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Emergent low-frequency activity in cortico-cerebellar networks with motor skill learning

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20 **Abstract**

21

22 The motor cortex controls skilled arm movement by recruiting a variety of targets in the nervous

23 system, and it is important to understand the emergent activity in these regions as refinement of

24 a motor skill occurs. One fundamental projection of the motor cortex is to the cerebellum.

25 However, the emergent activity in the motor cortex and the cerebellum that appears as a

26 dexterous motor skill is consolidated is incompletely understood. Here, we report on low-

27 frequency oscillatory (LFO) activity that emerges in cortico-cerebellar networks with learning the

28 reach-to-grasp motor skill. We chronically recorded the motor and the cerebellar cortices in rats

29 which revealed the emergence of coordinated movement-related activity in the local-field

30 potentials (LFPs) as the reaching skill consolidated. We found that the local and cross-area

31 spiking activity was coordinated with LFOs. Finally, we also found that these neural dynamics

32 were more prominently expressed during accurate behavior. This work furthers our understanding

33 on emergent dynamics in the cortico-cerebellar loop that underlie learning and execution of

34 precise skilled movement.

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37 **Keywords:** Motor cortex, cerebellum, oscillations, skill learning.

Introduction

The primary motor cortex (M1) is viewed as a driver for movement and an emerging view posits transient oscillatory dynamics- both at the level of spiking and local field potentials (LFPs) as the neural substrate for it[1–7]. There has been a particular interest in low-frequency quasi-oscillatory activity (LFOs) in M1, which can be brief (1-2 cycles) for rapid movements or longer for sustained movements, and it has been shown to be phase-locked to sub-movement timing[2,3,8,9]. Recent work showed that such oscillatory dynamics are coordinated in the M1 and dorsolateral striatum in the rodents as they learned a reach-to-grasp task[3]. One of M1's principal projections is to the cerebellum via the pons[10–13], but similar oscillatory dynamics have not been studied in cortico-cerebellar networks.

M1 is a key brain hub involved in voluntary forelimb movement: experimental lesions of M1 in animal models or neurological injury to M1 (such as stroke) impair dexterity[2,14–16], stimulation of M1 neurons evokes movement[17–19], spiking activity in M1 is closely linked to movement parameters[3,11,20–23] and optogenetic perturbation of M1 affects forelimb behaviors[18,20,24,25]. The cerebellum's role in the coordination of arm movements has also been extensively studied. Investigation of prehension/reaching tasks in animals have shown that cerebellar neurons – both in the cerebellar cortex and its deep nuclei are tuned to several movement-related events such as movement onset, cues leading to movement and its duration, limb position, velocity and muscle activity[26–31]. Besides coding for the above-listed features of limbs and associated movement parameters, other evidence indicates that the cerebellum participates in the formation of procedural memories, learning and retention of skills, habits, and conditioned responses[32,33]. Cerebellar lesions impair acquisition of skilled behaviors and patients with cerebellar disease show impaired reaching[34–36]. Furthermore, optogenetic perturbation of cerebellar nuclei or pontine inputs can cause a loss of endpoint precision in mice during reach-to-grasp behavior[13,37].

64   Additionally, electric stimulation over the cerebellum facilitates adaptive control of reaching[38,39].

65   Recent rodent work using two-photon imaging showed the emergence of shared neuronal-

66   dynamics in *M1*-cerebellar ensembles as animals learned to expertly control a manipulandum[11].

67

68   In this study, we have focused on transient oscillatory dynamics that emerge in M1 and the

69   cerebellum as a reaching skill is learned. We recorded neural activity in the M1 and contralateral

70   cerebellum (the primary M1 target through pons nuclei) throughout the learning of a reach-to-

71   grasp skill in rats. We observed emergent coordinated low-frequency oscillatory activity (1-4 Hz)

72   across M1 and cerebellum LFPs that was linked to increased success rates. We also found that

73   LFPs modulated spiking in both regions and that the spiking dynamics were conserved for

74   successful, accurate movements.

75 **Results**

76

77   We trained 13 rats on the Whishaw forelimb reach-to-grasp task[40,41] in our in-house built

78   automated training box that is compatible with electrophysiology (**Fig. 1A**)[2,4142]. We chose this

79   task due to its similarity to skilled learning tasks in humans[43,44] as well as extensive evidence that

80   this task is associated with multiple levels of neural plasticity in the M1 and the cerebellum.

81   Examples of this include changes in Long-Term Potentiation (LTP)[45], dendritic spine growth[46]

82   motor map plasticity in the M1[47], as well as patterned spiking in the cerebellar cortex[29] and more

83   recently, it has also been demonstrated that cerebellar associative learning underlies reach

84   adaptation[48]. Importantly, patients with neurologic injury in either region show impairment in this

85   skilled reaching behavior[36,49]. In a subset of rats ($n = 5$) that were monitored during reach-to-grasp

86   motor skill consolidation, we also recorded neural signals, including single-unit activity and local

87   field potentials (LFPs) in M1 and cerebellum (**Fig. 2A**). For the electrophysiology experiments,

88   microelectrodes were implanted (microwire arrays in M1 and tetrodes/ polytrodes in cerebellum,

89   see Materials and Methods; and **Supplementary Table 1**). In the animals that were recorded,

90   training began five days after electrode placement surgery.

91

92   **Measurement of Skilled Motor Performance**

93   As in other studies that employ the Whishaw forelimb reach-to-grasp task, we assessed motor

94   skill learning across two dimensions: speed and accuracy (**Fig. 1B-E**)[3,50]. Accuracy was measured

95   as percent success in retrieving the pellet and speed was assessed using the time the animal

96   took to perform the full reach-grasp-retract motor sequence. Training lasted for 5 days in

97   automated behavioral boxes[2,41], and animals performed 100–160 trials each day. Consistent with

98   past results[3,50] over 5 days of learning, the success rate increased and movements became faster

99   as measured through reach-grasp task completion duration or reach duration (see **Fig. 1**). On

100   average, success rates increased from 23.9 ± 4.7% to 49.8 ± 3.2% from early to late days (mean

101   ± s.e.m., mixed-effects model: $P = 1.87 \times 10^{-17}$) and reach duration came down from : 406 ± 57

102   ms on early days to 367 ± 48 ms on late days (mean ± s.e.m., mixed-effects model: $P = 2.15 \times$

103   10^{-5}).

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105   **Figure 1**
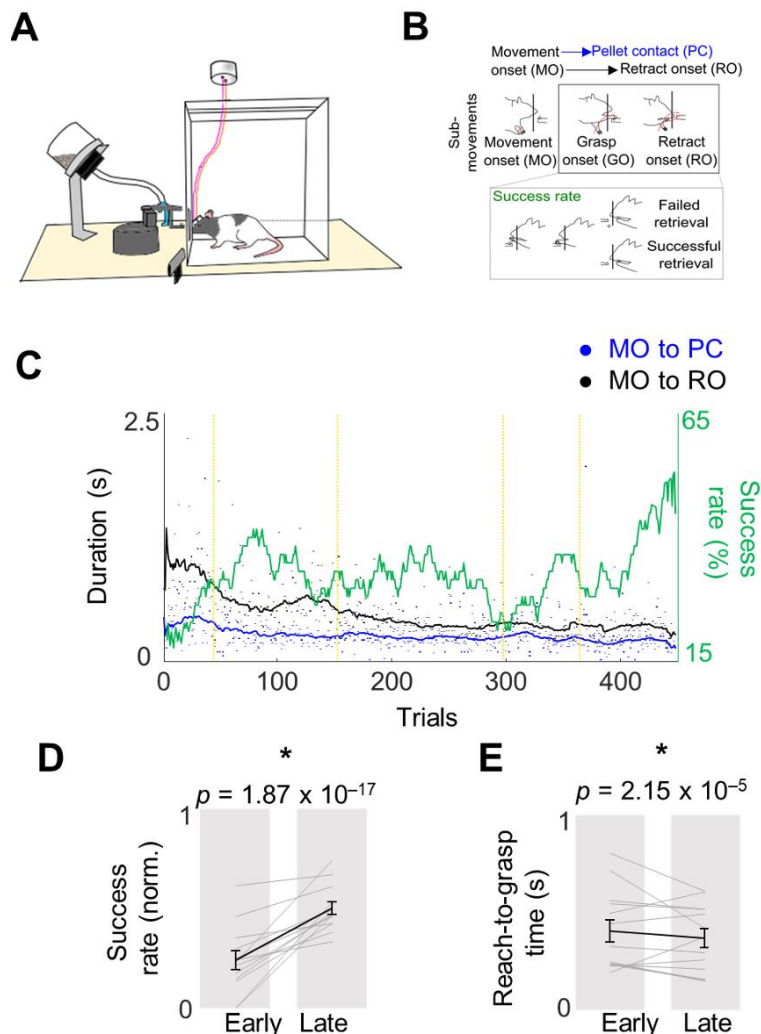
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108   **Figure 1.** Behavioral evaluation of the skilled reach -to-grasp task. **A,** The behavioral setup for
109   the skilled forelimb reaching task with simultaneous neurophysiological recording. **B,** Top:
110   Illustration of the reach-to-grasp task showing the three major parts of the reach movement: reach
111   onset, pellet contact, and retract onset. Bottom: Comparison of a failed trial and a successful trial.
112   **C,** Success rate and reach event timing from a sample animal. **D,E,** Difference in success rate
113   and reach duration from early training days to late training days (n = 13 animals). Gray lines
114   represent individual animals, and the black line is mean and s.e.m. across animals. P-values are
115   from mixed-effects models.
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118 **Coordinated movement-related activity emerges across M1 and cerebellum during skill**

119 **learning.**

120 We next evaluated the cerebellum in search of transient low-frequency oscillatory (LFO) dynamics

121 similar to those that were recently shown to emerge in the M1[2,3] while learning this skill. We

122 observed that coordinated LFO (1–4 Hz) activity appeared during movement across M1 and

123 cerebellum as performance improved (**Fig. 2**). This low-frequency activity was clearly observed

124 in movement-related LFP signals (**Fig 2B, C**). The movement-related LFP power in the LFO-band

125 increased from early to late days in both M1 and cerebellum (**Fig. 2C**; M1 baseline-normalized

126 power: 0.51 ± 0.15 on early days to 0.65 ± 0.16 on late days, mixed-effects model: $t(406) = 4.3$,

127 $P = 2.3 \times 10^{-5}$; cerebellum power: 0.43 ± 0.12 to 0.86 ± 0.25, mixed-effects model: $t(650) = 8.6$,

128 $P = 8.4 \times 10^{-17}$).

129

130 We also analyzed movement-related low-frequency LFP coherence between M1 and cerebellum

131 LFPs and we found that this also increased with increased task proficiency (**Fig. 2D**; 0.18 ± 0.02

132 coherence on early days to 0.21 ± 0.01 on late days, mixed-effects model: $t(5158) = 13.4$, $P = 4.5$

133 $\times 10^{-40}$). These increases in LFP power and coherence were not solely a by-product of faster and

134 more consistent movements, since these high LFP power and coherence were not present for

135 fast trials early in training, which we checked in a subset of animals.

136

137 With training, reaching sub-movements also became precisely phase-locked to 1–4 Hz LFP

138 signals in both M1 and cerebellum, consistent with what we would expect if this activity was

139 involved in generating sub-movements within this task (**Fig. 2E**; significant increase in inter-trial

140 coherence (ITC) of the M1 LFP locked to movement onset (*MO*): mixed-effects model: $t(406) =$

141 4.4, $P = 1.5 \times 10^{-5}$; pellet contact (*PC*, right at the time of grasp initiation): mixed-effects model:

142 $t(406) = 7.0$, $P = 9.2 \times 10^{-12}$; and retract onset (*RO*): mixed-effects model: $t(406) = 10.1$, $P = 1.5$

143 $\times 10^{-21}$; cerebellum LFP locked to movement onset: mixed-effects model: $t(650) = 4.5$, $P = 8 \times$

144   10^{-6}, pellet touch: mixed-effects model: $t(650) = 9.8$, $P = 1 \times 10^{-19}$, retract onset: mixed-effects

145   model: $t(650) = 9.1$, $P = 9.1 \times 10^{-19}$).

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149   **Figure 2**
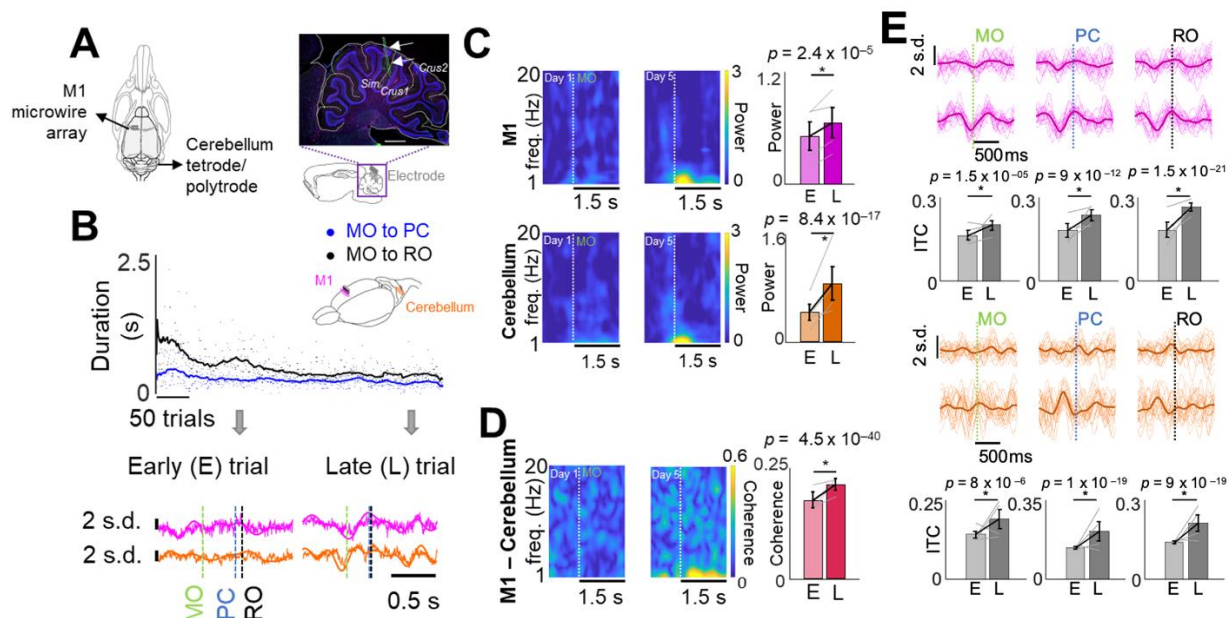
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152   **Figure 2. Coordinated movement-related mesoscopic activity emerges across M1 and**
153   **cerebellum during skill learning. A,** *Left:* Schematic of recording electrode locations in M1 and
154   contralateral cerebellum depicted from top; *Right:* Histological verification of recording location in
155   cerebellum (three markers used: Iba1 (green, microglia), GFAP (pink, astrocytes), DAPI (blue,
156   nuclei). Sagittal section shows cerebellar lobules and cortical layers. Scale bar: 1 mm. Electrode
157   shank is marked by two arrows. **B,** *Top:* Example time course and illustration of recording scheme
158   in M1 and the cerebellum from a frontal-side view. *Bottom*: neural and forearm muscle activity for
159   representative successful trials from days 1 and 8.**C,** *Left*: Spectrograms of example M1 and
160   cerebellar channels. *Right*: Difference in 1–4 Hz cerebellum and M1 power from early training to
161   late training. The gray lines represent the mean power from individual animals (*n* = 4 animals)
162   and the black lines represent the mean ± s.e.m. *P*-values are from mixed-effects models. **D,** Left:
163   Coherograms from an example M1 and cerebellum LFP channel pair. Right: difference in 1–4 Hz
164   M1-cerebellum coherence from early to late training sessions. The gray lines represent the mean
165   coherence from individual animals (*n* = 3 animals) and the black lines represent the mean and
166   s.e.m. *P*-values are from mixed-effects models. **E,** 1–4 Hz filtered LFP from example M1 and
167   cerebellum channels time-locked to reach events; individual trials with mean overlaid. Bar plots
168   depict changes in ITC from early trials to late trials (*upper row* for M1 and *lower row* for
169   cerebellum). The gray lines represent the mean ITC from individual animals (*n* = 4 animals) and
170   the black lines represent the mean and s.e.m. *P*-values from mixed-effects models.

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Coordinated spiking activity emerges across M1 and cerebellum during skill learning.

The emergence of coordinated low-frequency activity across M1 and cerebellum was also clearly observed in movement-related spiking activity across M1 and cerebellum. We quantified phase-locking of movement-related M1 and cerebellar spikes to 1–4 Hz LFP signals in each region by generating polar histograms of the LFP phase at which each spike occurred for a single unit and LFP channel (**Fig. 3A**). The non-uniformity of the distribution of phases (indicating phase-locking) was quantified using a Raleigh test of circular non-uniformity. We compared all task-related M1 and cerebellar units on day 1 and 5 to a representative LFP channel in M1 and cerebellum and observed an increase in the percentage of M1 and cerebellum units phase-locked to both M1 and cerebellum LFP signals with training (**Fig. 3B**; the black vertical dashed lines correspond to the P = 0.05 significance threshold of the natural log of the Z statistic; M1 unit – M1 LFP pairs: 39.1% day 1 to 59.9% day 5, $P = 8 \times 10^{-6}$, Kolmogorov–Smirnov test; M1 unit – cerebellum LFP pairs: 21.8–76.3%, $P = 1.4 \times 10^{-30}$, Kolmogorov–Smirnov test; cerebellum unit – M1 LFP pairs: 77.8–88.1%, $P = 0.3$, Kolmogorov–Smirnov test; cerebellum unit – cerebellum LFP pairs: 40.9–86.0%, $P = 2.3 \times 10^{-10}$, Kolmogorov–Smirnov test). All the pairs showed a significantly increased phase-locking, except cerebellum unit–cerebellum LFP pairs, although they also trended in same direction over days. These results further suggest that coordinated low-frequency activity emerges across M1 and cerebellum during skill learning.

Next, we also explored these relations for successful and unsuccessful trials on day 5. We found that all four pairs showed significant M1 and cerebellar units' phase-locking to 1–4 Hz M1 and cerebellum LFPs for successful trials (**Fig. 3C**; the black vertical dashed lines correspond to the $P = 0.05$ significance threshold of the natural log of the Z statistic; M1 unit – M1 LFP pairs: 34.6% for unsuccessful trials versus 44.1% for successful trials, $P = 0.013$, Kolmogorov–Smirnov test; M1 unit – cerebellum LFP pairs: 50.5–64.9%, $P = 6 \times 10^{-4}$, Kolmogorov–Smirnov test; cerebellum

200   unit – M1 LFP pairs: 61.0–86.4%, P = 1.6 × 10^{-4}, Kolmogorov–Smirnov test; cerebellum unit –

201   cerebellum LFP pairs: 80.7–84.2%, P = 2.3 × 10^{-10}, Kolmogorov–Smirnov test).

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204   **Figure 3**
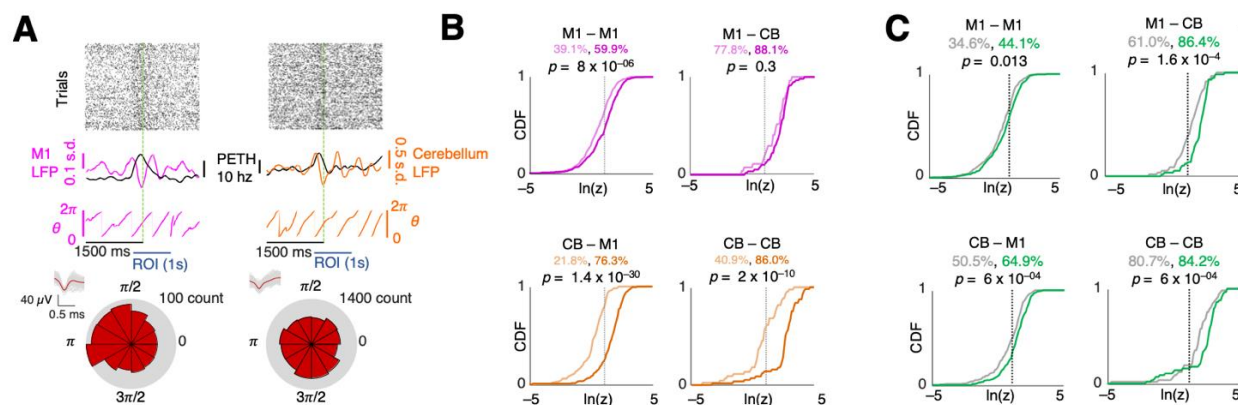
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207   **Figure 3. Coordinated spiking activity emerges across M1 and cerebellum during skill
208   learning. *A,*** Illustration of spike locking to LFP phase for M1 unit-M1 LFP (left) and cerebellum
209   unit- cerebellum LFP (right) pair examples. *Top*: raster plots of reach-centered spiking activity
210   from example single units. *Middle*: 1–4 Hz filtered LFP overlayed with PETH from example unit.
211   Below is the extracted phase from the filtered LFP. *Bottom*. Polar histograms of the spikes that
212   occurred at various LFP phases. ***B,*** Cumulative density functions (CDFs) of the z-statistic for
213   every LFP-unit pair across and within each region. The vertical dotted lines indicate the
214   significance threshold (p = 0.05). The percentage of the pairs with significant p-values is
215   displayed. Lighter colors indicate early trials and darker is later. n = 280 M1 unit-LFP pairs on day
216   1, n = 298 M1 unit-LFP pairs on day 5, n = 46 cerebellum unit-LFP pairs on day 1, n = 73
217   cerebellum unit-LFP pairs on day 5. *P*-values derived using a Kolmogorov-Smirnov test. ***C,***
218   Success/failure CDFs of the z-statistic for every LFP-unit pair within and across each region. The
219   vertical dotted lines indicate the significance threshold (p = 0.05). The percentage of the pairs
220   with significant p-values is displayed. Green indicate successful trials and gray is failures. *P*-
221   values derived using a Kolmogorov-Smirnov test.

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225   **Reorganization of neural dynamics in M1 and cerebellum with skill learning**

226   We also investigated the consistency of single-trial population spiking activity by computing the

227   correlations between single-trial neural activity and the trial-averaged template across all units in

228   a session (**Fig. 4**). In early sessions, trial-to-trial neural firing was more inconsistent compared to

229   later sessions, while later sessions were consistently associated with a stereotyped sequence of

230   unit activations that also matched peri-event time histograms (PETH). This was observed in both

231   M1 (**Fig. 4A**) and cerebellar (**Fig. 4C**) activity. Across the sessions from all rats, we observed a

232   significant increase in template correlation among trials (**Fig. 4B, D**; linear mixed-effects model.

233   M1: $t(770) = 8.2$, $P = 5 \times 10^{-3}$), cerebellum: $t(648) = 5.4$, $P = 8 \times 10^{-8}$) indicating that trial-to-trial

234   variability in M1 and cerebellum neural activity reduced with skill consolidation.

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237   **Figure 4**
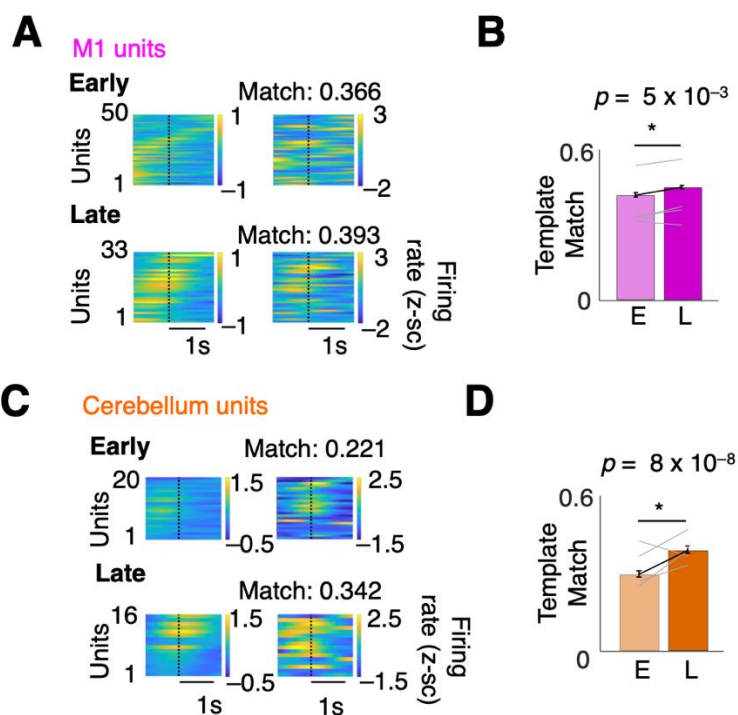
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240   **Figure 4. Changes in M1 and cerebellum neural dynamics with skill learning. *A,*** M1
241   successful trial averaged PETH from an example rat (*left*) and single trial PETH example (*right*)
242   for early (*top*) and late (*bottom*) training sessions. ***B,*** M1 PETH template match over training. Bars
243   indicate mean ± s.e.m. over trials. Gray lines indicate average per animal ($n = 4$ animals). *P*-
244   values are from mixed-effects models. ***C,*** Cerebellum successful trial-averaged PETH from an
245   example rat (left) and single trial PETH example (*right*) for early (*top*) and late (*bottom*) training
246   sessions. ***D,*** Cerebellum PETH template match over training. Bars indicate mean ± s.e.m. over
247   trials. Gray lines indicate average per animal ($n = 4$ animals).

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250   **Skilled movement representation in M1 and cerebellum**

251   Lastly, we explored the representation of successful and failed reaches in M1 and cerebellum.

252   We used Gaussian-process factor analysis (GPFA) to find low-dimensional neural trajectory

253   representations of population spiking activity in M1 and cerebellum on individual trials[3,51] (**Fig. 5A**)

254   and then compared trajectories for successful and unsuccessful trials in early and late learning.

255   We observed a difference between trajectories for successful and unsuccessful trials in M1 and

256   cerebellum. To compare successful and unsuccessful trials we computed the correlation between

257   the mean neural trajectory for successful trials, that is, the 'successful template', and each

258   individual trial's neural trajectory (**Fig. 5B**) during the period from 250 ms before movement onset

259   until 250ms after retract onset (**Fig. 5C**). This period encompassed the movement onset and pellet

260   contact for grasping and retraction of the forelimb. Since trials differed in the duration of this

261   period, we interpolated trajectories such that they were all the same length. Neural trajectories for

262   unsuccessful trials had significantly lower correlation than successful trials (**Fig. 5C**, Early M1: P

263    $= 8.5 \times 10^{-12}$, Early cerebellum: $P = 0.02$, Late M1: $P = 1.1 \times 10^{-8}$, Late cerebellum: 6.6×10^{-3}

264   mixed-effects model with Bonferroni correction for multiple comparisons). Together with Figure

265   3c, this provided further evidence that accurate reach-to-grasp task execution has M1 and

266   cerebellar reliance.

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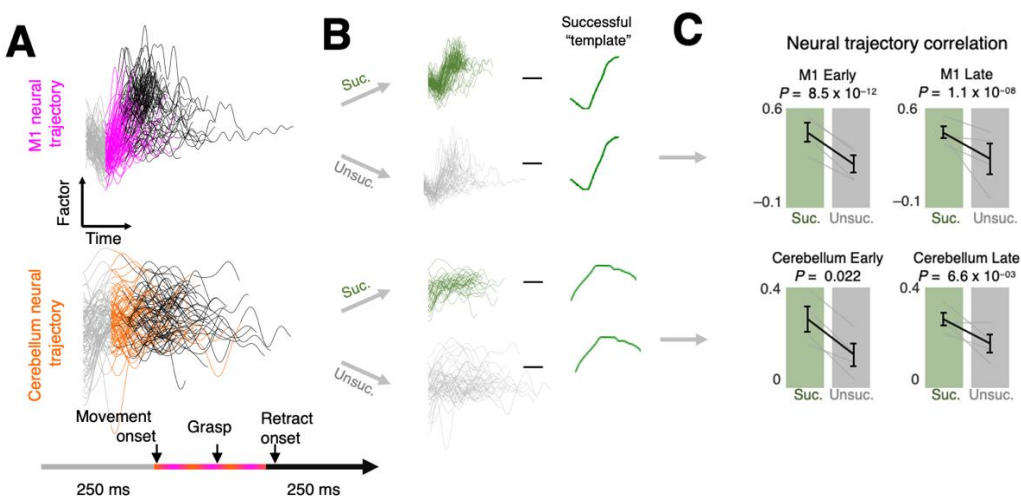270
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Figure 5

Figure 5. Skilled movement representation in M1 and cerebellum. *A,* Example GPFA neural trajectories from late training sessions for M1 (*top*) and cerebellum (*bottom*) in a single animal. ***B,*** Illustration of the process of comparing factor trajectories from successful and unsuccessful trials to the template (mean successful trajectory). ***C,*** Deviation from the template for M1 (*top*) and cerebellum (*bottom*) factors. Gray lines represent individual animals ($n = 4$ animals), and the black line is mean $\pm$ s.e.m. across animals. *P*-values are from mixed-effects models.

Discussion

In summary, we found that coordinated low-frequency activity emerged across M1 and cerebellum, which was linked to the emergence of faster reaching movements. We further found that coordinated spiking activity in both these regions was linked to accurate reach-to-grasp movements. Our work details the mesoscopic transmission in cortico-cerebellar networks and how it evolves with skill learning as well as how skilled reaching has a motor cortical and cerebellar cortical reliance.

Role of M1 and cerebellum in motor skill learning and execution

M1 has a well-established role in motor learning as well as movement execution[52]. In particular, M1 is critical for generation of skilled dexterous movement[3,20,43,52]. Our work is consistent with this notion as we also see that M1 activity is different for successful reaches (**Fig. 3C, 4A** and **5**). M1's projection to the cerebellum is thought to mediate fine-tuning of the movement. Cerebellar neurons in the cortex and in the deep nuclei are known to be modulated around several movement events. Perturbation of M1 input to cerebellum or direct manipulation of cerebellum itself is shown to delay movement initiation and to increase movement variability and duration[13,34,37,53]. Our work is also consistent with these observations as we found that precise, accurate movements had more consistent spiking activity in the cerebellum, and its coordination with LFOs in LFPs differed for successful and unsuccessful reaches (**Figs. 3C**, **4B** and **5**). Besides this role in increasing movement precision, cerebellar cortex is also theorized to contribute to task relevant dimensionality expansion that can aid in flexible computation and enhance learning[54–56]. This notion of dimensionality expansion was confirmed experimentally with the observations of high correlations among granule cells activity when mice expertly exerted pushing control over a manipulandum in a forelimb movement task[11]. This work also showed increase in emergent shared variance in M1 and cerebellar cells. Our increased M1-cerebellum LFP coherence with

322   skill learning is similar to this observation. Neural network models of cortico-cerebellar networks

323   show that cerebellar feedback improves rate of learning and cerebellar network also carries task

324   representation[57]. Our experimental data supports this notion as well. We observed that M1-

325   cerebellum LFP coherence increased with learning, and we observed movement-modulated units

326   in the cerebellum. One of our observations also showed that M1 LFP-cerebellar units showed

327   strong coordination in low-frequency range early on in training (**Fig. 3B**). This might suggest that

328   cerebellar activity was critical during reach-to-grasp skill acquisition and is consistent with the

329   notions of M1 being input-driven, and is also consistent with the cerebellar contributions to

330   acquisition of skilled volitional movements[24,32].

331

332   ***Coordinated oscillatory dynamics across motor networks***

333   One of our keys findings here is on low-frequency activity across M1 and cerebellum as an

334   important marker of skilled motor control. We found evidence of such activity at the level of neural

335   spiking and LFPs during the performance of dexterous task in rats. It is noteworthy that similar

336   LFOs were recently shown to be disrupted in M1 post-stroke and tracked recovery[2]. This work

337   also boosted M1 LFOs through electric stimulation to promote recovery. Recently, there has also

338   been an interest in cerebellar stimulation for stroke recovery[58–60], but a biomarker in cortico-

339   cerebellar networks that can be target for closed-loop electric stimulation for stroke recovery is

340   lacking. Future work can test if the LFOs we found in cortico-cerebellar networks of healthy

341   animals with skill consolidation here can also serve as a biomarker for motor function during

342   recovery from stroke. Mesoscopic biomarkers such as LFPs present a lower translational barrier

343   in clinical populations.

344

345   Cortical LFOs can be used to decode reach-related activity and predict spiking phase across

346   multiple behavioral states[9,61]. Such activity is also correlated with multiphasic muscle activations

347   and timing of movements[5,8,9,62]. Recent work also suggest that oscillatory dynamics reflect an

348   underlying dynamical system[5]. This previous work argues that LFOs represent an intrinsic

349   property of motor circuits associated with precise movement control. Our findings extend this body

350   of work by showing LFO dynamics in both M1 and cerebellum (**Fig. 2**). The exact origin of LFOs

351   and underlying generators remains unknown. While reach-related LFOs may have involved

352   striatum[3] or thalamocortical activity[63] so far, our results here raise the possibility of cerebellar

353   involvement. Further work can probe interactions between M1 and the broader motor network to

354   pinpoint the drivers of the electrophysiologic changes seen during skill learning.

355 **Materials and Methods**

356

357 **Animal care and surgery**

358 All procedures were in accordance with protocols approved by the Institutional Animal Care and

359 Use Committee at the Cedars-Sinai Medical Center. Adult male Long Evans rats (n = 13, 250–

360 400 g; Charles River Laboratories) were housed in a 14-h/10-h light–dark cycle. All experiments

361 were done during the light cycle. We used 8 rats for behavior only (**Fig. 1**) and 5 rats for behavior

362 and physiology (**Figs. 2** to **5**; see **Supplementary Table 1** for details). No statistical methods

363 were used to predetermine cohort size, but our sample sizes are similar to those reported in

364 previous publications[3,50,64–66] (3–9 animals per group). Animals were pair-housed prior to

365 electrode implantation or behavioral training and then single-housed after to prevent damage to

366 implants, or to implement food restriction, respectively.

367

368 All surgical procedures were performed using sterile techniques under 1%–4% isoflurane.

369 Surgery involved cleaning and exposure of the skull and preparation of the skull surface using

370 cyanoacrylate and then implantation of the skull screws for referencing and overall head-stage

371 stability. The analgesic regimen included the administration of 0.1 mg per kg body weight

372 buprenorphine, and 5 mg per kg body weight carprofen. Neural implanted rats were also

373 administered 2 mg per kg body weight dexamethasone and 33 mg per kg body weight sulfatrim

374 for 5 days. All neural implanted animals were allowed to recover for 5 days prior to further

375 behavioral training. Ground and reference screws were implanted posterior to lambda

376 contralateral to the recorded cerebellum, contralateral to the neural recordings. For M1

377 recordings, 32-channel arrays (33-µm polyamide-coated tungsten microwire arrays) were lowered

378 to a depth of ~1,200–1,500 µm in either the left or right M1 depending on handedness. These

379 were implanted centered at 0.5 mm anterior and 3 mm lateral to the bregma[3,50]. For cerebellar

380 recordings we used 32-64 channel tetrodes (Neuronexus, MI) or shuttle-mounted polytrodes

381 (Cambridge Neurophysiology, UK). The probes were lowered into the cerebellar cortex through a

382 craniotomy centered at 12.5 mm posterior and 2.5-3 mm lateral to bregma. Shuttle mounted

383 probes were moved across days and recorded from depths of 1.5-4 mm. Our target regions were

384 Simplex/ Crus I and Crus II areas of the cerebellum[67–69]. Activity in these areas has shown

385 modulation during upper limb motor behaviors and in response to corticofugal fiber and forelimb

386 stimulation . For the cerebellar recordings, we confirmed the location of electrode tips either

387 through: (i) Staining with the orange/red fluorescence stain DiI (ThermoFisher Scientific) or (ii)

388 three markers of Iba1 (microglia), GFAP (astrocytes), DAPI (nuclei) as shown in figure 2a (also

389 see details below).

390

391 **Supplementary Table 1**

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Animal	Camera Frame rate (Hz)	M1 Probe	Electrode details	Cb Probe	Electrode details
1	30	Yes	32 channel array	Yes	8x4 Tetrode
2	75	Yes	32 channel array	Yes	4x16 Polytrode
3	75	Yes	32 channel array	Yes	4x16 Polytrode
4	75	Yes	32 channel array	No	N/A
5	87	No	N/A	Yes	2x32 Polytrode
6	30	No	N/A	No	N/A
7	30	No	N/A	No	N/A
8	30	No	N/A	No	N/A
9	30	No	N/A	No	N/A
10	30	No	N/A	No	N/A
11	30	No	N/A	No	N/A
12	87	No	N/A	No	N/A
13	87	No	N/A	No	N/A

393
394
395 **Supp. Table 1. Number of rats used for experiments.** Tabulated list of animals and
396 behavioral monitoring camera frame rates and electrode used (see columns).
397
398
399

Behavior

Training

Rats were acclimated to the behavioral box for at least 2 days and then exposed to a reach-to-grasp task for 5-10 trials to establish hand-preference before neural probe implantation. Probe implantation was performed in the contralateral M1 and ipsilateral cerebellum to the preferred hand. Rats were allowed to recover for at least 5 days before the start of experimental sessions. During behavioral assessments, we monitored the animals and ensured that their body weights did not drop below 90% of their initial weight. We used an automated reach-box, controlled by custom MATLAB scripts and an Arduino microcontroller. This setup requires minimal user intervention, as described previously[41]. Each trial consisted of a pellet dispensed on the pellet tray, followed by an alerting beep indicating that the trial was beginning. They then had 15 s to reach their arms through the slot, grasp and retrieve the pellet. A real-time 'pellet detector' using an infrared detector centered over the pellet was used to determine when the pellet was moved, which indicated that the trial was over, and the door was closed. All trials were captured by video through a camera placed on the side of the behavioral box. The camera was synced with the electrophysiology data either using Arduino digital output or directly through TTL pulses to the TDT RZ2 system. In electrode implanted animals the video frame rate ranged from 75-87 Hz aside from 1 animal for which the framerate was 30 Hz (see **Supp. Table 1**). For behavior-only animals the framerate was 30Hz aside from two animals for which the framerate was 87 Hz.

Behavioral Testing

Rats began behavioral testing training 5 days after surgery by performing the same reach-to-grasp task. Electrophysiology recordings were taken throughout the full extent of the testing which consisted of one to two sessions of 60-100 trials per day for 5 days. Typically, each day would consist of a session of 100 trials followed by a session of 60 trials. Sessions within a day were spaced by a 2-hour resting block.

426

Behavioral analysis

428 Behavioral analysis was done based on video recorded during experimental sessions. Reach

429 videos were viewed and manually scored to obtain trial success, hand position and time points

430 for reach onset, pellet contact and retract onset. To characterize motor performance, we

431 quantified pellet retrieval success rate (percentage of pellets successfully retrieved into the box)

432 and reach duration (time from reach onset to retract onset).

433

434

In vivo electrophysiology

436 Units and LFP activity were recorded using a 128-channel TDT-RZ2 system (Tucker-Davis

437 Technologies). Spike data were sampled at 24,414 Hz and LFP data at 1,017.3 Hz. ZIF (zero

438 insertion force) clip-based digital head stages from TDT were used that interface the ZIF

439 connector and the Intan RHD2000 chip that uses 192x gain. Behavior-related timestamps (that

440 is, trial onset, trial completion) and video timestamps (that is, frame times) were sent to the RZ2

441 analog input channel using an Arduino digital board and synchronized to the neural data.

442

443

Neural data analysis

445 Analyses were conducted using custom-written scripts and functions in MATLAB 2018a

446 (MathWorks, MA).

447

Local field potential (LFP) analyses

449 Artifact rejection was first performed on LFP signals to remove broken channels and noisy trials.

450 LFPs were then z-scored and median referenced separately for M1 and cerebellum. There was

451 excessive noise detected in all cerebellum channels in 1 of the 4 animals with simultaneous M1

452   and cerebellum recordings. Hence, the cerebellar LFP activity from that animal was excluded

453   from analysis. A fifth animal with only cerebellum implants was included in the cohort. LFP power

454   was calculated on a trial-by-trial basis and then averaged across channels and animals, with

455   wavelet decomposition using the EEGLAB[70] function 'newtimef'. To characterize coordination of

456   activity across regions, we measured changes in movement-related spectral coherence between

457   LFP channels in M1 and cerebellum. For learning comparisons, coherence was measured for the

458   same channels on early and late days, and specifically for channels with an increase in power of

459   0.5 baseline-normalized unit from early to late days. Strong coherence in a specific frequency

460   band indicates a constant phase relationship in that frequency between two signals and is

461   theorized to indicate increased communication between regions[3,71,72]. M1-cerebellum LFP

462   coherence was calculated for each pair of channels using the EEGLAB function 'newcrossf' with

463   0.1s windows moving by 0.01s.

464

465   To determine whether the emergence of coordinated low-frequency activity during training was

466   attributable solely to faster movements, we compared LFP power and coherence between 'fast'

467   trials (trials with a movement duration less than 300 ms) on day 1 and 2 versus day 4 and 5.

468

469   In several instances, we filtered the LFP signals to isolate and display the low-frequency (1–4 Hz)

470   component of the signal (**Figs. 2** and **3**). Filtering was performed using the EEGLAB function

471   'eegfilt'[70]. In addition to display purposes, we also used filtered LFP to characterize the phase-

472   locking of spiking activity specifically to low-frequency LFP signals. For this we used the Hilbert

473   transform linear operator (MATLAB) to extract the phase information from low- frequency filtered

474   LFP signals (**Fig. 3**).

475

476   To quantify phase-locking of LFP signals to specific sub-movements (movement onset, pellet

477   contact and retract onset), we calculated the ITC of LFP signals across trials time-locked to these

478   sub-movements (**Fig. 2d**). ITC was measured and compared for the same channels on early and

479   late days across all channels (except those removed due to noise). ITC was computed using the

480   EEGLAB function 'newtimef'[70].

481

482   ***Spiking analyses***

483   Spike data was sorted offline after local median subtraction. The threshold for spiking activity was

484   set offline using the automated spike detection of Spyking Circus, and waveforms and timestamps

485   were stored for any event that crossed that threshold. Sorting was performed using a principal

486   component analysis (PCA)-based method followed by manual inspection and sorting. Clearly

487   identified units were selected for this analysis. All units were analyzed and not sorted into cell

488   type based on waveform shape. However, activity that was unambiguously multi-unit was

489   removed. Behavior-related timestamps (trial onset and trial completion) were sent to the RZ2

490   analog input channel using an Arduino digital board and synchronized to neural data.

491

492   ***Unit modulation and spike-LFP phase analysis***

493   Spikes were binned at 25 ms and time locked to behavioral markers. For visualization purposes,

494   the peri-event time histogram (PETH) was estimated by the MATLAB 'fit' function using smoothing

495   spines. To determine if a unit was significantly modulated during movement, a baseline firing rate

496   mean and standard deviation was taken within the period –4s to –2s from reach onset. If the mean

497   firing rate in the period from –350ms to –850ms relative to reach onset differed from the baseline

498   mean by more than 1.25 baseline standard deviations the unit was categorized as a reach-

499   modulated unit.

500

501   To characterize low-frequency spiking activity, we generated histograms of the LFP phases at

502   which each spike occurred for a single unit to a single LFP channel filtered in the 1–4 Hz band in

503   a 1-s window around movement (–250 ms before to 750 ms after movement onset) across all

504   trials of a session (**Fig. 3**). For learning comparisons, all units were compared to the same

505   selected M1 and DLS LFP channel on day 1 and 5. These histograms were generated for each

506   unit–LFP channel pair both within and across regions. For every pair, we then calculated the

507   Rayleigh's z-statistic for circular non-uniformity. These z-statistics were then used to calculate the

508   percentage of significantly non-uniform distributions across unit–LFP pairs with a significance

509   threshold of $P = 0.05$ (**Fig. 3**). A significantly nonuniform distribution signifies phase preference

510   for spikes of a unit to an LFP signal. This process was also performed to compare the successful

511   and unsuccessful trials of day 5 (**Fig. 3C**).

512

513   ***Single trial to template correlation***

514   Spikes from –4s to 4 s around pellet touch were binned at 20 ms, smoothed with a Gaussian

515   kernel with a standard deviation of 60 ms and then z-scored. Binned, smoothed and standardized

516   spike counts within the period of –1s to 1.25s for all units of a single trial were then concatenated

517   into one long vector. The correlation (measured using Pearson's r) between each concatenated

518   single trial neural activity and the mean template (mean of all successful trials) was computed

519   and the mean correlation for each session was reported (**Fig. 4**).

520

521   ***GPFA neural trajectory analyses***

522   To characterize single-trial representations of population spiking activity we used GPFA[3,51] to find

523   low-dimensional neural trajectories, which consisted of the first two factors, for each trial. GPFA

524   analyses were carried out using the MATLAB based graphical user interface DataHigh (version

525   1.2)[73], 10 ms time bins and a dimensionality of 5. We determined the magnitude of deviation for

526   each individual trial trajectory from the mean trajectory across all successful trials by taking the

527   absolute value of the difference between the trajectory of each trial and the mean trajectory across

528   all trials (**Fig. 5B, C**; computed in each dimension independently). This was performed specifically

529   for the period between 250 ms before movement onset and until 250 ms after retract onset. Since

530 this duration varied across trials, we interpolated each trial such that every epoch (reach onset to

531 touch and touch to retract onset) of each trial was the same length and then calculated the

532 average deviation.

533

534

535 **Immunohistochemistry**

536 After all experiments, rats were anesthetized and transcardially perfused with 1% phosphate-

537 buffered saline, followed by phosphate-buffered 4% formaldehyde (PFA). The harvested brains

538 were post-fixed for 72 h in PFA and immersed in 30% sucrose. For immunofluorescence staining

539 (**Fig. 2A**), sagittal cerebellar tissue cryostat sections (40 μm) were washed 3x in 1x Tris Buffered

540 Saline (TBS), followed by antigen retrieval with 0.1N hydrochloric acid (HCl). After 3 more washes

541 in 1xTBS, sections were blocked with 5% Normal Donkey Serum (NDS) in 0.1% TBS-T(Triton)

542 for 1 hour. Sections were then incubated in primary antibodies for astrocytes and microglia

543 overnight. The next day sections were washed 3 times in 1xTBS and then incubated with

544 fluorescent secondary antibodies for 2 hours. Sections were then washed 3 times in 1xTBS and

545 incubated with 300nM DAPI in 1xTBS for 7 min, before coverslipping with mounting media

546 (ProLongTM Glass Antifade Mountant, ThermoFisher cat# P36980). Primary antibodies used are

547 1:1000 Rat-anti-GFAP(ThermoFisher cat #13-0300) and 1:1000 Rabbit-anti-IBA1(Wako cat

548 #019-19741). Secondary antibodies used are 1:250 Alexa FluorTM 647 Donkey-anti Rat (Jackson

549 cat# 712-605-153) and 1:1000 Alexa FluorTM 488 Donkey-anti Rabbit 488(ThermoFisher cat #

550 A-21206). Fluorescent sections were imaged with a BZ-X700 Keyence microscope.

551

552

553 **Statistical analysis**

554 The linear mixed-effects model (implemented using MATLAB 'fitlme') was used in this study.

555 Using these models accounts for the fact that units, channels or trials from the same animal are

556   more correlated than those from different animals; thus, it is more stringent than computing

557   statistical significance over all units, channels or trials[3,74]. We fitted random intercepts for each rat

558   and reported the p values for the regression coefficients associated with successful or

559   unsuccessful outcome, early (that constituted days 1 and 2) or late (that constituted days 4 and

560   5) learning, or training session. Linear mixed effects models was used for testing significance in

561   **Figs 1D,E; 2C-E; 4B,D**; and **5C**. Two-sample Kolmogorov–Smirnov tests were used to test

562   whether spike-LFP phase-locking values on days 1 and 5 came from the same distribution (**Fig.**

563   **3C**). All statistical analyses were implemented within MATLAB. We fitted random intercepts for

564   each rat and reported the p values for the regression coefficients associated with successful or

565   unsuccessful outcome, early or late learning, or training session.

Author Contributions

P.J.F. and T.G. designed the study. P.J.F., A.A., A.W.F. and N.P.D. carried out the electrophysiology experiments. A.A., A.W.F., N.P.D. and T.G. performed the surgical procedures. P.J.F. carried out the analysis. A.A., A.W.F., N.P.D., R.S. and P.R.R. provided resources and assisted with analysis. A.W.F., N.P.D., R.S. and P.R.R. carried out histology. P.J.F. and T.G. wrote the manuscript. A.A. and A.W.F. edited the manuscript.
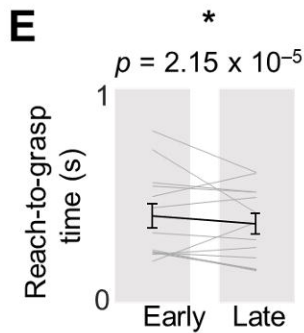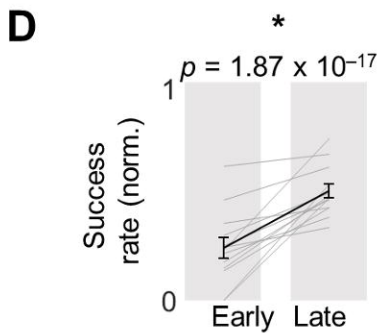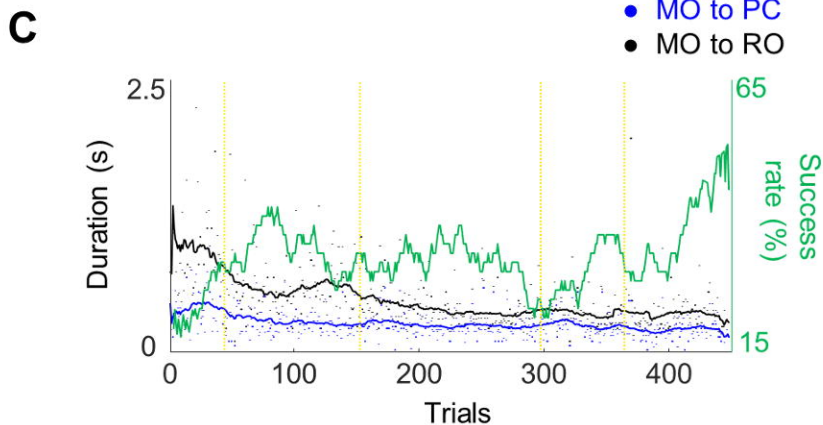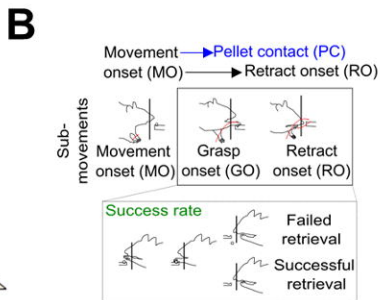
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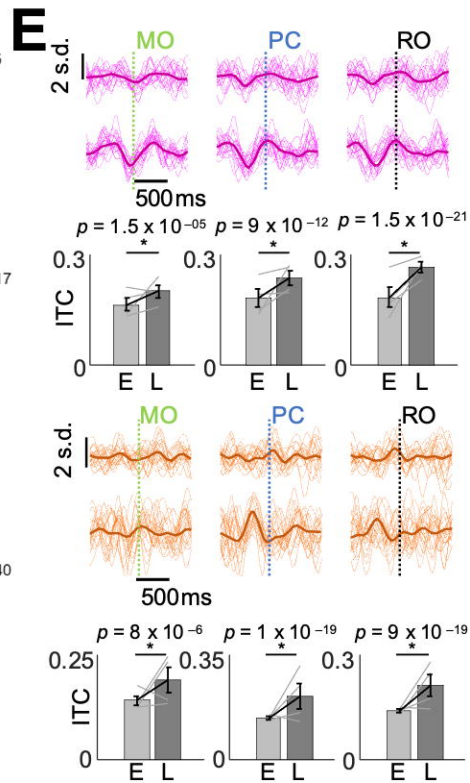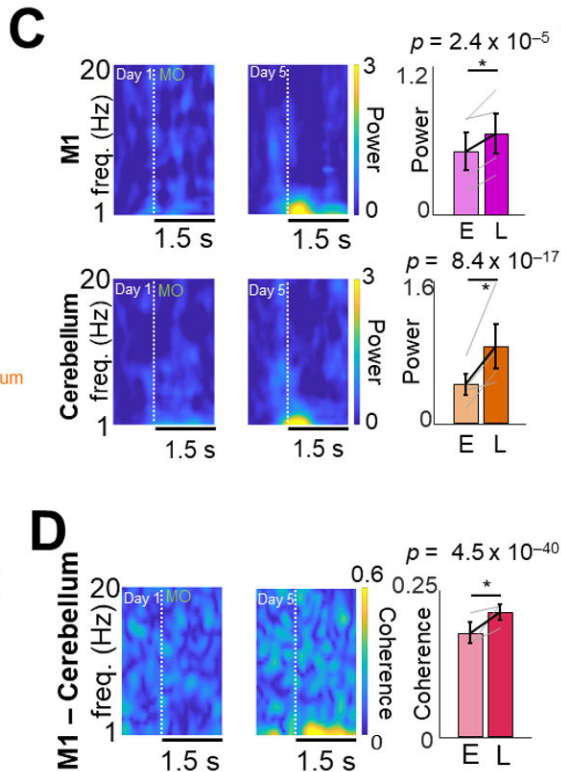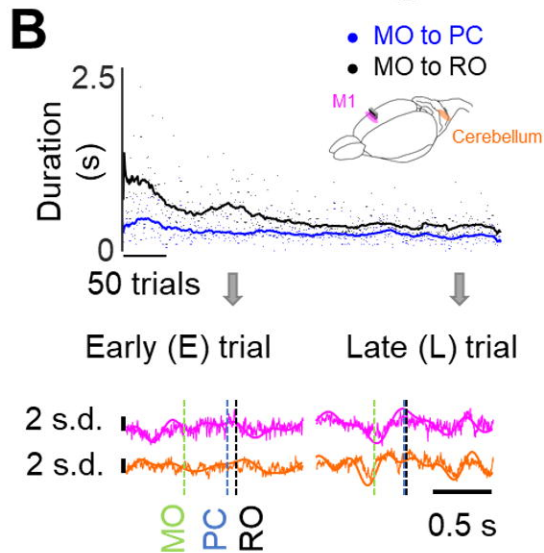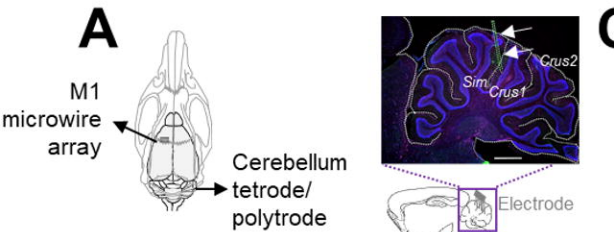
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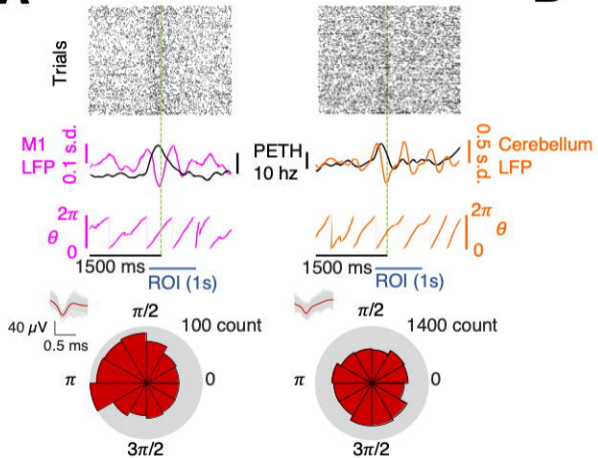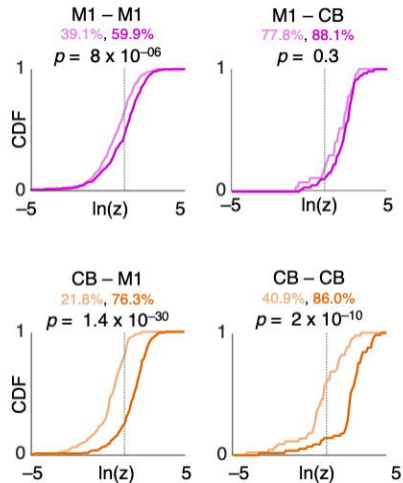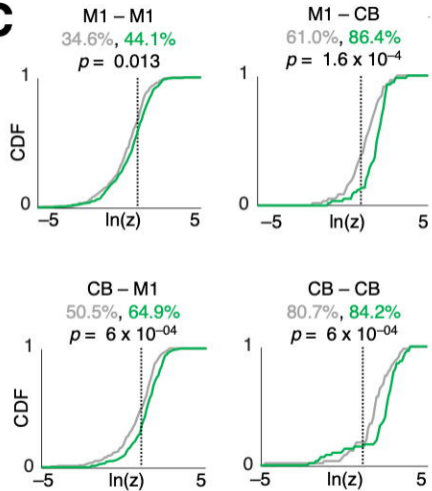
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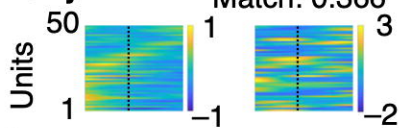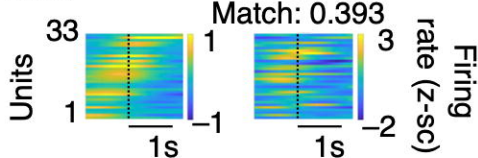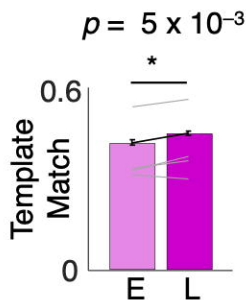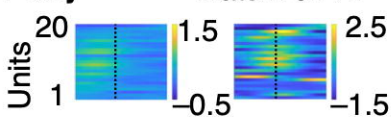
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753

A

B

Movement onset (MO) →(blue)▶ Pellet contact (PC)
Movement onset (MO) ——→▶ Retract onset (RO)

Sub-movements

Movement onset (MO) | Grasp onset (GO) | Retract onset (RO)

Success rate

Failed retrieval

Successful retrieval

C

● MO to PC
● MO to RO

D

*
$p = 1.87 \times 10^{-17}$

E

*
$p = 2.15 \times 10^{-5}$

A

M1 microwire array

Cerebellum tetrode/polytrode

Crus2
Sim
Crus1

Electrode

B

Duration (s)

• MO to PC
• MO to RO

M1

Cerebellum

50 trials

Early (E) trial   Late (L) trial

2 s.d.

2 s.d.

MO   PC   RO   0.5 s

C

M1

Day 1: MO   Day 5

freq. (Hz)

1.5 s   1.5 s

Power

p = 2.4 × 10⁻⁵

Power

E   L

Cerebellum

Day 1: MO   Day 5

freq. (Hz)

1.5 s   1.5 s

Power

p = 8.4 × 10⁻¹⁷

Power

E   L

D

M1 – Cerebellum

Day 1: MO   Day 5

freq. (Hz)

1.5 s   1.5 s

Coherence

p = 4.5 × 10⁻⁴⁰

Coherence

E   L

E

MO   PC   RO

2 s.d.

500ms

p = 1.5 × 10⁻⁰⁵   *p* = 9 × 10⁻¹²   *p* = 1.5 × 10⁻²¹

ITC   ITC   ITC

E   L   E   L   E   L

MO   PC   RO

2 s.d.

500ms

p = 8 × 10⁻⁶   *p* = 1 × 10⁻¹⁹   *p* = 9 × 10⁻¹⁹

ITC   ITC   ITC

E   L   E   L   E   L

A M1 units

Early — Match: 0.366

Units 50 → 1

1s

Late — Match: 0.393

Units 33 → 1

1s

Firing rate (z-sc)

B

$p = 5 \times 10^{-3}$

Template Match

0.6

0

E   L

C Cerebellum units

Early — Match: 0.221

Units 20 → 1

1s

Late — Match: 0.342

Units 16 → 1

1s

Firing rate (z-sc)

D

$p = 8 \times 10^{-8}$

Template Match

0.6

0

E   L

A

M1 neural trajectory

Factor

Time

Cerebellum neural trajectory

Movement onset — Grasp — Retract onset

250 ms | 250 ms

B

Suc.

Unsuc.

Suc.

Unsuc.

Successful "template"

C

Neural trajectory correlation

M1 Early
$P = 8.5 \times 10^{-12}$

0.6

-0.1

Suc. | Unsuc.

M1 Late
$P = 1.1 \times 10^{-08}$

0.6

-0.1

Suc. | Unsuc.

Cerebellum Early
$P = 0.022$

0.4

0

Suc. | Unsuc.

Cerebellum Late
$P = 6.6 \times 10^{-03}$

0.4

0

Suc. | Unsuc.