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Overnight Consolidation Aids the Transfer of Statistical Knowledge from the Medial Temporal Lobe to the Striatum

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Sleep is important for abstraction of the underlying principles (or gist) which bind together conceptually related stimuli, but little is known about the neural correlates of this process. Here, we investigate this issue using overnight sleep monitoring and functional magnetic resonance imaging (fMRI). Participants were exposed to a statistically structured sequence of auditory tones then tested immediately for recognition of short sequences which conformed to the learned statistical pattern. Subsequently, after consolidation over either 30 min or 24 h, they performed a delayed test session in which brain activity was monitored with fMRI. Behaviorally, there was greater improvement across 24 h than across 30 min, and this was predicted by the amount of slow wave sleep (SWS) obtained. Functionally, we observed weaker parahippocampal responses and stronger striatal responses after sleep. Like the behavioral result, these differences in functional response were predicted by the amount of SWS obtained. Furthermore, connectivity between striatum and parahippocampus was weaker after sleep, whereas connectivity between putamen and planum temporale was stronger. Taken together, these findings suggest that abstraction is associated with a gradual shift from the hippocampal to the striatal memory system and that this may be mediated by SWS.

Keywords: abstraction, consolidation, hippocampus, sleep, striatum

Introduction

In addition to direct retention benefits on both declarative (Gais et al. 2006; Hu et al. 2006; Rasch et al. 2007; Backhaus et al. 2008; Benedict et al. 2009; Mograss et al. 2009) and nondeclarative (Gais et al. 2000; Walker et al. 2002, 2003; Press et al. 2005; Robertson et al. 2005; Walker and Stickgold 2005; Fischer et al. 2007; Gais, Koster et al. 2008; Gais, Rasch et al. 2008) memory, sleep has been found to assist in the abstraction of shared elements in a set of related memories (Wagner et al. 2004; Fischer et al. 2006; Gomez et al. 2006; Djonlagic et al. 2009; Durrant et al. 2011b25b26b27b28b29b30b31) and integration of learned information (Dumay and Gaskell 2007; Eichenbaum 2007; Ellenbogen et al. 2007; Lau et al. 2010; Tamminen et al. 2010). Recent studies have shown that improvements in integration or abstraction can be predicted by the amount of slow wave sleep (SWS) obtained on the night following encoding (Lau *et al.* 2010; Durrant et al. 2011), further supporting an active role for sleep in these processes. In this report, we set out to extend these findings by examining the neuroplasticity associated with such sleep-related abstraction.

Existing work on sleep-related consolidation of declarative memories has drawn upon the concept of neural reorganization of memories as described by the standard model of system-level consolidation (Frankland and Bontempi 2005). This posits that the hippocampus binds together distributed cortical representations before direct cortico-cortical connections have been formed. A decrease in hippocampal involvement across time has been shown to depend upon the amount of SWS obtained (Takashima et al. 2006). More recent work has also described the reorganization that occurs as new neocortical connections are formed and hippocampal connections are lost (Takashima et al. 2009); this can also be seen in the context of an implicit/explicit trade-off in an insight task (Darsaud et al. 2011). Here, we aimed to determine whether such neural reorganization also occurs when underlying structure or 'gist' information is abstracted from a set of related stimuli during consolidation across sleep. To allow a full examination of this issue, we monitored brain activity using polysomnography (PSG) throughout the overnight retention interval.

Our study used a statistical learning paradigm (Durrant et al. 2011) involving the abstraction of an underlying statistical pattern from auditory tone sequences. This is a modification of the more widely used Saffran paradigm (Saffran et al. 1996, 1999; Saffran and Thiessen 2006; Pelucchi et al. 2009). Prior work with this task has shown that it consolidates strongly across sleep (Durrant et al. 2011), and that this consolidation is predicted by the amount of SWS obtained. Furthermore, this task allows us to vary the difficulty of the stimuli, and hence to determine whether or not sleep-dependent consolidation on this task varies with difficulty, as suggested for some tasks (Kuriyama et al. 2004) but not others (Debarnot et al. 2009). Previous research has shown that this task draws on both the medial temporal lobe (MTL) and the striatum (Turk-Browne et al. 2009, 2010), we therefore focused on these structures, both of which have also been shown to be involved in overnight consolidation, for instance, in motor sequence learning (Albouy et al. 2008).

Materials and Methods

Participants

All participants were right handed (a score of 80% or higher on the Edinburgh Handedness Inventory) and healthy volunteers, with no history of neurological or sleep disorders (evaluated by a screening questionnaire and an interview) and not taking any medication except for the contraceptive pill. Forty participants (20 female, 20 male) were randomly divided between the 2 experimental groups (30 min and 24 h); of these, 4 had to be excluded due to insufficient sleep (<4 h; 1 participant), equipment malfunction (1 participant), brain abnormality (1 participant), and excessive head movement (1 participant), leaving 36 participants equally divided between the 2 groups. Eighteen participants in the 30 min group (9 female, 9 male) were aged 19–36 years (mean: 24.167; standard error of mean [SEM]: 1.282) and 18 participants in the 24 h group (9 female, 9 male) were aged 19–30 years (mean: 23.833; SEM: 0.809).

Each subject gave informed consent for the experiment, which was approved by the Research Ethics Committee of the School of Psychological Sciences at the University of Manchester and the Research Ethics Committee of the University of Liverpool. Throughout the entire period of the experiment, participants were asked to abstain from alcohol, caffeine, and other drugs. In addition, participants were asked not to nap on the experiment days, sleep normally at night, and report the number of hours they slept. No participants had taken part in any previous version of the experiment.

Stimuli

The stimuli were made up of sequences of pure tones with 7 different frequencies (261.63, 288.86, 318.93, 352.12, 388.77, 429.24, and 473.92 Hz). This scale was created by dividing the octave into 7 equally spaced intervals, none of which sound familiar to listeners immersed in Western tonal music; this was used in order to avoid creating melodic fragments familiar to Western listeners. Each tone lasted 200 ms, with a 20-ms gap between tones. Tones were sampled with a frequency of 44 100 Hz, had a fixed amplitude and were Gaussian modulated to avoid aliasing edge effects which sound like clicks to listeners. The stimuli consisted of a single long exposure stream of 1818 tones (lasting 6 min and 40 s), and 168 short test streams each containing 18 tones (lasting 3.96 s). Half of the test sequences (the unstructured condition) were generated randomly (with an equal probability for each possible subsequent tone at every position in the sequence), while both the exposure stream and the other half of the test sequences (the structured condition) were determined by a transition matrix containing the probabilities for each potential transition between the current tone and the subsequent tone, forming a first-order Markov chain. This is shown in Figure 1, where each row corresponds to the current tone and each column corresponds to a possible identity of the next tone.

Each row–column combination in the matrix defines an entry that gives the probability that the tone associated with that row will be followed by the tone associated with that column. In the transition matrix used in these experiments, each row contained 1 high-probability transition (which we term a likely transition) ($P = 0.9$; shown in white color in Fig. 1), and 6 equal low-probability transitions (unlikely transitions; $P = 0.0167$; shown in black color in Fig. 1); this ensured that a given tone would be followed by a particular subsequent tone 90% of the time, but by any of the other 6 possible tones 10% of the time, making the sequences probabilistic. Importantly, this transition matrix was constructed such that all 7 tones had an equal chance of occurring overall (uniform zero-order transitions). This means that any discernible structure in the sequences is first order or higher, requiring participants to be aware of the relationship between successive tones rather than just how frequently individual tones may occur.

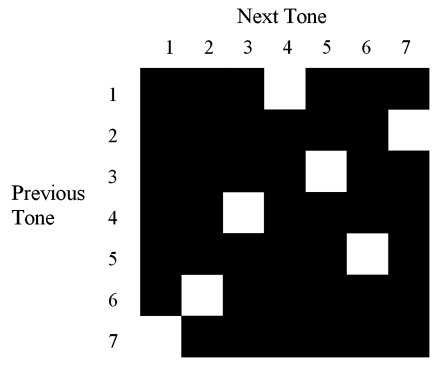

Figure 1. Transition matrix for the exposure stream and structured test sequences. Values are color-coded probabilities, with black = 0.0167 and white = 0.90. The row indexes the last tone that has occurred, the column indexes the next tone that could occur, and the grayscale value (black or white) gives the probability of this transition. The matrix is set up in such a way that tones occur overall with equal frequency, ensuring that this cannot provide additional structural information.

Structured sequences were generated by randomly sampling the transition matrix, but under an additional constraint. In order to evaluate the role of task difficulty in subsequent consolidation, 3 levels of difficulty were defined (easy, medium, and hard), which corresponded to different levels of structure within the sequence. To guarantee a good separation in difficulty between the categories (easy, medium, and hard), we constrained the number of high-probability transitions to be 16 in easy sequences, 13 in medium sequences, and 10 in hard sequences. This is equivalent to setting the likely transition probability to 0.941, 0.765, and 0.588, respectively.

Experimental Task and Design

The timeline of the experiment can be seen in figure 2*A*. It consisted of 2 sessions, the first of which was subdivided into a learning session and an immediate-recall session and the second of which was just a delayed-recall session; the first session was purely behavioral, whereas the second session also involved functional magnetic resonance imaging (fMRI) scanning. Participants were divided into 2 groups: 30 min and 24 h. Participants in the 24 h group undertook the first session at 3 PM (±1.5 h) and were invited to sleep overnight from 11 PM to 7 AM in a bedroom in the Sleep Research Laboratory at the University of Manchester, where they were monitored with PSG while they slept. On the following day, they undertook the second session at 3 PM (±1.5 h), which took place inside an fMRI scanner and included functional brain imaging. Participants in the 30 min group undertook the first session at 2 PM (±1 h) and immediately after were placed in the fMRI scanner where they undertook the second session (starting the tasks around 3 PM).

The structure of the sessions and trials is shown in Figure 2. Participants were made aware of this structure, and in particular the fact that they would have immediate and delayed test sessions, at the beginning of the experiment, as previous evidence suggests that this may be important for sleep-dependent consolidation (Saletin et al. 2011; Wilhelm et al. 2011). The experiment started with a learning session which involved presentation of the structured exposure stream for just under 7 min (400 s, 1818 tones in total), in order to familiarize the participant with the transition probabilities. During the exposure stream, the screen contained a centrally located prompt which instructed participants to listen. This was followed by an immediate-recall session containing 84 randomly ordered trials lasting approximately 9 s each (4-s sequence and 5-s response period) and consisting of a short sequence of 18 tones which was either structured (and sharing the transition probabilities with the exposure stream) or unstructured. The 84 trials consisted of 14 structured trials in each of the 3 levels of difficulty, and 42 unstructured trials. Participants were told in advance that half of the trials contained sequences similar to the long exposure stream (the structured sequences) and half contained unfamiliar sequences. On each trial, they were instructed to indicate whether or not the sequence sounded similar to the long exposure stream by pressing the appropriate response button as soon as they were sure, and always within a response window of 5 s from the end of the auditory presentation. During the trial, on the center of the screen participants were shown the trial number out of the total number ("Trial 53 of 84") and instructions on which buttons to press for a sequence that sounded "familiar" or "unfamiliar" in the context of the exposure stream. The delayed-recall session consisted of a further 84 trials analogous to the immediate-recall session, plus 21 rest trials lasting 9 s each in which no sequence was presented and participants were given an on-screen instruction to rest; these trials were included in order to facilitate estimation of baseline activity in fMRI. The structured sequences in this session were novel but again shared the transition probabilities with the exposure stream from the learning session (in other words, they had the same statistical structure as the exposure stream). The unpredictable sequences were also novel and generated randomly. The order of the sequences was randomized for each participant.

Equipment

This experiment was realized with custom-written scripts using Cogent 2000 developed by the Cogent 2000 team at the Functional

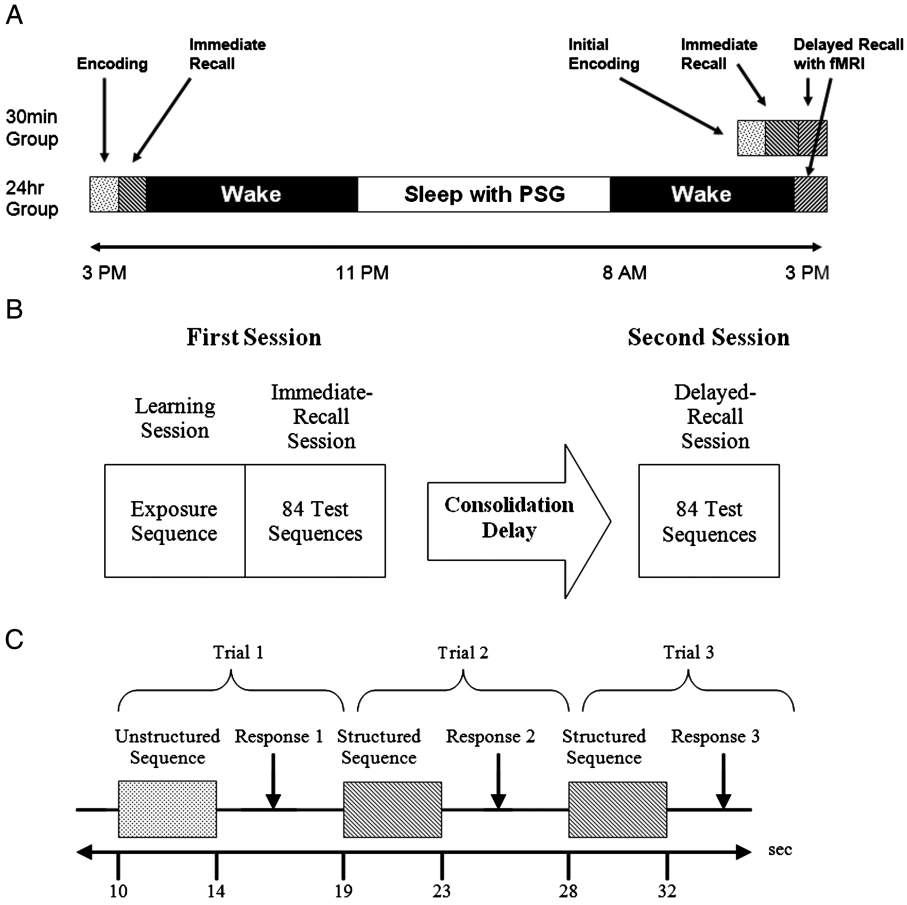

Figure 2. Experiment design. (*A*) The 24 h group encoded at 3 PM on Day 1, followed by an immediate recall test session. They returned at 11 PM to sleep overnight in a sleep laboratory where their sleep was monitored with PSG. At 3 PM on Day 2 they undertook a delayed recall session, 24 h after their initial encoding. The 30 min group encoded at 2 PM on Day 2, followed by an immediate recall test session and then a delayed recall test session with only a short break in between. (*B*) The first session is subdivided into a learning session, in which participants hear a single, continuous tone stream for 400 s, and an immediate test session in which participants have 84 test trials. After a retention interval of either 24 h (24 h group) or less than 30 min (30 min group), the second session consists of just a delayed test session containing a further 84 test trials, taking place inside an fMRI scanner. (*C*) Each trial consists of either a structured sequence or an unstructured sequence (in a pseudo-randomized order) lasting 4 s, and a fixed response period of 5 s in which participants are asked to indicate whether or not the sequence sounds similar to exposure sequence heard during encoding.

Imaging Laboratory and the Institute for Cognitive Neuroscience (University College, London), and Cogent Graphics developed by John Romaya at the Laboratory of Neurobiology at the Wellcome Department of Imaging Neuroscience (University College, London). It was written and executed using MATLAB© 6.5 running on a PC equipped with a dual-core processor. Sound was generated using the onboard SoundMAX© digital audio chip, and heard through a pair of Sennheiser© HD207 noise-cancelling headphones during the first (behavioral) session, and via an MR compatible audio setup (MR Confon©) during the second (fMRI) session. Responses were recorded using a serial multibutton box attached to a Domino 2 microcontroller from Micromint©, with a time resolution of approximately 1 ms.

Polysomnographic Monitoring

Polysomnographic monitoring was carried out using an Embla© N7000 sleep monitoring system, with Ag–AgCl electrodes attached using EC2© electrogel after the scalp was first prepared with NuPrep© exfoliating agent. Scalp electrodes were attached at 6 standard locations using the 10–20 system, C3, C4, F3, F4, O1, and O2, each referenced to the contralateral mastoid (A1 and A2). Left and right electrooculogram, left, right, and upper electromyogram, and a ground electrode were also attached. All electrodes were verified to have a connection impedance of less than 5 kΩ. In addition, monitoring of physiological signals including movement, pulse oximetry, and respiration was also carried out. All signals were digitally sampled at a rate of 200 Hz.

fMRI Data Acquisition

Functional MRI time series data were acquired using a 3T Allegra MR scanner (Siemens) with an 8-channel head coil. Blood oxygen level-dependent signal was recorded using T_2*-weighted fMRI images obtained with a gradient echo-planar sequence. Fifty oblique transaxial slices tilted at 15° were acquired in an ascending sequence with a voxel size of $3 \times 3 \times 2.8$ mm^3 including an interslice gap of 40%, matrix size of 64×64, time repetition (TR) of 2960 ms, time echo (TE) of 30 ms, and flip angle of 80°. A T_1-weighted structural image was also acquired in the same session for each participant using a 3D IR/GR sequence with a matrix size of $224 \times 256 \times 176$, cubic isovoxels of 1 mm^3, TR of 2040 ms, TE of 5.57 ms, and a flip angle of 8°.

Behavioral Data Analysis

Data were analyzed with a combination of SPSS© 15.0 statistical software and MATLAB© 6.5. In all our results, we consider $P < 0.05$ as significant and all tests are 2-tailed unless otherwise stated.

The sensitivity index (d') for detection of the structured sequences was calculated as $d' = z$-score (hits)—z-score (false alarms) for each session from the number of hits (correct identification of structured sequences) and the number of false alarms (incorrect identification of unstructured sequences as being structured). In cases where maximum hits or no false alarms occurred, we followed the common practice of reducing or increasing the proportion correct by the equivalent of half a trial (e.g. 0.5/84 when considering all test trials in 1 session) in order to avoid an infinite z-score while still allowing a

higher score than would have been achieved if 1 trial had been incorrect. The difference between performance on the 2 sessions gave a measure of consolidation. A 2-way mixed analysis of variance (ANOVA) with the within-subject factor session (immediate recall, delayed recall), the between-subject factor group (30 min, 24 h) and the dependent variable d', was used to test for differences in consolidation relating to the 2 retention intervals. Post hoc Bonferroni-corrected *t*-tests were used to explore the direction of such effects. In addition, one-sample *t*-tests were used on both groups in both sessions separately to ensure that performance was consistently above chance, and an independent samples *t*-test between the groups on the immediate-recall session d' was used to test group differences in baseline performance.

Analysis of performance on the 3 levels of difficulty in the stimuli was conducted by means of a second 2-way mixed ANOVA, containing a within-subjects factor difficulty (3 levels) and a between-subjects factor group (30 min, 24 h). Bonferroni-corrected posthoc *t*-tests were used to determine which difficulty levels were significantly different from each other.

Participants reported their subjective alertness at the start of each session using the Stanford Sleepiness Scale (SSS), a subjective measure of alertness (Glenville and Broughton 1978). Independent-samples *t*-tests between the response times of the 30 min and 24 h groups were used to test for differences in both SSS scores and response times, which provided an objective measure of alertness. In addition, a 2-way mixed ANOVA containing the between subject factor group (30 min, 24 h) and the within-subject factor accuracy (correct, incorrect) was performed on response times in each recall session. Accuracy was included in this ANOVA to ensure that response times provide a sensitive measure in this paradigm (participants provide faster responses on correct trials in statistical learning tasks; Kim et al. 2009), and group was included in order to look for possible between-group differences in vigilance. We also tested for a predictive relationship between alertness and sleep pressure by examining the Pearson correlations between response times and the amount of SWS obtained.

PSG Data Analysis

Sleep structure was analyzed using RemLogic© 1.1 software. Sleep data were organized into 30-s epochs, bandpass filtered between 0.3 and 40 Hz to remove low-frequency drift and high-frequency noise, and visually scored independently by 2 experienced sleep researchers on the referenced central electrodes (C3–A2 and C4–A1) according to the standardized sleep scoring criteria of Rechtschaffen and Kales (1968). The proportion of time in each sleep stage and the overall sleep duration were calculated from the hypnogram. The effect of sleep was measured by the correlation between the amount of consolidation (delayed d'—immediate d') and the duration of each of the 3 main sleep stages [stage 2, SWS, and rapid eye movement (REM)], Bonferroni corrected for multiple comparisons with an a priori hypothesis of a positive role for SWS based on previous results (Durrant et al. 2011).

fMRI Data Analysis

Functional imaging data were processed using the Statistical Parametric Mapping 8 software (SPM8; Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm). Functional images were realigned to correct for motion artifacts and corrected for slice acquisition time differences. The structural image was coregistered with the functionals, and then segmented into different tissue classes and normalized into the space of the Montreal Neurological Institute brain (MNI space) using the iterative combined segmentation-normalization algorithm in SPM8. The coregistered functional images were normalized to MNI space using the same parameters. Finally, a spherical Gaussian smoothing kernel with a full-width half-maximum of 8 mm was applied to the normalized data of each participant.

Analysis was conducted by means of a 2-level random effects general linear model (Friston et al. 1995). The design matrix for each participant at the first level was constructed with separate boxcar regressors for easy, medium, and hard structured sequences and unstructured sequences; these regressors were for blocks of approximately 4 s, coinciding with the onset and offset of the stimulus sequence in each trial. In order to avoid confounding with the level of performance and to minimize error-related activations, we adopted the common practice of including only trials with correct behavioral performance in the regressors. In addition, incorrect trials and button presses were modeled as regressors of no interest. Each regressor was convolved with a canonical hemodynamic response function. Alongside these convolved regressors, the movement parameters estimated during realignment of the time series were included as 6 non-convolved regressors of no interest, and finally a constant regressor was included to model baseline activation. Serial correlations were modeled with a first-order autoregressive model with added white noise, estimated using a restricted maximum likelihood algorithm. High-pass filtering of the data was implemented by the application of a discrete cosine transform to the design matrix with a cut-off of 128 s, effectively removing low-frequency drift in the time series.

Effects of interest were modeled by balanced linear *t*-contrasts at the first level for individual participants. These included one-sample *t*-tests for structured (all structured regressors, equally weighted) and unstructured (unstructured) regressors and one-sample *t*-tests for each level of difficulty separately (easy, medium, and hard). The contrast images resulting from these first-level analyses were taken forward to a pair of second-level mixed ANOVAs to look at group results. The first of these focused on the interaction of consolidation and structure, and contained factors group (30 min, 24 h) and structure (structured, unstructured). The second analysis focused on the interaction of group with levels of difficulty within the structured sequences, and contained factors group (30 min, 24 h) and difficulty (easy, medium, and hard).

Analyses were initially conducted at a whole-brain level with an uncorrected threshold of $P < 0.001$ and a minimum cluster extent threshold of $k = 5$ voxels. As the MTL and striatum bilaterally were designated as a priori regions of interest (ROIs) we also performed small volume-corrected analyses at $P < 0.05$ using Gaussian random field theory (Worsley et al. 1996) within each of these areas. This was carried out using masks from automatic anatomical templates (Tzourio-Mazoyer et al. 2002), as implemented in the WFU pickatlas software (Maldjian et al. 2003). The MTL template mask was formed from bilateral hippocampus and parahippocampal gyrus, and the striatal template mask was formed from bilateral caudate, putamen, and pallidum.

In order to determine whether responses detected in the above analyses were predicted by sleep parameters we performed a regression analysis in SPM8. To this end, the contrast (structured>unstructured) was performed at the first level. The resulting contrast images were then used in a second-level design matrix with a constant regressor (structured>unstructured) and 3 parametric regressors (%S2, %SWS, and %REM). For each active cluster, the first eigenvariate was extracted and regressed against sleep parameters (%S2, %SWS, and %REM) in SPSS in order to obtain the correlation coefficient. Where active clusters were also active in the (structured>unstructured) contrast (see Table 2), the cluster from that contrast was used in the SPSS correlation in order to ensure that any correlation detected was true of the task-related cluster as a whole.

Functional Connectivity

In addition to identifying localized differences in activation, we examined the functional connectivity between regions using psychophysiological interactions (PPIs). Three separate PPI analyses were performed, each with a different seed region. Each seed region was centered on the peak coordinate of the group response to the (structure>unstructured) contrast in 1 of our 3 ROIs and was spherical with a radius of 6 mm. For each subject, the physiological factor of the PPI was created by extracting and deconvolving the timecourse of activity for those voxels within the seed region which were activated in the (sequence>baseline) contrast at $P < 0.001$. This ensured that only those voxels involved in processing the auditory sequences were

included. Our psychological factor was the contrast (structured>unstructured). At the first level, our PPI design matrix contained 3 regressors: the physiological factor, the psychological factor, and the interaction (physiological × psychological) in addition to 6 regressors for motion correction. A one-sample *t*-test was used to create contrast images for the PPI regressor. These images represented regions whose functional connection with the seed region was sensitive to sequence structure and were taken forward to form a second-level random effects analysis in which 30 min and 24 h groups were compared. The results indicated whether modulation of connectivity by structure was significantly greater in 1 group than the other. The entire PPI analysis was performed separately for each of the 3 seed regions.

As previously, the PPI analyses were initially conducted at a whole-brain level with an uncorrected threshold of $P < 0.001$ and a minimum cluster extent threshold of $k = 5$ voxels. The MTL and the striatum bilaterally were again a priori designated as ROIs. Two additional areas of interest, the ventromedial prefrontal cortex and bilateral planum temporale, were also identified beforehand and examined using a 10-mm radius sphere centered on coordinates taken from previous findings. The ventromedial prefrontal cortex (–2, 32, –10; coordinates taken from Takashima et al. (2006)), has been shown in several previous studies to take over the binding role of the hippocampus after a period of consolidation including sleep (Takashima et al. 2006; Gais et al. 2007; Sterpenich et al. 2009), though other studies with a similar design have failed to find it (Takashima et al. 2009). The bilateral planum temporale (–61, –31, 12; 67, –21, 1; coordinates taken from Overath et al. (2007)), has been repeatedly implicated in the statistical processing of auditory sequences (Overath et al. 2007; Furl et al. 2010; Overath et al. 2010).

RESULTS

Behavioral

The main behavioral results are shown in Figure 3*A*. A 2-way mixed ANOVA with the within-subject factor session (immediate recall, delayed recall) and the between-subject factor group (30 min, 24 h) and *d'* [*z*(hits)–*z*(false alarms) for correct identification of structured sequences] as the dependent variable revealed a main effect of session ($F(1,34) = 4.266$, $P = 0.047$), a nonsignificant main effect of group ($F(1,34) = 2.777$, $P = 0.105$), and most importantly a strong interaction of group and session ($F(1,34) = 9.196$, $P = 0.005$). Bonferroni-corrected post hoc *t*-tests revealed that the interaction was driven by a significant improvement from the immediate-recall to the delayed-recall session in the 24 h group ($t(17) = 3.078$; $P = 0.007$), whereas the 30 min group showed no such improvement ($t(17) = –0.863$; $P = 0.400$).

Importantly, the overall performance in each recall session for each group was much greater than chance (all *t*-tests $P < 0.001$), demonstrating that participants in all conditions were

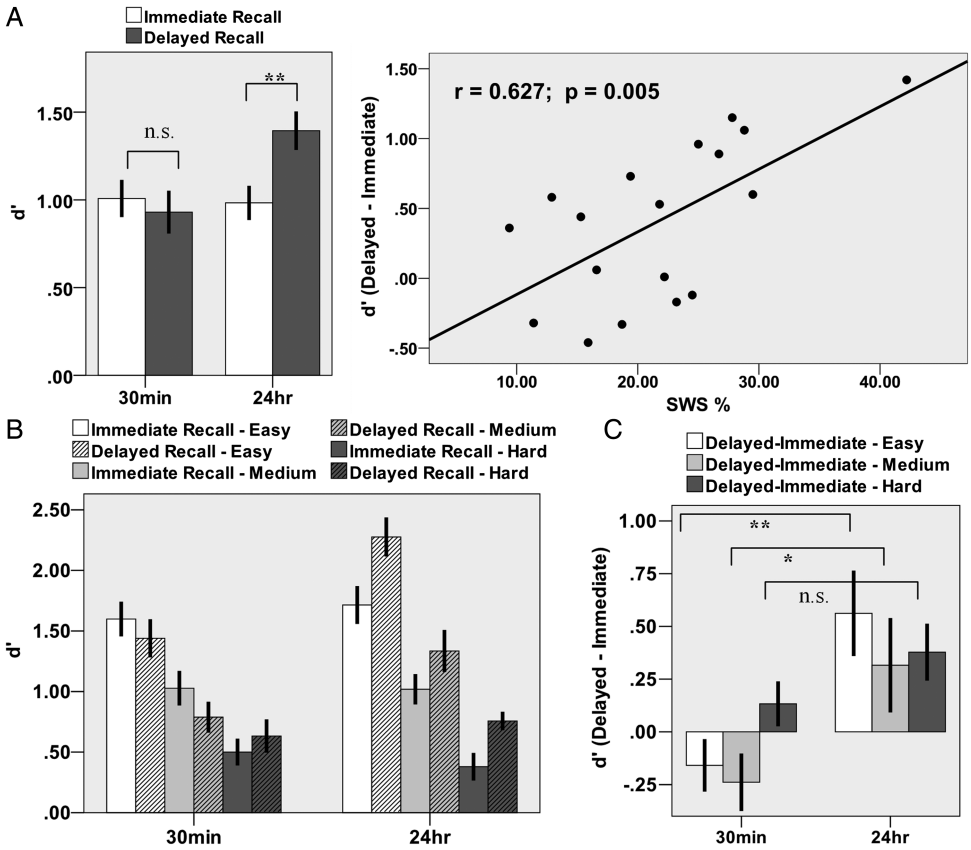

Figure 3. Behavioral results, with paired *t*-test statistics (*$P < 0.05$; **$P < 0.01$). (*A*) The 24 h group show a significant increase in correct recognition of structured and unstructured sequences after consolidation, whereas the 30 min group show no such improvement; the difference between the 2 groups is significant ($P = 0.005$). The improvement for participants in the sleep group is predicted by the amount of slow wave sleep obtained. (*B*) Both groups show similar performance at immediate recall, while the 24 h group shows greater performance at delayed recall for easy and medium items. Overall recognition is greater for easier items. (*C*) The improvement in the 24 h group is significantly greater than that in the 30 min group for easy and medium items.

able to do the task successfully. As expected, there was no significant difference between the performance of the 2 groups (30 min and 24 h) in the immediate-recall session ($t(34) = 0.173$, $P = 0.864$), indicating that both groups had equivalent ability.

Results as a function of level of difficulty, calculated using our second ANOVA which contained the within-subjects factor difficulty (3 levels) and the between-subjects factor group (30 min, 24 h), are shown in Figure 3*B*. The main effect of difficulty was strongly present in both the immediate-recall ($F(2,68) = 67.360$; $P < 0.0001$) and the delayed-recall ($F(2,68) = 75.652$; $P < 0.0001$) sessions. The interaction between group and difficulty was not significant for the immediate-recall session ($F(2,68) = 0.636$; $P = 0.514$), but was significant for the delayed-recall session ($F(2,68) = 6.863$; $P = 0.002$), with the 24 h group showing stronger performance than the 30 min group on the easy ($t(34) = 3.713$; $P = 0.001$) and medium items ($t(34) = 2.534$; $P = 0.016$), while performance on the hard items did not differ between the groups ($t(34) = 0.794$; $P = 0.433$). Improvement between the sessions showed a similar pattern (see Fig. 3*C*), with the improvement significantly greater for the 24 h group relative to the 30 min group on the easy items ($t(34) = 3.034$; $P = 0.005$) and the medium items ($t(34) = 2.118$; $P = 0.042$), but no difference between the groups in the improvement in the hard items ($t(34) = 1.423$; $P = 0.164$).

Overall, these results show that consolidation plays an important role in the detection of sequences which share underlying structural properties with a previously learned sequence. Sequences which share more structural properties with the learned sequence are more easily detected, and after consolidation this effect is even more pronounced.

Response Times and Alertness

In keeping with prior work on statistical learning (Kim et al. 2009; Durrant et al. 2011), response times (shown here in seconds) were faster on correct than incorrect trials for both the immediate-recall (correct: $M = 1.029 \pm 0.084$ SE; incorrect: $M = 1.232 \pm 0.093$ SE; comparison: $F(1,34) = 36.115$, $P < 0.0001$) and delayed-recall (correct: $M = 0.877 \pm 0.053$ SE; incorrect: $M = 0.966 \pm 0.060$ SE; comparison: $F(1,34) = 10.84$, $P = 0.002$) sessions, confirming that response time is a sensitive measure in our statistical learning paradigm.

In order to examine vigilance, which is often equated to alertness (Van Dongen and Dinges 2005), a 2-way mixed ANOVA containing within-subject factors response accuracy (correct, incorrect) and experiment group (30 min, 24 h) was performed on response time data in each of the 2 recall sessions. In the immediate recall session there was no significant main effect of group ($F(1,34) = 0.228$, $P = 0.636$) and no significant interaction between group and trial correctness ($F(1,34) = 0.003$, $P = 0.953$), confirming that both groups had similar patterns of response times. Similarly, in the delayed-recall session there was no significant main effect of group ($F(1,34) = 1.773$, $P = 0.192$) and no significant interaction between group and trial correctness ($F(1,34) = 0.128$, $P = 0.723$), once again confirming that both groups had similar patterns of response times. Finally, no deficit in alertness related to homeostatic sleep pressure was detected, since the amount of SWS obtained on the night after training did not correlate with response times in the immediate recall session for correct ($r = -0.057$; $P = 0.823$) or incorrect ($r = -0.165$; $P = 0.512$) items, or in the delayed recall session for correct ($r = -0.298$; $P = 0.230$), or incorrect ($r = -0.298$; $P = 0.229$) items.

In addition to objective response time data, alertness was measured subjectively and independently of memory using the SSS. In the immediate-recall session the SSS was not significantly different ($t(34) = 0.864$; $P = 0.394$) between the 30 min group ($M = 2.00 \pm 0.229$ SE) and the 24 h group ($M = 2.28 \pm 0.226$ SE) and showed that participants subjectively felt quite alert in the first session and did not differ in this regard. A similar pattern was obtained in the second session (30 min group: $M = 2.17 \pm 0.185$ SE; 24 h group: $M = 1.94 \pm 0.221$ SE; comparison of groups: $t(34) = 0.771$; $P = 0.446$).

These different measures taken together suggest that the subsequent results were not due to differences in alertness.

PSG

The main results of the PSG sleep analysis can be seen in Table 1. Figure 3*A* shows the significant correlation ($r = 0.627$; $P = 0.005$), between behavioral performance improvement (across all levels of difficulty combined) from immediate to delayed recall and the proportion of time spent in SWS. This correlation varied by the level of difficulty in a similar way to the overall improvement; the easy sequences showed a strongly significant correlation ($r = 0.656$, $P = 0.003$), the medium sequences showed a strong trend ($r = 0.460$; $P = 0.055$), whereas the hard sequences showed a small nonsignificant correlation ($r = 0.277$, $P = 0.266$). No other sleep stage showed a significant correlation (S1: $r = 0.114$, $P = 0.653$; S3: $r = -0.365$, $P = 0.136$; REM: $r = -0.381$, $P = 0.119$) for data combined

Table 1
PSG results

Parameter	24 h group
Sleep onset time (h : min ± min)	23:59 ± 10.47
Total sleep time (min)	421.58 ± 12.98
Stage 1 (%)	11.34 ± 1.45
Stage 2 (%)	46.92 ± 1.55
SWS (%)	21.74 ± 1.87
REM (%)	20.04 ± 1.79

Data are mean ± SE. See "Materials and Methods" for details of calculation.

Table 2
Main effect of structure—MTL and striatum

Anatomical region	MNI *x*, *y*, *z* (mm)	No. of voxels	Peak *Z*	Peak P_{SVC}
Medial temporal lobe				
Right hippocampus	21, –25, 8	42	5.36	<0.0001
Left hippocampus	–27, –13, –14	18	4.36	0.0052
Left parahippocampal gyrus	–24, –24, –26	12	4.02	0.0182
Striatum				
Right putamen	18, 11, 1	178	5.57	<0.0001
Right caudate	24, 2 10		5.17	0.0002
Right caudate	15, 2, 13		4.65	0.0018
Left putamen	–21, 2, –8	57	4.71	0.0014
Left pallidum	–9, 5, –2		4.55	0.0017
Left caudate	–9, 2, 7		4.49	0.0034
Left putamen	–21, –4, 7	5	4.29	0.0077

The main effect of structure in the medial temporal lobe and the striatum, with a voxel threshold of $P = 0.05$ (FWE corrected for the small search volume) and an extent threshold of $k = 5$ voxels. Local peaks within single clusters are shown to indicate the anatomical extent of the cluster. All active voxels are positive for the effect of structure (structured>unstructured).

across difficulty levels, or for any individual difficulty level. In conjunction with the behavioral group comparison, these correlation results suggest that SWS may play an active role in the consolidation process.

Functional Imaging

We used a 2-way mixed ANOVA containing the factors group (30 min, 24 h) and structure (structured, unstructured) to examine the neuroimaging data. The main effect of structure in this ANOVA (structured < > unstructured) involved an extensive network of activation (including areas such as bilateral hippocampus, bilateral striatum, left superior and inferior parietal lobules, and right middle and frontal gyri) listed in see Supplementary Table 1 and shown in Supplementary Figure 1, which subsequent one-tailed *t*-tests revealed to be entirely in favor of structured sequences; no voxels were active for the opposite contrast (unstructured>structured), which is consistent with previous results in statistical learning (Turk-Browne et al. 2010). Activation in our areas of particular interest, the MTL and the striatum, is shown in Table 2 at $P_{SVC}<0.05$ (corrected for small volume family-wise error). These results highlight the involvement of both the MTL and the striatum in this task, in keeping with previous findings (Turk-Browne et al. 2009).

The interaction between group and structure [30 min (structured< >unstructured) < > 24 h (structured < > unstructured)] represents how neural activation related to solving our task differs at 30 min and 24 h, presumably as a result of consolidation. Whole-brain results of this interaction at $P<0.001$ (uncorrected), $k=5$, are shown in Supplementary Table 3. The 30 min group showed a stronger response to structured sequences than the 24 h group in the left parahippocampal response. Conversely, the 24 h group showed a stronger response to structured sequences than the 30 min group in the left putamen, right caudate, and right planum temporale. Two-sample *t*-tests comparing structured and unstructured sequences within each group individually confirmed that these results were not due to baseline differences between the groups (Supplementary Table 2). These results may reflect the effect of consolidation on the MTL and the striatum as predicted by our hypotheses. The involvement of the right planum temporale, an area known to be closely associated with the statistical processing of auditory sequences (Overath et al. 2007), suggests that this type of processing is also influenced by consolidation.

Table 3
Group×structure interaction—MTL and striatum

Anatomical region	MNI *x*, *y*, *z* (mm)	No. of voxels	Peak *Z*	Peak P_{SVC}	First eigenvariate %
Medial temporal lobe (stronger for 30 min group)					
Left parahippocampal gyrus	–21, –25, –23	23	4.57	0.0022	82.98
Striatum (stronger for 24 h group)					
Right caudate	18, 17, 4	11	4.53	0.0014	95.77
Left putamen	–24, 17, –5	11	4.41	0.0024	95.79

Group×structure interaction in the medial temporal lobe and the striatum, with a voxel threshold of $P = 0.05$ (FWE corrected for the small search volume) and an extent threshold of $k = 5$ voxels. Three clusters were identified; 1 in the MTL, which had a stronger positive effect of structure for the 30 min group, and 2 in the striatum which had a stronger positive effect of structure for the 24 h group.

We performed a region of interest analysis in the bilateral MTL and striatum in order to more precisely determine how these structures responded to the interaction between structure and retention interval. The results of this analysis are shown in Table 3 and Figure 4 at $P_{SVC}<0.05$. In the striatum (Fig. 4*B*), structure-related responses that were significantly stronger at 24 h than 30 min included right caudate (18, 17, 4; peak $Z=4.53$) and left putamen (–24, 17, –5; peak $Z=4.41$). In the MTL (Fig. 4*A*), the structure-related response that was weaker at 24 h than 30 min was focused on the left parahippocampal gyrus (–23, –25, –21; peak $Z=4.57$). The parameter estimates for each cluster are plotted in Figure 4. The results exhibit a clear dissociation between the 30 min and 24 h groups and MTL and striatal memory systems. The left parahippocampal gyrus shows a stronger response for the 30 min group, while the right caudate and the left putamen show a stronger response for the 24 h group.

These task-related differences between the 30 min and 24 h groups could either be due to the specific effect of sleep, or to 24 h consolidation regardless of sleep. To test the former possibility, we conducted a whole-brain regression analysis in SPM using sleep parameters as covariates. This revealed that time spent in SWS predicted the degree of activation in left putamen (–24, 14, –2; peak $Z=4.29$). A small-volume-corrected analysis in our a priori ROIs revealed this same cluster. The correlation between activity in this cluster and SWS is shown in Figure 4 ($r=0.766$; $P=0.0002$) and indicates that larger amounts of SWS predict greater increase in structure-related activation after 24 h. No relationship to any other sleep stage or to total sleep time was observed, and no other brain region showed any relationship to sleep parameters.

In addition to the looking at structured versus unstructured sequences, we examined functional responses associated with levels of difficulty within the structured sequences. We used a 2-way mixed ANOVA, with factors group (30 min, 24 h) and difficulty (easy, medium, and hard). The main effect of difficulty revealed activation in the right caudate and right inferior frontal operculum, as well as left posterior and right anterior cerebellum at $P<0.001$ (uncorrected), $k=5$ voxels, shown in Supplementary Table 4. In each area, this activation was strongest for the most difficult sequences, most likely representing effortful processing of difficult stimuli (Gould et al. 2003; Lewandowska et al. 2010). The interaction between group and difficulty, however, produced no significant findings.

Functional Connectivity

In addition to identifying localized differences in activation, the functional connectivity of areas that showed sensitivity to consolidation and structure was examined. This was done using 3 separate PPI analyses seeded in the left parahippocampus, left putamen, and right caudate, respectively. Each analysis was examined using a separate second level *t*-test which compared the PPI results in 30 min and 24 h groups, revealing areas where the extent to which connectivity with the seed region was modulated by structure differed across this delay. Whole-brain results of these analyses are shown in Supplementary Table 5 and Figures 4*C* and *D*, at $P<0.001$ uncorrected, with a minimum cluster size of $k=5$ voxels. In order to specifically examine connectivity between our areas

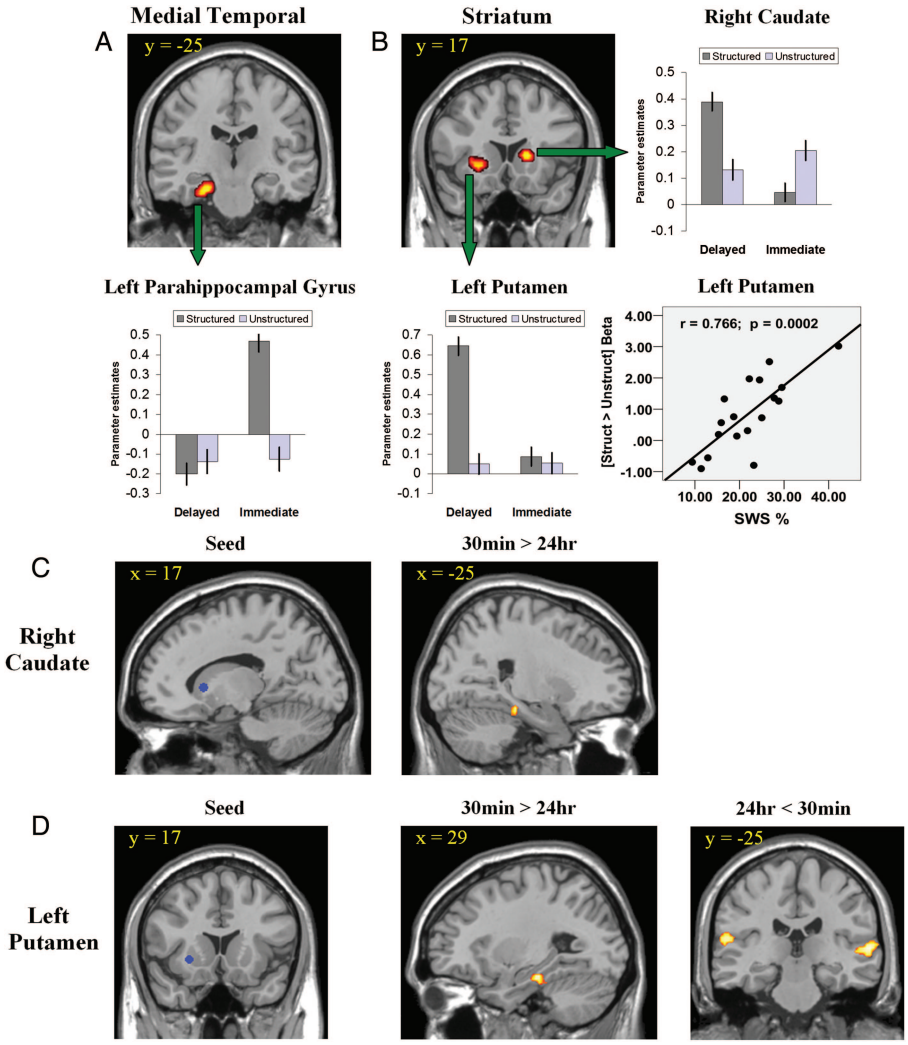

Figure 4. Neuroimaging results, shown with a voxel threshold of $P = 0.001$ (uncorrected) and an extent threshold of $k = 5$ voxels. Activation for group × structure interaction in (*A*) the MTL and (*B*) the striatum, reveals clusters in the left parahippocampal gyrus, the right caudate, and the left putamen. The correlation between the amount of SWS obtained and activation in the left putamen is shown, highlighting the involvement of sleep. A full list of the areas of activation is given in Table 3 and Supplementary Table 2. Functional connectivity with a PPI seed in (*C*) right caudate shows enhanced task-related connectivity with the left parahippocampal gyrus for the 30 min group more than the 24 h group. Functional connectivity with a PPI seed in (*D*) left putamen shows enhanced task-related connectivity with bilateral parahippocampal gyrus for the 30 min group more than the 24 h group, and bilateral planum temporale for the 24 h group more than the 30 min group. A full list of the areas of activation is given in Table 4 and Supplementary Table 5.

of interest, we tested for modulations in connectivity between the 3 seed regions and each of our 4 ROIs (MTL, striatum, ventromedial prefrontal cortex, and planum temporale) with a small-volume-corrected threshold of $P_{SVC} < 0.05$. These data (Table 4) show a clear dissociation between the 30 min and 24 h groups. The task-related connection between the striatum and the MTL, and in particular bilateral parahippocampal gyrus, was stronger for the 30 min group. Meanwhile, the 24 h group showed a much stronger direct connection between the left putamen and bilateral planum temporale which is known to be involved in processing statistical information in auditory sequences, bypassing the MTL.

Discussion

This study showed that the detection of structured and unstructured auditory sequences was greater after 24 h of consolidation than after just 30 min, and that this improvement was predicted by the amount of SWS obtained. We also showed evidence of neural reorganization related to sleep, with lower responses in MTL, and higher responses in striatum after overnight consolidation. Like the behavioral improvement, the greater striatal activity after 24 h was predicted by the amount of SWS obtained. Furthermore, we found greater connectivity between striatum and both MTL and ventromedial prefrontal cortex after 30 min, and greater connectivity between striatum and planum temporale after 24 h. These data provide the first evidence of neural reorganization related to abstraction through consolidation, and indicate that the MTL-striatal trade-off previously reported as a function of training can also occur as a function of consolidation.

Functional decreases in MTL activation as a result of consolidation have been observed in previous studies using declarative memory tasks (Takashima et al. 2006, 2009). These findings are often interpreted under the standard model of consolidation (Frankland and Bontempi 2005). This proposes

Table 4
PPI connectivity analysis—MTL, striatum, STG, and vmPFC

Anatomical region	MNI *x*, *y*, *z* (mm)	No. of voxels	Peak *Z*	Peak P_{SVC}	Contrast
Seed: left parahippocampal gyrus	–21, –25, –23				
No regions	—	—	—	—	—
Seed: left putamen	24, 17, –5				
Right planum temporale	63, –25, 4	70	3.80	0.007	24 h > 30 min
Left planum temporale	–60, –25, 13	48	3.60	0.011	24 h > 30 min
Right parahippocampal gyrus	30, –25, –20	7	3.94	0.007	30 min > 24 h
Seed: right caudate	18, 17, 4				
Left parahippocampal gyrus	–24, –31, –14	9	3.85	0.011	30 min > 24 h

PPI analysis for connectivity between 3 seed regions and regions of interest in the MTL, the striatum and the planum temporale, modulated by sequence structure (structured>unstructured), contrasted between 30 min and 24 h groups with a voxel threshold of $P = 0.05$ (FWE corrected for the small search volume) and an extent threshold of $k = 5$ voxels.

that the hippocampus initially links disparate neocortical areas, which direct connections between these cortical areas are gradually strengthened during consolidation, and that links from the hippocampus subsequently fade until the memory becomes hippocampal independent. The need for this initial involvement of the hippocampus is motivated by the complementary learning systems framework (McClelland et al. 1995) which posits that the hippocampus provides a limited-capacity rapid-encoding store while the neocortex forms cortico-cortical connections more slowly. In cases where a network of cortical connections already exists, a new memory may become independent of the hippocampus much more rapidly (Tse et al. 2007; van Kesteren et al. 2010), although some memory traces may never become entirely independent (Nadel and Moscovitch 1997). Some authors have proposed that this process takes place during sleep (Born et al. 2006; Walker 2009), benefitting not only from reduced external input but also from reduced internal connectivity (Massimini et al. 2005; Robertson 2009) which can prevent undesirable interactions between declarative and nondeclarative memory systems (Poldrack et al. 2001; Brown and Robertson 2007a,b).

The slow oscillations that occur during SWS have been suggested as the specific mechanism most directly involved in sleep-related transfer of connectivity away from the MTL (Diekelmann and Born 2010). Both systems consolidation (Born et al. 2006) and synaptic homeostasis (Tononi and Cirelli 2006; Tononi 2009) may be involved in this process (Walker 2009), and together these could lead to abstraction of underlying regularities while inessential details are lost (Lewis and Durrant 2011). Although the relationship between SWS and slow oscillations is indirect (Dijk et al. 1987), more time in SWS typically leads to more slow oscillations. Our observation that the amount of time spent in SWS predicts improvement on our task, which can be solved by abstraction of an underlying transition structure, is in keeping with these suggestions, as is the reduced MTL activation we observed after consolidation. An alternative explanation is that chunks of melodies rather than abstract transition statistics were encoded in declarative memory and consolidated across SWS. This reflects an ongoing debate regarding the nature of statistical learning (Perruchet and Pacton 2006). We cannot distinguish between these possibilities in the present dataset, but it seems likely that both chunks and statistical structure are learned to an extent (Kim et al. 2009). We have examined this issue in a separate experiment by presenting our sequence stimuli in different modalities at encoding and test, for example, training in the auditory modality and testing in the visual modality (Durrant et al. accepted). This paradigm was designed to ensure that explicit episodic memory for chunks could not aid test performance since the stimuli presented at test shared no superficial characteristics with those presented at training. Instead, the only shared characteristic was the underlying statistical structure which determined the sequence of stimuli. Subjects performed well above chance on this task, clearly demonstrating that they did not solve it using episodic memory for chunks, but instead relied on knowledge of the statistical structure. Importantly, performance on this task also improved across a night of sleep, again supporting a role for this state in the consolidation of statistical structure. In combination with existing literature on the role of sleep in related procedures (Stickgold and Walker 2004; Wagner et al. 2004; Gomez et al. 2006; Yordanova et al. 2008; Djonlagic et al. 2009; Yordanova et al. 2012), and a recent theoretical explanation (Lewis and Durrant 2011), these data suggest that abstraction is used in solving our task.

As well as a reduced MTL activation, we found greater striatal activation after overnight consolidation. This trade-off between memory systems has been found in several previous studies related to sequence learning (Poldrack and Packard 2003; Cartwright 2004; Poldrack and Rodriguez 2004; Reiss et al. 2005; Albouy et al. 2008; Poldrack and Foerde 2008; Rieckmann et al. 2010), and generally progresses with training, even after relatively few trials (Rieckmann et al. 2010). Our data show that this trade-off may also be achieved by consolidation over time, and in particular over sleep. The stronger MTL activation in the 30 min group and the stronger striatal activation and improved behavioral performance in the 24 h group together resemble the early- and late-training scenarios in the classical interpretation. The predictive relationship we observed between SWS and both behavioral improvement and striatal activation suggests that sleep may play an active role in this process.

Our functional connectivity analyses shed further light on the trade-off between MTL and striatum. The observed increase in functional connectivity between left putamen and bilateral planum temporale after consolidation is analogous to prior results (Takashima et al. 2009; see also Durrant and Lewis 2009). In that study, functionally relevant areas of posterior parietal cortex and fusiform face area showed increased interconnectivity, and decreased connectivity with MTL after consolidation. Our current study shows a broadly similar pattern, with task-related areas in bilateral planum temporale (Overath et al. 2007, 2010; Furl et al. 2010) and striatum exhibiting greater interconnectivity, and less connectivity with MTL (for striatum in particular) after 24 h than after 30 min.

Our results may be contrasted with those of Albouy et al. (2008), who looked at the hippocampus and striatum in consolidation of motor sequences and found a competitive relationship in functional connectivity during early training. There are several possible explanations for this difference. First, Albouy et al. focus on immediate relationships (the functional connectivity between different areas at the same time

point), while we focused on the development of relationships over time (how much activation in 1 area changes over time, whether activation in other areas follows the same or opposite pattern, and whether the functional connectivity between different areas evolves in a similar way). Second, our task uses perceptual statistical learning with no motor component and may therefore draw on a different neural system from that used in motor sequence learning (Remillard 2010). Third, the current study reports results in left parahippocampus rather than the hippocampus proper. This makes sense because the parahippocampus is critical for our task, which requires the formation (Eichenbaum and Lipton 2008) and successful retrieval (Yang et al. 2008) of temporal associations in our structured sequences. As it mediates these processes, parahippocampus could potentially act as gateway between hippocampus proper and superior temporal gyrus, which performs initial auditory processing of the sequence (Munoz-Lopez et al. 2010). In this account, decreases in parahippocampal response occur as temporal associations become integrated over sleep (Ellenbogen et al. 2007) and increases in striatal activation reflect a more automatic processing (Valentin et al. 2007; Rostami et al. 2009) in response selection (Peigneux et al. 2000). Meanwhile, the hippocampus itself shows a stronger response to structured than unstructured sequences regardless of consolidation, reflecting the continued involuntary response to novelty detection (Kumaran and Maguire 2006, 2007, 2009; Herdener et al. 2010) which may occur for unpredictable tones within structured sequences in this paradigm (Furl et al. 2010).

In relation to task difficulty, we found evidence that sequences with less obvious structure were more difficult to detect, and that this was modulated by sleep, with the easiest sequences showing the greatest improvement and having the strongest relationship with SWS. We also found a main effect of difficulty in our imaging results, with the greatest activation observed during the most difficult sequences. No sleep-related modulation of cerebral activity for levels of difficulty was found.

Studies which find different memory effects between groups and attribute the differences specifically to sleep (see Diekelmann and Born 2010, for a review) must take care to ensure that these findings cannot be explained by other differences between the groups (Siegel 2001). We controlled for circadian confounds related to functional imaging (Dang-Vu et al. 2007) by ensuring that encoding and recall sessions were conducted at the same time of day. Another possibility is that the consolidation results are due to time rather than sleep. A previous study with our task showed the existence of both sleep- and time-based consolidation processes (Durrant et al. 2011). In our current study, the predictive relationship between SWS and both the behavioral improvement and the stronger striatal activation also suggests that the consolidation process is not purely based on time although this possibility cannot be ruled out completely. Furthermore, our measures of alertness and vigilance showed no evidence of differences in homeostatic sleep pressure which might otherwise have confounded these findings. Finally, it is important to note that although our study measures consolidation by having 2 behavioral sessions for each participant, the different time conditions (30 min, 24 h) for that consolidation are between subjects. This means that our comparison of consolidation across different conditions is indirect; following the example of prior work (Kuriyama et al. 2004; Spencer et al. 2006; Backhaus et al. 2008; Doyon et al. 2009; Durrant et al. 2011) we examine differences in consolidation across groups. We believe this is a reasonable interpretation because the only systematic difference between the groups was the much longer retention interval in the 24 h group.

In summary, our data show an improvement in behavioral performance on an abstraction task that is predicted by the SWS obtained. Functional imaging reveals less dependence on MTL and a greater dependence on striatum after 24 h of consolidation, and the functional difference in striatum can also be predicted by the amount of SWS obtained. Before sleep, the striatum shows a greater connectivity with both MTL and ventromedial prefrontal cortex, while after sleep it is directly functionally connected to auditory areas involved in initially processing the stimuli. Overall, we provide evidence that sleep may be actively involved in neural reorganization to support a more automatic processing of stimuli based on underlying abstract properties.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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