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Time-dependent motor memory representations in prefrontal cortex

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ABSTRACT

How memories evolve over time is fundamental for understanding memory. Hippocampus-dependent episodic memories are generally assumed to undergo a time-dependent neural reorganization involving an increased reliance on neocortical areas. Yet, whether other forms of memory undergo a similar reorganization over time remains unclear. Here, we examined whether the neural underpinnings of motor sequence memories change over time. Participants were trained on a motor sequence learning task. Either 1d or 28d later, they performed a retention test for this task in the fMRI scanner. Sequence-specific motor memory was observed both 1d and 28d after initial training. Bayesian second-level fMRI analyses suggested a higher probability for task activity in the middle frontal gyrus and frontal pole 28d compared to 1d after initial motor learning. Searchlight representational similarity analysis indicated that areas in middle and superior frontal cortex were more involved in differentiating between multivariate activity patterns for old motor sequence memories and newly learned motor sequences in the 28d-group compared to the 1d-group. This increased involvement of lateral frontal areas during the task after 28 days was not paralleled by a decrease in those areas that were involved in performing the motor sequence retention task after 1d. These novel findings provide insights into how memories beyond the hippocampus evolve over time.

1. Introduction

Memory changes over time. For episodic and spatial memories, encoded by the hippocampus (Eichenbaum, 1999; O'Keefe and Nadel, 1978; Squire and Zola-Morgan, 1991), these time-dependent changes are known to be accompanied by a neural reorganization that is referred to as systems consolidation (Dudai et al., 2015; Frankland and Bontempi, 2005). It is assumed that during this consolidation process initially hippocampus-dependent memories are, as time proceeds, increasingly represented by neocortical areas (Squire and Alvarez, 1995; Squire et al., 2015) and it is debated whether the hippocampus is at all involved in remote episodic or spatial memories (Nadel et al., 2007; Squire and Bayley, 2007; Winocur and Moscovitch, 2011). The time-dependent reorganization of memories is fundamental for understanding memory. However, although it is well known that there are multiple memory systems beyond the hippocampus (Eichenbaum and Cohen, 2001; Squire, 2004; White et al., 2013), the long-term temporal dynamics of memory have been mostly investigated in (initially) hippocampus-dependent forms of memory (e.g. Bonnici et al., 2012; Furman et al., 2012; Gilboa et al., 2004). The time-dependent neural reorganization of other forms of memory, such as motor sequence memory, has only rather recently been discussed within the framework of the systems consolidation debate (Dudai et al., 2015) and studies so far focused on early systems consolidation processes or reorganization processes associated with repeated training (Albouy et al., 2008; Debas et al., 2010; Coynel et al., 2010; Dayan and Cohen, 2011).

Motor sequence learning relies mainly on cortico-striatal and cortico-cerebellar systems, including the putamen, caudate nucleus, cerebellum, thalamus as well as motor and somatosensory cortices (Doyon et al., 2003, 2009; Hardwick et al., 2013). It is well documented that motor memories undergo an initial synaptic consolidation process similar to the one known for hippocampal memories, with newly established memories being vulnerable to interference immediately after learning but not hours later (Brashers-Krug et al., 1996). This consolidation process is also paralleled by distinct neural changes at systems level within the first hours after learning (Shadmehr and Holcomb, 1997). Consolidation of motor sequence memory is further reflected in off-line gains in reaction times, i.e. improvements in motor task performance between two training sessions without further practice (Dayan and Cohen, 2011; Debas et al., 2014; Doyon and Benali, 2005; Robertson et al., 2004a). At least for explicit motor sequence memory, this off-line learning requires sleep (Debas et al., 2010; Robertson et al., 2004b). Elegant neuroimaging

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studies revealed that the sleep-dependent early systems consolidation of motor memories is linked to changes in the striatum (Albouy et al., 2008; Debas et al., 2010; Fogel et al., 2017; Vahdat et al., 2017) and greater between-regions interaction within the cortico-striatal system (Debas et al., 2014), pointing to a neural reorganization of motor memory after sleep, similar as for hippocampus-dependent memory (Born and Wilhelm, 2012; Diekelmann et al., 2009). While these studies point to an early overnight consolidation process for motor memories, several studies have also shown that extensive training of motor sequences over weeks results in a transfer of motor memories from an associative, premotor circuit to an sensorimotor circuit (Coynel et al., 2010; Dayan and Cohen, 2011; Floyer-Lea and Matthews, 2005; Lehericy et al., 2005; but see Kupferschmidt et al., 2017), and that these extensively trained motor skills can be retained over long periods of time, even without further training (Park and Sternad, 2015; Penhune and Doyon, 2002; Romano et al., 2010). Studies on extensive training of motor skills over weeks, however, provide only little insight into the spontaneous, i.e. training-independent, reorganization of motor memory over several weeks that has been shown for episodic memory (Squire and Alvarez, 1995; Squire et al., 2015). Behavioral studies demonstrate that motor memories can be retained over long time periods, even with only minimal training (Julius and Adi-Japha, 2015; Savion-Lemieux and Penhune, 2005). However, it remains unclear whether several weeks old remote motor sequence memories, that were not extensively trained, rely on the same neural circuits as more recent (e.g. one day old) motor memories. In other words, is there a prolonged systems consolidation-like process in motor sequence memory that goes beyond the early system consolidation processes seen after the first nights of sleep (Albouy et al., 2008; Debas et al., 2010; Fogel et al., 2017; Vahdat et al., 2017)?

In the present experiment, we tested whether motor sequence memories undergo a neuronal reorganization over several weeks. To this end, participants were first trained in a modified version of the implicit Serial Reaction Time Task (SRTT) that has been used since decades to test motor sequence learning and memory (Nissen and Bullemer, 1987; Robertson, 2007). In this task, changing visual cues are presented to the participants with the instruction to respond to each cue as fast as possible with a respective button press (Fig. 1A). Not known to the participants, a specific sequence of cues is repeated several times to produce a recurring movement of sequential button presses. Faster reaction times in these *target* trials compared to those in trials with *random* sequences reflect successful motor sequence learning, which is typically observed after only a few trials (Doyon et al., 2009; Doyon and Benali, 2005). After the initial SRTT learning phase on a first experimental day, participants completed a SRTT testing phase in a functional magnetic resonance imaging (fMRI) scanner on a second experimental day. Critically, for half of the participants the interval between motor learning and retention testing was one day (1d-group), whereas for the other half of the participants this interval was four weeks (28d-group). This experimental set-up allowed us to determine whether remote motor sequence memories recruit the same or different brain areas as recent motor sequence memories, without any interference due to repeated testing. In the testing phase, we additionally introduced a second repeating sequence, allowing a distinction between new sequence learning on experimental day 2 and sequence-specific motor memory for the sequence learned on day 1. Importantly, successful motor skill learning can lead to increasing or decreasing activity in the related brain areas (Dayan and Cohen, 2011; Huang et al., 2013; Wiestler and Diedrichsen, 2013). Decreasing activity, however, does not necessarily imply that the respective area is less involved in motor sequence learning and memory but may point to more efficient encoding of the motor sequences (Poldrack et al., 2005; Ungerleider et al., 2002; Wiestler and Diedrichsen, 2013). Therefore, it has been suggested to complement traditional, univariate fMRI analyses by multivariate analyses that allow the detection of specific multivariate activity patterns irrespective of an overall increase or decrease in activity (Wiestler and Diedrichsen, 2013; Wymbs and Grafton, 2015). Thus, we combined here univariate fMRI analysis and multivariate search-light representational dissimilarity analysis (RSA) to investigate time-dependent changes in the neuronal representation of motor sequence memories. Based on the proposed systems consolidation process for hippocampus-dependent episodic memory, we predicted a similar, time-dependent reorganization of remote (several weeks old), compared to recent (one day old), motor sequence memories, with an increase in neocortical memory representation, possibly paralleled by a decrease in regions subserving initial motor sequence learning.

2. Materials and methods

2.1. Participants

We tested 48 healthy, right-handed young adults with normal or corrected-to-normal vision (24 men, 24 women; age: mean = 23.85 years, SD = 3.28 years). Exclusion criteria comprised a lifetime history of any psychiatric or neurological disorder, medication intake or drug abuse and circumstances preventing a MRI scan. One participant had to be excluded due to technical problems during data acquisition leading to an incomplete data set, four participants due to extensive movement during the fMRI measurements (more than 3mm/3°), one participant due to strong task-related movement (correlation of task onsets and the 6th rigid body motion parameter of r = - 0.51) and three participants due to poor overall performance in the task (more than 34% error rate), thus leaving a final sample of 39 participants for analysis (age: mean = 23.44 years, SD = 3.11 years; 1d-group: 9 men, 9 women; 28d-group: 11 men, 10 women). The study protocol was approved by the ethics committee of the German Psychological Association (LS 062013_012015). Participants gave written informed consent before participation and received monetary compensation. All testing took place in the afternoon or early evening.

2.2. Experimental design

The study consisted of two experimental days: on Day 1, participants performed the learning phase of the serial reaction time task (SRTT) outside the scanner. On Day 2, participants completed the test phase of the SRTT in the fMRI scanner. Importantly, the time interval between the learning phase and the test phase depended on the experimental group: participants assigned to the 1d-group performed the test phase one day after learning, while participants assigned to the 28d-group performed the test phase four weeks after the learning phase. This between-subject design allowed us to compare recent and remote motor sequence memories without any interference due to repeated testing. Participants were pseudo-randomly assigned to the 1d-group or 28d-group (12 women and 12 men per group). The testing of participants of the two groups in the fMRI scanner took place intermixed, so potential group differences cannot be explained by systematic changes in the technical environment of the scanner over time. In addition to the SRTT, participants performed an unrelated explicit picture encoding task or picture recognition task immediately before the SRTT learning phase or test phase on experimental Day 1 or Day 2, respectively, the results of which are reported elsewhere (Dandolo and Schwabe, 2018).

2.3. Serial reaction time task (SRTT)

We adapted a modified version of the original SRTT (Nissen and Bullemer, 1987) that was introduced by Tzvi et al. (2015). In this task, participants saw changing visual cues and were instructed to respond to each cue as quickly as possible with a specific button press. Unbeknownst to the participants, a specific sequence of twelve cues was repeated several times. To allow an event-related design we modified the block design used in Tzvi et al. (2015) by introducing breaks between each sequence of twelve cues. More specifically, at the beginning of each trial, consisting of a sequence of twelve cues, four grey squares appeared in a horizontal array in the middle of a computer screen (see Fig. 1A). Each

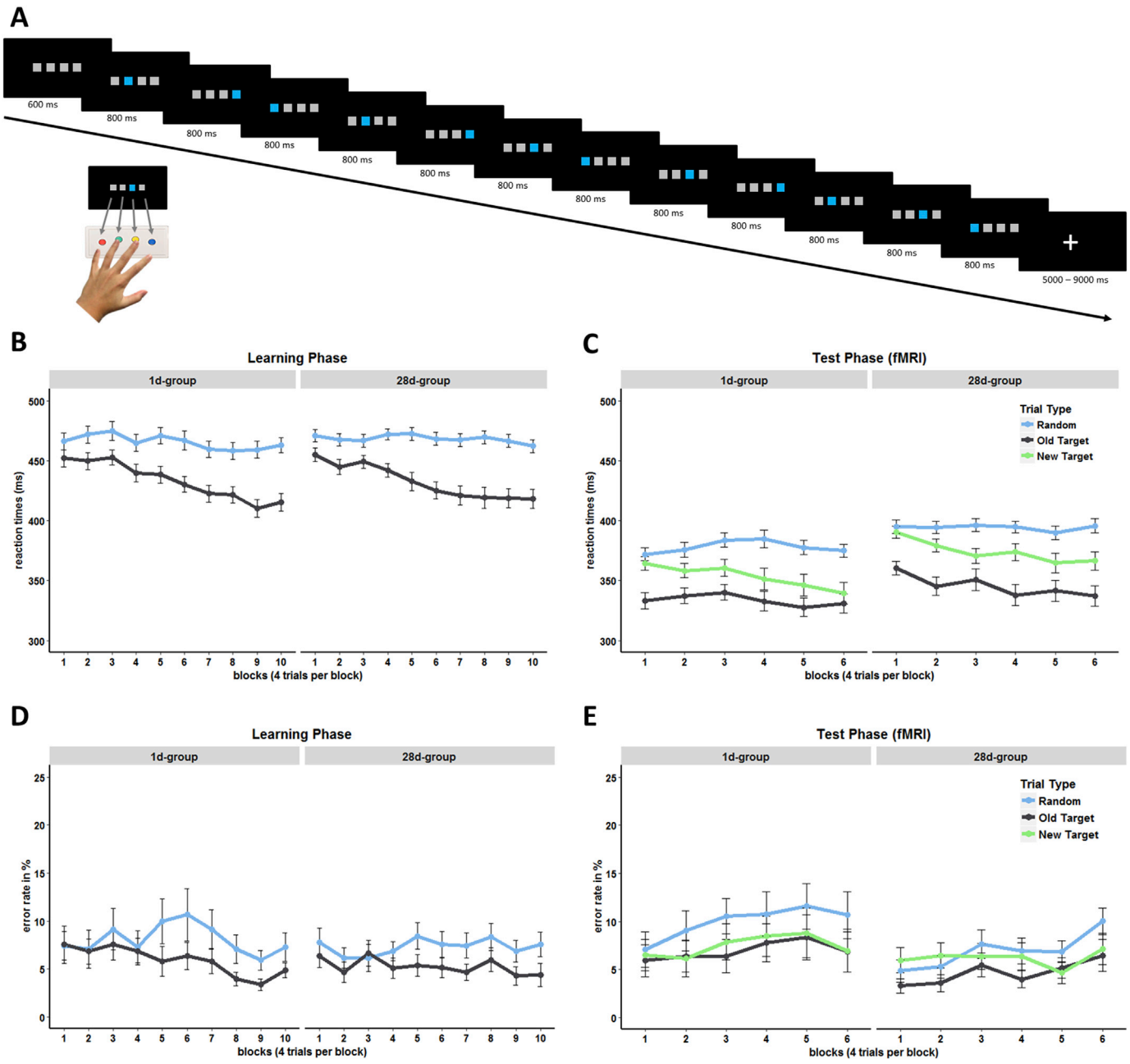

Fig. 1. (A) Schematic overview of one trial of the serial reaction time task (SRTT). First, four grey horizontal squares appeared on the screen for 600 ms to signal the start of a new trial. Then a sequence of 12 visual cues followed (800 ms each), with one of the squares turning blue each time to cue a corresponding finger press on a four-button response box using the left hand (see bottom left for visual cue-button-finger correspondence). Each finger was cued three times within one trial, but never twice in a row. A fixation cross was shown between trials. **(B) Reaction times in the learning phase.** Reaction times were faster for *old target* trials than for *random* trials and decreased throughout the blocks in both groups. Data from the 1d-group is presented in the left panel and data from the 28d-group in the right panel. The learning phase consisted of 10 blocks, with four trials per block for each trial type (*random* vs. *old target*), respectively. Error bars represent SEM. **(C) Reaction times in the test phase.** Reaction times for *old target* trials were, both for the 1d-group and for the 28d-group, faster than reaction times for both *random* and *new target* trials, in particular at the beginning of the test phase. Data from the 1d-group is presented in the left panel and data from the 28d-group in the right panel. The test phase consisted of 6 blocks, with four trials per block for each trial type (*random* vs. *old target* vs. *new target*) respectively. Error bars represent SEM. **(D) Error Rates in the learning phase**. We found a main effect of Trial Type with more errors in *random* trials than in *old target* trials, but no effects involving the factors Block or Group. Data from the 1d-group is presented in the left panel and data from the 28d-group in the right panel. The learning phase consisted of 10 blocks, with four trials per block for each trial type (*random* vs. *old target*) respectively. Error bars represent SEM. **(E) Error Rates in the test phase**. We found a main effect of Trial Type and a main effect of Block, but no interaction and no effects involving the factor Group. Data from the 1d-group is presented in the left panel and data from the 28d-group in the right panel. The test phase consisted of 6 blocks, with four trials per block for each trial type (*random* vs. *old target* vs. *new target*) respectively. Error bars represent SEM.

square was associated with a respective finger of the non-dominant (i.e., left) hand, placed on a response box (left square/button = small finger, second from left square/button = ring finger, second from right square/button = middle finger, right square/button = index finger). After 600 ms, one of the squares turned blue prompting participants to press the corresponding button on the response box with the corresponding finger. After 800 ms, a different square turned blue, cuing the next button press and so forth, until all twelve cues were presented. Within each trial, each of the four buttons was cued three times, with the same button never being cued twice in a row. We used a four-button fiber optic response box (Current Designs, Inc., Philadelphia, PA, USA) in both the learning phase outside the scanner and the test phase inside the scanner. The visual cues were presented and the button presses recorded using MATLAB and the Psychtoolbox (Brainard, 1997). Participants were instructed to press the correct buttons as quickly and as precisely as possible. They did not receive feedback about their performance during the task, neither during the learning nor during the test phase.

2.3.1. Learning phase

For each participant, an individual target sequence, consisting of 12 button presses, was generated at the beginning of the learning phase and unbeknownst to the participant this sequence was presented 40 times throughout the learning phase of the experiment, pseudo-randomly intermixed with 40 trials containing *random* sequences. The learning phase consisted of ten blocks in total, with four *target* trials and four *random* trials presented in random order in each block. This procedure assured that each trial type (*target* vs *random*) occurred at a similar rate throughout the learning phase. The blocks were presented directly one after another, without a break in between and without participants noticing a transition between blocks. Between trials a fixation cross was presented for 5 ± 2 s. Three random practice trials were presented before the learning phase to make sure participants understood the visual cue to finger correspondence.

2.3.2. Test phase

For the test phase we reused the *target* sequence generated for the respective participant on the first day, now referred to as *old target* sequence, and also generated a second *new target* sequence for each participant, again consisting of 12 button presses. The introduction of the *new target* sequence allowed us to differentiate between memory for the *old target* sequence and new learning processes during the test phase, which were likely to occur for both the *new target* and the *old target* sequence. Throughout the test phase the *old target* sequence was presented 24 times, pseudo-randomly intermixed with 24 *new target* sequences and 24 *random* sequences. The test phase consisted of six blocks in total, with four *old target* trials, four *new target* trials and four *random* trials presented in random order in each block. This procedure assured that each trial type (*old target* vs *new target* vs *random*) occurred at a similar rate throughout the test phase. The blocks were presented directly one after another, without a break in between and without participants noticing a transition between blocks. Between trials a fixation cross was presented for 7 ± 2 s.

2.4. Assessment of explicit awareness

After the test phase, we asked participants to reproduce the two visual cue sequences (*old target* and *new target*) that they had been presented with in the test phase by marking the respective presumed position of each visual cue on a paper sheet containing 12 rows of the horizontal grey squares array (one row for each cue in the sequence). We then compared these two reported sequences with both the *old target* and the *new target* sequence and noted the highest number of correctly recalled consecutive cues per sequence. Tzvi et al. (2015) used Monte Carlo simulations to find the number of consecutive correct hits that can be seen as "above chance level" and therefore interpreted as explicit awareness. In accordance with these simulations, we classified participants who correctly recalled six or more consecutive cues within a sequence as having gained explicit awareness of the respective sequence. In retrospect, ten participants were explicitly aware of at least one of the two target sequences, with three of these participants even recalling both target sequences correctly. We assessed if there were systematic differences in explicit awareness between the two groups (1d vs 28d) to make sure that potential group differences could not be explained by differences in explicit awareness. In retrospect, there were no significant differences in the number of participants with explicit awareness of either the *old target* sequence (4 out of 18 in the 1d group and 4 out of 21 in the 28d group, $p = 1$, Fisher's exact test) or the *new target* sequence (2 out of 18 in the 1d group and 3 out of 21 in the 28d group, $p = 1$, Fisher's exact test) between the two groups. Nevertheless, we further reanalyzed the data excluding the 10 participants with explicit awareness (leaving a sample of $n = 29$; 13 in the 1d-group and 16 in the 28d-group), to examine if the main results obtained in the analysis with all participants ($n = 39$) hold for the sample including only participants with implicit learning and memory ($n = 29$).

2.5. Assessment of patterns in target sequences

As we used different target sequences for each participant, we also assessed differences in target sequence difficulty, expressed by the potential occurrence of systematic patterns in the sequences. We checked for group differences and effects of the patterns on the behavioral results and could show that the behavioral effects were not driven by potential differences in target sequence difficulty (See Supplementary Results for a more detailed description of these analyses).

2.6. Behavioral data analysis

Behavioral data analyses were performed in R version 3.3.2 (https://www.r-project.org/). In case of a violation of the sphericity assumption in the ANOVAs, Greenhouse-Geisser corrections were applied.

2.6.1. Learning phase and test phase reaction times analyses

We analyzed the mean reaction time of all correct responses within a trial as our main behavioral parameter. For the learning phase, we subjected the reaction times to a mixed ANOVA with Block (10 blocks) and Trial Type (*target* vs *random*) as within-subjects factors and Group (1d vs 28d) as between-subjects factor. Likewise, for the test phase, we analyzed the reaction times by means of mixed ANOVAs with Block (6 blocks) and Trial Type (*old target* vs *new target* vs *random*) as within-subjects factors and again Group (1d vs 28d) as between-subjects factor.

2.6.2. Learning phase and test phase error rates analyses

In addition to reaction times, we analyzed the error rates defined as the percentage of incorrect and missing button presses within a trial. Error rates were subjected to the same ANOVAs as reaction times. Note that error rates overall were very low throughout the learning phase ($6.60\% \pm 0.22$ SEM) and the test phase ($6.92\% \pm 0.28$ SEM; i.e. in average less than one incorrect/missing button press per trial as 1 out of 12 would be 8.33%).

2.6.3. Differences between learning phase and test phase do not allow assessment of off-line learning

Previous studies have shown that, in addition to the fast online learning during the learning phase of a SRTT, there are also off-line learning effects, reflected in a decrease of reaction times for target sequences after learning even without further practice (Debas et al., 2014; Press et al., 2005). However, a direct assessment of off-line gains in our design was hardly possible due to differences in the experimental setup between our learning and test phases (different context and additional target sequences during the test session).

2.7. MRI acquisition

Whole-brain fMRI data were acquired on a 3T Skyra scanner (Siemens) equipped with a 32-channel head coil. For the functional images we used an echoplanar imaging (EPI) sequence, acquiring 513 vol with the following parameters: 36 slices, slice thickness = 3 mm, distance factor 20%, repetition time (TR) = 2500 ms, echo time (TE) = 30 ms, voxel size 3.0 mm isotropic. We also acquired a high-resolution T1-weighted anatomical image (TR = 2.5s, TE = 2.12 ms, 256 slices, voxel size = 0.8 × 0.8 × 0.9 mm) and a magnetic (B0) field map to unwarp the functional images.

2.8. fMRI data preprocessing

The fMRI data were preprocessed using MATLAB and SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). The first four functional images (10 s) were discarded to allow for T1 equilibration. The remaining 509 functional images were first spatially realigned and unwarped using the field maps (utilizing the SPM *Calculate VDM* and SPM *Realign & Unwarp* modules), then coregistered to the structural image, followed by a normalization to the MNI space. For the univariate analysis, the images were additionally spatially smoothed using an 8 mm full-width half-maximum Gaussian kernel.

2.9. General linear modeling and whole brain analysis

The data was analyzed using general linear modeling (GLM), in the form of a random effects analysis, as implemented in SPM12.

2.9.1. First level modelling in SPM

For each of the six blocks in the test phase we created regressors for each Trial Type (*old target, new target, random*), resulting in 18 regressors (6 Blocks × 3 Trial Types). Thereby each regressor contained 4 trials and each trial was modeled as a short block, using the time the first square turned blue as the onset of the block and 9.6 s as duration, thus equal to the total trial length (12 cues × 800 ms presentation of each cue). We therefore modelled all 72 trials in the test phase (4 trials per regressor x 18 regressors = 72 trials). Because the error rate was overall very low (mean error rate 6.92% ± 0.28 SEM per trial) and trials were analyzed as 'mini-blocks' of 12 button presses each, we did not exclude trials containing a single erroneous button press. The division of the trials into the six blocks was implemented to test new learning across the test phase, utilizing the fact that the task was programmed in a pseudo-random way, ensuring that each trial type occurred at a similar rate throughout the test phase. Although including the blocks in the analysis enabled us to examine changes within the test phase due to new learning, it should nevertheless be noted that alternative analyses examining the modulation of brain activity at the trial level instead of blocks may have resulted in a different pattern of results.

Note that we did not include movement regressors in the GLM, as we used the SPM unwarp function in the data preprocessing instead. A high-pass filter of 128 s was used to remove low-frequency drifts and serial correlations in the time series were accounted for using an autoregressive AR(1) model.

2.9.2. Second level modelling in SPM

We first looked at the overall task activity across all subjects (using the first-level main contrast comparing all trial types to the implicit baseline) to verify that the expected motor areas are active when performing the SRTT in general. We then analyzed the following difference contrasts from the first level across all participants: *old target* > *random*, *new target* > *random* and *old target* > *new target*. To take new learning processes during the test phase into account, we additionally examined the main effect of Block (six blocks), and the interaction effect of Trial Type (*old target, new target, random*) x Block by setting up the relevant t-contrasts on the first-level (5 contrast for the main effect of block, 10 for the interaction effect Trial Type x Block; created using the spm_make_contrasts function). Using a two-sample *t*-test design at second level modelling we then compared differences between the 1d-group and 28d-group in all the above contrasts.

2.9.3. Classical and Bayesian estimation methods

To estimate the second level models we used both the classical (Restricted Maximum Likelihood) estimation and, in a second step, the Bayesian estimation of second level models as implemented in SPM12. For the results of the classical estimation method, we first used a voxel wise threshold of $p < 0.05$ (family-wise error correction (FWE)) at the whole brain-level and, if no voxels survived this threshold, used the less conservative FWE cluster-thresholding implemented in SPM12. Importantly, we used a high cluster forming threshold of $p = 0.001$ combined with a FWE corrected cluster extent threshold (and not an arbitrary extent threshold such as e.g. $k = 10$). These thresholds have been shown to be sufficient (Flandin and Friston, 2017) to avoid the otherwise inflated false-positive rates (Eklund et al., 2016).

The Bayesian second level estimation of the models as implemented in SPM12 uses an Empirical Bayes algorithm with global shrinkage priors, which embodies a prior belief that on average across all voxels there is no experimental effect (see SPM12 documentation). For this Bayesian second level analysis, we used an effect size threshold of 0.5 (medium effect size) and a log odds bayes factor threshold of logBF = 5 (very strong evidence (Han and Park, 2018)) for the posterior probability maps (PPMs) to test for group differences in the overall task activity and differences in the activity for the *old target* sequence, the *new target* sequence and the *random* sequence separately. We also computed evidence for the null hypothesis (no group differences) by first defining a F-contrast with the vector [1 -1] then using the Bayesian estimation method to create a posterior probability map using a logBF of 3 and then using the *spm_bms_test_null* function to create a map containing the log bayes factors for the null hypothesis.

2.10. ROI analysis

In addition to the whole-brain analysis, we specifically looked at regions that have previously been discussed as being involved in motor sequence learning (Hardwick et al., 2013). We used the following anatomical masks from the Harvard-Oxford atlas (Desikan et al., 2006) using a probability threshold of 50%: caudate nucleus, putamen, pallidum, thalamus, hippocampus and superior parietal lobule (left and right respectively), juxtapositional lobule (formerly supplementary motor cortex) and anterior cingulate gyrus. We also used the following anatomical masks from the Juelich atlas (Eickhoff et al., 2007), again using a probability threshold of 50%: Primary motor cortex BA4a, Primary motor cortex BA4p, Primary somatosensory cortex BA1, Primary somatosensory cortex BA2, Primary somatosensory cortex BA3a, Primary somatosensory cortex BA3b and Premotor cortex (left and right respectively). In addition, we used masks created with MARINA (http://www.bion.de/eng/MARINA.php) for the left and right dorsolateral prefrontal cortex (dlPFC) and a cerebellum mask retrieved from the Diedrichsen Lab (http://www.diedrichsenlab.org/imaging/propatlas.htm). We performed small volume correction for these ROIs to test whether there were differences between trial types (*old target* > *random*, *new target* > *random* and *old target* > *new target*) or differences between the groups (1d vs 28d) that could be detected when correcting the FWE-threshold for the number of voxels in the ROIs in comparison to the whole brain. Thus, voxels were regarded as significant when falling below a corrected voxel threshold of 0.05 (FWE) adjusted for the small volume. We report all areas with $k > 10$ significant voxels.

2.11. Searchlight representational similarity analysis

2.11.1. Searchlight approach

In addition to the univariate analysis, we performed a whole-brain

searchlight Representational Similarity Analysis (RSA; Kriegeskorte et al., 2008) using the *rsatoolbox* (Nili et al., 2014). For each participant, we extracted a representational dissimilarity matrix (RDM) for each spherical searchlight (15 mm radius), based on the t-maps of the 18 regressors (6 blocks × 3 trial types) from a univariate GLM estimated on unsmoothed, normalized functional images. In each sphere, we extracted the activity pattern across the sphere for each regressor and calculated the dissimilarity between two activity patterns by correlation distances (1−r, Pearson linear correlation). Next, these dissimilarities based on each combination of the 18 regressors were placed into the respective cells of the 18 × 18 RDMs. Then, these brain RDMs were compared to one of six model RDMs (see Section 2.11.2 for description of the models) in each sphere using Spearman's rank correlation coefficient r. The resulting r estimates were assigned to the center voxels of each sphere, thus creating a whole-brain map of model fits for each model and subject. For each model, we then used the r-maps of each subject as input to a Second-Level SPM estimation to find main effects across the whole group of subjects and differences between the model fits of the two groups (1d vs 28d).

2.11.2. Model RDMs

We performed the searchlight RSA for six different models: (1) the *Old Target and New Target Stable* model expects two different activity patterns, one for all regressors based on *old target* sequence and one for all regressors based on *new target* sequence, that are dissimilar from each other, but stable across the blocks; (2) the *Old Target Stable and New Target Evolving* model expects similar activity patterns for all regressors based on *old target* trials from the beginning on, and a separate pattern for *new target* trials that slowly emerges across the blocks, i.e. we modeled a linear increase in pattern similarity across the blocks for the *new target* sequences reflecting a learning process; (3) the *Old Target and New Target Evolving* model expects two different activity patterns for the *old target* and the *new target* respectively, both becoming more and more consistent across the blocks; (4) the *Old Target Distinct* model expects similar activity patterns for all regressors based on *old target* trials, but no consistent patterns for *new target* trials; (5) the *New Target Distinct* model expects similar activity patterns for all regressors based on *new target* trials, but no consistent patterns for *old target* trials; (6) the *Old Target and New Target Same* model expects similar activity patterns for all regressors based on either *old target* trials or *new target* trials. None of the models expect consistent patterns for *random* trials. We hypothesized that the first three models (the *Old Target and New Target Stable; Old Target Stable and New Target Evolving; Old Target and New Target Evolving)* will all capture general differences between the representations of previously learned old motor memories (after consolidation) and newly learned motor memories (before consolidation). Differences between the 1d-group and the 28d-group in these models can then be related to differences between representations of recent motor memories after early systems consolidation and representations of remote motor memories after prolonged systems consolidation in comparison to newly learned motor memories, respectively. We expected model 2 (*Old Target Stable and New Target Evolving)* to show better model fits in areas that additionally represented new learning of the new sequence across the test phase, while model 3 (*Old Target and New Target Evolving)* was expected to show a better model fit in areas representing new learning of both sequences across the test phase. Models 4 (*Old Target Distinct)*, 5 (*New Target Distinct)* and 6 (*Old Target and New Target Same)* were included as control models, to show areas that only represented the old memories (4), the newly learned memories (5), or had the same representation for both sequences (6).

3. Results

3.1. Successful motor sequence learning

On a first experimental day, participants completed ten blocks of a SRTT (Nissen and Bullemer, 1987; Tzvi et al., 2015) in which they were requested to respond to changing visual cues with a corresponding button press (Fig. 1A). Unbeknownst to the participants, a specific sequence of cues (*target* sequence) was presented repeatedly, enabling motor learning. As expected, participants showed significantly faster reaction times in *target* trials than in *random* trials in the learning phase (main effect Trial Type: $F_{(1,37)} = 47.81$, $p = 3.68e\text{-}08$, generalized $\eta^2 = 0.095$) and a significant decrease of reaction times across the ten learning blocks in *target* trials (main effect Block for *target* trials: $F_{(3.94,149.77)} = 15.06$, $p = 2.86e\text{-}10$, generalized $\eta^2 = 0.055$), but not in *random* trials (main effect Block for *random* trials: $F_{(9,342)} = 1.20$, $p = 0.2968$, generalized $\eta^2 = 0.004$; interaction effect Block × Trial Type: $F_{(4.53,167.65)} = 7.82$, $p = 3.00e\text{-}06$, generalized $\eta^2 = 0.011$, Fig. 1B). Post-hoc paired t-tests comparing *target* trials to *random* trials in each block were significant in all blocks (all $t > 3.93$, all $p < 0.0003$), showing that the reaction times were faster for target compared to *random* sequences already in the first block. Thus, participants show very early gains in reaction times for the target sequence (after only 4 repetitions of the sequence) comparable to steep learning curves shown in other studies using similar tasks (Tzvi et al., 2015; Wymbs and Grafton, 2015). However, Fig. 1B, additionally shows that the difference between the *random* and *target* sequence still increased further across the blocks, as the reaction times for the *target* sequence consistently decreased. In the last block of the learning phase, the mean difference between *random* and *target* trials was significantly larger than in the first block (47 ms vs 17 ms; paired *t*-test comparing block 1 to block 10: $t(38) = -4.36$, $p = 9.58e\text{-}05$, Cohen's $d = 0.70$). Importantly, both groups learned the *target* sequence equally well (main effect Group: $F_{(1,37)} = 0.005$, $p = 0.9444$, generalized $\eta^2 = 0.0001$, no significant interaction effects involving Group: all $F < 0.68$, all $p > 0.727$).

The analysis of the error rates in the learning phase also showed a main effect of Trial Type ($F_{(1,37)} = 24.49$, $p = 1.65e\text{-}05$, generalized $\eta2 = 0.030$), with more errors for *random* trials than for *target* trials and no differences between the groups (main effect Group: $F_{(1,37)} = 0.27$, $p = 0.6093$, generalized $\eta^2 = 0.003$, Group × Trial Type: $F_{(1,37)} = 0.03$, $p = 0.8563$, generalized $\eta^2 = 0.00004$). There was only a trend for main effect of Block ($F_{(5.78,214.00)} = 1.83$, $p = 0.0969$, generalized $\eta^2 = 0.014$) and no interaction effects involving Block (all $F < 1.63$, all $p > 0.1370$), showing that the error rates stayed relatively constant throughout the learning phase (Fig. 1D). In sum, these data show that participants learned the target sequence very well on day 1, without any differences between the 1d- and 28d-groups.

3.2. Intact motor sequence-specific memory after 28 days

In the test phase, we introduced a *new target* sequence in addition to the *old target* sequence that was learned on day 1 in order to differentiate new sequence learning during the test phase from sequence-specific motor memory. The ANOVA showed a significant main effect of Trial Type ($F_{(2,74)} = 30.24$, $p = 2.52e\text{-}10$, generalized $\eta^2 = 0.105$), and a Block × Trial Type interaction ($F_{(5.83,215.69)} = 3.03$, $p = 0.0079$, generalized $\eta^2 = 0.005$; main effect Block: $F_{(2.40,88.94)} = 3.17$, $p = 0.0381$, generalized $\eta^2 = 0.006$). Most importantly, however, there were no interaction effects including the factor Group (all $F < 0.90$, all $p > 0.4247$) and no main effect of Group ($F_{(1,37)} = 1.09$, $p = 0.3017$, generalized $\eta^2 = 0.021$). Examining Fig. 1C shows that, for both groups, the reaction times for the *random* sequence remained rather constant across the test phase (main effect Block for *random* trials: $F_{(5,190)} = 1.05$, $p = 0.3899$, generalized $\eta^2 = 0.004$), while we found the expected learning effect for the *new target* sequence with reaction times decreasing across blocks (main effect Block for *new target* trials: $F_{(1.95,74.14)} = 4.41$, $p = 0.0162$, generalized $\eta^2 = 0.018$). Most importantly, however, the reaction times for the *old target* sequence that was trained on day 1 were consistently low throughout the testing phase. In particular in the first blocks the reaction times for the *old target* sequence were faster than not only the reaction times for the *random* sequence but also faster than the reaction times for the *new target* sequence, showing the expected

sequence-specific memory effect. Bonferroni-corrected post-hoc paired t-tests across both groups (0.05/18 tests = 0.0028 as significance threshold) showed that, in the first and second block, reaction times in the *old target* trials were significantly faster than in both the *random* trials (both $t > 5.98$, both $p < 0.0001$) and the *new target* trials (both $t > 4.21$, both $p < 0.0001$), while the *random* and *new target* trials did not differ significantly (both $t < 3.15$, both $p > 0.003$). In blocks four and five, the reaction times of *old target* trials were faster than the reaction times for *new target* trials and *random* trials, and the reaction times for *new target* trials were faster than the reaction times for *random* trials (all $t > 3.19$, all $p < 0.0028$). In blocks three and six, reaction times in *random* trials were significantly slower than both *old target* trials (both $t > 5.59$, both $p < 0.0001$) and *new target* trials (both $t > 3.58$, both $p < 0.0009$), while the *old target* and *new target* trials did not differ significantly (both $t < 3.03$, both $p > 0.004$). Although Fig. 1C suggests that across all trial types and blocks the reaction times in the 28d-group seemed to be somewhat slower than in the 1d-group, this difference was not significant (main effect of Group: $F_{(1,37)} = 1.09$, $p = 0.3017$, generalized $\eta^2 = 0.021$) and the pattern of results was clearly very similar in the 1d- and the 28d-groups. Thus, in both groups the reaction times were faster in the *old target* trials compared to both *random* and *new target* trials at the beginning of the test phase. This finding clearly shows intact sequence-specific motor memory in the 1d-group and the 28d-group.

For the error rates in the test phase, there was again a significant main effect of Trial Type ($F_{(2,74)} = 13.68$, $p = 8.79e\text{-}06$, generalized $\eta^2 = 0.023$), with more errors for *random* trials than for *old target* trials ($t(38) = -5.06$, $p = 1.09e\text{-}05$, Cohen's $d = -0.33$), and more errors for *random* trials than *new target* trials ($t(38) = -3.15$, $p = 0.0032$, Cohen's $d = -0.18$), and slightly less errors for *old target* trials than *new target* trials ($t(38) = 2.02$, $p = 0.0503$, Cohen's $d = 0.13$). There was also a main effect of Block ($F_{(3.84,142.04)} = 4.05$, $p = 4.37e\text{-}03$, generalized $\eta^2 = 0.014$), but no Trial Type × Block interaction ($F_{(6.77,250.56)} = 1.08$, $p = 0.3757$, generalized $\eta^2 = 0.005$). Importantly, there were again no differences between groups in the error rates (main effect Group: $F_{(1,37)} = 1.37$, $p = 0.2494$, generalized $\eta^2 = 0.023$, no interaction effects involving Group: all $F < 1.97$, all $p > 0.1051$, Fig. 1E).

3.3. Neural underpinnings of motor sequence learning and memory 1d and 28d after initial encoding

Our behavioral data from the test session on experimental day 2 suggest that sequence-specific motor memory was equally robust in participants tested one day after encoding and those tested 28 days after encoding. We next set out to determine whether the neural underpinnings of motor memory underwent time-dependent changes or not. In a first step, we analyzed overall task activity (for all trial types) against the implicit baseline across all participants to verify that overall the expected motor areas are involved during performance of the SRTT. This analysis showed, as expected, activity in areas implicated in motor sequence learning, including, for instance, the precentral gyrus, postcentral gyrus, caudate nucleus, putamen and cerebellum. Parts of the medial temporal lobe and frontal pole, in turn, showed a significant decrease in activation (compared to the implicit baseline) during the motor learning task ($p < 0.05$ (FWE); see Supplementary Fig. 1 for visualizations and Supplementary Table 1 for a complete list of increased and decreased activations). We then tested for differences between the trial types (*old target* > *random*, *new target* > *random* and *old target* > *new target*) across all participants at the whole-brain level and found higher activity for *old target* trials relative to *random* trials in the right caudate, the right putamen, the angular gyrus, the cuneal cortex and the frontal pole when applying a cluster forming threshold of $p < 0.001$ (unc.) and a cluster-extent of 254 voxels (see Supplementary Table 2 for exact coordinates and cluster extents). No areas survived this threshold for the *new target* > *random* and *old target* > *new target* contrasts. We then tested for effects related to the six different blocks within the testing phase and found a main effect of Block bilaterally in the lateral occipital cortex, inferior division (left: $k = 638$ voxels, t-value = 16.10, peak voxel: $x = -46$, $y = -70$ and $z = 2$; right: $k = 736$ voxels, t-value = 15.59, peak voxel: $x = 46$, $y = -68$ and $z = -2$) when applying a cluster forming threshold of $p < 0.001$ (unc.) and a cluster-extent of 165 voxels. However, no areas survived this threshold for the Trial Type × Block interaction. Next, we tested for group differences in all of the above described contrasts. These analyses, however, did not yield any significant voxels or clusters at the whole-brain level.

In a next step, we analyzed activity in a number of pre-defined ROIs that have been implicated in motor sequence memory before (see materials and method), using small volume correction for each ROI separately. Differences between *old target*, *new target*, and *random* sequences were obtained, across all participants, in the following regions (see Supplementary Table 3 for exact coordinates, p-values and number of voxels): we found higher activity for *old target* trials than *random* trials in the right caudate, left caudate, right putamen and left dlPFC, echoing the results of the whole-brain cluster-thresholded analysis for this contrast and suggesting that these areas are important for sequence-specific learning and memory. Further, we found higher activity for the *new target* trials than the *random* trials in the right caudate and the left hippocampus, suggesting that these areas are involved in new motor sequence learning. Finally, we found higher activity for *new target* trials than *old target* trials in the left primary somatosensory cortex BA2, suggesting that this area might be more involved in new motor sequence learning than in performing already trained motor sequences. Alternatively, this finding might also imply that the old sequence is already encoded more efficiently, leading to a decrease in activity, compared to the newly encoded sequence. Note, however, that after correcting for the number of ROIs used in these analyses, only the right caudate for the contrast *old target* > *random* remains significant. Most importantly, however, even before correcting for the number of ROIs in these small volume corrected analyses, we did not obtain evidence for any differences in brain activity between the 1d- and 28d-groups.

3.4. Bayesian analysis shows a higher probability of prefrontal involvement in motor sequence memory after 28 days

Our univariate analyses so far suggested that the neural underpinnings of motor memory are largely comparable in the 1d- and 28d-groups, implicating that the neural signature of motor memory remains, in contrast to episodic memory, stable over time (at least over 4 weeks). In order to explicitly test the evidence in favor of the null hypothesis (i.e. that there are no differences between the 1d- and 28d-groups) and the evidence in favor of the alternative hypothesis (i.e. that there are actually differences between the 1d- and 28d-groups), we run a Bayesian second level analysis. Bayesian second-level analysis has been shown to be more conservative than clusterwise FWE inference while being more sensitive than voxelwise FWE inference (Han and Park, 2018) and importantly also allows explicit testing of the null hypothesis. Using a logBF of 3 to create posterior probability maps for the null hypothesis we did, however, not find any evidence for the null hypothesis of comparable brain activity in the 1d- and 28d-groups, neither in the overall task activity nor in each trial type separately. On the contrary, when using an effect size threshold of 0.5 (medium effect size) and a log odds threshold of logBF = 5 (very strong evidence), we found that the probability that the 1d-group showed more activation than the 28d-group across all trial types was higher in the left post central gyrus (peak voxel: $x = -32$, $y = -38$, $z = 72$) and, conversely, the probability that the 28d-group showed more activation than the 1d-group across all trial types was higher in the bilateral middle frontal gyrus (peak voxel left: $x = -44$, $y = 26$, $z = 44$; peak voxel right: $x = 42$, $y = 34$, $z = 44$), the frontal pole (peak voxel: $x = -18$, $y = 68$, $z = 16$) and the occipital pole (peak voxel: $x = -14$, $y = -94$, $z = -2$; Fig. 2A). We then tested whether these group differences were related to new learning or memory processes and thus specific to certain trial types (i.e., specific to *old target* trials, *new target* trials and *random* trials). In *old target* trials, indicative of sequence-specific motor memory, there was a

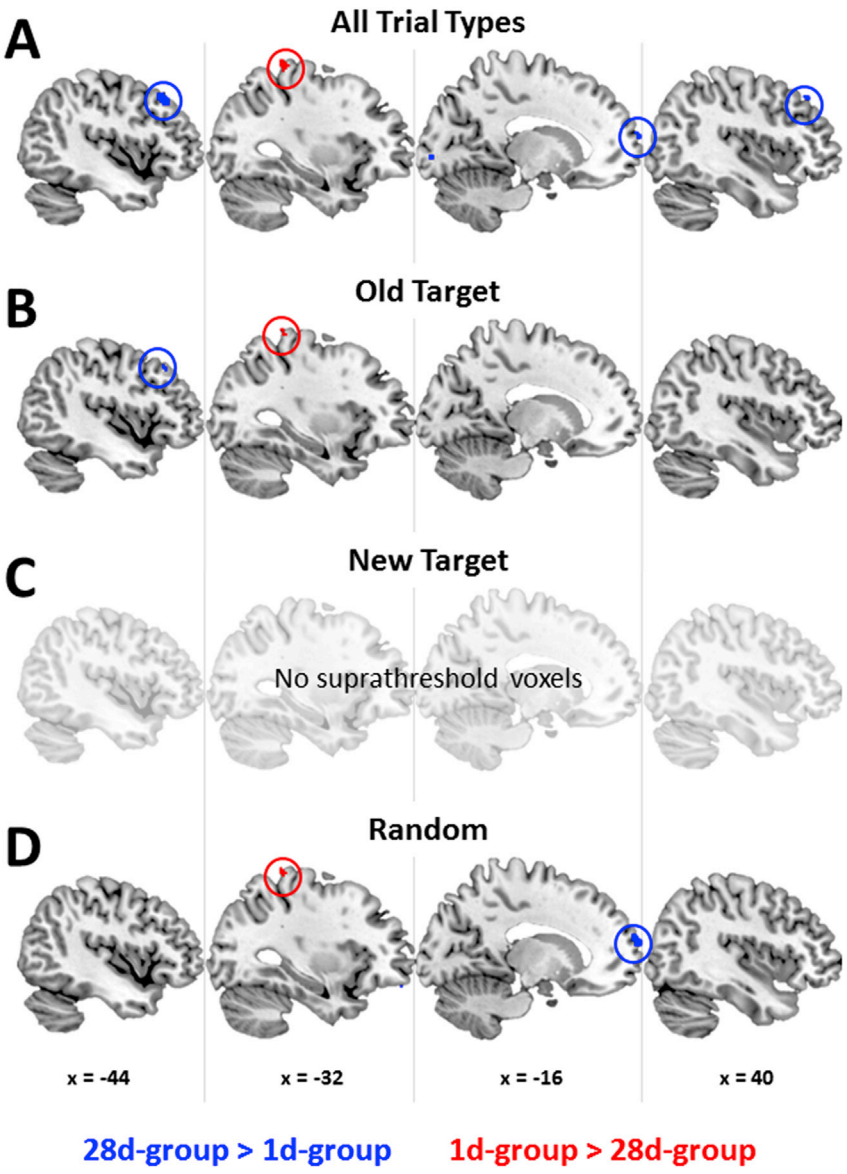

Fig. 2. Bayesian Second Level Group comparisons (n = 39). All voxels exceeding a threshold of logBF = 5 for PPMs created using an effect size threshold of 0.5 in the contrast 1d-group > 28d-group are coloured in red, and all voxels exceeding the same threshold in the contrast 28d-group > 1d-group are coloured in blue. Visualizations of these activations are superimposed on four sagittal slices (left hemisphere x = −44, −32, −16, right hemisphere x = 40) of a template image. Figures were created using MRIcron (https://www.nitrc.org/projects/mricron). **(A)** Group differences for the overall task activity (all trial types): the 1d-group showed a higher probability of activation compared to the 28d-group in the left postcentral gyrus (peak voxels: x = −32, y = −38, z = 72, k = 47; x = −30, y = −36, z = 50, k = 15), while there was a higher probability that the 28d-group showed more activation than the 1d-group in the left middle frontal gyrus (peak voxels: x = −44, y = 26, z = 44, k = 61; x = −32, y = 14, z = 66, k = 6), right middle frontal gyrus (peak voxel: x = 42, y = 34, z = 44, k = 13), occipital pole (peak voxel: x = - 14, y = −94, z = −2, k = 22) and frontal pole (peak voxel: x = −18, y = 68, z = 16, k = 12). Note that only areas with more than 5 voxels are explicitly listed here. **(B)** Group differences for *old target* trials: the 1d-group showed a higher probability of activation compared to the 28d-group in the left postcentral gyrus (peak voxel: x = −32, y = −38, z = 72, k = 11), while there was a higher probability that the 28d-group showed more activation than the 1d-group in the left middle frontal gyrus (peak voxel: x = −44, y = 26, z = 44, k = 7). **(C)** No voxels survived the threshold in the group comparisons of the *new target* trials. **(D)** Group differences for *random* trials: the 1d-group showed a higher probability of activation compared to the 28d-group in the left postcentral gyrus (peak voxel: x = −32, y = −38, z = 70, k = 16), while there was a higher probability that the 28d-group showed more activation than the 1d-group in the frontal pole (peak voxel: x = −16, y = 68, z = 16, k = 99) and the occipital pole (peak voxel: x = - 8, y = −92, z = −4, k = 8). Note that only areas with more than 5 voxels are explicitly listed here.

higher probability in the post central gyrus that the 1d-group showed more activation than the 28d-group (Fig. 2B). Yet, evidence for this difference (as well as a similar difference in the frontal pole and occipital pole) was also obtained for *random* trials (Fig. 2D), and thus seems to reflect differences between the groups in the general motor task rather than sequence-specific motor memory. Interestingly, however, there was selectively for *old target* trials a higher probability for activation in the left middle frontal gyrus in the 28d-group compared to the 1d-group, indicating that this area might be more strongly involved in sequence-specific memory after 28 days than after 1 day. In *new target* trials alone, there was no evidence for different activations in the two groups (Fig. 2C).

3.5. *Frontal cortex areas are more involved in separating between activity patterns for old sequence memories and patterns for newly learned sequences after 28 days than after 1 day*

The Bayesian Analysis showed a higher probability for the involvement of the middle frontal gyrus in motor memory after 28 days than 1 day after encoding. We also ran a searchlight RSA to find areas in the brain that show stable or evolving multivariate activity patterns for the *old* and/or *new target* sequence. In contrast to the mass univariate approach, the RSA allows the identification of information in the brain that is coded by patterns of activations in neighboring voxels. More specifically, we performed searchlight RSA comparing RDMs of each searchlight area to six different model RDMs reflecting different aspects of motor learning and memory: A first model reflected consistent multivariate representation of both the *old* learned sequence and the *new target* sequence throughout the test phase, reflecting differences between the two sequences without modeling any new learning processes across blocks (*Old Target and New Target Stable* model). The second model aimed to identify areas that show a consistent multivariate representation of the *old target* sequence throughout the test phase, reflecting an already established representation of the old sequence-specific motor memory, and a representation of the *new target* sequence that evolves over the course of the test phase, reflecting a new learning process (*Old Target Stable and New Target Evolving* model). Thus, this model reflects a representation of the motor memory of the target sequence learned on day 1, irrespective of any new learning processes for this *old target* sequence. The third model assumes also a re-learning process for the *old target* sequence, i.e. distinct representations for the *old target* and *new target* trials respectively that both become more consistent over the course of the test phase (*Old Target and New Target Evolving* model). The fourth

model assumed a specific and consistent multivariate representation of the *old target* sequence throughout the test phase that is clearly distinct from all other sequences, thereby not expecting any specific pattern for the *new target* sequence (*Old Target Distinct* model). The fifth model, on the other hand, assumed a specific and consistent multivariate representation of the *new target* sequence, without expecting any specific pattern for the *old target* sequence (*New Target Distinct* model). Finally, a sixth control model assumed consistent and indistinguishable multivariate representations for both target sequences (*Old Target and New Target Same* model), thereby not expecting the presence of sequence-specific information, but only a difference between re-occurring motor sequences and random sequences.

We first examined the main effects of model fits for each model, thereby searching for areas that showed, across all participants, a model fit that was significantly different from 0 (applying a $p < 0.05$ (FWE) threshold) and found that the first four models (*Old Target and New Target Stable* model, *Old Target Stable and New Target Evolving* model, *Old Target and New Target Evolving* model and *Old Target Distinct* model) all yielded positive results in a number of areas, including the putamen, thalamus, frontal pole, cerebellum, paracingulate gyrus, and temporal pole (Fig. 3A and Supplementary Tables 4–7 for complete lists of areas per model). However, for the *Old Target and New Target Same* model we found far less and smaller areas with significant model fits across all participants (Fig. 3A and Supplementary Table 8), while there were no areas with a significant model fit for the *New Target Distinct* model, demonstrating that a lot of areas involved in the task showed a specific multivariate activity pattern for the *old target* sequence that was distinct from the *new target* multivariate activity pattern. In a next step, we tested whether representations (i.e. model fits) were different between the 1d- and 28d-groups. When using a FWE cluster extent threshold (with a high cluster forming threshold of $p < 0.001$ unc.), we found two clusters, one in the right superior frontal gyrus (peak voxel: $x = 24$, $y = 20$, $z = 60$) and one in the right frontal pole extending into the middle frontal gyrus (peak voxel: $x = 38$, $y = 42$, $z = 42$) that showed significantly better model fits in the 28d-group in comparison to the 1d-group for the *Old Target and New Target Stable* model, *Old Target Stable and New Target Evolving* model and the *Old Target and New Target Evolving* model, i.e. those models that predict similar representational patterns for all regressors of the *old target* sequence and similar representational patterns for all regressors of the *new target* sequence respectively, that are, however, dissimilar from each other (see Fig. 3B and Supplementary Tables 9–11). Thus, these three models overlap to a certain extent and the reported clusters do not seem to differ between models that reflect an evolving learning process across the six blocks or a stable pattern across the six blocks. Importantly, however, we did not find group differences in these frontal cortex areas for the remaining three models (the *Old Target Distinct* model, the *New Target Distinct* model and the *Old Target and New Target Same* model), thus the decisive characteristic of a model that leads to differences between the 28d group and the 1d group in these frontal areas seems to be the separation between multivariate patterns for the old, consolidated motor sequence memory and patterns for a newly learned sequence. As this separation between the patterns of the two sequences seems to be higher after 28 days than after one day, one can assume that these frontal cortex areas are more involved in separating remote (4 week old) motor sequence memory representations from newly learned sequence representations than separating recent (1 day old) motor sequence memory representation from newly learned sequence representation. Notably, the cluster in the right frontal pole extending into the middle frontal gyrus included the right middle frontal area that showed a higher probability for an overall task-related involvement after 28d than after 1d in the univariate Bayesian analysis.

3.6. Results for subgroup with implicit awareness

In a last step, we examined whether the results obtained in the analysis with all participants ($n = 39$) held for a sample including only participants without explicit awareness of the sequences ($n = 29$; see methods section 2.4., Supplementary Figs. 1–3 and Supplementary Tables 12–19). Importantly, this analysis showed that the behavioral results remained largely comparable to those for the full sample (see Supplementary Fig. 2). In the Bayesian second level analysis, the results from the implicit sample showed a comparable pattern to that of the whole sample (Supplementary Fig. 3) for the overall task activity, although this time the higher probability of activation for the 28d-group in the frontal areas seemed to be especially reflected in *new target*trials and *random* trials. The search-light RSA results of the reduced sample, showed a comparable pattern to that of the whole sample (Supplementary Fig. 4), although the frontal pole clusters with a higher model fit in the 28d-group compared to the 1d-group (first three models) were located slightly inferior to those clusters found in the whole sample, yet all these clusters were located in the right frontal pole.

4. Discussion

Time-dependent neural reorganizations of hippocampus-dependent episodic or spatial memory have been a topic of intense scientific inquiry for decades (Dudai et al., 2015; Frankland and Bontempi, 2005; Moscovitch et al., 2016; Squire et al., 2015). Yet, if and how the neural representation of memories that are largely independent of the hippocampus changes over long time periods has received significantly less attention (Dayan and Cohen, 2011; Doyon et al., 2009). We tested here time-dependent changes in the neural representation of minimally trained motor sequence memories, known to rely mainly on cortico-striatal circuits (Dayan and Cohen, 2011; Doyon and Benali, 2005, but see Albouy et al., 2015; Albouy et al., 2013; Rose et al., 2011; Schendan et al., 2003 for evidence of an additional involvement of the hippocampus in implicit motor learning). Our behavioral findings show that even a single motor sequence learning session resulted in robust sequence-specific motor memory 28 days later. This motor memory was reflected in significantly faster reaction times for the target sequence learned during training compared to both a *random* sequence and a newly learned sequence during the test phase, which enabled us to separate actual motor memory from new learning during the test session. Our neuroimaging data are generally in line with previous findings implicating primarily cortico-striatal and cortico-cerebellar systems in motor learning tasks (Dayan and Cohen, 2011; Doyon et al., 2009; Doyon and Benali, 2005). Bayesian second-level fMRI analyses, which allowed us to directly test the evidence in favor and against the null hypothesis of similar motor memory-related activity after 1d and 28d, revealed a higher probability for overall task activity in the middle frontal gyrus and frontal pole 28d compared to 1d after initial motor learning. Further, searchlight RSA suggested that areas in the right middle frontal gyrus and frontal pole, including the area identified in the overall task-related Bayesian analysis, as well as areas in the right superior frontal gyrus are more involved in differentiating between multivariate activity patterns for old motor sequence memories and activity patterns of newly learned motor sequences in the 28d-group compared to the 1d-group. Together, these findings indicate time-dependent changes in the neural representation of motor sequence memory even without further training, in particular a stronger involvement of (lateral) prefrontal areas, mainly the middle frontal gyrus and the superior frontal gyrus, in differentiating remote motor sequence memories from new learning.

Although the middle frontal gyrus has been mainly linked to working memory (Leung et al., 2002; Ranganath et al., 2003) and inhibitory control processes (Garavan et al., 1999; Verbruggen and Logan, 2008), there is also some evidence for a role in motor learning and memory. Specifically, the middle frontal gyrus has been implicated in motor imagery (Decety et al., 1994) and in the initial acquisition of a motor skill (Shadmehr and Holcomb, 1997). Critically, however, the role of the middle frontal gyrus in the present study cannot be limited to the motor sequence learning process or the mere differentiation between two distinct motor sequences, as our findings show that the involvement of

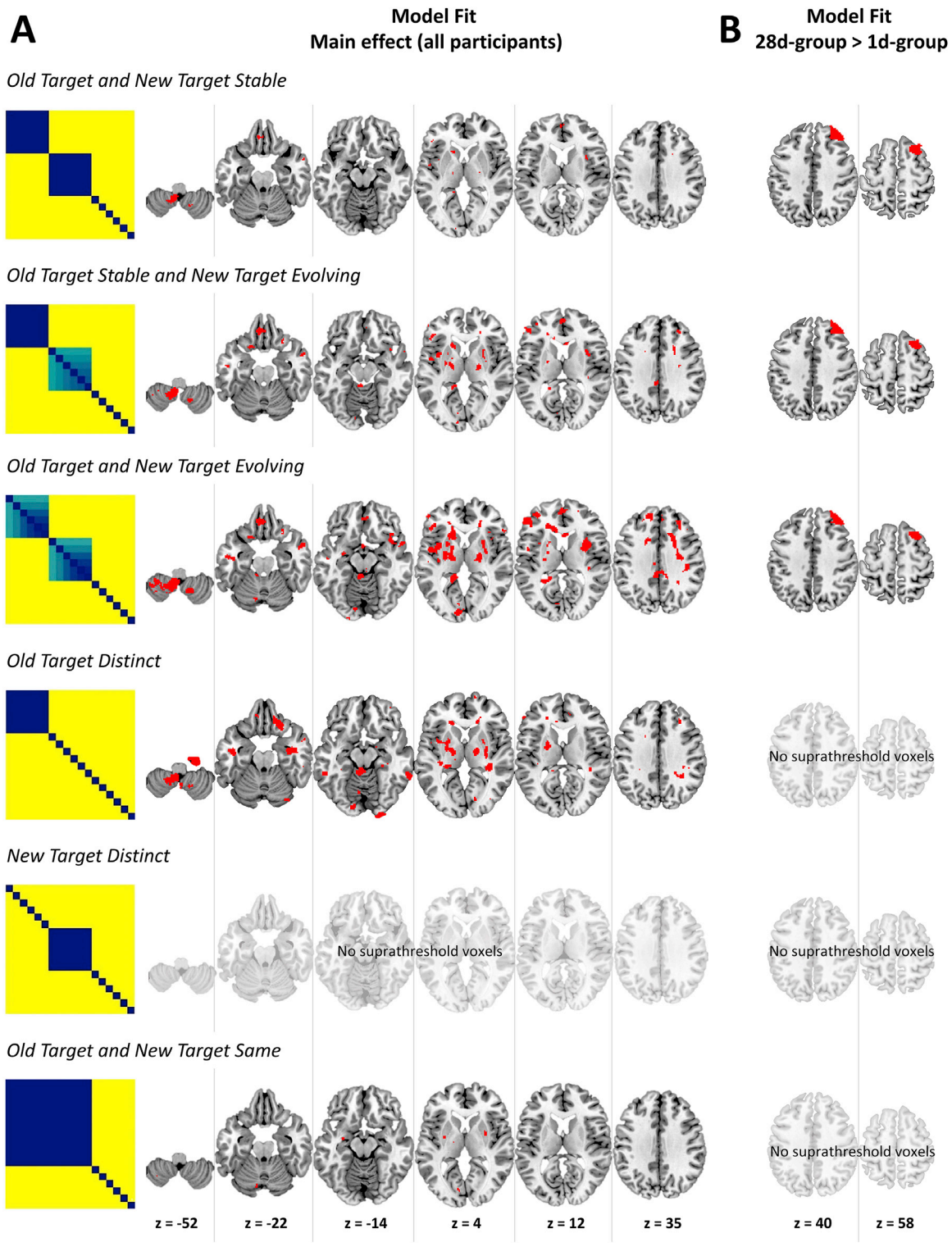

Fig. 3. Results from the RSA searchlight analysis (n = 39). **(A)** Main effects of the model fits (for all participants) for each of the six models separately: the *Old Target and New Target Stable* model in the first row, the *Old Target Stable and New Target Evolving* model in the second row, the *Old Target and New Target Evolving* model in the third row, the *Old Target Distinct* model in the fourth row, the *New Target Distinct* model in the fifth row and the *Old Target and New Target Same* model in the sixth row. All voxels surviving a threshold of $p < 0.05$ (FWE corrected) are coloured in red. For anatomical labels and coordinates see Supplementary Tables 4–8. **(B)** Group differences (28d-group > 1d-group) for each model. All voxels surviving a FWE cluster-threshold with a cluster forming threshold of $p = 0.001$ and a cluster-extent of 223 voxels (*Old Target and New Target Stable)*, 227 voxels (*Old Target Stable and New Target Evolving)* or 226 voxels (*Old Target and New Target Evolving*) are coloured in red. In right prefrontal areas, we obtained better model fits in the 28d-group compared to the 1d-group for the *Old Target and New Target Stable* model, the *Old Target Stable and New Target Evolving* model, and the *Old Target and New Target Evolving* model, but no suprathreshold voxels in the other three models. For anatomical labels and coordinates see Supplementary Tables 9–11. All visualizations are superimposed on axial slices of a template image. Figures were created using MRIcron (https://www.nitrc.org/projects/mricron).

the middle frontal gyrus (and superior frontal gyrus) in the differentiation of *old* and *new target* sequences was time-dependent. The separation of the old and new sequence representations was significantly more pronounced in the middle frontal gyrus (and superior frontal gyrus) after 28d than after 1d, indicating a time-dependent involvement of the middle frontal gyrus in the motor sequence memory representation.

The increased involvement of neocortical (prefrontal) areas across time is, in principle, in line with the proposed systems consolidation for hippocampus-dependent episodic memories (Dudai et al., 2015). However, for episodic memories, the time-dependent increase in the recruitment of the neocortex is thought to be accompanied by a decreased involvement and, ultimately, independence of the hippocampus (Frankland and Bontempi, 2005; Squire et al., 2015). Although we found decreased activity in the 28d-group compared to the 1d-group in the postcentral gyrus for the overall task activity, there were no areas in which the multivariate activity pattern for the *old target* sequence was more distinctly represented in the 1d-group than the 28d-group. In other words, the cortical, striatal, and cerebellar regions relevant for motor memory (and active in our analyses of overall task-related activity) after 1d appeared to be equally relevant for motor memory after 28d. Thus, our data suggest that there is no systems consolidation-like relocation of the motor sequence memories from some areas to others but instead an increased additional involvement of frontal areas in remote motor memories.

As noted above, several recent studies have suggested an additional involvement of the hippocampus during learning and early consolidation processes of a motor sequence task (Albouy et al., 2013, 2015; Rose et al., 2011; Schendan et al., 2003). We, however, found no increase in hippocampus activity during the overall performance of the task across both groups. On the contrary, some areas within the medial temporal lobe, including parts of the hippocampus, showed even reduced activation compared to the implicit baseline during performance of the task. Although, we did not focus on the involvement of the hippocampus in the present study and therefore cannot draw strong conclusions from these exploratory results, the reduced activation of the hippocampus during motor sequence learning may point to a competition between hippocampal areas, typically involved in episodic memory, and areas implicated in motor learning, such as the striatum (see also Poldrack et al., 2001; Poldrack and Packard, 2003). Future research is required to shed more light on the potential interaction of multiple memory systems during motor sequence learning. In addition, it is also important to note that our participants performed a declarative memory task before the motor sequence learning task and previous research suggested that declarative and procedural tasks performed one after another may influence each other (Keisler and Shadmehr, 2010; Robertson, 2012). Although group differences could hardly be explained by the prior performance of a declarative task because this task was performed by both groups in the same way, overall task-related activity (across groups) may have been influenced by the prior encoding task (Dandolo and Schwabe, 2018).

While we argue here that the representation of motor memories changes over time and that middle and superior frontal cortex areas represent, in addition to other cortico-striatal areas, remote motor memories, an alternative explanation might be that the increased involvement of these areas is due to an increased effort during the recall of the motor memories after 28d. Although lateral prefrontal areas have been associated with retrieval effort (Buckner and Wheeler, 2001; Henson et al., 1999), we consider this alternative rather unlikely. If participants had to show more effort to reproduce the learned sequence after 28d than after 1d, then this should be reflected in increased reaction times for the *old target* sequences in the 28 day group. Yet, we did not find a main effect of group or interaction effects including the factor group in the reaction time data. In addition, cognitive effort that is mediated by lateral prefrontal areas should be mainly relevant for the retrieval of explicit information. We used here, however, an implicit form of the SRTT and the vast majority of the participants were not explicitly aware of the *old target* sequence. Thus, retrieval effort may have been less relevant for most participants in the used task. Importantly, there were no differences between the 1d- and 28d-groups in terms of the number of participants that were explicitly aware of the target sequences and an additional analysis including only those participants without explicit awareness (see Supplementary Materials) showed mainly comparable results, although the area within the prefrontal cortex found in the RSA analyses was located more inferior in the sample of the participants without explicit awareness. However, we did not have enough participants to directly test whether the temporal dynamics are comparable for implicit vs. explicit motor sequence learning and future studies are needed to explicitly compare the areas involved in representing remote implicit or explicit motor memories. Overall, it should be noted that due to the necessary exclusion of nine participants (see Section 2.1.), the power of the study was lower than optimal, which makes it important for future research to run a replication study in a larger sample.

Furthermore, for episodic memories it has been suggested that the neuronal reorganization from hippocampus-dependent to more neocortical representations across time is accompanied by a transformation from rich, detailed memories to more semantic, gist-like representations (Moscovitch et al., 2016; Nadel et al., 2007; Winocur and Moscovitch, 2011). It would be very interesting to test whether the time-dependent changes in the neural representation of motor memories that we suggest here are also paralleled by a transformation in the nature or expression of motor sequence memories over time. Future studies might address this question by using new sequences in the test session that explicitly resemble the initially learned target sequence. Moreover, tracking the temporal dynamics of the reorganization of motor sequence memory representations is an important challenge for future research. We used here a 28d interval because earlier studies showed systems consolidation processes for episodic memories after several weeks (e.g. Takashima et al., 2006). However, the temporal profile of systems consolidation processes for motor memories may be different than what we know from episodic memory and testing parallels and differences between the reorganization of motor and episodic memories at different time intervals would be highly interesting. Finally, while our data showed more distinctive multivariate patterns for the target sequences in the 28d-group in the right, but not left, middle and superior frontal gyrus, it remains to be shown, for instance by employing brain stimulation techniques, whether the time-dependent involvement of lateral prefrontal cortex in motor memory is indeed lateralized.

In sum, we provide here evidence for time-dependent changes in the neural circuitry underlying motor sequence memory. More specifically, our findings show an increased involvement of lateral prefrontal cortex in the representation of remote compared to recent motor sequence memories. In contrast to the proposed systems consolidation of episodic or spatial memories (Dudai et al., 2015; Squire et al., 2015), however, the time-dependent increase in the involvement of neocortical areas after four weeks was not paralleled by a decrease in those cortico-striatal areas that supported initial motor learning. Instead, the additional recruitment of lateral prefrontal areas might contribute to a more distributed representation of remote motor memories. These findings provide insights into how memories beyond the hippocampus evolve over time.

Author contributions

L.C.D. collected the data, analyzed the data, and wrote the manuscript. L.S. conceived and designed the experiment, supervised the project, and wrote the manuscript.

Conflicts of interest

The authors declare no competing financial interests.

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Appendix A. Supplementary data

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