Behavioral/Cognitive

The Time Course of Task-Specific Memory Consolidation Effects in Resting State Networks

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Previous studies have reported functionally localized changes in resting-state brain activity following a short period of motor learning, but their relationship with memory consolidation and their dependence on the form of learning is unclear. We investigate these questions with implicit or explicit variants of the serial reaction time task (SRTT). fMRI resting-state functional connectivity was measured in human subjects before the tasks, and 0.1, 0.5, and 6 h after learning. There was significant improvement in procedural skill in both groups, with the group learning under explicit conditions showing stronger initial acquisition, and greater improvement at the 6 h retest. Immediately following acquisition, this group showed enhanced functional connectivity in networks including frontal and cerebellar areas and in the visual cortex. Thirty minutes later, enhanced connectivity was observed between cerebellar nuclei, thalamus, and basal ganglia, whereas at 6 h there was enhanced connectivity in a sensory-motor cortical network. In contrast, immediately after acquisition under implicit conditions, there was increased connectivity in a network including precentral and sensory-motor areas, whereas after 30 min a similar cerebello-thalamo-basal ganglionic network was seen as in explicit learning. Finally, 6 h after implicit learning, we found increased connectivity in medial temporal cortex, but reduction in precentral and sensory-motor areas. Our findings are consistent with predictions that two variants of the SRTT task engage dissociable functional networks, although there are also networks in common. We also show a converging and diverging pattern of flux between prefrontal, sensory-motor, and parietal areas, and subcortical circuits across a 6 h consolidation period.

Key words: consolidation; fMRI; ICA; motor learning; resting state

Introduction

Motor memories are acquired during practice of a particular task, and are then consolidated into long-term memories over a period of hours; they can be later recalled and potentially modified when the task is next performed (Walker et al., 2003; Lee et al., 2008). Changes in these memories over successive training sessions contribute to improvement in performance, and are the basis of motor learning. However, performance can also improve over an interval without further training, and evidence suggests "off-line" consolidation processes that modify the underlying motor memories, leading to improved performance on retesting of the skill (Robertson, 2009). Consolidation also leads to enhanced resistance of the memories to interference (Shadmehr and Holcomb, 1997). Memory consolidation is thus a complex phenomenon,

with parallel processes that appear to depend on separate neural pathways (Robertson, 2009).

To better understand these off-line processes, we have previously reported changes in the functional connectivity of the brain, by measuring resting-state BOLD activity using fMRI imaging. We have shown significant changes in resting state connectivity induced after a short period of training in a visuomotor adaptation task (Albert et al., 2009). Others (Daselaar et al., 2010; Ma et al., 2010) have shown similar results: learning alters subsequent brain activity, and the resting brain shows altered functional connectivity. These changes are assumed to contribute to, or be a signature of, the background consolidation of the acquired motor memories.

The networks engaged after the visuomotor learning task (Albert et al., 2009) appear to be members of previously identified resting-state networks (RSNs), reliably identified in both awake and sleeping human participants (Damoiseaux et al., 2006; Shehzad et al., 2009; Van Dijk et al., 2010). Smith et al. (2009) have also demonstrated a close correspondence between networks obtained from resting-state data and networks activated during active task performance. Hence, RSNs represent reproducible yet distinct networks that reflect segregated functional circuits, are a fundamental aspect of brain organization (Smith et al., 2009; Meindl et al., 2010), and are sensitive to the effects of learning.

However, although this work suggests that different motor learning tasks should engage different networks during acquisition, whether the subsequent consolidation processes are com-
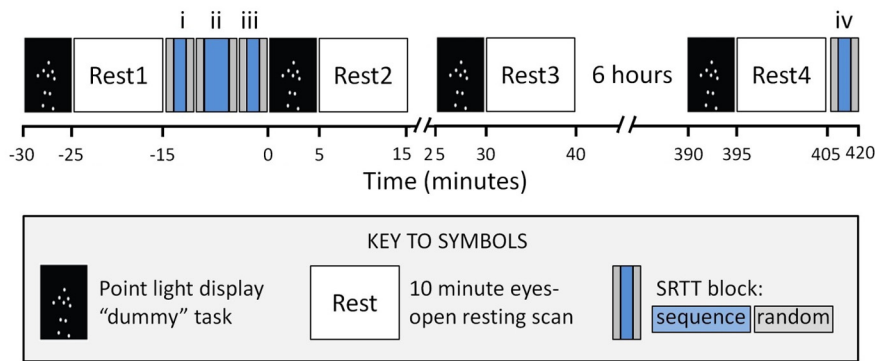
Figure 1. A timeline of the experiment (top): the morning session began with a dummy task with point light displays of human whole-body movements or scrambled versions, followed by a baseline rest condition (REST1), followed by exposure to the SRTT task in three blocks (i–iii). This was immediately followed by the second dummy and resting scans (REST2) and a further dummy and resting scan (REST3) timed to be completed 30 min after the SRTT task. Following a 6 h break of wakefulness, participants completed a second session. This afternoon session included the fourth dummy and rest scans (REST4), as well as the final SRTT block to retest performance after the consolidation period. Each block of the SRTT included a set of sequence trials sandwiched between two sets of random trials (bottom shows key to top).

mon or distinct has not yet been resolved. We address this question by measuring resting activity before and after learning a sequence task, the serial reaction time (SRT) task, in participants trained under implicit and explicit task conditions. We modified these tasks to ensure that both groups showed motor skill enhancement during awake consolidation (see Materials and Methods). Thus, we expect behaviorally measureable consolidation to take place within hours after task acquisition, even though there may be later sleep-dependent consolidation (Brown and Robertson, 2007a). Hence we predict dynamic changes in resting-state activity over a six-h daytime consolidation period, and we tested this by comparing resting state activity at three time points after serial reaction time task (SRTT) learning. We hypothesize that SRTT learning under implicit conditions will initially engage sensory motor circuits (Wilkinson et al., 2010), and learning under explicit conditions will also engage prefrontal cortex (Grafton et al., 1995; Yang and Li, 2012).

Materials and Methods

Participants and experimental protocol. Twenty-nine healthy volunteers (9 male, 23.6 ±5.2 (mean ± SD) years) participated in the experiment and gave written informed consent; the local ethics panel of the University of Birmingham approved the experiments. Participants completed the Edinburgh handedness questionnaire to confirm that they were right handed. Participants were then randomly allocated into one of two groups, learning a procedural sequential button-pressing task known as the SRTT under explicit or implicit presentation conditions. They performed the SRTT during an initial acquisition session (testing) and 6 h later (retesting). Five participants were retrospectively excluded from the study: two were removed due to the lack of significant learning in the explicit task; two were removed from the implicit task group due to their ability to declaratively describe the sequence, which implies that they became explicitly aware of the task, and one was removed due to excessive head movement in the MRI scanner. Overall, there were 24 remaining participants, with 12 in each group.

The participants lay with their right hand resting on a button response box which had buttons arranged in a horizontal array. They were scanned at rest, during 15 min of performance of the motor sequence learning task in the fMRI scanner, and scanned at rest again 0.1, 0.5, and 6 h after completion of the learning task (Fig. 1 shows a full timeline).

Resting-state scans. Participants lay in the scanner with their eyes open and were instructed to remain relaxed, with gaze held still, but without need either to force fixation or to suppress blinking. The button box was removed during the 10 min rest scans, to avoid any finger-to-button

contact. In addition, to ensure that participants had similar mental states at the onset of each resting state scan, and so reduce variability among and between those scans, each resting scan was preceded by a 5 min dummy task, in which the participant passively viewed dynamic point light displays of human whole-body movements (Albert et al., 2009). The first resting scan (REST1) was immediately followed by SRTT acquisition; a second dummy scan and REST2 then followed, with the resting scan running from approx. Five to 15 min from the end of the SRTT task. The next dummy scan and REST3 followed after a 10 min break, in which the participant remained at rest within the scanner, but with fMRI acquisition, so that REST3 ran between ~35 and 45 min from the end of the SRTT task. After REST3, they were brought out of the scanner, and asked to return 5 h later. Participants were then given a final dummy task, and REST4 starting 6 h after the end of the initial SRTT acquisition. A final SRTT block followed REST4, to allow assessment of consolidated task performance. After emerging from the MR scanner, all participants in the implicit task group were then questioned about their knowledge of the sequence, and asked to free recall any of the repeated sequence that they could remember.

The serial reaction time task. We used a modified version of the SRTT (Nissen and Bullemer, 1987). A solid square stimulus (20 mm, viewed from ~800 mm) appeared on a monitor at any one of four possible positions within an equally spaced horizontal array. Each of the four possible positions corresponded to one of four buttons on a response pad (LUMItouch, fMRI Optical Response keypad, Photon Control). When a target appeared, subjects were instructed to respond by pressing the appropriate button on the pad as quickly as possible. Subjects responded using the four fingers of their right hand, which rested on the four buttons. If the subject made an incorrect response, the stimulus remained until the correct button was selected. Once the correct response was made, the cue on the screen disappeared and was replaced by the next cue after a delay of 400 ms. Response time was defined as the interval between presentation of a stimulus and selection of the correct response. This measure included the time associated with making any earlier incorrect responses.

Two versions of the SRTT were used. In the explicit version, subjects were instructed that a change in the color of the stimuli from black to blue heralded the beginning of a repeating sequence (2-3-1-4-3-2-4-1-3-4-2-1). Subjects were neither told the sequence itself nor its length, and unlike previous uses of this task subjects were not told that they would be asked to declaratively recall the sequence at the end of the final session. Reducing the relevance of a memory can weaken its interference with other memories (Fischer and Born, 2009). So, by making the declarative knowledge irrelevant for future recall would, we predicted, minimize the interference between the declarative and motor skill memory, which has been observed in earlier studies, and so allow the explicit task to show off-line improvements (Brown and Robertson, 2007a,b; Robertson, 2009; Galea et al., 2010; Cohen and Robertson, 2011). Thus, the explicit task, like the implicit task should show off-line improvements during the daytime consolidation (Robertson et al., 2004). In the implicit version, the task was described to participants as a test of reaction times; however, in reality the position of each cue followed the same regular and repeating 12-item pattern. In the implicit group, no cues marked the beginning or the end of the sequence. Note that we can only assume implicit or explicit awareness of the SRTT sequences during the acquisition and testing phases. We refer to these tasks as "implicit" and "explicit" with this caveat in mind. However, verbal recall of the sequence was tested at the end of the experiment, and those participants able to successfully recall more than four items in the correct order were excluded from the implicit group.

The first session consisted of three blocks: a training block (Block ii) sandwiched between two test blocks (Blocks i and iii; Fig. 1). After 6 h, subjects performed a single retest (Block iv). For both the implicit and explicit tasks, the training block (Block ii) had 25 repetitions (300 trials) of the 12-item sequence. The two (pre- and post-training) test blocks and the re-test block had only 15 repetitions (180 trials). These test blocks were designed to be sufficiently long to allow a valid assessment of procedural skill without giving an opportunity to acquire further skill.

Fifty random trials preceded and followed the sequential trials in the training and test blocks, for both the implicit and explicit groups (Fig. 1). Within these random trials there were no item repeats (for example, 2-1-1-4 was illegal); there were few three of four item segments of the sequence; and each item had approximately the same frequency of appearance. Each set of random trials in the training and test blocks were unique. This minimized the chance that participants might become familiar with the random trials. However, the random sequences of trials used for the implicit group and explicit group were identical. This minimized still further the differences between the groups, allowing performance of the finger movement sequence to be compared with the response times of a common set of random trials.

For the explicit group only, we marked the introduction of the repeating sequence with a change in the color of the guiding visual cue from black to blue. In the implicit group, the visual cues remained black throughout all the trials. Others have successfully used a similar cueing strategy as a means to engage an explicit learning strategy (Curran, 1997, Robertson et al., 2004). Merely changing the color of the cue without altering its relationship with the response does not significantly impact learning in the SRTT (Robertson et al., 2004). The color change only marked the introduction of the sequence, not its removal. Hence, the onset of the final 50 random trials was unknown to the participants in both groups. Therefore, our measure of skill, the contrast between the response times of the final 50 sequential and the following 50 random trials, was comparable across the two groups.

Behavioral analysis. Accuracy in the SRT task is not a useful measure of skill because even with limited experience, error rates are extremely low (<1–2%). We therefore report average response times, defined as the interval between the appearance of the stimulus on the screen and the time of the correct response. Response times >2200 ms (top 1% of response times) were not included in this analysis. Response times are influenced not only by growing knowledge of the sequence but also by nonspecific factors, for example fatigue and circadian effects (Robertson, 2007). To factor out these influences, in both the implicit and explicit groups, we contrasted the response times for the final 50 sequential trials in each block against the following 50 random trials. This contrast was performed using a repeated-measures ANOVA, which was extended to explore the influence of the learning type (explicit vs implicit) upon off-line learning.

Neuroimaging procedures. MR scanning was performed at the University of Birmingham Brain Imaging Centre in a 3T Philips Achieva scanner (Koninklijke Philips Electronics) using a standard 8-channel head coil with SENSE factor 2. The scanning protocol consisted of structural and functional resting state scans in which subjects were instructed to lie still with their eyes open looking at a fixation cross on a screen (Fig. 1).

Gradient-echo echo-planar images were acquired with TR = 2.8 s/volume, TE = 0.035 s, flip angle = 85°, FOV = 240 mm × 147 mm × 240 mm (anterior–posterior, inferior–superior, left–right, respectively) and voxel size = 2.5 × 2.5 × 3 mm. Forty-nine horizontal slices of 3 mm thickness covering the entire brain including the cerebellum were acquired in ascending order from bottom to the top of the brain. In addition, whole brain T1-weighted anatomical scans were collected with 1 mm × 1 mm × 2 mm resolution (TR = 8.4 ms; TE = 3.8 ms; flip angle =
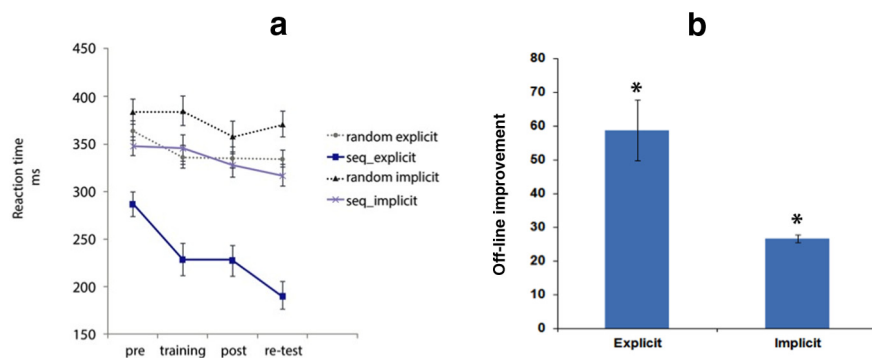
Figure 2. *a*, Group performance in the SRTT task. Each block of the SRTT included random, sequential, and random trials. The average reaction times for the last 50 sequence trials and the subsequent 50 random trials are shown for both groups, at all measurement points. Error bars represent SE of the mean. (SRTT Blocks i–iv; Fig. 1). Both groups show some nonspecific improvement in performance across the random conditions as they became more familiar with the task. However, the major change is the gradual and sustained improvement in reaction times to the sequential trials, indicating acquisition and consolidation of the sequential skill. *b*, Off-line learning, i.e., change in skill (difference in RTs from random to sequence) measured between post test and the afternoon session, showing significant off-line learning in both the explicit and implicit condition. Bars are group mean, error bars are SEM; *$p < 0.05$.

8°, FOV = 232 mm × 288 mm × 175 mm). The structural images were acquired for coregistration and normalization of the resting scans to the MNI-template in the data preprocessing stages.

Image analysis. The data analysis was conducted using FSL (FMRIB Software Library, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). Programs within this toolbox were used to perform standard preprocessing including brain extraction, head motion correction, and spatial smoothing.

Each brain volume was motion-corrected using MCFLIRT, high-pass filtered (0.01 Hz cutoff), masked to eliminate nonbrain voxels, spatially-smoothed using a Gaussian kernel of full width half maximum of 5 mm filter, demeaned on a voxel-by-voxel basis. For coregistration, the FSL-based nonlinear registration tool was applied to register each mean functional whole brain volume to the individual's structural scan and then to standard MNI average brain. Nonbrain structures were removed from the high-resolution structural image using the semiautomatic brain extraction tool and the transformation matrix used for the affine registration of the functional image to MNI standard structural image.

Probabilistic independent components analysis (PICA) of the BOLD signal allowed us to identify the networks present during rest and to measure changes in these components after motor learning. The FSL program MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) was used to identify independent components that were spatially consistent across the group, without requiring common temporal structure (Beckmann et al., 2005). First, we concatenated REST1 with each one of the three other rest conditions (REST2–4), within each task group, using a contrast model to dissociate the baseline sessions from the postlearning sessions. This allowed for the identification and analysis of RSNs that were found in common across both resting state sessions, within the same task group. The contrast between these two datasets restricted the selection to components with significantly different coefficients between the two sessions. Each independent component was visually inspected to ensure that they were spatially similar to previously identified resting networks. The multivariate ICA approach separates multiple signal sources from the mixtures within the time series, and is very likely to identify and separate signals from physiological sources as independent components from the resting state components. We visually inspected the spatial pattern, time course and frequency spectrum of the components of interest, to ensure they were not apparently contaminated by noise signals. Following visual inspection we calculated the spatial correlation between two corresponding RSN images using the Resting-State fMRI Data Analysis Toolkit (Song et al., 2011). Additionally, the power spectrum of the BOLD signal was inspected to confirm the expected low-frequency power profile typical of resting state network activity (Damoiseaux et al., 2006; Smith et al., 2009).
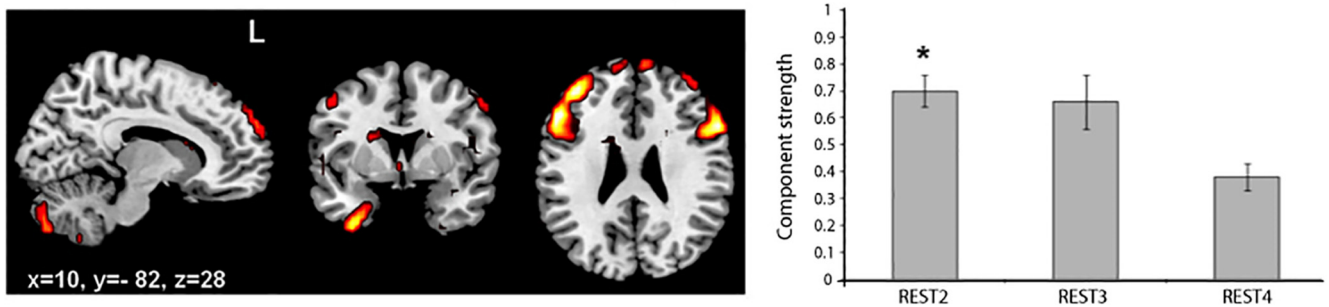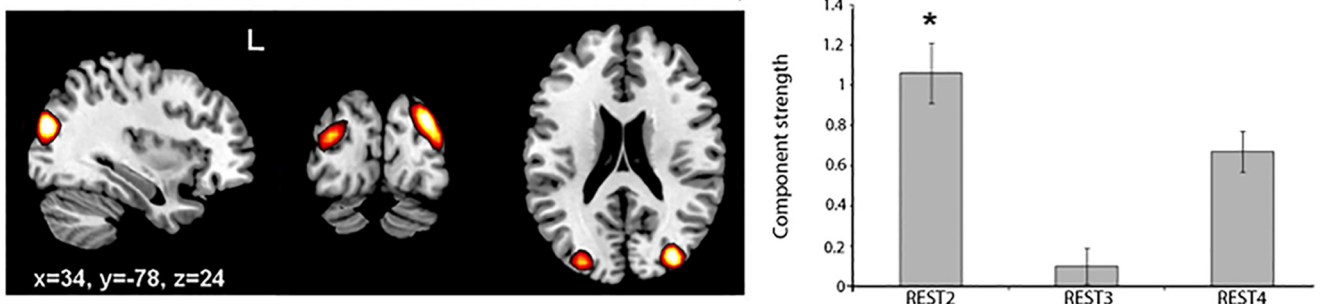
Figure 3. *a*, Group level ICA maps shows whole brain coverage of the executive frontal cerebellar RSN regional shown in sagittal, coronal, and axial slices. Bar charts depict the changes in strength for this RSN following the explicit serial reaction time task (REST2, REST 3, REST4) illustrating the most significant modulation in the earliest REST2 stage. *b*, Functional connectivity group level results for the Visual RSN shown in sagittal, coronal, and axial slices. The bar charts represent the changes in this RSN following the contrast between baseline and the three resting conditions after explicit task (group mean ± 1 SEM). The results highlight the visual RSN showed significant early changes in component strength for the REST 2 condition.

Table 1. Cerebellar-frontal executive network

Component local maxima	BA	Peak Z	Peak x	Peak y	Peak z
Frontal lobe					
L inferior frontal gyrus	46	6.17	−50	34	8
L middle frontal gyrus	44	4.84	−42	38	28
L orbital middle frontal gyrus	45	4.15	−46	46	0
L triangular inferior frontal gyrus	45	7.06	−42	22	32
R inferior frontal gyrus	46	7.06	−50	34	8
R triangular inferior frontal gyrus	45	5.32	−54	34	0
Parietal lobe					
L angular gyrus	39	4.74	−62	−54	12
L supramarginal gyrus	40	4.07	−50	−46	12
R angular gyrus	39	3.55	54	−46	16
Cerebellum					
R Crus II		5.14	22	−78	−48

Maximum activation peaks in MNI space, their anatomical labels and equivalent Brodmann areas (BA), as well as the corresponding Z value of the activation peaks for the cerebellar-frontal executive network identified under explicit conditions following a comparison between REST1 and REST2.

Table 2. Visual networks

Component local maxima	BA	Peak Z	Peak x	Peak y	Peak z
a, REST 1: REST2 EXPL					
L lateral occipital gyri (cortex)	18	14.82	−30	−86	20
R lateral occipital gyri (cortex)	18	19.30	30	−82	28
b, REST 3: IMPL & EXPL					
L lateral occipital gyri	18	11.45	−35	−80	24
R lateral occipital gyri	18	12.35	32	−84	20
c, Dual regression REST 3: IMPL & EXPL					
L lateral occipital gyri	18		−30	−74	23
R lateral occipital gyri	18		35	−83	22
d, REST4: IMPL & EXPL					
L V2	18	10.84	−10	−58	0.0
R V2	18	11.23	14	−58	0.0
L V1	17	13.11	−2	−70	4.0
R V1	17	10.69	22	−58	4.0

A similar labeling scheme to Table 1 but this time for visual networks which led to focal activations in the occipital cortex identified across (*a*) REST2, under the explicit conditions, (*b*) REST 3 following the comparison between implicit and explicit conditions, (*c*) following dual regression under the same condition as in (*b*), and finally in (*d*) REST 4 following the comparison between implicit and explicit conditions.

To test for comparable baseline activity for these identified components, we temporally concatenated the baseline rest (REST1) from the two groups (explicit and implicit), testing for differences in the identified components before learning. The final set of planned contrasts was between the explicit and implicit group data at each of the resting stages (e.g., REST2 Explicit vs Implicit, REST3 Explicit vs Implicit, etc.). In every case, we ran unconstrained PICA to identify the components.

Dual regression. To further investigate the between-group differences in functional connectivity, we performed a dual regression analysis on the resting state data (Beckmann et al., 2009). Dual regression uses the output of the temporally concatenated ICA to define regions of interest, and then creates individual subject-level connectivity maps for each component identified at the group level. Regression analyses between mean signal within each region of interest, found by regression of the group component onto the individual brain, against the whole brain activity, is then performed on the individual BOLD time-series. This results in subject-specific spatial components associated with each group level ICA map (Beckmann et al., 2009). In the final stage, the individual maps are combined into a group-level contrast between the conditions of interest, in our case comparison between REST1 and other REST sessions. The end result characterizes the between-session group differences in functional connectivity at the voxel level.

For visualization, thresholded statistical maps were superimposed on T1 structural MNI templates using FSL View based atlases (FMRIB Software Library), whereas the final images were produced with MRIcro (www.mricro.com).
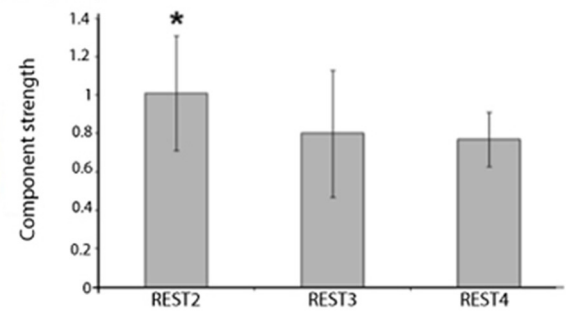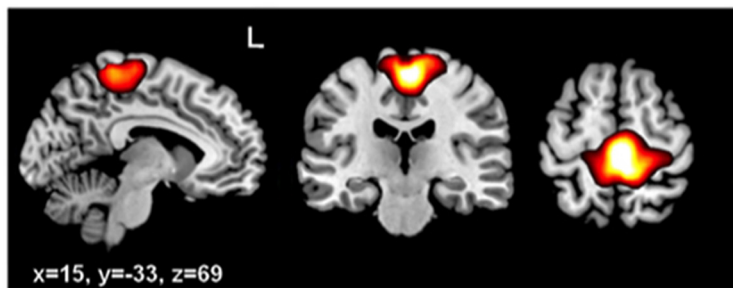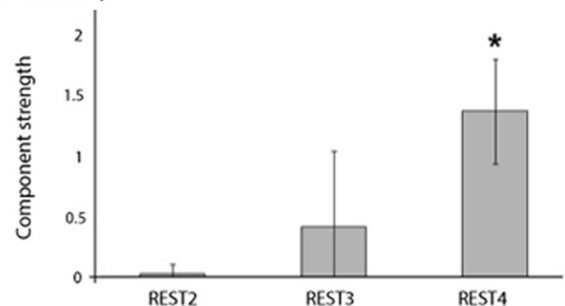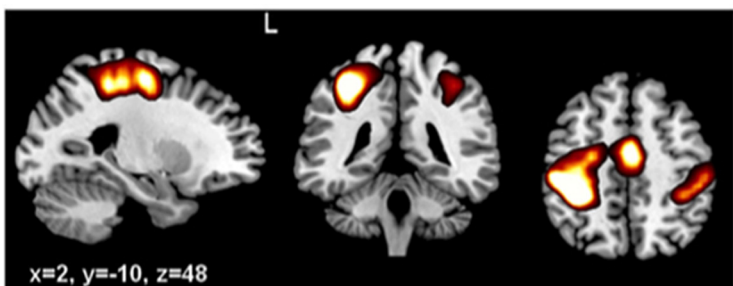
a Sensory Motor RSN (Implicit Rest conditions vs Baseline Rest)

b Sensory Motor RSN (Explicit Rest conditions vs Baseline Rest)

Figure 4. *a*. Group level ICA maps of the sensory motor RSN shown in sagittal, coronal and axial slices. The bar chart accompanying this figure highlights the early engagement of sensory motor networks activated, based on a comparison between the baseline rest and the three remaining rest condition following the implicit SRTT task. *b*, Group level ICA connectivity map shows the Sensorimotor RSN results following a comparison between baseline and the three rest stages following learning in the explicit SRTT task, the bar chart shows that and REST4 condition was significantly modulated (group mean ± 1 SEM).

Results

Behavioral results

All participants completed the full protocol, as indicated in Figure 1. After the final scan session in the afternoon, participants in the implicit group were asked to freely recall the sequence. We then excluded participants from this group who were able to recall more than four items of the 12-item sequence (see Materials and Methods). After this exclusion, the highest number of items recalled in the implicit group was 4 (median 0). On average those in the implicit group recalled 2.08 (±2) of the 12-item sequence. All subsequent analyses reported below use only data from these final implicit ($n = 12$) and explicit ($n = 12$) groups.

The initial naive level of performance of the two groups, tested during their responses to the first 50 random trials, was similar ($t_{(22)} = 0.06$, $p = 0.94$). The RTs for the random trials significantly reduced across the 4 blocks ($F_{(3,66)} = 5.124$, $p = 0.003$), but there was no significant group difference ($F_{(1,22)} = 1.131$, $p = 0.265$), nor a significant interaction ($F_{(3,66)} = 2.259$, $p = 0.09$). Thus, there was a nonspecific increase in response speed across both groups with practice. However, after even the initial exposure to the sequences, there was a clear difference between the performance of the two groups, with significantly shorter RTs measured in the sequence trials for the explicit group in the first test block ($t_{(22)} = 2.33$, $p = 0.02$). This was expected because of the participants' explicit knowledge that there was a sequence present, and so this group showed more rapid and more effective sequence acquisition. This difference was maintained and extended across the remainder of the initial training session, and after consolidation.

We define procedural skill as the difference in RTs for the last 50 sequence trials versus the subsequent random trials (Robertson, 2007). After the first acquisition Block i, both groups showed significant skill (1, sample *t* tests against skill = 0: implicit group $t_{(11)} = 3.94$, $p = 0.002$; explicit group $t_{(11)} = 3.54$, $p = 0.005$).

Next, a 2 × 4 mixed ANOVA comparing the repeated procedural skill measures from Blocks i–iv between the two groups (Fig. 2*a*) demonstrated a significant difference across the four blocks ($F_{(3,20)} = 6.808$, $p = 0.002$), and a significant group difference ($F_{(1,22)} = 9.996$, $p = 0.005$). Thus, both groups showed significant learning across the entire experiment, and a group difference. However there was no significant interaction ($F_{(3,66)} = 0.743$, $p = 0.53$).

Next, to assess change in performance over the 6 h consolidation period itself, we contrasted skill in the post-training test (Block iii) against skill at retest (Block iv) with a 2 × 2 ANOVA. As expected, the group difference reported above was maintained ($F_{(1,22)} = 8.07$, $p = 0.01$), because the level of procedural skill in the explicit group was greater than that in the implicit group. There was a significant main effect of time ($F_{(1,22)} = 12.113$, $p = 0.002$), demonstrating significant off-line improvement between testing and retesting, and *post hoc t* tests confirmed an increase in procedural skill for both implicit and explicit groups (implicit: $t_{(11)} = 2.36$, $p = 0.04$; explicit: $t_{(11)} = 2.70$, $p = 0.02$; Figure 2*b*). Thus, both groups demonstrated off-line consolidation of the sequence task. However, the interaction between group and time was not significant ($F_{(1,22)} = 1.72$, $p = 0.20$): the change in skill across the 6 h was roughly proportional to the difference in acquired skill after the initial session, and the mean difference in skill enhancement (delta-skill) was 32 ms. In our instructions to the participants in the explicit condition, we did not ask them to be able to verbally recall the sequence at retesting. By contrast, in earlier work participants have been asked to recall the sequence, which it is proposed, leads to interference between the declarative and motor skill memory for the sequence, and prevents enhancement of the motor skill memory during consolidation (Brown and Robertson, 2007a,b; Robertson, 2009; Galea et al., 2010; Cohen and Robertson, 2011; Robertson, 2012). However, when not instructed about later testing of declarative knowledge, there

Table 3. Sensorimotor networks

Component local maxima	BA	IMPLICIT REST1: REST2				EXPLICIT REST1: REST4			
		Peak Z	X	Y	X	Peak Z	X	Y	Z
L supplementary motor cortex	6	12.18	−3	−15	63	8.44	−1	−10	56
L primary motor area	4	11.36.90	−21	−27	6900	8.03	−34	−18	56
L primary somatosensory area	3	10.378	−24	−30	69	9.47	−34	−34	56
Parietal lobe									
L angular gyrus	3	3.59	−54	−54	24	4.93	−52	−48	32
L supramarginal gyrus	3	4.48	−50	−50	24	5.84	−55	−45	26
Dual regression									
Supplementary motor cortex	6		5	−12	57		−8	−15	60
Left amygdala			−18	−38	−12		−18	−38	−12

Highlights of the modulated sensorimotor networks using a similar labeling scheme as in Table 1. Left, Maximal peak activation in this network primarily effects the early implicit condition. Right, Highlights that the sensorimotor networks are particularly enhanced in the late explicit condition.

a Cerebellar Thalamus Basal Ganglia RSN (Explicit Rest conditions vs Baseline Rest)
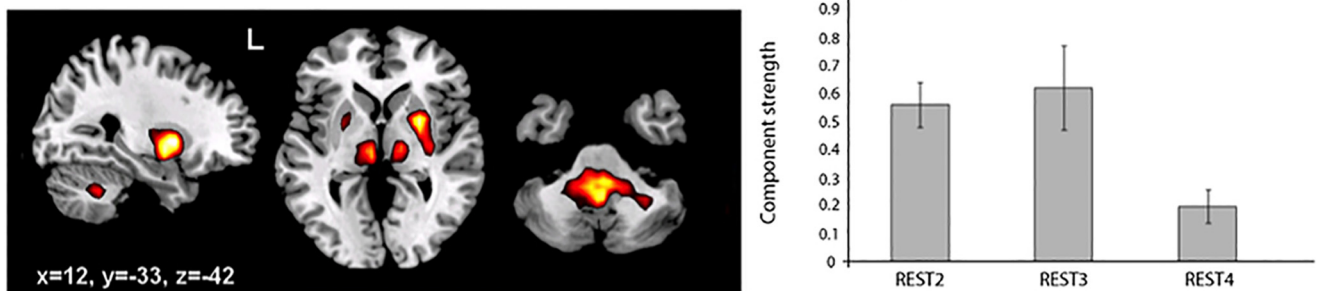
b Cerebellar Thalamus Basal Ganglia RSN (Implicit Rest conditions vs Baseline Rest)
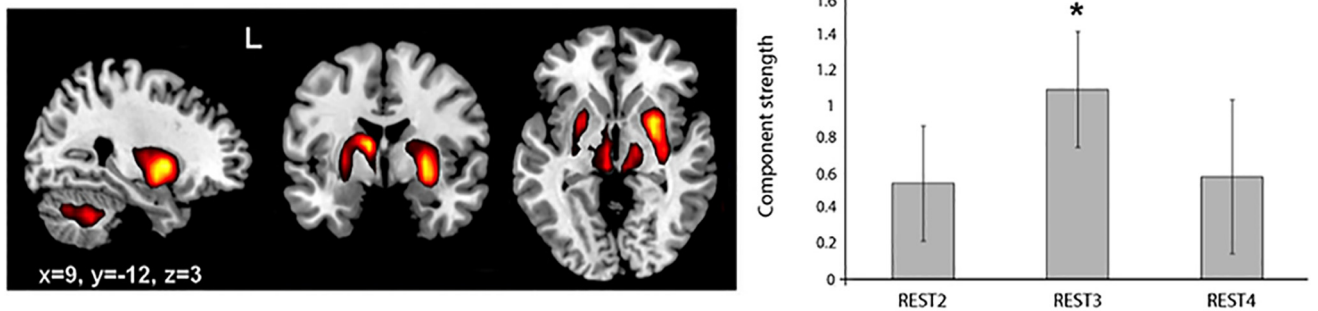
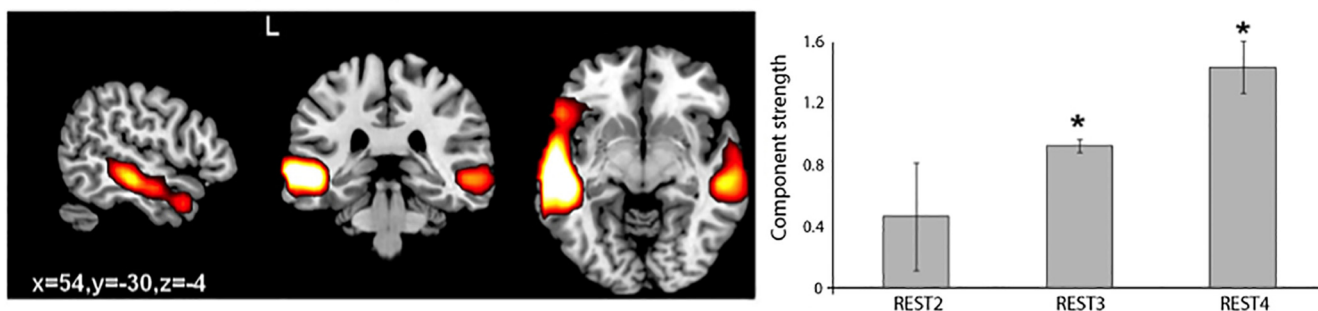**c** Medial Temporal RSN (Implicit Rest conditions vs Baseline Rest)

Figure 5. *a*, The figure exhibits functional connectivity group level ICA maps of the cerebellar thalamus basal ganglia RSN networks active following the explicit task shown in sagittal, coronal, and axial slices. The bar chart signifies the changes in strength for this RSN across the three conditions following the task. *b*, This figure also demonstrates group level functional connectivity ICA maps of the cerebellar thalamus basal ganglia networks active following the implicit task as shown in sagittal, coronal, and axial slices. The bar chart demonstrates the strength of the component across the three conditions following the task. *c*, Group level ICA connectivity maps representing the medial temporal RSN for the implicit task, whereas the accompanying bar charts show the significant modulation of this RSN in REST3 and REST4 (group mean ± 1 SEM).

should be minimal interference between the motor skill and declarative memory in the explicit task, and allow enhancement of the motor skill memory through consolidation. Indeed, daytime consolidation occurred in both our participant groups despite initial

acquisition of the SRTT in different modes (i.e., under explicit vs implicit conditions). This was important to allow contrast of the effects of learning mode on the subsequent consolidation processes, with similar amounts of consolidation in each group.

Neuroimaging results

Our initial contrasts compared the baseline rest condition, REST1, against the other three time points (REST2, REST3, and REST4), independently for the explicit and implicit groups. We found six main RSN components that were present in each of the three contrasts for the group that were significantly modulated from REST1 in a least one of the three contrasts. The remaining components were either physiologically relevant functional brain networks that were unaffected by the learning task, or reflected physiological or motion artifacts and were therefore discarded. The six RSNs of interest included the sensory-motor, medial temporal, frontoparietal, cerebellar-basal ganglia, cerebellar-frontal, and visual RSNs (Smith et al., 2009). To confirm that the networks identified by the ICA process in these pairs (REST1–REST2, REST1–REST3, and REST1–REST4) were similar, we tested their spatial similarity. Average spatial correlation between corresponding components of the six main RSN components showed a high spatial reproducibility (mean 0.64 ± 0.17 SD).

Rest 1 versus Rest 2

The contrast between REST1 and REST2 is the earliest stage at which we could test for resting state differences induced by the learning, and corresponds to the contrast reported by Albert et al. (2009). Following the explicit task, a cerebellar-frontal executive network (Habas et al., 2009) was significantly strengthened. This network includes the bilateral cerebellum, with a large region of right cerebellar cortex, including Crus II (Fig. 3a). There were also significant regions within the dorsolateral prefrontal and orbitofrontal cortex, as well as the angular and supramarginal cortex (Table 1). In addition, a separate component was identified closely matching the visual RSN, encompassing the superior and inferior divisions of the bilateral visual cortex (Table 2a), with the greatest significance over V2, i.e., bilateral BA18 (Fig. 3b). Dual regression of the cerebellar-frontal network highlighted further connections beyond the dorsolateral prefrontal and the orbitofrontal cortex, with significant enhanced connectivity between this network and the superior frontal gyrus (BA 10, MNI xyz coordinates 18, 6, 52 mm). In contrast, dual regression analysis for the visual RSN did not show any further regional engagement outside the visual cortex (Table 2a).

However, the implicit SRTT training induced early changes in a very different network involving the left sensorimotor motor areas including the supplementary motor cortex and primary sensory-motor cortex (M1/S1) as well as parietal areas including angular and supramarginal gyrus (Fig. 4a; Table 3, left). Additional dual regression analysis exposed enhanced connections to the supplementary motor cortex as well as the left amygdala (Table 3, left).

Rest 1 versus Rest 3

Thirty minutes following the end of the SRTT acquisition, the activation in the two components identified above (Fig. 3) had declined, and was no longer significantly different from REST1. For the cerebellar-frontal component, this was due to increased variance across the group, although the mean component strength had not reduced greatly (Fig. 3a, right). For the occipital component, the strength had dropped dramatically (Fig. 3b, right). Likewise, for the implicit group the sensory-motor component reduced in intensity and was no longer significantly different from REST1 (Fig. 4a, right). However, a new component with significant increase in strength between REST1 and REST3 was now found in the both the explicit and implicit groups (Fig. 5a,b), comprising a network of basal ganglia, thalamus and cerebellar dentate nuclei. The right putamen showed the strongest

Table 4. Cerebellar-thalamic basal ganglia network

Component local maxima	BA	EXPLICIT REST1: REST3				IMPLICIT REST1: REST3			
		Peak Z	X	Y	Z	Peak Z	X	Y	Z
Cerebellum									
L Crus I		7.6	−34	−54	−32	4.1	−26	−62	−36
Dentate nucleus		4.9	6	−64	−28	3.6	10	−46	−32
Thalamus									
L thalamus		7.12	−18	−18	8	6.32	−10	−18	8
R thalamus		4.83	10	−22	8	4.83	10	−22	8
Basal ganglia									
L putamen		11.38	−30	−14	0	3.85	−36	−2	−8
L pallidum		9.19	−22	−6	0	9.19	−22	−6	0
Dual regression									
L primary motor	4		−14	−6	68		34	−26	68
Supplementary motor cortex	6						2	−14	48
L angular gyrus	39		−22	−58	68		42	−50	12

A similar labelling scheme as the used in Table 1 for the cerebellar-thalamic basal ganglia network that were active for both the explicit (left) and implicit conditions (right) in REST 3.

Table 5. Medial temporal network

Component local maxima	BA	IMPL REST1: REST 3				IMPL REST1: REST4			
		Peak Z	X	Y	X	Peak Z	X	Y	Z
R superior frontal gyrus	6					5.2	26	18	44
L Crus I						4.0	−46	−74	−40
L middle temporal gyrus	21	9.03	−58	2	−24	10.17	−58	−38	0.0
R middle temporal gyrus	21	8.67	54	−2	0.0	4.35	62	−38	0.0
L superior temporal gyrus	22	5.84	−58	−6	−8	6.93	−58	−18	0.0
R superior temporal gyrus	22	3.98	62	−2	−8	4.01	62	−22	0.0
Dual regression									
L hippocampus			−26	−10	−28		−18	−34	−12
L somatosensory cortex			−30	−22	52		−50	−26	52
Supplementary motor cortex			−6	−14	64		−6	−6	59

Regions within the medial temporal network that were significantly more active during REST 3 (left) and REST 4 (right) under the implicit condition (the labelling scheme conforms to that of Table 1).

Table 6. The frontal parietal networks

Component local maxima	BA	REST 3 IMPL: EXPL				REST 4 IMPL: EXPL			
		Peak Z	X	Y	Z	Peak Z	X	Y	Z
R supramarginal gyrus	40	12.83	46	−42	48	13.2	46	−34	44
R superior parietal lobule	7	13.30	38	−46	44	10.2	34	−46	44
L angular gyrus	39	5.3	−38	−62	40	4.90	−58	−26	48
R angular gyrus	39	12.45	38	−62	40	9.26	62	−22	40
R DLPFC	44	7.79	50	10	24	4.77	54	10	24
R superior frontal	6	3.6	26	14	48	4.1	22	18	48
Dual regression									
L premotor	6		−54	−6	44		−2	−2	68
L superior parietal lobule	7		−46	−58	44		−14	−54	72

Regions within the frontal parietal networks following the comparison between the explicit and implicit conditions during REST 3 and REST 4 (the labelling scheme conforms to that of Table 1).

activation in this RSN (Table 4). Dual regression analysis of this network for both groups revealed further connections to the primary motor cortex, supplementary motor cortex and angular gyrus (Table 4). In addition, the implicit group showed significant engagement of a medial temporal component, with bilateral activity mainly in the anterior division of the temporal lobes (Fig. 5c; Table 5, left). Dual regression of this medial temporal network showed enhanced engagement with the postcentral gyrus, the hippocampus and frontal polar cortex (Table 5, left).
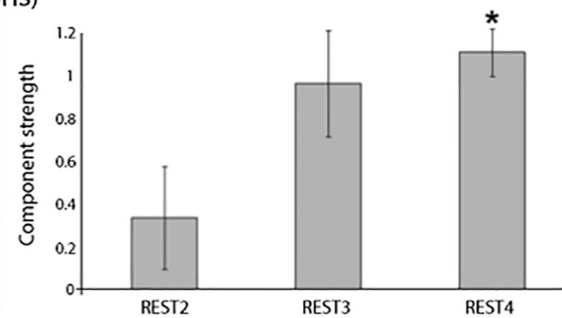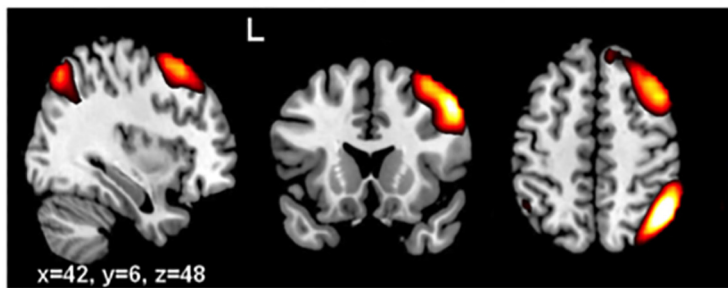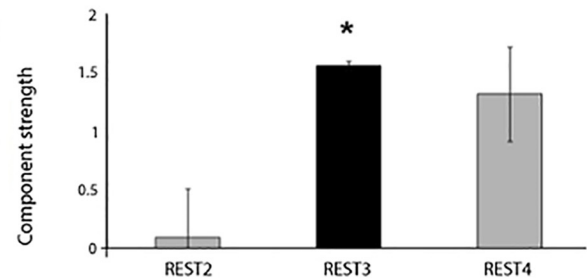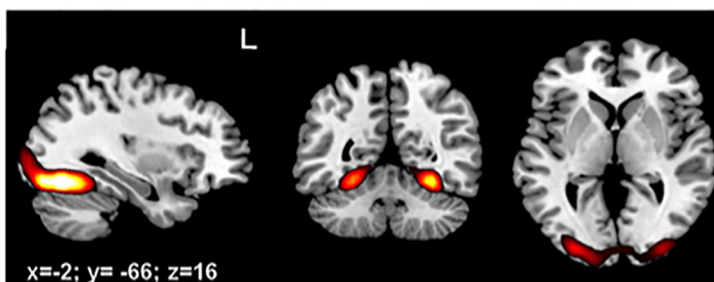
a   Fronto-Parietal RSN (Explicit vs Implicit Rest conditions)

x=42, y=6, z=48

b   Visual RSN (Explicit vs Implicit Rest conditions)

x=-2; y= -66; z=16

Figure 6. *a*, The figure depicts functional connectivity group results for the frontoparietal network in the sagittal, coronal, and axial slice views. The bar chart indicates the increase in component strength between the explicit and implicit conditions signifying the changes in the three rest conditions following the task and highlighting the significant change in the explicit condition in the afternoon session (REST4). *b*, The figure highlights the Visual RSN in three views while the bar charts exhibit the comparison between the explicit and implicit in all three rest comparisons after the tasks. The black bar represents an increase in strength in the implicit task, whereas the gray bar signifies that this increase is in the explicit condition.

Rest 1 versus Rest 4

The contrast between REST1 and REST4 was designed to highlight late changes in the resting networks, 6 h after acquisition. For the explicit group, all of the components mentioned above failed to reach significant difference from REST1 (Figs. 3a, right, b, 5a), and connectivity had declined from the significant peaks observed either immediately after learning (REST2) or 30 min later (REST3). However, we did now find that a sensory-motor RSN was actively engaged at this stage (Fig. 4b), including the sensorimotor cortex (M1/S1), as well as premotor cortex (BA 6) and the supplementary motor areas (Table 3, right). Dual regression analysis did not exhibit any extended cortical activations beyond this network (Table 3, right). For the implicit acquisition group, the late consolidation contrast between REST1 and REST4 identified further increased activation in the medial temporal network mentioned above (Table 5, right; Fig. 5c). Dual regression from medial temporal network highlights the right hippocampus and the frontal pole as well as the somatosensory cortex as the mainly affected areas (see Fig. 7b).

Comparison between implicit and explicit networks

Further analysis was conducted to compare activity between the explicit and implicit resting state conditions, using a comparison between the corresponding rest periods, as described below. During REST1, before learning, there were no significant differences, implying equivalent resting activity in the two groups at this baseline stage before SRTT acquisition. For REST2 there were no significant differences at this early stage, only some marked enhancements with an increase in SMA for the implicit condition in comparison with the explicit condition, whereas there was a greater increase in the prefrontal regions for the explicit condition. Thirty minutes after acquisition, the right frontoparietal network (Table 6, left) showed an increase in the explicit group, compared with the implicit group (Fig. 6a). Dual regression re-

veals that the left premotor cortex and superior parietal lobule were also significantly more connected with this network in the explicit group (Table 6, left). In contrast, the implicit group showed significantly greater activation of the visual occipital cortex compared with the explicit condition (Fig. 6b). However, dual regression for this visual RSN showed no significant connections outside the visual cortices.

Finally, in the late consolidation phase (REST4) the explicit group maintained the significant increase over the implicit group in the right frontoparietal network first seen in REST3 (Fig. 6a, right; Table 6, right). Dual regression for this frontoparietal network disclosed a shift in connectivity from the premotor cortex to SMA, whereas the connection with the superior parietal lobule in this network is maintained (Table 6, right). Additionally, this contrast between explicit and implicit groups 6 h after acquisition showed a near significant difference in the visual cortical RSN that included the occipital pole, extending laterally toward the occipitotemporal junction and secondary visual areas (Table 2d). A further resting state network that included premotor and parietal cortices not seen in the earlier contrasts was reliably identified in this comparison (Fig. 7a). This network included bilateral premotor cortex BA6 and bilateral superior and inferior parietal lobules, was more engaged in the implicit group (Table 7).

Discussion

We show by measuring response speeds, that two different forms of motor sequence learning, acquired under implicit and explicit conditions, lead to differential initial acquisition of the sequence. However, both groups showed significant motor skill consolidation after 6 h awake, and the initial response advantage in the explicit task was maintained (Fig. 2b). Note that we modified the explicit task from earlier studies to minimize interference between the motor skill and declarative memory, to allow motor skill enhancement during con-
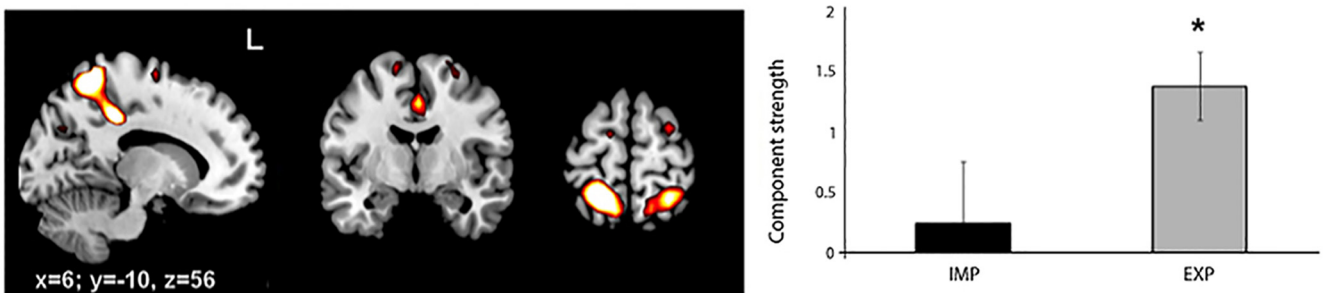
a Parietal Pre-motor RSN (Explicit vs Implicit Rest conditions)

b Right Hippocampus Network (Dual Regression Medial Temporal RSN Implicit Rest 4)

Figure 7. *a*, Resting state activity in the bilateral parietal premotor network. This group level component was identified following the contrast between the implicit and explicit task for REST 4. The absence of this of this network in the earlier rest comparisons suggests that it is likely to be related to consolidation. *b*, The figure highlights the voxelwise dual regression results of the medial temporal RSN network following the implicit task, illustrating that this RSN significantly enhances the right hippocampus for REST4 when compared with baseline. It also depicts the additional connections to this RSN in the sensory motor areas, although not visible from this slice layout the prefrontal areas also showed a significant increase.

Table 7. Parietal-motor network

Component local maxima	BA	Peak Z	Peak x	y	z
R superior parietal lobule	7	6.12	26	−54	68
L superior parietal lobule	7	8.16	−18	−50	68
L inferior parietal lobule	39	8.27	−62	−42	20
R inferior parietal lobule	39	7.02	62	−46	20
L premotor cortex	6	4.64	−14	−6	64
R premotor cortex	6	4.66	30	−6	64
SMA	6	5.55	2	−6	48

Regions within the unique parietal-motor network identified following a comparison between the explicit and implicit during REST4 sessions using the same labelling scheme as in Table 1.

solidation. Thus, the groups differed in acquisition, but both showed consolidation across the experiment.

We also found dissociable engagement of resting state networks immediately following learning, and these networks then evolved differentially over the consolidation period. Willingham et al. (2002) have examined effects of sequence awareness on the neural circuits involved in acquisition of the SRTT task. They showed that both implicit and explicit SRTT acquisition engaged a common network of brain areas that include right putamen, left inferior parietal and inferior/medial frontal gyrii. However, explicit sequence knowledge then recruited an additional broad network; this included bilateral posterior parietal areas, cingulate, precuneus, midfrontal cortex, caudate nucleus, and cerebellum. We see a similar pattern in the early resting state REST2, with engagement of the cerebellar-frontal executive RSN (Habas et al., 2009), as well as a network including dorsal prefrontal and orbitofrontal areas, the superior parietal, angular and supramar-

ginal cortex. We found increased striate and extrastriate engagement in the explicit group, suggesting that perceptual learning may be an important component of this task. Some earlier studies found little or no perceptual learning component; however, these studies were restricted to the implicit task (Willingham and Goedert-Eschmann, 1999). Lewis et al. (2009) found that resting state functional connectivity between visual cortex and frontal-parietal areas was significantly modified following training on a shape-identification task. Thus, despite the markedly different methods, the similarities between the two studies suggest that differences in task-driven activation under implicit and explicit acquisition conditions feeds into short-term differences within the resting brain in the subsequent 10–20 min.

In a study similar to ours, Albert et al. (2009) found a fronto-parietal network and a cerebellar network that were differentially engaged during postlearning rest, both networks that are engaged during learning of similar visuomotor tasks. Resting state analyses measure connectivity (correlations), and not simply activation levels (Cole et al., 2010), and by their design, the analysis of activation patterns are unconstrained by any task, albeit that our dummy task was designed to normalize mental states at the start of each scan. Hence, it seems that brain areas activated in task acquisition (but not in performance; Albert et al., 2009) are then expressed as more connected resting networks in the early consolidation phase; Cunha et al. (2004) report complementary EEG results. The strong engagement of the frontoparietal-cerebellar network in our explicit group, and of frontoparietal and cerebellar systems within the Albert et al. (2009) study suggests these areas are related to the state of explicit awareness, and potentially to the capture of attention (Grafton et al., 1995): the visuomotor rotation in

the Albert et al. (2009) learning condition was noticeable to the participants, even if the form of the perturbation was not understood.

Turning to the resting scan 30 min after acquisition, REST3, we found a different picture emerging. The components described above declined in significance, while a new network that comprised the cerebellar nuclei, thalamus, and basal ganglia became prominent in both learning groups. Dual regression identified engagement of M1 and angular gyrus, in both, and SMA in the explicit group. There was differential activation of medial temporal lobe and hippocampus in the implicit group. Thus, midterm consolidation appears to involve sensory motor cortical areas, and the two major subcortical motor systems, the basal ganglia and cerebellum: the consolidation process evolves over the first 30 min, shifting from frontal and parietal association areas toward cortical and subcortical motor circuits.

Last, in the final resting state scan 6 h after initial acquisition, clear differences re-emerged. A frontoparietal network was now predominant in the explicit group. This might reflect the explicit group bringing the learnt sequence back into declarative awareness. Alternatively, consolidation processes may be serial: our instructions emphasized the motor component of the SRT task (Daniels N, Sami S, Robertson EM, Miall RC, unpublished observations). Participants may consolidate this component first, and connectivity 30 min after learning was similar (as described above). After explicit learning, there may be late consolidation of the declarative component, and hence prefrontal activation. In contrast, for the implicit condition, the medial temporal network first seen 30 min postacquisition became further pronounced. Directly comparing explicit and implicit groups at this late state, we identified a unique network that represents bilateral activation in the parietal and premotor regions (Fig. 7a). This network materialized only at the late stage and may reflect the extra procedural learning skill that had developed in the explicit acquisition group.

We now briefly review the main functional networks exposed by our study.

The motor RSN
Our results provide evidence for dissociable consolidation processing affecting the sensory-motor cortex. For the explicit condition we found late changes in the motor RSN (Fig. 4b), whereas an RSN involving both motor and parietal cortex was most active in the early stage for the implicit condition (Fig. 4a). The latter is similar to event-related activation in sequence learning (Karni et al., 1998). TMS of M1 affects the early acquisition and retention of motor skills (Muellbacher et al., 2002; Wilkinson et al., 2010), whereas M1-TMS after consolidation does not (Muellbacher et al., 2002). This suggests that the implicit-group motor RSN is engaged in early procedural aspects of the task. The later engagement within our explicit learning group may reflect consolidation of other aspects of the task, when the component enlarges to encompass the supramarginal gyri and the SMA (Fig. 4b). Functional connectivity between left and right supramarginal gyrus is enhanced following a 4 week motor learning task (Ma et al., 2010), and Hikosaka et al. (1996) have shown SMA involvement in complex sequence movements. Hence, this regional expansion may be indicative of late motor consolidation. Finally, dual regression analysis of this motor network at REST4 indicates a further connection to left cerebellar Crus I, linked to both spatial and working memory function (Stoodley and Schmahmann, 2009).

Cerebellar-thalamic-basal ganglia RSN loop
Hoshi et al. (2005) have shown disynaptic connections from cerebellar output nuclei via the thalamus to the striatum, while

Bostan and Strick (2010) show a reciprocal projection from the subthalamic nucleus to the cerebellar cortex, Crus II, and HVIIb. We show significant engagement of this network during REST3 for both the explicit and implicit task (Fig. 5a,b). Several imaging studies have shown striatal activation during implicit sequence learning (Doyon et al., 2002; Schendan et al., 2003; Albouy et al., 2008). Moreover, Karabanov et al. (2010) showed that both implicit and explicit learning correlated negatively with dopamine in the associative and sensorimotor striatum, suggesting both subregions are involved in implicit as well as explicit learning. Doyon et al. (2002) have demonstrated a shift of motor representations from the associative to the sensorimotor territories of the striatum during the explicit learning of motor sequences, and from the cerebellar cortex to the dentate nucleus as subjects acquire implicit knowledge of a declaratively known sequence. In addition, an early frontocerebellar component seen after explicit learning (Fig. 3a) involved lateral cerebellum and prefrontal areas, which were correlated with the posterior parietal cortex and extended into medial temporal lobe and posterior cerebellum. This network is known for its contributions to higher cognitive function (Balsters and Ramnani, 2011). Shadmehr and Holcomb (1997) also reported a shift in motor representation from the cerebellar cortex to the deep cerebellar nuclei. Finally, our dual regression analysis of this cerebello-thalamo-basal ganglionic network identified increased connections with the sensory motor cortices, SMA, and angular gyrus.

Our interpretation of these results is that learning takes place initially in the cerebellar motor networks and that during a consolidation process that includes the cerebellar-thalamic-basalganglionic network, motor memories are converted to a more distributed representation.

The medial temporal lobe and the SRTT
Schendan et al. (2003) reported activation of the medial temporal lobes (MTL) in both explicit and implicit versions of the SRTT, whereas Fletcher et al. (2005) reported significantly greater activation in the implicit condition. Here we show that although the MTL is involved in the explicit task, later stages of consolidation of the implicit task show significantly greater MTL functional connectivity (REST3 and REST4). Dual regression analysis also highlighted that the MTL became more consistently connected to the hippocampus in both REST3 and REST4 (Fig. 7b). The MTL does not play a significant role in simple sequence learning but is involved in learning longer, complex sequences as used here (Hafting et al., 2008; Molter and Yamaguchi, 2008).

Summary
By contrasting two versions of SRTT acquisition we induced different levels of initial acquisition, although both groups showed significant consolidation across 6 h. Complementing results from a visuomotor adaptation task (Albert et al., 2009), we have shown that motor skill learning takes place in distinct, task-dependent, sensory motor loops. Moreover, during a 6 h consolidation period, a picture emerges of complex shifts in these networks, with differential engagement driven by explicit and implicit learning, but also with common activation of a cerebellar, thalamic, and basal ganglionic network in the middle stages.

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