Quantitative Evaluations of the Motor Functions of Patients With Cerebellar Ataxia Based on the B_r/K_r Ratio

Precise evaluations of motor functions of patients with neurological disorders are essential for both monitoring the progress of disease and evaluation of effects of treatment. Although several groups have tried to perform quantitative evaluations of cerebellar ataxia with arm movements (Nakanishi et al., 1992; Sanguineti et al., 2003; Menegoni et al., 2009), their evaluations are mostly limited to movement kinematics. The authors have reported some features of movement kinematics, such as more curved and irregular hand paths, with a more asymmetric speed profile, in ataxic patients. However, movement kinematics cannot tell much about causal muscle activities or motor commands due to the redundancy of the musculoskeletal system. In other words, muscle activities provide

more information than movement kinematics. Therefore, it is desirable to find anomalies of the motor commands directly (Diener and Dichgans, 1992; Manto, 1996) rather than the resultant movement anomalies. In this study, we evaluated the motor functions of patients with cerebellar ataxia based on the level of muscle activities (i.e., EMG signals). In particular, the decreased B_r/K_r ratio for the F1 component strongly reflected the pathophysiological changes in these patients (**Figures 5B**, **6B**, **8**). We will test this hypothesis by monitoring the B_r/K_r ratios for the F1 component of the pursuit task in ataxic patients for a long period.

CONCLUSION

In conclusion, the B_r/K_r ratio of the F1 component provides a unique parameter to characterize the accuracy in terms of predictive control of voluntary goal-directed motion. This method can be applied in the numerous forms of cerebellar ataxias encountered in daily practice.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the ethics committees of the Tokyo Metropolitan Institute of Medical Science, Tokyo Metropolitan Neurological Hospital, and Tokyo Medical University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committees of the Tokyo Metropolitan Institute of Medical Science, Tokyo Metropolitan Neurological Hospital, and Tokyo Medical University.

AUTHOR CONTRIBUTIONS

SK and JL conceived and designed the experiments. JL, SK, and HM conducted the experiments. JL, SK, HM, and HT analyzed the data. SK, JL, HM, HT, MM, and CH wrote the manuscript.

FUNDING

This research was supported by the Tokyo Metropolitan Institute of Medical Science and grants-in-aid from the Japan Science and Technology Agency (A-STEP) to SK (http://www.jst.go.jp/) and from the Ministry of Education, Culture, Sports, Science and Technology in Japan (http://www.mext.go.jp/) (Jp26120003, Jp14580784, Jp15016008, Jp16015212, Jp20033029, and Jp21500319) to SK and (Nos. 21700229 and 24650304) to Jl. This research was also supported by the AMED under the Grant Number 16ek0109048h0003 to SK. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

We thank Dr. Yasuo Ohashi (Statcom Co., Ltd.) for his invaluable advice on the use of CCA and discussions on the data analysis. We also thank Drs. Donna S. Hoffman and Koji Ito for their invaluable comments and discussions.

REFERENCES

Bastian, A. J. (2006). Learning to predict the future: the cerebellum adapts feedforward movement control. *Curr. Opin. Neurobiol.* 16, 645–649. doi: 10.1016/j.conb.2006.08.016

Beppu, H., Nagaoka, M., and Tanaka, R. (1987). Analysis of cerebellar motor disorders by visually-guided elbow tracking movement. 2. Contribution of the visual cues on slow ramp pursuit. *Brain* 110, 1–18. doi: 10.1093/brain/110.1.1

Blakemore, S. J., Frith, C. D., and Wolpert, D. M. (2001). The cerebellum is involved in predicting the sensory consequences of action. *Neuroreport* 12, 1879–1884. doi: 10.1097/00001756-200107030-00023

Crevecoeur, F., and Kurtzer, I. (2018). Long-latency reflexes for inter-effector coordination reflect a continuous state feedback controller. *J. Neurophysiol.* 120, 2466–2483. doi: 10.1152/jn.00205.2018

Crevecoeur, F., Munoz, D. P., and Scott, S. H. (2016). Dynamic multisensory integration: somatosensory speed trumps visual accuracy during feedback control. *J. Neurosci.* 36, 8598–8611. doi: 10.1523/JNEUROSCI.0184-16.2016

Davidson, P. R., and Wolpert, D. M. (2005). Widespread access to predictive models in the motor system: a short review. *J. Neur. Eng.* 2:S313.

Desmurget, M., and Grafton, S. (2000). Forward modeling allows feedback control for fast reaching movements. *Trends Cogn. Sci.* 4, 423–431. doi: 10.1016/s1364-6613(00)01537-0

Diener, H. C., and Dichgans, J. (1992). Pathophysiology of cerebellar ataxia. *Mov. Disord.* 7, 95–109. doi: 10.1002/mds.870070202

Ebner, T. J., and Pasalar, S. (2008). Cerebellum predicts the future motor state. *Cerebellum* 7, 583–588. doi: 10.1007/s12311-008-0059-3

Franklin, D. W., Franklin, S., and Wolpert, D. M. (2014). Fractionation of the visuomotor feedback response to directions of movement and perturbation. *J. Neurophysiol.* 112, 2218–2233. doi: 10.1152/jn.00377.2013

Franklin, S., Wolpert, D. M., and Franklin, D. W. (2017). Rapid visuomotor feedback gains are tuned to the task dynamics. *J. Neurophysiol.* 118, 2711–2726. doi: 10.1152/jn.00748.2016

Härdle, W. K., and Simar, L. (2003). "Canonical correlation analysis," in *Applied Multivariate Statistical Analysis* (New York, NY: Springer), 321–330.

Hoffman, D. S., and Strick, P. L. (1999). Step-tracking movements of the wrist. IV. Muscle activity associated with movements in different directions. *J. Neurophysiol.* 81, 319–333. doi: 10.1152/jn.1999.81.1.319

Ishikawa, T., Kakei, S., and Mitoma, H. (2015). Overlooked Holmes' clinical signs: reevaluation by recent physiological findings. *Cerebellum Ataxias* 2:13. doi: 10.1186/s40673-015-0033-z

Ishikawa, T., Tomatsu, S., Izawa, J., and Kakei, S. (2016). The cerebro-cerebellum: could it be loci of forward models? *Neurosci. Res.* 104, 72–79. doi: 10.1016/j.neures.2015.12.003

Ishikawa, T., Tomatsu, S., Tsunoda, Y., Lee, J., Hoffman, D. S., and Kakei, S. (2014). Releasing dentate nucleus cells from purkinje cell inhibition generates output from the cerebrocerebellum. *PLoS One* 9:e108774. doi: 10.1371/journal.pone.0108774

Kakei, S., Hoffman, D. S., and Strick, P. L. (1999). Muscle and movement representations in the primary motor cortex. *Science* 285, 2136–2139. doi: 10.1126/science.285.5436.2136

Kakei, S., Hoffman, D. S., and Strick, P. L. (2003). Sensorimotor transformations in cortical motor areas. *Neurosci. Res.* 46, 1–10. doi: 10.1016/s0168-0102(03)00031-2

Kawato, M. (1999). Internal models for motor control and trajectory planning. *Curr. Opin. Neurobiol.* 9, 718–727. doi: 10.1016/s0959-4388(99)00028-8

Kawato, M., Kuroda, T., Imamizu, H., Nakano, E., Miyauchi, S., Yoshioka, T., et al. (2003). Internal forward models in the cerebellum: fMRI study on grip force and load force coupling. *Prog. Brain Res.* 142, 171–188. doi: 10.1016/s0079-6123(03)42013-x

Koike, Y., and Kawato, M. (1995). Estimation of dynamic joint torques and trajectory formation from surface electromyography signals using a neural network model. *Biol. Cybern.* 73, 291–300. doi: 10.1007/s004220050185

Lacquaniti, F., Licata, F., and Soechting, J. F. (1982). The mechanical behavior of the human forearm in response to transient perturbations. *Biol. Cybern.* 1982, 35–46. doi: 10.1007/bf00353954

Lee, J., Kagamihara, Y., and Kakei, S. (2008). Quantitative evaluation of movement disorders in neurological diseases based on EMG signals. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2008, 181–184. doi: 10.1109/IEMBS.2008.4649120

Lee, J., Kagamihara, Y., and Kakei, S. (2013). Quantitative evaluation of cerebellar ataxia based on pathological patterns of the muscle activities. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2013, 902–905. doi: 10.1109/EMBC.2013.6609647

Lee, J., Kagamihara, Y., and Kakei, S. (2015). A new method for functional evaluation of motor commands in patients with cerebellar ataxia. *PLoS One* 10:e0132983. doi: 10.1371/journal.pone.0132983

Lee, J., Kagamihara, Y., Tomatsu, S., and Kakei, S. (2012). The functional role of the cerebellum in visually guided tracking movement. *Cerebellum* 11, 426–433. doi: 10.1007/s12311-012-0370-x

Lesage, E., Morgan, B. E., Olson, A. C., Meyer, A. S., and Miall, R. C. (2012). Cerebellar rTMS disrupts predictive language processing. *Curr. Biol.* 2012, R794–R795.

Mannard, A., and Stein, R. B. (1973). Determination of the frequency response of isometric soleus muscle in the cat using random nerve stimulation. *J. Physiol.* 229, 275–296. doi: 10.1113/jphysiol.1973.sp010138

Manto, M. (1996). Pathophysiology of cerebellar dysmetria: the imbalance between the agonist and the antagonist electromyographic activities. *Eur. Neurol.* 36, 333–337. doi: 10.1159/000117289

Menegoni, F., Milano, E., Trotti, C., Galli, M., Bigoni, M., and Baudo, S. (2009). Quantitative evaluation of functional limitation of upper limb movements in subjects affected by ataxia. *Eur. J. Neurol.* 16, 232–239. doi: 10.1111/j.1468-1331.2008.02396.x

Miall, R. C., Christensen, L. O., Cain, O., and Stanley, J. (2007). Disruption of state estimation in the human lateral cerebellum. *PLoS Biol.* 5:e316. doi: 10.1371/journal.pbio.0050316

Miall, R. C., Weir, D. J., and Stein, J. F. (1993a). Intermittency in human manual tracking tasks. *J. Mot. Behav.* 25, 53–63. doi: 10.1080/00222895.1993.9941639

Miall, R. C., Weir, D. J., Wolpert, D. M., and Stein, J. F. (1993b). Is the cerebellum a smith predictor? *J. Mot. Behav.* 25, 203–216. doi: 10.1080/00222895.1993.9942050

Miall, R. C., and Wolpert, D. M. (1996). Forward models for physiological motor control. *Neural Netw.* 9, 1265–1279. doi: 10.1016/s0893-6080(96)00035-4

Mitoma, H., Adhikari, K., Aeschlimann, D., Chattopadhyay, P., Hadjivassiliou, M., Hampe, C. S., et al. (2016). Consensus paper: neuroimmune mechanisms of cerebellar ataxias. *Cerebellum* 15, 213–232. doi: 10.1007/s12311-015-0664-x

Nakanishi, R., Yamanaga, H., Okumura, C., Murayama, N., and Ideta, T. (1992). A quantitative analysis of ataxia in the upper limbs. *Rinsho Shinkeigaku* 32, 251–258.

Nowak, D. A., Topka, H., Timmann, D., Boecker, H., and Hermsdörfer, J. (2007). The role of the cerebellum for predictive control of grasping. *Cerebellum* 6, 7–17. doi: 10.1080/14734220600776379

Pasalar, S., Roitman, A. V., Durfee, W. K., and Ebner, T. J. (2006). Force field effects on cerebellar purkinje cell discharge with implications for internal models. *Nat. Neurosci.* 9, 1404–1411. doi: 10.1038/nn1783

Popa, L. S., and Ebner, T. J. (2019). Cerebellum, predictions and errors. *Front. Cell Neurosci.* 12:524. doi: 10.3389/fncel.2018.00524

Pruszynski, J. A., Kurtzer, I., Nashed, J. Y., Omrani, M., Brouwer, B., and Scott, S. H. (2011). Primary motor cortex underlies multi-joint integration for fast feedback control. *Nature* 478, 387–390. doi: 10.1038/nature10436

Pruszynski, J. A., Omrani, M., and Scott, S. H. (2014). Goal-dependent modulation of fast feedback responses in primary motor cortex. *J. Neurosci.* 34, 4608–4617. doi: 10.1523/JNEUROSCI.4520-13.2014

Sanguineti, V., Morasso, P. G., Baratto, L., Brichetto, G., Luigi Mancardi, G., and Solaro, C. (2003). Cerebellar ataxia: quantitative assessment and cybernetic interpretation. *Hum. Mov. Sci.* 22, 189–205. doi: 10.1016/s0167-9457(02)00159-8

Schlerf, J., Ivry, R. B., and Diedrichsen, J. (2012). Encoding of sensory prediction errors in the human cerebellum. *J. Neurosci.* 32, 4913–4922. doi: 10.1523/JNEUROSCI.4504-11.2012

Scott, S. H., Cluff, T., Lowrey, C. R., and Takei, T. (2015). Feedback control during voluntary motor actions. *Curr. Opin. Neurobiol.* 33, 85–94. doi: 10.1016/j.conb.2015.03.006

Shadmehr, R., and Krakauer, J. W. (2008). A computational neuroanatomy for motor control. *Exp. Brain Res.* 185, 359–381. doi: 10.1007/s00221-008-1280-5

Shadmehr, R., Smith, M. A., and Krakauer, J. W. (2010). Error correction, sensory prediction, and adaptation in motor control. *Ann. Rev. Neurosci.* 33, 89–108. doi: 10.1146/annurev-neuro-060909-153135

Shin, D., Kim, J., and Koike, Y. (2009). A myokinetic arm model for estimating joint torque and stiffness from EMG signals during maintained posture. *J. Neurophysiol.* 101, 387–401. doi: 10.1152/jn.00584.2007

Soechting, J. F., and Lacquaniti, F. (1988). Quantitative evaluation of the electromyographic responses to multidirectional load perturbations of the human arm. *J. Neurophysiol.* 59, 1296–1313. doi: 10.1152/jn.1988.59.4.1296

Standenmann, D., Roeleveld, K., Stegeman, D. F., and van Dieën, J. H. (2010). Methodological aspects of SEMG recordings for force estimation – a tutorial and review. *J. Electromyogr. Kinesiol.* 20, 375–387. doi: 10.1016/j.jelekin.2009.08.005

Synofzik, M., Lindner, A., and Thier, P. (2008). The cerebellum updates predictions about the visual consequences of one's behavior. *Curr. Biol.* 18, 814–818. doi: 10.1016/j.cub.2008.04.071

Tanaka, H., Ishikawa, T., and Kakei, S. (2019). Neural evidence of the cerebellum as a state predictor. *Cerebellum* doi: 10.1007/s12311-018-0996-4 [Epub ahead of print].

Todorov, E., and Jordan, M. I. (2002). Optimal feedback control as a theory of motor coordination. *Nat. Neurosci.* 5, 1226–1235. doi: 10.1038/nn963

Tseng, Y. W., Diedrichsen, J., Krakauer, J. W., Shadmehr, R., and Bastian, A. J. (2007). Sensory prediction errors drive cerebellum-dependent adaptation of reaching. *J. Neurophysiol.* 98, 54–62. doi: 10.1152/jn.00266.2007

Wolpert, D. M., Ghahramani, Z., and Jordan, M. I. (1995). An internal model for sensorimotor integration. *Science* 269, 1880–1882. doi: 10.1126/science.7569931

Wolpert, D. M., Miall, R. C., and Kawato, M. (1998). Internal models in the cerebellum. *Trends Cogn. Sci.* 2, 338–347. doi: 10.1016/s1364-6613(98)01221-2

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cellular Neuroscience

REVIEW
published: 09 October 2019
doi: 10.3389/fncel.2019.00439

The Implementation of Predictions During Sequencing

M. Molinari and M. Masciullo*

IRCCS Fondazione Santa Lucia, Rome, Italy

Optimal control mechanisms require prediction capabilities. If one cannot predict the consequences of a motor act or behavior, one will continually collide with walls or become a social pariah. "Looking into the future" is thus one of the most important prerequisites for smooth movements and social interactions. To achieve this goal, the brain must constantly predict future events. This principle applies to all domains of information processing, including motor and cognitive control, as well as the development of decision-making skills, theory of mind, and virtually all cognitive processes. Sequencing is suggested to support the predictive capacity of the brain. To recognize that events are related, the brain must discover links among them in the spatiotemporal domain. To achieve this, the brain must often hold one event in working memory and compare it to a second one, and the characteristics of the two must be compared and correctly placed in space and time. Among the different brain structures involved in sequencing, the cerebellum has been proposed to have a central function. We have suggested that the operational mode of the cerebellum is based on "sequence detection" and that this process is crucial for prediction. Patterns of temporally or spatially structured events are conveyed to the cerebellum via the pontine nuclei and compared with actual ones conveyed through the climbing fibers olivary inputs. Through this interaction, data on previously encountered sequences can be obtained and used to generate internal models from which predictions can be made. This mechanism would allow the cerebellum not only to recognize sequences but also to detect sequence violations. Cerebellar pattern detection and prediction would thus be a means to allow feedforward control based on anticipation. We will argue that cerebellar sequencing allows implementation of prediction by setting the correct excitatory levels in defined brain areas to implement the adaptive response for a given pattern of stimuli that embeds sufficient information to be recognized as a previously encountered template. Here, we will discuss results from human and animal studies and correlate them with the present understanding of cerebellar function in cognition and behavior.

Keywords: sequencing, prediction error, forward internal model, cognition, emotions

OPEN ACCESS

Edited by:
Lisa Mapelli,
University of Pavia, Italy

Reviewed by:
Timothy J. Ebner,
University of Minnesota Twin Cities, United States
Egidio D'Angelo,
University of Pavia, Italy

****Correspondence:***
M. Molinari
m.molinari@hsantalucia.it

Specialty section:
This article was submitted to Cellular Neurophysiology, a section of the journal Frontiers in Cellular Neuroscience

Received: *08 February 2019*
Accepted: *17 September 2019*
Published: *09 October 2019*

Citation:
Molinari M and Masciullo M (2019) The Implementation of Predictions During Sequencing. Front. Cell. Neurosci. 13:439. doi: 10.3389/fncel.2019.00439

INTRODUCTION

Literature data have shown that the brain is constantly making predictions about future events. Several theories of prediction in perception, action and learning suggest that the brain serves to reduce the discrepancies between expectation and actual experience, i.e., by reducing the prediction error (Brown and Brüne, 2012).

Predictive ability may indeed map well to Prefrontal cortex (PFC) in addition to primary sensory areas, with significant portions of PFC specialized for reporting error as a deviation from predicted events (Alexander and Brown, 2018).

The idea that also the cerebellum is involved in predicting the effects of motor commands is well accepted in the neuroscience community (Bastian and Thach, 2002; Popa et al., 2012; D'Angelo and Casali, 2013; Pisotta and Molinari, 2014). The role of the cerebellum in cognition and emotion remains more heavily debated (Koziol et al., 2014), although it is almost generally accepted that the cerebellar structures are involved in cognition.

In the framework of cerebellar cognition, different studies, research groups and cerebellar clinical centers have provided sample data demonstrating cerebellar output to the cerebral cortex as the cornerstone for understanding basic cerebellar functioning (Molinari et al., 2005; Timmann et al., 2010).

Integration of cognitive and motor cerebellar functions forced a reconsideration of the basic operational mode of the cerebellum, and among the theories on cerebellar functioning (for a recent review on cerebellar theories see D'Angelo and Casali, 2013), sequencing has been considered suitable for describing cerebellar cognitive processing (Molinari et al., 2005).

In this context, sequence processing was suggested as the basic functional mechanism of the motor (Braitenberg et al., 1997) and cognitive (Molinari et al., 1997, 2009; Molinari, 2016) functions.

Sequencing has been defined as "the ability to perceive, represent and execute a set of actions (events) that follow a particular order" (Savalia et al., 2016). This is a sovramodal function present in virtually all human activities and even in many processes at neuronal level. According to this definition, sequencing can be recognized in the cellular capacity to detect a spike sequence as well as in recognizing a given firing in a neuronal network.

Eye Blink Classical conditioning can be considered the simplest unitary component of sequence planning and it represents one of the more productive area of cerebellar research; moreover, literature data from different groups provided evidence of sequence processing mechanisms at circuitry and cellular level (Bracha et al., 2009; Swain et al., 2011).

In this ability, the cerebellum with its peculiar anatomical organization is well equipped for paying a central role. As proposed by Braitenberg et al. (1997), cerebellar capacity to tag time and space characteristics of inputs is embedded in the cortico-nuclear microcomplex structure (D'Angelo and Casali, 2013). Signals traveling through the parallel fibers possess precise spatio-temporal features. These in turn determine the specificity of the cerebellar nuclei output. "What the beam passes on to the cerebellar nuclei is a sequence of signals produced by selected Purkinje cells at times specified by the moving wave of excitation." Particularly in the sensory domain, different experimental models were instrumental in depicting theories on cellular mechanisms for prediction of sensory events (Mauk and Ohyama, 2004; D'Angelo and Casali, 2013; Yamazaki and Lennon, 2019).

The hypothesis that sequence detection might represent the main contribution of cerebellar physiology to brain functioning is presented and discussed here.

CORTICO-CEREBELLAR CROSSTALK

The history of research into the connections between the cerebellum and the cerebral cortex is quite long, and many aspects still await clarification. Cerebellar terminals in the thalamus were described in non-human primates in the early 1980s (Asanuma et al., 1983) and corresponding areas were revealed in humans more than a decade later (Macchi and Jones, 1997). A clear step forward in experimental tract-tracing studies derived from the use of transneuronal transport of viruses. Experiments in primates indicated that the motor, premotor, prefrontal and parietal cortices receive cerebellar information via the thalamus (Strick et al., 2009). Functional connectivity magnetic resonance imaging studies confirmed widespread cortico-cerebellar interconnections well beyond motor areas (Allen et al., 2005; Palesi et al., 2017).

The cortico-cerebello-cortical loop is believed to be organized in parallel segregated modules (Ramnani, 2006). If this is true, then cerebello-cortical functional interactions can be quite specific and can be dynamically organized in continuously changing patterns allowing specific crosstalk between the cerebellum and cortex to meet the ever-changing requests needed to optimize brain activity.

Despite the well-advanced characterization of cerebro-cerebellar organization, its function remains poorly understood. Neurophysiological techniques, in healthy subjects and in patients, have been instrumental in clarifying interactions between the cerebral cortex and cerebellum (Tesche and Karhu, 1997, 2000; Ivry, 2000; Nixon, 2003; Molinari et al., 2005).

Thus, the quest to identify the cerebellar processes underlying the modulation of cortical activity is well under way. One of the main intriguing aspects, as noted by many since early times, is the apparent contradiction that cerebellar circuits organized in a uniform structure but involved in many different functions. Different theories have been put forward to identify the basic operational mode of the cerebellum and thus decode its influence on so many functional domains. Error detection (Marr, 1969; Albus, 1971; Ito, 1990), timing (Ivry and Keele, 1989), sensory processing (Bower and Parsons, 2003), and sequence detection (Braitenberg et al., 1997) are among the most widely accepted theories. In particular, the sequence detection hypothesis is advanced to highlight the peculiar role of the cerebellum in the functional organization of the predictive brain network. On the other hand, the same hypothesis has been proposed as the basic operation mode of the cerebellum in all the multifarious domains reported to be affected in patients with cerebellar damage. In summary, the sequence detection theory postulates that the cerebellum is capable of detecting and memorizing patterns, constructing internal models of the perceived patterns.

If an activity pattern resembles a memorized pattern, then precise expectations linked to the identified internal model are activated. The correctness of the prediction is estimated by confronting bottom-up incoming information with top-down expectations. If the prediction holds, the specific brain areas previously successfully used to respond to that stimulation pattern are selectively activated, thus allowing a more efficient

response. Conversely, violation of expectancy will induce general brain activation and thus a less efficient response (see **Figure 1**).

A study involving a large population with focal or degenerative cerebellar pathologies reported sequencing to be the most affected cognitive domain (Tedesco et al., 2011).

Interestingly, sequencing has been shown to be relevant for understanding the cerebellar role in pathophysiological mechanisms in different conditions, such as schizophrenia (Shergill et al., 2014) and autism (Larson and Mostofsky, 2008), in which impairments in patterns of information processing and disruptions in error signal prediction have been proposed.

CEREBELLUM AND ITS ROLE IN PREDICTING PERCEPTION

To achieve mind-world synchronization, our perceptual systems must constantly tune themselves to an ever-changing environment.

"Looking into the future" is one of the most significant concepts in neuroscience (Bubic et al., 2010). As recently argued by Pisotta and Molinari (2016), the brain is constantly required to predict future events. This process is critical for many aspects of information, such as perception, motor and cognitive control, decision-making, and theory of mind, to name just a few.

One of the main abilities allowing the brain to adapt to a changing environment is the capacity to correct errors. Within this framework, looking into the future represents the best way to avoid errors. Among the areas constituting the "predictive brain," the cerebellum and its ability to generate internal models are hypothesized to play a central role.

As elegantly stated by Ebner, 2013 (Cerebellum and Internal Models, Handbook of the Cerebellum and Cerebellar Disorders, 2013), "There are two general classes of internal models. Forward models use the commands for an action and information about the present state to predict the consequences of that action. Inverse models transform a desired outcome or effector state into the necessary commands to achieve that state."

We recently synthetized Ebner's theory, depicting two conditions: "(1) the cerebellum provides the motor system with the correct sensory information that is needed to adjust movements in real time, or (2) the cerebellum identifies sensorimotor patterns that fit into known motor sequences and thus can prepare the cortex for the next step. The first hypothesis postulates that cerebellar activity is related to ongoing motor or sensory information. In the second, cerebellar activity is related

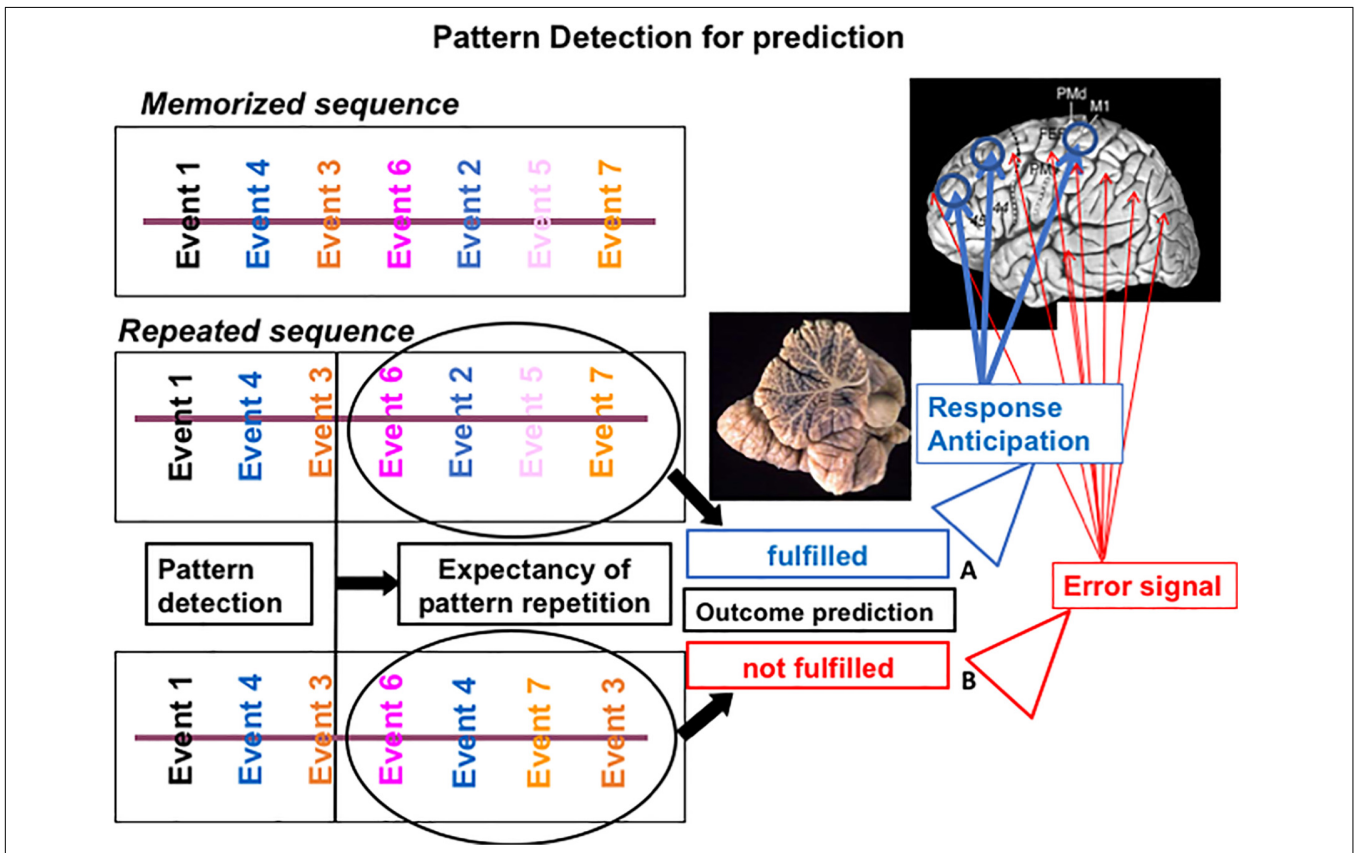

FIGURE 1 | Putative mechanism of cerebellar sequencing for prediction incoming events are continuously monitored in the cerebellar circuits. Relations between events are compared in the cerebellar circuits (Ito, 2006) and stored in a working memory area. When the sequences of new incoming events occur, they are compared with previously stored event ones. If a match is recognized **(A)**, then an expectancy of repetition is generated and the feedforward control can function efficiently. If prediction fails **(B)**, then an error signal is activated by the cerebellar output system, and feedforward control is interrupted or corrected.

more to the expectancy of future events than with the registration of ongoing activities" (Molinari et al., 2009).

Ebner and Pasalar, 2008 argued that "the spike discharge of monkey Purkinje cells does not have the dynamics-related signals required to be the output of an inverse dynamics model signals."

On the other hand, the neurophysiological data are more in line with the idea of a forward internal model. Overall, the cerebral cortex receives information on future events from Purkinje cell firing. Through this mechanism, the cortical modules needed to respond to the foreseen condition will be alerted in advance.

It must be noted that the preparatory function of the cerebellum cannot be limited to a single functional domain. Overall, the capacity of the cerebellum to predict incoming inputs (Tesche and Karhu, 2000), and thus alert specific brain circuits (Restuccia et al., 2007; Moberget et al., 2008) can be considered a supramodal function. Consequently, prediction capability affects whole-brain function, alerting the specific neural systems (e.g., sensory, motor, autonomic, memory, attention, affective, speech, and language) required to respond to a given context.

Tesche and Karhu (2000) analyzed the neural signals generated in the somatosensory cortex and cerebellum according to the predictability of a sensory stimulus. When the stimulus is absent, no activity is present in S1, as expected, whereas the cerebellar response is evident and is much larger than the one recorded when the stimulus is present. The most direct interpretation indicates that the cerebellum reacts to the absence of an expected somatosensory stimulus more than its presence. This response to the absence of a stimulus can be understood only as an indication that something that is expected does not appear (Ivry, 2000). When sensory patterns are recognized, prediction of sequence of events is possible, and consequently, the appropriate brain state can be established beforehand (Nixon, 2003). What is the content of such prediction? Somatosensory Evoked Potentials (SEPs) are presented in a fixed time frame; thus, cerebellar activity may signal the absence of an expected sensation as well as a deviation from expected timing (Ivry, 2000).

The theoretical framework to reconcile the two views is sequencing. By definition, relationships in time and space are the building element of a sequence (Molinari, 2016).

To test the role of the cerebellum in prediction vs. timing, Restuccia et al. (2007) adopted a somatosensory mismatch negativity (MMN) paradigm in which oddballs were generated by varying not the rhythm but the location of the stimuli (Restuccia et al., 2007). Oddball signals were generated by interspersing fifth-finger stimulation among frequent left-thumb stimulations. This s-MMN paradigm was studied in subjects with unilateral cerebellar lesions to exploit the possibility of testing cortical responses with and without cerebellar processing in the same subject. Because of the well-known crossed organization of cerebro-cerebellar circuits, unilateral cerebellar damage will affect only the cerebral cortex of the contralateral hemisphere (Di Lazzaro et al., 1994a,b, 1995; De Vico Fallani et al., 2016).

As we already argued in 2008 (Molinari et al., 2008), considering the involvement of the cerebellum in the prediction of sensory events (Nixon, 2003) and the old theory that it acts as a comparator (Ito, 2006), it is plausible that actual inputs and preceding stimuli are compared within the cerebellum and discordances are tested. If the incoming stimulus matches the predicted stimulus, cerebellar output is not significant; if a discrepancy–error signal is identified, then the output of the cerebellum increases, and a large area of the cerebral cortex is alerted by increasing its excitability."

PREDICTION IN LOCOMOTION

Locomotion is a complex act that involves, in addition to basic locomotor motor patterns provided by spinal interneuronal networks (CPGs), different control centers, both in subcortical and cortical areas (Takakusaki, 2013), including the cerebellum.

The role of the cerebellum in locomotor control and learning has been demonstrated in animals by electrophysiological studies. The spinocerebellum is one of the main structure that processes information conveyed by peripheral sensory signals and information from the spinal pattern generators through the spinocerebellar tracts (Arshavsky et al., 1983; Fedirchuk et al., 2013). Recordings of spinocerebellar neural activity revealed that step-related information is present in the activity of many cerebellar neuron types. An essential role for interlimb coordination, adaptation to external perturbation, is played by Purkinje cells, which tend to fire rhythmically with the stepping cycle (Udo et al., 1981; Armstrong and Edgley, 1984; Yanagihara and Kondo, 1996).

How the cerebellum normally contributes to locomotor behavior in humans is debated, although recent works suggest that it helps generate appropriate patterns of limb movement, dynamically regulate upright posture and balance, and adjust the feedforward control of locomotor output through error-feedback learning.

The role of the cerebellum in the timing and scaling of individual joint movements during gait was addressed by Earhart and Bastian (2001) (J Neurophysiol). The authors asked individuals with cerebellar lesions to step on an inclined surface while walking.

Based on the changes in inclination, healthy subjects presented systematic shifts in the timing of muscle activity and peak joint angles, thus mastering the task through several temporal strategies. Notably, subjects with cerebellar lesions presented appropriate timing shifts at most joints, thus demonstrating preservation of the basic timing of motor patterns. Conversely, relative joint movements were abnormal with movement decomposition, implicating the cerebellum in multiple joint adjustments, particularly when external constraints must be accommodated (Earhart and Bastian, 2001). With the sequencing theory in mind, it appears conceivable that, in presence of cerebellar damage, motor timing is preserved, while multi-joint coordination, requiring spatio-temporal sequence processing, is not.

At present, clinical and experimental data support the idea that cerebellum processes information for adaptive gait control, allowing constant recalibration of walking patterns to smoothly adapt to various terrains and environments. Subjects affected by cerebellar damage are impaired in locomotor tasks that

require prediction, whereas they have good control when reactive control is needed (Morton and Bastian, 2006). This evidence demonstrates that cerebellar adaptation is based not on sensory feedback information but on prediction.

Moreover, several studies investigated the biomechanical characteristics of patients with degenerative cerebellar atrophy (spinocerebellar ataxia, or SCA), finding these to consist of decreases in step length, gait speed, and ankle torque; increased step width; impaired interjoint coordination; and marked variability of all global segmental gait parameter values (Palliyath et al., 1998; Mitoma et al., 2000; Earhart and Bastian, 2001; Morton and Bastian, 2003; Serrao et al., 2012; Wuehr et al., 2013). Moreover, previous findings (Konczak and Timmann, 2007; Bastian, 2011; Goodworth and Peterka, 2012; Timmann et al., 2013) suggest that lesions of the cerebellum may induce abnormalities in the spatial and temporal pattern of muscle activation resulting in specification gait impairments. In this regard, Martino et al., 2014 (J Neurophysiol 2014) found that SCA patients showed a widening of muscle activation profiles as a consequence of improper motor planning (feedforward control) and processing of proprioceptive information (Bastian, 2011), leading to inaccurate movements.

Sequencing intervenes at various levels of locomotor control, providing the basic mechanism for sustaining prediction. As observed in sMMN paradigms (Restuccia et al., 2007), it can be argued that, during locomotion, the cerebellum recognizes fixed sequences of sensory information (Pisotta and Molinari, 2016) funneled by spinocerebellar fibers (Jankowska et al., 2011). Through this mechanism, a correct prediction of the neuromuscular requirements of the subsequent step is achieved. If the actual sequence does not match the predictive sequence, then the cerebellar output system will be enhanced, allowing cortical and brainstem locomotor regions to adapt.

In other words, advance information on subsequent step events (feedforward control) is achieved through cerebellar sequencing, further supporting the idea that sequencing is the basic operational mode of the cerebellum. Recent data in mice provide support to this hypothesis (Darmohray et al., 2019). Chemogenetic dissection of cerebellar circuitries using a split belt locomotion learning paradigm, indicated that spatial and temporal components of gait are both encoded by Purkinje cells (Darmohray et al., 2019). This evidence indicates that timing is not the only domain in which cerebellar control is exerted, indicating spatio-temporal sequencing the best candidate of basic cerebellar operational mode.

PREDICTION IN COGNITION

Since the last century, the ideas on cerebellar functioning have been completely transformed. Even in the 1990s, neurophysiology text books were still presenting an oversimplified functional view of cerebellar functioning with all cerebellar competencies restricted to the motor system. Currently, cerebellar circuits are identified as part of most brain networks, thus indicating involvement not only in motor control but also in virtually all aspects of cognition.

Notwithstanding early reports since Luciani's work (Manni and Petrosini, 1997), a consensus on the cognitive function of the cerebellum was only recently formed.

Anatomical and neuroimaging investigations on cortical-cerebellar connections provide the neurobiological basis for the cerebellar contribution to cognitive functions. Functional MRI studies revealed activation of the cerebellum during several cognitive tasks, particularly in experiments that employed working memory or executive functions (Durisko and Fiez, 2010; Marvel and Desmond, 2010; Chen et al., 2014; Castellazzi et al., 2018).

Cerebellar activation is not limited to this modality but is also present in tasks involving attention and timing (Akshoomoff and Courchesne, 1992; Xu et al., 2006). Regarding language, studies indicate prominent activation of the lateral cerebellar hemispheres (Stoodley and Schmahmann, 2009).

In addition to neuroimaging data, data from preclinical models and clinical studies document diverse cognitive deficits associated with cerebellar damage. The list includes impairments in executive function, procedural memory, declarative memory, and associative memory tasks such as eye blink conditioning, along with deficits in timing/attention (Schmahmann and Sherman, 1997, 1998; Ravizza et al., 2006; Gerwig et al., 2008; Koziol et al., 2014; Baumann et al., 2015).

Recently, in the context of an experimental work on the role of the cerebellum in a countermanding task, we had the opportunity to summarize our view defining the role of the cerebellum in error control across domains (Olivito et al., 2017). One prominent postulation concerning cerebellar involvement in non-motor domains is based on the idea that the cerebellum allows online prediction of upcoming occurrences and produces estimates of future states by implementing internal models (see **Figure 1**). This mechanism allows the system to anticipate predictable events and consequently modify behavior when these predictions are violated (Ivry and Spencer, 2004; Ghajar and Ivry, 2009; Molinari et al., 2009; Leggio and Molinari, 2015; Moberget and Ivry, 2016).

For example, several studies revealed that the cerebellum contributes to the decoding of errors and to the consequent behavioral adaptation in both cognitive and motor domains (Blakemore et al., 2001; Molinari et al., 2008, 2009).

In the results of Ide and Li (2011), the cerebellum emerges as an important structure strongly modulated after error experience in the countermanding task, in cooperation with the ventrolateral PFC and the thalamus (Li et al., 2008). Furthermore, specific impairments in subjects with focal or atrophic cerebellar damage have also been reported (Brunamonti et al., 2014; Olivito et al., 2017). Thus, together with the PFC, anterior cingulate cortices, basal ganglia, and supplementary motor areas, the cerebellum is part of a distributed network contributing to the elaboration of errors as "deviations from what is expected" and to performance monitoring in general (Chevrier and Schachar, 2010; Peterburs et al., 2015).

A previous work documented that subjects with cerebellar damage developed impairments in cognitive sequencing (Leggio et al., 2008). Leggio et al. (2008) using a card-sequencing test, analyzed the ability of patients 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 (Leggio et al., 2008). The patients presented with clear cognitive sequencing impairments independent of the material that was to be processed.

Consequently, the authors stated that the cerebellum identifies serial events as a sequence, finds a sequence violation, and is able to reconstruct the correct sequence of events. The hypothesis that pattern detection, prediction and processing of anticipation are cerebellum-dependent functions is similar to the sequence detection hypothesis in that it links the multifarious impairments that are reported in patients affected by cerebellar damage (Leggio et al., 2008; Molinari and Leggio, 2013).

PREDICTION IN BEHAVIOR

Behavior control relies on a complex network, and recently, cerebellar circuits have been considered relevant. Examining early reports, it has been observed since the 1800s that deviant and aberrant behaviors are present in patients affected by cerebellar anomalies (Schmahmann, 1991). Subsequent clinical studies (Cooper and Upton, 1978) reported a correlation between psychosis and cerebellar damage.

Schmahmann and Sherman (1998), in their initial description of cerebellar cognitive affective syndrome (CCAS), described significant behavioral disruption in 20 patients with cerebellar damage, with behavioral manifestations ranging from affective changes to behavioral disinhibition.

Several authors (Bower et al., 1981; Schmahmann and Sherman, 1998; Andreasen and Pierson, 2008) suggested that the cerebellum regulates mental operations in much the same way as it regulates movements.

The psychiatric literature provides many interesting data highlighting the role of the cerebellum in behavioral control, particularly in schizophrenia. Within the framework of cerebellar involvement in schizophrenia, the connections and cellular architecture of the cerebellum support an interesting theory explaining the different symptoms of this pathology. It is not conceivable that the only dysfunctional brain structure in schizophrenia is the cerebellum. Rather, schizophrenia is probably a disease involving the interaction between multiple components in distributed brain circuits. If this is true, then no structure is necessarily the primary pathological site. Conversely, the network-based theory implies that on any given occasion, or during any given task, different nodes of the network may malfunction in a way that affects the whole system. Alternatively, malfunction might be derived from altered interactions among nodes of the distributed circuits (e.g., cortical areas, thalamus, and cerebellum).

Clinical and experimental findings indicate that schizophrenic patients estimate time less accurately than healthy controls do (Giersch et al., 2016). Schizophrenia is associated with attention deficits and working-memory impairment (Cohen et al., 1997). Moreover, patients affected by schizophrenia can remember that an event occurred but do not know when it occurred. These data have been interpreted considering that patients do not lose memory but that time perception is disorganized (Capa et al., 2014). Overall, many researchers have indicated that time perception is impaired in schizophrenia (Cohen et al., 1997; Giersch et al., 2016).

On the other hand, it has been proposed that psychotic symptoms depend on the lack of coherence between internally perceived and externally generated signals (D'Angelo and Casali, 2013). This "mind-world synchronization" can be obtained when perceptual mechanisms are constantly tuned to an ever-changing environment (Paquette et al., 2013); thus, perceptual tuning is achieved when patterns are recognized and predictions fulfilled (Molinari et al., 2008).

As proposed by Braitenberg et al. (1997), we applied a "sequence detection model" to highlight the cerebellar operational mode in several domains, including the processing of emotions (Molinari et al., 2008; Lupo et al., 2015; Adamaszek et al., 2017; Clausi et al., 2018).

This theory states that the role of the cerebellum in proactive and flexible control of behavior (Miall, 1998; Schlerf et al., 2012) is achieved by implementing a forward model of the incoming sensory input (Wolpert and Kawato, 1998), in turn affecting the cortico-subcortical network involved in error processing and corrective behavior (Falkenstein et al., 2000; Ullsperger and von Cramon, 2006).

Starting from observations in subjects with alterations of cerebellar circuits because of atrophy, we hypothesized that cerebro-cerebellar interactions are altered through continuous error signaling due to misdetection of incoming sequencing. This will induce insertion of virtual errors in the forward control models, thus generating continuous correction of the ongoing motor program (Pisotta and Molinari, 2016).

This hypothesis, derived from observations in the motor system, could help in understanding schizophrenia symptoms. In this latter condition, it can be argued that an incorrect error signal could misguide a sequence/pattern of behavior during the adaptation of behavior to context.

Overall, at the behavioral level, despite the organization based on the function-specific input and networks, the cerebellum plays a unique role in acquiring and predicting sequences affecting not only the understanding of planned and observed actions but also the construction of internal mental models. The role of the cerebellum in this function would be more demanding when applied to novel or complex sequences. These hypotheses are admittedly still at an early stage.

CONCLUSION

Sequencing refers to the ability to acquire knowledge of the structure of sequences. This can be achieved incidentally acting on event sequences through experience or, in case of explicit efforts, intentionally. To learn a sequence means that the presentation and ordering rules of stimuli must be acquired. The working memory system comes into play by keeping the information on a single stimulus active, allowing comparison

with subsequent stimuli. In addition, the relationships among the temporal and spatial characteristics of the stimuli must be acquired. Of relevance is the need to store the sequence structure once identified.

Sequencing is not recognized as a discrete cognitive function. Sequencing abilities are relevant in various fields of cognitive neuroscience. The network subserving sequencing involves different regions, and functional hypotheses have been advanced. For example, predictive functions have been suggested for frontal regions (Bubic et al., 2010), spatial sequencing processing in the hippocampus (Iglói et al., 2010; Babayan et al., 2017) and spatial-temporal relationships in the cerebellum (Leggio et al., 2011; Molinari, 2016; Babayan et al., 2017). Overall, the relationship between sequencing and other functions such as working memory and timing is still elusive, and we can consider it supramodal. In line with this hypothesis, deficits in sequencing affects many discrete domains, and compensation is quite effective.

Within the framework reviewed in the previous paragraphs, sequencing and the cerebellum appear to be closely linked. Regardless of the material processed, comparisons among actual and preceding patterns, as well as detection of discrepancies, occur in the cerebellum (Molinari et al., 2009).

Data from animal and clinical studies converge in supporting this view of fundamental cerebellar operation. Nevertheless, it is still not clear whether cerebellar comparison focuses mainly on time as suggested by Ivry (2000) or integrates processing of spatial and temporal characteristics (Leggio et al., 2011; Darmohray et al., 2019). Another relevant aspect is where internal models coded as pattern/sequence information are stored. The cerebral cortex, basal ganglia and cerebellum are all likely candidates (Leggio et al., 2011). Similarly, experimental and clinical evidence are prompting cerebellar function models to take sequencing in consideration (Tanaka et al., 2019; D'Angelo and Casali, 2013; Molinari et al., 2018; Rowan et al., 2018). Further studies should address the specific roles of these structures in sequencing, particularly to better understand predictive brain mechanisms.

AUTHOR CONTRIBUTIONS

Both authors wrote the manuscript.

REFERENCES

Adamaszek, M., D'Agata, F., Ferrucci, R., Habas, C., Keulen, S., Kirkby, K. C., et al. (2017). Consensus paper: cerebellum and emotion. *Cerebellum* 16, 552–576. doi: 10.1007/s12311-016-0815-8

Akshoomoff, N. A., and Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. *Behav. Neurosci.* 106, 731–738. doi: 10.1037//0735-7044.106.5.731

Albus, J. S. (1971). A theory of cerebellar function. *Math. Biosci.* 10, 25–61. doi: 10.1016/0025-5564(71)90051-4

Alexander, W. H., and Brown, J. W. (2018). Frontal cortex function as derived from hierarchical predictive coding. *Sci. Rep.* 8:3843. doi: 10.1038/s41598-018-21407-9

Allen, G., McColl, R., Barnard, H., Ringe, W. K., Fleckenstein, J., and Cullum, C. M. (2005). Magnetic resonance imaging of cerebellar prefrontal and cerebellar parietal functional connectivity. *Neuroimage* 28, 39–48. doi: 10.1016/j.neuroimage.2005.06.013

Andreasen, N. C., and Pierson, R. (2008). The role of the cerebellum in schizophrenia. *Biol. Psychiatry* 64, 81–88. doi: 10.1016/j.biopsych.2008.01.003

Armstrong, D. M., and Edgley, S. A. (1984). Discharges of Purkinje cells in the paravermal part of the cerebellar anterior lobe during locomotion in the cat. *J. Physiol.* 352, 403–424. doi: 10.1113/jphysiol.1984.sp015300

Arshavsky, I. M., Gelfand Yu, I., and Orlovsky, G. N. (1983). The cerebellum and control of rhythmical movements. *Trends Neurosci.* 6, 417–422. doi: 10.3389/fneur.2015.00249

Asanuma, C., Thach, W. T., and Jones, E. G. (1983). Distribution of cerebellar terminations and their relation to other afferent terminations in the ventral lateral thalamic region of the monkey. *Brain Res.* 286, 237–265. doi: 10.1016/0165-0173(83)90015-2

Babayan, B. M., Watilliaux, A., Viejo, G., Paradis, A. L., Girard, B., and Rondi-Reig, L. (2017). A hippocampo-cerebellar centred network for the learning and execution of sequence-based navigation. *Sci. Rep.* 19:17812. doi: 10.1038/s41598-017-18004-7

Bastian, A. J. (2011). Moving, sensing and learning with cerebellar damage. *Curr. Opin. Neurobiol.* 21, 596–601. doi: 10.1016/j.conb.2011.06.007

Bastian, A. J., and Thach, W. T. (2002). "Structure and function of the cerebellum," in *The Cerebellum and its Disorders*, eds M. Manto, and M. Pandolfo (New York, NY: Cambridge University Press), 49–66. doi: 10.1017/cbo9780511666469.007

Baumann, O., Borra, R. J., Bower, J. M., Cullen, K. E., Habas, C., Ivry, R. B., et al. (2015). Consensus paper: the role of the cerebellum in perceptual processes. *Cerebellum* 14, 197–220. doi: 10.1007/s12311-014-0627-7

Blakemore, S. J., Fonlupt, P., Pachot-Clouard, M., Darmon, C., Boyer, P., Meltzoff, A. N., et al. (2001). How the brain perceives causality: an event-related fMRI study. *Neuroreport* 12, 3741–3746. doi: 10.1097/00001756-200112040-00027

Bower, J. M., Beermann, D. H., Gibson, J. M., Shambes, G. M., and Welker, W. (1981). Principles of organization of a cerebro-cerebellar circuit. Micromapping the projections from cerebral (SI) to cerebellar (granule cell layer) tactile areas of rats. *Brain Behav. Evol.* 18, 1–18. doi: 10.1159/000121772

Bower, J. M., and Parsons, L. M. (2003). Rethinking the lesser brain. *Sci. Am.* 289, 50–57. doi: 10.1038/scientificamerican0803-48

Bracha, V., Zbarska, S., Parker, K., Carrel, A., Zenitsky, G., and Bloedel, J. R. (2009). The cerebellum and eye-blink conditioning: learning versus network performance hypotheses. *Neuroscience* 162, 787–796 doi: 10.1016/j.neuroscience.2008.12.042

Braitenberg, V., Heck, D., Sultan, F., Arbid, M. A., Spoelstra, J., Bjaalie, J. G., et al. (1997). The detection and generation of sequences as a key to cerebellar function: experiments and theory. *Behav. Brain Sci.* 20, 229–277.

Brown, E. C., and Brüne, M. (2012). The role of prediction in social neuroscience. *Front. Hum. Neurosci.* 6:147. doi: 10.3389/fnhum.2012.00147

Brunamonti, E., Chiricozzi, F. R., Clausi, S., Olivito, G., Giusti, M. A., Molinari, M., et al. (2014). Cerebellar damage impairs executive control and monitoring of movement generation. *PLoS One* 9:e85997. doi: 10.1371/journal.pone.0085997

Bubic, A., von Cramon, D. Y., and Schubotz, R. I. (2010). Prediction, cognition and the brain. *Front. Hum. Neurosci.* 4:25. doi: 10.3389/fnhum.2010.00025

Capa, R. L., Duval, C. Z., Blaison, D., and Giersch, A. (2014). Patients with schizophrenia selectively impaired in temporal order judgments. *Schizophr. Res.* 156, 51–55. doi: 10.1016/j.schres.2014.04.001

Castellazzi, G., Bruno, S. D., Toosy, A. T., Casiraghi, L., Palesi, F., Savini, G., et al. (2018). Prominent changes in cerebro-cerebellar functional connectivity during continuous cognitive processing. *Front. Cell. Neurosci.* 12:331. doi: 10.3389/fncel.2018.00331

Chen, J.-C., Hämmerer, D. D., Ostilio, K., Casula, E. P., Marshall, L., Tsai, C.-H., et al. (2014). Bi-directional modulation of somatosensory mismatch negativity with transcranial direct current stimulation: an event related potential study. *J. Physiol.* 592(Pt 4), 745–757. doi: 10.1113/jphysiol.2013.260331

Chevrier, A., and Schachar, R. J. (2010). Error detection in the stop signal task. *Neuroimage* 53, 664–673. doi: 10.1016/j.neuroimage.2010.06.056

Clausi, S., Lupo, M., Olivito, G., Siciliano, L., Contento, M. P., Aloise, F., et al. (2018). Depression disorder in patients with cerebellar damage: awareness of the mood state. *J. Affect Disord.* 245, 386–393. doi: 10.1016/j.jad.2018.11.029

Cohen, J. D., Dunbar, K. O., Barch, D. M., and Braver, T. S. (1997). Issues concerning relative speed of processing hypotheses, schizophrenic performance deficits, and prefrontal function: comment on Schooler et al. *J. Exp. Psychol. Gen.* 126, 37–41. doi: 10.1037/0096-3445.126.1.37

Cooper, I. S., and Upton, A. R. (1978). Use of chronic cerebellar stimulation for disorders of disinhibition. *Lancet* 1, 595–600. doi: 10.1016/s0140-6736(78)91038-3

D'Angelo, E., and Casali, S. (2013). Seeking a unified framework for cerebellar function and dysfunction: from circuit operations to cognition. *Front. Neural Circuits* 6:116. doi: 10.3389/fncir.2012.00116

Darmohray, D. M., Jacobs, J. R., Marques, H. G., and Carey, M. R. (2019). Spatial and temporal locomotor learning in mouse cerebellum. *Neuron* 102, 217–231.e4. doi: 10.1016/j.neuron.2019.01.038

De Vico Fallani, F., Clausi, S., Leggio, M., Chavez, M., Valencia, M., Maglione, A. G., et al. (2016). Interhemispheric connectivity characterizes cortical reorganization in motor-related networks after cerebellar lesions. *Cerebellum* 16, 358–375. doi: 10.1007/s12311-016-0811-z

Di Lazzaro, V., Molinari, M., Restuccia, D., Leggio, M. G., Nardone, R., Fogli, D., et al. (1994a). Cerebro-cerebellar interactions in man: neurophysiological studies in patients with focal cerebellar lesions. *Electroencephalogr. Clin. Neurophysiol.* 93, 27–34. doi: 10.1016/0168-5597(94)90088-4

Di Lazzaro, V., Restuccia, D., Molinari, M., Leggio, M. G., Nardone, R., Fogli, D., et al. (1994b). Excitability of the motor cortex to magnetic stimulation in patients with cerebellar lesions. *J. Neurol. Neurosurg. Psychiatry* 57, 108–110. doi: 10.1136/jnnp.57.1.108

Di Lazzaro, V., Restuccia, D., Nardone, R., Leggio, M. G., Oliviero, A., Profice, P., et al. (1995). Motor cortex changes in a patient with hemicerebellectomy. *Electroencephalogr. Clin. Neurophysiol.* 97, 259–263. doi: 10.1016/0013-4694(95)00110-k

Durisko, C., and Fiez, J. A. (2010). Functional activation in the cerebellum during working memory and simple speech tasks. *Cortex* 46, 896–906. doi: 10.1016/j.cortex.2009.09.009

Earhart, G. M., and Bastian, A. J. (2001). Selection and coordination of human locomotor forms following cerebellar damage. *J. Neurophysiol.* 85, 759–769. doi: 10.1152/jn.2001.85.2.759

Ebner, T. J. (2013). "Cerebellum and internal models," in *Handbook of the Cerebellum and Cerebellar Disorders*, eds M. Manto, J. D. Schmahmann, F. Rossi, D. L. Gruol, and N. Koibuchi (Dordrecht: Springer), 1279–1295. doi: 10.1007/978-94-007-1333-8_56

Ebner, T. J., and Pasalar, S. (2008). Cerebellum predicts the future motor state. *Cerebellum* 7, 583–588. doi: 10.1007/s12311-008-0059-3

Falkenstein, M., Hoormann, J., Christ, S., and Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: a tutorial. *Biol. Psychol.* 51, 87–107. doi: 10.1016/s0301-0511(99)00031-9

Fedirchuk, B., Stecina, K., Kristensen, K. K., Zhang, M., Meehan, C. F., Bennett, D. J., et al. (2013). Rhythmic activity of feline dorsal and ventral spinocerebellar tract neurons during fictive motor actions. *J. Neurophysiol.* 109, 375–388. doi: 10.1152/jn.00649.2012

Gerwig, M., Esser, A. C., Guberina, H., Frings, M., Kolb, F. P., Forsting, M., et al. (2008). Trace eyeblink conditioning in patients with cerebellar degeneration: comparison of short and long trace intervals. *Exp. Brain Res.* 187, 85–96. doi: 10.1007/s00221-008-1283-2

Ghajar, J., and Ivry, R. B. (2009). The predictive brain state: asynchrony in disorders of attention? *Neuroscientist* 15, 232–242. doi: 10.1177/1073858408326429

Giersch, A., Lalanne, L., and Isope, P. (2016). Implicit timing as the missing link between neurobiological and self disorders in schizophrenia? *Front. Hum. Neurosci.* 10:303. doi: 10.3389/fnhum.2016.00303

Goodworth, A. D., and Peterka, R. J. (2012). Sensorimotor integration for multisegmental frontal plane balance control in humans. *J. Neurophysiol.* 107, 12–28. doi: 10.1152/jn.00670.2010

Ide, J. S., and Li, C. S. (2011). Error-related functional connectivity of the habenula in humans. *Front. Hum. Neurosci.* 5:25. doi: 10.3389/fnhum.2011.00025

Iglói, K., Doeller, C. F., Berthoz, A., Rondi-Reig, L., and Burgess, N. (2010). Lateralized human hippocampal activity predicts navigation based on sequence or place memory. *Proc. Natl. Acad. Sci. U.S.A.* 107, 14466–14471. doi: 10.1073/pnas.1004243107

Ito, M. (1990). A new physiological concept on cerebellum. *Rev. Neurol.* 146, 564–569.

Ito, M. (2006). Cerebellar circuitry as a neuronal machine. *Prog. Neurobiol.* 78, 272–303. doi: 10.1016/j.pneurobio.2006.02.006

Ivry, R. (2000). Exploring the role of the cerebellum in sensory anticipation and timing: commentary on Tesche and Karhu [comment]. *Hum. Brain Mapp.* 9, 115–118. doi: 10.1002/(sici)1097-0193(200003)9:3<115::aid-hbm1>3.0.co;2-5

Ivry, R., and Keele, S. (1989). Timing functions of the cerebellum. *J. Cogn. Neurosci.* 1, 136–152. doi: 10.1162/jocn.1989.1.2.136

Ivry, R. B., and Spencer, R. M. (2004). The neural representation of time. *Curr. Opin. Neurobiol.* 14, 225–232.

Jankowska, E., Nilsson, E., and Hammar, I. (2011). Do spinocerebellar neurones forward information on spinal actions of neurones in the feline red nucleus? *J. Physiol.* 589, 5727–5739. doi: 10.1113/jphysiol.2011.213694

Konczak, J., and Timmann, D. (2007). The effect of damage to the cerebellum on sensorimotor and cognitive function in children and adolescents. *Neurosci. Biobehav. Rev.* 31, 1101–1113. doi: 10.1016/j.neubiorev.2007.04.014

Koziol, L. F., Budding, D., Andreasen, N., D'Arrigo, S., Bulgheroni, S., Imamizu, H., et al. (2014). Consensus paper: the cerebellum's role in movement and cognition. *Cerebellum* 13, 151–177. doi: 10.1007/s12311-013-0511-x

Larson, J. C. G., and Mostofsky, S. H. (2008). Evidence that the pattern of visuomotor sequence learning is altered in children with autism. *Autism Res.* 1, 341–353. doi: 10.1002/aur.54

Leggio, M., and Molinari, M. (2015). Cerebellar sequencing: a trick for predicting the future. *Cerebellum* 14, 35–38. doi: 10.1007/s12311-014-0616-x

Leggio, M. G., Chiricozzi, F. R., Clausi, S., Tedesco, A. M., and Molinari, M. (2011). The neuropsychological profile of cerebellar damage: the sequencing hypothesis. *Cortex* 47, 137–144. doi: 10.1016/j.cortex.2009.08.011

Leggio, M. G., Tedesco, A. M., Chiricozzi, F. R., Clausi, S., Orsini, A., and Molinari, M. (2008). Cognitive sequencing impairment in patients with focal or atrophic cerebellar damage. *Brain* 131, 1332–1343. doi: 10.1093/brain/awn040

Li, C. S., Yan, P., Chao, H. H., Sinha, R., Paliwal, P., Constable, R. T., et al. (2008). Error-specific medial cortical and subcortical activity during the stop signal task: a functional magnetic resonance imaging study. *Neuroscience* 155, 1142–1151. doi: 10.1016/j.neuroscience.2008.06.062

Lupo, M., Troisi, E., Chiricozzi, F. R., Clausi, S., Molinari, M., and Leggio, M. (2015). Inability to process negative emotions in cerebellar damage: a functional transcranial doppler sonographic study. *Cerebellum* 14, 663–669. doi: 10.1007/s12311-015-0662-z

Macchi, G., and Jones, E. G. (1997). Toward an agreement of nuclear and subnuclear division of the motor thalamus. *J. Neurosurg.* 86, 670–685. doi: 10.3171/jns.1997.86.4.0670

Manni, E., and Petrosini, L. (1997). Luciani's work on the cerebellum a century later. *Trends Neurosci.* 20, 112–116. doi: 10.1016/s0166-2236(96)10077-1

Marr, D. (1969). A theory of cerebellar cortex. *J. Physiol.* 202, 437–470. doi: 10.1113/jphysiol.1969.sp008820

Martino, G., Ivanenko, Y. P., Serrao, M., Ranavolo, A., d'Avella, A., Draicchio, F., et al. (2014). Locomotor patterns in cerebellar ataxia. *J. Neurophysiol.* 112, 2810–2821. doi: 10.1152/jn.00275.2014

Marvel, C. L., and Desmond, J. E. (2010). The contributions of cerebro-cerebellar circuitry to executive verbal working memory. *Cortex* 46, 880–895. doi: 10.1016/j.cortex.2009.08.017

Mauk, M. D., and Ohyama, T. (2004). Extinction as new learning versus unlearning: considerations from a computer simulation of the cerebellum. *Learn. Mem.* 11, 566–571. doi: 10.1101/lm.83504

Miall, R. C. (1998). The cerebellum, predictive control and motor coordination. *Novartis Found. Symp.* 218, 272–284.

Mitoma, H., Hayashi, R., Yanagisawa, N., and Tsukagoshi, H. (2000). Characteristics of parkinsonian and ataxic gaits: a study using surface electromyograms, angular displacements and floor reaction forces. *J. Neurol. Sci.* 174, 22–39. doi: 10.1016/s0022-510x(99)00329-9

Moberget, T., and Ivry, R. B. (2016). Cerebellar contributions to motor control and language comprehension: searching for common computational

principles. *Ann. N. Y. Acad. Sci.* 369, 154–171. doi: 10.1111/nyas.13094

Moberget, T., Karns, C. M., Deouell, L. Y., Lindgren, M., Knight, R. T., and Ivry, R. B. (2008). Detecting violations of sensory expectancies following cerebellar degeneration: a mismatch negativity study. *Neuropsychologia* 46, 2569–2579. doi: 10.1016/j.neuropsychologia.2008.03.016

Molinari, M. (2016). "Sequencing," in *Essentials of Cerebellum and Cerebellar Disorders: A Primer For Graduate Students*, eds D. L. Gruol, N. Koibuchi, M. Manto, et al. (Cham: Springer International Publishing), 397–402.

Molinari, M., Chiricozzi, F., Clausi, S., Tedesco, A., De Lisa, M., and Leggio, M. (2008). Cerebellum and detection of sequences, from perception to cognition. *Cerebellum* 7, 611–615. doi: 10.1007/s12311-008-0060-x

Molinari, M., Leggio, M. G., Solida, A., Ciorra, R., Misciagna, S., Silveri, M. C., et al. (1997). Cerebellum and procedural learning: evidence from focal cerebellar lesions. *Brain* 120, 1753–1762. doi: 10.1093/brain/120.10.1753

Molinari, M., Masciullo, M., Bulgheroni, S., D'Arrigo, S., and Riva, D. (2018). Cognitive aspects: sequencing, behavior, and executive functions. *Handb. Clin. Neurol.* 154, 167–180. doi: 10.1016/B978-0-444-63956-1.00010-2

Molinari, M., Restuccia, D., and Leggio, M. G. (2005). Cerebellar information flow in the thalamus: implications for cortical functions. *Thalamus Relat. Syst.* 3, 141–146.

Molinari, M., Restuccia, D., and Leggio, M. G. (2009). State estimation, response prediction, and cerebellar sensory processing for behavioral control. *Cerebellum* 8, 399–402. doi: 10.1007/s12311-009-0112-x

Molinari, M., and Leggio, M. G. (2013). "Cerebellar sequencing for cognitive processing," in *Handbook of the Cerebellum and Cerebellar Disorders*, eds M. Manto, J. D. Schmahmann, F. Rossi, D. L. Gruol, and N. Koibuchi (Dordrecht: Springer), 1701–1716.

Morton, S. M., and Bastian, A. J. (2003). Relative contributions of balance and voluntary leg-coordination deficits to cerebellar gait ataxia. *J. Neurophysiol.* 89, 1844–1856. doi: 10.1152/jn.00787.2002

Morton, S. M., and Bastian, A. J. (2006). Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. *J. Neurosci.* 26, 9107–9116. doi: 10.1523/jneurosci.2622-06.2006

Nixon, P. D. (2003). The role of the cerebellum in preparing responses to predictable sensory events. *Cerebellum* 2, 114–122. doi: 10.1080/14734220309410

Olivito, G., Brunamonti, E., Clausi, S., Pani, P., Chiricozzi, F. R., Giamundo, M., et al. (2017). Atrophic degeneration of cerebellum impairs both the reactive and the proactive control of movement in the stop signal paradigm. *Exp. Brain Res.* 235, 2971–2981. doi: 10.1007/s00221-017-5027-z

Palesi, F., De Rinaldis, A., Castellazzi, G., Calamante, F., Muhlert, N., Chard, D., et al. (2017). Contralateral cortico-ponto-cerebellar pathways reconstruction in humans in vivo: implications for reciprocal cerebro-cerebellar structural connectivity in motor and non-motor areas. *Sci. Rep.* 7:12841. doi: 10.1038/s41598-017-13079-8

Palliyath, S., Hallett, M., Thomas, S. L., and Lebiedowska, M. K. (1998). Gait in patients with cerebellar ataxia. *Mov. Disord.* 13, 958–964.

Paquette, S., Mignault Goulet, G., and Rothermich, K. (2013). Prediction, attention, and unconscious processing in hierarchical auditory perception. *Front. Psychol.* 4:955. doi: 10.3389/fpsyg.2013.00955

Peterburs, J., Thürling, M., Rustemeier, M., Göricke, S., Suchan, B., Timmann, D., et al. (2015). A cerebellar role in performance monitoring - evidence from EEG and voxel-based morphometry in patients with cerebellar degenerative disease. *Neuropsychologia* 68, 139–147. doi: 10.1016/j.neuropsychologia.2015.01.017

Pisotta, I., and Molinari, M. (2014). Cerebellar contribution to feedforward control of locomotion. *Front. Hum. Neurosci.* 8:475. doi: 10.3389/fnhum.2014.00475

Pisotta, I., and Molinari, M. (2016). "Cerebro-Cerebellar Networks," in *Essentials of Cerebellum and Cerebellar Disorders: A Primer For Graduate Students*, eds D. L. Gruol, N. Koibuchi, M. Manto, et al. (Cham: Springer International Publishing), 385–389. doi: 10.1007/978-3-319-24551-5_52

Popa, L. S., Hewitt, A. L., and Ebner, T. J. (2012). Predictive and feedback performance errors are signaled in the simple spike discharge of individual purkinje cells. *J. Neurosci.* 32, 15345–15358. doi: 10.1523/JNEUROSCI.2151-12.2012

Ramnani, N. (2006). The primate cortico-cerebellar system: anatomy and function. *Nat. Rev. Neurosci.* 7, 511–522. doi: 10.1038/nrn1953

Ravizza, S. M., McCormick, C. A., Schlerf, J. E., Justus, T., Ivry, R. B., and Fiez, J. A. (2006). Cerebellar damage produces selective deficits in verbal working memory. *Brain* 129, 306–320. doi: 10.1093/brain/awh685

Restuccia, D., Marca, G. D., Valeriani, M., Leggio, M. G., and Molinari, M. (2007). Cerebellar damage impairs detection of somatosensory input changes. A somatosensory mismatch-negativity study. *Brain* 130, 276–287. doi: 10.1093/brain/awl236

Rowan, M. J. M., Bonnan, A., Zhang, K., Amat, S. B., Kikuchi, C., Taniguchi, H., et al. (2018). Graded control of climbing-fiber-mediated plasticity and learning by inhibition in the cerebellum. *Neuron* 99, 999–1015.e6. doi: 10.1016/j.neuron.2018.07.024

Savalia, T., Shukla, A., and Bapi, R. S. (2016). A unified theoretical framework for cognitive sequencing. *Front. Psychol.* 7:1821. doi: 10.3389/fpsyg.2016.01821

Schlerf, J., Ivry, R. B., and Diedrichsen, J. (2012). Encoding of sensory prediction errors in the human cerebellum. *J. Neurosci.* 32, 4913–4922. doi: 10.1523/JNEUROSCI.4504-11.2012

Schmahmann, J. D. (1991). An emerging concept. The cerebellar contribution to higher function. *Arch. Neurol.* 48, 1178–1187.

Schmahmann, J. D., and Sherman, J. C. (1997). Cerebellar cognitive affective syndrome. *Int. Rev. Neurobiol.* 41, 433–440.

Schmahmann, J. D., and Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain.* 121, 561–579. doi: 10.1093/brain/121.4.561

Serrao, M., Pierelli, F., Ranavolo, A., Draicchio, F., Conte, C., Don, R., et al. (2012). Gait pattern in inherited cerebellar ataxias. *Cerebellum* 11, 194–211. doi: 10.1007/s12311-011-0296-8

Shergill, S. S., White, T. P., Joyce, D. W., Bays, P. M., Wolpert, D. M., and Frith, C. D. (2014). FUnctional magnetic resonance imaging of impaired sensory prediction in schizophrenia. *JAMA Psychiatry* 71, 28–35.

Stoodley, C. J., and Schmahmann, J. D. (2009). The cerebellum and language: evidence from patients with cerebellar degeneration. *Brain Lang.* 110, 149–153. doi: 10.1016/j.bandl.2009.07.006

Strick, P. L., Dum, R. P., and Fiez, J. A. (2009). Cerebellum and nonmotor function. *Annu. Rev. Neurosci.* 32, 413–434. doi: 10.1146/annurev.neuro.31.060407.125606

Swain, R. A., Kerr, A. L., and Thompson, R. F. (2011). The cerebellum: a neural system for the study of reinforcement learning. *Front. Behav. Neurosci.* 5:8. doi: 10.3389/fnbeh.2011.00008

Takakusaki, K. (2013). Neurophysiology of gait: from the spinal cord to the frontal lobe. *Mov. Disord.* 28, 1483–1491. doi: 10.1002/mds.25669

Tanaka, H., Ishikawa, T., and Kakei, S. (2019). Neural evidence of the cerebellum as a state predictor. *Cerebellum* 18, 349–371. doi: 10.1007/s12311-018-0996-4

Tedesco, A. M., Chiricozzi, F. R., Clausi, S., Lupo, M., Molinari, M., and Leggio, M. G. (2011). The cerebellar cognitive profile. *Brain* 134, 3672–3678. doi: 10.1093/brain/awr266

Tesche, C. D., and Karhu, J. (1997). Somatosensory evoked magnetic fields arising from sources in the human cerebellum. *Brain Res.* 744, 23–31. doi: 10.1016/s0006-8993(96)01027-x

Tesche, C. D., and Karhu, J. J. (2000). Anticipatory cerebellar responses during somatosensory omission in man [see comments]. *Hum. Brain Mapp.* 9, 119–142. doi: 10.1002/(sici)1097-0193(200003)9:3<119::aid-hbm2>3.0.co;2-r

Timmann, D., Drepper, J., Frings, M., Maschke, M., Richter, S., Gerwig, M., et al. (2010). The human cerebellum contributes to motor, emotional and cognitive associative learning. A review. *Cortex* 46, 845–857. doi: 10.1016/j.cortex.2009.06.009

Timmann, D., Kaulich, T., Föhre, W., Kutz, D. F., Gerwig, M., and Kolb, F. P. (2013). Comparison of the classically conditioned withdrawal reflex in cerebellar patients and healthy control subjects during stance: I. electrophysiological characteristics. *Cerebellum* 13, 12108–12126. doi: 10.1007/s12311-012-0400-8

Udo, M., Matsukawa, K., Kamei, H., Minoda, K., and Oda, Y. (1981). Simple and complex spike activities of Purkinje cells during locomotion in the cerebellar vermal zones of decerebrate cats. *Exp. Brain Res.* 41, 292–300.

Ullsperger, M., and von Cramon, D. Y. (2006). How does error correction differ from error signaling? An event-related potential study. *Brain Res.* 1105, 102–109. doi: 10.1016/j.brainres.2006.01.007

Wolpert, D. M., and Kawato, M. (1998). Multiple paired forward and inverse models for motor control. *Neural Netw.* 11, 1317–1329. doi: 10.1016/s0893-6080(98)00066-5

Wuehr, M., Schniepp, R., Ilmberger, J., Brandt, T., and Jahn, K. (2013). Speed-dependent temporospatial gait variability and long-range correlations in cerebellar ataxia. *Gait Posture* 37, 214–218. doi: 10.1016/j.gaitpost.2012.07.003

Xu, D., Liu, T., Ashe, J., and Bushara, K. O. (2006). Role of the olivo-cerebellar system in timing. *J. Neurosci.* 26, 5990–5995. doi: 10.1523/jneurosci.0038-06.2006

Yamazaki, T., and Lennon, W. (2019). Revisiting a theory of cerebellar cortex. *Neurosci. Res.* 148, 1–8. doi: 10.1016/j.neures.2019.03.001

Yanagihara, D., and Kondo, I. (1996). Nitric oxide plays a key role in adaptive control of locomotion in cat. *Proc. Natl. Acad. Sci. U.S.A.* 93, 13292–13297. doi: 10.1073/pnas.93.23.13292

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership