

# Disentangling acute motor deficits and adaptive responses evoked by the loss of cerebellar output

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## eLife Assessment

Using a unique cerebellar disruption approach in non-human primates, this study provides **valuable** new insight into how cerebellar inputs to the motor cortex contribute to reaching. Evidence for many claims is **solid**, but several analyses - especially with respect to control at the end of the reaches - could be expanded or clarified. Additional details about the behavioral task and a clearer description about the limits of the disruption approach with respect to selectivity are also warranted.

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## Abstract

Cerebellar patients exhibit various motor impairments, but the sequence of primary and compensatory processes leading to these deficits remains unclear. To investigate this, we reversibly blocked cerebellar outflow in monkeys performing planar reaching. The block caused a spatially tuned reduction in hand velocity due to decreased muscle torque, especially in movements with high coupling torques. Examining repeated movements to the same target revealed that during multi-joint reaching movements, the reduced velocity was driven by an acute deficit superimposed on a gradually emergent strategic slowing aimed at minimizing passive inter-joint interactions. However, the reduced velocity did not explain the decomposed and variable trajectories observed during the cerebellar block. Our findings suggest that loss of cerebellar signals leads to motor impairments through insufficient muscle torques and an altered control strategy to compensate for the impaired control of limb dynamics. However, impaired feedforward control also increases motor noise, which cannot be strategically eliminated.

## Introduction

The ability to coordinate well-timed movements greatly relies on the cerebellum as evident from studies of individuals with cerebellar ataxia (Beppu, Suda et al. 1984). The cerebellum regulates the timing of movements by predicting the mechanical interactions between adjacent joints (Ivry and Keele 1989, Manto, Bower et al. 2011), a computation that requires an internal model of feedforward control (Shidara, Kawano et al. 1993, Shadmehr and Mussa-Ivaldi 1994, Wolpert, Ghahramani et al. 1995, Wolpert, Miall et al. 1998, Kawato 1999, Sainburg, Ghez et al. 1999, Popa, Hewitt et al. 2013). However, motor impairments exhibited by individuals with cerebellar deficits extend much beyond poor motor timing. For example, during the acute phase of cerebellar injury, there is a loss of muscle tone and weakness of voluntary movements (Holmes 1917, Goldstein 1927, Holmes 1939). Cerebellar patients also exhibit movement-related sensory deficits such as an impaired visual perception of stimulus movement and perception of the limb position sense (i.e., proprioception or state estimation) during active movements (Therrien and Bastian 2015, Weeks, Therrien et al. 2017). Accumulating clinical data collected from cerebellar patients provide conflicting findings regarding the underlying pathophysiology resulting from a loss of cerebellar signals. Some researchers attribute them to an inability to compensate for inter-joint interactions (Bastian, Martin et al. 1996, Bastian, Zackowski et al. 2000), while others emphasize insufficient muscle torque generation as the core issue (Topka, Konczak et al. 1998, Boose, Dichgans et al. 1999). These conflicting reports are likely due to the heterogeneity of individuals with chronic cerebellar deficits, where the primary and secondary effects are inseparable. Therefore, the sequence of events leading to the observed motor impairments in cerebellar patients remains unclear.

To address this question, we trained monkeys to perform a planar reaching task with the arm supported by an exoskeleton. Cerebellar output to the motor cortex was reversibly blocked using high-frequency stimulation (HFS) through the superior cerebellar peduncle and the effect of this manipulation was measured during subsequent movements. Previously we have shown that HFS can effectively and reversibly interfere with the normal outflow of cerebellar signals (Nashef, Cohen et al. 2019) since this perturbation accurately replicated the behavioral deficits identified in cerebellar patients (Bastian 1997) and the changes in motor cortical activity that appear after dentate cooling in monkeys (Meyer-Lohmann, Conrad et al. 1975). In the present study, we found that the loss of cerebellar outflow led to reduced hand velocity during reaching movements reflecting two parallel underlying mechanisms. First, there was a reduction in muscle torques, even for movement directions where inter-joint interactions were low. Second, the reduction in hand velocity exhibited a spatial tuning and was greater in directions that generated large inter-joint interactions, thereby reflecting an inability to compensate for limb dynamics. The time course of these two mechanisms was identified by analyzing sequence of movements made to the same target during the cerebellar block. During such movements, hand velocity was low initially, reflecting a primary muscle torque deficit, and declined further in successive trials, revealing an adaptive motor strategy to minimize inter-joint interactions. Finally, we found that the decrease in velocity during cerebellar block could not fully explain the noisy and decomposed movements observed under these conditions, which may be due to an impaired state estimate of the limb that leads to the faulty feedforward control of inter-joint interactions. Taken together, we show that cerebellar output is essential for generating sufficient muscle torques to allow for fast and stereotypical movements while overcoming the complex inter-joint interactions inherent in such actions. The loss of this output triggers a sequence of early primary effects followed by compensatory responses aimed at mitigating these impairments. Together these processes result in significantly slower movements.

## Results

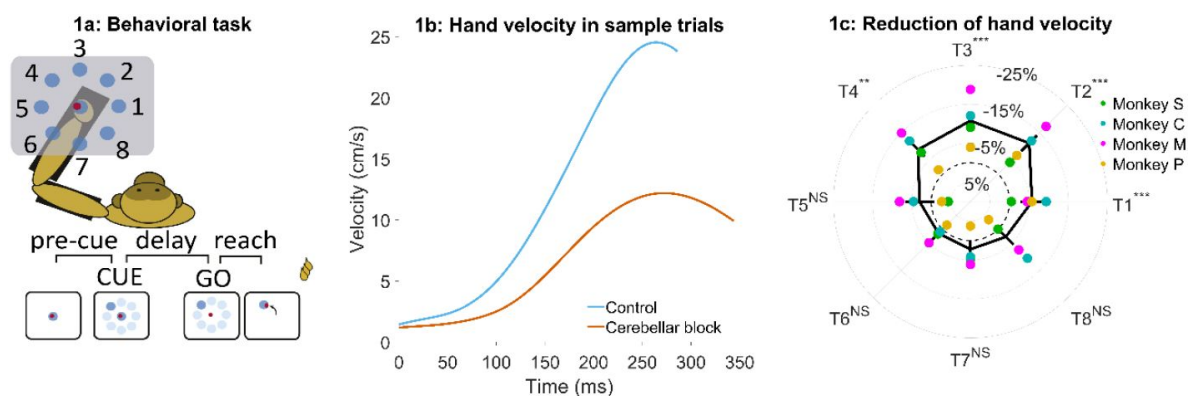
### Slower reaching movements in cerebellar block are due to weakness and impaired limb dynamics

We trained four adult monkeys (*Macaca fascicularis*) to sit in a primate chair with their upper limb supported by an exoskeleton (KINARM system) and perform planar center-out movements (**Figure 1a**). The spatial location of the targets enabled us to dissociate between shoulder-dominant (lateral targets) vs. shoulder-elbow movements (diagonal and straight targets respectively).

Cerebellar block significantly reduced the ability of the monkeys to perform the task as measured by the success rate across all the recorded sessions (mean success rate in control = 86.5%, CI [85.8, 87.2] vs. cerebellar block = 75.3%, CI [73.9, 76.7],  $p < 0.001$ ; **Supplementary table S1**). Since the monkeys had to meet strict timing criteria to perform the movements successfully during the task, we began by examining the hand kinematics. **Figure 1b** shows profiles of hand velocity in sample trials collected during the control (blue) and cerebellar block (vermillion) conditions. This example shows that movements exhibited a significant reduction in the peak hand velocity during cerebellar block. However, when compared across the targets, we found that the reduction in hand velocity was strongly modulated by the target direction (1-way ANOVA of the change in peak hand velocity, the effect of cerebellar block:  $p = 0.01$ , the effect of targets:  $p < 0.001$ ; **Supplementary table S2**). *Post hoc* comparisons further revealed that the effect of cerebellar block on outward reaching movements i.e., movements to targets 1-4 was significantly higher than on inward reaching movements i.e., movements to targets 5-8 (**Figure 1c**; mean decrease of 9.7%, CI [8.2, 11.2],  $p < 0.001$  for targets 1-4 compared to mean decrease of 2.5%, CI [0.9, 4.0],  $p = 0.21$  for targets 5-8) even though there was no difference in the peak hand velocity between the movements to the two target groups during control ( $p = 0.88$ , **Supplementary tables S3a and b**).

In the task used in our study, hand movements were made by controlling the muscle torque at the shoulder and elbow joints (Scott 2004). However, simultaneous movements of both joints also generated coupling torques due to passive interactions between limb inertial properties and joint velocities (Bernshtein 1967, Hollerbach and Flash 1982). To identify the target-specific muscle and coupling torques, we employed an inverse dynamics model of the upper limb (Fagg, Ojakangas et al. 2009) which enabled us to distinguish between the different contributions to the net torque experienced by each joint. According to this model, the net torque at each joint is the sum of both the active muscle torque and the passive coupling torque acting at that joint (see Methods section for details).

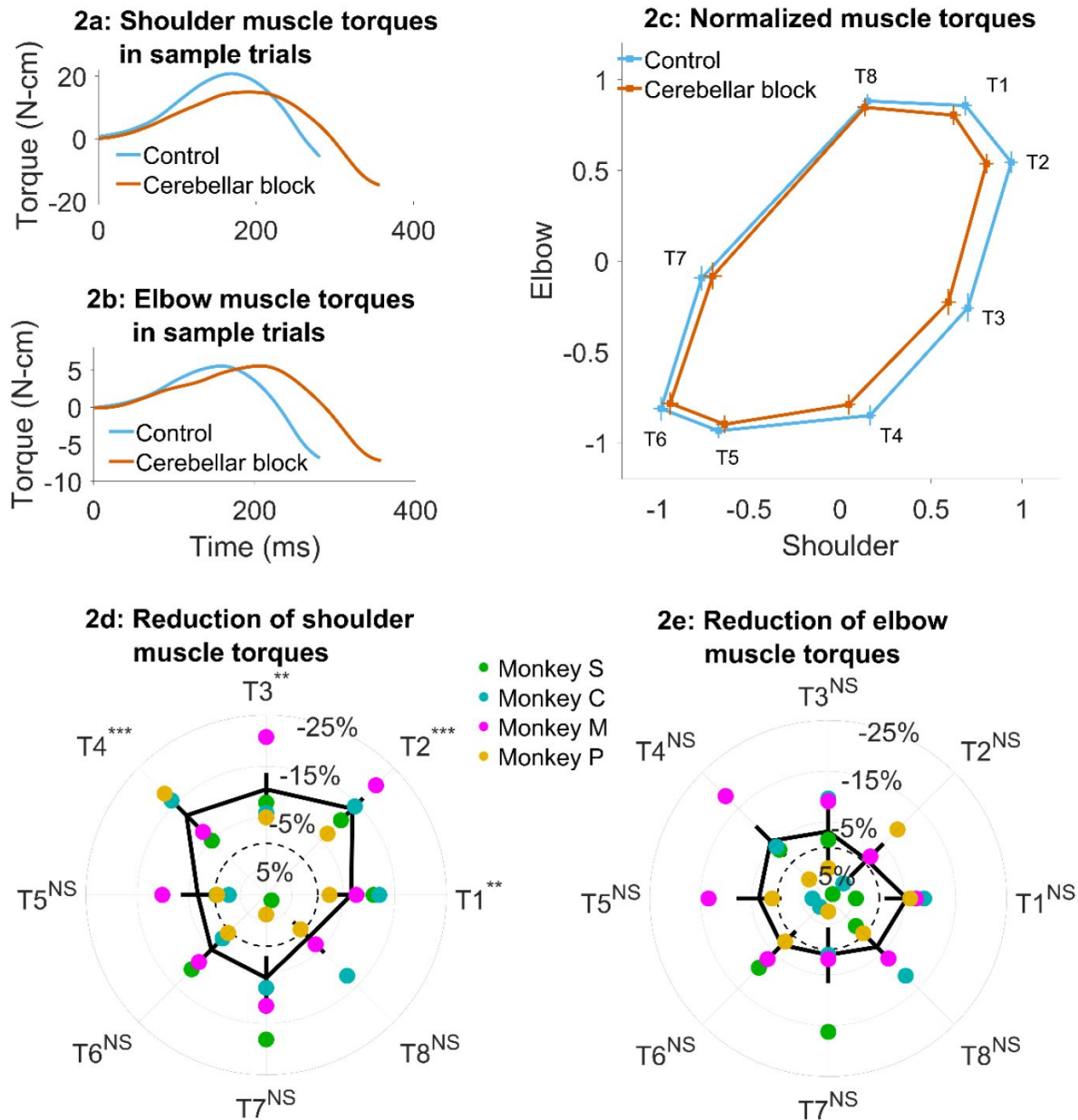
Using the inverse dynamics model, we found that the target-specific reduction in hand velocities was produced by changes in muscle commands (e.g., **Figures 2a, b**). Specifically, we observed that the muscle torque impulses, calculated by integrating the torque profiles over the early phase of movements when acceleration was positive, were reduced in a target-specific manner during the cerebellar block (**Figure 2c**; **Supplementary table S4-5**). This reduction was particularly pronounced at the shoulder joint. Furthermore, as in the case of hand velocities, *post hoc* comparisons revealed that the shoulder joint experienced a significantly greater reduction in muscle torque for targets 1-4 vs. 5-8 (**Figure 2d**; mean decrease of 10.6%, CI [9.0, 11.2],  $p < 0.001$  for targets 1-4 compared to mean decrease of 3.3%, CI [-1.3, 5.2]  $p = 0.21$  for targets 5-8). In contrast, the slight reduction in elbow torques due to the cerebellar block did not reach significance for any of the targets (**Figure 2e**). Collectively, these findings indicate that during the cerebellar block, there is a reduction in shoulder muscle torque specifically for targets involved in outward reaching movements, which leads to the target-specific reduction in hand velocity.



**Figure 1**

### Effect of cerebellar block on peak hand velocity.

(a) Schematic of the monkey performing the delayed reaching task in the KINARM exoskeleton to eight peripheral targets on the horizontal plane. The locations of the eight targets are numbered. (b) Movement-onset aligned hand velocity profiles during a sample control and cerebellar block trial performed by monkey C to target 2. Entry of the control cursor into the peripheral target marked the end of the trial. (c) Target-wise effect of the cerebellar block on peak hand velocity. For each session, the target-wise reduction in the median peak hand velocity during the cerebellar block trials was computed relative to that of control trials. The depicted values are the means  $\pm$  95% confidence intervals across all sessions pooled from all the four monkeys. The means of individual monkeys are overlaid. The dashed circle indicates no change. Statistical significance is denoted as follows:  $p \geq 0.05$ NS,  $p < 0.05$ \*,  $p < 0.01$ \*\*,  $p < 0.001$ \*\*\*. [T1-8: Targets 1-8]



**Figure 2**

### Effect of cerebellar block on muscle torques.

Movement-onset aligned shoulder (a) and elbow (b) muscle torque profiles during a sample control and cerebellar block trial performed by monkey C to target 2. Entry of the control cursor into the peripheral target marked the end of the trial. (c) Normalized muscle torque impulse at the shoulder vs. elbow per target during control and cerebellar block. For each session, we computed the target-wise median muscle torque impulse during the acceleration phase of the movement across the control and cerebellar block trials. They were then normalized by the maximum absolute torque impulse across all the targets. The depicted values are the means across all the sessions pooled from the data of all four monkeys. The 95% confidence interval of the means is indicated by the horizontal and vertical bars for the shoulder and elbow joints respectively. Target-wise effect of cerebellar block on shoulder (d) and elbow (e) muscle torque impulse. For each session, the target-wise reduction in the median torque impulse during the cerebellar block trials was computed relative to the maximum absolute value of the target-wise medians observed during the control trials. The depicted values are the means  $\pm$  95% confidence intervals across all sessions pooled from all four monkeys. The means of individual monkeys are overlaid. The dashed circle indicates no change. Statistical significance is denoted as follows:  $p \geq 0.05$ NS,  $p < 0.05$ \*,  $p < 0.01$ \*\*,  $p < 0.001$ \*\*\*. [T1-8: Targets 1-8]

Several studies have shown that individuals with cerebellar deficits exhibit an inability to correctly compensate for inter-joint interactions (Bastian, Martin et al. 1996 [↗](#), Bastian, Zackowski et al. 2000 [↗](#)). Therefore, we asked whether the reduction in muscle torques and hand velocities due to the cerebellar block could be associated with the coupling torques generated during movements in various directions. **Figures 3a [↗](#) and b [↗](#)** show the coupling torque profiles at the shoulder and elbow joints respectively during sample trials. We observed that the coupling torque impulses varied in a target-dependent manner during both the control and cerebellar block conditions (**Figure 3c [↗](#)**). Furthermore, the reduction in peak hand velocities during cerebellar block was correlated to the net coupling torque impulse (calculated as the sum of absolute coupling torque impulses at both joints) during control, particularly for the outward reaching movements (**Figure 3d [↗](#)**; targets 1-4:  $\rho = 0.33$ , CI [0.25, 0.38],  $p < 0.001$ ). This indicated that the effect of the cerebellar block on hand velocity during the outward reaching movements was strongest for targets with high coupling torques. Nevertheless, despite the significant correlation between the reduced hand velocity and coupling torques, the cerebellar block reduced the hand velocity even in the single-joint outward reaches (i.e., movements to target 1, mean reduction in hand velocity = 5.8%, CI [2.8, 8.7],  $p < 0.001$ ) where the elbow was stationary. This finding indicated a reduction in the motor command which occurred in addition and beyond the effect attributable to the impaired control of coupling torques alone.

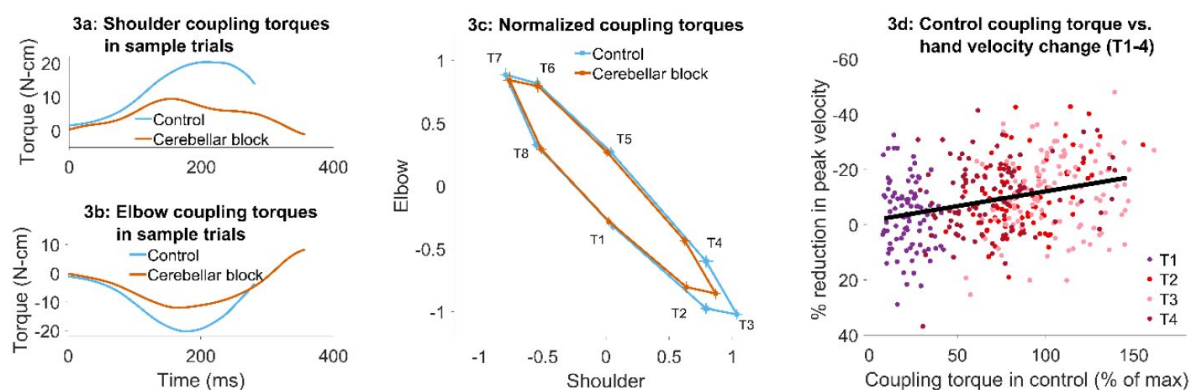
Overall, the cerebellar block produced a significant impact on the kinematics and dynamics of outward reaching movements. Specifically, the cerebellar block caused slower hand velocities due to a systematic, target- and joint-specific reduction in muscle torques for these movements, which strongly correlated with the coupling torques. Additionally, a reduction in muscle torques was also observed during the single-joint outward reaching movements, indicating an additional component of muscle torque insufficiency that further exacerbated motor impairment following cerebellar block.

## Hand velocity exhibits an adaptive trend during repeated movements to the same target during cerebellar block

The advantage of using a reversible cerebellar block in an animal model is the ability to track the temporal profile of motor impairments induced by this condition, allowing us to distinguish between primary and compensatory effects. To this end, we assessed changes in hand kinematics produced by the cerebellar block across successive trials. Specifically, we examined the evolution of peak hand velocities for single-joint (target 1) vs. dual-joint outward reaches (data pooled for movements to targets 2-4) during blocks of control and cerebellar block trials. **Figure 4a [↗](#)** illustrates this procedure. Since the targets were presented in a pseudorandom order during each block of trials, we collected for each block the tested target, while keeping its order of presentation to generate a temporally accurate sequence of trials, all directed towards the same single target.

We found that during the control condition, peak hand velocity remained stable across successive trials. In contrast, cerebellar block affected hand velocity in a trial- and target-dependent manner (**Figure 4b, c [↗](#)**). For movements to target 1 (i.e., single-joint movements), hand velocity was lower than control but unaffected by the temporal sequence of target presentation (trial type  $\times$  trial sequence interaction effect:  $p = 0.69$ , **Supplementary Table S6 [↗](#)**). However, for movements to targets 2-4, hand velocity was lower than control in the early trials and declined further with successive trials (trial type  $\times$  trial sequence interaction effect:  $p = 0.007$ , **Supplementary Table S7 [↗](#)**).

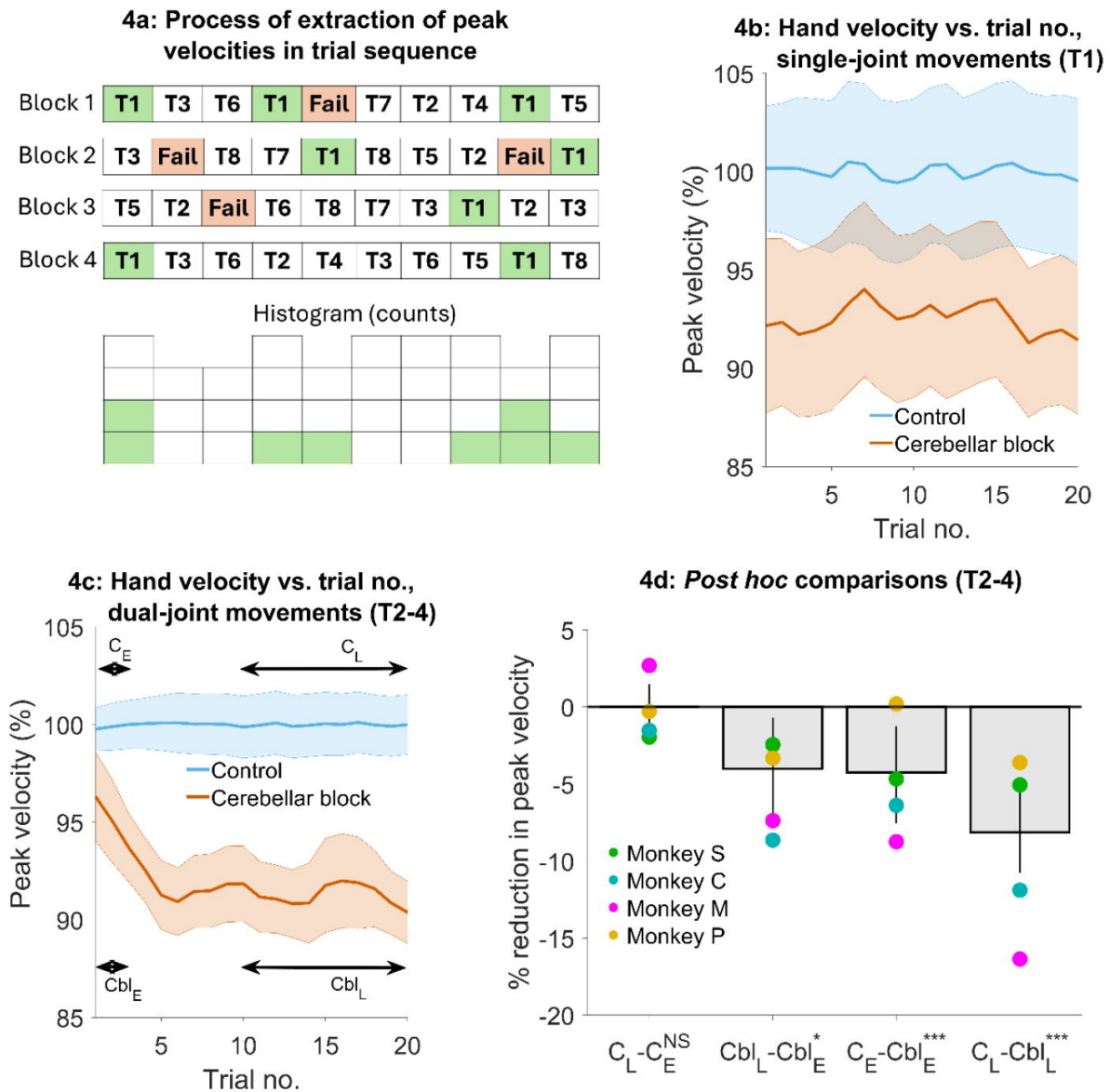
To further quantify the effect of trial sequence on movements to targets 2-4, we performed *post hoc* comparisons (**Figure 4d [↗](#)**). These comparisons revealed that during the cerebellar block, hand velocity was 4.3% (CI [1.0, 7.3],  $p < 0.001$ ) lower than control during the first 1-2 trials. With successive trials, the hand velocity declined further before reaching an asymptote during the late trials 11-20 at 8.2% (CI [5.7, 10.7],  $p < 0.001$ ) lower than the control.



**Figure 3**

### Effect of cerebellar block on coupling torques.

Movement-onset aligned shoulder (a) and elbow (b) coupling torque profiles during a sample control and cerebellar block trial performed by monkey C to target 2. Entry of the control cursor into the peripheral target marked the end of the trial. (c) Normalized coupling torque impulse at the shoulder vs. elbow per target during control and cerebellar block. For each session, we computed the target-wise median coupling torque impulse during the acceleration phase of the movement across the control and cerebellar block trials. They were then normalized by the maximum absolute torque impulse across all the targets. The depicted values are the means across all the sessions pooled from the data of all four monkeys. The 95% confidence interval of the means is indicated by the horizontal and vertical bars for the shoulder and elbow joints respectively. (d) Change in peak hand velocity due to cerebellar block plotted against the coupling torque in control for each session for the reaching movements (T1-4). The target-wise reduction in the median peak hand velocity during the cerebellar block trials was computed relative to that of control trials. The target-wise median coupling torque during the control trials of each session was normalized to the median across all trials of all sessions per monkey. The depicted data contains all the sessions pooled from all four monkeys. The black line overlayed on the scatter indicates the least-squares linear regression fit to the data points. [T1-8: Targets 1-8]



**Figure 4**

### Effect of the cerebellar block on hand velocity across successive trials.

(a) Schematic of the process of extraction of peak hand velocity for movements to a particular target from blocks of control/cerebellar block trials while preserving the order in which the target was presented. For each block, the peak velocity for movements to a particular target (in this example target 1) was extracted while retaining the trial numbers in which it was presented in the block. This enabled us to examine the evolution of the peak velocity across the sequence of presentation of the target during control vs. cerebellar block. (b) Mean  $\pm$  95% confidence intervals of the peak hand velocity for movements to target 1 across all the trial blocks pooled from all four monkeys. For each monkey, the peak hand velocities were normalized to the median peak velocity of the early trials 1-2 from all the control blocks. (c) Same as in (b) but for targets 2-4. (d) Post hoc comparisons between early trials 1-2 and late trials 11-20 during control and cerebellar block. Statistical significance is denoted as follows:  $p \geq 0.05$ NS,  $p < 0.05^*$ ,  $p < 0.01^{**}$ ,  $p < 0.001^{***}$ . [E: Early, L: Late, C: Control, Cbl: Cerebellar block; T1-8: Targets 1-8]

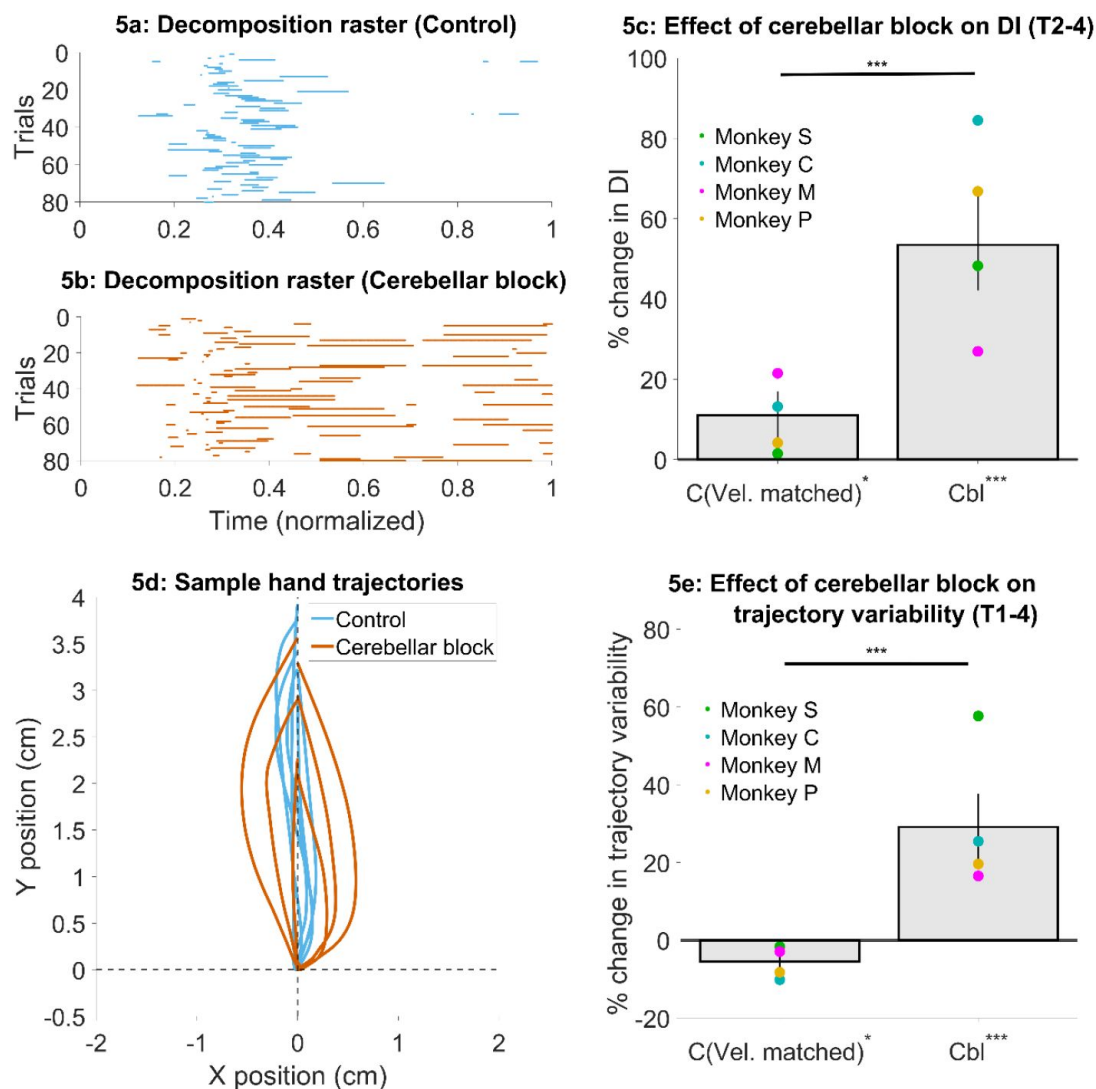
Taken together these results reveal that the hand velocity of dual-joint outward reaching movements during cerebellar block was already low initially, reflecting a primary deficit. Over and above this, there was a further progressive decline of the hand velocity during successive movements, most likely due to an adaptive response to the inability to compensate for coupling torques. Furthermore, this adaptive response was not observed in the case of single-joint movements where the coupling torques were low, and therefore inter-joint interactions did not play a significant role.

## Slow movements during the cerebellar block cannot fully account for the impaired motor timing

Individuals with cerebellar deficits suffer from poorly timed movements, including asynchronous activation of joints during multi-joint movements leading to movement decomposition (Bastian, Martin et al. 1996 [↗](#)) or spatial variability in their movement trajectories across trials (Day, Thompson et al. 1998 [↗](#)). However, these properties of movement are also velocity-dependent (Bastian, Martin et al. 1996 [↗](#), Osu, Morishige et al. 2015 [↗](#)). Therefore, it is conceivable that the combination of primary deficit and adaptive reduction in velocity to reduce the effects of coupling torque observed in our results is the main driver of abnormal motor timing. To evaluate this, we examined movement decomposition and trajectory variability during the outward reaching movements (which exhibited a significant reduction in hand velocity during cerebellar block) and measured the impact of hand velocity on these measures.

To quantify movement decomposition, we normalized the movement times of individual trials to range from 0 to 1 and identified the bins where either the shoulder or the elbow joint paused (angular velocity  $< 20^\circ/\text{s}$ ) while the other joint continued moving (Bastian, Martin et al. 1996 [↗](#)). In control trials, decomposition was primarily observed during the early phase of movement, where joint velocities are low making this measure more sensitive (Figure 5a [↗](#)). However, during cerebellar block trials, decomposition occurred throughout the movement (Figure 5b [↗](#)) similar to individuals with cerebellar deficits (Bastian, Martin et al. 1996 [↗](#)). To quantify this effect, we calculated a decomposition index for each trial, representing the proportion of movement time during which the movement was decomposed, as defined above. Overall, the cerebellar block increased movement decomposition by 53.5% (CI [42.2, 66.0],  $p < 0.001$ ). Next, we asked whether movement decomposition was mainly due to lower hand velocities. We therefore selected a subset of control trials that matched the cerebellar block trials in their peak velocities. However, even though movement decomposition in these control trials was higher (11.0%, CI [5.2, 17.0],  $p = 0.03$ ) compared to all control trials, it was still significantly lower ( $p < 0.001$ ) than the velocity-matched cerebellar block trials (in three out of the four monkeys as shown in Figure 5c [↗](#)). This indicates that even at matched velocities, movements during cerebellar block were more decomposed relative to the control.

Next, we assessed the effect of cerebellar block and hand velocity on trajectory variability. To this end, we first aligned the hand trajectories to have the same starting position, and then rotated them so that their endpoint was located on the positive Y-axis (Figure 5d [↗](#)). Subsequently, we defined the error in each trajectory as the maximal perpendicular distance from the Y-axis. The standard deviation of the errors across all trials was used to quantify the trial-to-trial trajectory variability. Normally, slower movements are also less variable due to the speed-accuracy tradeoff (Plamondon and Alimi 1997 [↗](#)). Therefore, we selected the subset of control trials that matched the cerebellar block trials in their peak velocities. Indeed, the trajectory variability in this subset of slower control trials was 5.5% (CI [0.9, 9.9],  $p = 0.02$ ) lower than that of all control trials. However, when we compared the subset of velocity matched control and cerebellar block trials, we found that cerebellar block exhibited 34.6% (CI [26.2, 43.2],  $p < 0.001$ ) higher trajectory variability (Figure 5e [↗](#)). In other words, despite slower movements, cerebellar block increased trajectory variability.



**Figure 5a-c**

### Effect of the cerebellar block on the decomposition of dual-joint movements.

(a) Binary decomposition raster of sample trials for movements made to target 2 by monkey C during control. The duration of each trial was normalized to 0-1 (bin width = 0.001) and then decomposition was computed for each bin based on whether either (but not both) of the shoulder or the elbow joint velocity was less than 20°/s. (b) Same as in (a) but for movements to target 2 by monkey C during cerebellar block. (c) Change in decomposition index (i.e., the proportion of the movement time during which the movement was decomposed, as defined above) for movements to targets 2-4 during velocity-matched control and cerebellar block trials relative to all control trials. The change in median decomposition was computed for each session. The depicted values are the mean  $\pm$  95% confidence intervals across all sessions pooled from all four monkeys. The individual means of each monkey are overlaid. **Figure 5d-e: Effect of the cerebellar block on inter-trial trajectory variability.** (d) Sample hand trajectories during control vs. cerebellar block trials for movements to target 2 by monkey C. The starting point of the trajectories was shifted to the origin and then they were rotated about the origin so that their endpoints lie on the positive Y-axis. (e) Change in Inter-trial trajectory variability for movements to targets 2-4 during velocity-matched control and cerebellar block trials relative to all control trials. The trajectory variability was measured as the standard deviation of the maximum perpendicular distance of the trajectories from the Y-axis after transforming them as in (d). The change in trajectory variability for the cerebellar block trials was computed relative to the control trials for each session. The depicted values are the mean  $\pm$  95% confidence intervals across all sessions pooled from all four monkeys. The individual means of each monkey are overlaid. Statistical significance is denoted as follows:  $p \geq 0.05$ NS,  $p < 0.05^*$ ,  $p < 0.01^{**}$ ,  $p < 0.001^{***}$ . [C: Control, Cbl: Cerebellar block; T1-8: Targets 1-8; DI: Decomposition index]

## Discussion

Individuals with cerebellar deficits exhibit altered motor behavior related mostly to poor timing and coordination of voluntary movements. Understanding the impairments that follow cerebellar lesions is often complicated by the fact that the studies of this question mostly rely on a heterogeneous population due to various levels and types of cerebellar pathologies. Here we addressed this question by using high-frequency stimulation to reversibly block cerebellar output to the motor cortex in behaving monkeys wearing an exoskeleton (Nashef, Cohen et al. 2019) and comparing the post-block motor behavior to control conditions. Our results indicate that cerebellar block leads to decreased hand velocity, particularly during the outward reaching movements via two mechanisms: a reduction in muscle torques suggesting motor weakness, and spatially tuned decreases in velocity in targets where large inter-joint interactions occur, indicating a failure to compensate for limb dynamics. Analyzing the time course of these impairments revealed partially overlapping processes: an initial reduction in hand velocity due to the inability to generate sufficient muscle torques, followed by a further progressive decline in hand velocities during subsequent movements during the cerebellar block. This secondary decline was observed only in the case of dual-joint movements, suggesting an adaptive strategy to minimize inter-joint interactions. Finally, we observed increased motor noise in terms of movement decomposition and trial-to-trial trajectory variability which were independent of the slower movements observed during the cerebellar block.

### Target-dependent reduction in hand velocity and coupling torques during reaching movements during the cerebellar block

Cerebellar block led to a target-specific reduction in hand velocity, even though the arm was fully supported by the exoskeleton and thus the limb weight did not play any role. This observation replicates findings made in previous studies that have documented the slowing of movements in individuals with cerebellar lesions (Wild and Dichgans 1993, Topka, Konczak et al. 1998, Konczak, Schoch et al. 2005) as well as in monkeys that underwent dentate cooling (Tsujimoto, Gemba et al. 1993). It was argued that the reduction in hand velocity may be a compensatory strategy to counteract the impaired ability to manage inter-joint coupling torques in the absence of cerebellar input to the motor cortex (Wild and Dichgans 1993, Bastian and Thach 1995, Bastian, Martin et al. 1996, Beer, Dewald et al. 2000). Since coupling torques in multi-joint movements are generated in a velocity-dependent manner (Hollerbach and Flash 1982, Virji-Babul and Cooke 1995), slowing down the movement not only simplifies its kinetics (by reducing the impact of coupling torques) but also allows more time for slower visual feedback to aid in guiding the movement (Jeannerod 1988). Our findings, which demonstrate a correlation between the extent of hand velocity reduction during cerebellar block and the magnitude of coupling torque under control conditions, further corroborate this hypothesis and confirms our approach for reversible inactivation of cerebellar output as a model for ataxia. Furthermore, our model enabled us to study this effect rigorously and systematically while dissociating it from the other primary effects of cerebellar block as discussed below.

### Muscle torque deficit is an acute response to the cerebellar block

Poor compensation for coupling torque is a fundamental deficit in cerebellar ataxia (Bastian, Zackowski et al. 2000). However, early studies have reported the occurrence of muscle weakness (asthenia) and hypotonia acutely following cerebellar injury in humans (Haines, Manto et al. 2007) or experimental lesions in animals (Luciani 1893, Bremer, Roger et al. 1935, Fulton and Dow 1937, Granit, Holmgren et al. 1955). Both Luciani (Luciani 1893) and Holmes (Holmes 1917) described a triad of cerebellar deficits to be atonia (low muscle tone), asthenia (weakness of voluntary movements), and astasia (oscillation of the head and trunk). Importantly,

muscle weakness is typically characteristic of the acute phase of injury, especially in the upper extremity, and tends to normalize gradually over weeks to months, depending on the severity of the injury (Konczak, Pierscianek et al. 2010 [↗](#)). It is therefore conceivable that studies in humans with cerebellar deficits, which often included subjects at the chronic stage of the lesion, may have underestimated the contribution of muscle weakness which by that time was already less pronounced.

We explored the acute outcome of the cerebellar block, a phase in which muscle weakness may play a more prominent role. Importantly, we showed that muscle torque deficits appear immediately after the cerebellar block, resulting in lower hand velocity already in the first few trials of both single- and dual-joint movements. This kind of fast response is less likely to be a strategic response aimed at mitigating the loss of cerebellar signals. This finding is consistent with the initial weakness followed by a gradual recovery of function observed in acute lesions of other neural structures involved in movement control, including the primary (Pressman and Rosen 2015 [↗](#)) and premotor cortices (Freund 1985 [↗](#), Freund and Hummelsheim 1985 [↗](#)). It also aligns with the understanding that cerebellar output provides a strong excitatory drive to the motor cortex (Shinoda, Yamazaki et al. 1982 [↗](#), Hore and Flament 1988 [↗](#), Nashef, Cohen et al. 2018 [↗](#)) and several subcortical descending motor systems (Ruigrok 2013 [↗](#)), beyond its well-known role in motor timing and coordination. Following the initial reduction in hand velocity observed in our study, there was a further gradual decline across subsequent trials specifically for the dual-joint movements, a behavior profile that is more consistent with strategic effort, most likely in response to the inability to compensate for limb dynamics.

Therefore, the slower movements in the absence of cerebellar signals are likely due to two main factors: (i) a primary inability to generate sufficient muscle torques due to the lack of synchronized recruitment of the cortical and sub-cortical descending motor systems via the cerebellar output, and (ii) a secondary adaptive strategy aimed at compensating for the impaired prediction of limb dynamics due to the loss of feedforward control signals from the cerebellum.

## Insufficient muscle torques vs. poor inter-joint coordination

Unlike most previous clinical studies that examined motor deficits in individuals with chronic cerebellar injuries, our study utilized a reversible model of cerebellar block. This approach enabled us to track the temporal evolution of motor deficits from the onset of the block within the same study participant. Although several studies have explored the nature of motor deficits following cerebellar injuries, there remains considerable debate regarding the fundamental mechanisms driving these deficits. Some studies have suggested that the inability to compensate for inter-joint interactions is the primary driver of the observed motor abnormalities in cerebellar injury (Bastian, Martin et al. 1996 [↗](#), Bastian, Zackowski et al. 2000 [↗](#)). In contrast, other studies have emphasized the inability to generate sufficient muscle torques as the core deficit in cerebellar ataxia while claiming that inter-joint coordination is unaffected following cerebellar lesions (Topka, Konczak et al. 1998 [↗](#), Boose, Dichgans et al. 1999 [↗](#)). Given these conflicting findings, our study aimed to systematically explore the entire spectrum of motor deficits using a model of reversible cerebellar block. First, we found that the deficits in muscle torque are more pronounced for the reaching movements as compared to the retrieval movements. We identified both an acute insufficiency in muscle torque generation and the inability to compensate for coupling torques as potential mechanisms underlying the observed slowness during the reaching movements. Moreover, we delineated the time course of these deficits, providing insights into their evolution from the onset of cerebellar block.

## The asymmetric effect of cerebellar block on outward vs. inward reaching movements

We observed a notable distinction in the impact of cerebellar blockage on outward vs. inward reaching movements. At a collective level, this variance could be attributed to the disparity in magnitude of coupling torque impulse, with movements towards targets 2-4 exhibiting 18.7% (CI [13.1, 24.1],  $p = 0.008$ ) higher coupling torque impulse compared to those towards targets 6-8. However, this explanation does not hold consistently when examined at the individual target level. For instance, while the coupling torque was higher for movements towards target 7, the effects of cerebellar blockage were less pronounced compared to those observed for target 1, where the coupling torques are considerably lower. There are two possible explanations for this discrepancy. One possibility is that the effect of cerebellar block exhibits a bias in the direction of shoulder flexion (i.e., for movements to targets 1-4). In fact, several early studies in cats (Hare, Magoun et al. 1936 [\[1\]](#), Chambers 1947 [\[2\]](#)), non-human primates (Magoun, Hare et al. 1935 [\[3\]](#)) and humans (Nashold and Slaughter 1969 [\[4\]](#)) have all reported a bias towards the activation of ipsilateral flexors of the arm following stimulation of the deep cerebellar nuclei and the superior cerebellar peduncle. Furthermore, lesioning of these structures led to the reduction of ipsilateral flexor tone and power (Schneider and Crosby 1963 [\[5\]](#), Nashold and Slaughter 1969 [\[4\]](#)). The cerebellar output influences the excitability of spinal interneurons either directly (Bantli and Bloedel 1975 [\[6\]](#), Asanuma, Thach et al. 1980 [\[7\]](#), Sathyamurthy, Barik et al. 2020 [\[8\]](#)) or via indirect relays in the subcortical descending motor systems like the rubrospinal and the reticulospinal pathways (Ruigrok 2013 [\[9\]](#)). Since the spinal interneurons influence the activity of flexor muscles twice as often as extensor muscles (Perlmutter, Maier et al. 1998 [\[10\]](#)), this might explain why the cerebellar block had a stronger effect on movements involving shoulder flexion (i.e., outward reaching movements) relative to shoulder extension (i.e., inward reaching movements) in our study. Alternatively, the initial position of the limb in our experimental setup (i.e., on the central target) might have been favorable for movements in the direction of shoulder extension, thereby making them easier to perform.

## Asynchronous joint movements and motor variability are unaffected by the movement velocity in cerebellar block

Abnormally high motor variability (Day, Thompson et al. 1998 [\[11\]](#), Timmann, Watts et al. 1999 [\[12\]](#), Schlerf, Xu et al. 2012 [\[13\]](#)) and decomposition of multi-joint movements (Bastian, Martin et al. 1996 [\[14\]](#)) are core deficits in cerebellar patients. We showed that the cerebellar block decomposed the dual-joint movements into temporally isolated single-joint actions and led to an increased trial-to-trial spatial noise. These two measures can be affected by the reduction in movement velocities. Our results showed that even though movement decomposition increased with a reduction in velocity in control trials, they were still significantly lower than that of velocity-matched cerebellar block trials. Second, the trial-to-trial spatial noise in hand trajectories increased during cerebellar block despite the slower movement speeds. The cerebellum is known to participate in the planning of movements by providing an internal model of the limb which is necessary for predicting the sensory outcomes of motor commands (Wolpert, Miall et al. 1998 [\[15\]](#)). For this purpose, the cerebellum aids in estimating the state of the limb by integrating the sensory information of its last known state with predictions of its response to the latest motor command (Miall, Christensen et al. 2007 [\[16\]](#), Miall and King 2008 [\[17\]](#)). Therefore, in the absence of cerebellar signals, there are programming errors in the feedforward command required to launch the limb accurately toward a target (Day, Thompson et al. 1998 [\[11\]](#)). These feedforward errors may in turn translate into the noisy joint activation patterns and variable hand trajectories observed in our results. Moreover, the persistence of these deficits independently of the movement speeds observed during cerebellar block indicates that they cannot be compensated for, unlike the impaired prediction of inter-joint interactions which are strategically dealt with by reducing the movement velocity.

In summary, our study systematically investigated the temporal progression and distinct mechanisms of motor deficits in a controlled, reversible animal model of cerebellar block. These include an acute onset muscle torque deficit, impaired compensation of limb dynamics, and increased motor noise. We aim to further explore the neural correlates of these deficits in future studies.

## Materials and Methods

### Experimental subjects

This study was performed on four adult female monkeys (*Macaca fascicularis*, weight 4.5-8 kg). The care and surgical procedures of the subjects will be in accordance with the Hebrew University Guidelines for the Use and Care of Laboratory Animals in Research, supervised by the Institutional Committee for Animal Care and Use.

### Behavioral task

Each monkey was trained to sit in a primate chair and perform planar, center-out movements. During the task, the left upper arm was abducted 90° and rested on cushioned troughs secured to links of a two-joint exoskeleton (KINARM, BKIN Technologies Ltd.). The sequence of events in each trial of this task was as follows. First, the monkey located a cursor (projected on a horizontal screen immediately above its arm) within a central target. After 500-800 ms, a randomly selected peripheral target (out of 8 evenly distributed targets) was displayed. The monkey had to wait until the central target disappeared (i.e., the 'go' signal) and then reached the cued peripheral target. This delay between the cue and the 'go' signal was 450-600 ms. The monkey was rewarded with a drop of applesauce if it moved the cursor to the correct target within 1 s of the 'go' signal.

### Insertion of the stimulating electrode into the superior cerebellar peduncle

After the training was completed, a square recording chamber (24×24 mm) was attached to the monkey's skull above the upper limb-related area of the motor cortex in a surgical procedure under general anesthesia. To insert a chronic stimulating electrode into the ipsilateral superior cerebellar peduncle (SCP), a round chamber (diameter = 19 mm) was also implanted above the estimated insertion point (as per stereotactic measurements) during the surgery for the cortical chamber implantation. Subsequently, a post-surgery MRI was used to plan the trajectory for the electrode insertion into the SCP. After a recovery and re-training period, a bi-polar concentric electrode (Microprobes for Life Science Inc.) was inserted through the round chamber along the planned trajectory. During the process of insertion, the evoked multi-unit activity in the primary motor cortex was simultaneously monitored to identify the precise location where the stimulating electrode should be secured (Nashef, Cohen et al. 2018 [DOI](#), Nashef, Rapp et al. 2018 [DOI](#)).

### High frequency stimulation to block the cerebellar outflow to the motor cortex

The superior cerebellar peduncle was blocked using high-frequency stimulation (HFS). This stimulation protocol consisted of a train of biphasic rectangular-pulse stimuli (where each phase was 200  $\mu$ s) applied at 130 Hz. Each train was delivered at a fixed intensity of 150-250  $\mu$ A. In our earlier study, we demonstrated that by using this manipulation we can successfully replicate the impaired motor timing and coordination characteristic of cerebellar ataxia (Nashef, Cohen et al. 2019 [DOI](#)). Furthermore, we also demonstrated that at the motor cortical level, this manipulation leads to a loss of response transients at movement onset and decoupling of task-related activity, similar to findings observed in studies where the dentate nucleus was cooled (Meyer-Lohmann, Conrad et al. 1975 [DOI](#)). Deep brain stimulation (DBS) is a perturbation similar in properties to the

HFS we used, which is routinely used in clinical practice for similar purposes of interfering with neural circuitries that underwent pathological changes (Perlmutter and Mink 2006) although in both applications there is no accurate measure for the extent of the block (i.e., the fraction of fibers which become ineffective in these conditions) other than the behavioral consequences. HFS probably imposes only a partial block of the CTC system, but the behavioral outcomes we found here during an adaptation task further confirm the validity of this approach.

## Data collection protocol

Each monkey performed the experimental task for several days (sessions). A total of 46, 29, 36, and 54 sessions of data were collected from Monkeys S, C, M, and P, respectively. Each session was divided into three or four sub-sessions. Each sub-session included blocks of control trials (~80 trials) and trials with the superior cerebellar peduncle blocked using high-frequency stimulation (~50 trials) as described above. During the task performance, the following behavioral data was obtained at 1000 Hz using the KINARM's motor encoders: (i) Hand position in the x-y plane of movement, (ii) Elbow and shoulder joint angular positions, velocities, and accelerations. The lengths of the upper arm and forearm of each monkey were measured as the distances from the head of the humerus to the lateral epicondyle and from the lateral epicondyle to the palm, respectively. The inertial properties of the upper limb were estimated using the monkey's body weight (Cheng and Scott 2000).

## Processing of the behavioral data

All data analysis was performed in MATLAB R2021b (MathWorks Inc.). The raw kinematic data was low-pass filtered by using a second order Butterworth filter (cutoff = 10Hz) and then epoched into trials. For this purpose, the start and end events were taken as the time of presentation of the cue (i.e., the peripheral target) and the time of entry of the control cursor into the peripheral target, respectively. This cutoff meant that a major portion of the extracted segment of each trial was the acceleration phase of the movement. The movement onset was defined as the time when the radial hand velocity exceeded 5% of its peak. Subsequently, all the trials were zero-centered around the calculated movement onset. We then applied a two-link inverse dynamics model of the upper arm to the kinematic data to compute the coupling and muscle torques acting on the elbow and shoulder joints (Fagg, Ojakangas et al. 2009). The inverse dynamics equations of motion for the combined system consisting of the monkey's arm and the associated moving components of the KINARM were used to compute the joint torques:

$$T_{me} = T_{ne} - T_{ce} \quad (i)$$

$$T_{ms} = T_{ns} - T_{cs} \quad (ii)$$

where  $T_{ne}$  and  $T_{ns}$  are the net torques (proportional to the joint's acceleration),  $T_{ce}$  and  $T_{cs}$  are passive coupling torques, and  $T_{me}$  and  $T_{ms}$  are the active muscle torques acting at the elbow and shoulder joints respectively. The expanded formulas for computing each of the above terms are provided by equations 1a-2e in the methods section C (Fagg, Ojakangas et al. 2009). It must be noted that the 'muscle' torques computed here include the effects of the actively generated muscle forces as well as the viscoelastic effects that result from the musculoskeletal system and the KINARM (Smith and Zernicke 1987).

## Statistical analysis

We used linear mixed effects analysis to evaluate the effects of predictor variables of interest on the computed response variables. This allowed us to account for the variability across the monkeys which was modeled as a random effect. Each data sample for this model was obtained by

calculating the median of all the trials for each unique combination of the response variable(s) per session. We computed the change in the measured outcome variable due to the cerebellar block per session using the following formula:

$$\frac{\text{Median response during cerebellar block} - \text{median response during control}}{\text{Median response during control}} \times 100$$

For post-hoc comparisons, we used the ‘coefTest’ function from MATLAB’s ‘fitlme’ to perform hypothesis testing on the fixed effects. This involved specifying the contrast matrices to evaluate specific hypotheses regarding the differences in the response variables across the levels of the predictor variables. The ‘coefTest’ function allowed us to obtain p-values for these comparisons. The computed p-values were then corrected using the Benjamini-Hochberg procedure to control the false discovery rate for multiple post-hoc comparisons, wherever applicable (Haynes 2013 [↗](#)). A significance level of 0.05 was used for all comparisons in this study. For estimation of the group means and their confidence intervals, we pooled the per session data from all monkeys after ensuring that effects are consistent across the monkeys. For further clarity, we have also overlaid the means of the measured variables from individual monkeys on all our plots of summary statistics.

## Data availability statement

Data and code used in this manuscript is available publicly as a GitHub repository (Sinha et al. 2024 [↗](#)).

## Acknowledgements

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## Additional files

**Supplementary tables** [↗](#)

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**Reviewer #1 (Public review):**

Summary:

In a previous work, Prut and colleagues had shown that during reaching, high-frequency stimulation of the cerebellar outputs resulted in reduced reach velocity. Moreover, they showed that the stimulation produced reaches that deviated from a straight line, with the shoulder and elbow movements becoming less coordinated. In this report, they extend their previous work by the addition of modeling results that investigate the relationship between the kinematic changes and torques produced at the joints. The results show that the slowing is not due to reductions in interaction torques alone, as the reductions in velocity occur even for movements that are single joints. More interestingly, the experiment revealed evidence for the decomposition of the reaching movement, as well as an increase in the variance of the trajectory.

Strengths:

This is a rare experiment in a non-human primate that assessed the importance of cerebellar input to the motor cortex during reaching.

Weaknesses:

My major concerns are described below.

If I understand the task design correctly, the monkeys did not need to stop their hand at the target. I think this design may be suboptimal for investigating the role of the cerebellum in control of reaching because a number of earlier works have found that the cerebellum's contributions are particularly significant as the movement ends, i.e., stopping at the target. For example, in mice, interposed nucleus neurons tend to be most active near the end of the reach that requires extension, and their activation produces flexion forces during the reach (Becker and Person 2019). Indeed, the inactivation of interposed neurons that project to the thalamus results in overshooting of reaching movements (Low et al. 2018). Recent work has also found that many Purkinje cells show a burst-pause pattern as the reach nears its endpoint, and stimulation of the mossy fibers tends to disrupt endpoint control (Calame et al. 2023). Thus, the fact that the current paper has no data regarding endpoint control of the reach is puzzling to me.

Because stimulation continued after the cursor had crossed the target, it is interesting to ask whether this disruption had any effects on the movements that were task-irrelevant. The reason for asking this is because we have found that whereas during task-relevant eye or tongue movements the Purkinje cells are strongly modulated, the modulations are much more muted when similar movements are performed but are task-irrelevant (Pi et al., PNAS 2024; Hage et al. Biorxiv 2024). Thus, it is interesting to ask whether the effects of stimulation were global and affected all movements, or were the effects primarily concerned with the task-relevant movements.

If the schematic in Figure 1 is accurate, it is difficult for me to see how any of the reaching movements can be termed single joint. In the paper, T1 is labeled as a single joint, and T2-T4 are labeled as dual-joint. The authors should provide data to justify this.

Because at least part of this work was previously analyzed and published, information should be provided regarding which data are new.

<https://doi.org/10.7554/eLife.105152.1.sa3>

#### **Reviewer #2 (Public review):**

This manuscript asks an interesting and important question: what part of 'cerebellar' motor dysfunction is an acute control problem vs a compensatory strategy to the acute control issue? The authors use a cerebellar 'blockade' protocol, consisting of high-frequency stimuli applied to the cerebellar peduncle which is thought to interfere with outflow signals. This protocol was applied in monkeys performing center outreaching movements and has been published from this laboratory in several preceding studies. I found the take-home-message broadly convincing and clarifying - that cerebellar block reduces muscle activation acutely particularly in movements that involve multiple joints and therefore invoke interaction torques, and that movements progressively slow down to in effect 'compensate' for these acute tone deficits. The manuscript was generally well written, and the data was clear, convincing, and novel. My comments below highlight suggestions to improve clarity and sharpen some arguments.

Primary comments:

(1) Torque vs. tone: Is it known whether this type of cerebellar blockade is reducing muscle tone or inducing any type of acute co-contraction that could influence limb velocity through mechanisms different than 'atonia'? If so, the authors should discuss this information in the discussion section starting around line 336, and clarify that this motivates (if it does) the focus on 'torques' rather than muscle activation. Relatedly, besides the fact that there are joints involved, is there a reason there is so much emphasis on torque per se? If the muscle is deprived of sufficient drive, it would seem that it would be more straightforward to conceptualize the deficit as one of insufficient timed drive to a set of muscles than joint force. Some text better contextualizing the choices made here would be sufficient to address this concern. I found statements like those in the introduction "hand velocity was low initially, reflecting a primary muscle torque deficit" to be lacking in substance. Either that statement is self-evident or the alternative was not made clear. Finally, emphasize that it is a loss of self-generated torque at the shoulder that accounts for the velocity deficits. At times the phrasing makes it seem that there is a loss of some kind of passive torque.

(2) Please clarify some of the experimental metrics: Ln 94 RESULTS. The success rate is used as a primary behavioral readout, but what constitutes success is not clearly defined in the methods. In addition to providing a clear definition in the methods section, it would also be helpful for the authors to provide a brief list of criteria used to determine a 'successful'

movement in the results section before the behavioral consequences of stimulation are described. In particular, the time and positional error requirements should be clear.

(3) Based on the polar plot in Figure 1c, it seemed odd to consider Targets 1-4 outward and 5-8 inward movements, when 1 and 5 are side-to-side. Is there a rationale for this grouping or might results be cleaner by cleanly segregating outward (targets 2-4) and inward (targets 6-8) movements? Indeed, by Figure 3 where interaction torques are measured, this grouping would seem to align with the hypothesis much more cleanly since it is with T2,T3,and T4 where clear coupling torques deficits are seen with cerebellar block.

4. I did not follow Figure 3d. Both the figure axis labels and the description in the main text were difficult to follow. Furthermore, the color code per animal made me question whether the linear regression across the entire dataset was valid, or would be better performed within animal, and the regressions summarized across animals. The authors should look again at this section and figure.

(5) Line 206+ The rationale for examining movement decomposition with a cerebellar block is presented as testing the role of the cerebellum in timing. Yet it is not spelled out what movement decomposition and trajectory variability have to do with motor timing per se.

<https://doi.org/10.7554/eLife.105152.1.sa2>

### Reviewer #3 (Public review):

#### Summary:

In their manuscript, "Disentangling acute motor deficits and adaptive responses evoked by the loss of cerebellar output," Sinha and colleagues aim to identify distinct causes of motor impairments seen when perturbing cerebellar circuits. This goal is an important one, given the diversity of movement-related phenotypes in patients with cerebellar lesions or injuries, which are especially difficult to dissect given the chronic nature of the circuit damage. To address this goal, the authors use high-frequency stimulation (HFS) of the superior cerebellar peduncle in monkeys performing reaching movements. HFS provides an attractive approach for transiently disrupting cerebellar function previously published by this group. First, they found a reduction in hand velocities during reaching, which was more pronounced for outward versus inward movements. By modeling inverse dynamics, they find evidence that shoulder muscle torques are especially affected. Next, the authors examine the temporal evolution of movement phenotypes over successive blocks of HFS trials. Using this analysis, they find that in addition to the acute, specific effects on muscle torques in early HFS trials, there was an additional progressive reduction in velocity during later trials, which they interpret as an adaptive response to the inability to effectively compensate for interaction torques during cerebellar block. Finally, the authors examine movement decomposition and trajectory, finding that even when low-velocity reaches are matched to controls, HFS produces abnormally decomposed movements and higher than expected variability in trajectory.

#### Strengths:

Overall, this work provides important insight into how perturbation of cerebellar circuits can elicit diverse effects on movement across multiple timescales.

The HFS approach provides temporal resolution and enables analysis that would be hard to perform in the context of chronic lesions or slow pharmacological interventions. Thus, this study describes an important advance over prior methods of circuit disruption, and their approach can be used as a framework for future studies that delve deeper into how

additional aspects of sensorimotor control are disrupted (e.g., response to limb perturbations).

In addition, the authors use well-designed behavioral approaches and analysis methods to distinguish immediate from longer-term adaptive effects of HFS on behavior. Moreover, inverse dynamics modeling provides important insight into how movements with different kinematics and muscle dynamics might be differentially disrupted by cerebellar perturbation.

#### Weaknesses:

The argument that there are acute and adaptive effects to perturbing cerebellar circuits is compelling, but there seems to be a lost opportunity to leverage the fast and reversible nature of the perturbations to further test this idea and strengthen the interpretation. Specifically, the authors could have bolstered this argument by looking at the effects of terminating HFS - one might hypothesize that the acute impacts on muscle torques would quickly return to baseline in the absence of HFS, whereas the longer-term adaptive component would persist in the form of aftereffects during the 'washout' period. As is, the reversible nature of the perturbation seems underutilized in testing the authors' ideas.

The analysis showing that there is a gradual reduction in velocity during what the authors call an adaptive phase is convincing. That said, the argument is made that this is due to difficulty in compensating for interaction torques. Even if the inward targets (i.e., targets 6-8) do not show a deficit during the acute phase, these targets still have significant interaction torques (Figure 3c). Given the interpretation of the data as presented, it is not clear why disruption of movement during the adaptive phase would not be seen for these targets as well since they also have large interaction torques. Moreover, it is difficult to delve into this issue in more detail, as the analyses in Figures 4 and 5 omit the inward targets.

The text in the Introduction and in the prior work developing the HFS approach overstates the selectivity of the perturbations. First, there is an emphasis on signals transmitted to the neocortex. As the authors state several times in the Discussion, there are many subcortical targets of the cerebellar nuclei as well, and thus it is difficult to disentangle target-specific behavioral effects using this approach. Second, the superior cerebellar peduncle contains both cerebellar outputs and inputs (e.g., spinocerebellar). Therefore, the selectivity in perturbing cerebellar output feels overstated. Readers would benefit from a more agnostic claim that HFS affects cerebellar communication with the rest of the nervous system, which would not affect the major findings of the study.

The text implies that increased movement decomposition and variability must be due to noise. However, this assumption is not tested. It is possible that the impairments observed are caused by disrupted commands, independent of whether these command signals are noisy. In other words, commands could be low noise but still faulty.

Throughout the text, the use of the term 'feedforward control' seems unnecessary. To dig into the feedforward component of the deficit, the authors could quantify the trajectory errors only at the earliest time points (e.g., in Figure 5d), but even with this analysis, it is difficult to disentangle feedforward- and feedback-mediated effects when deficits are seen throughout the reach. While outside the scope of this study, it would be interesting to explore how feedback responses to limb perturbation are affected in control versus HFS conditions. However, as is, these questions are not explored, and the claim of impaired feedforward control feels overstated.

The terminology 'single-joint' movement is a bit confusing. At a minimum, it would be nice to show kinematics during different target reaches to demonstrate that certain targets are indeed single joint movements. More of an issue, however, is that it seems like these are not actually 'single-joint' movements. For example, Figure 2c shows that target 1 exhibits high

elbow and shoulder torques, but in the text, T1 is described as a 'single-joint' reach (e.g. lines 155-156). The point that I think the authors are making is that these targets have low interaction torques. If that is the case, the terminology should be changed or clarified to avoid confusion.

The labels in Figure 3d are confusing and could use more explanation in the figure legend.

In Figure 3d, it is stated that data from all monkeys is pooled. However, if there is a systematic bias between animals, this could generate spurious correlations. Were correlations also calculated for each animal separately to confirm the same trend between velocity and coupling torques holds for each animal?

In Table S1, it would be nice to see target-specific success rates. The data would suggest that targets with the highest interaction torques will have the largest reduction in success rates, especially during later HFS trials. Is this the case?

<https://doi.org/10.7554/eLife.105152.1.sa1>

## Author response:

### Public Reviews:

#### Reviewer #1 (Public review):

##### Summary:

*In a previous work, Prut and colleagues had shown that during reaching, high-frequency stimulation of the cerebellar outputs resulted in reduced reach velocity. Moreover, they showed that the stimulation produced reaches that deviated from a straight line, with the shoulder and elbow movements becoming less coordinated. In this report, they extend their previous work by the addition of modeling results that investigate the relationship between the kinematic changes and torques produced at the joints. The results show that the slowing is not due to reductions in interaction torques alone, as the reductions in velocity occur even for movements that are single joints. More interestingly, the experiment revealed evidence for the decomposition of the reaching movement, as well as an increase in the variance of the trajectory.*

##### Strengths:

*This is a rare experiment in a non-human primate that assessed the importance of cerebellar input to the motor cortex during reaching.*

##### Weaknesses:

*My major concerns are described below.*

*If I understand the task design correctly, the monkeys did not need to stop their hand at the target. I think this design may be suboptimal for investigating the role of the cerebellum in control of reaching because a number of earlier works have found that the cerebellum's contributions are particularly significant as the movement ends, i.e., stopping at the target. For example, in mice, interposed nucleus neurons tend to be most active near the end of the reach that requires extension, and their activation produces flexion forces during the reach (Becker and Person 2019). Indeed, the inactivation of interposed neurons that project to the thalamus results in overshooting of reaching movements (Low et al. 2018). Recent work has also found that many Purkinje cells show a burst-pause pattern as the reach nears its endpoint, and stimulation of the mossy fibers*

*tends to disrupt endpoint control (Calame et al. 2023). Thus, the fact that the current paper has no data regarding endpoint control of the reach is puzzling to me.*

We appreciate the reviewer's point that cerebellar contributions can be particularly critical near the endpoint of a reach. In our current task design, monkeys were indeed required to hold at the target briefly—100 ms for Monkeys S and P, and 150 ms for Monkeys C and M—before receiving a reward. However, given the size of the targets and the velocity of movements, it often happened that the monkey didn't have to stop its movement to obtain a reward. Importantly, we relaxed the task's requirements (by increasing target size and reducing temporal constraints) to allow monkeys to perform the task under cerebellar block conditions as we found that the strict criteria in these conditions yield a low success rate. This design is suboptimal for studying endpoint accuracy which, as we now appreciate, is an important aspect of cerebellar control. In our revision, we will clarify these aspects of the task design and acknowledge that it is sub-optimal for examining the role of cerebellum in end-point control. Future studies will explicitly address this point more carefully.

*Because stimulation continued after the cursor had crossed the target, it is interesting to ask whether this disruption had any effects on the movements that were task-irrelevant. The reason for asking this is because we have found that whereas during task-relevant eye or tongue movements the Purkinje cells are strongly modulated, the modulations are much more muted when similar movements are performed but are task-irrelevant (Pi et al., PNAS 2024; Hage et al. Biorxiv 2024). Thus, it is interesting to ask whether the effects of stimulation were global and affected all movements, or were the effects primarily concerned with the task-relevant movements.*

This is a very interesting suggestion. Although our main analysis focused on target-directed reaching movements, we have the data for the between-trial movements under continuous stimulation (e.g., return to center movements). In our revised supplementary material, we will examine the effect of cerebellar block on endpoint velocities in inter-trial movements versus task-related movements.

*If the schematic in Figure 1 is accurate, it is difficult for me to see how any of the reaching movements can be termed single joint. In the paper, T1 is labeled as a single joint, and T2-T4 are labeled as dual-joint. The authors should provide data to justify this.*

The reviewer is right and movements to all targets engages shoulder and elbow but the single joint participation varied in a target-specific manner. In the manuscript, we used the term “single-joint” to indicate a target direction in which one joint remains stationary, resulting in minimal coupling torque at the adjacent joint. Specifically, for Targets 1 and 5 in our experiments, the net torque (and thus acceleration) at the elbow was negligible, and hence the shoulder experienced correspondingly low coupling torque (as illustrated in Figure 3c of our manuscript). To avoid confusion, we will use the term ‘predominantly single-joint’ movements in our revised manuscript to indicate targets with low coupling torques. We will also include an additional figure in the revised supplementary material displaying the net torques at the shoulder and elbow, similar to Figures 2c and 3c. Our goal is to demonstrate that movements to targets 1 and 5 are characterized by predominantly one-joint engagement (i.e., the elbow is stationary with low net torque) and low coupling torques, rather than implying a purely isolated, single-joint motion.

*Because at least part of this work was previously analyzed and published, information should be provided regarding which data are new.*

We will include a clear statement in the Methods section specifying which components of the dataset and analyses are entirely new. While some of the same animals and stimulation

protocol were presented in prior work, the inverse-dynamics modeling, analyses of progressive movement changes across trials under stimulation and invariance of motor noise to movement velocity are newly reported in this manuscript.

**Reviewer #2 (Public review):**

*This manuscript asks an interesting and important question: what part of 'cerebellar' motor dysfunction is an acute control problem vs a compensatory strategy to the acute control issue? The authors use a cerebellar 'blockade' protocol, consisting of high-frequency stimuli applied to the cerebellar peduncle which is thought to interfere with outflow signals. This protocol was applied in monkeys performing center outreaching movements and has been published from this laboratory in several preceding studies. I found the take-home-message broadly convincing and clarifying - that cerebellar block reduces muscle activation acutely particularly in movements that involve multiple joints and therefore invoke interaction torques, and that movements progressively slow down to in effect 'compensate' for these acute tone deficits. The manuscript was generally well written, and the data was clear, convincing, and novel. My comments below highlight suggestions to improve clarity and sharpen some arguments.*

*Primary comments:*

*(1) Torque vs. tone: Is it known whether this type of cerebellar blockade is reducing muscle tone or inducing any type of acute co-contraction that could influence limb velocity through mechanisms different than 'atonia'? If so, the authors should discuss this information in the discussion section starting around line 336, and clarify that this motivates (if it does) the focus on 'torques' rather than muscle activation. Relatedly, besides the fact that there are joints involved, is there a reason there is so much emphasis on torque per se? If the muscle is deprived of sufficient drive, it would seem that it would be more straightforward to conceptualize the deficit as one of insufficient timed drive to a set of muscles than joint force. Some text better contextualizing the choices made here would be sufficient to address this concern. I found statements like those in the introduction "hand velocity was low initially, reflecting a primary muscle torque deficit" to be lacking in substance. Either that statement is self-evident or the alternative was not made clear. Finally, emphasize that it is a loss of self-generated torque at the shoulder that accounts for the velocity deficits. At times the phrasing makes it seem that there is a loss of some kind of passive torque.*

We appreciate the reviewer's emphasis on distinguishing reduced muscle tone and altered co-contraction patterns as possible explanations for decreased limb velocity. Our focus on torques arises from previous studies suggesting that the core deficit in cerebellar ataxia is impaired prediction of coupling torques. This point will be added in the discussion section of our revised manuscript where we will explain why we prioritize muscle torques and how muscle-level activation collectively contributes to net joint torques. Also, we will underscore that the observed velocity deficits primarily reflect a reduction of self-generated torque at the shoulder (whether acute or adaptive), rather than any reduction in passive torques.

*(2) Please clarify some of the experimental metrics: Ln 94 RESULTS. The success rate is used as a primary behavioral readout, but what constitutes success is not clearly defined in the methods. In addition to providing a clear definition in the methods section, it would also be helpful for the authors to provide a brief list of criteria used to determine a 'successful' movement in the results section before the behavioral consequences of stimulation are described. In particular, the time and positional error requirements should be clear.*

Successful trials were trials in which monkeys didn't leave the center position before the go signal and reached the peripheral target within a specific time criteria. These values varied in different monkeys. We will include detailed definitions of our success criteria in the revised methods section of our manuscript. Specifically, we will update our methods section to include (i) the timing criteria of each phase of the trials and (ii) the size of the peripheral targets indicating the tolerance for endpoint accuracy.

*(3) Based on the polar plot in Figure 1c, it seemed odd to consider Targets 1-4 outward and 5-8 inward movements, when 1 and 5 are side-to-side. Is there a rationale for this grouping or might results be cleaner by cleanly segregating outward (targets 2-4) and inward (targets 6-8) movements? Indeed, by Figure 3 where interaction torques are measured, this grouping would seem to align with the hypothesis much more cleanly since it is with T2,T3,and T4 where clear coupling torques deficits are seen with cerebellar block.*

We acknowledge the reviewer's observation regarding Targets 1 and 5 being side-to-side rather than strictly "outward" or "inward." In the first section of our results, we grouped the targets in this way to emphasize the notably stronger effect of the cerebellar block on targets involving shoulder flexion ('outward') as compared to those involving shoulder extension ('inwards'). For subsequent analyses we focused on the effects of cerebellar block on outward targets where movements were single-joint (Target 1) vs. multi-joint (Targets 2-4). To clarify this aspect, in our revised manuscript we will explain the rationale for grouping T1-T4 as "outward" and T5-T8 as "inward," including how we defined them.

*(4) I did not follow Figure 3d. Both the figure axis labels and the description in the main text were difficult to follow. Furthermore, the color code per animal made me question whether the linear regression across the entire dataset was valid, or would be better performed within animal, and the regressions summarized across animals. The authors should look again at this section and figure.*

We will revise the figure labels and legend to clarify how each axis is defined. Please note that pooling the data was done after confirming that data from each animal expressed a similar trend. Specifically, the correlation coefficients were all positive but statistically significant in 3 out of the 4 monkeys. Moreover, following the reviewers' feedback, we also did a partial correlation analysis (which controls for the variability across monkeys) and found a significant correlation ( $r = 0.33$ ,  $p < 0.001$ ). These points will be described in the revised manuscript.

*(5) Line 206+ The rationale for examining movement decomposition with a cerebellar block is presented as testing the role of the cerebellum in timing. Yet it is not spelled out what movement decomposition and trajectory variability have to do with motor timing per se.*

The reviewer is right and the relations between timing, decomposition and variability need to be explicitly presented. In our revision, we will explain how decomposed movements may reflect impaired temporal coordination across multiple joints—a critical cerebellar function. We will also clarify how increased variability in joint coordination can result in increased trial-to-trial variability of trajectories.

### **Reviewer #3 (Public review):**

*Summary:*

*In their manuscript, "Disentangling acute motor deficits and adaptive responses evoked by the loss of cerebellar output," Sinha and colleagues aim to identify distinct causes of motor impairments seen when perturbing cerebellar circuits. This goal is an important one, given the diversity of movement-related phenotypes in patients with cerebellar lesions or injuries, which are especially difficult to dissect given the chronic nature of the circuit damage. To address this goal, the authors use high-frequency stimulation (HFS) of the superior cerebellar peduncle in monkeys performing reaching movements. HFS provides an attractive approach for transiently disrupting cerebellar function previously published by this group. First, they found a reduction in hand velocities during reaching, which was more pronounced for outward versus inward movements. By modeling inverse dynamics, they find evidence that shoulder muscle torques are especially affected. Next, the authors examine the temporal evolution of movement phenotypes over successive blocks of HFS trials. Using this analysis, they find that in addition to the acute, specific effects on muscle torques in early HFS trials, there was an additional progressive reduction in velocity during later trials, which they interpret as an adaptive response to the inability to effectively compensate for interaction torques during cerebellar block. Finally, the authors examine movement decomposition and trajectory, finding that even when low-velocity reaches are matched to controls, HFS produces abnormally decomposed movements and higher than expected variability in trajectory.*

#### *Strengths:*

*Overall, this work provides important insight into how perturbation of cerebellar circuits can elicit diverse effects on movement across multiple timescales.*

*The HFS approach provides temporal resolution and enables analysis that would be hard to perform in the context of chronic lesions or slow pharmacological interventions. Thus, this study describes an important advance over prior methods of circuit disruption, and their approach can be used as a framework for future studies that delve deeper into how additional aspects of sensorimotor control are disrupted (e.g., response to limb perturbations).*

*In addition, the authors use well-designed behavioral approaches and analysis methods to distinguish immediate from longer-term adaptive effects of HFS on behavior. Moreover, inverse dynamics modeling provides important insight into how movements with different kinematics and muscle dynamics might be differentially disrupted by cerebellar perturbation.*

#### *Weaknesses:*

*The argument that there are acute and adaptive effects to perturbing cerebellar circuits is compelling, but there seems to be a lost opportunity to leverage the fast and reversible nature of the perturbations to further test this idea and strengthen the interpretation. Specifically, the authors could have bolstered this argument by looking at the effects of terminating HFS - one might hypothesize that the acute impacts on muscle torques would quickly return to baseline in the absence of HFS, whereas the longer-term adaptive component would persist in the form of aftereffects during the 'washout' period. As is, the reversible nature of the perturbation seems underutilized in testing the authors' ideas.*

We agree that our approach could more explicitly exploit the rapid reversibility of high-frequency stimulation (HFS) by examining post-stimulation 'washout' periods. However, for the present dataset, we ended the session after the set of cerebellar block trials. We plan to study the effect of cerebellar block on immediate post-block washout trials in the future.

*The analysis showing that there is a gradual reduction in velocity during what the authors call an adaptive phase is convincing. That said, the argument is made that this is due to difficulty in compensating for interaction torques. Even if the inward targets (i.e., targets 6-8) do not show a deficit during the acute phase, these targets still have significant interaction torques (Figure 3c). Given the interpretation of the data as presented, it is not clear why disruption of movement during the adaptive phase would not be seen for these targets as well since they also have large interaction torques. Moreover, it is difficult to delve into this issue in more detail, as the analyses in Figures 4 and 5 omit the inward targets.*

The reviewer is right and movements to Targets 6–8 (inward) were seemingly unaffected despite also involving significant interaction torques. In fact, we have already attempted to address this issue in the discussion section of the version 1 of our manuscript. Specifically, we note that while outward targets (2–4) tend to involve higher coupling torque impulses on average, this alone does not fully explain the differential impact of cerebellar block, as illustrated by discrepancies at the individual target level (e.g., target 7 vs. target 1). We proposed two possible explanations: (1) a bias toward shoulder flexion in the effect of cerebellar block—consistent with earlier studies showing ipsilateral flexor activation or tone changes following stimulation or lesioning of the deep cerebellar nuclei; and (2) a posture-related facilitation of inward (shoulder extension) movements from the central starting position.

*The text in the Introduction and in the prior work developing the HFS approach overstates the selectivity of the perturbations. First, there is an emphasis on signals transmitted to the neocortex. As the authors state several times in the Discussion, there are many subcortical targets of the cerebellar nuclei as well, and thus it is difficult to disentangle target-specific behavioral effects using this approach. Second, the superior cerebellar peduncle contains both cerebellar outputs and inputs (e.g., spinocerebellar). Therefore, the selectivity in perturbing cerebellar output feels overstated. Readers would benefit from a more agnostic claim that HFS affects cerebellar communication with the rest of the nervous system, which would not affect the major findings of the study.*

The reviewer is right that the superior cerebellar peduncle carries both descending and ascending fibers, and that cerebellar nuclei project to subcortical as well as cortical targets. However, it is also important to note that in primates the cerebellar-thalamo-cortical (CTC) pathway greatly expanded (on the expanse of the cerebello-rubro-spinal tract) in mediating cerebellar control of voluntary movements (Horne and Butler, 1995). The cerebello-subcortical pathways lost its importance over the course of evolution (Nathan and Smith, 1982, Padel et al., 1981, ten Donkelaar, 1988). In our previous study we found that the ascending spinocerebellar axons which enter the cerebellum through the SCP are weakly task-related and the descending system is quite small (Cohen et al, 2017). However, we cannot rule out an effect of HFS mediated in part through other systems. In the revised introduction section, we will clarify this point and use more careful language about the scope of our stimulation, emphasizing that HFS disrupts cerebellar communication broadly, rather than solely the cerebello-thalamo-cortical pathway.

*The text implies that increased movement decomposition and variability must be due to noise. However, this assumption is not tested. It is possible that the impairments observed are caused by disrupted commands, independent of whether these command signals are noisy. In other words, commands could be low noise but still faulty.*

We recognize the reviewer's concern about linking movement decomposition and trial-to-trial trajectory variability with motor noise. As presented in our discussion section, we

interpret these motor abnormalities as a form of motor noise in the sense that they are generated by faulty motor commands. We draw our interpretation from the findings of previous research work which show that the cerebellum aids in the state estimation of the limb and subsequent generation of accurate feedforward commands. Therefore, disruption of the cerebellar output may lead to faulty motor commands resulting in the observed asynchronous joint activations (i.e., movement decomposition) and unpredictable trajectories (i.e., increased trial-to-trial variability). Both observed deficits resemble increased motor noise.

*Throughout the text, the use of the term 'feedforward control' seems unnecessary. To dig into the feedforward component of the deficit, the authors could quantify the trajectory errors only at the earliest time points (e.g., in Figure 5d), but even with this analysis, it is difficult to disentangle feedforward- and feedback-mediated effects when deficits are seen throughout the reach. While outside the scope of this study, it would be interesting to explore how feedback responses to limb perturbation are affected in control versus HFS conditions. However, as is, these questions are not explored, and the claim of impaired feedforward control feels overstated.*

We agree that to strictly focus on feedforward control, we could have examined the measured variables in the first 50-100 ms of the movement which has been shown to be unaffected by feedback responses (Pruszynski et al. 2008, Todorov and Jordan 2002, Pruszynski and Scott 2012, Crevecoeur et al. 2013). However, in our task the amplitude of movements made by our monkeys was small and therefore the response measures we used were too small in the first 50-100 ms for a robust estimation. Also, fixing a time window led to an unfair comparison between control and cerebellar block trials, in which velocity was significantly reduced and therefore movement time was longer. Therefore, we used the peak velocity, torque-impulse at the peak velocity and maximum deviation of the hand trajectory as response measures. We will acknowledge this point in the discussion section of our revised manuscript. We will also tone down references to feedforward control throughout the text of our revised manuscript as suggested by the reviewer.

*The terminology 'single-joint' movement is a bit confusing. At a minimum, it would be nice to show kinematics during different target reaches to demonstrate that certain targets are indeed single joint movements. More of an issue, however, is that it seems like these are not actually 'single-joint' movements. For example, Figure 2c shows that target 1 exhibits high elbow and shoulder torques, but in the text, T1 is described as a 'single-joint' reach (e.g. lines 155-156). The point that I think the authors are making is that these targets have low interaction torques. If that is the case, the terminology should be changed or clarified to avoid confusion.*

Indeed, as reviewer #1 also noted, movements to target 1 and 5 are not purely single-joint but rather have relatively low coupling torques. Our intention while using the term “single-joint” was to indicate a target direction in which one joint remains stationary, resulting in minimal coupling torque at the adjacent joint. Specifically, for Targets 1 and 5 in our experiments, the net torque (and thus acceleration) at the elbow was negligible, and hence the shoulder experienced correspondingly low coupling torque (as illustrated in Figure 3c of our manuscript). To avoid confusion, we will use the term ‘predominantly single-joint’ movements in our revised manuscript to indicate targets with low coupling torques. We will also include an additional figure in the revised supplementary material displaying the net torques at the shoulder and elbow, similar to Figures 2c and 3c. Our goal is to demonstrate that movements to targets 1 and 5 are characterized by predominantly one-joint engagement (i.e., the elbow is stationary with low net torque) and low coupling torques, rather than implying a purely isolated, single-joint motion.

*The labels in Figure 3d are confusing and could use more explanation in the figure legend.*

*In Figure 3d, it is stated that data from all monkeys is pooled. However, if there is a systematic bias between animals, this could generate spurious correlations. Were correlations also calculated for each animal separately to confirm the same trend between velocity and coupling torques holds for each animal?*

We will revise the figure legend and main-text explanation for Figure 3d. Please note that pooling the data was done after confirming that data from each animal expressed a similar trend. Specifically, the correlation coefficients were positive but significant for 3 out of the 4 monkeys. Moreover, following the reviewers' feedback, we also did a partial correlation analysis (which controls for the variability across monkeys) and found a significant correlation ( $r = 0.33$ ,  $p < 0.001$ ). These points will be described in the revised manuscript.

*In Table S1, it would be nice to see target-specific success rates. The data would suggest that targets with the highest interaction torques will have the largest reduction in success rates, especially during later HFS trials. Is this the case?*

We will provide a breakdown of the success rates as a function of targets. However, one should note that success/failure may depend on several factors beyond impaired limb dynamics. In a previous study (Nashef et al. 2019) we identified several causes of failure such as (i) not entering the central target in time, (ii) moving out too early from the peripheral target, (iii) Reaction time longer than permitted, or (iv) premature exit from the central target before permitted.

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