1 **The cerebellum does more than sensory-prediction-error-based learning in**

2 **sensorimotor adaptation tasks**

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Abstract

Individuals with damage to the cerebellum perform poorly in sensorimotor adaptation paradigms. This deficit has been attributed to impairment in sensory-prediction-error-based updating of an internal forward model, a form of implicit learning. These individuals can, however, successfully counter a perturbation when instructed with an explicit aiming strategy. This successful use of an instructed aiming strategy presents a paradox: In adaptation tasks, why don't individuals with cerebellar damage come up with an aiming solution on their own to compensate for their implicit learning deficit? To explore this question, we employed a variant of a visuomotor rotation task in which, prior to executing a movement on each trial, the participants verbally reported their intended aiming location. Compared to healthy controls, participants with spinocerebellar ataxia (SCA) displayed impairments in both implicit learning and aiming. This was observed when the visuomotor rotation was introduced abruptly (Exp. 1) or gradually (Exp. 2). This dual deficit does not appear to be related to the increased movement variance associated with ataxia: Healthy undergraduates showed little change in implicit learning or aiming when their movement feedback was artificially manipulated to produce similar levels of variability (Exp. 3). Taken together the results indicate that a consequence of cerebellar dysfunction is not only impaired sensory-prediction-error-based learning, but also a difficulty in developing and/or maintaining an aiming solution in response to a visuomotor perturbation. We suggest that this dual deficit can be explained by the cerebellum forming part of a network that learns and maintains action-outcome associations across trials.

New and noteworthy

Individuals with cerebellar pathology are impaired in sensorimotor adaptation. This deficit has been attributed to an impairment in error-based learning, specifically, from a deficit in using sensory prediction errors to update an internal model. Here, we show that these individuals also have difficulty in discovering an aiming solution to overcome their adaptation deficit, suggesting a new role for the cerebellum in sensorimotor adaptation tasks.

Introduction

Visuomotor rotation tasks, which induce a discrepancy between movements of the limb and visual feedback, are a powerful tool for elucidating principles of motor learning (for a review see Krakauer, 2009). While learning in these tasks has typically been thought to be implicit, reflecting the training of an internal forward model via sensory prediction errors (Mazzoni & Krakauer 2006; Tseng et al., 2007; Schlerf et al., 2012), it has become clear that multiple processes can contribute to performance. These include reinforcement learning (Huang et al., 2011; Nikooyan and Ahmed, 2015; Galea et al., 2011), use-dependent plasticity (Diedrichsen et al., 2010; Verstynen and Sabes, 2011; Huang et al., 2011), and instructed aiming strategies (Mazzoni and Krakauer, 2006; Benson et al., 2011; Taylor and Ivry, 2011).

Most relevant to the current study is our recent work dissociating changes in performance that arise from modifications in aiming, which can be explicitly reported, and learning processes that are implicit, such as sensory-prediction-error-based learning (Taylor et al., 2014; Bond & Taylor, 2015; McDougle et al., 2015). The latter has been associated with the cerebellum, with compelling evidence coming from studies showing that individuals with cerebellar pathology display significant impairments in a range of sensorimotor adaptation tasks (Martin et al., 1996; Weiner et al., 1983; Rabe et al., 2009; Schlerf et al., 2013; Smith & Shadmehr, 2005). For example, in visuomotor rotation tasks, people with spinocerebellar ataxia (SCA) exhibit a reduced ability to counter experimentally-imposed perturbations. Importantly, they show attenuated aftereffects when the perturbation is removed (Schlerf et al., 2013; Werner et al., 2009). This is consistent with the idea that an intact cerebellum is required to compute sensory prediction errors via a forward model (Izawa et al., 2012; Miall & Wolpert, 1996; Haruno et al., 2001). This hypothesis is further supported by neuroimaging in humans (Schlerf et al., 2012) and neurophysiology in non-human species (Brooks et al., 2015) showing cerebellar activity that is correlated with sensory prediction errors.

In the context of a visuomotor rotation, we define aiming as choosing to move the hand towards a location other than the target, with the goal of having the cursor land on the target. *A priori,* there is no reason to believe that aiming is cerebellar dependent. Indeed, when individuals with cerebellar degeneration are provided with an explicit

96   aiming strategy and visual cues to support the implementation of that strategy, they

97   show near perfect performance in a visuomotor adaptation task (Taylor et al., 2010).

98   Given their ability to use an instructed strategy, it is puzzling that individuals with

99   cerebellar damage are impaired in visuomotor rotation tasks when they are not provided

100   with an explicit strategy. That is, why do they fail on their own to come up with an aiming

101   solution to compensate for their impaired implicit learning, especially given that the

102   perturbation results in a salient error that remains for many trials? This paradox

103   suggests that the cerebellum may be necessary, not only for implicit learning, but also

104   for discovering, implementing, and/or adjusting an appropriate aiming solution when it is

105   not provided directly through instruction (see also, Vaca-Palomares et al., 2013).

106   We have developed a simple method to assess trial-by-trial fluctuations in aiming

107   during visuomotor rotation tasks (Taylor et al., 2014) that allows for continuous

108   assessment of aiming behavior and implicit learning. In the current set of experiments,

109   we employed this method to determine the source(s) of impairment in individuals with

110   cerebellar damage.

111

112   **Materials and Methods**

113   *Participants*

114   Experiment 1: Ten individuals with spinocerebellar ataxia (SCA, average age =

115   53.7, SD = 12.6 years; 2 female; 5 right-handed) were recruited for the study at the

116   2012 National Ataxia Foundation Annual Meeting (San Antonio, TX) and from the

117   Berkeley, California community. SCA participants were only included if they did not

118   exhibit clinical signs of cerebellar-type multiple system atrophy or evidence of moderate

119   cognitive impairment. Four of the SCA group had a confirmed genetic subtype; for the

120   others, the diagnosis was sporadic adult onset ataxia of unknown etiology (Table 1).

121   The severity of ataxia was assessed with the International Cooperative Ataxia Rating

122   Scale (ICARS, Trouillas et al., 1997). The SCA participants had an average ICARS

123   score of 26.5 (SD = 14.7) out of a maximum score of 100. The participants were also

124   screened for cognitive impairment with the Montreal Cognitive Assessment (MOCA;

125   average = 28.1, SD = 1.5; all scored within normal range of 26-30) (Nasreddine et al.,

126   2005).

127   Twelve age-matched control participants were recruited from the Berkeley or

128   Princeton, New Jersey communities. These participants, based on self-reports, had no

129   known neurological conditions. The data from two of the controls were not included in

130   the final analysis: One consistently moved too slowly and the other failed to report the

131   aiming locations on many trials (see below). Thus, the control group consisted of ten

132   participants (average age = 59.7, SD = 14.7; SD = 1.4; 4 female; 10 right-handed). The

133   control participants were also administered the MOCA (average = 27.6, SD = 2.2), with

134   two scoring just below the normal range cutoff of 26 (23 and 25). They were included in

135   the analyses given that their performance was similar to the other control participants on

136   the experimental task.

137   Experiment 2: Twelve individuals with SCA were recruited from the Princeton

138   community and from the Columbia University Medical Center (CUMC). These

139   participants were selected after a clinical assessment determined that they did not

140   exhibit symptoms of extra-cerebellar pathology (Parkinson's disease, cerebellar-type

141   multiple system atrophy). One individual was excluded from the analysis after failing to

142   provide aiming reports, and a second was unable to complete the task in the time

143   allotted, resulting in a final dataset of ten participants (average age = 48.1, SD = 16.2

144   years; average years of education = 17, SD = 1.6; 4 female; 8 right-handed; 6 confirmed

145   genetic subtype; Table 1). The severity of ataxia symptoms was evaluated with the

146   Scale for the Assessment and Rating of Ataxia Severity (Schmitz-Hubsch et al., 2006).

147   The SCA participants had an average SARA score of 10.6 (SD = 6.2) out of a maximum

148   score of 40. The SARA scale was used in experiment 2 reflected the preference of the

149   CUMC neurologists. Due to time constraints, the MOCA was not administered to one of

150   the SCA participants. Surprisingly, eight of the nine remaining SCA participants scored

151   below the normal range on the MOCA (average score: 22.7, SD 4.8). In part, this may

152   reflect the fact that, for four of these participants, English was a second language. It is

153   also possible that this reflects a more severely compromised sample (although this is

154   not supported by their ataxia scores), or more stringent scoring criteria. Ten age-

155   matched control participants were recruited from the Princeton community (average age

156   = 53.3, SD = 10.5 years; 5 female; 10 right-handed). The control participants were

157 administered the MOCA (average = 25.5, SD = 1.1); five participants scored just below

158 the normal range (three 25 and two 24).

159   Experiment 3: Twenty young adults were recruited from the research participation

160 pool of the Department of Psychology at Princeton University (average age = 19.7, SD

161 = 1.5; 9 female; 20 right-handed).

162   The experimental protocols were approved by the Institutional Review Boards at

163 the University of California, Berkeley (experiment 1), CUMC (experiment 2), and

164 Princeton University (experiments 2 and 3). All participants provided written informed

165 consent. Participants in experiments 1 and 2 were paid an honorarium of $20 per hour,

166 while participants in experiment 3 were compensated with class credit or $12.

167

168 *Experimental Apparatus*

169   In all three experiments, participants made 7 cm horizontal reaching movements to

170 visual targets. The targets were displayed on a 15-inch (Exp. 1) or 17-inch (Exps. 2 and

171 3) LCD monitor. The monitor was mounted horizontally, positioned approximately 25 cm

172 above a digitizing tablet (Intuous Pro Large, Wacom). Given the position of the monitor,

173 vision of the limb was occluded. All participants, regardless of handedness, were tested

174 with their right hand. A digitizing pen was held in the right hand - regardless of

175 handedness preference - and the movement required sliding the pen across the surface

176 of the tablet. Feedback of hand position, when provided, was displayed in the form of a

177 circular cursor displayed on the monitor.

178

179 *Procedure*

180   We employed a variant of a visuomotor rotation task which requires participants to

181 verbally report their aiming location on each trial. This procedure has been described in

182 detail in a previous report (Taylor et al., 2014). At the start of each trial, a white ring was

183 presented, indicating the distance of the participant's hand from a start position (5 mm

184 circle at center of screen). By continually making the ring smaller the participant could

185 guide his or her hand to the start position. When the hand was within 1 cm of the center

186 of the start position, the ring was replaced by a cursor, allowing the participant to

187 precisely position the hand inside the start circle (Figure 1A).

188   After maintaining the start position for 1s, a green target circle (7 mm diameter)

189 was presented. The target appeared at one of eight locations, separated by 45° along

190 an invisible ring (radial distance from start circle of 7 cm). Each of the eight locations

191 was presented within a block of eight trials and, within a block, the locations were

192 randomly selected.

193   Participants were instructed to make a ballistic reaching movement, with the goal

194 of getting the feedback cursor to appear at the target location. Participants were

195 encouraged to reach beyond the target location, effectively shooting through the target.

196 We chose to have the participants reach past the target to minimize the impact of

197 intention tremor on accuracy, given that this symptom can become pronounced at the

198 end of a rapid movement. Feedback was presented as an endpoint location in

199 experiments 1 and 3. In these experiments, the cursor disappeared when the movement

200 amplitude exceeded the 5 mm start circle and did not reappear until the amplitude

201 reached 7 cm. Endpoint feedback was presented for 1.5 s at this location (subject to the

202 visual perturbation— see below) in the form of a red cursor (3.5 mm diameter). In

203 experiment 2, the cursor was visible during the outbound portion of the reach (online

204 feedback). Once the amplitude reached 7 cm, the cursor position was frozen for 1.5 s.

205 In all experiments, a pleasant "ding" sound was played if the feedback cursor

206 intersected the target region; otherwise a mildly aversive "buzz" sound was played.

207   To encourage participants to make fast movements, a digital vocal sample saying

208 "too slow" was played if the movement time was more than 400 ms. The movement

209 protocol, involving an emphasis on fast movements with limited feedback (Exps. 1 and

210 3), was adopted to minimize feedback corrections, a problem for individuals with SCA

211 (Tseng et al., 2007).

212   The visual workspace included a ring of numbered "landmarks", spaced at regular

213 intervals of 5.6° (Figure 1A). The numbers increased and decreased in the clockwise

214 and counterclockwise directions, respectively, from the target. As such, the order of the

215 landmarks rotated with the target. Prior to each movement on aiming report trials, the

216 participant verbally reported the landmark they planned to reach towards. These verbal

217 reports were recorded by the experimenter. Trials in which the participants failed to

218 report their aim were excluded from the analysis. In experiment 1, the SCA participants

219   failed to provide a report on 15.0% of the report trials, while control participants failed to

220   provide a report on 1.8% of the trials. In experiment 2, the percentage of failed reports

221   dropped to 1.6% and 0.4% for the SCA and control participants, respectively. In

222   experiment 3, the college-age controls failed to provide reports on 1.1% and 1.0% of the

223   trials for the No-Variance and Variance-Added groups, respectively. Refinements in the

224   clarity of task instructions are likely responsible for the higher response rate in

225   experiments 2 and 3.

226   The experiment was divided into five blocks: baseline, baseline-report, rotation,

227   washout no-feedback, and washout with feedback. The participants first completed a

228   baseline block of 48 trials with veridical feedback (Figure 1B). The report task was then

229   described and participants completed eight trials, verbally reporting the aiming landmark

230   prior to each reach. Feedback was veridical on these trials (and participants almost

231   always reported the aiming location as "zero").

232   The visual rotation was introduced in the rotation block. In experiment 1, this was a

233   45° counterclockwise rotation, imposed for 128 trials. In experiment 2, the rotation was

234   introduced gradually over 320 trials, with 0.144° added on each trial until the full 45°

235   counterclockwise rotation was achieved. For experiment 3, a counterclockwise rotation

236   was present for 128 trials. For one group of participants (No-Variance), the size of the

237   rotation was constant at 45°; for a second group of participants, the size of the rotation

238   on a given trial was drawn from a Gaussian distribution with a mean of 45° and a

239   standard deviation of 11° (Variance-Added). In all three experiments, participants

240   reported the aiming location prior to making their reach.

241   Following the rotation block, participants made an additional 40 reaches, but the

242   rotation, cursor feedback, and the aiming landmarks were removed (washout no-

243   feedback). For this block, participants were explicitly instructed to aim directly to the

244   green target. Neutral auditory feedback, in the form of a 'knock' sound, indicated when

245   the reach amplitude exceeded 7 cm, but otherwise provided no information related to

246   target accuracy. Veridical feedback was restored for a final 40-trial block (washout with

247   feedback).

248

249   *Movement analysis.*

250   All initial data analyses were performed using Matlab (MathWorks) and statistical

251   analyses were performed in SPSS (IBM, 2011). Task performance was assessed by

252   calculating the angular difference between the target and the initial heading angle of the

253   hand. A participants' hand location could drift within the start circle during the report

254   period of the trial, therefore we computed heading angle relative to the location where

255   their hand left the start circle. This was done by fitting a straight line between samples

256   taken at 1 and 3 cm from the start position (Taylor et al., 2014). We used initial heading

257   angle rather than endpoint angle to allow for a visual comparison between the online

258   and endpoint feedback conditions. The initial heading angle is also less susceptible to

259   noise that might come about from the SCA participants' ataxia.

260   For averaging across trials, movement trajectories were rotated to a common axis

261   (e.g., as though the target was always located at 0°). With this convention, a positive

262   angle indicates a deviation in the clockwise direction and a negative angle indicates a

263   deviation in the counterclockwise direction. Note that the heading angles are reported in

264   hand space rather than as target error. With this convention, hand heading angle will

265   change in the opposite direction of the rotation as performance improves.

266   The mean hand heading angle was calculated on an individual basis for four

267   different epochs: 1) The last eight trials of the baseline block, 2) the first and 3) last

268   eight trials of the rotation block (early and late rotation), and 4) the first eight trials of the

269   no-feedback washout block (washout). Trials were binned into groups of eight trials, we

270   report the mean and standard error of the mean for each bin. Since the eight targets

271   were presented in a random order within each cycle, this ensured that all targets were

272   equally represented in each bin. In experiment 1, one participant with SCA failed to

273   complete the last eight trials of the rotation block so the mean of their second to last bin

274   of eight trials was used. We did not fit an exponential function to the time series of hand

275   heading angles during the rotation block given the non-monotonic nature of the aim

276   report data (Taylor et al., 2014).

277   To obtain an estimate of implicit learning, the reported aiming angle was

278   subtracted from the measured hand heading angle on each trial. We refer to this

279   measure as implicit learning, since it could contain a number of processes in addition to

280   error-based updating of a forward model, such as use-dependent learning and

281 reinforcement learning. The mean aiming angle and implicit learning was calculated for

282 three different epochs: 1) The last eight trials of the baseline block, 2) the first and 3)

283 last eight trials of the rotation block (early and late rotation).

284   In terms of kinematics, we measured velocity and movement time. Velocity was

285 computed by submitting the hand position data to a fourth-order Savitzky-Golay filter

286 (Savitzky & Golay, 1964; Smith et al., 2000). Movement onset could not always be

287 based on the time at which the hand left the start circle because the hand occasionally

288 wandered from this position during the report phase. As such, movement onset was

289 estimated by a two-part procedure. We first identified the point in the time series where

290 the movement amplitude reached 2 cm from the start position. From this point, the time

291 series was searched backwards to find the time point when the participant either left the

292 start circle, or when the movement started from outside the start position, the time point

293 with the minimum radial distance from the start position.

294   We also excluded trials from the rotation block if the implicit learning estimate for

295 that trial was more than 3 standard deviations outside the median implicit learning

296 estimate for that participant. We used this criterion as a proxy to identify trials in which

297 the participant may not have provided an accurate report of their aiming location, or that

298 the movement itself was highly discrepant. Using this criterion, less than 1% of the trials

299 were excluded for the SCA participants over experiments 1 and 2 and control

300 participants in experiment 2. In experiment 1, control participants had 2.1% of trials

301 excluded. For experiment 3, 1.5% and 1.6% of the trials were excluded for the

302 Variance-Added and No-Variance groups, respectively.

303

304 *Power Analysis*

305   We performed a power analysis to estimate the minimum sample size required to

306 obtain an expected effect size, using the dataset from Taylor et al. (2010). Specifically,

307 we focused on two "pure" measures of implicit learning, the extent of hand angle drift

308 when participants were provided with an aiming strategy, and the magnitude of the

309 aftereffect, comparing these measures between SCA and control participants. Power

310 was estimated for an independent samples t-test, using a two-tailed α of 0.05 and power

311 of 0.95. Based on the group means and standard deviations from the measure of

312   implicit learning (i.e., drift) in Taylor et al. (2010), the effect size is d = 2.63 ($\mu_{Control}$ =

313   11.3°, $\sigma_{Control}$ = 2.2°, μ_{SCA} = 5.9, σ_{SCA} = 1.9°). From this value, a minimum sample size

314   of five participants is required in each group. A similar estimate of sample size is

315   obtained using the aftereffect values ($\mu_{Control}$ = 6.2°, $\sigma_{Control}$ = 2.4°, μ_{SCA} = 0.3, σ_{SCA} =

316   1.6°, d = 2.89). To be conservative, we doubled this number and recruited a minimum of

317   10 participants for each group for all of the experiments (Button et al., 2013).

318

319   **Results**

320   ***Experiment 1: Cerebellar damage impairs both aiming and adaptation to an***

321   ***abrupt rotation***

322   Following a baseline block with veridical endpoint feedback, we introduced the

323   aiming report task, requiring participants to indicate the number corresponding to the

324   aiming location prior to each movement (Figure 1A). For the first eight trials in which

325   feedback remained veridical (baseline-report block), participants in both groups tended

326   to report aiming directly at the target (Control: -0.5 ± 0.3°; SCA: -0.3 ± 0.4°; group

327   comparison: t_{18} = 0.5, p = 0.65). Consistent with their aiming reports, the heading angles

328   of the reaches were directed towards the target with a small clockwise bias (Control: 2.9

329   ± 0.9°; SCA: 2.0 ± 1.8°; group comparison: t_{18} = 0.5, p = 0.65). In sum, the behavior

330   during the baseline phase was similar between the two groups.

331   The introduction of the perturbation (rotation block) induced changes in heading

332   angle from baseline for both groups (Figure 2A). To examine the initial phase of

333   learning, we focused on the first eight trials. Participants with SCA displayed smaller

334   heading angles (5.0 ± 3.8°) over these trials compared to the control participants (20.7 ±

335   3.5°; Figure 2D). The difference in performance was even more pronounced at the end

336   of the rotation block. Over the final eight trials, the controls had almost completely

337   countered the perturbation (41.3 ± 5.0°); in contrast, SCAs were only partially

338   countering the perturbation (16.5 ± 7.9°). To determine whether there were any

339   differences in performance over the course of the rotation block, we performed a mixed

340   factorial repeated measures ANOVA with factors of Group (Control and SCA) and Time

341   (Early Rot and Late Rot). A main effect of time is expected, since participants should

342   compensate for more of the perturbation at the end of the rotation block than in the

343   beginning. There are two, non-mutually exclusive, ways in which SCA participants'

344   performance could differ from controls. SCA participants might be generally impaired in

345   compensating for the perturbation, relative to controls, in which case a main effect of

346   group would be expected. Additionally, SCA participants could be slower to respond to

347   the perturbation, in which case an interaction would be expected. The ANOVA revealed

348   a main effect of group ($F_{(1,18)}$ = 12.6, p = 0.002) and a main effect of time ($F_{(1,18)}$ = 10.4, p =

349   0.005). No Group X Time interaction was present ($F_{(1,18)}$ = 0.8, p = 0.37). Thus, the

350   performance of both groups improved (cursor terminated closer to the target) over the

351   course of the rotation block, and the performance improvement was considerably

352   greater for the controls compared to the SCAs.

353   To measure the size of the aftereffect, participants completed a no-feedback block

354   in which they were instructed to aim directly to the target. Feedback in this block was

355   limited to an auditory tone, indicating when the movement amplitude had exceeded 7

356   cm. A comparison of the first eight trials of this block to the 8 baseline trials revealed a

357   reliable aftereffect for both controls (12.2 ± 1.3°; t_9 = 5.5, p = 0.0004) and SCAs (7.1 ±

358   2.2°; t_9 = 3.0, p = 0.02; Figures 2A, 2D). However, when comparing the two groups, the

359   magnitude of the aftereffect was significantly larger in the control group compared to the

360   SCA group (t_{18} = 2,0, p = 0.03). Additionally, our measure of implicit learning provides

361   complementary evidence that this process is impaired in the SCA group (see below).

362

363   *Verbal Reports*

364   The time series of the aiming reports revealed that a large portion of the

365   performance changes for the controls was due to a change in their reported aiming

366   location (Figure 2B). For control participants, the mean aiming location was shifted from

367   13.3 ± 3.3° over the first eight trials to 22.1 ± 5.9° by the last eight trials of the rotation

368   block. On average, these values were attenuated in the SCA participants (Figure 2E).

369   Here, the early and late aiming angles were shifted from the target location by 1.6 ± 2.8°

370   and 13.3 ± 7.0°, respectively. As with hand heading angle, to determine whether there

371   were any differences in the verbal aiming reports over the rotation block, the aiming

372   reports for early and late in the rotation block were submitted to a mixed factorial

373   ANOVA with the same factors of Group (Control and SCA) and Time (Early Rot and
374   Late Rot). The ANOVA revealed an effect of Time ($F_{(1,18)}$ = 6.3, p = 0.03), suggesting
375   aiming angles increased over the rotation block, but only a trend for an effect of Group
376   ($F_{(1,18)}$ = 3.2, p = 0.09). No Group X Time interaction ($F_{(1,18)}$ = 0.1, p = 0.74) was present.
377   From visual inspection of the aiming time series, control participants appeared to have
378   an initial large shift in aiming angle, which then began to decrease slowly over the
379   course of the rotation block. Given this non-monotonic nature of the aiming report time
380   series, as well as the high variance in the initial trials, we performed an additional *post-*
381   *hoc* analysis comparing the aim reports for the two groups across the whole rotation
382   phase. On this composite measure, the aiming reports indicated larger shifts in aiming
383   location for control (25.7 ± 3.8°) compared to SCA participants (11.2 ± 5.1°; t_{18} = 2.3, p =
384   0.035).
385   To estimate implicit learning, we subtracted the reported aiming angle from the
386   hand heading angle for each trial (Figure 2C). We again focused on the mean for the
387   first and last eight trials. For control participants, the estimate of implicit learning
388   increased from 2.8 ± 1.4° early in the rotation block to 14.6 ± 2.3° by the end. By
389   comparison, SCA participants had an estimate of no implicit learning (0.6 ± 2.1) early in
390   the rotation block, which only barely increased to 2.9 ± 3.4° by the end of the block. As
391   was done for hand heading angle and the verbal aim reports, to compare changes in
392   implicit learning over the rotation block, these values were submitted to an ANOVA with
393   factors of Group and Time. The ANOVA revealed significant main effects of Group ($F_{(1,18)}$
394   = 5.6, p = 0.03), resulting from generally impaired implicit learning for SCA participants,
395   and Time ($F_{(1,18)}$ = 17.7, p = 0.001), due to implicit learning estimates increasing from
396   early to late in the rotation block. A Group x Time interaction ($F_{(1,18)}$ = 8.1, p = 0.01) was
397   also present, suggesting the impaired implicit learning in SCA participants differed
398   relative to control participants between early and late in the rotation. As can be seen in
399   Figure 2F, the estimate of implicit learning was markedly lower for the SCAs, an effect
400   that was especially pronounced late in the rotation block. Thus, using both the estimate
401   of implicit learning during the rotation block and the aftereffect measure, adaptation was
402   impaired in SCA participants compared to controls.

403   In summary, the individuals with spinocerebellar ataxia exhibited a performance
404   impairment when presented with a 45° visuomotor rotation, similar to that observed in
405   previous studies of sensorimotor adaptation (e.g., Martin et al., 1996; Schlerf et al.,
406   2013). By obtaining verbal reports, we were able to dissociate adjustments in aiming
407   from implicit learning. The results indicate a dual-impairment: Not only was implicit
408   learning attenuated in the SCA participants, but they also tended to aim to locations
409   closer to the target during the early stages of the rotation block compared to controls.
410   While SCA participants did modify their aim, these adjustments failed to effectively
411   counter the rotation such that their overall performance only compensated for about half
412   of the perturbation by the end of training. Thus SCA participants were impaired in self-
413   discovery of an aiming strategy, which stands in contrast to our previous finding that
414   SCA participants are quite competent in carrying out strategy if it is provided by
415   instruction (Taylor et al 2010).
416

417   ***Experiment 2: Gradually introducing a rotation fails to alleviate the impairment in***
418   ***aiming and adaptation as a result of cerebellar damage***
419   With an abruptly introduced rotation, there appears to be two stages of aiming: an
420   initial large change in aim to compensate for the salient error induced by the
421   perturbation, followed by small trial-to-trial adjustments to maintain accurate
422   performance in the presence of small errors. It is likely that this first initial stage is the
423   selection and implementation of an explicit general aiming strategy, however, the extent
424   to which this second smaller adjustment phase is explicitly generated is less clear. It
425   may be that the small trial-to-trial adjustments are achieved by something like implicit
426   aiming, where an implicit mechanism is used to generate the adjustment to which
427   explicit access is gained afterwards. Providing an instructed aiming strategy would
428   direct the initial large change in aim, however, as adaptation increases and
429   compensates for more of the perturbation, to maintain accurate performance and offset
430   adaptation, small adjustments in aim may be necessary from trial-to-trial. Given that
431   when SCA individuals are provided with an instructed aiming strategy they can counter
432   an abrupt rotation, and maintain performance, they may not be impaired when only
433   small trial-to-trial changes in aim are necessary. To investigate this, in Exp. 2, we

434   introduced the perturbation gradually over the rotation block. Note, we extended the

435   rotation block from 128 to 320 trials and provided online cursor feedback as the

436   participants reached towards the target to increase the contribution of implicit learning.

437   For the first eight trials of aiming under veridical feedback (baseline-report block),

438   participants in both groups tended to report aiming towards the target (Control: -2.4 ±

439   2.2°; SCA: -0.9 ± 1.2°; group comparison: t_{18} = 0.6, p = 0.56). Consistent with their aim

440   reports, the heading angles for these first eight baseline trials were directed towards the

441   target with a small clockwise bias (Control: 1.4 ± 0.6°; SCA: 3.9 ± 1.6°; group

442   comparison: t_{18} = 1.5, p = 0.15). As in experiment 1, the emphasis on participants

443   making quick slicing movements towards the target resulted in relatively similar

444   behavior for both groups of participants.

445   Following the baseline block, a 45° counterclockwise visuomotor rotation was

446   gradually introduced over 320 trials. The small perturbation (only 1.15° on the 8th trial)

447   did not induce reliable changes from baseline in hand heading angle over the first eight

448   trials of the rotation block for either the controls (-0.7 ± 2.8°) or the SCA participants (1.6

449   ± 1.2°; Figure 3D). By the end of the rotation block, when the full 45° rotation was

450   present, both groups had adjusted their hand heading angles in response to the

451   perturbation (Figure 3A). This change, averaged over the last eight trials, was

452   substantially larger in the controls (35.8 ± 1.3°) compared to the SCA participants (18.2

453   ± 4.2°). As in experiment 1, to compare performance over the rotation block these

454   values were submitted to a mixed factorial ANOVA. The ANOVA revealed a main effect

455   of Group $F_{(1,18)}$ = 8.8, p = 0.008), a main effect of Time ($F_{(1,18)}$ = 93.9, p < 0.0001) and a

456   Time X Group interaction ($F_{(1,18)}$ = 13.3, p = 0.002). Thus, as in experiment 1, the main

457   effect of Group reveals that SCA participants compensated less for the perturbation

458   than did control participants, showing that their performance impairment is observed

459   with both abrupt and gradual perturbations (see Schlerf et al., 2013). Additionally, the

460   presence of an interaction suggests that the relative impairment of SCA participants to

461   controls differed between early and late in the rotation. Visual inspection suggests the

462   difference in performance was larger late in the rotation block, which is expected given

463   that the gradual introduction of the perturbation resulted in only a ~1° perturbation

464   during this early phase.

465   On the no-feedback washout block, cursor feedback was withheld and the

466   participants were instructed to aim directly for the target. Comparing the first eight trials

467   of this block to the eight baseline trials revealed a reliable aftereffect for the controls

468   (26.0 ± 1.5°; t_9 = 15.8, p < 0.0001) and SCAs (16.6 ± 1.8°; t_9 = 5.2, p = 0.0005).

469   However, the magnitude of the aftereffect was smaller in SCA compared to control

470   participants (t_{18} = 4.0, p = 0.0004; Figures 3A, 3D). Thus, on this measure of implicit

471   learning, the SCA participants were impaired relative to the control group.

472

473   *Verbal Reports*

474   In contrast to experiment 1, the time series of the aiming reports revealed that only

475   a small portion of the change in hand heading angle for the controls was due to a

476   change in their aiming location (Figure 3B). Over the first eight trials of the rotation

477   block, their mean aiming location was -2.4 ± 2.3°. Note that this shift is in the

478   counterclockwise direction and would effectively increase the perturbation; we assume

479   this reflects noise or an attempt to negate the effects of intrinsic bias (Gibo et al., 2013;

480   Vindras et al., 1998 & 2005; Ghilardi et al.,1995). By the last eight trials, the aim was

481   shifted by 5.3 ± 3.1° in the clockwise direction, effectively helping to counter the rotation.

482   In contrast, the SCA participants did not consistently shift their aiming location over the

483   course of the rotation block (Figure 3E). Compared to baseline, they showed a shift of -

484   1.7 ± 0.8° over the first eight trials and a shift of -0.6 ± 0.4° over the last eight trials.

485   When comparing the verbal aiming reports with an ANOVA, the effect of Time was

486   significant ($F_{(1,18)}$ = 6.1, p = 0.024), but the effect of Group was not ($F_{(1,18)}$ = 1.5, p = 0.24).

487   There was a trend towards a Time X Group interaction ($F_{(1,18)}$ = 3.3, p = 0.085).

488   We performed two additional post-hoc comparisons to quantify the extent of

489   aiming in the control and SCA participants. First, to determine whether aiming direction

490   changed over the course of the rotation block, a within subject *t*-test was conducted,

491   comparing aiming during the last 8 baseline trials and the last 8 rotation trials. By this

492   measure, the control participants adjusted their aim by the end of the rotation block (t_9 =

493   2.2, p = 0.051), although this was only marginally significant. In contrast, the SCA

494   participants did not exhibit a reliable shift in aim (t_9 = 0.3, p = 0.79). Second, to compare

495   overall aiming between the two groups, a *t*-test was performed comparing the aim

16

496   reports averaged across the entire rotation phase. Using this measure, we observed a
497   reduced shift in aiming direction for the SCA group compared to the controls (t_{18} = -2.1, p
498   = 0.047). Thus, despite the relatively small changes in aiming observed for the control
499   participants, these comparisons suggest larger changes in aim for the control
500   participants compared to SCA participants. Indeed, the SCA participants failed to adjust
501   their aim in a consistent manner during the rotation block, despite the fact that the target
502   error became quite pronounced by the end of the block.
503   We employed the subtractive procedure to estimate implicit learning (Figure 3C),
504   and focused on the first and last eight trials during the rotation block for our statistical
505   analysis (Figure 3F). For control participants, the estimate of implicit learning increased
506   from 3.8 ± 2.1° early in the rotation block to 33.1 ± 4.5° by the end. By comparison, SCA
507   participants had an estimate of no implicit learning (-2.3 ± 3.1) early in the rotation
508   block, which increased to 13.2 ± 5.5° by the end of the block. An ANOVA on these
509   values revealed main effects of both Group ($F_{(1,18)}$ = 7.0, p = 0.016) and Time ($F_{(1,18)}$ =
510   59.7, p < 0.0001). The main effect of group results from smaller implicit learning
511   estimates overall for SCA participants compared to controls. In addition, the Group X
512   Time interaction was significant ($F_{(1,18)}$ = 5.6, p = 0.030), reflecting the fact that the control
513   participants had a larger increase in implicit learning over the course of the rotation
514   block compared to the SCA participants. This result converged with that observed in the
515   measure of the aftereffect, replicating the impaired adaptation for SCA participants
516   shown in experiment 1.
517   While our results are comparable across experiments 1 and 2, we caution against
518   drawing any strong inferences from any differences in results between the experiments.
519   First, there is the problematic nature of null results (the lack of a difference between
520   controls and SCA participants on the aftereffect data in experiment 1). Second, there
521   are substantial differences between the two tasks. In experiment 2, participants
522   completed more than twice as many rotation trials as in experiment 1, and received
523   online cursor feedback. We would expect both factors to enhance implicit learning (in
524   controls), offering greater sensitivity when comparing their performance to the SCA
525   participants.

526   The results of experiment 2 demonstrate that the SCA participants were impaired

527 in responding to a 45° gradual visuomotor rotation. As in experiment 1, their deficit

528 appears to be manifest in measures of both implicit learning and aiming. The aiming

529 deficit was apparent in experiment 2, even though only small adjustments in aiming

530 location are necessary from trial-to-trial to maintain performance. We note that, for both

531 groups, the amount of aiming was markedly attenuated in this experiment, and this may

532 have contributed to the fact that the target error remained substantial at the end of the

533 experiment. For controls, the final error was around 9°; for the SCA group, the final error

534 was around 27°. Despite this large error, the SCA participants failed to alter their aiming

535 locations; they were unable to compensate for their impairment in implicit learning by

536 deploying an aiming solution.

537   Given the variable performance of SCA participants in experiments 1 and 2, and

538 that SCA leads to highly heterogeneous damage to the cerebellum, it may be tempting

539 to map behavior to damage in cerebellar subregions or with specific subtypes of SCA.

540 However, given this variability, a larger sample size than we have here would be

541 necessary (see Kansal et al., 2016). With the current dataset, any conclusions involving

542 SCA subtypes, or more specific regions of the cerebellum, would likely be driven by

543 lesions and performance in only a few participants, where lesion reconstruction is

544 unlikely to yield reliable results (Rorden et al., 2007; Kimberg et al., 2007). Additionally,

545 correlating behavioral deficits to damage in cerebellar subregions is likely to be best

546 tested in individuals with focal lesions, where the pathology is more localized than the

547 broad deterioration in SCA.

548

549 ***Experiment 3: Higher motor variability does not account for the aiming and***

550 ***adaptation deficits due to cerebellar damage***

551   A feature of spinocerebellar ataxia is the presence of increased movement

552 variability. Indeed, even though we focused on the initial heading angle in experiments 1

553 and 2, the reaching movements for the SCA participants were more variable than the

554 controls. For example, limiting the analysis to the initial baseline block of experiment 1

555 (before the aiming task was introduced), the standard deviation of the heading angles

556 for the SCA and control groups were 11° and 5°, respectively. This increase in

18

557   movement variability may make it difficult for individuals with SCA to develop a reliable

558   aiming solution because they cannot converge on a consistent direction. To make this

559   concrete, consider the situation where an individual, after encountering a 45° clockwise

560   perturbation as in experiment 1, opts to aim to a location that is 30° in the

561   counterclockwise direction. Evaluating the utility of this aiming solution will be hampered

562   if the reach deviates widely from the selected trajectory (independent of adjustments

563   induced by implicit learning). Similarly, increased motor variability in experiment 2 might

564   make it difficult for the SCA participants to gauge the effects of the increasing

565   perturbation.

566   The impact of motor variance on learning has been explored in previous studies of

567   visuomotor adaptation (Wu et al., 2014; Therrien et al., 2015, He et al., 2016). In terms

568   of the effects of cerebellar pathology, Schlerf et al. (2013) found that individuals with

569   SCA exhibited impaired implicit learning, even when one considers how increased

570   motor variability might impinge upon learning and performance. Here we ask how an

571   increase in motor variability might influence the discovery of an aiming solution. Rather

572   than create conditions in which we directly manipulate motor variability, we added noise

573   to the movement feedback presented to adults and examined the effect this had as they

574   learned to respond to a 45° perturbation.

575   College-aged adults were randomly assigned to one of two groups in experiment

576   3. In the No-Variance group, the procedure was identical to experiment 1 with the

577   participants exposed to a constant 45° counterclockwise perturbation during the rotation

578   block. In the Variance-Added group, we (crudely) simulated the effects of ataxia by

579   pseudo-randomly varying the size of the rotation on each trial during the rotation block

580   (Figure 4). To this end, a noise term was added to the 45° perturbation. The size of the

581   rotation on each trial was based on a random sample from a Gaussian distribution with

582   a mean of 45° and standard deviation of 11°. The value of 11° was chosen because it is

583   the mean of the individual standard deviations of the hand heading angle for the SCA

584   participants in Experiment 1. Given that feedback is limited to the reach endpoint (at 7

585   cm), the participants in the Variance-Added group would experience a noisy 45°

586   perturbation.

587   During the initial baseline block (prior to reporting aim) the two groups had similar

588   standard deviations of their heading angles (No-Variance: 6.3 ± 0.4°; Variance-Added:

589   6.4 ± 0.9°; t_{18} = 0.04, p = 0.97), suggesting there were no baseline differences in

590   movement variance between the two groups. For the first eight trials of aiming with

591   veridical feedback (baseline-report block), the participants in both groups tended to

592   report aiming towards the target (No-Variance: -1.1 ± 0.6°; Variance-Added: 0.1 ± 0.2°;

593   group comparison: t_{18} = 0.6, p = 0.56). The hand heading angles were in the direction of

594   the target, although the Variance-Added group exhibited a significant, albeit small

595   clockwise bias (2.7 ± 0.7°) that was not observed in the No-Variance group (0.0 ± 0.5°,

596   t_{18} = 3.1, p = 0.01). Given that the two groups received identical (veridical) feedback in

597   these first two blocks, this difference likely represents chance variation in the

598   participants' baseline reaching bias (Ghilardi et al., 1995).

599   The 45° perturbation was introduced in the rotation block, along with the increase

600   in endpoint variance for the Variance-Added group. Both groups displayed adjustments

601   in heading angle in response to the perturbation (Figure 5A). These adjustments were

602   similar for the No-Variance and Variance-Added participants, both early (No-Variance

603   mean: 12.6 ± 4.5°; Variance mean: 11.7± 6.2°) and late in the rotation block (No-

604   Variance mean: 44.2 ± 1.2°; Variance-Added mean: 41.8 ± 6.6°; Figure 5D). As in

605   previous experiments, a mixed factorial ANOVA was used to compare learning over the

606   rotation blocks, although in this case the factor of Group is comparing Variance-Added

607   and No-Variance groups. There was a main effect of Time ($F_{(1,18)}$ = 76.1, p < 0.0001), but

608   no effect of Group ($F_{(1,18)}$ = 0.07, p = 0.80) nor a Group X Time interaction ($F_{(1,18)}$ = 0.04, p

609   = 0.84), thus no differences in performance were present between the groups. The

610   groups also exhibited similar aftereffects in the no-feedback block in which they were

611   instructed to aim directly for the target. Both groups exhibited a significant aftereffect

612   (No-Variance: 6.3 ± 0.9°; t_9 = 4.8, p = 0.0009; Variance-Added: 7.9 ± 0.8°; t_9 = 5.2, p =

613   0.0006), and the magnitude of the aftereffect was similar for the two groups (t_{18} = 1.4, p

614   = 0.90). These results suggest that the imposition of added endpoint variance did not

615   impact overall performance in response to a visuomotor perturbation.

616   Per experimenter instructions, participants in both groups moved rapidly, and there
617 was no difference in movement duration between the groups during the rotation block
618 (No-Variance: 274 ± 57 ms; Variance-Added: 214 ± 14 ms; t_{18} = 1.02, p = 0.32).
619

620 *Verbal Reports*

621   The aiming report data reveals that a large portion of learning was due to an
622 adjustment in aiming location (Figure 5B), and that this effect was comparable for the
623 two groups. For the No-Variance group, the mean aiming location was shifted 7.3 ± 5.0°
624 over the first eight trials, and increased to 34.8 ± 1.4° by the last eight trials of the
625 rotation block. Participants in the Variance-Added group had an initial shift of 12.3 ±
626 5.0°, which increased to 30.8 ± 5.8° by the last eight trials of the rotation block. A mixed
627 factorial ANOVA comparing aiming over the rotation block revealed the main effect of
628 Time was significant ($F_{(1,18)}$ = 33.3, p < 0.0001), with participants increasing the angle of
629 their aiming over the course of the rotation block (Figure 5E). However, there was no
630 main effect of Group ($F_{(1,18)}$ = 0.01, p = 0.92) nor a Group X Time interaction ($F_{(1,18)}$ = 1.3, p
631 = 0.27). While the overall pattern suggests that the aiming shift over the entire rotation
632 block was larger for the No-Variance group (33.7 ± 2.3°) compared to the Variance-
633 Added (29.0 ± 3.9°) group, this difference was not significant (comparison of means
634 taken over the whole rotation block: t_{18} = 1.0, p = 0.31). Indeed, the group difference
635 reflects the performance of one participant in the Variance-Added group who only
636 reported small aiming angles.
637   Implicit learning was estimated for each trial by subtracting the aiming angle from
638 the hand heading angle (Figures 5C, 5F). Participants in the No-Variance group had an
639 estimate of implicit learning that increased from 5.3 ± 1.5° early in the rotation block to
640 9.4 ± 1.3° by the end. In the Variance-Added group participants had an estimate implicit
641 learning that increased from 0.0 ± 1.6 early in the rotation block to 9.4 ± 1.4° by the end
642 of the block. Implicit learning was compared with an ANOVA based on the first and last
643 eight trials of the rotation block, revealing a main effect of Time ($F_{(1,18)}$ = 26.0, p =
644 0.0001), but no main effect of Group ($F_{(1,18)}$ = 2.9, p = 0.11) and only a trend for an
645 interaction between these factors ($F_{(1,18)}$ = 4.2, p = 0.055). While the group effect and
646 interaction were not significant, a post-hoc comparison of the groups early (t_{18} = 2.5, p =

647   0.02) and late (t_{18} = 0.0, p = 0.99) in the rotation block, suggests that while participants in

648   the Variance-Added group may have initially had less implicit learning early during the

649   rotation block, their implicit learning caught up to the No-Variance group by the end of

650   the rotation. When a further post-hoc comparison is made of implicit learning estimates

651   averaged across the entire rotation block, no difference was present between the No-

652   Variance group (7.2 ± 0.9) and the Variance-Added group (6.5 ± 1.2; t_{18} = 0.5, p = 0.62),

653   confirming no difference in overall implicit learning was present.

654   In summary, the results of experiment 3 show that the injection of random endpoint

655   noise had only a modest effect on performance. Interestingly, the effect of noise was, at

656   least in terms of overall performance, limited to a possible slight reduction in the

657   magnitude of implicit learning as estimated early during the rotation block, but no

658   differences were present late in the rotation block, nor in aftereffect. There were also

659   differences between the groups in how they modified their aim on a trial-by-trial basis,

660   with the Added-Variance group continually modifying their aiming location in response

661   to the added noise. Nonetheless, these participants were able to learn the mean of the

662   45° rotation and they changed their mean aiming angle to a similar degree as

663   participants who experienced a constant perturbation. Taken together, these results

664   suggest that an increase in endpoint variability does not result in profound deficits in

665   implicit and aiming components of visuomotor learning. Thus, the difficulty exhibited by

666   individuals with SCA in adopting an appropriate aiming solution is likely unrelated to

667   their increased movement variability.

668

669   **Discussion**

670   Previous work has repeatedly demonstrated that individuals with damage to the

671   cerebellum are impaired in sensorimotor learning. The emphasis in this literature has

672   focused on implicit deficits in error-based learning. However, here we have shown that

673   SCA also leads to an impairment in the ability to discover and maintain an aiming

674   solution to offset a visuomotor perturbation.

675

676   Impaired aiming in SCA

677   To study the use of aiming behavior, participants reported their aiming location
678 prior to each reach (Taylor et al., 2014). This task provides a direct probe on the use
679 and evolution of an aiming solution and, by subtractive logic, a continuous estimate of
680 implicit learning. We observed a dual-deficit in participants with SCA when presented
681 with a visuomotor rotation. Not only did the SCA group exhibit impaired implicit learning,
682 they also showed a failure to aim to counter the observed target error. They adjusted
683 their aim across the perturbation block, choosing locations that tended to be in the
684 appropriate direction to counter the rotation, but failed to fully compensate for the
685 perturbation.
686   This aiming deficit helps answer the question posed in the Introduction: If people
687 can compensate for a rotation through a multiplicity of processes, why do individuals
688 with SCA not compensate for an implicit learning deficit through an increased reliance
689 on aiming? The current results indicate that the ability to discover an aiming solution is
690 also compromised.
691   This dual-deficit was not only observed when a 45° perturbation was introduced
692 abruptly (Exp 1), but also when the 45° perturbation was introduced gradually (Exp 2). It
693 has been assumed that aiming makes a minimal contribution to performance when the
694 perturbation is introduced in a gradual manner. However, this assumes that implicit
695 learning – the form arising from sensory-prediction-error-based learning – will be
696 sufficient to compensate for the perturbation. The current data, as well as a recent
697 report (Bond and Taylor, 2015), suggest that implicit learning is insufficient to achieve
698 good performance when the perturbation is large (for controls, as well as SCA
699 participants), and thus, the endpoint error will grow over the course of the rotation block.
700 In experiment 2, the control participants began to adjust their aim, with deviations in the
701 aiming location becoming consistent after approximately 150 trials into the rotation
702 block. In contrast, the SCA group failed to invoke compensatory aiming even when the
703 error became quite large. A priori, we might have expected the SCA participants to have
704 larger aiming angles than the controls in order to compensate for their impaired implicit
705 learning.
706   The inclusion of participants with SCA types 1 and 2 in our sample may be a point
707 of concern given previous reports indicating greater extra-cerebellar involvement in

708 these groups compared to other subtypes of SCA (Burk et al., 2003). In particular, might

709 the aiming deficit in the SCA group analyses arise from pathology in these extra-

710 cerebellar regions? The SCA2 participants in experiment 1 exhibited some of the

711 greater impairments in aiming. However, analyses conducted after removal of these

712 three participants in experiment 1, as well as the three SCA1 and one SCA2

713 participants in experiment 2, yields a similar trend as in the reported analyses, in terms

714 of overall performance, aberrant aiming and attenuated implicit adaptation. If aiming

715 processes remained intact we would expect to see comparable overall performance, as

716 SCA participants could use larger changes in aim to compensate for their impaired

717 implicit adaptation. This was not observed in any of the participants, nor in the literature

718 where cerebellar damage has consistently been linked with impairments in both overall

719 performance and aftereffects (Martin et al., 1996; Weiner et al., 1983; Rabe et al., 2009;

720 Schlerf et al., 2013; Smith & Shadmehr, 2005), suggesting they are not effectively using

721 aiming or other compensatory strategies to make up for their impaired implicit

722 adaptation. Most relevant to our experiments, to minimize the chance of extracerebellar

723 involvement in our sample, we only included SCA participants with pure cerebellar

724 symptoms, excluding any participants with resting tremor, rigidity, or bradykinesia,

725 which would suggest parkinsonism and basal ganglia involvement. Additionally, the

726 SCA participants in experiment 2 were examined in detail by a movement disorders

727 specialist (SHK).

728 It is also important to note that the SCA2 participants who showed aiming

729 impairments also tended to have more advanced ataxia as measured in the

730 neurological assessment (Table 1 ataxia scale). As such, we cannot dissociate disease

731 progression from SCA subtype. Moreover, the patterns of pathology show considerable

732 overlap at more advanced disease stages, independent of subtype, and the extra-

733 cerebellar pathology in SCA1 and SCA2 is not evident in areas associated with

734 executive function or strategy use (Seidel et al., 2012). When measured

735 macroscopically, the extra-cerebellar pathology is primarily in the brainstem, with

736 occasional extension to midbrain regions (Mascalchi et al., 2014; Nave et al., 2008;

737 Paulson, 2009; Seidel et al., 2012).

738   We are not making the claim that the aiming deficits reported here should be taken

739   to mean that aiming is solely dependent on cerebellar function. There is extensive

740   evidence that cortico-cerebellar networks encompass almost the entire neocortex, with

741   prominent projections to prefrontal cortex (Buckner et al., 2011; Bostan et al., 2013;

742   Caligiore et al., 2017; Kelly and Strick, 2003). Even if the pathology in our sample was

743   limited to just the cerebellum, behavioral changes likely reflect disruption in a network

744   that spans cerebellar and extra-cerebellar regions. Indeed, this point is made clear in

745   studies of diaschisis showing hypometabolism of frontal cortex in patients with

746   cerebellar degeneration (Meyer et al., 1993).

747   One could take the position that the deficits in planning, including something like

748   the implementation of an aiming strategy, in individuals with SCA, should be attributed

749   to brain areas such as prefrontal cortex known to be essential for these aspects of

750   cognition. This inference (Klinke et al., 2010) however, seems questionable when we

751   consider that complex processes such as those subsumed by the term "executive

752   function" surely require a network perspective. It is likely that the neuropsychological

753   impairments observed in individuals with SCA reflect a disruption of cerebello-cortical

754   networks. More generally, concerns with using lesion methods to make direct structure-

755   function inferences are relevant for all neuropsychological research in humans and non-

756   human species. Although it is important to keep these issues in mind, it is also clear that

757   there is some degree of commonality in patients with cerebellar degeneration,

758   supporting the idea that despite their heterogeneity, we can learn something about

759   cerebellar function through the study of this group.

760   Taken together, experiments 1 and 2 demonstrate that SCA participants have

761   difficulty adjusting their aim to counter a visuomotor rotation. Thus, in addition to an

762   impairment in sensory-prediction-error-based learning, these individuals have difficulty

763   using the feedback to develop and implement an appropriate aiming solution. Below, we

764   consider possible explanations for this impairment in aiming.

765

766   <u>Increased movement variability does not account for impairments in aiming</u>

767   In experiment 3, the addition of trial-by-trial noise to a constant perturbation was

768   used to test the hypothesis that the observed aiming impairment is due to ataxia-related

769 movement variability. This manipulation, however, only had a modest effect on the
770 performance of the young healthy adults. Most relevant to the current study, the
771 additional variability did not produce a significant effect on either overall performance or
772 on aiming behavior. The Variance-Added group altered their aiming direction shortly
773 after the onset of the (noisy) perturbation. While they continued to make aiming
774 adjustments across the rotation block, the asymptotic size of the aiming shift was
775 statistically indistinguishable from that observed in the No-Variance group.

776   We recognize that our noise manipulation is, at best, a weak approximation of the
777 consequences of ataxia. We assume the college students attribute the increased
778 variability to the environment, and not their motor system. Moreover, the increased
779 variance is transient, unlike the chronic nature of ataxia. Nonetheless, the results of
780 experiment 3 suggest that an inability to develop an appropriate aiming solution is not
781 solely due to the motor variability associated with ataxia.

782   The Variance-Added group did exhibit a small, reduction in the estimate of implicit
783 learning early the rotation block. However, there was no difference in the implicit
784 learning estimate by the end of the rotation block, nor when compared across the entire
785 rotation block. However, this delayed onset of implicit learning is likely distinct from the
786 implicit learning deficit observed in SCA. Under conditions of high external noise, the
787 learning rate should be reduced (Kalman, 1960; He et al., 2016). Moreover, using a
788 computational model, Schlerf and colleagues (2013) reported that the slower learning
789 rates in SCA are unlikely to be the result of increased motor noise. Indeed, when
790 directly examined, minimal correlation is found between impairments in visuomotor
791 learning and the severity of ataxia (Martin et al., 1996; Schlerf et al., 2013).

792

793 <u>Flexibility in aiming is not directly driven by sensory prediction errors</u>

794   A second hypothesis is that sensory prediction errors are necessary to form an
795 effective aiming solution. While some form of performance error would be needed to
796 adjust aiming, it is unlikely that a sensory prediction error is the primary signal. A
797 sensory prediction error occurs whenever there is a mismatch between the expected
798 and actual consequences of a movement. This sensory prediction error is used to
799 update a forward model to improve prediction. In a standard visuomotor rotation task,

800   this error is defined as the difference between the cursor position and target (when
801   taken as a proxy of the location for expected feedback). However, when participants
802   use an instructed aiming strategy to counter the rotation, their hand slowly drifts away
803   from the aiming location across trials (Mazzoni and Krakauer 2006). This occurs
804   because a persistent sensory prediction error, the mismatch between the cursor
805   position and aiming location in this context, continues to result in implicit updating of a
806   forward model. Eventually, this implicit learning leads to poor performance (i.e., large
807   target errors) and participants have to change their aim to offset continued implicit
808   learning (Taylor and Ivry 2011). Models of performance in this aiming task suggest that
809   changes in aim are driven by performance error, the difference between the target and
810   cursor feedback locations, rather than sensory prediction error (Taylor and Ivry 2011;
811   Taylor et al 2014). Sensory prediction errors, on the other hand, appear to lead to
812   implicit learning even when irrelevant to the task goal (Mazzoni and Krakauer 2006;
813   Schaefer and Thoroughman 2011; Morehead et al 2014).
814   Another problem with the hypothesis that the aiming deficit is related to an
815   impairment in learning from sensory prediction errors is that the time course of aim
816   reports looks quite different than that observed for implicit learning. First, with large
817   perturbations (e.g., experiment 1), the aim reports are non-monotonic, with an initial
818   large increase and then a gradual reduction over the course of the rotation block.
819   Second, while the average data might look smooth, the aiming reports for individuals
820   can change abruptly and in either direction, behavior that is reminiscent of exploration
821   (see Taylor et al., 2014). This stands in contrast, to the slow, monotonic updating of an
822   internal model that is considered to be the hallmark of motor adaptation (Huberdeau et
823   al., 2015). Thus, it seems unlikely that the output of a forward model is the driving force
824   for finding an aiming solution.

826   An action-outcome maintenance account of impaired aiming in SCA
827   A third hypothesis considers less direct ways in which the cerebellum might
828   support learning, and by extension, the cognitive capacity required for discovering an
829   aiming solution. The cerebellum is known to be highly connected with much of the
830   cerebral cortex, including prefrontal cortex (Buckner et al., 2011), and damage to the
831   cerebellum can produce a constellation of neuropsychological impairments similar,

832   albeit in milder form, to that observed in patients with lesions of prefrontal cortex

833   (Buckner et al., 2013; Bodranghien et al., 2016). Drawing on ideas developed in

834   perceptual domains (Cohen et al., 1997; Prabhakaran et al., 2000; Gazzaley et al.,

835   2005), we have proposed that a network including prefrontal cortex and cerebellum

836   forms something akin to a motor working memory system, one essential in the action

837   domain (Ivry & Fiez, 2000; Spencer and Ivry, 2009). By this idea, the cerebellum helps

838   represent and/or maintain task-relevant stimulus-response associations across trials.

839   Theories of prefrontal cortex function have suggested a role in implementing and

840   maintaining task sets across trials (Dosenbach et al., 2006 and 2007), possibly in a

841   hierarchical manner where abstraction increases rostrally, allowing for the simultaneous

842   search for action rules at multiple levels of abstraction (Badre and D'Esposito, 2009;

843   Badre et al., 2010). By extension, the task set implemented by the prefrontal cortex

844   would include the task relevant action-outcome associations, a network involving the

845   cerebellum. Consistent with this theory, Spencer and Ivry (2009) showed that the impact

846   of SCA on sequence learning was considerable when the task involved indirect,

847   arbitrary S-R associations, but that SCA participants performed as well as controls in

848   sequence learning when the S-R associations were direct.

849   An extension of this hypothesis may account for the aiming deficit observed in the

850   current study. Converging on an appropriate aiming solution entails a cyclic process of

851   hypothesis testing, generating possible solutions and then evaluating their efficacy. This

852   process would require the maintenance of stimulus-response associations or, perhaps

853   in the case of visuomotor rotations, action-outcome associations.

854   Moreover, the memory demands are likely greatly increased when there are eight

855   target locations, especially with a visuomotor rotation (Krakauer et al., 2000) where

856   implicit generalization appears quite narrow (Heuer and Hegele, 2011). Here an aiming

857   hypothesis generated in response to an action at one target, may appear appropriate

858   when applied to neighboring targets, but fail miserably when applied to distant targets.

859   For example, aiming above the target location would be effective in countering a

860   clockwise rotation for targets presented on the right side of the display but would be

861   counterproductive if applied to targets on the left side of the display. Thus, the

862   participant would need to maintain action-outcome associations at multiple target

863 locations to eventually learn that the solution to the perturbation is common to all target
864 locations in a polar coordinate reference frame. This idea would suggest that if the SCA
865 participants had a compromised ability to maintain action-outcome association, then
866 they would naturally have an impaired ability to counter a visuomotor rotation across the
867 workspace.

868   Our action-outcome maintenance hypothesis makes three predictions. First, we
869 would expect that the ability to employ an aiming solution might be related to the
870 individual's cognitive status. Second, we would expect that individuals with SCA would
871 be able to develop an appropriate aiming solution if the perturbation was simpler. For
872 example, these individuals might be able to use aiming to compensate for a
873 translational perturbation. Third, we would predict that individuals with ataxia would
874 disproportionately benefit if the demands on working memory were reduced, say by
875 displaying the previous aim choice for each target, or by the use of only a single target
876 location. These last two predictions can motivate future work on the multi-faceted
877 contribution of the cerebellum to sensorimotor learning. At present, the results
878 presented here underscore a role for the cerebellum, not only in implicit aspects of
879 motor performance, but also when those tasks require a more explicit association to link
880 a stimulus with an appropriate response to meet task goals.

881   Here we observed a dual-deficit in sensory-prediction-error-based learning (e.g., a
882 forward model) and aiming. While at first glance the latter may seem odd, it perhaps
883 shouldn't be all that surprising given the cerebellum's involvement in learning for many
884 different types of tasks, from eye-blink conditioning to sequence learning. Indeed, the
885 nearly uniform circuitry of the cerebellum, along with its connections to many areas of
886 the rest of the brain (Buckner et al., 2011), suggests that it may be contributing to
887 learning processes in a generalized manner that remains to be determined.

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1109

1110 **Figure legends**

1111

1112 Figure 1 - General task outline

1113 A) On each trial a single target appeared at one of eight possible locations arranged

1114 equally around the start position. After the target appeared, but before moving,

1115 participants were asked to verbally report which number they were aiming towards for

1116 the current trial. B) In all three experiments, participants first completed 56 baseline

1117 trials with veridical feedback. This was followed by a rotation block in which the visual

1118 feedback was rotated about the start position. Finally, participants completed a no

1119 feedback washout block, where both visual and auditory feedback were withheld. In

1120 experiments 1 and 3 participants completed 128 rotation trials for a total of 264 trials,

1121 while in experiment 2 participants completed 220 rotation trials for a total of 456 trials.

1122

1123 Figure 2 - Experiment 1: Abrupt Rotation performance metrics.

1124
1125 The top row depicts group averaged data for A) hand heading angle, B) aim reports,

1126 and C) estimates of implicit learning (Hand heading angle - Aim). The data are based on

1127 averages taken over bins of 8 trials for each participant, and then averaged across

1128 participants for each group. Shaded lines represent confidence intervals around the

1129 mean. Bins are marked with the trial number of the last trial of that bin. The bottom row

1130 shows individual participant data (dots) and group means (horizontal bar) for D) hand

1131 heading angle, E) aim report, and F) implicit learning estimate, with the data averaged

1132 over the first 8 trials of the rotation block, the last 8 trials of the rotation block, or the first

1133 8 trials of no-feedback washout block.

1134

1135   Figure 3 - Experiment 2: Gradual Rotation performance metrics.

1136

1137   The top row depicts group averaged data for A) hand heading angle, B) aim reports,

1138   and C) estimates of implicit learning (Hand heading angle - Aim). The data are based on

1139   averages taken over bins of 8 trials for each participant, and then averaged across

1140   participants for each group. Shaded lines represent confidence intervals around the

1141   mean. Bins are marked with the trial number of the last trial of that bin. The bottom row

1142   shows individual participant data (dots) and group means (horizontal bar) for D) hand

1143   heading angle, E) aim report, and F) implicit learning estimate, with the data averaged

1144   over the first 8 trials of the rotation block, the last 8 trials of the rotation block, or the first

1145   8 trials of no-feedback washout block.

1146

1147

1148   Figure 4 – Sample perturbation schedule for Variance-Added group in experiment 3.

1149

1150   The visuomotor rotation for each trial in the rotation block was was drawn from a

1151   gaussian distribution with a mean of 45° and standard deviation of 11°. The variance of

1152   the gaussian was based on the mean variance in hand heading angle seen in

1153   participants with ataxia in experiment 1. Participants in the No-Variance *control* group

1154   experienced a constant 45° rotation on all trials in the rotation block (not shown).

1155
1156   Figure 5 - Experiment 3: Abrupt Rotation with variable rotation performance metrics

1157

1158   The top row depicts group averaged data for A) hand heading angle, B) aim reports,

1159   and C) estimates of implicit learning (Hand heading angle - Aim). The data are based on

1160   averages taken over bins of 8 trials for each participant, and then averaged across

1161   participants for each group. Shaded lines represent confidence intervals around the

1162   mean. Bins are marked with the trial number of the last trial of that bin. The bottom row

1163   shows individual participant data (dots) and group means (horizontal bar) for D) hand

1164   heading angle, E) aim report, and F) implicit learning estimate, with the data averaged

1165   over the first 8 trials of the rotation block, the last 8 trials of the rotation block, or the first

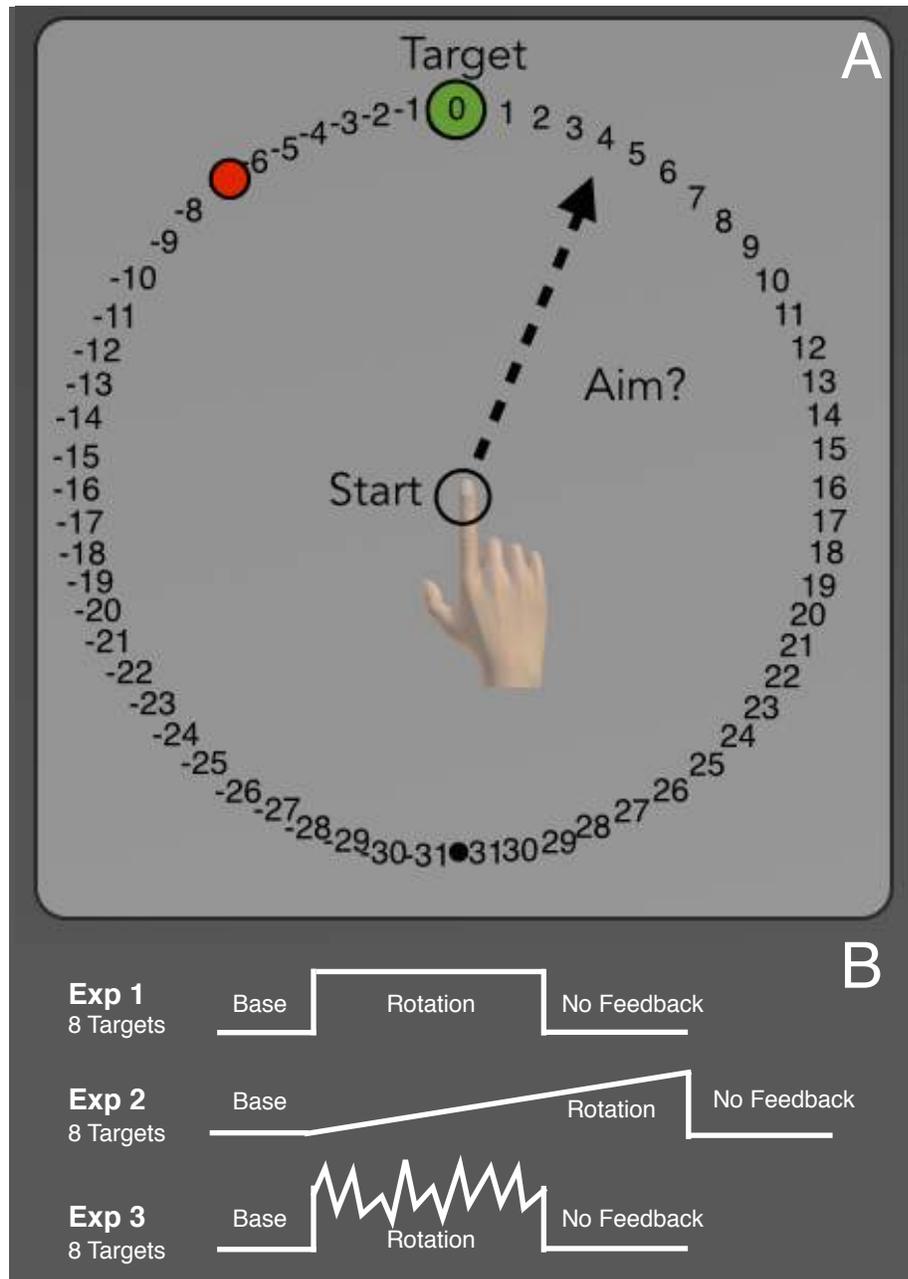1166   8 trials of no-feedback washout block.

Figure 1 - General task outline

A) On each trial a single target appeared at one of eight possible locations arranged equally around the start position. After the target appeared, but before moving, participants were asked to verbally report which number they were aiming towards for the current trial. B) In all three experiments, participants first completed 56 baseline trials with veridical feedback. This was followed by a rotation block in which the visual feedback was rotated about the start position. Finally, participants completed a no feedback washout block, where both visual and auditory feedback were withheld. In experiments 1 and 3 participants completed 128 rotation trials for a total of 264 trials, while in experiment 2 participants completed 220 rotation trials for a total of 456 trials.
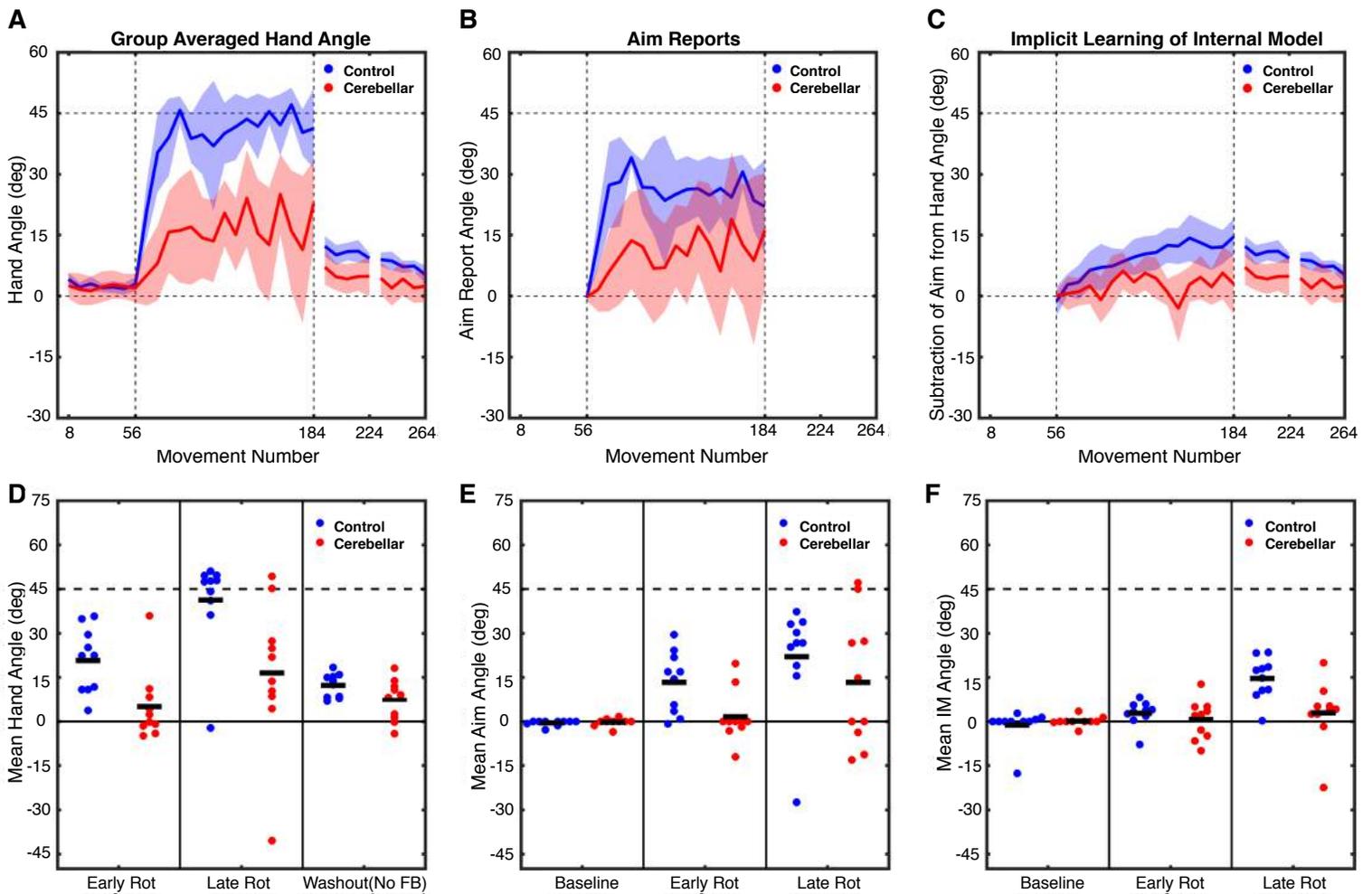
Figure 2 - Experiment 1: Abrupt Rotation performance metrics.

The top row depicts group averaged data for A) hand heading angle, B) aim reports, and C) estimates of implicit learning (Hand heading angle - Aim). The data are based on averages taken over bins of 8 trials for each participant, and then averaged across participants for each group. Shaded lines represent confidence intervals around the mean. Bins are marked with the trial number of the last trial of that bin. The bottom row shows individual participant data (dots) and group means (horizontal bar) for D) hand heading angle, E) aim report, and F) implicit learning estimate, with the data averaged over the first 8 trials of the rotation block, the last 8 trials of the rotation block, or the first 8 trials of no-feedback washout block.
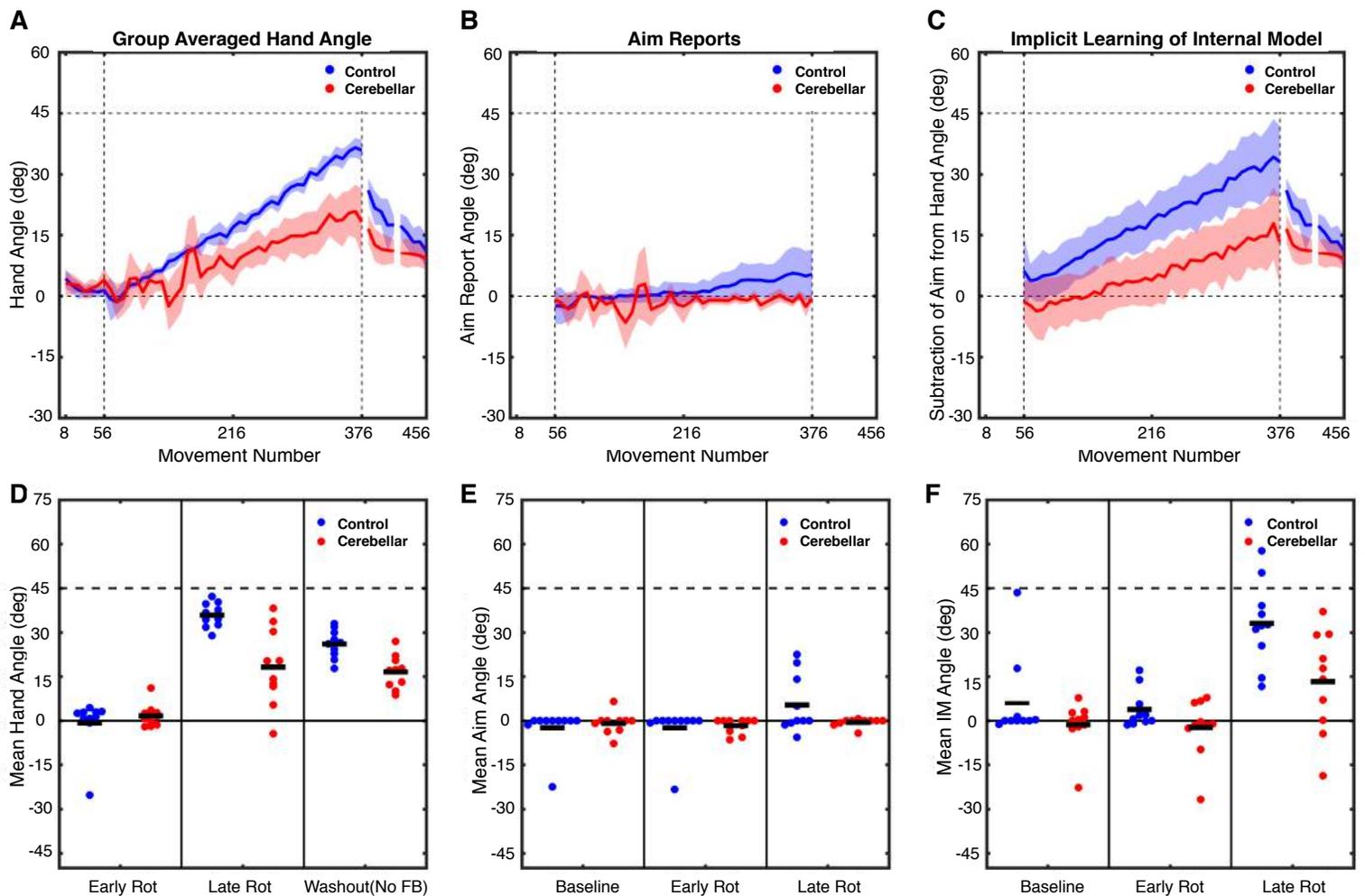
Figure 3 - Experiment 2: Gradual Rotation performance metrics.

The top row depicts group averaged data for A) hand heading angle, B) aim reports, and C) estimates of implicit learning (Hand heading angle - Aim). The data are based on averages taken over bins of 8 trials for each participant, and then averaged across participants for each group. Shaded lines represent confidence intervals around the mean. Bins are marked with the trial number of the last trial of that bin. The bottom row shows individual participant data (dots) and group means (horizontal bar) for D) hand heading angle, E) aim report, and F) implicit learning estimate, with the data averaged over the first 8 trials of the rotation block, the last 8 trials of the rotation block, or the first 8 trials of no-feedback washout block.
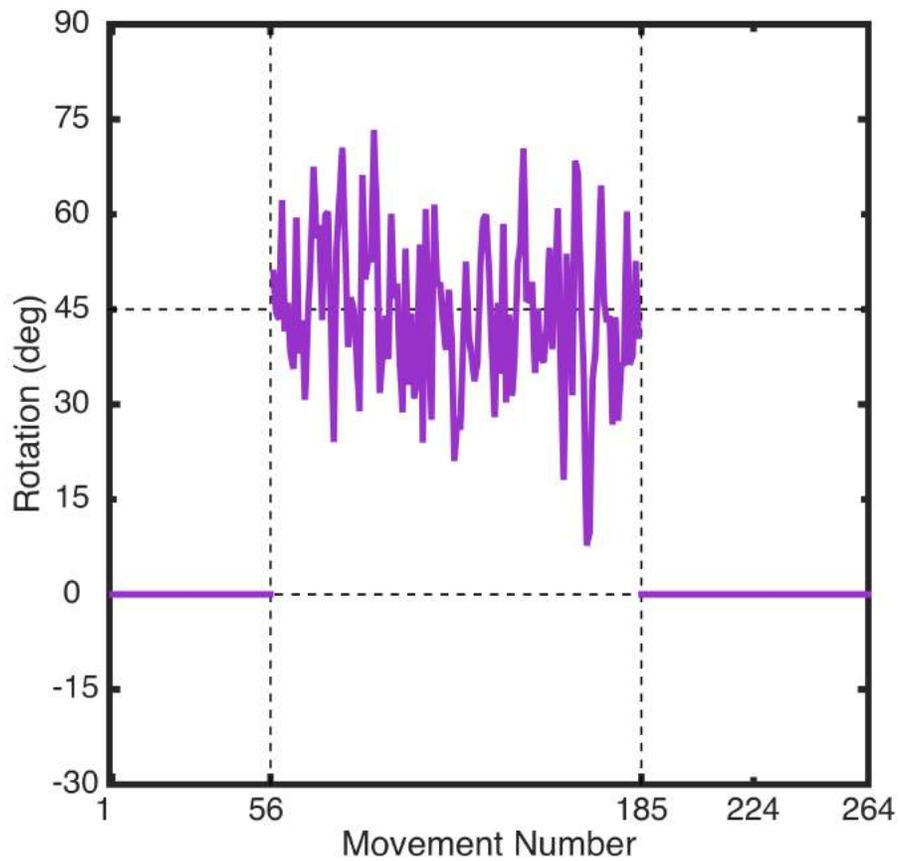
Figure 4 - Sample perturbation schedule for Variance-Added group in experiment 3.

The visuomotor rotation for each trial in the rotation block was was drawn from a gaussian distribution with a mean of 45° and standard deviation of 11°. The variance of the gaussian was based on the mean variance in hand heading angle seen in participants with ataxia in experiment 1. Participants in the No-Variance control group experienced a constant 45° rotation on all trials in the rotation block (not shown).
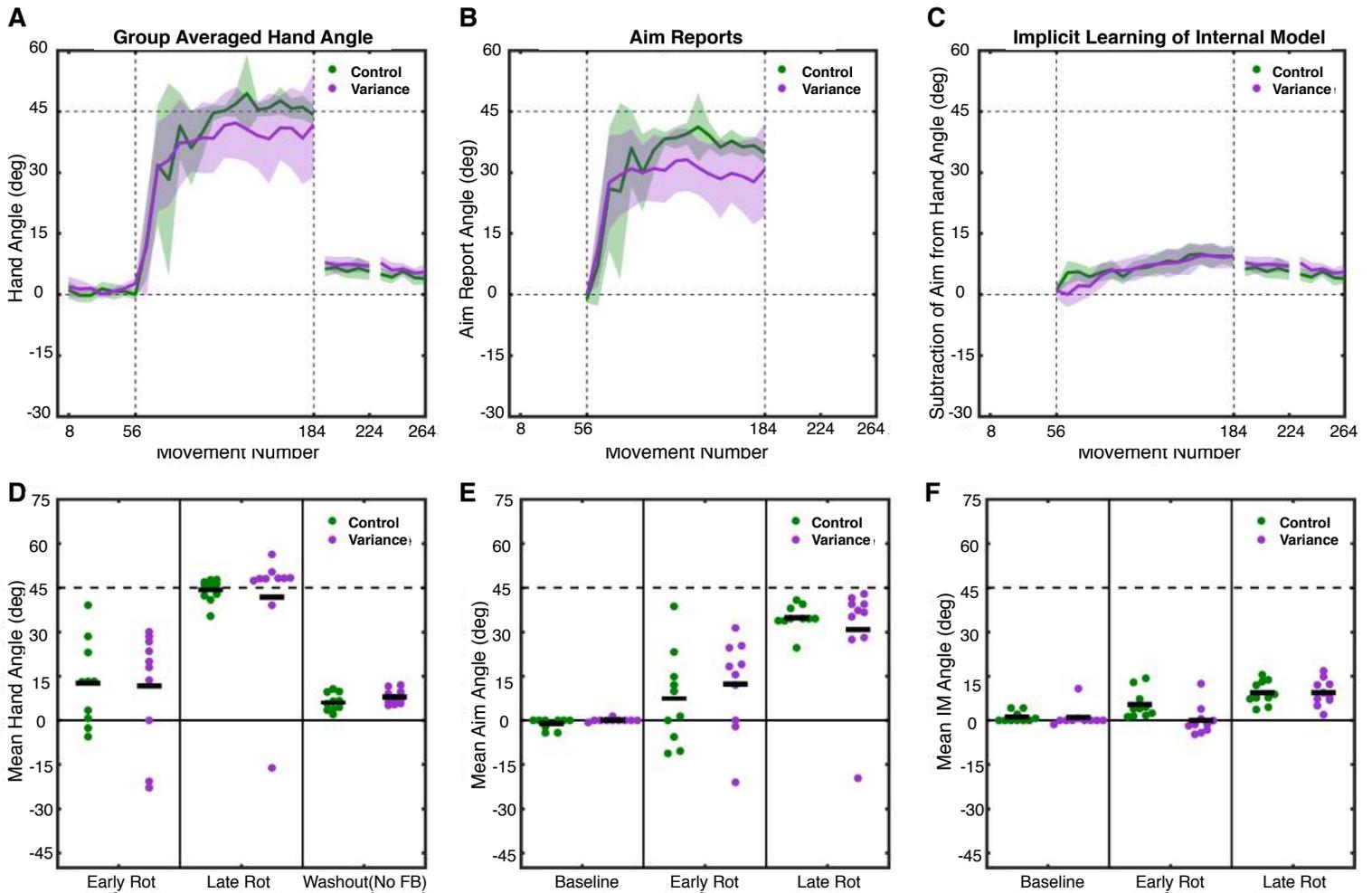
Figure 5 - Experiment 3: Abrupt Rotation with variable rotation performance metrics

The top row depicts group averaged data for A) hand heading angle, B) aim reports, and C) estimates of implicit learning (Hand heading angle - Aim). The data are based on averages taken over bins of 8 trials for each participant, and then averaged across participants for each group. Shaded lines represent confidence intervals around the mean. Bins are marked with the trial number of the last trial of that bin. The bottom row shows individual participant data (dots) and group means (horizontal bar) for D) hand heading angle, E) aim report, and F) implicit learning estimate, with the data averaged over the first 8 trials of the rotation block, the last 8 trials of the rotation block, or the first 8 trials of no-feedback washout block.

Participant	Gender	Age	Ed (years)	Handedness	Type	Diag (years)	Ataxia scale	MOCA
Abrupt								
ARSCA1	Female	63	16	Left	SCA8	11	----	27
ARSCA2	Male	73	20	Left	SAOA	4	20.5	28
ARSCA3	Male	41	16	left	SAOA	19	27	29
ARSCA4	Female	55	14	Right	SCA2	13	48	26
ARSCA5	Male	47	16	Left	SAOA	19	22	29
ARSCA6	Male	42	16	Right	SCA2	2	41	28
ARSCA7	Male	62	19	Right	SAOA/MSA	4	12	30
ARSCA8	Male	70	16	Right	SAOA/Family Hist	9	11	27.5
ARSCA9	Male	44	22	Left	SAOA/MSA	2	12	30
ARSCA10	Male	40	16	Right	SCA2	11	45	26
Gradual								
GRSCA1	Female	35	17	Right	SCA1	4	6*	24
GRSCA2	Female	30	17	Left	SCA2	3	17*	----
GRSCA3	Male	44	17	Right	SCA1	1	9*	19
GRSCA4	Male	79	13	Right	SAOA	6	11*	14
GRSCA5	Male	46	17	Right	ADCA	1	7*	20
GRSCA6	Male	41	17	Right	SAOA	----	23.5*	23
GRSCA7	Male	49	17	Right	SAOA	3	8*	22
GRSCA8	Male	36	17	Right	SCA1	3	10.5*	25
GRSCA9	Female	69	19	Left	SAOA	8	3*	30
GRSCA10	Female	52	22	Right	SCA6	14	1	28
							* SARA, otherwise ICARS	

Table 1: SCA neuropsychology and demographic information