

Neural Correlates of Sensory Prediction Errors in Monkeys: Evidence for Internal Models of Voluntary Self-Motion in the Cerebellum

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Abstract During self-motion, the vestibular system makes essential contributions to postural stability and self-motion perception. To ensure accurate perception and motor control, it is critical to distinguish between vestibular sensory inputs that are the result of externally applied motion (exafference) and that are the result of our own actions (reafference). Indeed, although the vestibular sensors encode vestibular afference and reafference with equal fidelity, neurons at the first central stage of sensory processing selectively encode vestibular exafference. The mechanism underlying this reafferent suppression compares the brain's motor-based expectation of sensory feedback with the actual sensory consequences of voluntary self-motion, effectively computing the sensory prediction error (i.e., exafference). It is generally thought that sensory prediction errors are computed in the cerebellum, yet it has been challenging to explicitly demonstrate this. We have recently addressed this question and found that deep cerebellar nuclei neurons explicitly encode sensory prediction errors during self-motion. Importantly, in everyday life, sensory prediction errors occur in response to changes in the effector or world (muscle strength, load, etc.), as well as in response to externally applied sensory stimulation. Accordingly, we hypothesize that altering the relationship between motor commands and the actual movement parameters will result in the updating in the cerebellum-based computation of exafference. If our hypothesis is correct, under these conditions, neuronal responses should initially be increased—consistent with a sudden increase in the sensory prediction error. Then, over time, as the internal model is updated, response modulation should decrease in parallel with a reduction in sensory prediction error, until vestibular reafference is again suppressed. The finding that the internal

model predicting the sensory consequences of motor commands adapts for new relationships would have important implications for understanding how responses to passive stimulation endure despite the cerebellum's ability to learn new relationships between motor commands and sensory feedback.

Keywords Primate · Cerebellum · Motor learning · Vestibular · Efference copy · Corollary discharge · Internal models

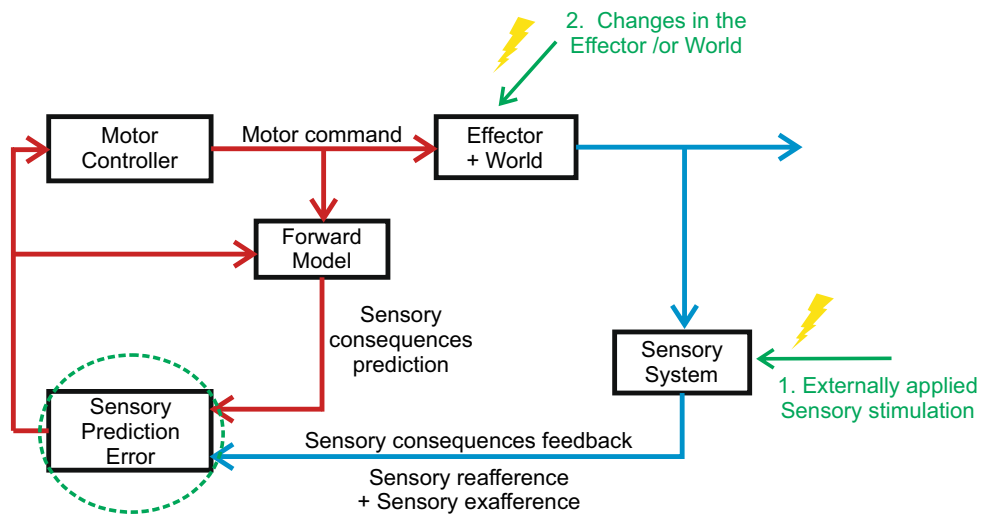
Introduction

To acquire new skills and maintain mastered skills, in response to changes in the internal and external environment, our brain must coordinate changes in the responses of neurons and neural circuits, with motor performance. There is accumulating evidence that the brain does this by computing an estimate of the expected sensory consequences of movement (forward model) and then comparing this estimate to the actual sensory feedback to compute a sensory prediction error (Fig. 1a).

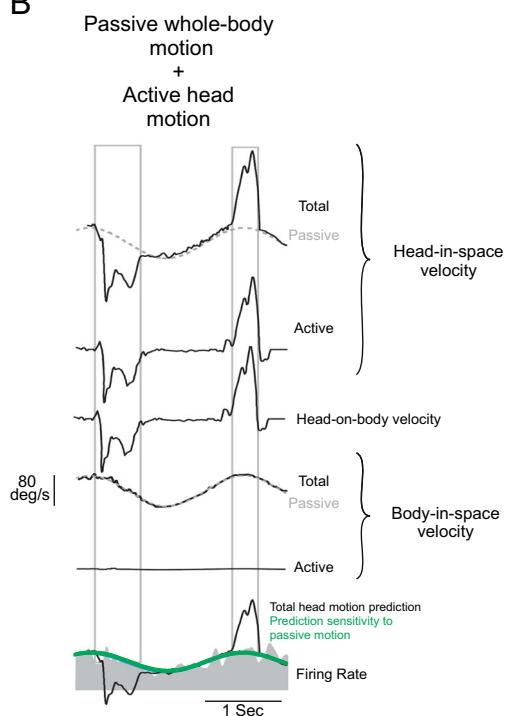
In everyday life, sensory prediction errors can occur for several reasons, most notably, (1) they may occur when sensory stimulation is externally generated rather than self-generated (e.g., sensory exafference versus reafference) or (2) result because of changes in the effector or world (muscle strength, load, etc.). In a series of recent studies, Ebner and colleagues found that the activity of Purkinje neurons in the cerebellar cortex is consistent with a forward model. When a force was applied as monkeys manually tracked a target, Purkinje cell responses were linked to the motion produced rather than specific kinematics (forces and torques) and encoded error-related signals. In addition, Popa et al., most recently found evidence for a bimodal (with respect to time) distribution of error signals in these neurons [reviewed in 1]. The authors have proposed that this dual representation of error (with opposing

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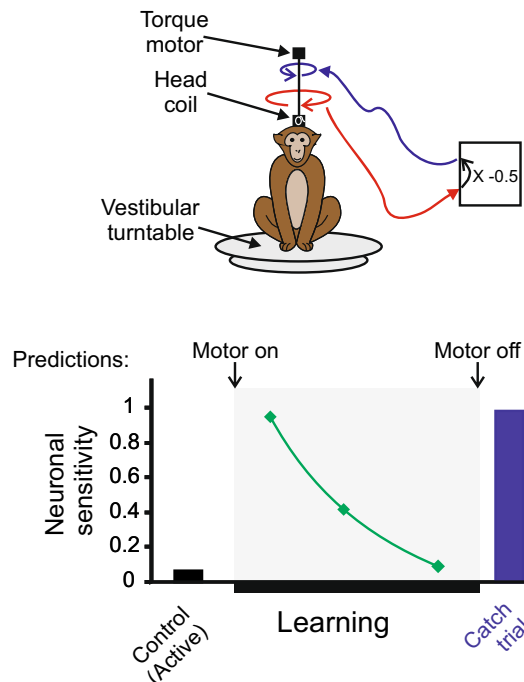


Fig. 1 a. Schematic of the relationship between motor command, sensory feedback, and sensory prediction errors. Sensory prediction errors occur in response to both (1) externally applied sensory stimulation and (2) changes in the motor apparatus and or world. **b.** In response to combined actively generated and externally (passively) motion rostral fastigial neurons selectively encode passive motion. **c.** *Top:* experimental

set up in which torque applied to the head can be used to establish a new relationship between motor commands and resulting head movements. *Bottom:* predicted sensitivity of rostral fastigial neurons during control active movements, during a sustained time period where the torque is applied and during catch trials

modulation of the simple spike firing) is consistent with the signals needed to generate sensory prediction errors used to update an internal model. However, to date, a neural correlate for sensory prediction error has not yet been found.

In this manuscript, we discuss the results and implications of recent experiments done in our laboratory aimed at

understanding the signals encoded by neurons at the next stage of processing—in the deep cerebellar nuclei—during voluntary movements. Specifically, we focus on the relatively simple sensory-motor pathway with a well-described organization that mediates postural control. Single-unit recordings made in the most medial of the deep cerebellar nuclei

(fastigial), which constitutes a major output target of the cerebellar cortex, and in turn sends strong projections to the vestibular nuclei, reticular formation, and spinal cord to ensure accurate posture and maintenance of balance.

Encoding of Sensory Prediction Errors in the Rostral Fastigial Nucleus

The cerebellum is generally thought to act as a forward model that predicts the sensory consequences of self-generated movement [reviewed in 2]. To date, this idea has been mainly considered in relation to the fine-tuning of motor commands necessary for motor learning. In this context, the cerebellum computes an error signal by comparing a prediction of the sensory consequences of an action to the sensory stimulation produced by the actual movement. This error signal in turn guides updating of both the motor program as well as forward model (Fig. 1). Consistent with this idea, recent behavioral studies in humans have shown sensory prediction errors drive motor learning [3]. Furthermore, clinical studies with neurologic patients [4] and using brain stimulation [5] suggest a role for cerebellum-dependent mechanisms.

Importantly, however, it is important to consider that sensory prediction errors will occur not only in conditions that require motor learning but also occur whenever we experience externally produced sensory stimuli (i.e., sensory exafference). When sensory stimulation is unexpected, the computation of sensory prediction errors effectively enables the brain to distinguish between the consequences of our self-generated actions (sensory reafference) and stimulation that is externally produced (sensory exafference). Work in the vestibular system has provided concrete evidence that indeed such a computation is performed. While vestibular afferents similarly encode vestibular reafference and exafference during self-motion, neurons at the subsequent stage of sensory processing preferentially respond to vestibular exafference [6]. Taken together, these findings suggest that the brain computes vestibular prediction error signals during active motion, thereby allowing the selective encoding of sensory exafference.

Despite long-standing interest in the computations required for accurate motor control and the role of the cerebellum in these computations, the neural mechanisms underlying the computation of sensory exafference had remained unclear. It had been proposed that our brain constructs an internal model of the expected sensory consequences of movement based on an efference copy of the self-produced motor command [7]. This idea is supported by single-unit recording studies in the fish electrosensory system showing that their cerebellum-like circuitry computes predictions about the sensory consequences of the animals' own behavior [8]. However, while single-unit recording studies in primates [9] and imaging studies in normal humans have shown increased activity in

the cerebellum when sensory feedback does not match what is expected [10, 11], the proposal that the cerebellum computes an explicit estimate of the sensory consequences of unexpected movement had not been tested. Notably, in everyday life, exafference and reafference are often experienced simultaneously, making it crucial to address whether neurons encode sensory prediction errors demonstrating the anticipation and cancelation of reafferent effects under conditions in which active and passive stimulation are concurrent.

To address this, we recently completed a series of experiments in which recordings were made from individual neurons in the rostral fastigial nucleus (rFN), which constitutes a major output target of the cerebellar cortex [12] and sends strong projections to the vestibular nuclei, reticular formation, and spinal cord [12, 13] to regulate postural control. We found that neurons in the rostral FN that faithfully encode passive head and body motion are greatly suppressed during actively generated movements of the head and body. Moreover, when active and passive motion occurs simultaneously, the externally applied component of the movement is selectively encoded (Fig. 1b). Thus, neuronal responses do not encode a representation of absolute head or body motion but rather provide an estimate of unexpected motion required for the maintenance of posture and accurate spatial orientation. These findings show for the first time that neurons in the cerebellum explicitly encode sensory prediction errors detailing the time course of externally applied self-motion.

Further Studies

Our current hypothesis is that neurons in the deep cerebellar nuclei (fastigial) encode sensory prediction errors in response to externally applied self-motion (i.e., scenario 1 in Fig. 1a). Moreover, to date, our experimental evidence is consistent with the proposal that suppression of sensory reafference occurs when proprioceptive feedback matches that expected as a result of the motor command (as during normal active movements) [7, 14]. If this is true, then reafferent suppression should not occur when the relationship between motor commands and sensory reafference is altered (i.e., scenario 2 in Fig. 1a). In real life, the relationship between the brain's motor command and the resulting movement (and thus sensory feedback) will change over time due to, for example, development, injury, or other external factors [3].

Studies have suggested that in order to deal with such challenges, the brain updates its internal model of the consequences of movements in order to adapt to the new circumstances [15]. We hypothesize that the cerebellum-mediated mechanism that suppresses vestibular reafference can be updated to account for changes in the relationship between motor commands and resulting head motion. This question can be addressed by evaluating rostral FN neuron responses and head

movement behavior in a learning protocol where the relationship between the motor command to move the head and the actual head movement are experimentally controlled by applying a load to the head during actively generated movements (Fig. 1c). This added torque would create a new yet consistent relationship between motor command and the actual head movement produced. If our hypothesis is correct, then we would expect that when faced with changes in the relationship between the motor command and actual movement, responses of rostral FN neurons would initially be increased (i.e., have a head velocity sensitivity similar to that observed during passive head motion), but that over time, their response modulation would decrease such that vestibular reafference was once again suppressed as the internal model is updated.

Furthermore, previous motor learning studies have further used “catch trials” (which refers to removal of the experimentally induced perturbation unexpectedly for single trials during a learning paradigm) as a way to assess whether an internal model has been updated [15]. If the behavioral response to the catch trials produces a movement that is the mirror image of the initial change in response caused by the imposed perturbation, this provides evidence that the motor system has incorporated the perturbation into its internal motor plan and thus updated its internal model of the consequences of its motor command. According to our hypothesis, we predict that the sensitivity of rostral FN neurons to these catch trials, once learning of the new relationship has occurred and the neuronal sensitivity to actively generated head movement under these new conditions is once again suppressed, should be increased (i.e., comparable to sensitivities observed during passive head motion).

Finally, it is noteworthy that the responses of neurons in the cerebellar cortex often significantly lead or lag movement during movements such as reaching or manual tracking [reviewed in 1]. In contrast, FN neuron responses are tightly coupled to externally applied self-motion. Interestingly, neurons in regions of the vestibular cerebellar cortex (i.e., flocculus and nodula/uvula) also show tight coupling to applied motion. One possibility is that precise linkage to movement is a characteristic of particular regions of cerebellar cortex. For example, it has been recently reported that neurons in lateral crus I of the rodent cerebellum respond robustly (<10 ms) and selectively to stimulation of whisking-related areas of sensory and motor cortex [16]. We speculate such direct connectivity between sensory inputs/motor outputs, and these specific cerebellar regions are essential for the construction of forward models.

Conclusion

Continued reafference suppression in the face of sustained changes in the relationship between motor commands and sensory feedback is essential to the vestibular system’s contribution to both vestibulo-spinal reflexes and self-motion

perception. The finding that the internal model predicting the sensory consequences of motor commands can adapt for new relationships between motor commands, and actual head movements would have important implications for understanding how responses to passive stimulation endure despite the ability to learn new relationships between motor commands and sensory feedback.

Conflict of Interest There are no potential conflicts of interest in our submission.

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