




# The Cerebellum and Implicit Sequencing: Evidence from Cerebellar Ataxia

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## Abstract

The cerebellum recognizes sequences from prior experiences and uses this information to generate internal models that predict future outcomes in a feedforward manner [Front Hum Neurosci 8: 475, 2014; Cortex 47: 137–44, 2011; Cerebellum 7: 611–5, 2008; J Neurosci 26: 9107–16, 2006]. This process has been well documented in the motor domain, but the cerebellum's role in cognitive sequencing, within the context of implicit versus explicit processes, is not well characterized. In this study, we tested individuals with cerebellar ataxia and healthy controls to clarify the role of the cerebellum sequencing using variations on implicit versus explicit and motor versus cognitive demands across five experiments. Converging results across these studies suggest that cerebellar feedforward mechanisms may be necessary for sequencing in the implicit domain only. In the ataxia group, rhythmic tapping, rate of motor learning, and implicit sequence learning were impaired. However, for cognitive sequencing that could be accomplished using explicit strategies, the cerebellar group performed normally, as though they shifted to extra-cerebellar mechanisms to compensate. For example, when cognitive and motor functions relied on cerebellar function simultaneously, the ataxia group's motor function was unaffected, in contrast to that of controls whose motor performance declined as a function of cognitive load. These findings indicated that the cerebellum is not critical for all forms of sequencing per se. Instead, it plays a fundamental role for sequencing within the implicit domain, whether functions are motor or cognitive. Moreover, individuals with cerebellar ataxia are generally able to compensate for cognitive sequencing when explicit strategies are available in order to preserve resources for motor function.

**Keywords** Ataxia · Cerebellum · Motor · Implicit · Explicit · Sequencing

## General Introduction

The cerebellum's role in motor function has been well studied. Notably, it contributes to the timing and coordination of voluntary movements [1]. The cerebellum is uniform in structure, composed of “micro-modules” that include Purkinje cells and parallel fibers throughout the

entire structure. Accordingly, it is believed that the cerebellum is also uniform in its function [2]. Because the cerebellum interconnects with various cortical regions via the thalamus, function is determined by whether a cerebellar region communicates with motor or cognitive cortical regions to support motor or cortical functions, respectively [3–5].

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The “sequencing hypothesis” posits that the cerebellum recognizes spatial and temporal relationships from prior experiences and uses this information to predict future outcomes in a feedforward manner [6–9]. The cerebellum then compares the predicted versus actual outcomes. If these do not match, the cerebellum adjusts its output to the cortex accordingly [9–11]. While this concept has been generally accepted within the motor domain, the sequencing hypothesis is thought to extend more broadly to include cognition [4]. The ability to sequence enables one to understand the order in which sensory events occur, to generate and execute motor responses, and to predict the sensory consequences of an intended action. This function may be applied within the cognitive domain as well, because the temporal order of thoughts must be organized such that cognitive functions are executed in a purposeful way. The concept of “dysmetria of thought” has been used to describe a disruption of coordination within cognition [5]. Along these lines, cerebellar damage has been reported to disrupt a variety of cognitive processes that involve temporal relations, including perceptual timing [12, 13], rhythmic movement [14, 15], strategy formation [16], sequence detection [8, 17], language [18–20], logical sequencing [21], and reasoning [22]. The cerebellum may also contribute to the creation of internal motor traces that support cognitive function, and these motor traces presumably also rely on sequencing [23]. Thus, the notion that the cerebellum supports the *sequencing* of thoughts, comparable to how it supports the sequencing of motor control, can be extrapolated from a wide variety of experimental paradigms.

Sequencing can occur in the explicit and implicit domains with separate underlying neural mechanisms. For example, explicit sequencing often draws upon neocortical areas, such as the prefrontal cortex [24–27], thought to be involved with working memory, attention, and volitional intent to learn or retrieve sequential information. Implicit processing refers to a class of learning and memory phenomena in which behavior is influenced by prior experiences, without conscious recollection of those experiences. One type of implicit learning is the acquisition of motor skills, often referred to as procedural learning. Implicit learning can also occur in the cognitive domain, in which it involves processing patterns of stimuli, or structural relations between events in the environment, so that information regarding these regularities may be applied to subsequent novel events [28, 29]. Thus, implicit learning facilitates adaptive behavior because it enables one to predict upcoming events and generate appropriate anticipatory responses. Underlying neural mechanisms of implicit sequence learning include the basal ganglia and cerebellum [30–32].

Despite the research conducted to date, the contribution of the cerebellum to cognitive sequencing is unclear. For example, does the cerebellum underlie all forms of sequencing *per se*? Does it support a specific aspect of sequencing that contributes to explicit and implicit domains equally? By studying individuals with cerebellar pathology, we can examine how a disruption in feedforward mechanisms might impact sequencing abilities. Moreover, we can explore whether the cerebellar contributions are more critical to implicit versus explicit domains.

In this series of experiments, we set out to clarify the role of the cerebellum in sequencing skills, within the implicit and explicit domains, with a particular interest in cognitive sequencing, which has been less studied. We administered five paradigms to individuals with cerebellar ataxia and healthy controls to measure sequencing ability when the cerebellar predictive feedforward system was disrupted by cerebellar degeneration. We hypothesized that impairments primarily would be related to timing, ordering, and sequencing abilities in the implicit domain given that explicit sequencing could rely on extra-cerebellar mechanisms to compensate. Experiment 1 tested timing abilities by asking participants to tap along with a flashing cue at four speed frequencies. This paradigm relied on the ability to predict the timing of future events. Experiment 2 directly compared implicit procedural learning (repeatedly drawing a figure) to explicit sequence learning (immediate recall of letter sequences). Both tasks were administered separately and in a dual-task condition to examine how cerebellar functional integrity impacted each, and whether one domain was prioritized over the other. Experiment 3 tested implicit sequence learning by asking participants to indicate the location of a stimulus as it followed a probabilistic, rule-based pattern of changing locations. This paradigm fundamentally relied on implicit learning of non-motor sequences, and we were, moreover, able to isolate the rate of motor versus non-motor sequence learning for comparison, even though both occurred within the implicit domain. Experiment 4 examined cognitive sequencing of different kinds of information using cards that depicted verbal, spatial, and behavioral sequences (following Leggio et al. (2008) [21]). This paradigm involved “top down” processes for understanding contextual information, and was considered to primarily involve explicit sequencing skills. Finally, Experiment 5 tested the ability to understand and express the abstract meaning of common proverbs. The paradigm relied upon one’s tacit ability to marshal thoughts prior to the verbal expression of those thoughts. Together, these five experiments were designed to investigate cerebellar sequencing abilities by utilizing tasks that involved a combination of motor and

cognitive demands within implicit and explicit domains for comparison.

## General Methods

### Participants

Individuals with cerebellar ataxia ( $n = 119$ ) and healthy controls ( $n = 73$ ) participated. The five experiments took place over the course of 2 years (except Experiment 2, which spanned 4 years). While there was some degree of overlap, not all participants completed all experiments. Study demographics are presented in Table 1. Participants were recruited through the Johns Hopkins Ataxia Center, the National Ataxia Foundation Annual Ataxia Conferences (AAC, 2018 and 2019), the University of Iowa Department of Psychiatry, and flyers posted in the local community. Participants were tested at Johns Hopkins University, the AAC, or the University of Iowa. People were included in the ataxia group if they had been diagnosed with progressive cerebellar degeneration when other causes, including stroke, virus/bacteria, or environmental factors had been ruled out. Exclusion criteria included history of (1) diagnosis of a major psychotic disorder, (2) substance use disorder, (3) neurologic disorder aside from ataxia (e.g., epilepsy, autism, attention deficit hyperactivity disorder), learning disability, and head injury with loss of consciousness longer than 5 min.

Cerebellar ataxia diagnoses were verified by a trained movement disorders neurologist (LR) who categorized cases as spinocerebellar ataxia (SCA) of a known subtype, autosomal dominant cerebellar ataxia (ADCA), or cerebellar ataxia of unknown etiology (CAUE) based on information from personal and family health histories, clinical examination data, genetics, and neuroimaging. It should be noted, however, that brain pathology may not have been restricted to the cerebellum in all of the cerebellar ataxia patients in this study, due to heterogeneity of the disease [33]. This research was approved by the Johns Hopkins University School of Medicine and the University of Iowa Institutional Review Boards and were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki. All participants gave their written informed consent prior to inclusion in the study and were paid for their participation.

### Supplemental Measures (Cerebellar Ataxia Group Only)

The Center of Epidemiologic Studies Depression Scale (CES-D) [34] was used to explore the influence of depressive state on performance. A score of 16 or higher suggests active depression. In addition, the International Cooperative Ataxia Rating Scale (ICARS) [35] was administered to quantify

neurological impairment across a range of categories, including posture and gait, kinetic function, speech, and eye movement.

Participants who were tested at the University of Iowa ( $n = 13$ ) received a slightly different test battery from the rest of the participants. They were administered the Scale for the Assessment and Rating of Ataxia (SARA) [36], which is a rating scale of neurologic signs of ataxia similar to the ICARS, and did not receive the CES-D. Additional protocol differences are described in Experiment 5.

### Statistical Analyses

Our data contained continuous and ordinal variables. To compare groups on normally distributed continuous variables, we used independent samples  $t$  tests or mixed-design ANOVAs, making appropriate considerations in cases of unequal variability. To compare groups on ordinal or non-normal data, we used Mann-Whitney  $U$  tests. We used Pearson and Spearman rank correlations for continuous and ordinal variables, respectively. When correction for multiple comparisons was appropriate,  $p$  values were adjusted using the Bonferroni-Holm method. For repeated measures ANOVAs, Mauchly's Test of Sphericity was applied, and if the assumption of sphericity was violated, a Greenhouse-Geisser correction was applied to adjust the degrees of freedom. For  $t$  tests, Levine's Test for Equality of Variances was used. Degrees of freedom followed whether equal variances were assumed or not. Statistics for Experiments 1, 4, and 5 were performed using  $R$  [37]; statistics for Experiments 1 (partial), 2 and 3 were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA).

## Experiment 1

### Introduction

A fundamental role for the cerebellum in time perception and timing of movements has been discussed and debated within the cerebellar research field [15, 38–40]. Lesions of the cerebellum can impact not only motor timing (e.g., rhythmic tapping) but also time perception (e.g., duration judgments) [13]. However, it has been suggested that the cerebellum's role is not central to timing because patients with cerebellar degeneration can entrain to new auditory rhythms normally despite variability in motor output [15]. One model suggests that the cerebellum's role in timing is instead related to monitoring input from the cortex to compare intended versus actual outcomes [41]. This model implicates the cerebellum's function as an intermediary of timing, rather than as a clock timer. If the cerebellum is involved in timing, it may also matter whether the time scale is of sub-second or supra-second durations.

**Table 1** Demographics of study participants

Experiment	Group	N	Sex M:F	Age Mean (SD)	Education Mean (SD)	CES-D Mean (SD)	ICARS Mean (SD)	SARA Mean (SD)	Subtype Counts							
									SCA1	SCA2	SCA3	SCA5	SCA6	SCA8	ADCA	CAUE
1: Tapping/Timing	Ataxia	17	6:11	62.1 (10.19)	16.29 (2.34)	12.24 (7.9)	37.18 (14.7)	–	1	2	1	1	2	0	1	9
	Control	17	9:8	61.26 (13.14)	17 (2.21)	–	–	–	–	–	–	–	–	–	–	–
2: Figure 8, Experiment A	Ataxia	23	11:12	56.57 (11.54)	16.14 (2.62) <i>[n = 19]</i>	10.30 (8.81)	30.84 (14.91) <i>[n = 16]</i>	–	0	0	4	0	4	2	10	3
	Control	28	11:17	59.43 (8.47)	15.91 (2.66)	–	–	–	–	–	–	–	–	–	–	–
Figure 8, Experiment B	Ataxia	24	9:15	59.46 (12.18)	15.71 (2.74)	14.50 (9.68)	41.35 (15.3) <i>[n = 23]</i>	–	1	3	1	1	2	0	2	14
	Control	24	9:15	55.67 (12.18)	16.44 (2.28)	–	–	–	–	–	–	–	–	–	–	–
3: Implicit Sequence Learning	Ataxia	32	10:22	55.72 (10.85)	16.34 (1.7)	12.68 (8.2) <i>[n = 31]</i>	36.5 (12.26)	–	3	5	4	2	2	1	3	12
	Control	30	15:15	54.97 (17.07)	17.07 (2.02)	–	–	–	–	–	–	–	–	–	–	–
4: Card sequencing	Ataxia	43	17:26	56.21 (11.1)	15.67 (2.22)	12.29 (7.99) <i>[n = 34]</i>	37.48 (12.81) <i>[n = 31]</i>	14.89 (7.02) <i>[n = 9]</i>	4	5	7	2	7	1	7	10
	Control	16	6:10	56.24 (13.92)	16.06 (2.18)	–	–	–	–	–	–	–	–	–	–	–
5: Proverb Interpretation	Ataxia	38	20:18	56 (12.6)	15.4 (2.4)	11.2 (7.9) <i>[n = 14]</i>	38 (11.8) <i>[n = 25]</i>	15 (6.6) <i>[n = 13]</i>	2	2	12	1	5	1	6	9
	Control	25	10:15	56.9 (14.2)	16.4 (2)	–	–	–	–	–	–	–	–	–	–	–

Demographics are described for each experiment and study group. Where data are available for only a subset of participants, the number of datapoints *n* is indicated in italics. Appropriate statistical tests found no significant differences between groups in terms of sex, age, or education within any experiment at alpha = 0.05

*M*, male; *F*, female; *ICARS*, International Cooperative Ataxia Rating Scale; *CES-D*, Center of Epidemiologic Studies Depression Scale; *WRAT*, Wide Range Achievement Test. *Units for age and education*, years

For example, temporal ordering of supra-second events involves the frontal lobe [42], whereas durations in the sub-second range, such as in eyeblink conditioning, involve the cerebellum [43]. Moreover, many tests rely on auditory stimuli, which can influence the auditory cortex to synchronize directly with motor output [44]. By contrast, visual rhythms may provide a better way to examine cerebellar timing by bypassing the auditory system. A PET study in healthy controls indicated that tapping to a visual cue elicited greater cerebellar activity than did tapping to auditory cues [40].

In this study, we tested how cerebellar feedforward mechanisms contribute to timing. To the extent that timing is an integral component of sequencing, we reasoned that repeated exposure to a visually timed cue (that required a concomitant motor response) would lead to development of an internal model that anticipated future events. This task design was predominantly a motor task of procedural learning, and therefore aligned primarily with the implicit domain. However, the ability to perceive the visual cue and attempt to tap along with it presumably also involved the influence of explicit processes, especially at the slower speeds. Moreover, we included constant visual feedback that indicated whether the participant was tapping too fast or slow relative to the target speed. This also involved an explicit component that allowed the participant to perceive their performance and make adjustments. We hypothesized that the ataxia group would show impairments in predicting upcoming events, leading to inaccurate tapping in relation to the visual cue. We tested at three sub-second speeds (2, 3, and 4 Hz) and at 1 Hz, and expected tapping accuracy to be most impaired at the faster speeds, with cortical compensatory mechanisms assisting at the slower speeds.

## Methods

**Participants** Individuals with cerebellar ataxia ( $n = 20$ ) and healthy controls ( $n = 17$ ) who were equated for age, sex, and level of education participated. Three individuals with ataxia were excluded from analysis due to (1) subsequent diagnosis of HSP7, (2) recent electroconvulsive therapy, and (3) a technical error in which data were not recorded. Thus, the final patient group's  $n = 17$ .

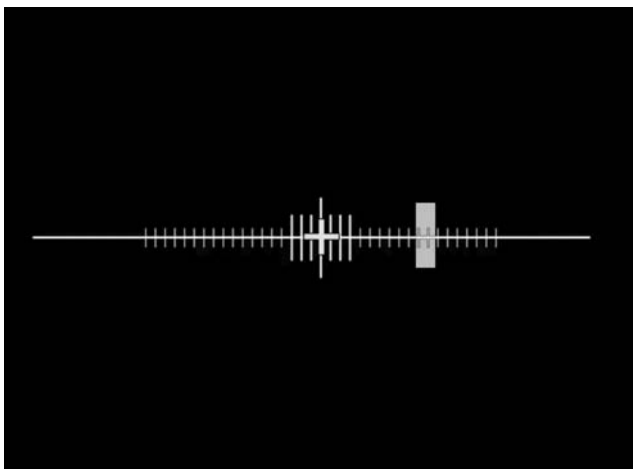
**Task** This task was adapted from a previous functional MRI experiment [45]. Participants were asked to direct their gaze at a cross in the center of the screen, which was either flashing at 1, 2, 3, or 4 Hz or not flashing (Fig. 1). When the cross was not flashing, participants were instructed not to tap. When the cross was flashing, participants were asked to tap in sync with the flash. Participants sat at a desk while viewing stimuli on a computer screen. They pressed the “down” arrow on a standard keyboard to perform the task. They were informed that they could make use of visual feedback. This consisted of a rectangular vertical bar that would slide to the left as

participants tapped slower than target and to the right as they tapped faster than target. Participants were administered a practice session that consisted of two 20s blocks at 1 and 2 Hz. Following practice, the full task was administered, consisting of 12 blocks, each 15 s long, separated by 5 s blocks of rest (4 min total). Only one target frequency was presented during each block. The order of block-frequency was generated pseudo-randomly with the constraints that each frequency should be presented an equal number of times, and that the task would begin with the frequencies 1, 2, 3, and 4 Hz in ascending order. The task was created in Python using VisionEgg [46]. Variables of interest were tapping speed, measured as inter-tap intervals or seconds/tap, and tapping accuracy, measured by root-mean-squared error (RMSE) relative to target.

## Results

To evaluate differences in tapping speed across groups and target frequencies, we conducted a  $4 \times 2$  mixed-design analysis of variance (ANOVA) with median tapping speed at each frequency (4: 1, 2, 3, and 4 Hz) as a within-subjects variable and group (2: ataxia versus control) as a between-subjects variable. The ANOVA indicated an expected main effect of frequency ( $F(1.31, 41.94) = 435, p < .001$ ), in which tapping speed increased with target speed. There was no main effect of group, ( $F(1, 32) = 0.045, p = .833$ ). However, there was an interaction of frequency  $\times$  group ( $F(1.31, 41.94) = 8.07, p < .005$ ), which prompted post hoc testing. Within each group, there was a main effect of frequency (ataxia,  $F(1.19, 19.1) = 94.0, p < 0.001$ ; controls,  $F(1.74, 27.84) = 1128, p < 0.001$ ). One-sample  $t$  tests comparing each group to target speed indicated that both controls and ataxia participants tapped faster than target at 1 Hz (ataxia,  $M = 0.85$  s/tap,  $SD = 0.16, t(16) = -3.79, p < 0.002$ ; controls,  $M = 0.96, SD = 0.05, t(16) = -3.35, p < 0.005$ ), and that ataxia participants tapped slower than target at 4 Hz ( $M = 0.33, SD = 0.12, t(16) = 2.68, p < 0.02$ ). Independent  $t$  tests confirmed that ataxia participants tapped faster than controls did at 1 Hz (ataxia,  $M = 0.85, SD = 0.16$ ; controls,  $M = 0.96, SD = 0.05$ ;  $t(18.7) = 2.69, p < 0.02$ ), and slower than controls did at 4 Hz (ataxia,  $M = 0.33, SD = 0.12$ ; controls,  $M = 0.25, SD = 0.03$ ;  $t(18.4) = 2.42, p < 0.03$ ). These results, together with visual inspection, suggested that the interaction of frequency  $\times$  group was driven by ataxia participants' tapping more quickly at 1 Hz, and more slowly at 4 Hz, than controls (Fig. 2).

A similar analysis was conducted to test differences in accuracy between groups and across target frequencies. A 4 (frequency) by 2 (group) ANOVA using tapping accuracy (RMSE) indicated a main effect of group ( $F(1, 32) = 10.72, p < .005$ ) in which controls tapped more accurately overall, and of frequency ( $F(1.71, 54.84) = 47.45, p < .001$ ), indicating that accuracy improved at higher frequencies. There was no



**Fig. 1** Participants were instructed to tap in sync with the turquoise cross, which flashed rhythmically in the center of the screen. Subjects could make use of the rectangular bar, which hovered to the right if they were tapping too quickly and to the left if they were tapping too slowly

interaction of group  $\times$  frequency ( $F(1.71, 54.84) = 2.12, p = .14$ ). Exploratory analyses were conducted to evaluate whether there were group differences in accuracy at each frequency. *T* tests indicated that RMSE was higher (i.e., accuracy was lower) in the ataxia group versus controls at 1 Hz (ataxia participants,  $M = 0.29, SD = 0.12$ ; controls,  $M = 0.19, SD = 0.091, t(30.35) = 2.60, p < 0.03$ ), 3 Hz (ataxia participants,  $M = 0.13, SD = 0.072$ ; controls,  $M = 0.074, SD = 0.027, t(20.44) = 3.09, p < 0.03$ ), and 4 Hz (ataxia participants,  $M = 0.14, SD = 0.10$ ; controls,  $M = 0.064, SD = 0.028, t(18.42) = 3.14, p < 0.03$ ), but not at 2 Hz (ataxia,  $M = 0.17, SD = 0.062$ ; control,  $M = 0.14, SD = 0.052; t(31.1) = 1.56, p = 0.128$ ).

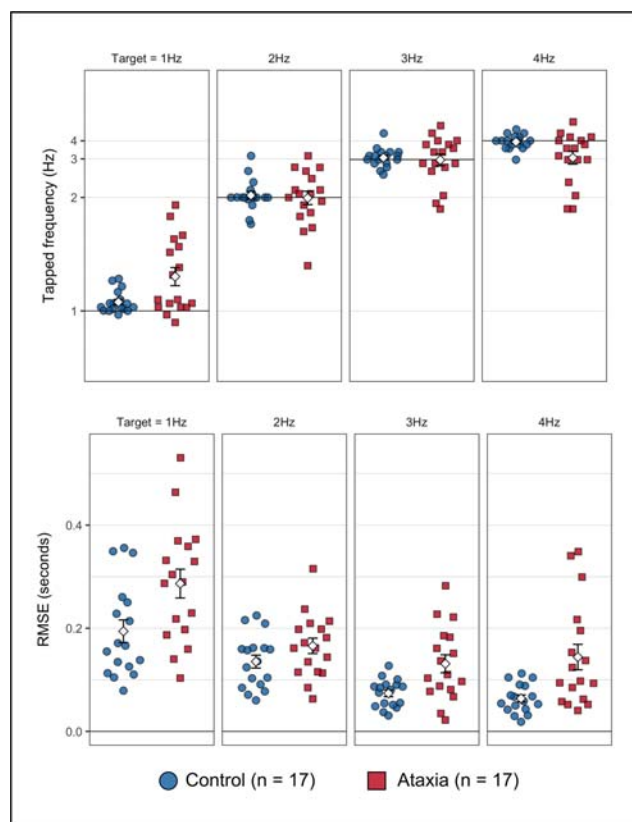
We conducted a follow-up experiment in order to determine whether the feedback from the vertical bar altered tapping behavior, such as by adding explicit components that helped participants improve their performance. We tested 18 ataxia patients and 6 healthy controls on the test again, this time without feedback. However, the flashing cross remained the same, at 1, 2, 3, and 4 Hz target frequencies (see Supplement #1 for results).

To test the differences in tapping speed groups between the two feedback conditions, a  $4 \times 2$  mixed-design ANOVA was performed with median tapping speed at each frequency (4) as a within-subjects variable and condition (2: feedback versus no feedback) as a between-subjects variable. For ataxia participants, the ANOVA replicated a main effect of frequency ( $F(1.29, 42.68) = 347, p < .001$ ), in which tapping speed increased with target speed. Interestingly, there was a main effect of condition, ( $F(1, 33) = 4.35, p < .05$ ), indicating that ataxia participants tapped faster in the feedback versus no feedback condition. There was no interaction of frequency  $\times$  condition ( $F(1.29, 42.68) = 2.69, p = .099$ ). Conducting the same test within controls yielded similar results. Tapping increased with target speed ( $F(1.87, 39.33) = 1248, p < .001$ ,

and there was a marginal main effect of condition ( $F(1, 21) = 4.02, p = .058$ ), indicating that control participants tapped faster in the feedback versus no feedback condition. There was no interaction of frequency  $\times$  condition ( $F(1.87, 39.33) = .808, p = .446$ ). Thus, it appeared that removing the feedback vertical bar slowed tapping speed for both groups.

A similar analysis was conducted to examine differences in accuracy within groups between the two feedback conditions using a  $4 \times 2$  mixed-design ANOVA for tapping accuracy (RMSE). For ataxia participants, accuracy was not affected by feedback conditions, ( $F(1, 33) = .508, p = .481$ ), and there was no interaction of feedback condition  $\times$  frequency, ( $F(1.98, 65.46) = 1.06, p = .354$ ). For controls, results were similar: accuracy was not affected by feedback conditions, ( $F(1, 21) = 1.44, p = .243$ ), and there was no interaction of feedback condition  $\times$  frequency, ( $F(1.56, 32.72) = 1.94, p = .168$ ).

Finally, we conducted between-groups analyses. A 4 (frequency)  $\times$  2 (condition)  $\times$  2 (group) mixed-design ANOVA was performed with median tapping speed at each frequency. This ANOVA revealed a main effect of condition, supporting the within-group findings of faster tapping in the



**Fig. 2** Mean speed (shown here as Hz, reported in the text as seconds/tap) and mean tapping accuracy (RMSE) for control and ataxia groups at each of the four target frequencies (1, 2, 3, and 4 Hz). The ataxia group showed increased speed at 1 Hz, and decreased speed at 4 Hz, relative to controls, and lower accuracy (higher RMSE) at 1 Hz, 3 Hz, and 4 Hz. Error bars denote standard error

presence of feedback, ( $F(1, 54) = 5.69, p < .03$ ), with no other main effects or interactions (all  $p$  values  $> .10$ ). A similar  $4 \times 2 \times 2$  mixed-design ANOVA was performed on tapping accuracy (RSME), which revealed a main effect of group, indicating that the ataxia group was less accurate than were controls ( $F(1, 54) = 17.19, p < .001$ ). There was a marginal interaction of frequency  $\times$  group, ( $F(1.89, 101.97) = 2.55, p < .086$ ). There were no other main effects or interactions (all  $p$  values  $> .10$ ).

Speed and accuracy at 1 Hz were of special interest to us because of the increased speed and lower accuracy by the ataxia group in the earlier with-feedback condition. We, therefore, compared speed and accuracy performance between-groups in the 1 Hz no-feedback condition. Independent  $t$  tests of median tapping speed at 1 Hz indicated no group difference (ataxia participants,  $M = 0.96, SD = 0.08$ ; controls,  $M = 0.98, SD = 0.02, t(22) = .683, p = .502$ ). By contrast, an independent  $t$  test of accuracy (RSME) at 1 Hz indicated a marginal group difference, (ataxia participants,  $M = 0.24, SD = 0.11$ ; controls,  $M = 0.13, SD = 0.09, t(22) = 2.075, p = .05$ ). This persistent accuracy impairment by the ataxia group at 1 Hz in the no-feedback condition explained the marginal group  $\times$  frequency interaction in the no-feedback  $4 \times 2 \times 2$  ANOVA accuracy results. Thus, even though the ataxia participants slowed their speed in the no-feedback condition, it did not improve their accuracy at 1 Hz.

**Correlations with Supplemental Measures** To evaluate how tapping speed and accuracy might be linked to neurological signs in those with cerebellar ataxia, Spearman rank correlations were conducted between ICARS scores and tapping accuracy (RMSE) and speed in the with-feedback condition. ICARS total scores positively correlated with RMSE ( $r(17) = .50, p < .05$ ) (i.e., higher symptom severity was associated with more error) and negatively correlated with speed ( $r(17) = -0.71, p < .005$ ) (i.e., higher symptom severity was associated with slower speed).

To assess whether depressive state influenced performance, Spearman rank correlations were conducted on the CES-D total scores and speed and RMSE (overall and at each frequency) in the with-feedback condition. There was no correlation between CES-D and accuracy ( $r(34) = 0.27, p = .24$ ); however, there was a marginal negative correlation between CES-D and speed ( $r(34) = -0.40, p = .07$ ).

## Discussion

The ataxia group showed impaired tapping speed at the 1 Hz and 4 Hz intervals. At 4 Hz, ataxia participants' slow tapping may be explained by an inability to tap fast enough, which would be consistent with the correlation between ICARS

severity and slower tapping speeds. However, this did not explain ataxia participants' level of impairment at 1 Hz, which was associated with tapping *faster* than the target.

Unexpectedly, the ataxia participants performed normally at the 2 and 3 Hz intervals. This coincided with a general shift toward better accuracy with faster target frequencies. It is possible that shorter intervals left less room for tapping variability, and this improved accuracy for both groups. It is notable that 3 Hz intervals fall within the range of intention tremors often experienced in ataxia (3–5 Hz) [47]. Thus, as tremors and tapping range coincided, it is possible that tapping rate averaged zero distance error from the target due to consistent over and under corrections to the target interval [15].

Ataxia participants tapped faster than needed at the 1 Hz interval despite getting visual feedback on every trial, which they could have used to slow down tapping speed. There are two interpretations of this behavior. First, a disrupted feedforward mechanism could have blocked the ability to predict timing intervals and refine motor sequences accordingly. These effects were potentially masked at 2 and 3 Hz intervals for reasons described above, and at the 4 Hz interval, the ataxia participants were simply unable to tap that quickly. A second interpretation is that, without full reliance on cerebellar function, other neural pathways compensated for timing performance. Molinari et al. (2003) found that when comparing musicians to non-musicians on timed rhythmic tapping, musicians relied more on the cerebellum, whereas non-musicians relied more on cortical areas, although both groups tapped with equal accuracy [38]. This suggests that the cerebellum supported tapping when rhythmicity (familiar timing) has been learned, but that without such learning, cortical regions are helpful for control of the tapping. Thus, instead of an inability to predict timing intervals, results of this experiment may reflect the ataxia participants' reliance on compensatory mechanisms (e.g., cortical regions) for tapping at 1 Hz, which enabled them to perform the task, albeit with greater error and a propensity to tap faster than necessary.

In order to further evaluate the contribution of explicit processing to timed tapping abilities, we administered a variation of the task that did not show feedback to a second set of participants. We speculated that removing this feedback would result in decreased accuracy for the ataxia group relative to controls because explicit contributions should provide benefit. However, we found that accuracy was unchanged. Feedback, however, motivated both groups to tap faster overall. We interpret this speed/accuracy dissociation in the context of feedback to reflect several findings. First, it confirmed that explicit feedback impacted task performance, i.e., faster tapping. Second, although we anticipated that feedback would aid performance, instead it hindered speed performance at 1 Hz because people, and the ataxia group in particular, tapped too quickly at 1 Hz with feedback. Third, removing the explicit feedback component laid bare implicit motor processes

related to motor execution. In the ataxia group, this revealed their tapping inaccuracies. Thus, even though tapping slowed to normal at 1 Hz, their over and under corrections, captured by the RSME, remained in play. In this interpretation, participants with ataxia may be able to use cortical networks to change their overall speed when prompted by explicit feedback, but these mechanisms for explicit control cannot override fundamental deficits in implicit sequencing and feedforward control.

## Experiment 2

### Introduction

Evidence suggests that the motor system, including the cerebellum, supports verbal working memory, especially when task demands are high [48–53], possibly by establishing covert motor traces that support an individual's phonological rehearsal of verbal content [23, 50, 51] and internally representing the temporal organization of words, syllables, and phonemes [54]. Thus, because the cerebellum is involved in motor (e.g., implicit procedural learning) and cognitive (e.g., verbal working memory) functions, we wondered how dependent each of these domains were upon cerebellar feedforward mechanisms, and how this relationship held up when both domains relied upon the cerebellum at the same time.

Two studies have examined patients with cerebellar damage in a dual-task paradigm that taps both motor and cognitive processes. Lang and Bastian (2002) [55] examined motor function in SCA6 patients versus healthy controls. Participants performed a motor and cognitive task, under single- and dual-task conditions: (1) performing a figure-8 movement with the arm (motor task) and (2) performing an auditory vigilance test (cognitive task of attention). SCA6 patients showed a motor deficit, but not a cognitive deficit, in the single-task conditions. When SCA6 patients were required to divide their resources between motor and cognitive demands in a dual-task condition, motor performance (specifically) got worse and did not improve with practice. Controls maintained high motor and cognitive performance under dual-task conditions and continued to improve motor control with practice. The cognitive demands in this study were low, relative to the motor demands. It is possible that cognitive load was insufficient to reveal a cognitive deficit in the dual-task condition for either group. In a separate study by Ilg et al. (2013), patients with cerebellar focal lesions were examined in a dual-task motor-cognitive paradigm in which motor and cognitive demands ranged from easy to complex (motor demands: sitting, walking, tandem walking; cognitive demands: n-back at 0-, 1-, 2-, 3-, and 4-back) [56]. Both groups showed a reduction in motor and cognitive

performance under dual-task conditions. However, in this study, cerebellar patients were disproportionately impaired on cognitive performance and motor performance under dual-task conditions, as a function of task difficulty.

These studies suggest that when motor and cognitive functions are required simultaneously, this leads to exacerbated motor deficits in cerebellar patients. We wondered if different cognitive performance results in the two studies reflected study design differences, such as differences in cognitive sequencing demands or differences in the cerebellar pathology. We also wondered whether motor versus cognitive function was more contingent upon intact cerebellar feedforward mechanisms. To find out, we administered single- and dual-task paradigms that assessed motor learning and verbal working memory, separately and simultaneously. We measured motor learning across repeated trials. Similarly, we incrementally increased cognitive demands across trials in an explicit verbal working memory task involving letter sequences. We hypothesized that verbal working memory would be impaired in the ataxia group when cognitive demands were high, which is when the cerebellum contributes the most. When motor and cognitive demands were needed simultaneously, we hypothesized that both groups' motor and cognitive performance would be affected, with a disproportionate drop in performance observed by the ataxia group. However, because motor learning is implicit, whereas the verbal working task in this paradigm relied on explicit processes, it was also possible that both groups could compensate on the latter task by using extra-cerebellar pathways.

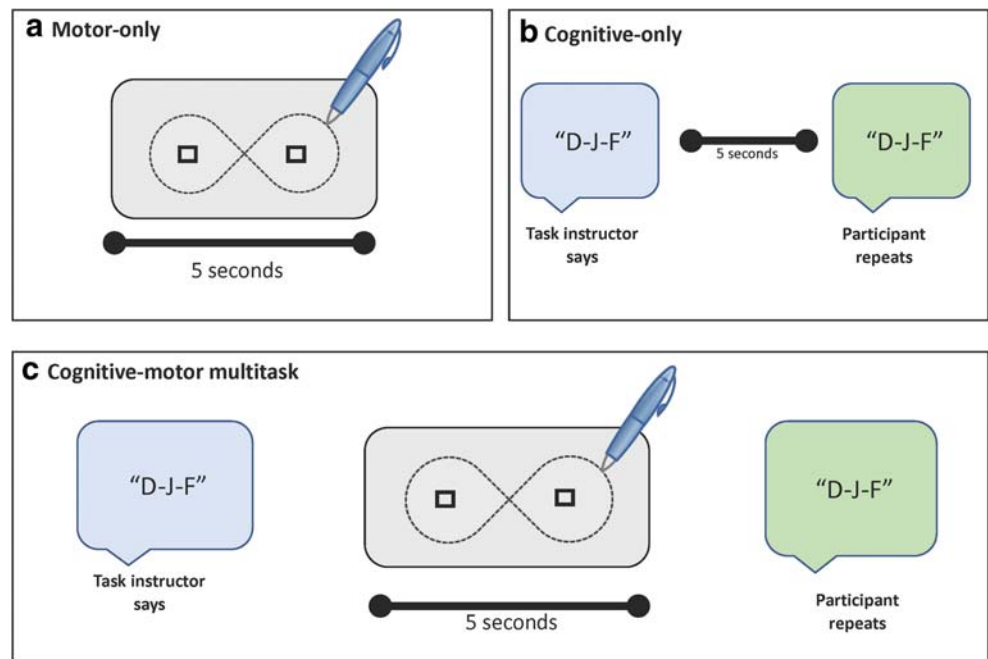
### Methods

**Participants** Individuals with cerebellar ataxia ( $n = 48$ ) and healthy controls ( $n = 56$ ) participated in Experiments 2A and 2B. To ensure that ages were equated between groups, controls under 30 years of age were excluded from analysis. Experiment 2A included 24 ataxia participants and 29 controls. One ataxia participant was excluded due to subsequent diagnosis of multiple systems atrophy (MSA), and one control was excluded due to age, leaving 23 ataxia participants and 28 controls. Experiment 2B included 24 ataxia participants and 28 controls. Of these, three controls were excluded due to age, and one control was excluded due to a subsequently discovered history of alcoholism, such that 24 controls were included in analyses.

**Experiment 2A Tasks** This study comprised two single tasks and one dual task. First, participants were asked to draw continuous (Fig. 8) loops as quickly and accurately as possible for durations of 5 s, across eight trials ("motor-only" condition, Fig. 3). Every trial was followed by a 3-s break. The duration of trials was controlled by MovAlyzeR software (Neuroscript LLC, Tempe, AZ, USA). The program automatically initiated



**Fig. 3** Task design in Experiment 2A. **A. Motor-only.** Participants drew figure-8 loops as quickly as they could for 5 s, across eight repeated trials. **B. Cognitive only.** Participants were read a sequence of three to eight letters out loud, and prompted to recall them after 5 s of silent rehearsal. **C. Cognitive-motor dual task.** Participants first listened to the letter sequences, drew figure-8 s while mentally rehearsing the letters for 5 s, and then recalled the letter sequences, across twelve repeated trials. In Experiment 2B, the motor-only condition was followed by a 5-min break, and then a second, 12-trial, motor-only condition



a 5-s trial when the subject began to draw and beeped to indicate when recording was finished, at which point no further data were recorded within the trial. Participants used rectangular markers on the tablet as guides for the position of their drawn loops.

Following the motor-only task, participants completed a “cognitive-only” verbal working memory task (Fig. 3). Each subject was read a series of three to eight distinct consonants and then were asked to recall as many letters as they could after 5 s of silent rehearsal. They were asked to recall the letters in sequence if possible or out of sequence for partial credit. Each participant was given two trials of each letter span, beginning with three items, increasing by one letter after two trials at a given span, for 12 trials total. Letter responses were recorded manually by the experimenter.

Finally, the motor and cognitive tasks were combined as a dual task paradigm. Here, participants were read a series of three to eight letters at the start of the trial. Then, they proceeded to draw loops for 5 s while simultaneously engaging in silent rehearsal of the letters. After these 5 s of drawing, subjects were asked to recall the letters in sequence (or out of sequence if needed). Subjects completed 12 5-s trials.

**Experiment 2B Tasks** In Experiment 2A, motor performance under dual-task conditions may have been affected by the additional cognitive demands of letter rehearsal, fatigue, or both. Therefore, in order to isolate motor performance with extended practice, without the influence of simultaneous cognitive demands, Experiment 2B served as a “motor control” condition. Here, the motor-only task was administered as in Experiment 2A and was then followed again by a second round of the motor-only condition, following a 5-min delay

to simulate the break that would have occurred when the verbal working memory task would have been given. During this delay, questionnaires were given (e.g., acquiring demographic information). Following the protocol of Experiment 2A, there were eight trials before the delay, and 12 trials after the delay, with every trial lasting 5 s.

All drawings were recorded on a digital tablet (Wacom Intuos 13”) using a stylus. Data were processed in real-time using MovAlyzeR software (Neuroscript LLC, Tempe, AZ, USA), which was used to run the task (following Kronemer et al. [57]). Motor performance was measured by the number of loops drawn in each 5-s trial, rounded down to the nearest 1/8 loop. This was computed for each subject across trials, and the mean number of loops per trial was computed within each group. The variable of interest in the verbal working memory task was the number of letters stated in sequence on each trial, expressed as a percentage of the total number of letters. We also computed the total number of letters given, regardless of sequence, also expressed as a percentage of the total number of letters. Errors of commission were not penalized. Because each letter span consisted of two trials, we averaged performance within a letter span for each participant, and the mean letter scores per span was computed within each group.

## Results

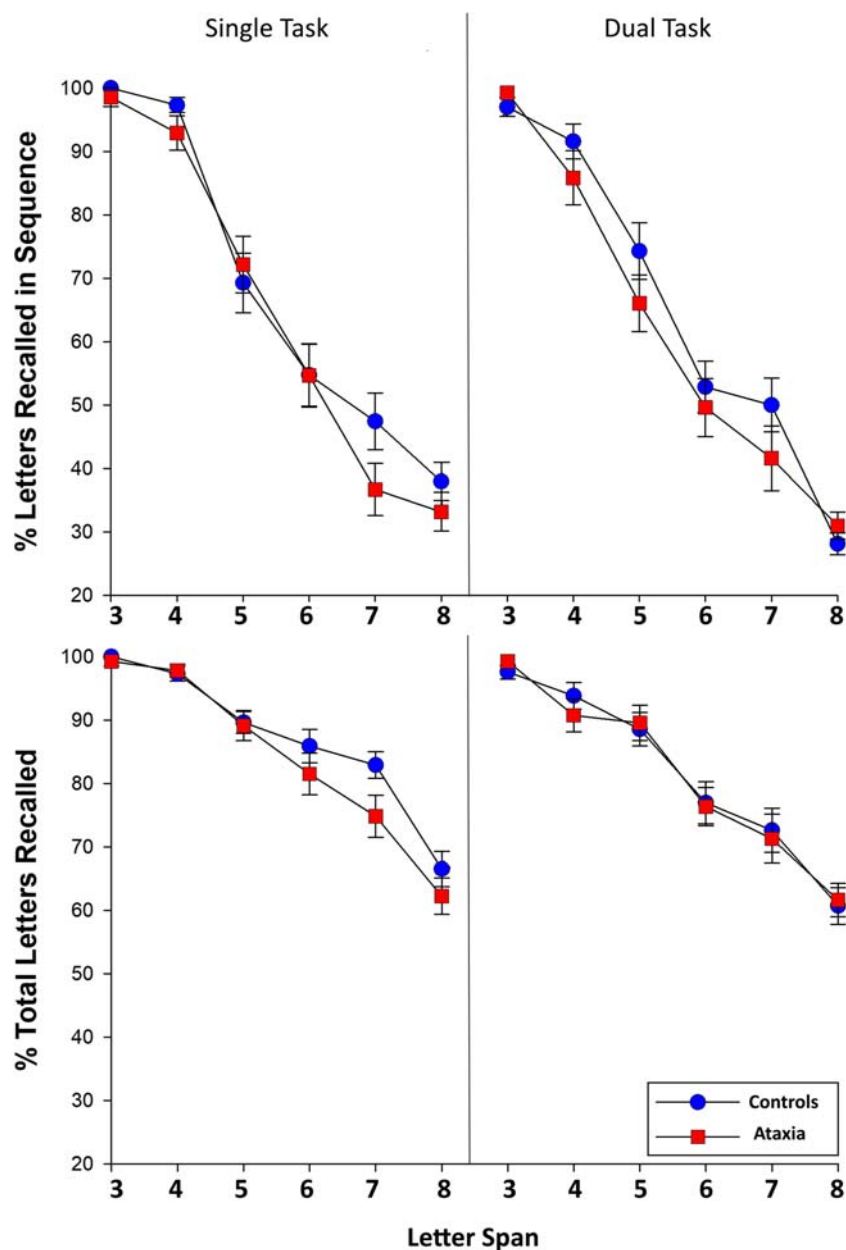
**Cognition** To examine verbal working memory, we conducted a mixed-design 2 (group: controls vs. ataxia)  $\times$  6 (spans: 3–8)  $\times$  2 (condition: single vs. dual task) ANOVA, with group and condition as the between-subjects factors and percentage of maximum letters recalled in sequence (relative to total number of letters) as the within-subjects factor. This revealed a main

effect of span (decreased performance with longer spans),  $F(3.47, 169) = 241, p < .001$ , and of condition (decreased performance with dual task),  $F(1, 49) = 5.03, p < .001$ . However, there was no main effect of group, and no interactions of span  $\times$  group, condition  $\times$  group, span  $\times$  condition, or span  $\times$  condition  $\times$  group (all  $p$  values  $> .10$ ) (Fig. 4). The same ANOVA was run for percentage of total letters recalled (regardless of sequence) with similar results, yielding a main effect of span,  $F(3.44, 169) = 139, p < .001$ , and of condition,  $F(1, 49) = 27.5, p < .001$ , without further effects or interactions, except for a marginal condition  $\times$  group interaction ( $F(1, 49) = 3.08, p = .086$ ). While performance declined in the dual task overall, the rate of decline was equivalent between groups. Taken together, these results indicated that both groups were equally

affected by cognitive load and by combining cognitive load with motor demands.

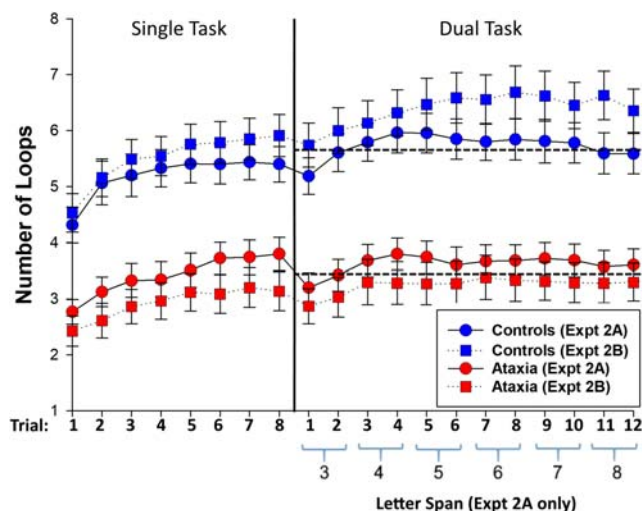
**Motor Performance** In Experiment 2A, a single (motor-only) task was followed by a dual task (combined with cognitive load). In Experiment 2B, two consecutive single tasks (motor-only) were administered. Given that the two conditions did not contain an equal number of trials, they could not be loaded into the same ANOVA and were therefore analyzed separately. First, we analyzed the single task condition by conducting a mixed-design 2 (group)  $\times$  8 (trials: 1–8)  $\times$  2 (experiment: 2A vs. 2B) ANOVA, with group and experiment as the between-subjects factors and number of loops drawn on each trial as the within-subjects factor. This revealed a main effect of trial,

**Fig. 4** Cognitive performance (as mean percentage of letters recalled in sequence, and mean total percentage of letters recalled, for each letter span) across single task and dual task conditions in Experiment 2A. The ataxia group showed lower performance in the single task overall, and both groups' performance was adversely but equally impacted by dual tasking. Error bars denote group means and standard error for each letter span



$F(3.15, 299) = 86.2, p < .001$ , indicating that the number of loops increased across trials. There was also a main effect of group  $F(1, 95) = 63.1, p < .001$ , with ataxia participants drawing fewer loops than did controls. There was an interaction of trial  $\times$  group,  $F(7, 665) = 4.23, p < .001$ . There was no main effect of experiment and no interactions of trial  $\times$  experiment, group  $\times$  experiment, or trial  $\times$  group  $\times$  experiment, all  $p$  values  $> .10$ . A post hoc 2(experiment)  $\times$  8(trials) ANOVA within each group revealed that both groups increased performance across trials (controls:  $F(3.17, 158) = 57.5, p < .001$ ; ataxia:  $F(2.86, 128) = 31.9, p < .001$ ). To find out which group increased trials more in the trial  $\times$  group interaction, we computed the difference between number of loops drawn in the first versus last trials. An independent-samples  $t$  test indicated that the delta was significantly greater for controls ( $M = 1.32, SD = 0.83$ ) than for ataxia participants ( $M = 0.86, SD = 0.83$ ),  $t(97) = 2.75, p < .01$ . Thus, controls showed a greater overall increase in motor performance than did the ataxia group. (Fig. 5).

In the dual task condition, we conducted a mixed-design 2(group)  $\times$  12(trials)  $\times$  2(experiment: 2A vs. 2B) ANOVA. As in the single task condition, this yielded a main effect of trial,  $F(4.59, 436) = 18.78, p < .001$ , and of group  $F(1, 95) = 76.8, p < .001$ . There was a trial  $\times$  experiment interaction,  $F(11, 95) = 2.31, p < .01$ , and a marginal trial  $\times$  group interaction,  $F(11, 95) = 1.78, p = .053$ . There was no main effect of experiment and no interactions of group  $\times$  experiment or trial  $\times$  group  $\times$  experiment, all  $p$  values  $> .10$ . A post hoc mixed-design 2(group)  $\times$  12(trials) ANOVA was conducted within each experiment to understand the trial  $\times$  experiment



**Fig. 5** Motor performance (measured by mean number of loops drawn for each trial) across single and dual task conditions. Note that in Experiment 2B, the “dual task” was replaced by a second motor-only condition. In controls, increase in loop count across trials was greater in Experiment 2B (without a simultaneous cognitive task) than in the corresponding dual task condition of Experiment 2A. Dashed horizontal lines in dual task indicate the mean number of loop counts at the end of single task within each group. Error bars denote standard error

interaction. However, both experiments contained significant trial effects (Experiment 2A:  $F(4.16, 204) = 10.6, p < .001$ ; Experiment 2B:  $F(4.31, 198) = 10.5, p < .001$ ). We further examined the marginal trial  $\times$  group interaction because visual inspection of the plots in Fig. 5 suggested that the controls performed differently across trials and also by experiment, which may have driven the trial  $\times$  experiment interaction. We conducted a 12(trial)  $\times$  2(experiment) repeated-measures ANOVA within each group. In controls, loop drawing increased across trials,  $F(3.50, 180) = 12.1, p < .001$ , and this increase was greater in Experiment 2B, when there was no simultaneous cognitive load,  $F(11, 550) = 2.13, p < .02$ . In the ataxia group, loop drawing also increased across trials,  $F(4.86, 219) = 8.07, p < .001$ , but this did not differ between experiments,  $F(11, 495) = 0.80, p = .64$ . Thus, in the dual task condition, the experiment  $\times$  trial and the marginal trial  $\times$  group interactions indicated that controls increased loop drawing across trials, and this increase was disproportionately greater in the absence of cognitive load. By contrast, the ataxia group showed equivalent motor performance with or without a cognitive load. This was further corroborated by one-sample  $t$  tests that were run within each group separately for Experiments 2A and 2B within the dual task condition. The test value in each case was the mean number of loops drawn in the single task trial 8. We therefore compared the number of loops drawn on each trial in the dual task (by experiment) against a baseline of where the group had left off at the end of the single task condition. In controls Experiment 2A, the number of loops drawn did not differ from baseline on any trials 1–12, (test value of 5.75, all  $p$  values  $> .10$ ). On Experiment 2B, however, the number of loops significantly differed from baseline on trials 6–9 and 11 ( $df = 23, t$  values = 2.28, 2.19, 2.31, 2.24, 2.46, respectively, all  $p$  values  $< .04$ ), and they differed marginally on trials 5, 10, and 12 ( $t$  values = 1.83, 2.07, 2.00, and  $p$  values = .08, .05, .058, respectively), uncorrected. In the ataxia group, the number of loops drawn did not differ from baseline on any trials for either Experiment 2A or 2B (test value of 3.34, all  $p$  values  $> .10$ ). Thus, the combination of motor and cognitive demands impacted motor performance for controls but not for ataxia participants.

Finally, we examined the transition from single to dual task across experiments. This analysis compared the initial adjustment to loop drawing in combination with added cognitive demands (Experiment 2A) versus simple resumption of loop drawing (Experiment 2B) by comparing performance on single task trial 8 versus dual task trial 1. A mixed-design 2(condition)  $\times$  2(group)  $\times$  2(experiment) ANOVA yielded a main effect of condition, indicating that loops decreased between the last trial of the single task and the first trial of the dual task,  $F(1, 95) = 25.9, p < .001$ . There was also a main effect of group,  $F(1, 95) = 68.3, p < .001$ , as the ataxia group drew fewer loops overall. Importantly, there was an interaction of condition  $\times$  experiment, reflecting that performance between

trials declined more for Experiment 2A (motor-cognitive) than for Experiment 2B (motor-only),  $F(1, 95) = 4.67, p < .04$ . [Post hoc paired-samples  $t$  tests were run between trials within Experiment 2A:  $M = 4.68, SD = 1.76$  versus  $M = 4.28, SD = 1.79, t(50) = 4.85, p < .001$ ; Experiment 2B:  $M = 4.52, SD = 2.17$  versus  $M = 4.34, SD = 2.24, t(47) = 2.11, p < .04$ .] There was a marginal interaction of condition  $\times$  group,  $F(1, 95) = 3.29, p = .073$ . There was no main effect of experiment and no interactions of group  $\times$  experiment or condition  $\times$  group  $\times$  experiment (both  $p$  values  $> .10$ ). Thus, transitioning from a single motor task to a dual motor-cognitive task led to a drop in motor performance that was above and beyond simply re-summing loop drawing at the start of a new task. However, motor performance rebounded for both groups as they returned to baseline (single task trial 8 performance). For controls, in the absence of cognitive load, motor performance continued to increase beyond baseline, whereas the ataxia group never exceeded single task baseline performance, regardless of cognitive load.

**Correlations with Supplemental Measures** We examined the relation between motor impairment and loop drawing using Spearman's correlations between ICARS total scores and several performance measures. The number of loops drawn on single trial session 1 reflected initial motor performance prior to learning. This measure was negatively correlated with ICARS scores,  $r(39) = -.57, p < .001$ . The difference between trials 1 versus 8 (delta) on the single task also negatively correlated with ICARS scores,  $r(39) = -.46, p < .005$ . Thus, greater neurological signs of ataxia corresponded with slower loop drawing at the start of the task and with less improvement across trials. CES-D scores marginally and negatively correlated with improvement across trials,  $r(47) = -.29, p = .052$ . We therefore conducted a partial correlation between ICARS scores and the delta measure to rule out the possibility that psychomotor slowing was responsible for lower rates of improvement across trials. The correlation remained,  $r(36) = -.42, p < .01$ .

## Discussion

In this study, our initial hypothesis that verbal working memory would be impaired in the ataxia group was not supported. We found that dual task conditions that combined loop drawing with phonological rehearsal led to fewer letters recalled in sequence, especially at longer spans; however, the magnitude of this decrement did not differ between groups. This is consistent with a study by Lang & Bastian (2002) in which cognitive load was unaffected in SCA6 participants while performing a motor task [55]. It is, however, inconsistent with another study by Ilg et al. (2013) of cerebellar lesion patients in which their cognitive performance declined with increasing cognitive and motor demands [56]. The verbal working

memory task in this study was closer in design to that used by Ilg et al. than by Lang & Bastian. The latter involved a vigilance test with relatively low and consistent cognitive load. Ilg and colleagues administered the n-back working memory task at various difficulty levels. This task relies on an ability to hold information in mind (the current stimulus trial) while also recalling stimuli on prior trials and making decisions about whether the new and old stimuli match. Differences between the current study results and those of Ilg et al. can be attributed to several possibilities. First, the sequencing demands required for the n-back test may have been greater than those needed for the temporary storage of letter spans across 5-s intervals. Second, the focal regions affected by cerebellar stroke in the Ilg et al. study may have impacted cognitive networks differently than did cerebellar degeneration in the patients of the present study. Third, attentional demands of the cognitive and motor tasks may have been higher in the Ilg et al. study. There is a fair bit of attention required at the higher memory loads of the n-back task. Ilg et al. also required participants to perform increasingly more difficult postural tasks that are known to be particularly difficult in people with cerebellar damage. Ataxia patients have noted that their movement automaticity diminishes with progression of the disease, and a great amount of attention is needed to control movement. One patient in Holmes (1939) noted, "The movements of my left arm are done subconsciously, but I have to think out each movement of the right (affected) arm" [1] (p. 22). Therefore, if a cognitive process requires a high degree of attention, this would lead to rapid depletion of attentional resources needed for motor function, and that synergy may have led to cognitive and motor impairments by patients in the study by Ilg et al. In the current study, however, motor function was not impacted by cognitive load observed in the ataxia group, suggesting that their attentional resources for motor function were maintained in the dual task condition.

The motor task yielded several group differences. First, motor performance (i.e., number of loops drawn per trial) was impaired in the ataxia group in all conditions, which was expected. Second, the rate of improvement was higher in controls than in the ataxia group. In ataxia, lower rates of improvement were associated with greater severity of neurological signs. Third, motor performance declined with cognitive load for controls but not for ataxia participants. This was revealed by a motor-only control condition, in which controls continued to improve motor performance in the absence of simultaneous cognitive demands. By contrast, motor performance with and without cognitive load was identical in the ataxia group.

Behavior in the control group supported the expectation that dual task conditions would impact motor and cognitive performance. When both tasks relied on cerebellar function, resources were depleted, resulting in fewer loops drawn across

trials and fewer letters recalled in sequence, relative to when those same tasks were performed under single task conditions. It was somewhat surprising, therefore, to observe that motor function was unaffected in the ataxia group. Moreover, their cognitive function was impacted by the dual task condition, but not disproportionately so. Taken together, these results lead us to believe that when cerebellar circuitry is disrupted by degeneration, cognition is achievable through compensatory means that do not include the cerebellum. Such re-routing of mechanisms would preserve resources for cerebellar motor functions. Thus, even though the ataxia group drew fewer loops overall, their resources for doing so were not further depleted by simultaneous verbal working memory demands.

These results do not support the idea that cerebellar function is specific to sequencing *per se*. Indeed, the ataxia group's sequencing abilities were unimpaired in the explicit domain. By contrast, their implicit procedural learning (i.e., loop drawing across trials) was impaired, in terms of productivity and rate of improvement. This argues in support of the notion that cerebellar feedforward mechanisms preferentially support processes within the implicit domain.

## Experiment 3

### Introduction

Individuals with cerebellar injuries have demonstrated impaired sequence learning on paradigms designed to measure implicit learning [17, 58–61]. Sequence learning is often tested by using a variation of the serial reaction time task (SRTT) developed by Nissen and Bullemer (1987). This design includes a repeating sequence of visual stimuli that cue participants to press buttons that correspond to the sequence. For example, an asterisk may appear in one of four locations, with each location corresponding to buttons 1, 2, 3, and 4, and the sequence might be: 4-2-3-1-3-2-4-3-2-1 [62].

In the typical SRTT, sequence learning is indicated by decreased response times (RT) as the participant acquires sequence knowledge and begins to anticipate upcoming stimuli. RT also decreases due to motor learning as people gain familiarity with the task procedure overall. The SRTT begins and ends with a block of non-sequence, or “random” trials. This enables comparison of the RT between the first and last block of trials to compute overall motor learning. As well, RT reductions are compared between the last block of sequence trials and the last block of random trials to isolate the magnitude of sequence learning.

As sequences are presented repeatedly, however, participants often gain declarative knowledge of them. Indeed, in the original Nissen and Bullemer study (1987), 11 of 12 healthy participants explicitly recalled the sequence by the end of the test [62]. This represents a confound for implicit

sequence learning measurements using SRTT because those with explicit sequence knowledge may be able to use declarative processes to improve their RT above and beyond that gained by implicit processes alone. Moreover, patients with cerebellar damage, when probed after the SRTT, tend to show little to no declarative sequence knowledge, in contrast to that of controls [17, 59, 61, 63]. Two studies examined the use of declarative knowledge during SRTT in patients with cerebellar lesions [61] and those with cerebellar degeneration [17]. In both studies, patients and healthy controls were trained to memorize the sequence immediately before testing on the SRTT, which was validated by verbal recall. Healthy controls benefitted from declarative sequence knowledge by improving RTs, to the point of responding within 30 ms due to stimulus anticipation rather than to stimulus reaction [17]. Interestingly, the two patient groups responded differently: patients with cerebellar lesions were able to improve RT performance as a function of a priori declarative sequence knowledge, whereas the patients with cerebellar degeneration could not. Because neither patient group showed SRTT learning when they were naïve to the sequence, Molinari et al. (1997) reasoned that differing results between the two patient groups (i.e., improved RT performance by the cerebellar lesion group only) suggested that the role of the cerebellum was more important for detecting a sequence than for executing it. However, the question remains whether the impaired SRTT learning, as reflected by RT performance, in any group with cerebellar damage has resulted from deficits in implicit sequence learning or from an inability to naturally and gradually form declarative sequence knowledge. For example, if controls were able to develop declarative sequence knowledge whereas the patients could not, this would have conferred an unfair RT advantage for the controls and driven group RT differences.

In the current study, we embedded random items inside of a repeating sequence. This variation on the serial reaction time task (SRTT) [62] enabled us to mask the sequence in a way that greatly diminished declarative sequence knowledge formation [25, 64, 65]. Moreover, it enabled us to isolate the development of motor learning from the acquisition of sequence learning continuously across blocks [31, 32, 64–67]. We hypothesized that, in the absence of declarative sequence knowledge by controls, the ataxia group would unambiguously show impaired implicit sequence learning, which would be consistent with disrupted predictive feedforward modeling.

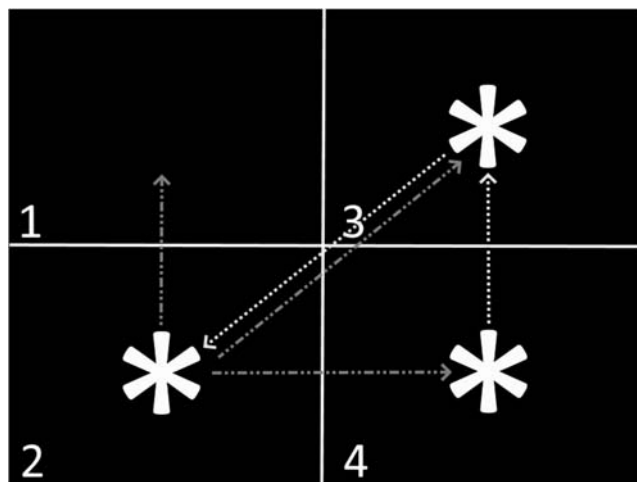
### Methods

**Participants** Individuals with cerebellar ataxia ( $n = 34$ ) and healthy controls ( $n = 30$ ) who were equated for age, sex, and level of education participated. Two ataxia participants were excluded from analysis due to a subsequent diagnosis of (1)

hereditary spastic paraplegia type 7 and (2) probable MSA. Thus, the final patient group's  $n = 32$ .

**Implicit Sequence Learning Task** White asterisks were presented on a black background and moved across four spatial locations according to a three-step pattern that was undisclosed to participants (Fig. 6). Random target locations were embedded within the pattern [31, 32, 65] as every fourth location. The target, however, could not remain in the same location for two consecutive trials. Thus, the target appeared in one of the remaining three locations, one of which was consistent with the pattern (i.e., “pattern consistent”), which represented 8.3% (1/3 of 25%) of all trials in the task. The remaining 16.7% represented random locations. Pattern and pattern-consistent trials were collapsed during analysis and compared against random trials.

The study design consisted of 12 blocks of 102 trials each. The first and twelfth blocks consisted of entirely random locations. Blocks 2–11 consisted of pattern and random trials. Response time (RT) and accuracy of the button press responses were recorded for each trial. Feedback was provided at the end of each block in the form of mean accuracy and RT. If accuracy was 90% or above, participants were encouraged



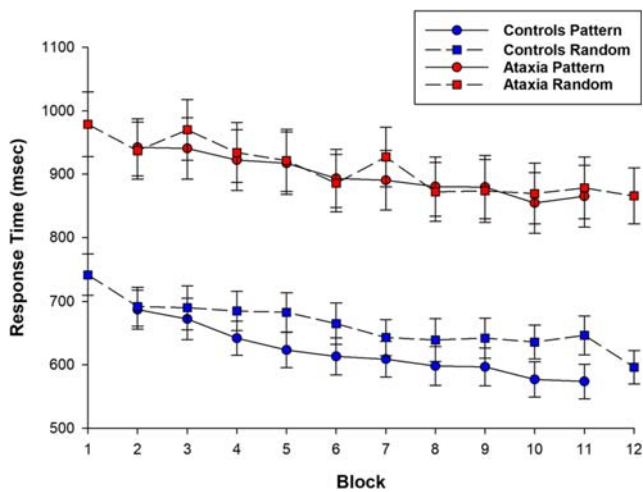
**Fig. 6** Participants indicated the asterisk's location as quickly and accurately as possible by using a response box and pressing the index and middle fingers of both hands to indicate whether the target appeared in locations 1, 2, 3, or 4 (keys “z,” “x,” “,” and “/,” respectively). Position of the asterisk on each trial was determined by a set of rules: a vertical “line” (created by two consecutively presented targets that appeared in locations above or below one another), followed by a diagonal “line” (created by two consecutively presented targets that appeared in locations above or below and contralateral to one another), followed by a horizontal “line” (created by two consecutively presented targets that appeared in locations to the right or left of one another). The 4th location was determined randomly, and then the pattern repeated. In this depiction, the asterisk moved from location 4 to 3 to 2 (indicated by blue dotted lines). The 4th location may be location 1, 3, or 4 (indicated by gray dash/dotted lines). If the asterisk moves to location 4, this would be considered “pattern-consistent” by following the rule, whereas locations 1 and 3 would be considered “random”. (adapted from [32])

to focus on speed. Otherwise, they were encouraged to focus on accuracy. We computed the median RT per block per trial type for each participant and used these medians during RT analyses. Pattern learning was computed as the difference in RT between pattern and random trials within Blocks 2–11. Overall motor learning was calculated as the difference in RT between Block 1 minus Block 12. Stimuli were delivered electronically using E-Prime Professional 2.0 [68].

**Post-experimental Tasks** Three post-experimental tasks were administered to probe for explicit knowledge of the rule-based pattern, following Marvel et al. (2007) [32]. (1) Verbal report: participants were asked whether they noticed any regularities in the location of the “stars” and if so, to describe them. They were asked how often such regularities occurred and whether they were able to use this knowledge to improve their performance. (2) Generation: participants were shown the asterisk moving from one quadrant to another and asked to indicate in which quadrant the asterisk would appear next. Because in the test, the asterisk never appeared in the same quadrant twice in a row, we determined chance response to be 33%. Correct responses were counterbalanced across all four quadrants. Twelve trials were administered. (3) Recognition: participants were shown a split screen with four quadrants on each side, with three consecutive stimulus locations shown in each. Participants were asked to indicate which series of locations occurred more often throughout the test. Correct responses were counterbalanced between left and right (i.e., chance = 50%). Twelve trials were administered.

## Results

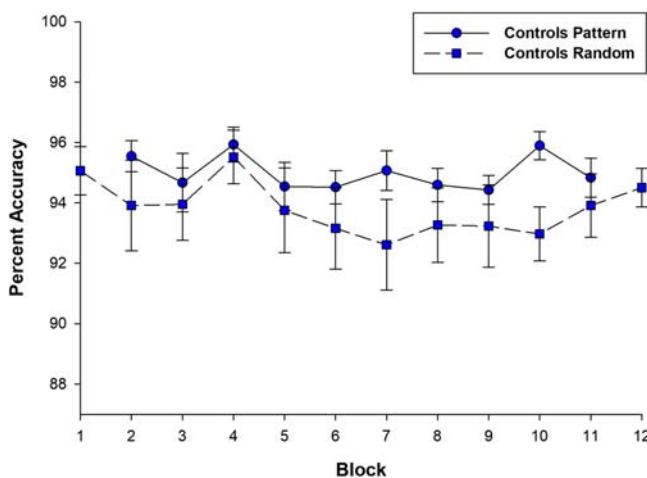
**Implicit Sequence Learning** We performed a mixed-design  $2 \times 10 \times 2$  ANOVA with trial type (2: pattern vs. random) and block (10: Blocks 2–11) as within-subjects factors and group (2: control vs. ataxia) as a between-subjects factor on the RT data. This revealed a main effect of trial type,  $F(1, 60) = 20.4, p < .001$ , in which RT for random trials was slower than for pattern trials (Fig. 7). There was a main effect of block,  $F(4.34, 261) = 18.7, p < .001$ , in which participants increased speed across blocks and a main effect of group,  $F(1, 60) = 23.7, p < .001$ , in which ataxia participants' RT was slower than that of controls. There was a two-way interaction of trial type  $\times$  group,  $F(1, 60) = 9.22, p < .005$ , in which controls showed greater RT separation between random and pattern trials than did ataxia participants. There was no trial type  $\times$  block interaction,  $F(6.74, 404) = 1.59, p = .141$ . However, there was a marginal three-way interaction of trial type  $\times$  block  $\times$  group,  $F(6.74, 404) = 1.85, p = .079$ , in which controls trended toward increasing the RT separation between random and pattern trials across blocks more than ataxia participants did. Interestingly, there was no two-way interaction of block  $\times$  group, indicating that the ataxia and control groups



**Fig. 7** Mean response times as a function of group, block, and trial type. Blocks 1 and 12 consisted of random trials only. Blocks 2–11 consisted of pattern and random trials. Although the ataxia group was slower in general, their rate of motor learning was equal to that of controls. However, controls showed a RT separation between pattern and random trials, indicative of pattern learning, that was not observed in the ataxia participants. Error bars denote standard error

showed an equivalent overall rate of RT improvement (i.e., motor learning) on Blocks 2–11  $F(4.34, 261) = 0.532$ ,  $p = .727$ .

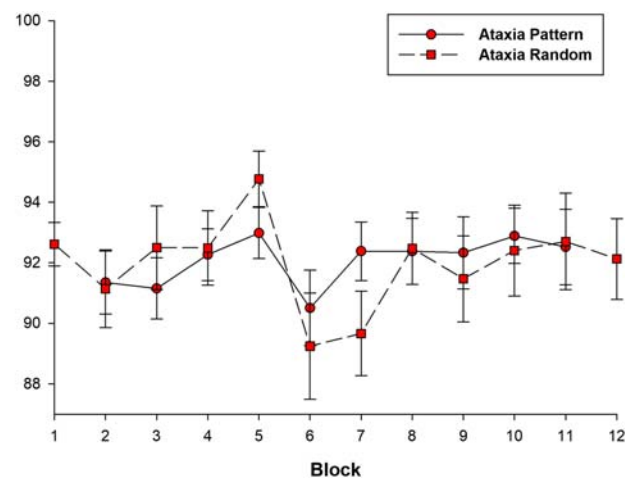
To examine accuracy, groups were compared using a mixed-design  $2 \times 10 \times 2$  ANOVA with trial type (2) and block (10) as within-subjects factors and group (2) as a between-subjects factor on the accuracy data. There was a main effect of trial type [accuracy was higher for pattern than random trials,  $F(1, 60) = 4.82$ ,  $p < .04$ ] and group [controls were more accurate than were ataxia participants,  $F(1, 60) = 7.03$ ,  $p < .02$ ]. There was no main effect of block, nor interactions of trial type  $\times$  group, trial type  $\times$  block, block  $\times$  group, or trial



**Fig. 8** Percent accuracy as a function of group, block, and trial type. As in Fig. 7, blocks 1 and 12 consisted of random trials only, and blocks 2–11 consisted of pattern and random trials. Accuracy was relatively high for both groups, but significantly higher for controls than for ataxia

type  $\times$  block  $\times$  group (all  $p$  values  $> .10$ ) (Fig. 8). However, visual inspection of the data suggested that groups performed differently and were subsequently analyzed separately by conducting a  $2(\text{trial type}) \times 10(\text{block})$  ANOVA within each group. In controls, this analysis yielded a trial type difference,  $F(1, 29) = 5.12$ ,  $p < .04$ . There was no main effect of block or interaction of trial type  $\times$  block [both  $p$  values  $> .10$ ]. We interpreted this trial type effect as a secondary measure of pattern learning, which has been observed in other SRTT tasks with random stimuli embedded within the pattern [65]. That is, as people learned the pattern, they became more likely to commit errors when presented with random stimuli, expecting pattern-consistent stimuli instead. In the cerebellar ataxia group, accuracy for pattern and random trials did not differentiate across trials or blocks, and there was no interaction of trial type  $\times$  block (all  $p$  values  $> .10$ ). Thus, the trial type effect that was first observed in the omnibus ANOVA was driven by controls. This is consistent with the RT data showing that implicit sequence learning occurred in the control group but not in the cerebellar ataxia group.

Working memory capacity may assist in sequence detection by maintaining multiple targets in mind at once [69], which is a function that involves the cerebellum [23, 51]. Thus, participants with slower RTs may have been challenged by having fewer items in mind within a given time frame. To find out, we performed the mixed-design  $2(\text{trial type}) \times 10(\text{block}) \times 2(\text{group})$  ANOVA again, this time using RT from Block 1 as a covariate. Accounting for individual speed, there was no longer a main effect of block,  $F(4.49, 265) = 1.68$ ,  $p = .147$  and only a marginal effect of trial type,  $F(1, 30) = 3.71$ ,  $p = 0.059$ . The main effect of group remained, as expected,  $F(1, 59) = 8.38$ ,  $p < .01$ , and so did the important trial type  $\times$  group interaction,  $F(1, 59) = 5.62$ ,  $p < .03$ . Again, there was no block  $\times$  group interaction,  $F(4.49, 265) = 1.02$ ,  $p = .401$ . In



participants. A trial-type separation was observed in controls, which represents another form of pattern learning. Error bars denote standard error

this analysis, there was a new two-way interaction of trial type  $\times$  block,  $F(6.92, 408) = 2.53$ ,  $p < .02$ , as pattern vs. random RTs differentiated increasingly across blocks. However, there was no longer a three-way interaction of trial type  $\times$  block  $\times$  group,  $F(6.92, 408) = 0.589$ ,  $p = .763$ . Thus, consideration of RT impacted findings related to motor learning (i.e., block effects), but evidence of impaired sequence learning in the ataxia group persisted (i.e., the trial type  $\times$  group interaction).

When pattern-consistent trials occurred multiple times in a row (odds =  $1/3 \times 1/3 \times 1/3$ , etc.), this created a repeated triangular stimulus trajectory that became visually obvious and provided an opportunity for speeded responses. Given that the control group was faster than the ataxia group, this potential advantage would have benefitted the controls more. In order to remove the influence of this conspicuous sequence, we identified trials in which the triangular trajectory occurred three or more times in a row and removed them from RT analyses. All of the original findings were upheld in this mixed-design 2 (trial type)  $\times$  10 (block)  $\times$  2 (group) ANOVA: main effect of trial type,  $F(1, 60) = 15.0$ ,  $p < .001$ , block,  $F(4.29, 257) = 18.8$ ,  $p < .001$ , and group,  $F(1, 60) = 23.6$ ,  $p < .001$ ; a two-way interaction of trial type  $\times$  group,  $F(1, 60) = 8.87$ ,  $p < .005$ ; and marginal three-way interaction of trial type  $\times$  block  $\times$  group,  $F(6.88, 413) = 1.79$ ,  $p = .089$ . As before, there was no interaction of trial type  $\times$  block or block  $\times$  group (both  $p$  values  $> .10$ ). Thus, any potential advantages derived from pattern repetition did not drive group differences within the implicit sequence learning results.

**Post-experimental Questionnaires** None of the participants described the pattern as a function of the rules (i.e., could not indicate that vertical movement was followed by diagonal, etc.), although some reported noticing occasional “triangles,” but could not elaborate beyond that. In the Generation task, one-sample  $t$  tests indicated that controls performed significantly above chance level of 33% ( $M = 46.4$ ,  $SD = 15.7$ ),  $t(29) = 4.66$ ,  $p < .001$ ). The ataxia group performed marginally above chance ( $M = 38.5$ ,  $SD = 16.8$ ),  $t(31) = 1.87$ ,  $p = .071$ ). This resulted in a marginal group difference,  $t(60) = 1.90$ ,  $p = .063$ . Neither group performed above chance (50%) in the Recognition task (controls:  $M = 51.4$ ,  $SD = 13.5$ ,  $t(29) = .56$ ,  $p = .578$ ; ataxia participants:  $M = 49.7$ ,  $SD = 13.1$ ,  $t(31) = -.11$ ,  $p = .911$ ), and the group scores did not differ ( $t(60) = .487$ ,  $p = .628$ ).

**Correlations with Supplemental Measures** Pattern learning (RT trial type difference on Block 11), motor learning (RT for Block 1 minus Block 12), Generation score, and Recognition score were compared to the ataxia participants’ CES-D and ICARS scores. No significant correlations were observed (all  $p$  values  $> .10$ ). Generation scores did not confer a pattern learning advantage for controls or ataxia participants (both  $p$  values  $> .10$ ).

## Discussion

The ataxia group was impaired at sequence learning even though their rate of motor learning was intact. If the pattern had been learned, RTs would have been faster on pattern than random trials. We propose that ataxia participants did not show RT trial type differences because they never learned the sequence. The difference in performance between motor versus sequence learning observed here demonstrated an interesting dissociation between cerebellar feedforward predictive models within motor versus cognitive domains.

Our approach differed from three prior studies [17, 61, 70] in that we applied a probabilistic, rule-based formula to the stimulus locations that mitigated opportunities for explicit sequence learning, whereas prior studies have used a repeating sequence that usually, over time, becomes explicit to healthy participants. Our results are consistent with the overall findings of prior studies, which also reported impaired SRTT performance by the ataxia groups. Unlike those studies, however, our ataxia group showed normal RT improvements from the beginning to the end of the task, indicating intact motor learning. Our paradigm separated motor learning from cognitive sequence learning, and found that the ataxia group was specifically impaired on the cognitive sequential aspects of the task. Normal procedural learning in the ataxia group was a surprising observation, especially in contrast to our own results in Experiment 2. However, the current study differed from those three prior studies in several important ways that may have affected motor learning. First, participants in our study completed 1224 trials total. By contrast, the prior studies included only 480–864 trials. Thus, ataxia participants in the current task received more practice. Second, two of the prior studies imposed 500-ms inter-trial intervals that only advanced to the subsequent trial after the participant responded correctly [17, 61]. The current study imposed no delay such that any response triggered the start of the next trial. Thus, it is possible that rapid response-stimulus intervals, in the absence of imposed delays, facilitated motor learning in the current paradigm. Regarding implicit sequence learning in the cognitive domain, our findings are also consistent with a recent study of SCA3 patients showing impairments on the SRTT alongside intact recall of temporal ordering for word lists and intact learning on a weather prediction probabilistic classification task [70]. The temporal ordering task was explicit, supporting the notion that extra-cerebellar mechanisms can help compensate (as we speculated from our results in Experiment 2). The classification task was designed to promote implicit learning of probabilities (i.e., a visual cue was associated with the probability of rainy weather). However, the task involved feedback after each trial. When feedforward prediction is disrupted, but sensorimotor feedback is available, ataxia patients can overcome deficits through explicit methods of compensation [9, 71]. Thus, feedback provided an



opportunity for the ataxia group to correct implicit learning deficits. The current study did not provide trial-by-trial feedback, which forced participants to learn the sequence purely through repeated exposure.

We administered two supplementary tasks to probe for explicit sequence knowledge. In the Generation task, controls performed above chance. However, scores on the Generation task did not correlate with sequence learning. On the Recognition task, both groups scored at chance. On the open-ended questionnaire, no participant expressed explicit knowledge of the rule-based sequence. Despite the fact that the Generation task was designed to probe for explicit sequence knowledge, it may have been a sensitive probe for implicit sequence knowledge. For example, the Generation task required active anticipation of an upcoming location/response, which was similar to the demands of the actual task, whereas the recognition task involved the passive observation of location sequences. Perhaps implicit sequence knowledge enabled controls to perform above-chance on the Generation task.

In sum, the ataxia group showed impaired implicit sequence learning when explicit strategies were unavailable. Interestingly, their motor learning was normal. This dissociation between the two forms of implicit learning suggests that cognitive implicit sequencing may be more sensitive to cerebellar disruption of feedforward mechanisms when explicit strategies are not available.

## Experiment 4

### Introduction

In order to test whether the cerebellum contributes to cognitive sequencing when task demands are explicit and sequencing requires conscious attention, we leveraged a card sequencing task developed by Leggio et al. (2008), in which participants were required to arrange verbal, spatial, and behavioral information in sequential order [21]. Leggio et al. found that individuals with cerebellar injury, both focal and atrophic, were impaired in this task. Furthermore, those with lateralized cerebellar lesions were found to be differentially impaired on verbal or non-verbal sequencing, depending on whether the lesion was located in the left or right cerebellar hemifield, respectively. Because this task required participants to explicitly identify and generate sequences, we interpreted this finding as supporting the hypothesis that the cerebellum contributes to sequencing of explicitly represented information, and that this ability was disrupted in cerebellar degeneration. Here, we set out to corroborate these hypotheses by attempting to replicate the findings of Leggio et al. in our cohort of participants with cerebellar degeneration.

We adapted the task created in Leggio et al. (2008) so that stimuli were presented and manipulated using a computer and mouse, rather than using physical cards. Computer administration enabled us to record response times, as well as the number of moves participants made to put the cards in the desired sequence. Number of moves served as a secondary measure of sequencing ability, in addition to accuracy of participant's final responses. Furthermore, in initial, informal pilot testing of three subjects using physical cards, we found that participants with ataxia had difficulty manipulating the cards, and particularly in placing the cards neatly (i.e., at right angles and parallel to one another). Computer administration ensured that participants were able to place the cards in precise alignment, which was especially important for spatial sequences.

### Methods

**Participants** In this experiment, 49 individuals with cerebellar ataxia and 19 controls participated, equated for age, sex, and education level. Six ataxia participants were excluded from analysis due to (1) subsequent diagnosis of Ataxia with Vitamin E Deficiency (AVED); (2) visual impairment resulting in difficulty seeing stimuli in the behavioral condition; (3) a technical error corrupting task data; and (4–6) unintentional moves (described below) not recorded. Three controls were excluded due to (1) a technical error corrupting task data, and (2–3) unintentional moves not recorded. Accordingly, the final groups comprised 43 ataxia participants and 16 controls. ICARS scores were unavailable for three ataxia participants tested at Johns Hopkins University and nine tested at the University of Iowa. As such, these 12 individuals' scores were excluded from analyses that involved the ICARS.

**Task** The task was a computerized adaptation of the card-sequencing task presented in Experiment 2 of Leggio et al. (2008), which generously made task stimuli available [21]. In each trial, participants were shown a series of six shuffled cards in evenly spaced locations on the bottom of the screen, and then asked to place each card in symmetrical locations at the top of the screen, in what they believed was the most logical order. Participants re-arranged the digital cards by clicking on them with a mouse button to pick them up, and clicking again to place them in the desired location. For each trial, response duration and number of moves were recorded. A move was defined as an instance of picking up and placing a card. To account for the possibility that motor impairment could result in accidental or mis-placed clicks, an administrator manually recorded the number of times individuals made an obviously unintentional move (for example, if a participant accidentally clicked on a card and immediately attempted to put it back down), and this number was subtracted from the raw number of moves for each trial. Following Leggio et al.,

an accuracy score was calculated as “ratio to repetition” (RR) [72], where  $RR = ((\text{correctly sequenced cards}) - (\text{correctly sequenced fragments})) / (\text{total number of cards} - 1)$  [21].

Card stimuli presented three different kinds of material to be sequenced: verbal (e.g., “Lucy called a friend.” “she asked him to go dancing,” “he agreed”...), spatial (abstract lines that formed a cohesive pattern when in the correct order), and behavioral (cartoon drawings that form a narrative) [21]. Verbal stimuli were copied verbatim and the translation edited by OM and CM; spatial and behavioral stimuli were traced by hand and edited in Adobe Photoshop to ensure a clear appearance. A control trial comprised cards with 1–6 dots, created in Adobe Illustrator. In pilot testing, seven participants with ataxia and five controls completed a computerized task with four verbal trials, three spatial trials, and four behavioral trials, corresponding to the 11 trials reported in Leggio et al. This pilot group was different from the group of three that completed a pilot with physical cards. After pilot testing, we excluded one stimulus each from the verbal and behavioral conditions (Supplement #2), such that each of the three conditions contained three trials, for a total of nine trials plus one control trial. Measures of interest were response time, number of moves, and accuracy score, which were compared between groups. [21].

## Results

As expected, participants with ataxia showed longer trial durations than did controls in each condition (all  $p$  values  $< 0.05$ ; see Table 2). However, participants with ataxia did not show significant deficits in number of moves or accuracy score in any condition (all  $p$  values  $> 0.10$ ; see Table 2).

**Correlations with Supplemental Measures** The ataxia participants’ task performance was compared to the severity of clinical signs by correlating the ICARS total score with number of moves, accuracy score, and trial durations for each condition. ICARS total score correlated positively with trial duration for the verbal condition ( $r(29) = 0.44$ ,  $p < 0.04$ ) and marginally for the spatial condition ( $r(29) = 0.40$ ,  $p = 0.053$ ), but not for the behavioral condition ( $r(29) = 0.267$ ,  $p = 0.15$ ). ICARS total score and CES-D score did not correlate with accuracy score or number of moves for any of the conditions (all  $p$ -values  $> 0.10$ ).

## Discussion

In contrast to Leggio et al. (2008), our study found no evidence for impairment of explicit sequencing ability in cerebellar ataxia, either across all participants with cerebellar degeneration [21]. Participants did not show lower accuracy scores, nor did they need to take more moves to achieve a satisfactory result, than did controls. This is surprising, given that our experimental set-up closely reproduces that described in Leggio et al., except for the fact that our task was computerized. One possible explanation for the difference in results is that the computerization of the task made it easier for both controls and ataxia participants, to an extent that group differences could no longer be detected. However, one-sample  $t$  tests confirmed that performance in each group in every non-control condition was significantly different from ceiling for both accuracy score and number of moves (all  $p$  values  $< 0.005$ ). Besides, the cognitive processes that the task aims to probe should be elicited across different modes of administration. Furthermore, controls’ scores in the present study were

**Table 2** Experiment 4: group comparisons

Measure	Condition	Control ( $n = 16$ )		Ataxia ( $n = 43$ )		Statistic	$p$ (uncor.)	$p$ (cor.)
		Median	Mean (SD)	Median	Mean (SD)			
Score	Control	1	1 (0)	1	1 (0)	–	–	–
	Verbal	0.97	0.9 (0.12)	1	0.93 (0.13)	$U = 282$	0.21	0.63
	Spatial	0.87	0.85 (0.19)	0.93	0.83 (0.21)	$U = 351.5$	0.90	1.0
	Behavioral	0.83	0.78 (0.22)	0.87	0.79 (0.22)	$U = 332$	0.84	1.0
Number of Moves	Control	6	6.56 (2.25)	6	6.30 (0.89)	$U = 313$	0.38	1.0
	Verbal	6.33	6.56 (0.61)	6.33	6.70 (0.92)	$U = 335.5$	0.89	1.0
	Spatial	9.33	11.31 (5.37)	9	10.33 (3.71)	$U = 352$	0.90	1.0
	Behavioral	7.67	8.15 (2.34)	7.67	8.27 (2.38)	$U = 344$	1.0	1.0
Duration (seconds)	Control	24.20	27.54 (11.8)	42.30	48.72 (29.66)	$U = 141.5$	$< 0.001$	$0.001$
	Verbal	33.02	35.04 (9.13)	50.57	58.12 (25.75)	$U = 97$	$< 0.001$	$< 0.001$
	Spatial	60.29	72.27 (46.01)	92.1	100.20 (52.99)	$U = 200.5$	0.015	0.015
	Behavioral	53.32	58.21 (22.51)	79.8	89.58 (35.11)	$U = 134.5$	$< 0.001$	$0.001$

Results of between-group comparisons in Experiment 4. Italicized  $p$  values indicate significance at  $\alpha = 0.05$

comparable to those reported in Leggio et al., which suggests that modes of administration did not differentially impact performance. Another possible explanation is differences in composition of the ataxia groups between studies. Our group of participants with cerebellar degeneration was qualitatively similar to the “idiopathic cerebellar ataxia (ICA)” group in Leggio et al. However, it is possible that there was heterogeneity of pathology between patient groups of the two studies that influenced results. Finally, the computerized administration of the task ensured that all participants in both groups were able to place the cards in precise spatial alignment, which removed a potential disadvantage for the ataxia group. Given these considerations, we interpret our null result as supporting the hypothesis that cerebellar degeneration specifically impacts implicit, but not explicit, sequencing [21].

## Experiment 5

### Introduction

Cerebellar cognitive affective syndrome (CCAS) refers to a collection of non-motor deficits that includes difficulties in executive function, visuo-spatial skills, language, and affect in individuals with cerebellar injury [4]. These impairments may arise from the cerebellum’s inability to properly organize thoughts as part of a “dysmetria of thought” [73]. In Experiment 5, we used word similarities and proverb interpretation tasks to test cerebellar sequencing. In addition to abstract thinking, this task requires unconscious “sequential logical reasoning” [22] in order to coherently construct and express meaningful statements. This unconscious sequencing of thought can be seen as internal predictive modeling in a cognitive domain, supporting the internal marshaling of thoughts prior to expression. Cerebellar injury has been associated with difficulties in abstract thinking [4, 74, 75]. However, it is possible that impairments of linguistic expression, as a function of sequential reasoning, may interfere with patients’ ability to reply in a meaningful way. We hypothesized that individuals with cerebellar ataxia would be impaired at proverb interpretation when it came to expression of thoughts, independent of their abstract thinking skills and ability to recognize correct interpretations of proverbs.

### Methods

**Participants** Individuals with cerebellar ataxia ( $n = 39$ ) and healthy controls ( $n = 25$ ) who were equated for age, sex, and level of education, participated. One ataxia patient was unable to provide any response for one of the proverbs, which prohibited accurate scoring for that individual, and was removed from analysis. Thus, the final patient group’s  $n = 38$ . All participants in Experiment 5 were native English speakers.

**Word Similarities and Proverb Interpretation Tasks** We administered the “Difficulty in Abstract Thinking” item from The Structured Clinical Interview-Positive and Negative Syndrome Scale (PANSS) [76]. This item of the PANSS contains two parts: (1) word similarities and (2) proverb interpretations. First, participants were asked to explain how word pairs were similar (e.g., “a bus and a train”). Second, participants were asked to explain the deeper meaning of a proverb (e.g., “Don’t put all of your eggs in one basket.”). Four trials of each task were administered. Both tasks required participants to think abstractly. However, responses for the similarities task were conducive to concise responses (e.g., “modes of transportation”). By contrast, interpretation of proverbs was open-ended and emphasized the marshaling of one’s thoughts while expressing the proverb’s deeper meaning.

All responses were transcribed and subsequently scored by consensus by raters who were blind to diagnosis (OM, MS, KI, CM). A score was given, following conventional PANSS scoring criteria, which took into consideration responses from similarities and proverbs. PANSS anchors included symptom severity scores from 1 (absent) to 7 (extreme).

We also endeavored to further identify difficulties in expressing meaningfulness, independent of abstract thinking. Therefore, we re-scored responses by considering abstraction and meaningfulness separately [77, 78], as depicted in Table 3. For each proverb trial, possible scores were 0 (deficit absent), 1 (partial deficit), or 2 (deficit present) for abstraction and meaningfulness. We counted the number of words per response, not including filler words like “um,” “hmm,” and “like.” We also counted the number of words that were repeated from the original proverb per response by pre-identifying the primary nouns and verbs of the proverb and computing the proportion of repetitions (i.e., number of repetitions to total words) used during proverb interpretation. We reasoned that elevated repetition would reflect a diminished ability to search beyond the words that had been provided by the experimenter and thereby expose limitations of thought coordination.

**Proverb Meaning Recognition Task** Following similarities/proverb interpretation tasks, we administered a multiple-choice assessment to test whether participants could recognize a meaningful and abstract interpretation. The paradigm was a four-alternative, forced choice approach. One option represented the correct proverb interpretation, and three lures followed these guidelines [77, 78]: (1) abstract but meaningless, (2) concrete but meaningful, and (3) concrete and meaningless. (See Supplement #3 for test stimuli.)

Participants at the two test sites received slightly different test batteries, consistent with local protocols. Specifically, 13 ataxia participants tested at the University of Iowa were not given word pairs (similarities task) from the PANSS and were administered the Scale for the Assessment and Rating of Ataxia (SARA) [36] rather than the ICARS. As such, these

**Table 3** Scoring criteria for meaningfulness and concreteness of proverb interpretations

		Meaningfulness		
		0	1	2
Concreteness	0	“Diversify”	“Do not rely on one aspect of something to deliver everything you need.”	“Complacency kills.”
	1	“Do not spend all of your money in one place. Go to different places.”	“Do not put all of your choices in one thing-one basket.”	“You could lose all of your money. So, it’s better to not have any money at all.”
	2	“If you drop it you might break it.”	“Do not get too excited about having a full basket because it could break at any time.”	“Separate new from old because they spoil. It refers to chicken care.”

Example responses are shown for the proverb “Do not put all of your eggs in one basket.” Scores of 0, 1, or 2 were given for “concreteness” and “meaningfulness” according to the following criteria: “Concreteness” measured whether the response was abstract (0), contained abstract and concrete elements (1), or was completely concrete (2). “Meaningfulness” measured whether the response’s meaning was consistent with the content of the proverb (0), mostly consistent with the content of the proverb (1), or not consistent with the meaning of the proverb (2)

13 individuals’ scores were excluded from analyses that involved the similarities task or the ICARS. All participants received the proverb interpretation and recognition tasks. Scores were compared between groups on the PANSS ratings and proverb recognition tasks. Groups were also compared on meaningfulness and concreteness scores, total word counts, and proportion of repetitions.

## Results

Overall, the cerebellar ataxia group did not show impairments of abstract thinking. Groups did not differ on severity scores for the PANSS ratings (ataxia participants,  $M = 2.08$ ,  $SD = 0.91$ ; controls,  $M = 2.00$ ,  $SD = 0.91$ ,  $U = 326$ ,  $p = .79$ ) or on level of concreteness (ataxia participants,  $M = 1.76$ ,  $SD = 1.99$ ; controls,  $M = 1.8$ ,  $SD = 1.55$ ,  $U = 437$ ,  $p = .59$ ). Consistent with intact abstract thinking skills, the ataxia group successfully recognized the abstract meaning of a proverb among concrete and meaningless lures (ataxia participants,  $M = 92.9\%$ ,  $SD = 14.3\%$ ; controls,  $M = 95.0\%$ ,  $SD = 13.1\%$ ,  $U = 323$ ,  $p = .51$ ). To confirm that recognition scores were not at ceiling, one-sample  $t$  tests were conducted to determine if a statistically significant difference existed between the recognition score and 100% for each group (ataxia participants:  $t(34) = -2.95$ ,  $p < 0.005$ ; controls:  $t(19) = -1.71$ ,  $p = 0.052$ ). Despite intact abstraction skills, the patient group’s ability to express a proverb’s meaning was impaired. This was evidenced by higher scores in the ataxia participants versus controls for proverb meaningfulness (ataxia participants,  $M = 1.63$ ,  $SD = 1.32$ ; controls,  $M = 0.88$ ,  $SD = 1.05$ ,  $U = 650$ ,  $p < .05$ ) despite having equivalent scores for total number of words (ataxia participants,  $M = 66.29$ ,  $SD = 39.14$ ; controls,  $M = 74.52$ ,  $SD = 31.25$ ,  $U = 372$ ,  $p = 0.45$ ) and proportion of word repetitions (ataxia participants,  $M = 0.07$ ,  $SD = 0.04$ ; controls,  $M = 0.06$ ,  $SD = 0.03$ ,  $U = 571$ ,  $p = 0.45$ ).

**Correlations with Supplemental Measures** ICARS total scores were compared with the following performance measures: PANSS rating, meaningfulness, concreteness, number of words, and proportion of word repetitions. ICARS total score positively correlated with PANSS rating ( $r(25) = .51$ ,  $p < .02$ ), concreteness ( $r(25) = .55$ ,  $p < .05$ ) and proportion of repeated words ( $r(25) = .48$ ,  $p < .05$ ). No other correlations were significant (all  $p$  values  $> .10$ ). Correlations between CES-D total scores and performance measures failed to yield any significant results (all  $p$  values  $> .10$ ).

## Discussion

Contrary to prior reports [4, 74, 75], our study observed unimpaired abstract thinking skills in individuals with cerebellar damage. The ataxia group showed intact performance on the global PANSS scoring for the word similarities, proverb interpretations, and proverb recognition tasks. However, we found that ataxia participants were impaired at expressing the *meaning* of proverbs. Responses were often partially or fully inconsistent with the content of the proverb. Because ataxia participants were able to recognize the proverb’s meaning, their deficit appeared to be directly related to the generation and expression of thoughts, rather than toward understanding abstract concepts. While it is possible that proverb recognition was easier to complete than proverb interpretation, performance did not differ between groups, and both groups performed below ceiling. Rather, the proverb recognition task did not require one to internally marshal thoughts prior to responding while the proverb interpretation task did. Although our results did not reflect impairments of abstract thinking in ataxia, we found associations between the severity of neurological signs and concrete thinking, suggesting that cerebellar damage can interfere with abstract thinking ability as well. Thus, within the theoretical framework of sequencing,

which was the focus of the study, our interpretation is that impairments of meaningful expressions may have been a consequence of the cerebellum's inability to properly organize one's thoughts.

Poor mental coordination can lead to difficulty in prioritizing and coordinating thoughts, which confuses the expression of those thoughts. As stated in Schmahmann et al. (2019), "Cerebellar injury disrupts modulation but not generation of ... language (resulting in metalinguistic deficits but not aphasia)" [5] (p. 352). In its extreme form, dysmetria of thought may lead to psychiatric disturbances, such as disorganized thinking (e.g., derailment, tangentiality, and incoherence) [79, 80]. Although the ataxia group's deficits found in the current study were far from the level of psychiatric disturbance, the notion that cerebellar feedforward mechanisms disrupt thought coordination was supported.

## General Discussion

This study was designed to examine sequencing ability within implicit versus explicit domains in order to characterize the role of cerebellar feedforward mechanisms in support of cognitive and motor functions. Given that feedforward mechanisms are thought to apply to cognition analogously to motor function [5], we hypothesized that cerebellar feedforward mechanisms would be important for cognitive sequencing, but primarily within the implicit domain because extra-cerebellar strategies could be used to compensate within the explicit domain. Taken together, results from these five experiments supported this hypothesis.

We observed in Experiment 1 that the ataxia group was impaired when tapping at 1 and 4 Hz when given a visual cue and real-time feedback. It might be expected that ataxia participants would tap too slowly, as they did at 4 Hz, given their movement disorder. However, their tapping too quickly at 1 Hz suggested a problem with timing and prediction of tap intervals. Severity of neurological signs was associated with tapping accuracy and speed. These results suggest that disruption of cerebellar functions prohibited proper timing and that explicit strategies were unable to fully compensate for this deficit. This interpretation was supported in a follow-up experiment in which feedback cues were removed. In that paradigm, participants tapped slower overall, but the ataxia group remained less accurate than controls at 1 Hz, despite tapping at an equivalent speed as controls. The dissociation between changes in speed but not accuracy in the absence of explicit feedback suggested an inherent disruption to feedforward timing mechanisms that reside specifically within the implicit domain.

In Experiment 2, procedural learning was compared to explicit cognitive sequencing when both tasks were administered under single versus dual task conditions. Sequencing disruptions were observed in the motor domain by the ataxia group's reduced rate of motor learning, which correlated with severity of neurological

signs. There was no evidence of cognitive sequencing impairments in the explicit domain. Interestingly, controls' motor performance was impacted by cognitive load in the dual task condition, which was not observed in the ataxia group. We interpreted this as exemplifying how implicit and explicit sequencing can be supported by intact cerebellar function, but when cerebellar feedforward mechanisms are disrupted, sequencing shifts to explicit strategies to compensate. Thus, the cerebellum's support of sequencing is critical within the implicit domain, but is not necessary for sequencing within the explicit domain.

In Experiment 3, ataxia participants revealed implicit sequence learning impairments despite showing normal rates of motor learning. Impaired sequence learning by the cerebellar ataxia group, therefore, was specific to the cognitive and sequential nature of the task, which was confined to the implicit domain. While it was unusual to observe intact motor learning in ataxia, this dissociation suggested that cognitive sequencing within the implicit domain is more vulnerable to disruptions of cerebellar feedforward mechanisms relative to procedural learning.

In Experiment 4, participants with cerebellar ataxia did not show impaired performance in a cognitive task that required the explicit production and detection of sequences, whether the items to be sequenced were verbal, spatial, or behavioral. As such, this experiment did not find evidence that explicit cognitive sequencing ability is impacted in cerebellar ataxia. This null result further suggests that sequencing abilities supported by the cerebellum may be specific to the implicit domain.

Finally, in Experiment 5, the ataxia group exhibited difficulty expressing the meaning of proverbs in their own words, even though their abstract thinking skills were otherwise intact. Importantly, we observed that ataxia participants could recognize the non-literal meaning of a proverb from among several alternatives (including meaningless and concrete lures). Because marshaling one's thoughts would be critical to providing a meaningful verbal response, these results suggested that the ataxia participants experienced cognitive sequencing deficits that impacted linguistic expression.

A limitation of this study was that we included individuals with various cerebellar ataxia subtypes, which included cerebellar ataxia types of variable etiology and pathology outside of the cerebellum [33]. All cerebellar ataxia participants had either been genetically confirmed or diagnosed with cerebellar ataxia by a clinician and exhibited signs of cerebellar dysfunction. Thus, the common overlapping issue with each of the ataxia participants was cerebellar damage and was, therefore, the mostly likely explanation for their performance. However, our sample size was not large enough to compare subtypes or to focus our analyses on individuals with "cerebellar pure" pathology (e.g., SCA6), which would be a valuable future research direction. A second limitation of the study was that we were unable to make within-subjects comparisons across studies because the patient groups between each task were different. For example, it would be

useful to track how the rate of motor learning compared across Experiments 2 and 3 to better understand the difference in outcomes of those two studies. As such, the finding that patients performed similar to controls in some tasks but not others could have been related to clinical differences between the patient groups. Future research would also benefit from brain imaging analysis of the structure and function of the ataxia participants to find out what brain pathways are used to compensate. Such knowledge would not only shed light on cerebellar function but also provide insight into novel therapeutic directions that take advantage of these compensatory behaviors.

In summary, converging results from five experiments support the notion that cerebellar feedforward mechanisms are necessary for sequencing in the implicit domain. The cerebellum is not critical, however, for all forms of sequencing, especially for cognitive functions that can be accomplished using explicit strategies. Notably, when the cerebellum is needed for motor and cognitive sequencing at the same time, cognitive functions may be reallocated to extra-cerebellar mechanisms whenever explicit strategies are available. One possible interpretation is that individuals with ataxia appear to capitalize on this compensatory method to retain their resources for motor function as best as possible.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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