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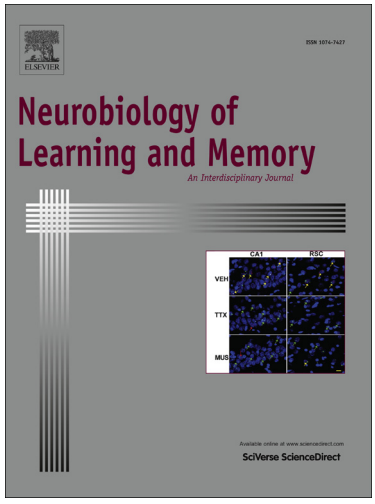

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Schema-Conformant Memories are Preferentially Consolidated During REM Sleep

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Abstract

Memory consolidation is most commonly described by the standard model, which proposes an initial binding role for the hippocampus which diminishes over time as intracortical connections are strengthened. Recent evidence suggests that slow wave sleep (SWS) plays an essential role in this process. Existing animal and human studies have suggested that memories which fit tightly into an existing knowledge framework or schema might use an alternative consolidation route in which the medial prefrontal cortex takes on the binding role. In this study we sought to investigate the role of sleep in this process using a novel melodic memory task. Participants were asked to remember 32 melodies, half of which conformed to a tonal schema present in all enculturated listeners, and half of which did not fit with this schema. After a 24-hour consolidation interval, participants were asked to remember a further 32 melodies, before being given a recognition test in which melodies from both sessions were presented alongside some previously unheard foils. Participants remembered schema-conformant melodies better than non-conformant ones. This was much more strongly the case for consolidated melodies, suggesting that consolidation over a 24-hour period preferentially consolidated schema-conformant items. Overnight sleep was monitored between the sessions, and the extent of the consolidation benefit for schema-conformant items was associated with both the amount of REM sleep obtained and EEG theta power in frontal and central regions during REM sleep. Overall our data suggest that REM sleep plays a crucial role in the rapid consolidation of schema-conformant items. This finding is consistent with previous results from animal studies and the SLIMM model of van Kesteren et al (2012), and suggest that REM sleep, rather than SWS, may be involved in an alternative pathway of consolidation for schema-conformant memories.

1. Introduction

Over the past century, a body of evidence has accumulated confirming the importance of consolidation as a key memory process (McGaugh, 2000; Dudai, 2012). Consolidation is a process that can take place over a timescale of second, hours, days or even years (Dudai, 2004), with a general distinction made between cellular synaptic consolidation which takes place within seconds of encoding, and systems level consolidation which is believed to start after minutes or hours, and may last much longer.

Consolidation at the systems level is most commonly described by the so-called standard model (Frankland & Bontempi, 2005), though alternatives such as the multiple trace model (Moscovitch & Nadel, 1998; Nadel & Moscovitch, 1997) have also been proposed. The wide variation in the timescale of consolidation has led to criticism of the vague details of the standard model (Meeter & Murre, 2004), and in response there has been a move to clarify and elucidate some of the specific processes involved (Frankland & Bontempi, 2006).

The standard model of consolidation proposes that the hippocampus initially plays a binding role on disparate neocortical areas which are involved in encoding a particular stimulus. Over time, the hippocampal role is reduced as the neocortical areas form direct connections, until in some cases at least, the memory trace eventually becomes independent of the hippocampus (Frankland & Bontempi, 2005; Nadel, Hupbach, Gomez, & Newman-Smith, 2012).

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In recent years there have been two significant developments of the standard model. First, the importance of sleep in systems level consolidation has been elucidated in a number of studies (Abel, Havekes, Saletin, & Walker, 2013; Rasch & Born, 2013). In particular, there is a growing body of evidence that hippocampal replay during sleep acts as a means of reactivating and strengthening the links between the neocortical areas involved, with slow waves playing a coordinating role synchronising the relevant activation (Born, Rasch, & Gais, 2006; Walker, 2008).

Second, a converging line of evidence from research into schema theory in humans has long since confirmed that items which fit well within an existing schema are generally remembered better (Bransford & Johnson, 1972; Chase, Simon, & Chase, 1973; Goldstein & Chance, 1980; Mandler, 1984; Royer & Perkins, 1977). In a series of recent studies, van Kesteren and colleagues (van Kesteren, Rijpkema, Ruiter, & Fernández, 2010; van Kesteren et al., 2013; van Kesteren, Fernández, et al., 2010) have attempted to elucidate the mechanisms underlying this, and have confirmed that the medial prefrontal cortex (mPFC) appears to at least partly take over the hippocampal binding role for schema-conformant items.

An intriguing study of rats in 2007 by Tse and colleagues (Tse et al., 2007) suggested that these two developments could be linked. The authors found that consolidation of food location information, as measured by memory following induced lesion of the hippocampus, was much more rapid when the rats had previously developed a schema (over a period of weeks) in the form of a mental map of their environment. Although sleep was not measured explicitly in the study, it was a possible mechanism in the consolidation process as 48 hours was allowed for consolidation. However, differing interpretations of these results have led to some controversy as to whether these findings relate to systems consolidation (Squire, 2007) or cellular consolidation (Rudy & Sutherland, 2008).

In this study, we sought to resolve this controversy and provide the first evidence of an equivalent process in humans. Specifically, an investigation of schemata and consolidation in humans should demonstrate: (1) the benefit of schemata for memory; (2) the benefit of a schema for rapid consolidation; (3) the possible role of sleep in this process. Of these, the first has previously been demonstrated in humans, the second only conclusively in animals and the third not at all. Our study aimed to investigate all three.

To achieve this, we made use of an existing strongly-established musical schema. Western enculturated listeners growing up in an environment in which music is omnipresent develop a schema for Western tonal music (Speer & Meeks, 1985) on a pure exposure basis, to the extent that even by the age of 5 years, musically untrained children reliably exhibit this schematic knowledge, which persists throughout adulthood (Krumhansl, 1990), and to which musical training makes relatively little difference. The tonality schema is involuntarily activated by hearing Western tonal music and creates expectations as to the tone distribution structure of the music. By creating a set of stimuli which manipulate this structure, we were able to control the use of this schema in processing the stimuli.

Our study compared schema-conformant and non-conformant items, some of which had been consolidated overnight and some of which had not. This enabled us to examine the interaction between the use of a schema in mental processing, and the benefit of consolidation. We also monitored overnight sleep with polysomnography after the first encoding session, enabling us to observe the role of specific sleep stages in this process. We expected to see a memory benefit for

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schema-conformant items, in keeping with previous literature. We also expected to see a benefit of consolidation, which we predicted would be greater for schema-conformant items. Finally, we expected to see a specific role for sleep, and in particular either slow wave sleep or REM sleep.

2. Materials and Methods

2.1 Participants

Participants were required to be healthy individuals aged between 18 and 45, with normal hearing and no history of sleep or neurological disorders (evaluated by a questionnaire and an interview). They were also required to have grown up in Western Culture with their principal musical interest in Western pop or classical music, but with no formal musical education in the previous five years. 20 participants volunteered to take part in the experiment. Of these, one participant was subsequently excluded for an existing neurological condition and one excluded due to insufficient sleep (five hours or fewer on the experiment night). Data is reported from the remaining 18 participants, who consisted of 9 males aged 18-26 years (mean age = 20.7 years, SD ± 2.87) and 9 females aged 19-23 years (mean age = 20.1 years, , SD ± 1.27).

Participants were required to have a normal sleep schedule with no shift work within the previous six months, and to have maintained strictly regular sleep hours for the week prior to the experiment, which was assessed by a sleep diary and completion of a customised sleep questionnaire. No participant reported an existing medical conditions and none were taking medication with the exception of the female contraceptive pill.

For the entire duration of the experiment participants were asked to abstain from alcohol, caffeine and other drugs, and refrain from taking daytime naps. Participants were paid £50 for their participation. Each participant gave informed consent for the experiment, which was approved by the Research Ethics Committee of the University of Manchester.

2.2. Stimuli

In order to evaluate the role of schemata in memory consolidation, we exploited an existing schema universally present in Western enculturated music listeners (Dowling & Harwood, 1986). Tonality describes a music theoretic concept in Western tonal music (Piston & DeVoto, 1978) in which certain musical tones are given more prominence than others within a given key. This is reflected in the frequency of occurrence of those tones (Knophoff & Hutchinson, 1983; Youngblood, 1958), and exists as a mental structure (Krumhansl & Shepard, 1979; Krumhansl, 1990) which governs the perception of tonal music (Krumhansl & Kessler, 1982). This mental structure qualifies as a schema (Mandler, 1984) for three important reasons: (1) it is acquired early in life on the basis of exposure (Speer & Meeks, 1985), probably through a mechanism of statistical learning (Durrant, Taylor, Cairney, & Lewis, 2011; Saffran, Johnson, Aslin, & Newport, 1999); (2) it can be triggered by a variety of key contexts but once activated remains intact and independent of the specific form of the

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trigger(Krumhansl, 1990); (3) it creates a set of schematic expectations about what will come next (Bharucha, 1987, 1994).

One of the authors (SJD), a trained and qualified musician, created 96 melodies , 48 of which were tonal, containing a tone distribution pattern clearly designed to trigger the tonality schema. The other 48 melodies used a system called serialism, developed in the early 20th century by Arnold Schoenberg (1978/1922) in opposition to tonal music, which specifically aims to avoid giving a sense of key (and hence not triggering the tonality schema). This is achieved by ensuring that as far as possible, all 12 semitones in the Western octave are equally represented, and no tone appears for a second time before every other tone has been encountered. Music created with this system is frequently called atonal, which we will adopt here.

We therefore had 48 tonal melodies, which conformed with the tonal schema and were designed to trigger it, and 48 atonal melodies which violated the tonal schema. In order to eliminate any other differences between the melodies which may have influenced how memorable they were, the 48 atonal melodies were adapted from the tonal melodies by moving individual pitches to the nearest available pitch in accordance with the serial rule. All pitch changes were within an octave and none changed the overall contour pattern of a melody. In this way, the set of 48 tonal melodies shared identical rhythms and other features with the 48 atonal melodies, and differed only by tonality. All the melodies consisted of four bars of music with four beats per bar and all were exactly 8 seconds in duration.

In order to verify the tonal qualities of the melodies, we used the key-finding algorithm developed by Krumhansl and Schmuckler (described in Krumhansl 1990, ch.4), implemented as part of the MIDI toolbox (Eerola & Toiviainen, 2004) running in MATLAB© 6.5. This algorithm matches the tone distribution of a given melody, weighted by the metrical position (i.e. the rhythmic importance) of the tone, to the perceptually-derived tone profiles of Krumhansl and Kessler (1982) in order to find the best match. As well as identifying the nearest key, the algorithm provides the strength of the match, which represents the tonal strength of the melody, i.e. the extent to which is likely to be heard as tonal rather than atonal. The average key strength of the tonal melodies was 0.799 (± 0.092 SEM) while the average key strength of the atonal melodies was 0.546 (± 0.137 SEM); the difference between the two was strongly significant ($t(94)=10.63$, $p<0.001$). Finally, all 96 melodies were played in a randomised order to three professional musicians who were asked to indicate whether a melody was tonal or atonal. All three musicians confirmed the tonal and atonal labels for all 96 melodies.

2.3. Experimental Protocol

The structure of the experiment can be seen in Figure 1. Participants attended the first session at the Manchester Sleep Laboratory at 1.45pm (± 1 hour at most) on Day 1. They were first asked to read a participant information sheet giving the detailed procedure, but not the purpose, of the experiment, and invited to ask any questions. This was followed by completion of a written consent form, submission of their sleep diary (which had been sent to them previously and completed during the preceding seven days), and completion of further experiment documentation including a background screening questionnaire (to check for existing health conditions or medication), sleep

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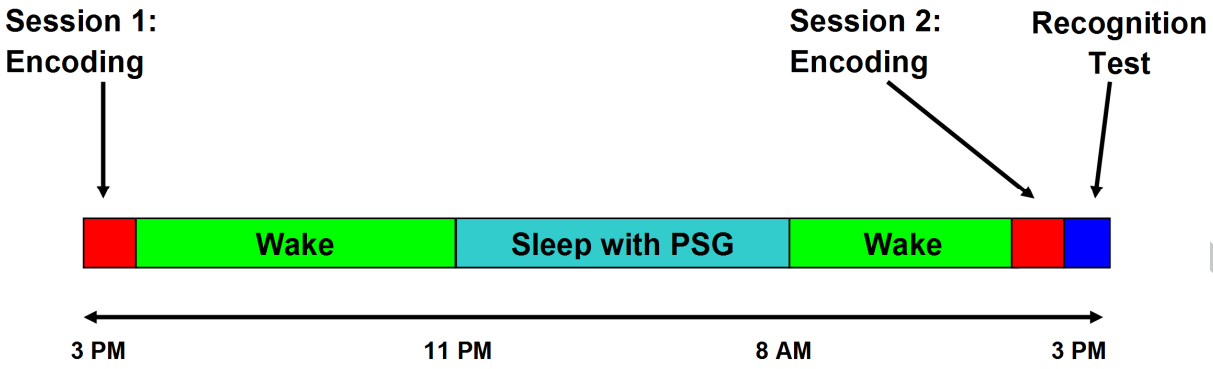

Figure 1: Experiment Design. Participants undertook an initial encoding session at 3pm on Day 1, followed by a 24-hour consolidation interval containing both wake and overnight sleep. Sleep was monitored with polysomnography. A second encoding session at 2pm on Day 2 was followed by a recognition test in which memory for both sets of stimuli was tested. Schema-conformant tonal melodies and non-conformant atonal melodies were presented in all sessions.

log (indicating detailed sleep activity for the previous three nights as an additional measure to the sleep diary), the Stanford Sleepiness Scale and a visual analogue sleepiness scale (both to measure tiredness in the session). This part of the session took approximately 15 minutes.

The main encoding task started at 2pm. This consisted of listening to a set of 32 melodies (16 tonal, 16 atonal) presented 9 times each in total, with a timbre detection attention task. The 32 melodies were pseudo-randomised and divided into two blocks of 16 melodies (containing 8 tonal and 8 atonal in each block). Within both blocks, each melody was repeated 3 consecutive times with a 2s gap between each presentation, once with a flute timbre, once with a violin timbre, and once with a clarinet timbre (randomly ordered for each melody). Participants were asked to indicate during the task which timbre they heard on each repetition by pressing the appropriate button on a keyboard, as instructed both verbally before the experiment and on-screen during the task; prior to the task they had been familiarised with the individual timbres by hearing some scales and intervals in each and told which timbre was which. This task served to maintain participant attention to the melodies, to monitor attention levels, and to identify any major hearing problems not indicated on the screening form. The first block, therefore consisting of 3 consecutive repetitions of each of 16 melodies, was itself repeated 3 consecutive times before moving on to the second block (which has an identical pattern of repetitions for the second set of 16 melodies). Participants therefore heard all 32 melodies a total of 9 times each, in a mixed configuration which combined consecutive and spaced repetition, which pilot testing suggested would give an appropriate level of memory encoding. Participants were allowed to take a short break between each block repetition if they wished; the task typically lasted around 50 minutes in total.

Following completion of the encoding task, participants were allowed to leave the lab and went about their usual business for the remainder of the day, in order to create as realistic a scenario as possible. At 10pm, they returned to the lab for overnight sleep monitoring. This consisted of application of electrodes and a patient unit to allow for full polysomnography (please see section on polysomnography below for further details). Lights were turned out at 11.30pm, and participants were woken the following morning at 8am by one of the experimenters, providing a sleep window of

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8½ hours with the expectation that sleep would last approximately seven hours (participants with fewer than five hours were excluded from subsequent analysis). After removal of the electrodes in the morning, participants were once again allowed to leave the lab and go about their business, with instructions to return for the second behavioural session during the afternoon. No behavioural task was carried out during the overnight session.

The second behavioural session took place at 3pm on Day 2, and consisted of both encoding and retrieval tasks. The encoding task in this session was identical to the one on Day 1, but with 32 new melodies (meaning that participants encoded a total of 64 melodies across the two days). Following encoding and a short 30-minute break, participants undertook the final retrieval task. This consisted of listening to 96 pseudo-randomised melodies in total, divided into two blocks of 48 melodies with a short break in between. The 96 melodies consisted of the 64 learned melodies (32 tonal, 32 atonal) and 32 unlearned foil melodies (16 tonal and 16 atonal). Participants were instructed to indicate whether or not they had heard the melody in either of the encoding sessions by pressing the appropriate button. They were also asked to rate the confidence of their decision on a 3-point scale (3 being most certain, 1 being least certain). Participants were given 3s to make their decision, and a further 3s to indicate their level of confidence. The retrieval task lasted around 25 minutes in total.

Finally, participants were given a debrief which included an explanation of the purpose of the experiment and the structure of the stimuli, and invited to ask questions and give feedback.

2.4. Equipment

The melodies were initially created as Midi files using Sibelius© 7.0 software (Avid, 2011) and subsequently rendered into audio using the General Midi instrument bank of a Creative Labs SoundBlaster™ X-Fi Elite Pro soundcard. Stimuli were presented via Sennheiser HD207 headphones connected to a Samsung Q430 laptop with a Core i5 processor, using the on-board Realtek High Definition Audio chip and 14" 1280 x 1024 resolution display operating at 60Hz (for instruction messages). Stimulus presentation and data collection used custom-written scripts running in MATLAB© 6.5 with Cogent 2000, developed by the Cogent 2000 team at the FIL and the ICN and Cogent Graphics developed by John Romaya at the LON at the Wellcome Department of Imaging Neuroscience. Responses in the timbre detection task during the encoding sessions were via the keyboard; responses in the retrieval task used a serial button box attached to a Micromint Domino 2 controller to give a better resolution of approximately 1ms when monitoring response times.

2.5. Polysomnography

Overnight sleep monitoring was carried out in the University of Manchester sleep laboratory using Embla© N7000 polysomnography systems. Ng-NgCl electrodes were attached at six standard locations using the 10-20 system (C3, C4, F3, F4, O1, O2) using EC2© electrogel, after first preparing the scalp for application with NuPrep© exfoliating agent. Left and right electrooculogram (LOC, ROC) and left, right and upper electromyogram (EMG1, EMG2, EMG3) were also attached. Scalp and

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eye electrodes were referenced to the contralateral mastoid (A1,A2), and a ground electrode was attached to the central forehead, giving 14 electrodes attached in total. In addition, the Patient Unit and a number of additional sensors were attached in order to record physiological signals including movement, heart rate, pulse oximetry and respiration. All electrodes were tested and confirmed to have an impedance level of less than 5Kohms at the start of the sleep session, and all signals were digitally sampled at a rate of 200Hz.

Each participant's sleep data was subsequently divided into 30s epochs and scored using RemLogic© 1.1 according to the standardised criteria laid down by Rechtschaffen and Kales (1968), grouping together stages 3 and 4 under the umbrella term of SWS as recommended by the American Academy of Sleep Medicine (Ancoli-Israel, Chesson, & Quan, 2007). This gave the proportion of time spent in each sleep stage (N1, N2, SWS, REM) for each participant, as well as measures of sleep efficiency and total sleep time.

2.6. Behavioural Data Analysis

A within-subjects design was used to minimise the impact of individual differences in polysomnography, given the strong heritability of characteristic EEG patterns (Smit, Posthuma, Boomsma, & Geus, 2005) and individual differences in musical background.

In order to reduce the influence of chance results, it was decided *a priori* to exclude trials with the lowest certainty rating from subsequent analyses. Data from the remaining trials, which were on average 78.8% (± 2.5% SEM) of all trials for each participant, were first converted to d' scores (the difference in the z-scores of hits and false alarms), a signal detection process widely used in memory studies as a way to account for response bias (MacMillan & Creelman, 2005).

As our hypotheses were concerned with the effects of schema conformity and consolidation the results were categorised according to these factors (tonal consolidated, tonal unconsolidated, atonal consolidated, atonal unconsolidated), and each condition tested against chance level to verify that participants were able to successfully perform the task.

Our main analysis used a 2 x 2 repeated-measures ANOVA. It was hypothesised that melodies from the first session, 24 hours before the test, had consolidated, while those from the second session just 30 minutes before the test would not have consolidated to the same extent. To test this, the first factor in the ANOVA was consolidation (consolidated, unconsolidated); the hypothesis predicted a main effect of this factor. It was further hypothesised that the schema-conformant tonal melodies would not only be more strongly remembered than the atonal melodies, but that they would also be more strongly consolidated. In order to test this, the second factor included in the ANOVA was tonality (tonal, atonal), and the hypothesis predicted that both a main effect and an interaction would be found, with the interaction driven by stronger consolidation of tonal items

Differences in alertness in the two experiment sessions could explain a difference in the encoding and subsequent retrieval of the consolidated and unconsolidated stimuli without reflecting a difference in consolidation. In order to test this possibility, data from the Stanford Sleepiness Scale and visual analogue sleepiness scales were analysed with paired-samples t-tests to check for

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differences in alertness between the two sessions. We also analysed sleep diaries for evidence of potential sleep deprivation or abnormal sleep on the experiment night amongst any of our participants, as a means of data quality control.

Similarly, differences in attention between the tonal and atonal stimuli (as a consequence of the tonal stimuli sounding more pleasant, for example), may also confound the effect of schema conformity. To test this, we examined performance on the timbre detection task in both encoding sessions, and tested for differences between sessions, and between tonal and atonal melodies within sessions, using Wilcoxon signed rank tests.

2.7. Sleep Data Analysis

The role of particular stages of sleep in consolidation was investigated by planned non-parametric correlation tests between the proportion of time spent in N2, SWS and REM, all of which have been implicated in sleep-dependent consolidation (Born & Wilhelm, 2012; Fogel, Smith, & Cote, 2007; Smith, 2001), and the retrieval difference between consolidated and unconsolidated items, separately for tonal and atonal melodies. These were Bonferroni-corrected for multiple comparisons to ensure that only the most reliable effects are shown. Differences in correlations for tonal and atonal melodies were tested using Steiger's Z-test, which has been shown to be an improvement upon the more commonly-encountered Hotelling's t-test (Meng, Rosenthal, & Rubin, 1992).

In addition, power spectral analyses and sleep spindle analyses were conducted to look at the role of specific neural oscillations in the consolidation process. Power spectral analysis was carried out in a standard manner using Welch's method, with the EEG trace for each channel divided into 8 segments, windowed with 50% overlap using a Hamming window and subsequently averaged after computing the Fourier transform. A spectral power estimate was obtained at each 0.25Hz interval and averaged across frequencies in a number of bands of interest including slow wave activity (0.5-2.0Hz), delta power (1-4Hz), theta power (5-8Hz) and alpha power (8-13Hz) bands. Estimates within a band were computed separately for each sleep stage of interest (SWS for slow wave activity and delta power, REM sleep for theta power), and separately for frontal, central and occipital electrodes (and averaged over electrodes within each of these regions). Absolute PSD estimates were finally normalised to give relative power at each electrode and control for overall power differences between participants. The relationship between power spectral density and behavioural performance was measured with specific Bonferroni-corrected non-parametric correlation tests looking at theta power during REM sleep and slow wave activity and delta power during SWS; these were selected as the defining power bands of these sleep stages and driven by the hypotheses of the study. For completeness, correlations between behavioural performance and delta, theta, alpha and spindle power bands for N2 were also computed.

Sleep spindles were calculated in stages N2 and SWS by first bandpass filtering the signal at 11-15Hz using an FIR filter implemented in EEGLAB v12 (Delorme & Makeig, 2004) and then applying the automatic spindle detection algorithm of Ferrarelli et al (2007). This algorithm takes the filtered signal and detects amplitude fluctuations of eight or more times the mean channel value and has been used in a number of previous studies (Cairney, Durrant, Hulleman, & Lewis, 2014; Nishida &

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Walker, 2007; Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010). Spindle measures derived were the total number of spindles, the spindle density (number per minute) and the integrated spindle amplitude (which effectively represents the combination of total spindle duration and mean spindle amplitude). The relationship between these three measures taken separately in N2 and SWS, and behavioural performance, was measured with non-parametric correlation tests Bonferroni-corrected within each set.

3. Results

3.1. Alertness and Attention

Participants gave two measures of alertness at the start of both experiment sessions: the Stanford Sleepiness Scale (SSS) and a visual analogue sleepiness scale (VASS). The SSS rating did not differ ($t(17)=1.00$, $p=0.331$) between the first session ($M=2.22$, $SEM=0.129$) and the second session ($M=2.06$, $SEM=0.127$). Similarly, the VASS rating did not differ ($t(17)=0.238$, $p=0.814$) between the first session ($M=29.56$, $SEM=1.86$) and the second session ($M=28.72$, $SEM=2.74$). Together these results indicate that there were no differences in alertness between the two sessions, and alertness can be reasonably discounted as a source of inter-session variability in melody encoding. A comparison of the two measures revealed a significant correlation between them in both session one ($\rho=0.629$, $p=0.005$) and session two ($\rho=0.549$, $p=0.018$), suggesting that participants were using them in a meaningful way.

Attention was good overall with 84.1% ($SEM=3.91\%$) correct responses in the timbre task in the first session, and 93.9% ($SEM=1.72\%$) correct responses in the second session. The difference between the sessions was significant ($Z=-3.726$, $p<0.001$); this partly reflected a learning curve with a significant difference seen between the first two blocks of the first session ($Z=-3.18$, $p=0.001$), but also partly a consolidation effect related to this task (performance in the first block of the second session was significantly higher than the last block of the first session: $Z=-2.85$, $p=0.004$). There was, however, no difference between attention to the tonal and atonal stimuli in either the first session (tonal: $M=83.4\%$, $SEM=4.36\%$; atonal: $M=84.8\%$, $SEM=3.55\%$; $Z=-0.518$, $p=0.604$) or the second session (tonal: $M=93.9\%$, $SEM=1.99\%$; atonal: $M=93.8\%$, $SEM=1.62\%$; $Z=0.79$, $p=0.431$), confirming that attention differences during encoding could not explain any difference in retrieval performance between tonal and atonal melodies.

3.2. Memory Consolidation and Schema Conformity

Participants overall recognition performance suggested that they were clearly able to recognise many, but not all, of the learned melodies, with an average correct recognition of 41.0 melodies (out of a possible 64) with just 8.2 false alarms. This consisted of an average of 13.3 ($SEM=0.42$) tonal consolidated, 9.7 ($SEM=0.66$) tonal unconsolidated, 10.0 ($SEM=.74$) atonal unconsolidated, and 8.0 ($SEM=.79$) atonal unconsolidated melodies, with 3.8 tonal ($SEM=.66$) and 4.4 atonal false alarms respectively. d' was calculated in order to account for response bias and used in subsequent hypothesis tests. Results were categorised according to their consolidation and schema status,

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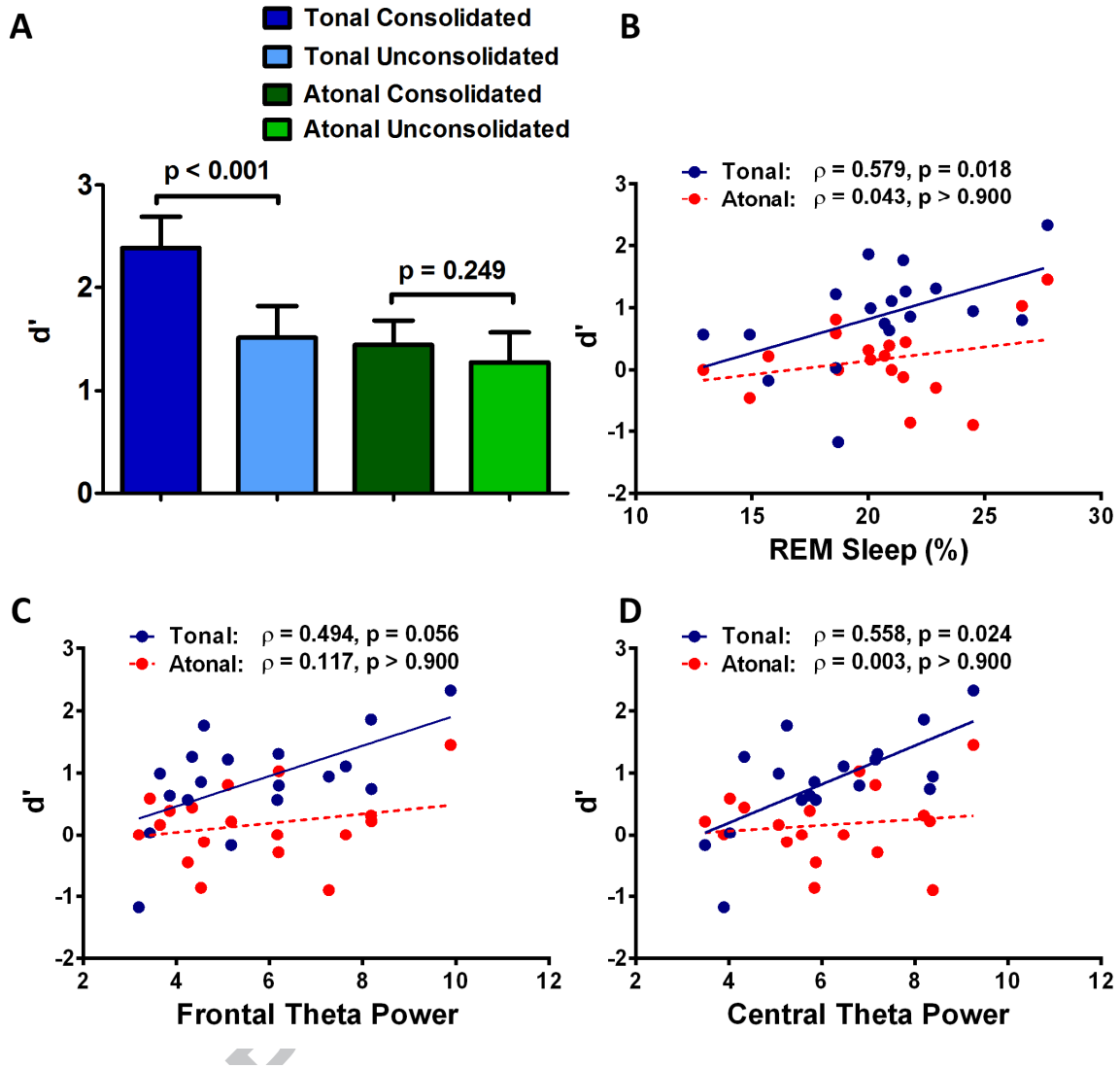

Figure 2: Behavioural results. A: d' scores for each of the four conditions in the study. The consolidated schema-conformant tonal melodies were recognised significantly better than the unconsolidated tonal melodies. By contrast, there was no difference between the consolidated and unconsolidated atonal melodies. B: The % of REM sleep obtained predicted the difference in d' scores between consolidated and unconsolidated tonal melodies. C: Frontal theta power predicted d' scores for consolidated tonal melodies, but not consolidated atonal melodies. D: Central theta power also predicted d' scores for consolidated tonal melodies, but not consolidated atonal melodies.

giving four conditions per participant – tonal consolidated, atonal consolidated, tonal unconsolid ated and atonal unconsolidated (shown in figure 2a). A series of one-sample t-tests against chance level (a d' score of 0) confirmed that participants were able to successfully remember melodies in all four conditions (all $t(17)>4.422$, all $p<0.001$).

In order to evaluat e the respective roles of consolidation and schema conformity on memory retrieval, and especially whether or not schema-conformant tonal melodies were consolidated more effectively than the non-conformant atonal melodies, we conducted a 2 x 2 ANOVA, with factors consolidation and tonality, on the retrieval d' scores. The results offered support for the

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hypotheses. We found a strong main effect of consolidation ($F(1,17)=16.07$, $p=0.001$), with consolidated melodies ($M=1.912$, $SEM=0.238$) remembered much better than unconsolidated melodies ($M=1.394$, $SEM=0.248$), in spite of having been heard 24 hours earlier rather than just 30 minutes before the test. We also found a main effect of schema ($F(1,17)=4.45$, $p=0.05$), with the schema-conformant tonal melodies ($M=1.946$, $SEM=0.289$) remembered better than the non-conformant atonal melodies ($M=1.359$, $SEM=0.254$). Importantly, our data showed a significant interaction between consolidation and schema ($F(1,17)=11.47$, $p=0.004$), with the difference in retrieval of tonal and atonal melodies much greater for consolidated ($d'=0.868$) than unconsolidated items ($d'=0.168$). Post hoc paired-samples t-tests confirmed that there was a significant difference between the consolidated and unconsolidated tonal melodies ($t(17)=4.649$, $p<0.001$), but no difference between the consolidated and unconsolidated atonal melodies ($t(17)=1.193$, $p=0.249$). In other words, the benefit of consolidation appears to be limited to the schema-conformant tonal melodies; the non-conformant atonal melodies did not seem to benefit significantly from consolidation. Similarly, analysing the data within session rather than within schema category, we found a significant difference between consolidated tonal and atonal melodies ($t(17)=3.580$, $p=0.002$), but no significant difference between unconsolidated tonal and atonal melodies ($t(17)=0.722$, $p=0.480$). This suggests that the difference in retrieval of the consolidated tonal and atonal melodies was as a result of consolidation rather than any difference in initial memory encoding.

3.3. Sleep Parameters

Participants slept for an average of 7 hours and 34 minutes (± 15.7 minutes SEM) on the night of the experiment; this was not significantly different ($t(17)=0.254$, $p=0.802$) to their average of 7 hours and 29 minutes across the previous seven nights, indicating that they experienced relatively typical sleep during the experiment in spite of the laboratory setting. Polysomnography showed that participants slept very efficiently in the sleep lab ($M=92.6\%$, $SEM=1.56\%$), and exhibited a typical hypnogram (Lorenzo & Barbanoj, 2002) with 11.6% (± 1.56% SEM) N1 sleep, 42.3% (± 1.88% SEM) N2 sleep, 26.1% (± 0.96% SEM) N2 sleep, and 20.5% (± 0.88% SEM) REM sleep.

In order to investigate the relationship between specific sleep stages and consolidation, the correlation between the specific consolidation benefit (consolidated – unconsolidated) and the proportion of N2, SWS and REM respectively was investigated, for both tonal and atonal melodies. No relationship was found between consolidation benefit and N2 for either tonal ($\rho(18)=-0.418$, $p=0.126$) or atonal ($\rho(18)=-0.082$, $p>0.900$) melodies. Similarly, SWS showed no relationship with consolidation benefit for the tonal ($\rho(18)=-0.432$, $p=0.110$) or atonal ($\rho(18)=-0.317$, $p=0.299$) melodies. However, a greater amount of REM sleep was associated with greater consolidation benefit for the tonal melodies ($\rho(18)=0.579$, $p=0.018$; see Figure 2b), while showing no significant relationship with the atonal melodies ($\rho(18)=0.043$, $p>0.900$; see Figure 2b); this difference was significant ($Z(15)=1.735$, $p=0.041$). This effect was driven in particular by better retrieval of the consolidation melodies for individuals with a greater amount of REM sleep ($\rho=0.439$, $p=0.029$), rather than reduced retrieval of the unconsolidated melodies ($\rho=0.057$, $p>0.900$). This pattern of results suggests REM sleep-related consolidation of the memories which conform to the schema, with no such relationship for the non-conformant melodies.

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To further elucidate the role of sleep, the underlying neural oscillations were investigated with power spectral density analysis in characteristic frequency bands (theta band for REM sleep, slow wave activity and delta band for SWS; delta, theta, alpha and spindle bands for N2). The broad topography (frontal, central, occipital) and correlation of the power spectral measures with the specific consolidation benefit (consolidated – unconsolidated) were computed in order to determine what neural oscillations may be involved in consolidation of schematic memory. Frontal theta power ($\rho(18)=0.494$, $p=0.056$; see figure 2c) and central theta power ($\rho(18)=0.558$, $p=0.024$; see figure 2d) during REM sleep predicted consolidation of the tonal melodies with at least marginal significance after Bonferroni correction, while occipital power during REM sleep exhibited no such relationship ($\rho(18)=0.189$, $p=0.679$). Consolidation of the atonal melodies showed no relationship with theta power in REM sleep in frontal ($\rho(18)=0.117$, $p>0.900$; see figure 2c), central ($\rho(18)=0.003$, $p>0.900$; see figure 2d) or occipital ($\rho(18)=-0.311$, $p=0.313$) electrodes; the difference in correlations for tonal and atonal melodies was signficant for central electrodes ($Z(15)= 1.768$, $p=0.039$) while not quite reaching signficance for frontal electrodes ($Z(15)=1.204$, $p=0.11$). These results offer further support to the involvement of REM sleep in consolidation of the memories which conform to the schema, particularly as the relationship is confined to regions likely to be involved in consolidation of schema-conformant auditory stimuli (frontal and central), with primarily visual regions (occipital) showing no such relationship.

During SWS, slow wave activity in frontal, central and occipital regions did not show any relationship with consolidation of tonal melodies (frontal: $\rho(18)=-0.271$, $p=0.414$; central: $\rho(18)=0.228$, $p=0.544$; occipital: $\rho(18)=0.036$, $p>0.900$) or atonal melodies (frontal: $\rho(18)=0.047$, $p>0.900$; central: $\rho(18)=$ $\rho(18)=-0.026$, $p>0.900$; occipital: $\rho(18)=0.138$, $p=0.879$). Similarly, delta power during SWS also failed to show any relationship with consolidation of tonal melodies (frontal: $\rho(18)=-0.249$, $p=0.479$; central: $\rho(18)=0.321$, $p=0.291$; occipital: $\rho(18)=0.307$, $p=0.324$) or atonal melodies (frontal: $\rho(18)=0.100$, $p>0.900$; central: $\rho(18)=0.073$, $p>0.900$; occipital: $\rho(18)=0.299$, $p=0.342$). Spectral power in stage N2 sleep also failed to show any relationship to consolidation in any combination of region and power band (all $p>0.2$).

Finally, sleep spindles in both SWS and N2 were analysed for a potential role in consolidation of the tonal or atonal melodies. During SWS, neither the total number of spindles (tonal: $\rho(18)=-0.118$, $p>0.900$; atonal: $\rho(18)=0.025$, $p>0.900$), spindle density (tonal: $\rho(18)=-0.009$, $p>0.900$; atonal: $\rho(18)=$ $\rho(18)=0.113$, $p>0.900$) or integrated spindle amplitude (tonal: $\rho(18)=-0.013$, $p>0.900$; atonal: $\rho(18)=0.187$, $p=0.686$) showed any relationship with the consolidation of either the tonal or atonal melodies. During N2 the total number of spindles (tonal: $\rho(18)=-0.297$, $p=0.346$; atonal: $\rho(18)=0.308$, $p=0.320$), spindle density (tonal: $\rho(18)=-0.162$, $p=0.781$; atonal: $\rho(18)=0.233$, $p=0.529$) or integrated spindle amplitude (tonal: $\rho(18)=-0.228$, $p=0.544$; atonal: $\rho(18)=-0.063$, $p>0.900$) again showed any relationship with the consolidation of either the tonal or atonal melodies. These findings, in combination with the spectral power data and the absence of any relationship between the behavioural data and the amount of time in spent in either SWS or N2, suggest that in this study SWS and N2 may have played a less important role than REM sleep in consolidation of the schematic memories.

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4. Discussion

We examined the respective roles of memory consolidation and use of a schema, in order to understand whether or not schema-conformant items consolidate more rapidly than non-conformant items. In particular we had three hypotheses: that schema-conformant items would be remembered better than non-conformant items in general, that consolidated items would be remembered better than unconsolidated items, and that schema-conformant items would be consolidated better than non-conformant items within the 24-hour period of the study. Our data support all three of these hypotheses. In particular, we found that the tonal melodies were remembered better than the atonal melodies, and that melodies overall were remembered better after 24 hours of consolidation. Crucially, however, these effects are driven by an interaction: only the schema-conformant tonal melodies appeared to consolidate within the 24-hour window; the atonal melodies showed no such improvement.

The benefit of a schema in memory encoding and retrieval has been well established for a number of years (Bransford & Johnson, 1972; Chase & Simon, 1973; Goldstein & Chance, 1980; Mandler, 1984; Royer & Perkins, 1977). However, our results are, to our knowledge, the first demonstration of an interaction between schema conformity and speed of consolidation in humans. This pattern of results has been seen in a previous study with rats, however (Tse et al., 2007). In that study, rats learned flavour-location associations over time when searching for food within their environment, gradually developing a schema. New associations were rapidly consolidated (becoming independent of the hippocampus) if introduced afterwards, but only if the environment schema was active. For rats without such an active schema (from being in an inconsistent environment, for example), no rapid consolidation of new associations took place. The authors of that study, and some subsequent commentators, interpreted the data as evidence of rapid systems level consolidation in rats (Squire, 2007). Others, however, suggested that their results could be due to a slow cellular consolidation process instead (Rudy & Sutherland, 2008), especially in view of the disruptive effect of the neurotoxins used in the study to disable the hippocampus, although the authors reject this suggestion (Tse et al., 2008). Our human data, for which no hippocampal lesions were used, tentatively support the systems consolidation hypothesis; we cannot rule out a slow cellular consolidation process in this case, but it seems unlikely given the timeframe and ample evidence for systems level consolidation in humans over similar time periods (Durrant, Cairney, & Lewis, 2013; Rasch & Born, 2013; Takashima et al., 2006).

Given the potential for the unconsolidated melodies encoded in the second session to interfere with the similar-sounding melodies learned in the first session, the stronger performance on the consolidated melodies suggests that both stabilisation and enhancement of the memories took place. It has been suggested that these processes may be distinct components of consolidation (Walker, 2005) and previous studies using paired associate learning have shown that sleep specifically protects against interference in a way not seen during wakefulness (Ellenbogen, Hulbert, Jiang, & Stickgold, 2009; Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006). We cannot measure the relative strength of stabilisation/protection from interference and enhancement in our design due to the lack of a feasible wake control group; however, from our 24-hour behavioural data it seems likely that both were present.

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In addition to our core behavioural results, we found a significant positive association between the consolidation benefit for tonal melodies, and the amount of REM sleep. No such relationship was observed for the atonal melodies, which did not benefit from consolidation, suggesting that this is a consolidation-specific effect for the schema-conformant items. No relationships with the duration of stage N2 sleep, or SWS, were observed. We also found a relationship with the amount of EEG theta power in frontal and central regions during REM sleep, but not in occipital regions. No relationships with spindles in N2 or SWS, or slow wave activity or delta power in SWS (or any spectral power band in N2) were found. As our study used auditory stimuli, the absence of a role for occipital theta power is to be expected. Consolidation-related theta power from central electrodes is likely to represent the reprocessing of auditory stimuli. On the other hand, consolidation-related theta power in frontal areas, and the fact that the results point consistently towards a specific role for REM sleep and not SWS, may appear strange at first glance, and at odds with the standard model of consolidation. However, a recent series of studies by van Kesteren et al (van Kesteren, Rijpkema, et al., 2010; van Kesteren et al., 2013; van Kesteren, Fernández, et al., 2010) looking at the neural mechanisms underpinning the consolidation of schema-conformant items, suggest a possible modification of the standard model to take into account how well new memories fit with existing schemata, with tightly linked memories following a more rapid consolidation path.

Van Kesteren et al (van Kesteren, Fernández, et al., 2010) manipulated the presence of a story schema by scrambling the order of the first part of a movie such that one group activated a schema for the movie plot, while the other group did not. Both subsequently encoded the final part of the movie in its original order. It was found that coupling between the hippocampus and medial prefrontal cortex (mPFC) was greater in those that did not have an active schema, reflecting the greater difficulty in integrating the final part of the movie for those participants. This greater coupling persisted after a 15-minute rest period, suggesting a possible consolidation mechanism related to the mPFC, although consolidation was not manipulated as part of the study. Following on from this, van Kesteren and colleagues (van Kesteren, Rijpkema, et al., 2010) adopted a consistency paradigm in which arbitrary visual motifs were associated with couplings of on-screen objects and physical fabrics which were either congruent (such as leather and a jacket) or incongruent (such as lace and an umbrella). Congruent information was assumed to be more compatible with existing schemata, and hence the congruency manipulation was designed to test integration of memory for the objects with differing levels of schema-compatibility. Schema-related memory was tested by way of an associative memory test with the visual motifs cueing recognition of the objects. The authors found better memory for congruent than incongruent items, suggesting a schema benefit similar to our own findings in this study. Once again, they also observed an important role for the mPFC, in this case an enhanced coupling between mPFC and somatosensory cortex (implicated in memory for the fabric). The final study by van Kesteren et al (van Kesteren et al., 2013) used a similar but slightly simplified congruency paradigm, in this case directly looking at object-scene pairings which were congruent or not, with functional neuroimaging of retrieval. This study once again revealed an enhanced role for the mPFC for schema-dependent items, and also found a decreased role for the hippocampus for these items.

On the basis of these findings, van Kesteren and colleagues developed the SLIMM model (van Kesteren et al., 2012). This model suggests that neocortical memory representations which are congruent resonate, and this resonance creates activation in the mPFC, which consequently further

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strengthens the cortico-cortical synaptic connections. The model also suggests that under these circumstances, the mPFC inhibits the medial temporal lobe (MTL), which would otherwise play an active binding role for the neocortical representations as in the standard model of consolidation. In other words, SLIMM suggests that the standard model should be modified such that for items which fit well with an existing schema, the mPFC rather than the MTL, will play the binding role, and it may be reasonably assumed that this intra-cortical consolidation of resonant representations will happen more rapidly than standard MTL-driven consolidation (Frankland & Bontempi, 2006; Tse et al., 2007).

The van Kesteren studies do not include any measurement of sleep and hence the SLIMM model is also silent on the topic of sleep-dependent consolidation. The standard model of consolidation, however, proposes that MTL-based consolidation occurs during slow-wave sleep, with slow waves coordinating hippocampal sharp-waves associated with episodic replay (Bendor & Wilson, 2012; Louie & Wilson, 2001; Ramadan, Eschenko, & Sara, 2009), and spindles associated with cortical plasticity (Born et al., 2006; Diekelmann & Born, 2010). The association of REM sleep, rather than SWS, with rapidly-consolidated schema-conformant memories found in our data, suggests that the mPFC intracortical strengthening may occur during REM sleep rather than SWS. Support for this idea comes from research on immediate early genes in which the zif268 gene has been found to be associated with learning during and subsequent upregulation at night specifically during REM sleep, and outside of the MTL (Ribeiro, 1999; Ribeiro et al., 2002, 2007). In a follow-up to their original schema study, Tse et al (2011) found that zif268 was upregulated in the mPFC, and most strongly for rats which had learned new flavour-location pairs and integrated them rapidly into an existing schema. Rats which learned new pairs without a schema, and rats which simply used existing information, showed significantly less mPFC zif268 expression.

Although there is still only very limited data available from both rodents and humans, the converging evidence suggests a possible modification of the standard model of consolidation. We propose that when consolidating items which fit well with an existing schema, not only is there rapid systems-level consolidation driven by the mPFC, but that this may happen during REM sleep, and be associated specifically with an upregulation of the zif268 gene. This proposal awaits further investigation in humans. In practice, most memories which require consolidation fit to some extent with an existing schema, but rarely to the extent seen for a very strongly established schema such as tonality. We would therefore expect to see both REM and SWS, and the mPFC and the MTL, involved in declarative memory consolidation on many tasks. It may even be that SWS, which occurs earlier in the night, is involved in strengthening or even forming schemata, as suggested by the recent iOtA model (Lewis & Durrant, 2011), and REM sleep follows on the same night taking advantage of the new schema in a multi-step process as suggested by Stickgold and colleagues (Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000).

One important line of research which should be pursued in the future relates to the amount of time available for consolidation. Our study, in common with the many other studies on sleep-dependent consolidation, used a 24-hour period, which proved sufficient for consolidation of the schema-conformant tonal melodies. The atonal melodies, however, showed no sign of consolidation across this interval. One possible explanation for this is that there was not sufficient time for consolidation of these melodies, which do not fit easily into any schema a participant is likely to possess. An alternative explanation is that items which do not fit into any schema will require the formation of a

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new schema through repeated exposure and abstraction of common elements (Lewis & Durrant, 2011), and that without such a schema consolidation cannot take place at all. There was neither sufficient time nor exposure in this experiment for this type of schema formation to reasonably take place, and there is evidence that humans struggle to develop schemata for atonal music even with a large amount of exposure due to the stimulus structure and fundamental limitations of working memory capacity (Krumhansl, 1987). Further studies, ideally incorporating a substantially longer time period, are required to address this important question. It is also worth noting that the 24-hour period in our study was chosen in order to minimise circadian effects (all encoding and retrieval took place at the same time of day), and the role of sleep was elucidated through overnight polysomnography. However, such a design cannot allow a direct sleep-wake comparison, since any wake group would be severely sleep deprived. This means that although we believe the correlation between behaviour and both the amount of REM sleep obtained and frontal and central theta power during REM sleep suggest a specific role of sleep in consolidation, we cannot rule out the possibility that a wake group would show a similar improvement.

In addition to an extended timeline, our results suggest a number of areas for further investigation. Parametric control of the strength of the schema which is activated has the potential to yield strong evidence for or against the modified model of consolidation. We would predict that greater activation in mPFC, reduced activation in the MTL, and more rapid consolidation of schema-conformant items, would correspond with greater schema strength in a graded effect. Parametric control of the extent to which a stimulus fits an existing schema is another development which would help clarify the role of sleep; we would also expect increased REM involvement and decreased SWS involvement in consolidation as the stimulus fits better with an existing schema. Finally, the genetic basis for schema-dependent consolidation in humans should be investigated; it seems likely that such an investigation will have implications for the standard model of consolidation.

In summary, our study has shown that melodies which fit which with an existing schema are consolidated on the first night after encoding, and show a strong benefit for recognition memory the following day. By contrast, melodies which do not fit which an existing schema show no such benefit. Consolidation appears to be related to REM sleep, showing a relationship with both the amount of REM sleep obtained and frontal and central EEG theta power during REM sleep. These results offer support to the SLIMM modification of the standard model of consolidation, and suggest a further modification in which consolidation of schema-conformant items happens during REM sleep, perhaps as a result of enhanced expression of the zif268 gene. Overall, our findings suggest a clear pattern of results in which consolidation and schemata are inextricably linked.

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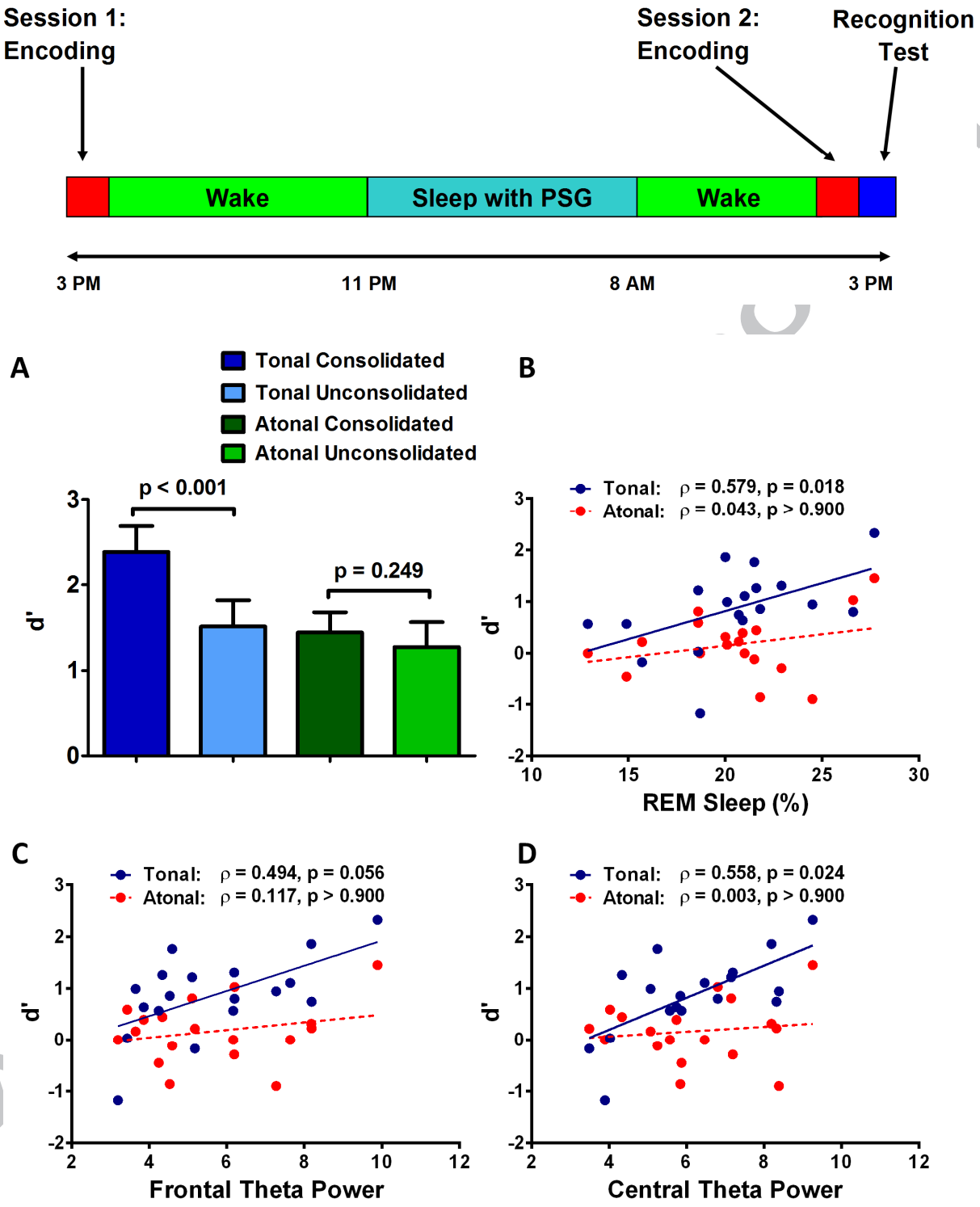

Schema-Conformant Memories are Preferentially Consolidated During REM Sleep

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Highlights

- Schema-conformant memory consolidates rapidly over 24hrs.
- Non-schema-conformant memory does not consolidate over 24hrs.
- Schematic memory consolidation is predicted by the amount of REM sleep obtained.
- Schematic memory consolidation is predicted by frontal and central REM theta power.

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