

1 Consolidation alters motor 2 sequence-specific distributed 3 representations.

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12 **Abstract** FMRI studies investigating the acquisition of sequential motor skills in humans have revealed learning-related functional reorganizations of the cortico-striatal and cortico-cerebellar motor systems in link with the hippocampus. Yet, the functional significance of these activity level changes is not fully understood as they convey the evolution of both sequence-specific knowledge and unspecific task expertise. Moreover, these changes do not specifically assess the occurrence of learning-related plasticity. To address these issues, we investigated local circuits tuning to sequence-specific information using multivariate distances between patterns evoked by consolidated or newly acquired motor sequences production. Results reveal that representations in dorsolateral striatum, prefrontal and secondary motor cortices are greater when executing consolidated sequences than untrained ones. By contrast, sequence representations in the hippocampus and dorsomedial striatum are less engaged. Our findings show, for the first time in humans, that complementary sequence-specific motor representations evolve distinctively during critical phases of skill acquisition and consolidation.

28 Introduction

29 Animals and humans are able to acquire and automatize new sequences of movements, hence allowing them to expand and update their repertoire of complex goal-oriented motor actions for long-term use. To investigate the mechanisms underlying this type of procedural memory in humans, a large body of behavioral studies has used motor sequence learning (MSL) tasks designed to test the ability to perform temporally ordered and coordinated movements, learned either implicitly or explicitly and has assessed their

36 performances in different phases of the acquisition process (Korman et al. 2003; Abra-
37 hamse et al. 2013; Diedrichsen and Kornysheva 2015; Verwey et al. 2015). While practice
38 of an explicit MSL task leads to substantial within-session execution improvements, there
39 is now ample evidence indicating that between-session maintenance, and even increases,
40 in performance can be observed after a night of sleep (Nettersheim et al. 2015; Landry et
41 al. 2016), while performance are unstable and tends to decay during an equal period of
42 wake (Doyon et al. 2009b; Brawn et al. 2010; Nettersheim et al. 2015; Landry et al. 2016).
43 Therefore, it is thought that sleep favors reprocessing of the motor memory trace, thus
44 promoting its consolidation for long-term skill proficiency (Fischer et al. 2002; see King et
45 al. 2017; Doyon et al. 2018 for recent in-depth reviews).

46 Functional magnetic resonance imaging (fMRI) studies using General-Linear-Model (GLM)
47 contrasts of activation have also revealed that MSL is associated with the recruitment of an
48 extended network of cerebral (Hardwick et al. 2013), cerebellar and spinal regions (Vahdat
49 et al. 2015), whose contributions differentiate as learning progresses (Karni et al. 1998;
50 Dayan and Cohen 2011; Doyon et al. 2018). In fact, critical plastic changes (Ungerleider et
51 al. 2002; Doyon and Benali 2005) are known to occur within the initial training session,
52 as well as during the offline consolidation phase, the latter being characterized by a
53 functional “reorganization” of the nervous system structures supporting this type of
54 procedural memory function (Rasch and Born 2008; Born and Wilhelm 2012; Albouy et al.
55 2013b; Bassett et al. 2015; Dudai et al. 2015; Fogel et al. 2017; Vahdat et al. 2017). More
56 specifically, MSL practice is known to activate a cortical, associative striatal and cerebellar
57 motor network which is assisted by the hippocampus during the initial “fast-learning”
58 phase (Albouy et al. 2013b). Yet, when approaching asymptotic behavioral performance
59 after longer practice, activity within the hippocampus and cerebellum decreases while
60 activity within the sensorimotor striatum increases (Doyon et al. 2002), both effects
61 conveying the transition to the “slow-learning” phase. The same striatal regions are
62 reactivated during sleep spindles (Fogel et al. 2017) contributing to the progressive
63 emergence of a reorganized network (Debas et al. 2010; Vahdat et al. 2017), which is
64 further stabilized when additional MSL practice extending over multiple days is separated
65 by consolidation periods (Lehéricy et al. 2005).

66 A critical issue typically overlooked by previous MSL neuroimaging research using GLM-
67 based activation contrasts, however, is that learning-related changes in brain activity do
68 reflect the temporal evolution of recruited processes during blocks of practice, only some
69 of which may be specifically related to plasticity induced by MSL. For instance, increases in
70 activity could not only signal a greater implication of the circuits specialized in movement
71 sequential learning *per se*, but could also result from the inherent faster execution of
72 the motor task. Likewise, a decrease in activity could either indicate some form of
73 optimization and greater efficiency of the circuits involved in executing the task (Wu et
74 al. 2004), or could show the reduced recruitment of non-specific networks supporting
75 the acquisition process. Therefore, even with the use of control conditions to dissociate
76 sequence-specific from non-specific processes (Orban et al. 2010), the observed large-
77 scale activation differences associated with different learning phases do not necessarily
78 provide direct evidence of plasticity related to the processing of a motor sequence-specific
79 representation (Berlot et al. 2018). Furthermore, it is also conceivable that these plastic
80 changes could even occur locally without significant changes in the GLM-based regional

81 activity level. Finally, in most studies investigating the neural substrate mediating the
82 consolidation process of explicit MSL, the neural changes associated with this mnemonic
83 mechanism are assessed by contrasting brain activity level of novice participants between
84 their initial training and a delayed practice session. Therefore, they measure not only
85 plasticity for sequence-specific (e.g. optimized chunks), but also task-related expertise
86 (e.g. habituation to experimental apparatus, optimized execution strategies, attentional
87 processes). The latter expertise is notably observed when participants practice two
88 motor sequences in succession and the initial performance during sequence execution is
89 significantly better for the subsequent than for the first sequence.

90 To address these specificity limitations, multivariate pattern analysis (MVPA) has been pro-
91 posed to evaluate how local patterns of activity are able to reliably discriminate between
92 stimuli or evoked memories of the same type over repeated occurrences, hence allowing
93 to test information-based hypotheses that GLM contrasts cannot inquire (Hebart and
94 Baker 2017). In the MSL literature, only a few studies have used such MVPA approaches to
95 identify the regions that specialize in processing the representation of learned motor se-
96 quences (Wiestler et al. 2011; Wiestler and Diedrichsen 2013; Kornysheva and Diedrichsen
97 2014; Nambu et al. 2015; Yokoi et al. 2017). These studies, however, mainly focused on
98 extensively practiced sequences over multiple training sessions across multiple days. For
99 instance, in a recent study covering dorsal cerebral cortices only (Wiestler and Diedrichsen
100 2013), cross-validated classification accuracy was measured separately on activity patterns
101 evoked by the practice of trained and untrained sets of sequences. The authors showed
102 that the extended training increased sequence discriminability in a network spanning
103 bilaterally the primary and secondary motor as well as parietal cortices. In another study
104 (Nambu et al. 2015) that aimed to analyze separately the preparation and execution of se-
105 quential movements, representations of extensively trained sequences were identified in
106 the contralateral dorsal premotor and supplementary motor cortices during preparation,
107 while representations related to the execution were found in the parietal cortex ipsilater-
108 ally, the premotor and motor cortices bilaterally as well as the cerebellum. In both studies,
109 the regions carrying sequence-specific representations overlapped only partly with those
110 identified using GLM-based measures, hence illustrating the fact that coarser differences
111 in activation between novel and trained sequences does not necessarily provide evidence
112 of plasticity for sequential information. However, the classification-based measures they
113 used may have biased their parametric statistical results by violating both the normality
114 assumption and theoretical null-distribution (Allefeld et al. 2015; Combrisson and Jerbi
115 2015; Jamalabadi et al. 2016; Varoquaux 2017) and may have thus been suboptimal in
116 detecting representational changes (Walther et al. 2016).

117 As a part of a larger research program, the present study aimed to address both the
118 critical issues overlooked by previous research investigating the early phases of MSL
119 consolidation with GLM-based approach described above, as well as the limitations
120 encountered when using classifier-based MVPA methods. Specifically, we employed a
121 recently developed MVPA approach (Nili et al. 2014) that is unbiased and more sensitive
122 to continuous representational changes (Walther et al. 2016), such as those that occur
123 in the early stage of MSL and consolidation (Albouy et al. 2013c). Our experimental
124 manipulation allowed to isolate sequence-specific plasticity, by extracting patterns evoked
125 through practice of both consolidated and new sequences at the same level of task

126 expertise and by computing this novel multivariate distance metric using a searchlight
 127 approach over the whole brain in order to cover cortical and subcortical regions critical
 128 to MSL. Based on theoretical models (Albouy et al. 2013b; Doyon et al. 2018) derived
 129 from imaging and invasive animal studies, we hypothesized that offline consolidation
 130 following training would induce greater cortical and striatal as well as weaker hippocampal
 131 sequence-specific representations.

132 Results

133 To investigate changes in the neural representations of motor sequences occurring during
 134 learning, young healthy participants ($n=18$) practiced two 5-element sequences of finger
 135 movements (executed through button presses) separately on two consecutive days. On
 136 the third day, participants were required to execute again the same two sequences, then
 137 considered to be consolidated, together with two new 5-element untrained sequences.
 138 This practice session consisted in 64 pseudo-randomly ordered short blocks split in two
 139 runs, with 16 blocks of each sequence. All four sequences were executed using their
 140 non-dominant left hand while functional MRI data was acquired.

141 Behavioral performance

142 We analyzed the behavioral performance related to the four different sequences using a
 143 repeated-measure mixed-effects model. As expected, new sequences were performed
 144 more slowly ($\beta = .365, SE = 0.047, p < .001$) and less accurately ($\beta = -0.304, SE = 0.101, p <$
 145 $.001$) than the consolidated ones. Significant improvement across blocks was observed
 146 for new sequences as compared to consolidated sequences in term of change of speed
 147 ($\beta = -0.018, SE = 0.002, p < .001$), thus showing an expected learning curve visible in
 148 fig. 1. Yet accuracy did not show significant improvement ($\beta = 0.014, SE = 0.010, p = 0.152$)
 149 likely explained by the limited precision of this measure that ranges discretely from 0 to
 150 5. By contrast, the consolidated sequences did not show significant changes in speed
 151 ($\beta = -0.006, SE = 0.005, p = 0.192$) nor accuracy ($\beta = -0.006, SE = 0.057, p = 0.919$), the
 152 asymptotic performances being already reached through practice and the consolidation
 153 process.

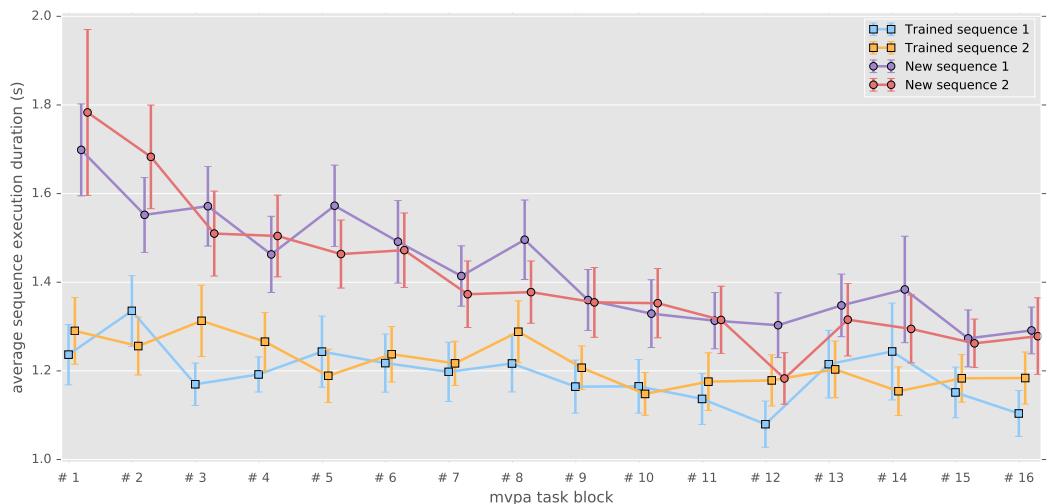


Figure 1. Correct sequence durations (average and standard error of the mean) across the MVPA task blocks.

154 Importantly, there were also no significant differences between the two consolidated se-
 155 quences in term of speed ($\beta = 0.031, SE = 0.026, p = 0.234$) and accuracy ($\beta = -0.030, SE =$
 156 $0.111, p = 0.789$), nor between the two new sequences speeds ($\beta = 0.025, SE = 0.045, p =$
 157 0.577) and accuracies ($\beta = -0.245, SE = 0.138, p = 0.076$).

158 **A common distributed network for sequence representation irre-
 159 spective of learning stage**

160 From the preprocessed functional MRI data we extracted patterns of activity for each
 161 block of practice, and computed a cross-validated Mahalanobis distance (Nili et al. 2014;
 162 Walther et al. 2016) using a Searchlight approach (Kriegeskorte et al. 2006) over brain
 163 cortical surfaces and subcortical regions of interest. Such multivariate distance, when
 164 positive, demonstrate that there is a stable difference in activity patterns between the
 165 conditions compared, and thus reflect the level of discriminability between these condi-
 166 tions. To assess true patterns and not mere global activity differences, we computed this
 167 discriminability measure for sequences that were at the same stage of learning, thus sepa-
 168 rately for consolidated and new sequences. From the individual discriminability maps, we
 169 then measured the prevalence of discriminability at the group level, using non-parametric
 170 testing with a Threshold-Free-Cluster-Enhancement approach (TFCE) (Smith and Nichols
 171 2009) to enable locally adaptive cluster-correction.

172 To extract the brain regions that show discriminative activity patterns for specific sequence
 173 during both learning stages, we then submitted these separate group results for the
 174 consolidated and new sequences to a minimum-statistic conjunction. A large distributed
 175 network (fig. 2) displayed significant discriminability, including the primary visual, as well
 176 as the posterior parietal, primary and supplementary motor, premotor and dorsolateral
 177 prefrontal cortices.(see the statistical maps for each learning stage separately in the
 178 Supplementary material (fig. S1,fig. S2).

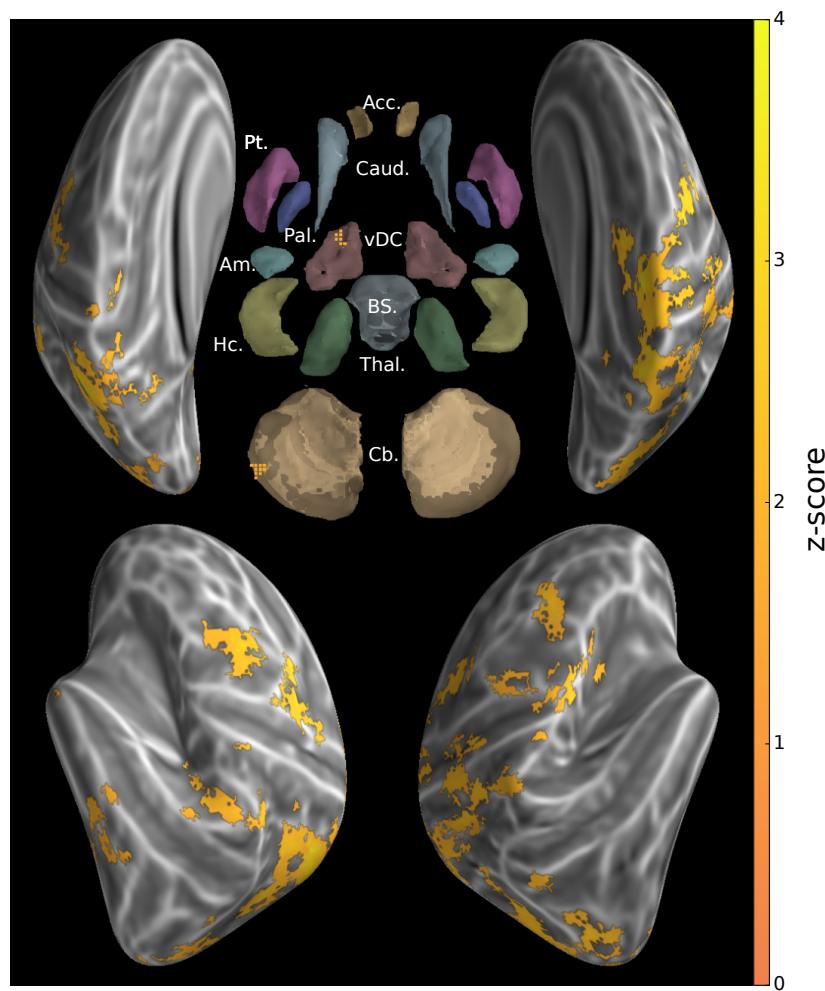


Figure 2. Group searchlight conjunction of new and consolidated sequences discriminability maps (z-score thresholded at $p < .05$ TFCE-cluster-corrected) showing a large distributed cortical network showing sequence discriminative patterns at both learning stages; Regions of interest with Freesurfer colors: Acc.:Accumbens; Pt.:Putamen; Caud.:Caudate; Pal.:Pallidum; vDC:ventral Diencephalon; Am.:Amygdala; Hc.:Hippocampus; Thal.:Thalamus; Cb.:Cerebellum; BS:brain-stem

179 **Reorganization of the distributed sequence representation after**
 180 **memory consolidation**

181 In order to evaluate the reorganization of sequence representation undergone by con-
 182 solidation at the group level, the consolidated and new sequence discriminability maps
 183 from all participants were submitted to a non-parametric pairwise t-test with TFCE. To
 184 ascertain that a greater discriminability in one stage versus the other was supported by a
 185 significant level of discriminability within that stage, we then calculated the conjunction of
 186 the contrast maps with the consolidated and new sequences group results, respectively
 187 with the positive and negative contrast differences (fig. 3).

188 Discriminability between the consolidated sequences was significantly higher than that
 189 between the new sequences in bilateral sensorimotor putamen, thalamus and anterior

190 insula, as well as in the ipsilateral cerebellar lobule IX, posterior cingulate and parietal
 191 cortices, and contralaterally in the lateral and dorsal premotor, supplementary motor,
 192 frontopolar and dorsolateral prefrontal cortices in addition to cerebellar Crus I. By con-
 193 trast, the pattern dissimilarity was higher for the new sequences in bilateral hippocampi
 194 as well as the body of the caudate nuclei, subthalamic nuclei, and cerebellar Crus II
 195 ipsilaterally. Although striatal activity patterns differentiating newly acquired sequences
 196 were found in contralateral putamen (fig. S1), this discriminability was significantly larger
 197 for consolidated sequences in sensorimotor regions of the putamen bilaterally.

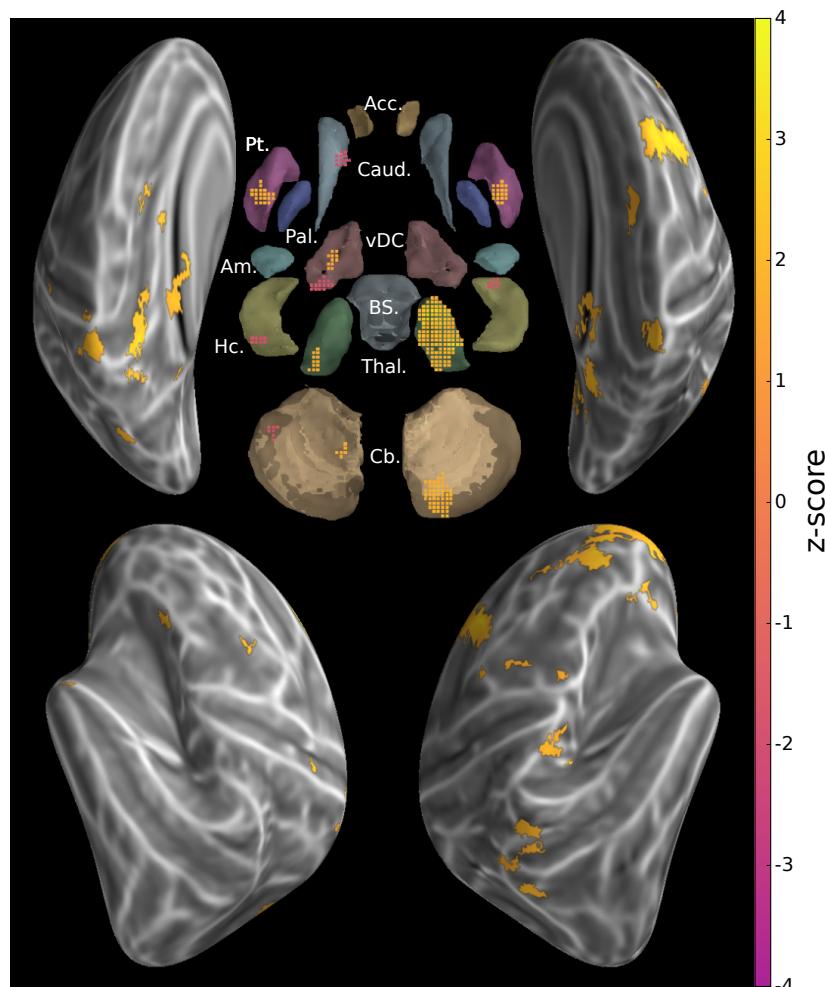


Figure 3. Conjunction of group searchlight contrast (paired t-test) between consolidated and new sequences discriminability maps and separate group discriminability maps for new and consolidated sequences (z-score thresholded at $p < .05$ TFCE-cluster-corrected) showing a reorganization of the distributed memory trace between these two stages; Acc.: Accumbens; Pt.:Putamen; Caud.:Caudate; Pal.:Pallidum; vDC:ventral Diencephalon; Am.:Amygdala; Hc.:Hippocampus; Thal.:Thalamus; Cb.:Cerebellum; BS:brain-stem

198 Discussion

199 In the present study, we aimed to identify the brain networks whose activity patterns
 200 differentiate between representations of multiple motor sequences during their exe-
 201 cution in different phases of learning (newly learned vs consolidated). Using an MVPA
 202 approach, we considered that stable local patterns of activity could be used as proxy for
 203 the specialization of neuronal circuits supportive of the efficient retrieval and expression
 204 of sequential motor memory traces. To investigate the differential pattern strength, we
 205 computed novel unbiased multivariate distance and applied robust permutation-based
 206 statistics with adaptive cluster correction.

207 **A distributed network for the representation of finger motor se-
 208 quence**

209 Our results provide evidence for an extended network of brain regions that shows re-
 210 liable discrimination of sequence-specific activity patterns for both the consolidated
 211 and novel sequences. At the cortical level, we found a network encompassing the sup-
 212 plementary motor and premotor areas as well as posterior parietal cortices bilaterally
 213 and contralateral somatosensory motor cortex. These findings are consistent with ear-
 214 lier MVPA investigations (Wiestler and Diedrichsen 2013; Nambu et al. 2015). Indeed,
 215 similar discriminative power of motor sequence representations within the ipsilateral
 216 premotor and parietal cortices has previously been described (Wiestler and Diedrichsen
 217 2013; Waters-Metenier et al. 2014; Waters et al. 2017), notably when the non-dominant
 218 hand is used for fine dexterous manual skills. Interestingly, we also found significant
 219 neural representations for both learning stages in the contralateral primary motor and
 220 somatosensory (M1/S1) cortices, more specifically around the hand knob area (Yousry
 221 et al. 1997) for which finger somatotopy is measurable using fMRI (Ejaz et al. 2015). The
 222 latter results suggest that these primary cortical regions play a critical role in building
 223 experience-related motor sequence memory traces. Yet such an interpretation must be
 224 taken with caution, as it has recently been reported that the capacity to discriminate
 225 between sequences based upon signals from these regions could simply be due to the
 226 stronger activity evoked by the first finger press in the sequence, and not to activity from
 227 the whole finger sequence (Yokoi et al. 2017). Yet although conjectural, we do not believe
 228 that such an effect can explain our pattern of results because, while the newly learned
 229 sequences began with different fingers, both consolidated sequences were discriminated
 230 despite the fact that the first finger presses were the same. Finally, while being located
 231 around the hand knob, the spatial extent of the M1/S1 representation in our study was
 232 smaller compared to that found by Wiestler and Diedrichsen (2013). This may be due,
 233 however, to differences in our design, notably in the uninterrupted repetition of the motor
 234 sequence during practice, and in the fact that none of our sequences engaged the thumb,
 235 which has a more distinctive M1/S1 cortical representation than the individual fingers
 236 (Ejaz et al. 2015).

237 The conjunction of new and consolidated sequences discriminability maps further re-
 238 vealed that a common cortical processing network, including non-motor primary and
 239 associative regions, carries sequential information across learning stages, that can orig-
 240 inate from visually presented instruction and short-term-memory to motor sequence

241 production. Herein, the visual occipital cortices, likely reflecting processing of the visual
 242 stimuli as low-level visual mapping of shapes (Miyawaki et al. 2008; Pilgramm et al. 2016),
 243 as well as the ventro-temporal regions, known to support higher level Arabic number
 244 representation (Shum et al. 2013; Peters et al. 2015) were found to discriminate between
 245 sequences in both stages of learning (fig. 2). The dorsolateral prefrontal cortex (DLPFC),
 246 which also exhibited pattern discriminability, was suggested previously to process the
 247 sequence spatial information in working memory, preceding motor command (Robertson
 248 et al. 2001). In fact, we believe that the cognitive processing required in our task, implying
 249 notably to switch between sequences, to maintain them in working memory and to inhibit
 250 competing ones, could have magnified this frontal associative representation in our study.

251 In sum, the regions found to carry sequence information regardless of the learning phase
 252 in the present study show some overlap with the network known to be implicated in MSL,
 253 such as primary and secondary motor cortices, as typically revealed in activation-based
 254 studies (Doyon et al. 2009b; Dayan and Cohen 2011; Hardwick et al. 2013). However,
 255 we also found significant representations in the occipital, temporal and insular cortices.
 256 This discrepancy can be attributable to the shift from an activation-based inference to
 257 one based on the presence of sequential information in activity patterns, but also by the
 258 recruitment of additional regions for the processing of this information in stimuli and its
 259 maintenance in working memory required by the task.

260 **Cortico-subcortical representational reorganization underlying 261 memory consolidation following MSL**

262 By contrasting the maps of multivariate distances for consolidated and newly acquired
 263 sequences, we identified the networks that reveal increased versus decreased discrim-
 264 inability of sequential representations in the early stages of the MSL consolidation (fig. 3).

265 At the cortical level, we found that the contralateral premotor and bilateral parietal regions
 266 showed a stronger representation for consolidated sequences. This pattern likely reflects
 267 that the tuning of these neural populations to coordinated movements is consolidated
 268 early after learning (Pilgramm et al. 2016; Makino et al. 2017; Yokoi et al. 2017), as
 269 was previously observed when contrasting sequence that underwent a longer training
 270 to new ones (Wiestler and Diedrichsen 2013). Importantly, no significant changes in
 271 representational magnitude were found in the contralateral primary somatosensory
 272 cortex after consolidation. This is in line with the fact that M1 representational geometry
 273 has been shown to be strongly shaped by ecological finger co-activations (Ejaz et al.
 274 2015), and to be resistant to extensive training of a sequence built on a new co-activation
 275 structure (Beukema et al. 2018). While the role of the motor cortex in MSL is undeniable,
 276 its plasticity in consolidation is still debated (Omrani et al. 2017). In fact, recent results
 277 revealed that after a M1 insult or even rapidly after M1 inactivation, a trained motor skill
 278 can still be expressed (Kawai et al. 2015; Bollu et al. 2018) arguing for its complementary,
 279 redundant and partially independent representation in subcortical regions.

280 Interestingly, significant differences at the subcortical level were found in bilateral puta-
 281 men and more specifically in their sensorimotor regions. This is consistent with findings
 282 from activation studies that reported increased functional activity after consolidation in

283 this structure (Debas et al. 2010, 2014; Albouy et al. 2013b; Fogel et al. 2017; Vahdat et
284 al. 2017). Significant representational changes were also found in the bilateral thalamus,
285 and could reflect the relay of information between the cortex and cerebellum, striatum or
286 spinal regions (Doyon et al. 2009a; Haber and Calzavara 2009). Finally, representation
287 changes were detected in the cerebellum, including ipsilateral Lobule IX, shown to corre-
288 late with sequential skill performance (Orban et al. 2010; Tomassini et al. 2011) as well as
289 contralateral Crus II which connectivity with prefrontal cortex is thought to support motor
290 functions (Ramnani 2006). However, no significant difference was observed in Lobule V of
291 the cerebellum that is known to carry finger somatotopic representations (Wiestler et al.
292 2011) and to show global activation during practice (Doyon et al. 2002).

293 Concurrently with the representational increase in the above-mentioned network, we
294 found only a few disparate regions that showed decreased sequence discrimination,
295 namely the caudate nuclei, subthalamic nuclei and cerebellar Crus II ipsilaterally as
296 well as bilateral hippocampi. Hippocampal activation in early learning has formerly
297 been hypothesized to support the temporary storage of novel explicitly acquired motor
298 sequence knowledge and to contribute to the reactivations of the distributed network
299 during offline periods and sleep in particular. Yet such contribution of the hippocampus
300 has been shown to be progressively disengaging afterward (Albouy et al. 2013b), and
301 thus our results are consistent with the idea of the hippocampus playing a transient
302 supportive role in early MSL, notably in encoding sequential information (Davachi and
303 DuBrow 2015). Our findings of a differential implication of dorsomedial and dorsolateral
304 striatum in sequence representation during learning and expression of a mastered skill
305 specifies the changes in activity in these regions in the course of MSL described by earlier
306 studies (Lehéricy et al. 2005; François-Brosseau et al. 2009; Jankowski et al. 2009; Reithler
307 et al. 2010; Corbit et al. 2017; Fogel et al. 2017; Kupferschmidt et al. 2017). Indeed,
308 our results uncover that this shift in activity purports a genuine reorganization of circuits
309 processing sequence-specific information, similar to what was reported at the neuronal
310 level in animals (Miyachi et al. 2002; Costa et al. 2004; Yin et al. 2009).

311 While our results show that the topology of the network representing motor sequential
312 information differs between consolidated and newly acquired memory traces, the present
313 study was not designed to investigate the information-content of hippocampal, striatal or
314 cerebellar sequence representations. These were previously assessed at cortical level for
315 finger sequences (Kornysheva and Diedrichsen 2014; Wiestler et al. 2014) as well as for
316 larger forearm movements (Haar et al. 2017). However, the hypothesized extrinsic and
317 intrinsic skill encoding in the respective hippocampal and striatal systems (Albouy et al.
318 2013a) remains to be assessed with a dedicated experimental design similar to that used
319 by Wiestler et al. (2014) to investigate such representations at the cortical level.

320 Importantly, our study investigated the change in neural substrates of sequence repre-
321 sentation after limited training and following sleep-dependent consolidation. This is in
322 contrast to previous investigations that studied sequences trained intensively for multiple
323 days (Nambu et al. 2015) and compared their discriminability to that of newly acquired
324 ones (Wiestler and Diedrichsen 2013). Therefore, in our study, the engagement of these
325 representations for expressing the sequential skill may further evolve, strengthen or
326 decline locally with either additional training or offline memory reprocessing supported
327 in part by sleep.

328 Methodological considerations

329 To limit the level of difficulty and the duration of the task, only four sequences were
 330 performed by participants, two consolidated and two newly acquired. This low number
 331 of sequence per condition could be a factor limiting the power of our analysis, as only
 332 a single multivariate distance is assessed for each of these conditions. Moreover, ini-
 333 tial training sessions of the consolidated sequences were each comprised of a single
 334 sequence performed in blocks longer than in the present task, designed for multivari-
 335 ate investigation. The current task, by requiring additional cognitive resources (such as
 336 instruction processing, retention in working memory, switching and inhibition of other se-
 337 quences), could have triggered some novel learning for the consolidated sequences. This
 338 seems unlikely however, as this was not reflected in performance changes throughout
 339 the task. The switching component could partly explain the pattern of results found here,
 340 as shifting between overlapping sets of motor commands has been shown to further
 341 implicate the dorsal striatum in collaboration with the prefrontal cortex (Monchi et al.
 342 2006).

343 Another potential limitation relates to the fact that the present representational analysis
 344 disregarded the behavioral performance. Nevertheless, the chained non-linear relations
 345 between behavior, neural activity and BOLD signal were recently established to have
 346 limited influence on the representational geometry extracted from Mahalanobis cross-
 347 validated distance in primary cortex, sampled across a wide range of speed of repeated
 348 finger-presses and visual stimulation (Arbuckle et al. 2018). Therefore, despite behavioral
 349 variability and potential ongoing evolution of the memory trace, we assumed that the
 350 previously encoded motor sequence engrams were nevertheless retrieved during this
 351 task as supported by the significant differences in activity pattern discriminability and the
 352 persistent behavioral advantage observed for the consolidated sequences.

353 Finally, our results also entail that it is possible to investigate learning-related representa-
 354 tional changes in a shorter time-frame and with less extended training than what was
 355 investigated before (Wiestler and Diedrichsen 2013; Nambu et al. 2015), including in
 356 subcortical regions where neuronal organization differs from that of the cortex. The
 357 use of a novel multivariate distance could have contributed to obtain these results by
 358 achieving increased sensitivity and statistical robustness (Walther et al. 2016).

359 Conclusion

360 Our study shows that the consolidation of sequential motor knowledge is supported
 361 by the reorganization of newly acquired representations within a distributed cerebral
 362 network. We uncover that following learning, local activity patterns tuned to represent
 363 sequential knowledge are enhanced not only in extended cortical areas, similarly to those
 364 shown after longer training (Wiestler and Diedrichsen 2013), but also in dorsolateral stria-
 365 tum, thalamus and cerebellar regions. Conversely, a smaller network showed a decrease
 366 of sequence specific patterned activation after consolidation, occurring specifically in
 367 dorsomedial striatum that supports cognitive processing during early-learning (Doyon et
 368 al. 2018) as well as in the hippocampus which carries explicit encoding of motor sequen-
 369 tial extrinsic representation (Albouy et al. 2013b; King et al. 2017) and play a significant

370 role in the offline reprocessing. Despite discrepancies with GLM-based activity changes
 371 observed previously, the results of our novel representational approach corroborate their
 372 interpretations that the differential plasticity changes in the latter regions subtend MSL
 373 consolidation (Albouy et al. 2015). Importantly, these results reveal for the first time in
 374 humans that such changes are determined by the local implementation of distributed
 375 neural coding of sequential information. Yet such consolidation-related representational
 376 changes need to be further investigated through exploration of the dynamic mechanism
 377 mediating this sleep-dependent mnemonic process, which is known to reorganize pro-
 378 gressively the cerebral network by repeatedly reactivating the memory trace (Fogel et al.
 379 2017; Vahdat et al. 2017; Boutin et al. 2018).

380 Materials and methods

381 Participants

382 Right-handed young ($n = 34, 25 \pm 6.2$ yr.) healthy individuals (19 females), recruited by
 383 advertising on academic and public website, participated in the study. Participants were
 384 excluded if they had a history of neurological psychological or psychiatric disorders,
 385 scored 4 and above on the short version of Beck Depression Scale (Beck et al. 1961), had
 386 a BMI greater than 27, smoked, had an extreme chronotype, were night-workers, had
 387 traveled across meridians during the three previous months, or were trained as musician
 388 or professional typist for more than a year. Their sleep quality was subjectively assessed,
 389 and individuals with score to the Pittsburgh Sleep Quality Index questionnaire (Buysse et
 390 al. 1989) greater or equal to 5, or daytime sleepiness Epworth Sleepiness Scale (Johns
 391 1991) score greater than 9, were excluded.

392 Participants included in the study were also instructed to abstain from caffeine, alcohol
 393 and nicotine, to maintain a regular sleep schedule (bed-time 10PM-1AM, wake-time 7AM-
 394 10AM) and avoid taking daytime nap for the duration of the experiment. In a separate
 395 screening session, EEG activity was also recorded while participants slept at night in a
 396 mock MRI scanner and gradients sounds were played to both screen for potential sleep
 397 disorders and test their ability to sleep in the experimental environment; 18 participants
 398 were excluded for not meeting the criterion of a minimum of 20min. in NREM2 sleep.
 399 After this last inclusion step, their sleep schedule was assessed by analyzing the data
 400 obtained from an actigraph (Actiwatch 2, Philips Respironics, Andover, MA, USA) worn on
 401 the wrist of the non-dominant hand for the week preceding as well as during the three
 402 days of experiment, hence certifying that all participants complied to the instructions.

403 Among the 34 participants, one did not show within-session improvement on the task,
 404 two didn't sleep on the first experimental night, three were withdrawn for technical
 405 problems, one did not show up on first experimental session, one presented novel MRI
 406 contraindication. Thus, among the 26 participants that completed the research project, a
 407 group of 18 which, by design, followed the appropriate behavioral intervention for the
 408 present study, were retained for our analysis.

409 All participants provided written informed consent and received financial compensation
 410 for their participation. This study protocol was approved by the Research Ethics Board

411 of the "Comité mixte d'éthique de la recherche - Regroupement en Neuroimagerie du
 412 Québec" (CMER-RNQ).

413 **Procedures and tasks**

414 The present study was conducted over 3 consecutive evenings and is part of an experi-
 415 ment that aimed to investigate the neural substrates mediating the consolidation and
 416 reconsolidation of motor sequence memories during wakefulness and sleep that will be
 417 reported separately. On each day, participants performed the experimental tasks while
 418 their brain activity was recorded using MRI. Their non-dominant hand (left) was placed on
 419 an ergonomic MRI-compatible response pad equipped with 4-keys corresponding to each
 420 of the fingers excluding the thumb.

421 On the first day (D1), participants were trained to perform repeatedly a 5-element se-
 422 quence (TSeq1: 1-4-2-3-1 where 1 indicate the little finger and 4 the index finger). The
 423 motor sequence was performed in blocks separated by rest periods to avoid fatigue.
 424 Apart for a green or a red cross displayed in the center of the screen, respectively in-
 425 structing the participants to execute the sequence or to rest, there were no other visual
 426 stimuli presented during the task. Participants were instructed to execute the sequence
 427 repeatedly, and as fast and accurately as possible, as long as the cross was green. They
 428 were then instructed to rest for the period of 25 sec. as indicated by the red cross. During
 429 each of the 14 practice blocks, participants performed repeatedly 12 motor sequences
 430 (i.e. 60 keypresses per block). In case participants made a mistake during sequence
 431 production, they were instructed to stop their performance and to immediately start
 432 practicing again from the beginning of the sequence until the end of the block. After
 433 completion of the training phase, participants were then administered a short retention
 434 test about 15min later, which consisted of a single block comprising 12 repetitions of
 435 the sequence. Then the participants were scanned with concurrent EEG and fMRI for
 436 approximately two hours while instructed to sleep.

437 On the second day (D2), participants were first evaluated on the TSeq1 (1 block retest) to
 438 test their level of consolidation of the motor sequence, and were then trained on a new
 439 sequence (TSeq2: 1-3-2-4-1) which was again performed for 14 blocks of 12 sequences
 440 each, similarly to TSeq1 training on D1. Again, they were then scanned during sleep while
 441 EEG recordings were simultaneously acquired.

442 Finally, on the third day (D3), participants first performed TSeq1 for 7 blocks followed by 7
 443 blocks of TSeq2, each block including 12 repetitions of the sequence or 60 keypresses.
 444 Following this last testing session, participants were then asked to complete an experi-
 445 mental task (here called MVPA task) specifically designed for the current study, similar
 446 to a previous study that investigated sequence representation by means of multivariate
 447 classification (Wiestler and Diedrichsen 2013). Specifically, participants performed short
 448 practice blocks of 4 different sequences, including TSeq1 and TSeq2 that were then con-
 449 solidated, as well as two new finger sequences (NewSeq1: 1-2-4-3-1, NewSeq2: 4-1-3-2-4).
 450 In contrast to Wiestler and Diedrichsen (2013), however, all four sequences used only
 451 four fingers of the left-hand, excluding the thumb. Also, as for the initial training, se-
 452 quences were instead repeated uninterruptedly and without feedback, in order to probe
 453 the processes underlying automatization of the skill.

454 Each block was composed of an instruction period of 4 seconds during which the se-
 455 quences to be performed was displayed as a series of 5 numbers (e.g. 1-4-2-3-1), that
 456 could easily be remembered by the participant. The latter was then followed by an execu-
 457 tion phase triggered by the appearance of a green cross. Participants performed 5 times
 458 the same sequence (or a maximum of 25 key-presses), before being instructed to stop
 459 and rest when the red cross was displayed.

460 The four sequences were assigned to blocks such as to include all possible successive
 461 pairs of the sequences using De-Brujin cycles (Aguirre et al. 2011), thus preventing the
 462 systematic leakage of BOLD activity patterns between blocks in this rapid design. As
 463 a 2-length De-Brujin cycle of the 4 sequences has to include each sequence 4 times,
 464 this yielded a total of 16 blocks. In our study, two different De-Brujin cycles were each
 465 repeated twice in two separate scanning runs separated by approximately 5 minutes of
 466 rest, hence resulting in a total of 64 blocks (4 groups of 16 practice blocks for a total of 16
 467 blocks per sequence). The blocks were synchronized to begin at a fixed time during the
 468 TR of the fMRI acquisition.

469 **Behavioral statistics**

470 Using data from the MVPA-task, we entered the mean duration per block of correctly
 471 performed sequences into a linear mixed-effect model with a sequence learning stage
 472 (new/consolidated) by block (1-16) interaction to test for difference in their performance
 473 level, as well as the evolution during the task, with sequences and blocks as random
 474 effects and participants as the grouping factor. The same model was run with the number
 475 of correct sequences as the outcome variable. Two other models were also used on
 476 subsets of data to test separately if there was any significant difference in performance
 477 (speed and accuracy) between the two consolidated sequences and between the two new
 478 sequences. Full models outputs are reported in supplementary materials.

479 **MRI data acquisition**

480 MRI data were acquired on a Siemens TIM Trio 3T scanner with two different setups. The
 481 first used a 32-channel coil to acquire high-resolution anatomical T1 weighted sagittal
 482 images using a Multi-Echo MPRAGE sequence (MEMPRAGE; voxel size=1mm isometric;
 483 TR=2530ms; TE=1.64,3.6,5.36,7.22ms; FA=7; GRAPPA=2; FoV=256 × 256 × 176mm) with the
 484 different echoes combined using a Root-Mean-Square (RMS).

485 Functional data were acquired with a 12-channel coil, which allowed to fit an EEG cap to
 486 monitor sleep after training, and using an EPI sequence providing complete cortical and
 487 cerebellum coverage (40 axial slices, acquire in ascending order, TR=2160ms;FoV=220 ×
 488 220 × 132mm, voxel size=3.44 × 3.44 × 3.3mm, TE=30ms, FA=90, GRAPPA=2). Following task
 489 fMRI data acquisition, four volumes were acquired using the same EPI sequence but with
 490 reversed phase encoding to enable retrospective correction of distortions induced by B0
 491 field inhomogeneity.

492 MRI data preprocessing

493 High-resolution anatomical T1 weighted images were preprocessed with Freesurfer (Dale
 494 et al. 1999; Fischl et al. 1999, 2008) to segment subcortical regions, reconstruct cortical
 495 surfaces and provide inter-individual alignment of cortical folding patterns. Pial and
 496 grey/white matter interface surfaces were downsampled to match the 32k sampling of
 497 Human Connectome Project (HCP) (Glasser et al. 2013). HCP subcortical atlas coordinates
 498 were warped onto individual T1 data using non-linear registration with the Ants software
 499 (Avants et al. 2008; Klein et al. 2009).

500 A custom pipeline was then used to preprocess fMRI data prior to analysis and relied on
 501 an integrated method (Pinsard et al. 2018) which combines slice-wise motion estimation
 502 and intensity correction followed by the extraction of BOLD timecourses in cortical and
 503 subcortical gray matter. This interpolation concurrently removed B0 inhomogeneity
 504 induced EPI distortion estimated by the FSL Topup tool using the fMRI data with reversed
 505 phase encoding (Andersson et al. 2003) acquired after the task. BOLD signal was further
 506 processed by detecting whole-brain intensity changes that corresponded to large motion,
 507 and each continuous period without such detected event was then separately detrended
 508 to remove linear signal drifts.

509 Importantly, the fMRI data preprocessing did not include smoothing, even though the
 510 interpolation inherent to any motion correction was based on averaging of values of
 511 neighboring voxels. This approach was intended to minimize the blurring of data in order
 512 to preserve fine-grained patterns of activity, with the resolution of relevant patterns being
 513 hypothetically at the columnar scale.

514 Multivariate Pattern Analysis

515 Samples

516 Each block was modeled by two boxcars, corresponding to the instruction and execution
 517 phases respectively, convolved with the single-gamma Hemodynamic Response Func-
 518 tion. Least-square separate (LS-S) regression of each event, which have been shown to
 519 provide improved activation patterns estimates for MVPA (Mumford et al. 2012), yielded
 520 instruction and execution phases beta maps for each block that were further used as
 521 MVPA samples.

522 Cross-validated multivariate distance

523 Similarly to Wiestler and Diedrichsen (2013) and Nambu et al. (2015), we aimed to uncover
 524 activity patterns that represented the different sequences performed by the participants.
 525 However, instead of calculating cross-validated classification accuracies, we opted for a
 526 representational approach by computing multivariate distance between activity patterns
 527 evoked by the execution of sequences, in order to avoid ceiling effect and baseline drift
 528 sensitivity (Walther et al. 2016). In the current study, we computed the cross-validated
 529 Mahalanobis distance (Nili et al. 2014; Diedrichsen et al. 2016; Walther et al. 2016), which
 530 is an unbiased metric that uses multivariate normalization by estimating the covariance
 531 from the GLM fitting residuals and regularizing it through Ledoit-Wolf optimal shrinkage

532 (Ledoit and Wolf 2004). This distance, which measures discriminability of conditions, was
 533 estimated separately for pairs of sequences that were in a similar acquisition stage, that
 534 is, for the newly acquired and consolidated sequences.

535 Searchlight analysis

536 Searchlight (Kriegeskorte et al. 2006) is an exploratory technique that applies MVPA
 537 repeatedly on small spatial neighborhoods covering the whole brain while avoiding high-
 538 dimensional limitation of multivariate algorithms. Searchlight was configured to select
 539 for each gray-matter coordinate their 64 closest neighbors as the subset of features for
 540 representational distance estimation. The neighborhood was limited to coordinates in
 541 the same structure (hemisphere or region of interest), and proximity was determined
 542 using respectively Euclidian and geodesic distance for subcortical and cortical coordinates.
 543 The extent of the searchlight was thus kept to such a local range to limit the inflation of
 544 false positive or negative results (Etzel et al. 2012, 2013).

545 Statistical testing

546 To assess statistical significance of multivariate distance and contrasts, group-level Monte-
 547 Carlo non-parametric statistical testing using 10000 permutations was conducted on
 548 searchlight distance maps with Threshold-Free-Cluster-Enhancement (TFCE) correction
 549 (Smith and Nichols 2009). The statistical significance level was set at $p < .05$ (with confi-
 550 dence interval $\pm .0044$ for 10000 permutations) with a minimum cluster size of 10 features.
 551 TFCE enabled a locally adaptive statistics and cluster size correction that particularly fitted
 552 our BOLD sampling of sparse gray-matter coordinates, as well as the large differences in
 553 the sizes of the structures that were investigated.

554 The MVPA analysis was done using the PyMVPA software (Hanke et al. 2009) package with
 555 additional development of custom samples extraction, cross-validation scheme, efficient
 556 searchlight and multivariate measure computation, optimally adapted to the study design
 557 and the anatomy-constrained data sampling.

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 560 analysis.

561 Author contributions

- 562 • Conceptualization: BP, AB, EG, HB, JD
- 563 • Investigation: AB, EG, BP
- 564 • Analysis: BP
- 565 • Software development: BP
- 566 • Writing: BP
- 567 • Review and editing: BP, AB, EG, OL, HB, JD

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571 **Supplementary materials**

572 **Behavioral linear mixed-effect model outputs**

573 Test for differences in speed as mean duration to perform a correct se-
 574 quence per block

575

```
576 mean_seq_duration ~ seq_new * blocks + (blocks+sequences | participants)
577 =====
578 Model: MixedLM Dependent Variable: mean_seq_duration
579 No. Observations: 1146 Method: REML
580 No. Groups: 18 Scale: 0.0368
581 Min. group size: 62 Likelihood: 165.9658
582 Max. group size: 64 Converged: Yes
583 Mean group size: 63.7
584 -----
585 Coef. Std.Err. z P>|z| [0.025 0.975]
586 -----
587 Intercept 1.269 0.076 16.790 0.000 1.121 1.417
588 seq_new[T.True] 0.365 0.047 7.776 0.000 0.273 0.457
589 blocks -0.006 0.005 -1.304 0.192 -0.016 0.003
590 seq_new[T.True]:blocks -0.018 0.002 -7.403 0.000 -0.023 -0.013
591 Intercept RE 0.132 0.246
592 Intercept RE x sequences[T.NewSeq2] RE -0.004 0.051
593 sequences[T.NewSeq2] RE 0.007 0.021
594 Intercept RE x sequences[T.TSeq1] RE -0.039 0.098
595 sequences[T.NewSeq2] RE x sequences[T.TSeq1] RE 0.001 0.024
596 sequences[T.TSeq1] RE 0.025 0.056
597 Intercept RE x sequences[T.Tseq2] RE -0.038 0.092
598 sequences[T.NewSeq2] RE x sequences[T.Tseq2] RE 0.001 0.023
599 sequences[T.TSeq1] RE x sequences[T.Tseq2] RE 0.023 0.049
600 sequences[T.Tseq2] RE 0.022 0.048
601 Intercept RE x blocks RE -0.005 0.010
602 sequences[T.NewSeq2] RE x blocks RE 0.000 0.002
603 sequences[T.TSeq1] RE x blocks RE 0.002 0.005
604 sequences[T.Tseq2] RE x blocks RE 0.002 0.004
605 blocks RE 0.000 0.001
606 =====
```

607 Test for differences in accuracy as the number of correct sequences over
 608 the 5 repetitions in a block

609

610	num_correct_seq ~ seq_new * blocks + (blocks+sequences participants)	=====						
611	====	Model:	MixedLM	Dependent Variable:	num_correct_seq			
612	No. Observations:	1152		Method:	REML			
613	No. Groups:	18		Scale:	0.6018			
614	Min. group size:	64		Likelihood:	-1409.7169			
615	Max. group size:	64		Converged:	No			
616	Mean group size:	64.0						
617	-----							
618	-----	Coef.	Std.Err.	z	P> z	[0.025	0.975]	
619	-----							
620	-----							
621	Intercept	4.691	0.079	59.215	0.000	4.536	4.846	
622	seq_new[T.True]	-0.304	0.101	-3.003	0.003	-0.503	-0.106	
623	blocks	-0.006	0.057	-0.101	0.919	-0.117	0.106	
624	seq_new[T.True]:blocks	0.014	0.010	1.434	0.152	-0.005	0.034	
625	Intercept RE	0.002	0.021					
626	Intercept RE x sequences[T.NewSeq2] RE	-0.003	0.019					
627	sequences[T.NewSeq2] RE	0.016	0.028					
628	Intercept RE x sequences[T.TSeq1] RE	-0.005	0.022					
629	sequences[T.NewSeq2] RE x sequences[T.TSeq1] RE	0.019	0.032					
630	sequences[T.TSeq1] RE	0.026	0.047					
631	Intercept RE x sequences[T.Tseq2] RE	-0.004	0.025					
632	sequences[T.NewSeq2] RE x sequences[T.Tseq2] RE	0.017	0.042					
633	sequences[T.TSeq1] RE x sequences[T.Tseq2] RE	0.027	0.058					
634	sequences[T.Tseq2] RE	0.034	0.089					
635	Intercept RE x blocks RE	-0.001	0.021					
636	sequences[T.NewSeq2] RE x blocks RE	0.001	0.016					
637	sequences[T.TSeq1] RE x blocks RE	0.002	0.018					
638	sequences[T.Tseq2] RE x blocks RE	0.002						
639	blocks RE	0.038						
640	=====							

641 Test for differences in speed and accuracy between the new sequences

642

```

643 mean_seq_duration ~ sequences*blocks + (1|participants)
644 =====
645 Model: MixedLM Dependent Variable: mean_seq_duration
646 No. Observations: 571 Method: REML
647 No. Groups: 18 Scale: 0.0655
648 Min. group size: 30 Likelihood: -76.5056
649 Max. group size: 32 Converged: Yes
650 Mean group size: 31.7
651 -----
652 Coef. Std.Err. z P>|z| [0.025 0.975]
653 -----
654 Intercept 1.630 0.071 22.931 0.000 1.490 1.769
655 sequences[T.NewSeq2] 0.025 0.045 0.558 0.577 -0.063 0.113
656 blocks -0.023 0.003 -7.157 0.000 -0.030 -0.017
657 sequences[T.NewSeq2]:blocks -0.005 0.005 -1.174 0.241 -0.015 0.004
658 groups RE 0.073 0.102
659 -----
660
661 num_correct_seq ~ sequences*blocks + (1|participants)
662 =====
663 Model: MixedLM Dependent Variable: num_correct_seq
664 No. Observations: 571 Method: REML
665 No. Groups: 18 Scale: 0.6209
666 Min. group size: 30 Likelihood: -689.3501
667 Max. group size: 32 Converged: Yes
668 Mean group size: 31.7
669 -----
670 Coef. Std.Err. z P>|z| [0.025 0.975]
671 -----
672 Intercept 4.553 0.102 44.450 0.000 4.353 4.754
673 sequences[T.NewSeq2] -0.245 0.138 -1.772 0.076 -0.517 0.026
674 blocks -0.007 0.010 -0.728 0.467 -0.027 0.012
675 sequences[T.NewSeq2]:blocks 0.028 0.014 1.936 0.053 -0.000 0.056
676 groups RE 0.018 0.017
677 -----

```

678 Test for differences in speed and accuracy between the consolidated se-
 679 quences

680

```
681 mean_seq_duration ~ sequences*blocks + (1|participants)
682 =====
683 Model: MixedLM Dependent Variable: mean_seq_duration
684 No. Observations: 575 Method: REML
685 No. Groups: 18 Scale: 0.0222
686 Min. group size: 31 Likelihood: 226.1710
687 Max. group size: 32 Converged: Yes
688 Mean group size: 31.9
689 -----
690 Coef. Std.Err. z P>|z| [0.025 0.975]
691 -----
692 Intercept 1.256 0.057 21.949 0.000 1.144 1.368
693 sequences[T.TSeq2] 0.031 0.026 1.191 0.234 -0.020 0.082
694 blocks -0.008 0.002 -4.023 0.000 -0.011 -0.004
695 sequences[T.TSeq2]:blocks -0.000 0.003 -0.165 0.869 -0.006 0.005
696 groups RE 0.053 0.125
697 =====
698
699 num_correct_seq ~ sequences*blocks + (1|participants)
700 =====
701 Model: MixedLM Dependent Variable: num_correct_seq
702 No. Observations: 575 Method: REML
703 No. Groups: 18 Scale: 0.4050
704 Min. group size: 31 Likelihood: -569.8356
705 Max. group size: 32 Converged: Yes
706 Mean group size: 31.9
707 -----
708 Coef. Std.Err. z P>|z| [0.025 0.975]
709 -----
710 Intercept 4.694 0.081 58.093 0.000 4.535 4.852
711 sequences[T.TSeq2] -0.030 0.111 -0.267 0.789 -0.248 0.188
712 blocks -0.012 0.008 -1.414 0.157 -0.028 0.004
713 sequences[T.TSeq2]:blocks 0.014 0.012 1.207 0.228 -0.009 0.036
714 groups RE 0.006 0.010
715 =====
```

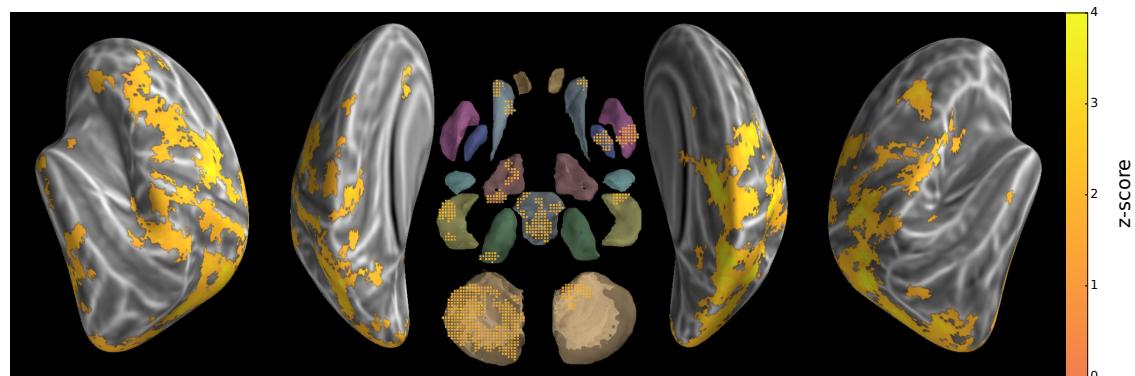
716 **Representational distance maps**

Figure S1. Group searchlight map of cross-validated Mahalanobis distance between the two new sequences (z-score thresholded at $p < .05$ TFCE-cluster-corrected)

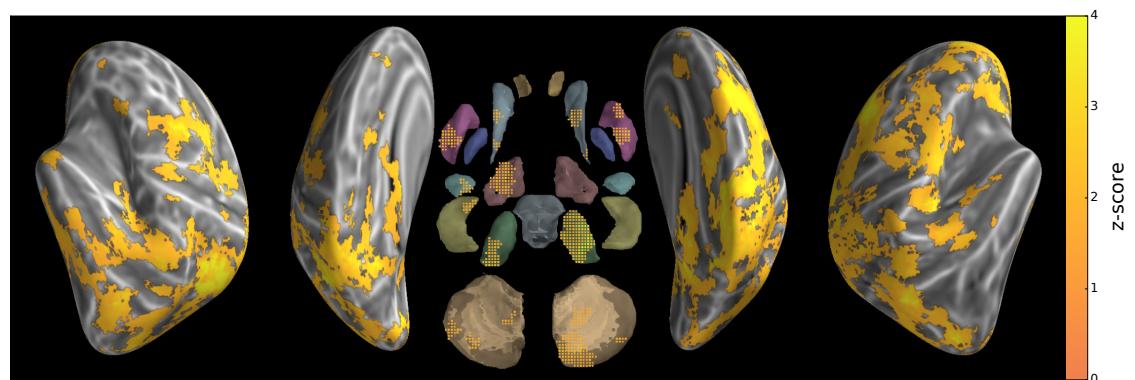


Figure S2. Group searchlight map of cross-validated Mahalanobis distance between the two consolidated sequences (z-score thresholded at $p < .05$ TFCE-cluster-corrected)

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