Review

Biological Psychiatry: CNNI

Corollary Discharge Signals in the Cerebellum

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ABSTRACT

The cerebellum is known to make movements fast, smooth, and accurate. Many hypotheses emphasize the role of the cerebellum in computing learned predictions important for sensorimotor calibration and feedforward control of movements. Hypotheses of the computations performed by the cerebellum in service of motor control borrow heavily from control systems theory, with models that frequently invoke copies of motor commands, called corollary discharge. This review describes evidence for corollary discharge inputs to the cerebellum and highlights the hypothesized roles for this information in cerebellar motor-related computations. Insights into the role of corollary discharge in motor control, described here, are intended to inform the exciting but still untested roles of corollary discharge in cognition, perception, and thought control relevant in psychiatric disorders.

Keywords: Cerebellar, Corollary discharge, Efference copy, Mossy fibers, Motor control, Reafference

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ORIGIN OF A CONCEPT

A major effort in cerebellar research is understanding the mechanistic basis of behavioral effects of cerebellar damage and disease. In the motor domain, cerebellar dysfunction leads to a prominent motor deficit called dysmetria, characterized by persistent overshoot or undershoot of effectors (e.g., eyes, limbs) that prompt repeated corrective responses, ultimately resembling oscillations. These oscillatory symptoms relate directly to control systems problems encountered in engineering of feedback-controlled mechanisms, such as thermostats, cruise controls, and assembly line workflow (1). Long sensory feedback delays, such as a thermostat detecting distant room temperature, produce oscillatory outputs because the feedback acted on by the controller is out of date (2,3). Analogous to these engineered systems, the brain experiences delayed sensory feedback during movements, such as the >100-ms delay of visually detecting the limb at a target; thus, both engineers and the brain monitor output signals, called corollary discharge (CD) signals or efference copies, to perform computations that improve output stability through predictive control (Figure 1).

Before discussing further the role of CD in cerebellar computations, it is important to clarify the definition of the term and its origins. In this short review, I will use the term CD to mean a motor signal sent upstream—away from muscles—used synonymously with the term efference copy (4). Some conceptual frameworks have argued that the term CD should refer strictly to sensory expectations referenced to motor commands and that CD signals should not produce or affect movement directly (4,5). These views are mainly valuable in certain brain regions, such as cerebral cortex, where recurrent networks are so vast that naming specific pathways as carrying CD is not always fruitful. Within the context of the cerebellum, I will argue that broader definitions of CD are convenient, as they permit interrogation of the control systems theories of cerebellar function that invoke CD-like signals. For instance, I would argue that collateral pathways from premotor neurons along the efferent motor path should be considered to constitute a form of CD, even though their manipulation produces direct motor consequences. This usage hews closely to the original work defining CD: CD signals and the synonymous term efference copy were first studied mechanistically in optokinetic circling induced by eye rotation in either flies or fishes. Under normal conditions, self-generated turning does not elicit optokinetic following. However, in the face of eye rotation, self-generated movements elicited optokinetic reflexes leading to circling behavior. The phenomenon predicted a signal present in the brain that suppressed optokinetic following during self-generated movement that became maladaptive in the face of eye rotation. Sperry (6) tested where such a signal might originate in a type of puffer fish, reporting that the maladaptive optokinetic phenomenon was abolished with tectal lesions. Thus, Sperry localized a central signal in the vertebrate brain that accounted for the phenomenon and proposed that "a corollary discharge of motor patterns into the sensorium may play an important role in the visual perception of movement" (6). Here it was clear that the motor patterns could be used to interpret sensory information; importantly, it was not suggested that they represented the sensory information per se or were defined by that purpose.

In which ways might CD information influence perception? Motor output copies (i.e., CD) are hypothesized to interact with reafferent signals such that mismatches in the total reafference signal relative to the CD will result in a residual bias that feeds back to the controller or interpreter (7). This idea had its roots in observations stemming back centuries: it seemed obvious that our brains take into account our own actions when interpreting the world. For instance, when we move, we do not interpret the world moving before us, but rather ourselves moving within it.

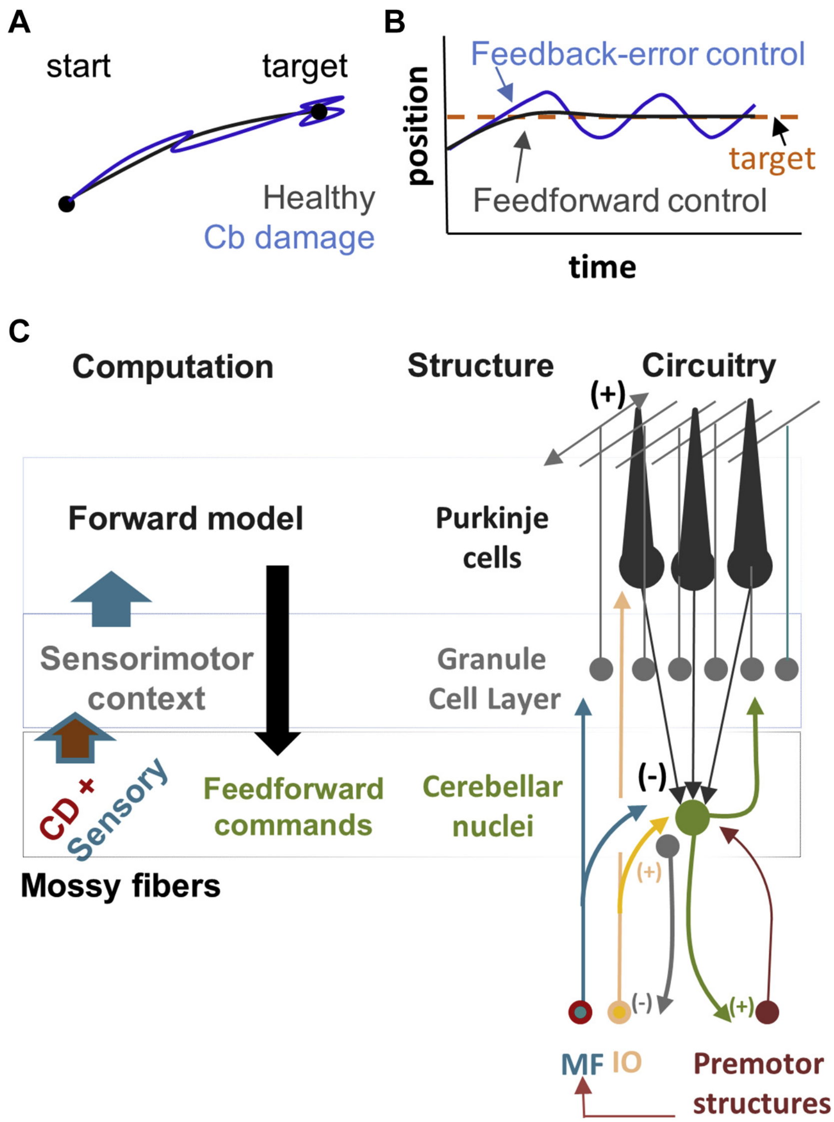

Figure 1. How corollary discharge (CD) signals to the cerebellum relate to motor control deficit hypotheses. **(A)** Schematic representation of dysmetric reaching movement trajectories, characterized by oscillatory movements around a target (dot), which emerges with cerebellar (Cb) damage. **(B)** Comparison of slow feedback-error control systems, which resemble dysmetric movements, with feedforward control. Feedforward control uses predictive output to drive movement, avoiding oscillation. **(C)** Hypothesized framework for cerebellar use of CD in predictive forward model computations. Panel **(C)** aligns computations in the first column with structures and circuitry, representing regions of the cerebellum that produce these signals. Starting at the bottom left, following arrows: CD and sensory information enter the cerebellum via mossy fibers. Information is re-expressed in granule cells and scaled at Purkinje neurons through associative plasticity mechanisms under the control of climbing fibers. Together, this plasticity is hypothesized to produce Purkinje patterning that matches sensory or kinematic predictions. Purkinje neurons project to the output structures of the cerebellum, the cerebellar nuclei, which send axons out of the cerebellum to influence downstream targets. One implementation of feedforward control uses these codes, called forward models, in conjunction with sensory feedback to identify mismatches of expected from actual outcomes to perform corrections, interpret sensory information, and learn. IO, inferior olive; MF, mossy fiber.

Interestingly, in the context of this review, in the 19th century, Purkinje [of Purkinje neuron fame, among other achievements (8)] is credited as among the first to propose a cancellation mechanism between postulated CD and reafferent signals (9,10). He further suggested that the two signals should be oppositely signed and temporally adjusted for comparison (9). While he could not have known that cerebellar Purkinje neurons themselves would become a candidate player in such cancellation, it is perhaps illuminating to recognize the extent to which current concepts derive from early physiologists. As discussed below, cerebellar studies have provided compelling evidence for the cerebellum mediating motor-to-sensory reference frame shifts.

SOURCES OF CD IN THE CEREBELLUM

Given the long-standing recognition of CD signaling as potentially important to cerebellar computations (see below), it is somewhat surprising that few empirical tests of the role of this information have been done. Ideally, one could record Purkinje neurons with and without CD information present to identify the contribution of CD information to Purkinje signaling. One challenge that has plagued progress into these questions is simply identifying CD pathways to the cerebellum. Numerous sources have been suggested, but owing in part to the challenges of definitions discussed above, many of these sources of motor information, however compelling theoretically, are referred to merely as feedback pathways, which sometimes obscures their potential unique computational utility. Another key challenge is the limitation of experimental tools available to specifically inhibit axonal pathways, including pathways conveying CD information. Insofar as some CD pathways are constituted from collaterals of outgoing motor command pathways, the limitations of terminal inhibition become prominent. In particular, optogenetic collateral inhibition has been viewed with general skepticism (11) despite meeting some success in published studies, including within the cerebellum (12).

Setting these concerns aside, there are numerous putative sources of motor information to the cerebellum. A number of major candidates convey motor information tuned to multiple effectors and derive from sources across the brain, including cerebral cortex, via relay in the basilar pontine nuclei (13–16). Other major brainstem sources of motor information are the lateral reticular nucleus (17–21), conveying information on cervical and limb musculature; the nucleus hypoglossis prepositus and nucleus reticularis tegmenti pontis, both encoding parameters of oculomotor control (22–24); the magnocellular red nucleus (25–27), involved in limb and facial movement; the cerebellar nuclei (12,28–30), mediating control of diverse effectors; and the ventral/rostral spinocerebellar tract (31–36), reporting activity of spinal motor neurons. Each of these putative sources of motor information could contribute to Purkinje neuron signaling, most clearly in analogous motor domains as the motor CD. Each source, however, could also be challenged in a strict sense as a source of CD, owing to potential for mixed sensorimotor signals (basilar pontine nuclei), equivocal evidence for a commanding role in movement (cerebellar nuclei), or whether they reflect proprioceptive rather than command signals (lateral reticular nucleus), as discussed in van Kan *et al.* (37). In the next three paragraphs, I look at several potential sources more carefully, discussing the considerations of whether each mossy fiber pathway should be considered to convey CD information.

The pontine nuclei are an interesting test case in the definitional challenges of CD entering the cerebellum. They are clearly a major route for motor information entering the cerebellum, relaying information from motor cortex, superior colliculus, and red nucleus among other areas, yet they themselves do not form a substantial output pathway toward muscles. They also receive massive inputs from nonmotor domains of cerebral cortex (38,39). Furthermore, evidence exists for some mixing of afferents within the basilar pontine nuclei. Within motor cortex-recipient zones, axons from some sensory regions are also present (40–45), but caudal zones receive increasingly dense afferents from sensory cortex as well as relays from nonmotor cortical regions (45). Additionally, pontine neurons themselves integrate and filter their synaptic inputs. As reviewed in Schwarz and Thier (45), pontine neurons possess intrinsic properties that preclude strict relaying of afferent input, including action potential accommodation, strong afterhyperpolarization properties, lack of spontaneous activity, high pass filtering properties, facilitating excitatory postsynaptic potentials, and intrinsic inhibitory circuitry. Thus, they proposed a functional role of pontine neurons in binding information suitable for cerebellar computations. The extent to which these characteristics transform motor cortical information is not well understood, and future studies should relate the extent of pontine information transformation to ideas of CD in service of refining computational models that use pure CD information. Despite these caveats, the cerebellar cortex is hypothesized to use cortical and collicular motor commands relayed through the pontine nuclei to sculpt volitional movements, and such signals are reasonably termed CD or efference copy in numerous models (5,46). Thus, with noted caveats, motor regions of the pontine nuclei should be considered as sources of CD to the cerebellum.

The cerebellar nuclei could be another source of CD to the cerebellar cortex. Among many other behaviors, the cerebellar nuclei are thought to drive conditioned eyelid closures, and aberrant overactivity in the nuclei has been linked to dystonic drive of muscle groups (47–49), demonstrating clear relationships with motor commands. It has been known for some time that the nuclei project back to the cerebellar cortex, but recently it was confirmed that among the mossy fiber projections are collaterals of premotor output neurons (12,30,50). The fact that collaterals of efferent neurons form mossy fibers conforms to the idea that motor patterns should be fed to areas computing internal models, a hypothesized role for Purkinje cells. Nevertheless, it is not believed that cerebellar premotor output neurons constitute the final common pathway of motor neuronal patterning; thus, downstream targets of the nuclei will transform cerebellar output toward the periphery before reaching muscles. Thus, once again, the input to the cerebellar cortex is unlikely to be a pure copy of motor neuronal activity, but it could nevertheless be essential motor information for predictive computations (51).

Brainstem cranial motor nuclei, their afferents, and spinal cord are other key candidates for CD information to the cerebellum. For instance, eye position is conveyed via the nucleus prepositus hypoglossi. This oculomotor structure contains principal neurons that project densely to abducens motor neurons. Among its diverse cell types, all appear to project to the cerebellum. Thus, nucleus prepositus input to the cerebellar cortex likely includes CD information as well as other computations made by nonprincipal neurons from this source (22,23,52,53). The medial vestibular nucleus itself is another key example of a cranial motor nucleus presynaptic to oculomotor nuclei that projects to the cerebellum. This projection has been well documented, but its cerebellar inputs are unlikely to derive from collaterals of premotor output neurons based on mismatches between peak firing rates of precerebellar neurons and output cells (54,55). The ventral spinocerebellar tract has been argued to carry CD information based on physiological observations that antidromically identified ventral spinocerebellar tract neurons show phasic modulation during stimulation-induced locomotion in deafferented cats (32,56).

Although this is a limited snapshot of the range of CD sources to the cerebellum, taken together, it highlights themes that motor information from across the brain with diverse somatotopic tuning enters the cerebellum with varying degrees of intermixed sensory information. While this sensory mixing could in theory disqualify a given site as providing a source of CD, in fact, such contamination of motor information with sensory information seems to reflect the inherent organization of the nervous system.

ROLES FOR CD IN THE CEREBELLUM

The cerebellum remains enigmatic in terms of its roles in behavior. An undisputed theme, however, is its importance in motor learning. The cerebellar cortex is proposed as a key site of plasticity; thus, many hypotheses of cerebellar function focus on its specific computations. Each of its principal neurons, the Purkinje cells, receives thousands of synapses from granule cells, which form the input layer of the cerebellar cortex (Figure 1). Granule cells receive mossy fiber inputs from diverse regions across the brainstem, some of which are described above carrying CD information. Other mossy fiber sources carry sensory information, e.g., from structures such as the external cuneate nucleus, or relay information from association and frontal cortices via subregions of the basilar pontine nuclei. Granule cells perform varying degrees of afferent mixing depending on the density of specific mossy fiber afferents in a region (16,57,58) and therefore relay sensorimotor information to Purkinje neurons. Coincident activation of granule cell axons (called parallel fibers) with a second Purkinje cell afferent, called climbing fibers, induces use-dependent changes in Purkinje firing rates that relate to motor learning (59). Many hypotheses of cerebellar function invoke this form of associative plasticity as a mechanism for motor learning. Because CD is conveyed via mossy fibers and therefore impinges on Purkinje neurons via parallel fibers, it is believed that motor information can be used as a rapid contextual cue on which Purkinje neurons can learn associative corrections. Moreover, as individual mossy fibers conveying putative CD information ramify widely (60,61), Purkinje neurons associated with a given effector, such as the eye, may receive diversely tuned CD information, such as limb-related signals, which may influence motor coordination across body parts.

One of the ideas proposed for the role of CD information in the brain that has clear psychiatric ramifications is its potential role in interpreting the self from others (62–64). The cerebellum and cerebellar-like structures have been a testing ground for some of these ideas. For instance, excellent headway has been made in understanding CD-based sensory interpretation in cerebellar-like structures of electric fish; thus, these structures provide interesting data to compare with studies of cerebellum. In the posterior lateral line lobule in electric fish, cerebellar cortical circuit architecture is repeated but lacks a climbing fiber system. This brain area is therefore referred to as a cerebellar-like structure, acknowledging the differences from cerebellum. In classic work on sensorimotor prediction in electric fish, Bell *et al.* (65–67) uncovered signals in Purkinje-like neurons that resemble negative images of sensory predictions. To show this, Bell recorded from principal neurons (akin to Purkinje cells) in the posterior lateral line lobule and paired electric organ activation (mimicking CD) with sensory electroreceptor activation (mimicking sensory reafference). Over time, this pairing reduced posterior lateral line lobule responsiveness to sensory activation. In other words, the pairing of effector activation with sensory activation led to a cancellation of the sensory responsiveness. Active cancellation was illustrated after pairing by omitting the sensory stimulation, which revealed a negative image within the Purkinje-like cell—such that when the sensory input was present, the cell's firing rate no longer changed. Thus, within the principal cells, a type of cancellation mechanism was revealed. More recent work in this system has revealed that negative image computations enhance sensory detection of unexpected stimuli, including preylike stimuli (68,69). This finding is in line with the variety of roles proposed for forward sensory reafference predictions based on motor commands, including blanking or nulling potentially disruptive reafferent input, selective enhancement of meaningful reafferent input, decoding of reafferent latency as a measure of stimulus intensity, and detection of novelty (65). Moreover, similar mechanisms have been uncovered in cerebellar-like structures in mammals; work in the dorsal cochlear nucleus has shown that Purkinje-like cartwheel cells learn to cancel self-generated sounds (70). Thus, in cerebellar-like structures in both fish and mammals, clear evidence exists linking CD and sensory reafference prediction, used to enhance sensory processing.

Whereas cerebellar-like structures reveal striking evidence of sensory cancellation from CD, similar signals have not been clearly observed in cerebellar Purkinje neurons. Rather, tantalizing evidence for such a canceling computation has been observed downstream of Purkinje neurons in the cerebellar nuclei. In a seminal study, Brooks *et al.* (71) made recordings from the rostral fastigial nucleus (rFN) while monkeys made rotational head movements. Ordinarily, a motor command to turn the head is naturally associated with vestibular reafference. To dissociate these motor and vestibular reafferent signals, a variable torque motor was attached to the head, such that the experimentalist was able to enhance, restrict, or passively generate head movements and thereby manipulate the vestibular feedback associated with movement. Before training, rFN neurons were selectively engaged during passive rotations yet showed little activity during active movements, even though the vestibular feedback was identical. This observation raised the question of what signals were present during active movements that suppressed the self-generated vestibular responses. To test this, they applied a load to the head via the torque motor, such that when the monkey voluntarily turned his head, the head would move only half as much as before. In this way, the motor command was paired with novel vestibular feedback. In early trials, rFN neurons showed activity during active head turning, in contrast to the unmanipulated state. This suggests that signals in the rFN were tuned to match predicted sensory feedback from actual sensory feedback, associated with a given motor command. Indeed, as training proceeded and the monkey experienced more head turns with altered vestibular feedback, the rFN signals that were initially activated during head turning went away, as if an internal model had learned to predict and cancel self-generated vestibular signals.

An obvious question is whether Purkinje neurons could perform this internal model computation. Indeed, many studies have proposed that Purkinje neurons compute and encode internal models, stemming from early models from Robinson studying the oculomotor system (72). The essential idea is that motor commands sent to effector organs such as the eye are fed into the cerebellum where, through adaptive mechanisms, a prediction of the future sensory/kinematic state of the effector is made. This computation is known as a forward model (5). Inverse models, which compute motor commands necessary to achieve a goal represented in sensory inputs, and hybrid forward-inverse models have also been proposed as a computation by the cerebellum (46,73), all of which use CD information in their computations. The utility of forward models in other computations is diverse. For instance, they have been proposed to serve as the basis of rapid feedback control of effectors, as they bypass the need for sensory reafference to guide movements (5,74). Relatedly, they can predict current state essential for updating the motor plan without relying on slow sensory reafference. Additionally, they can be used in conjunction with sensory feedback to produce online corrections by rapidly identifying discrepancies between predicted and actual motor output—an idea anticipated by early pioneers of CD and cerebellar control of movement alike (7,72,74). Such corrections can be fed back to the internal model as grist for sensorimotor adaptation, maintaining accurate performance of the body in the face of ever-changing levels of fatigue and motivation (51,59,72,75,76). These ideas have been extensively reviewed and nicely elaborated in a series of papers [including (5,52,72,74,77)].

Evidence in support of these ideas has appeared in recordings from Purkinje neurons in both oculomotor and limb control studies (75,78). For instance, in recordings of Purkinje neurons during adaptive changes in eye movements, several groups have described eye velocity signals in Purkinje neurons, a phenomenon that has been continually examined and elaborated on for many years (75,79). Although these signals are not the only computation of Purkinje neurons (80,81), models suggest how CD information is used in their computation, and this will be the focus here. Velocity tuning in oculomotor vermis Purkinje neurons represents an internal model, as eye velocity is not directly encoded by motor commands. Instead, brainstem saccade generator circuitry generates commands that activate extraocular muscles with burst-pause sequences, overcoming eye inertia (82). Recordings of mossy fibers made during saccadic eye movements showed activity resembling motor patterns, and anatomical work described above provides strong support for the idea that CD enters the cerebellum via mossy fiber pathways (52,83–86). As a more concrete example, Purkinje neurons have been shown to encode linear combinations of head and eye velocity, even though no mossy fiber pathways convey velocity information specifically, indicating that this is a computation specific to the Purkinje cell based on putative CD signals (83). This conjecture is difficult to test mechanistically, owing to methodological limitations. However, recent supporting evidence for this idea stems from analysis of Purkinje whisker movement tuning in mice. In an elegant experiment, it was found that kinematic encoding of whisker movements was unaffected by local anesthesia of the whisker pads, which would eliminate sensory reafference, strongly suggesting that a CD signal for reflexive whisking was sufficient to drive kinematic predictions in Purkinje cells (87).

The above discussion focuses heavily on CD information entering the cerebellum via mossy fibers to the cerebellar cortex, neglecting the potential role for the cerebellar nuclei as potential independent information processing centers. However, CD can target the cerebellar output nuclei as well, and increasing evidence indicates that this input can be fairly selective. Indeed, we and others have shown that some afferents target the nuclei exclusively (and vice versa). Moreover, of the two nuclear-selective afferents that have been described, both are putative CD pathways. One is constituted from collaterals of rubrospinal neurons and targets the cerebellar interposed nucleus in mice almost exclusively (25–27). Another originates in the median reticular formation in the rostrodorsal medulla and targets the lateral nucleus and parvocellular ventral part of the posterior interposed (88). These CD afferents to the nuclei represent deviations from control systems diagrams that use CD in forward model computations alone. The roles for these pathways are unknown but suggest that nuclear activity could follow both command signals from the motor system and predictive signals from Purkinje internal model computations (25). Interestingly, given the clear hypotheses of Purkinje neuronal suppression of predicted signals, nuclear neurons are typically active during movements, even those that have been conditioned, which would not be expected if the well-trained system should suppress reafference or goal-based signals. These observations therefore raise new questions for future research on CD, testing its roles both in computing forward models and in directly sculpting motor commands (37,48,87,89–92).

CONCLUSIONS

Taken together, the sources of CD to the cerebellum constitute a wide variety of motor-related information extending from preprocessed relays of cortical efferents to sources within one synapse of motor neurons. Psychiatric disease is often comorbid with soft motor signs, suggesting potential mechanistic overlap. By examining the roles of CD in motor behaviors, we hope to uncover general principles of how the brain handles internally generated signals in service of perception and behavior that may be informative in understanding cognitive and emotional dysfunction.

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ARTICLE INFORMATION

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