Schema-dependent hippocampo-prefrontal connectivity during memory encoding and early consolidation in humans

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Abstract

The ability to remember our past and to integrate the present and future with these past experiences is crucial for dealing with the complex world around us. Integrating novel information into established cortical memory networks (also known as systems consolidation) has been found to be faster and more efficient when the new information better fits the present cortical memory network (the schema). Slow wave sleep is generally acknowledged to support declarative memory consolidation, making neocortical representations hippocampally independent by replaying memory-related spiking activities. However, several studies have suggested that this hippocampo-cortical replay is already present during post-learning resting periods, and the (ventro)medial prefrontal cortex (vmPFC) has been demonstrated to be involved in this process. To explore the role of hippocampal-vmPFC connectivity on human declarative memory encoding and early consolidation in post-learning rest, we presented the last part of a movie to two groups of participants having either a clear or an unclear schema about the storyline of this movie in the MRI scanner. Subsequently, participants performed memory tests interleaved by a resting period. This paradigm allowed us to investigate the role of functional brain connectivity during natural viewing of the movie (encoding) and the subsequent rest period (early consolidation). Behavioral results showed successful selective schema manipulation, but no differences in memory performance after viewing the second part of the movie. Imaging results revealed group differences in hippocampal connectivity to the vmPFC, with the non-schema group demonstrating higher connectivity. Furthermore, better schema comprehension resulted in higher intersubject synchronization in hippocampus and vmPFC during movie viewing. These results reveal that neural encoding and systems consolidation mechanisms (dependent on existing schemata incorporated in neocortical memory networks) are reflected by hippocampal-vmPFC connectivity. This study is the first to examine early human online and offline mnemonic processes using schema manipulation and functional connectivity measurements.

Keywords: systems consolidation, replay, schemata, natural viewing, resting-state, functional connectivity, hippocampus, ventromedial prefrontal cortex

Introduction

Understanding the consolidation of memories from initially unstable and vulnerable traces in the hippocampus into a robust, secured framework situated in the neocortex is a key challenge for the cognitive neurosciences. It has long been thought that memory consolidation is a passive and long-lasting process, occurring mainly during sleep. Recent research however, has revealed that consolidation occurs earlier and faster (Axmacher, Haupt, Fernandez, Elger, & Fell, 2008; Takashima et al., 2006), is present beyond sleep states (Foster & Wilson, 2006; Peigneux et al., 2006), and is influenced by context and pre-existing knowledge (Tse et al., 2007). It thus seems that the consolidation of memory traces is a more active, permanent, and intricate process than was assumed up to now. Online human hippocampal connectivity to the neocortex underlying the earliest stages of memory consolidation however remains largely unknown.

Memory consolidation is generally explained as the process by which recent memories are crystallized into long-term memory (McGaugh, 2000). Research into deficits in long-term memory formation such as retrograde and anterograde amnesia following damage to the medial temporal lobe (particularly the hippocampus) have led researchers to reveal bits and pieces about the underlying mechanisms of memory consolidation. In particular, retrograde amnesia is found to degrade temporally, implying that more distant (or better consolidated) memories are less vulnerable to forgetting (Squire & Alvarez, 1995). Based on these findings, it has been hypothesized that the hippocampus acts as a modulator in reorganizing and transferring incoming information into neocortical long-term memory networks by strengthening hippocampo-cortical and cortico-cortical connection. Once fully incorporated, memory traces become stable and are more resistant to extinction than memories that are more hippocampal-based (Marr, 1970; Squire & Bayley, 2007). This process is generally referred to as *systems* or *network* consolidation (Frankland & Bontempi, 2005; Qin, McNaughton, Skaggs, & Barnes, 1997; Takashima et al., 2006). Systems consolidation and subsequent retrieval involves hippocampal and prefrontal brain functioning, in particular in the (ventro)medial prefrontal (Euston, Tatsuno, & McNaughton, 2007; Gais et al., 2007; Sterpenich et al., 2007; Takashima et al., 2006) or orbitofrontal cortex (Ross & Eichenbaum, 2006), which is additionally thought to be involved in a variety of higher-order top-down functions, for example novelty detection, deviation from expectation (Petrides, 2007), and comprehension (Maguire, Frith, &

Morris, 1999). Additionally, it has been argued that the vmPFC is taking over the integrative function of the hippocampus in time (Frankland & Bontempi, 2006).

Systems consolidation has been reported to mainly occur during offline periods such as sleep, in particular slow wave sleep (SWS) (Maquet, 2001; Peigneux et al., 2004; Stickgold, 2005), since the amount of obtained SWS is shown to correlate with subsequent (declarative) memory performance. The strengthening and reactivation of memory traces (Rasch & Born, 2007; Rasch, Buchel, Gais, & Born, 2007) is believed to be generated by replay: a lower-level cellular process underlying systems consolidation. Animal research has shown that pyramidal neurons in the hippocampal complex show a replay of the same spiking patterns of activity that were observed during the performance of a certain task (Pavlides & Winson, 1989; Skaggs & McNaughton, 1996; M. A. Wilson & McNaughton, 1994). During sleep this process is shown to exist in a fast-forward manner (Euston et al., 2007) while during awake resting, sequential reversed replay already occurs immediately after encoding (Foster & Wilson, 2006; Kudrimoti, Barnes, & McNaughton, 1999). Additionally, these offline replay patterns have been found to be present both in hippocampal-cortical and cortico-cortical networks (Ji & Wilson, 2007; Qin et al., 1997), including the medial prefrontal cortex (mPFC) (Euston et al., 2007; Siapas & Wilson, 1998). Also in humans, effects of prior state on subsequent consolidation mechanisms are observed during offline resting periods (Peigneux et al., 2006; Waites, Stanislavsky, Abbott, & Jackson, 2005), and patterns observed during sleep are shown to be related to rest patterns (Horovitz et al., 2007). These studies imply that systems consolidation is not only a process occurring during sleep, but that it is possibly conjoined with ongoing brain activity throughout the day, particularly during offline resting periods.

Evidence for a functional relation of these replay processes to subsequent memory performance is emerging. An association between weak replay and lower behavioral performance has been found in aging rats (Gerrard, Burke, McNaughton, & Barnes, 2008), and in humans replay activity and its relevance to memory consolidation and subsequent improved memory performance has been indirectly demonstrated by the discovery of ripples (high-frequency oscillations that have been linked to replay) in the human hippocampus using iEEG recordings (Axmacher, Elger, & Fell, 2008; Axmacher, Haupt et al., 2008). These findings support the notion that also in humans memory performance is enhanced when the hippocampus replays activity patterns similar to those observed during the actual experience, both during sleep and offline resting throughout the day. Based on these data, we can thus suggest a relation between replay, early consolidation, and subsequent memory improvement and link these processes to connectivity between the hippocampus and the vmPFC.

Besides a more active and permanent nature of systems consolidation mechanisms, it has also recently been shown to be dependent on pre-existing knowledge. Particularly, the process is demonstrated to be accelerated when incoming information can more easily be incorporated into the memory framework existing in the neocortex (Tse et al., 2007). This suggests that when novel information better fits existing memory traces in the brain, the hippocampo-cortical connections need less strengthening than when this information does not fit. In psychology the presence of pre-existing knowledge has been shown to improve subsequent memory, and is mainly known as schema theory (McVee, Dunsmore, & Gavelek, 2005), mental models (Johnson-Laird, 1983) or situation models (Zwaan & Radvansky, 1998). Also in psycholinguistics an analogous process is described as narrative comprehension or discourse (Mar, 2004). Hereafter, the concept of this network of established memory traces will be referred to as the *schema.* Once more, vmPFC activity has been indicated to be involved in processing schema-related information (Maguire et al., 1999; Mar, 2004). However, in the cognitive neurosciences, a clear relation between schemata, systems consolidation mechanisms and hippocampo-vmPFC connectivity is currently absent (Morris, 2006). In this study, we therefore applied manipulation of prior schema to investigate in-vivo online encoding during natural viewing and subsequent early consolidation during rest. We examined this by using functional Magnetic Resonance Imaging (fMRI) and combining the use of model-free functional connectivity analysis methods with (neuro)psychological theories regarding systems consolidation and schemata.

Using a between-subjects design in which one group was exposed to the first part of a movie in normal order (schema) while the second group viewed the same movie in a temporally scrambled order (non-schema), we provided participants with either a clear or a confused idea about the storyline of this movie. After a night of sleep we used fMRI to measure brain connectivity patterns during natural viewing of the second part of the movie (encoding) and a subsequent resting period (early consolidation). The use of these model-free paradigms offer an ecologically valid measurement of spontaneous brain activity (Fox & Raichle, 2007), and the additional opportunity to look at connectivity patterns underlying online encoding and early consolidation processes. Additionally, we

tested memory performance to both quantify successful selective schema manipulation and to be able to correlate brain activity during both conditions to external measures.

First, we predicted to find equal memory performance on item recognition tests and between-group differences in schema knowledge and behavioral performance after viewing the second part of the movie. Second, we predicted between-group differences in neural mechanisms underlying memory encoding and early consolidation, particularly in hippocampal connections to the vmPFC (shown to be involved in schema comprehension, replay, consolidation, and retrieval of long-term memory). We furthermore expected the schema group to be able to incorporate novel information faster and more efficiently into their existing schemata than the non-schema group, reflected by less hippocampo-vmPFC connectivity during natural viewing. Moreover, we expected to find equivalent, persistent connectivity patterns during the subsequent resting period, indicating that during offline rest the brain is still integrating recently encountered memories into the schema. Finally, we predicted to find a relation between these connectivity measures and external behavioral measures of memory performance. To control for global connectivity enhancement, hippocampal connectivity to the ventral-visual stream (which provides the hippocampus with bottom-up visual information: Ungerleider & Haxby, 1994) was also considered.

Methods

Participants

We obtained informed consent from 31 native Dutch right-handed healthy participants (12 men) without self-reported hearing, visual, or neurological problems or diseases. Further inclusion was determined by a Beck Depression Inventory (BDI: Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) score below 11. All participants were students in the age range of 18-31 with a mean age of 22.17 who stated they did not see the movie before. They were paid for participation and were notified that they could earn extra money for better performance. Ethical approval was obtained from the institutional review board (CMO Region Arnhem-Nijmegen, The Netherlands). One participant had to be excluded for not being able to adequately perceive the movie and falling asleep during the rest period, so in total we acquired data of 15 participants per group. Possible confounding factors (age, gender, hours of sleep, time of day, and English language skills (tested by means of the Oxford placement test: Allan, 1992) were equal over groups.

Design and general procedure

We employed a mixed factorial design with SCHEMA as between-subject factor and CONDITION (movie and rest) as within-subject factor (see figure 1). The first day participants watched the first part of the movie (1 hour and 20 minutes) either in normal (schema) or temporally scrambled (non-schema) order, and were instructed to pay attention because they would get detailed questions about the movie on the next day. On the second day, they were first tested on their memory for the movie by means of an item recognition test (test 1a) and a test with open questions about the schematic content of the movie (test 1b). They were then placed in the MRI-scanner and were instructed to watch the second part of the movie (15 minutes and 34 seconds, in normal order) and again pay attention because they would get questions about this part as well. Subsequently, they were asked to complete two sets of item recognition (tests 2a and 3a) and multiple choice tests (tests 2b and 3b) about this second part of the movie, interleaved by a rest period of the same length as the movie. During this rest period participants were instructed to lie still, close their eyes, think of nothing in particular and try not to fall asleep. In total, this session lasted around 1.5 hours. Functional scans were obtained only during watching of the movie and the rest period.

We controlled for two additional confounds that could possibly influence performance. First, to control for consolidation time, participants were always tested 20 to 25 hours (average 23.4 hours) after viewing the movie, counterbalanced over groups. Second, to verify that participants could optimally perceive the sound of the movie in contrast to the scanner noise, we employed a more silent EPI sequence (for details see fMRI scanning parameters section), earplugs, and headphones (Commander XG, Magnetic Resonance Technology, Northridge, CA, USA). Before starting the movie, we performed a sound test to verify whether participants could easily discriminate movie-related sounds from the scanner noise. After the experiment, participants were once more asked whether they had trouble hearing the movie (on a scale from 1 to 5). Overall, participants reported that they had little trouble perceiving the sound of the movie (average: 1.9) and subsequent memory performance was not significantly related to ratings.

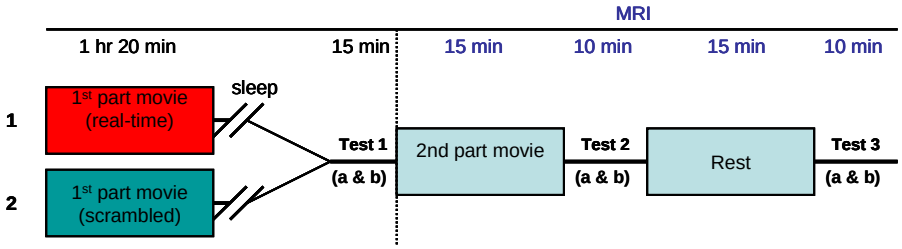

Figure 1. Experimental design: group 1 (schema) viewed the movie in real-time while the schema for group 2 (non-schema) was manipulated by temporal scrambling of the movie. The next day, both groups performed memory tests, viewed the second part of the movie inside the MRI scanner and subsequently performed two extra memory tests interleaved by a rest period.

Materials and apparatus

Movie

To manipulate schema knowledge while not altering input, we manipulated the first part of a movie using Windows Movie Maker version 5.1 (Microsoft Corporation, Redmont, WA, USA), by temporally scrambling scenes of minimally 20 seconds and maximally 2:24 minutes of length. The movie we used was named *Go* (Banner Entertainment, Columbia Pictures, and Saratoga Entertainment, 1999), and was chosen based on an important constraint: the movie contains three complex storylines that merge together at the end of the movie, making it possible to separate it into two parts. The first part (1 hour and 20 minutes) makes up a schema with which the second part (15:34 minutes) can subsequently be integrated, depending on initial schema comprehension. Without a clear schema, it is hard to understand the second part of the movie, since it consists of an integration of events that occurred in the first part of the movie.

Memory tests

Memory regarding the movie was tested using different memory tests: item recognition tests (to verify that both groups received and processed the input), open questions (to test schematic knowledge about the movie and confirm that schema manipulation was successful) and multiple choice questions (reflecting either a schematic or non-schematic background). We conducted a preceding pilot using the same setup (see figure 1) to test and subsequently adjust all questions.

The first item recognition test (test 1a) consisted of 60 still frames, 30 extracted from the movie and 30 lures from other movies that were selected according to their similarity in setting, actors or type of scenery. The stimuli were all equal in size and luminance, and contrast settings were equalized using Adobe Photoshop 7.0 (Adobe, San Jose, CA, USA) to control for recognition through these features. They were presented for 500 ms using Presentation 10.2 (Neurobehavioral systems, Albany, CA, USA). Participants were instructed to indicate whether the still frame was taken from the movie they saw the day before (yes or no). The item recognition tests (tests 2a and 3a) for the second part of the movie had the same setup, but contained only 40 still frames (20 movie frames and 20 lures) extracted from the second part of the movie. The 20 open questions (test 1b) were constructed to reflect comprehension of the storyline of the movie. Names of characters and objects were explicitly named and not explained. Furthermore, the questions did not contain any clues related to events in the second part of the movie. Participants were instructed to write the answers to the questions on a paper answer sheet and to recall as much as they could remember concerning the question.

Since the questions about the second part of the movie were to be answered inside the MRI scanner, we constructed 70 multiple choice questions (test 2b and 3b) for this part of the study. The questions were mainly created using the constraints described in a previous study reflecting memory for movies (Furman, Dorfman, Hasson, Davachi, & Dudai, 2007): the questions targeted distinct events and all questions together covered the whole content of the second part of the movie. Using 70 questions in total this means that approximately every 13 seconds of the movie was covered by a question. Additionally, we applied constraints particularly related to this study: questions could not be answered based only on the first part of the movie but could be answered based only on the second part of the movie. Furthermore, questions were divided into two distinct categories (containing 34 and 36 questions each) reflecting either detailed (non-schema) or schema-related (schema) questions. Each multiple choice question was displayed together with a still frame of the movie and three answer options, again using Presentation 10.2. Participants were instructed to indicate the answer (a, b, or c) and subsequently their confidence level (not sure, fairly sure, or very sure). The two question sessions

were divided so they both contained equal amounts of non-schema (17) and schema questions (18) and reflected the entire time period of the second part of the movie.

Statistical analyses

We analyzed behavioral data using SPSS 15.0. Item recognition scores (test 1a, 2a, and 3a) were reflected by hit minus false alarms (hit/old – false alarms/new) calculations. Performance on open questions (test 1b) was calculated using the percentage of correct answers provided. Group data for these tests were compared using independent samples t-tests. For multiple choice questions (test 2b and 3b), performance was again calculated using the percentage of correct answers, both overall and separately for both types of questions (schema or non-schema). Statistical analyses on these tests were carried out using a 2 X 2 repeated-measures ANOVA with SCHEMA as a between-group factor and CONDITION (movie versus rest) and TYPE (schema versus non-schema) as within-group factors. Alpha levels were always set at .05.

fMRI scanning parameters

Participants were scanned using a 1.5 Tesla Siemens Magnetom Avanto system, an 8 channel phased array head coil (MR Devices), and a T2* weighted gradient echo EPI sequence (ascending slice order). For each volume, 34 slices of 3.5 mm each were acquired at resolution 3.3x3.3x3.85 mm, matrix size 64*64, flip angle of 90°, TR of 2.31 s and TE of 35 ms. Slices (FoV = 212 mm) were angulated individually in an oblique axial manner to be able to reach whole brain coverage for each participant. To reduce the gradient acoustic noise, we used a relatively low readout bandwidth of 1396 Hz/pixel which is able to halve the amplitude of the readout gradient (de Zwart, van Gelderen, Golay, Ikonomidou, & Duyn, 2006) together with a GRAPPA parallel acceleration factor of 2 (Griswold et al., 2002). To ensure reaching a steady state condition and to let participants become accustomed to the scanner noise, the first 11 scans were discarded. Additionally, T1 weighted anatomical scans at 1 mm isotropic resolution were acquired using an MP-RAGE sequence with TR of 2250 ms, TI of 850 ms, flip angle of 15º and FOV of 256 x 256 x 176 mm. Acquisition time was again reduced by using GRAPPA with acceleration factor 2 and 24 reference lines.

fMRI data analyses

Raw fMRI data were preprocessed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). First, motion correction was performed by using iterative rigid body realignment to minimize the residual sum of square between the first and all further functional scans, and subsequent rigid body co-registration to corresponding individual T1 images using mutual information optimization. Subsequently, data were spatially normalized into a common space, defined by the Montreal Neurological Institute (MNI) 152 T1 image (voxel size = 2x2x2) and smoothed by convolving the data with an 8 mm FWHM 3D kernel (only for the cross-correlation analysis). The first 11 scans were excluded, which left 409 scans per condition (movie and rest) for analysis.

Partial correlations analysis using the normalized data was performed using in-house software written in Matlab (The Mathworks, Inc., Natick, MA, USA). This analysis was carried out using partitioning of the scans into the AAL (Automatic Anatomical Labeling) template (Tzourio-Mazoyer et al., 2002) and the approach proposed by Salvador (Salvador et al., 2005). Partial correlations for fMRI data were obtained by calculating the unique variance between the BOLD time series of two brain areas, while controlling for the effect that the BOLD times series of all other areas introduce to this time series. Specifically, after calculating the average time series for all AAL areas for each subject, individual covariance matrices were constructed, containing covariance measures between average time series of all AAL areas and all other AAL areas. Subsequently, these covariance matrices were used to calculate partial correlation matrices with the same arrangement as the covariance matrices.

We merged right and left hippocampi (defined by the AAL-template) into one area, reflecting bilateral hippocampus, to prevent the high partial correlations between both hippocampi from reducing the unique variance. After calculating partial correlation matrices, partial correlations were extracted from bilateral hippocampus to the vmPFC (comprised of bilateral AAL areas Frontal Superior Orbital, Frontal Mid Orbital, Frontal Medial Orbital and Rectus) and the ventral-visual stream (comprised of bilateral AAL areas Lingual Gyrus, Inferior Temporal Gyrus, Fusiform Gyrus, and Parahippocampus) during both conditions for each subject. These values were then further analyzed using SPSS 15.0 by applying a 2x8 repeated-measures ANOVA with SCHEMA as a between-group factor and CONDITION (movie and rest) and AREA as within-group factors. Furthermore, to look at interactions between vmPFC and ventral-visual regions, a 2x2 repeated measures ANOVA with SCHEMA as between-group factor and CONDITION and PATHWAY (vmPFC and ventral-visual) as within-group factors was used.

Finally, to link behavioral measures to the brain data, bivariate Pearsons correlations were calculated. Alpha levels were always set at .05.

A second data analysis method we used was based on a voxelwise intersubject cross-correlation analysis method (Hasson, Nir, Levy, Fuhrmann, & Malach, 2004). This method uses cross-correlation of the time series per voxel across participants to estimate synchronous activity present in all participants. Instead of using one brain as a model for activity patterns in another brain (see Hasson et al., 2004), the BOLD time-course of a certain voxel with the average of the BOLD time-course of the same voxel of all other participants in the group was calculated, which made it possible to perform between-group analyses on data obtained during viewing of the movie. Software necessary to perform these analyses was once more written in Matlab. In particular, preprocessed data (normalized and smoothed) were high-pass filtered (cut-off frequency = .01 Hz) and individual realignment parameters were used to correct for motion. Second, the non-selective component (the average time series of the whole brain, reflecting global brain activity) of all gray-matter voxels (abstracted by using a gray-matter mask based on the tissue probability map of the International Consortium for Brain Mapping (ICBM), which is included in SPM5 ($p > .45$)) for each participant was calculated. This non-selective component was then temporally smoothed (by taking the average of each time point with the preceding and subsequent time points), normalized, and regressed out of each voxels time series to control for the influence of global activity on more regionally distinct components. Third, the correlation coefficient of the time series for each participant for every voxel to the same voxel in all the other participants in the group was calculated and stored in a cross-correlation map.

Finally, we used these cross-correlation maps to perform group analyses in SPM5. Independent two-sample t-tests were conducted using cluster-level statistics with an initial threshold of $p < .001$, uncorrected (based on Gaussian random field theory). Small volume corrections (SVCs) were performed on regions of interests (ROIs) using predetermined masks of the vmPFC based on the same AAL regions as used for the partial correlations analysis. Additionally, SVCs constructed by using spherical regions of interest (radius = 10 mm) centered on voxels described in corresponding literature concerning retrieval mechanisms (Takashima et al., 2006) were carried out. For all SVCs, only clusters at $p < .05$ (corrected for multiple comparisons) were considered significant and local maxima were reported as MNI coordinates.

Results

Memory performance

Item recognition scores (tests 1a, 2a and 3a) did not show any significant group differences, indicating equal input processing for both groups during both parts of the movie. On the contrary, open questions (test 1b) about the first part of the movie did reveal a significant group difference ($t(2,28) = 3.383$; $p < .01$, higher for schema), demonstrating successful schema manipulation (figure 2). After watching the second part of the movie however, performance on the multiple choice questions (test 2b and 3b) did not yield any significant main effects or interactions.

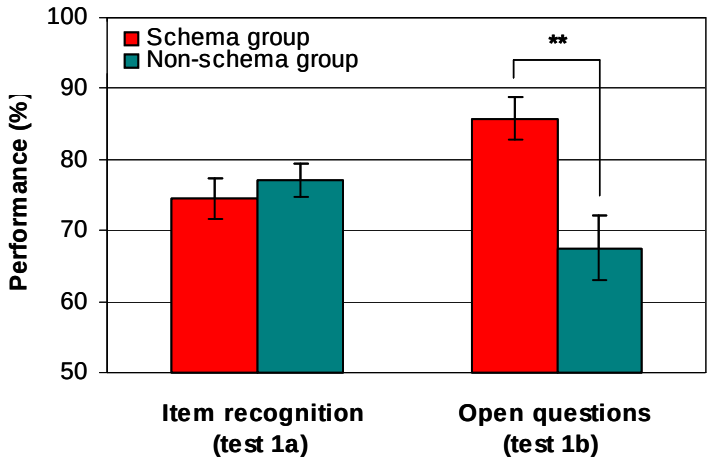

Figure 2. Memory performance on tests about the first part of the movie. Test 1a (item recognition) did not show a significant group difference, while test 1b (open schema questions) did, indicating equal processing of the movie and successful schema manipulation (** = $p < .01$).

Neuroimaging results

Partial correlations

At first, repeated measures ANOVA analyses comparing hippocampal partial connectivity to both the vmPFC and the ventral-visual stream show a significant main effect of PATHWAY ($F(1,28) = 123.312$, $p < .001$, higher for to the ventral-visual stream), and a PATHWAY * GROUP ($F(1,28) = 6.28$, $p < .05$) interaction. Further repeated measures ANOVA analyses on partial connectivity from hippocampus to the vmPFC exposed a main effect of SCHEMA ($F(1,28) = 13.919$, $p = .001$, higher for the non-schema group). Moreover, a main effect of CONDITION ($F(1,28) = 6,754$, $p < .05$) and AREA ($F(1,28) = 3.308$, $p < .01$) was found, but no significant interaction effects were apparent, showing no evidence for significant effects between underlying areas. The main SCHEMA effect was furthermore significant for both the movie condition ($F(1,28) = 5.458$, $p < .05$) and the rest condition ($F(1,28) = 7.218$, $p < .05$) (figure 3a). The non-schema group thus showed higher connectivity between hippocampus and vmPFC during both conditions. In addition, performance on open questions (test 1b) for the non-schema group showed a significant negative correlation with hippocampal partial connectivity to the vmPFC during the movie condition ($r = -.607$, $p < .05$), while this effect was not evident for the schema group ($r = .234$, $p > .05$) (figure 4). These results imply a relation between schema comprehension and subsequent connectivity measures: more comprehension resulted in lower hippocampo-vmPFC connectivity.

Repeated measures ANOVA analyses on hippocampal connectivity to the ventral-visual stream (figure 3b) showed a main effect of AREA ($F(1,28) = 48.004$, $p < .001$) and an AREA * GROUP interaction ($F(1,28) = 2.584$, $p < .05$), justifying further testing per area. This revealed significant effects both in the left fusiform ($F(1,28) = 6.333$, $p < .05$) and the right inferior temporal gyrus ($F(1,28) = 9.813$, $p < .01$), higher for the schema group. Hippocampal connectivity to parts of the ventral-visual stream thus demonstrated opposite group effects to those of connectivity to the vmPFC (figure 3b).

Cross-correlations

Cluster-level statistics on cross-correlation measures during watching of the movie in the vmPFC showed four significant clusters for the schema versus non-schema contrast, centered at peak voxels [-4,24,-24] ($p(SVC) < .001$, $k = 114$), [-4,40,-22] ($p(SVC) < .05$, $k = 34$), [-18,60-16] ($p(SVC) < .05$, $k = 33$), and [-46,56,-6] ($p(SVC) < .05$, $k = 31$) (figure 3c). Furthermore, ROIs centered on coordinates extracted from existing literature (Takashima et al., 2006) revealed a trend at a vmPFC cluster centered at [-10,36,-12] ($p = .052$, $k = 5$) and a significant hippocampal cluster centered at [36,-6,-26] ($p < .01$, $k = 29$). All these clusters were not identified for the opposite contrast (non-schema versus schema), indicating more synchronization in memory-related brain areas for the schema group.

Discussion

Using a between-subjects fMRI design consisting of two conditions (movie and rest) we investigated brain connectivity patterns underlying encoding and early memory consolidation through manipulation of prior schema knowledge. Results revealed that connectivity from the hippocampus to the vmPFC is dependent on prior schema. Less initial schema resulted in higher connectivity measures, indicating that connectivity between these brain areas is possibly related to more effort necessary to comprehend novel incoming information. Furthermore, better schema was associated with higher synchronization over participants, indicating more coherent processing of newly encountered information when prior schema is more consistent. We can thus associate connectivity between and synchronization in hippocampus and vmPFC with systems consolidation mechanisms

As expected, behavioral data showed successful selective schema manipulation and equivalent processing of input for both groups. Furthermore, partial correlations analyses on fMRI data showed a significant main effect of schema in hippocampal connectivity to the vmPFC, higher for the non-schema group. This effect illustrates that stronger connectivity is necessary during encoding to integrate novel incoming information that does not fit the current schema, and that this larger connectivity pattern persists during early consolidation mechanisms in post-learning rest. Moreover, performance on schema-related questions about the first part of the movie correlated negatively with this connectivity during the movie condition, once more showing a relation between schema comprehension and hippocampo-prefrontal connectivity. Intersubject cross-correlation analyses revealed larger synchronization over participants in hippocampus and vmPFC for the schema group,

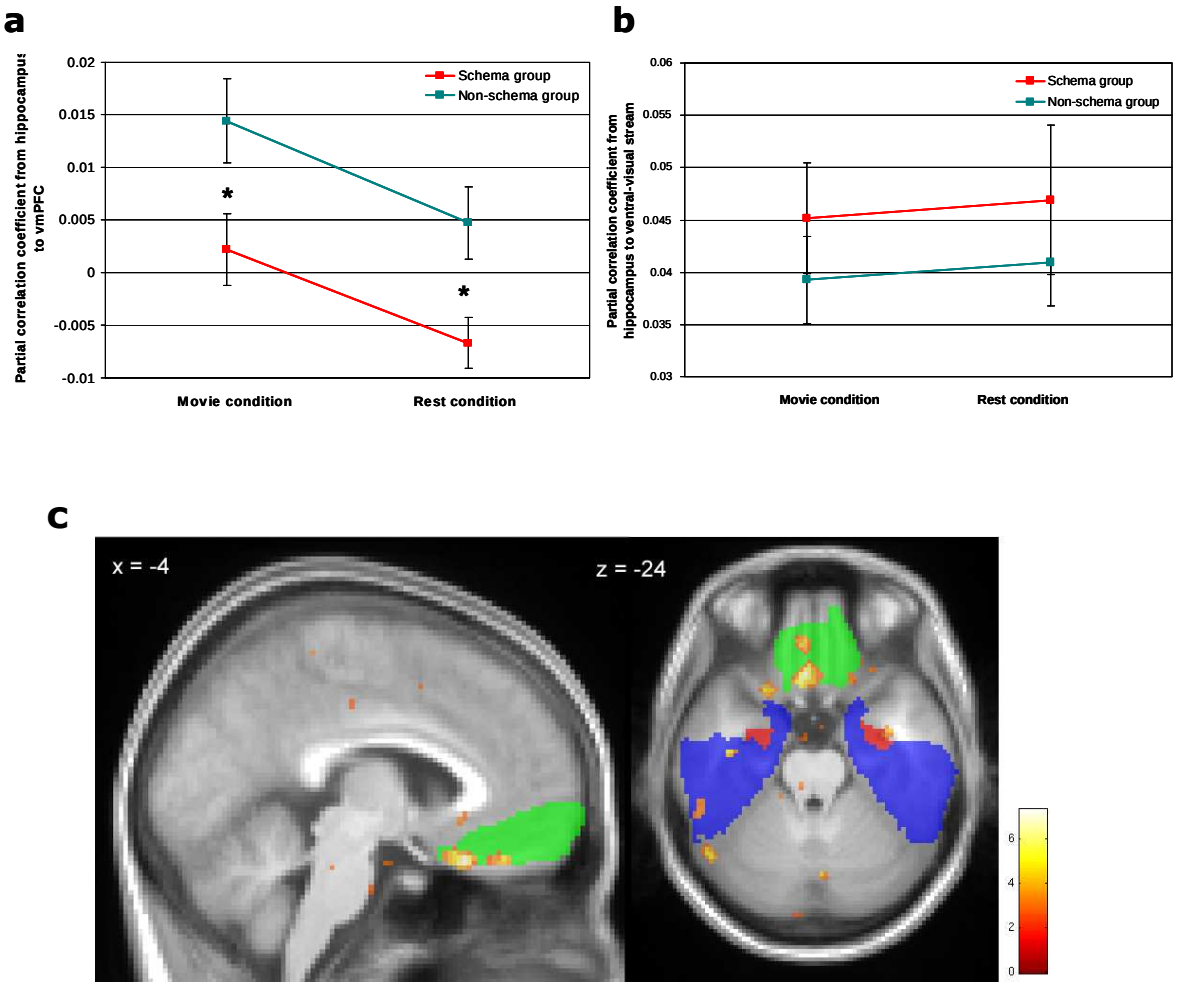

Figure 3. fMRI data showed higher connectivity from the hippocampus (red) to the vmPFC (green) for the non-schema group during both conditions (a, c). On the contrary, this effect was not present in hippocampal connectivity to the ventral-visual stream (blue) (b, c). Finally, higher synchronous activity in the schema group is present in the hippocampus and the vmPFC (c) (* = $p < .05$)

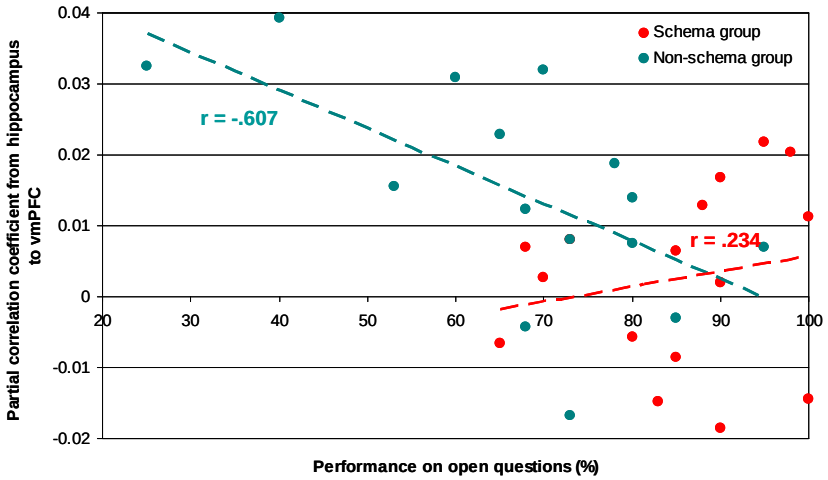

Figure 4: Performance on open questions for the non-schema group showed significant negative correlation to partial connectivity from the hippocampus to the vmPFC for the movie condition (r = -.607), indicating a relation between schema comprehension and subsequent connectivity measures. This relation is not present for the schema group (r = .234).

reflecting that in this group brain activity across participants is more consistent than in the non-schema group. Greater resemblance in understanding of the storyline of the movie in the schema group could possibly have resulted in more consistent neural processes underlying the integration of novel information into the existing schema. Since coordinates of significant clusters are adjacent to coordinates that have been related to comprehension, consolidation, and retrieval, higher synchronization is presumably related to these cognitive mechanisms.

Although one cannot discover direct replay mechanisms using indirect fMRI measurements, differences in connectivity observed in this study closely agree with current literature and hypotheses about replay patterns observed in hippocampal and neocortical structures. Differences in hippocampal connectivity to the vmPFC possibly are indirectly related to underlying replay of patterns present during encoding. Our partial correlation data then contribute to direct recordings of ripples, shown to be indirectly related to replay patterns in the medial temporal lobe, that predicted subsequent memory performance in humans (Axmacher, Elger et al., 2008). However, the noninvasive and indirect nature of human neuroscientific research obstructs direct replay recordings. To be able to examine human replay patterns in the future, we will thus have to either improve noninvasive neuroimaging methods or interpret indirect recordings and cautiously assume a link between particular observed patterns and underlying replay mechanisms.

The hippocampo-vmPFC connectivity differences observed in this study contribute to the systems consolidation theory and add support to the view that the vmPFC takes over the integrative function of the hippocampus in time (Frankland & Bontempi, 2006). According to this view, schema-related information would require less hippocampal interference since it is consolidated faster and more efficiently, resulting in less connectivity to the vmPFC. Our data and the possibility to use manipulation of schema and subsequent functional connectivity analyses in memory research open exciting new possibilities for further research into systems consolidation mechanisms.

Schemata and their influence on memory performance and brain mechanisms

Early research concerning schema-related understanding and subsequent memory discovered that once prior schemata are present, subsequent memory performance related to the schema improves (Bower & Morrow, 1990; Bransford & Johnson, 1972; Johnson-Laird, 1983). Although criticized (Alba & Hasher, 1983), schema theory is acknowledged to adequately explain comprehension, learning and memory mechanisms and it importantly influences educational sciences (McVee et al., 2005). Neuroscientific research regarding schema theory has mainly flourished in psycholinguistics, where it is referred to as discourse or comprehension (for review see: Ferstl, Neumann, Bogler, & von Cramon, 2008; Mar, 2004). In general, these studies revealed a schema-related brain network comprised of medial and lateral prefrontal, temporoparietal, anterior temporal and posterior cingulate areas to be generally active while comprehending text and narratives. Particularly, dorsomedial PFC (dmPFC) is uncovered to be involved in comprehension of narratives (Hasson, Nusbaum, & Small, 2007; Sieborger, Ferstl, & von Cramon, 2007; Xu, Kemeny, Park, Frattali, & Braun, 2005; Yarkoni, Speer, & Zacks, 2008), and is believed to reflect an endogenous, top-down process that integrates information (Ferstl, Rinck, & von Cramon, 2005; Hasson et al., 2007), rather than a process driven by exogenous stimuli. This idea generally complies with our data, but rather reflects online comprehension related to more dorsally oriented ROIs, while the vmPFC we found appears to be more related to influences of prior encountered schemata, already (partly) consolidated into the neocortex.

Apart from one rodent study linking schemata to faster consolidation of memory traces (Tse et al., 2007), no relation between schemata and consolidation mechanisms has been established in humans. The only study that, to our knowledge, investigated prior schema influence in humans (Maguire et al., 1999), indicated increased medial orbitofrontal cortex (analogous to vmPFC) activation to be related to increased comprehension. Coordinates of this activity greatly resemble the locations of high synchronization discovered for the schema group in this study. Although synchronization, connectivity and activity are hard to compare in this respect, it does seem apparent that the vmPFC is involved in comprehension of schema-dependent novel information. Our data suggest the interesting possibility that existing schemata exert influence on encoding and early consolidation mechanisms of incoming information. Future research will need to address the discrepancy between dorsomedial (involved in online comprehending) and ventromedial (dependent on prior schemata) activity to reach a clear understanding about brain structures underlying comprehension and consolidation of schema-related information and their interconnectivities.

Model-free methodology in fMRI

Applying a model-free natural viewing fMRI paradigm (for review see: Spiers & Maguire, 2007a) and subsequent functional connectivity analyses (for review see: Rogers, Morgan, Newton, & Gore, 2007) offers interesting possibilities. At first, natural viewing is more ecologically valid than event-related designs. Second, it makes it possible to consider the time course of the BOLD response (relevant for consolidation mechanisms) instead of activation profiles limited to a certain time point. Finally and most importantly, next to brain mechanisms driven by external stimuli, also intrinsically driven processes (such as top-down linking of schema-related knowledge to novel information) can be captured using this approach. Examples of natural viewing paradigms are freely viewing movies (Bartels & Zeki, 2004a, 2004b, 2005; Hasson et al., 2004; Malinen, Hlushchuk, & Hari, 2007), navigating through a virtual city (Spiers & Maguire, 2006, 2007b) or playing video games (Mathiak & Weber, 2006). The cross-correlation analysis applied in this study is able to analyze consistent intersubject brain activity while perceiving real-world settings and is shown to be able to extend traditional networks related to several cognitive processes (Hasson, Furman, Clark, Dudai, & Davachi, 2008; Hasson et al., 2007; Hejnar, Kiehl, & Calhoun, 2007; S. M. Wilson, Molnar-Szakacs, & Iacoboni, 2008). In combination with the partial correlation results, we can thus suggest that natural viewing paradigms are a promising novel application in fMRI research.

We furthermore adopted a resting-state paradigm. When resting, the brain reverts to networks, mostly reflected by low-frequency spontaneous fluctuations (Fox & Raichle, 2007), that are also apparent during sleep and are suppressed during cognitive functioning. One of the major networks consistently discovered during rest is known as the default mode network (DMN), comprised of vmPFC, dmPFC, posterior cingulate cortex (PCC), inferior parietal lobule (IPL), lateral temporal cortex (LTC) and hippocampus (for review see: Buckner, Andrews-Hanna, & Schacter, 2008). Opinions vary about the function of the DMN. For example, it has been attributed to self-projection (Buckner & Carroll, 2007), mind-wandering (Mason et al., 2007), autobiographical memory and theory of mind (Spreng, Mar, & Kim, 2008). Also areas discovered to make up the schema-related network however, largely overlap with this DMN. It has thus been suggested that the DMN is involved in memory encoding and can furthermore be modulated by the semantic properties of incoming information (Hasson et al., 2007; S. M. Wilson et al., 2008). Combined with rodent resting replay patterns in the mPFC and the connectivity differences observed in this study, it is plausible that rest in general and the DMN in particular is related to replay mechanisms and memory consolidation. However, further research will be necessary to unravel the exact function of the DMN and its possible contribution to mnemonic processes.

Computational modeling

To understand why cognitive processes are structured in a certain way, several attempts have been made to computationally model these processes, mainly using connectionist approaches that, in essence, are in accordance with the complex functioning of neurons and their interplay. Particularly the ideas of James McClelland (McClelland, McNaughton, & O'Reilly, 1995) have been of great influence in understanding how the memory consolidation process might be structured. Computational models, while a simplistic representation of the truth, are often helpful in bridging the gap between data and theory (for review see: Vogels, Rajan, & Abbott, 2005). Since memory consolidation appears to be highly dependent on the interplay between several neuronal groups and brain areas, computational models can aid when trying to fit novel data to current hypotheses (Hasselmo & McClelland, 1999). More explicitly, the model described by McClelland makes inferences about the interplay between the hippocampus (as a fast learner) and the neocortex (as a slow learner). It suggests that the hippocampus plays a modulatory role in adequately storing novel information among already present knowledge patterns in the neocortex.

This idea can be further illustrated by categorization and incorporation of novel information that does not fit existing categories. When only learning according to the fast hippocampal principle, incoming information that cannot be incorporated in present categories will lead to *catastrophic interference*, totally altering present categories. Information that does fit these categories however can be faster and more easily processed using this principle. The slow neocortical principle of *interleaved learning*, handles exceptions to the rule in a better way, preserving existing categories and better fitting new information. According to this model, the brain thus accomodates two different systems for learning: a hippocampal system that enables fast encoding of information that fits the prior categories and a neocortical system (connected to the hippocampal system) that needs to slowly incorporate interfering novel information. Through repeated reactivation and strengthening of

hippocampo-cortical and cortico-cortical connections, this system eventually aids the memory to become hippocampally independent (as also suggested by the systems consolidation theory).

This model can be easily linked to our data when assuming that hippocampal connections to the vmPFC constitute the pathway through which interleaved learning is managed. When incoming information does not fit the present schema, novel information can be less easily integrated, making it necessary to strengthen hippocampo-cortical connections. When a sufficient schema is present however, these connections need less strengthening, because interleaved learning is less necessary, resulting in faster and easier incorporation of novel information into the neocortex. Yet, further computational modeling is necessary to adequately test this hypothesis and to be able to apply the (adjusted) model to future data concerning systems consolidation mechanisms.

Shortcomings, implications, and directions for future research

Although expected, no significant between-group differences in memory performance were evident subsequent to viewing the second part of the movie. This suggests that the larger effort that the non-schema group made to integrate the novel information into their manipulated schema resulted in subsequent equal performance for both groups. Yet, no direct relation is detected between these memory performance measures and hippocampal connectivity to the vmPFC, possibly due to large intersubject variance. While it would be interesting to link brain connectivity measures to differential performance on the multiple choice questions and open questions about the first part of the movie, it is hard to interpret differences between these measures due to the different manner in which they were constructed. Differences in arousal are another explanation for the observed larger connectivity and subsequent equal performance. However, analyses regarding hippocampal connectivity to the ventral-visual stream revealed significantly higher connectivity for the schema group in two subregions (left fusiform and right inferior temporal gyrus). We thus do not have a definite reason to assume that the observed hippocampo-vmPFC connectivity was merely reflected by larger global brain activity caused by heightened arousal in the non-schema group. Therefore, we do not suppose that possible arousal differences affected subsequent memory performance, but assume that the extra effort displayed by the non-schema group (reflected by larger hippocampo-vmPFC connectivity) resulted in the observed equalization of performance after the integration of novel information. Future research using a more clear-cut design is needed to directly relate hippocampo-vmPFC connectivity to subsequent memory improvement.

These data interestingly contribute to existing knowledge regarding encoding and early consolidation of memory traces since they once more challenge the concept of memory consolidation as a passive, long-lasting process. Data show an interesting role for hippocampal connectivity to the vmPFC in encoding and early consolidation of novel information, depending on existing schemata captured in the neocortex. Furthermore, they suggest that consolidation mechanisms are presumably already present during resting periods, pointing to a faster, more active and permanent nature of these mechanisms, as was previously discovered in rodents. This insight can greatly contribute to adjusting present models or producing novel models concerning the role of vmPFC connectivity in consolidation and long-term memory, such as the systems consolidation model and computational models. Furthermore, it can aid to gain more insight into memory-related deficits such as amnesia and Alzheimer's disease. Moreover, since these data show an important influence of schemata on brain mechanisms underlying easier understanding of novel information, they can be utilized in constructing better educational strategies in order to more efficiently learn and incorporate study material. In sum, further research could compare and evaluate hippocampo-vmPFC connectivity, subsequent memory performance and educational strategies to further clarify neural mechanisms underlying the integration of novel information and to eventually verify the most efficient way to learn about the complex world around us.

Conclusions

In this study we manipulated prior schema knowledge to investigate the differences in underlying brain mechanisms during online encoding and early consolidation of novel information. Hippocampal connectivity to the vmPFC is shown to be enhanced when novel information does not fit the existing schema, indicating more effort necessary to incorporate this information. This effect persisted during a post-learning rest period, indirectly indicating early consolidation mechanisms. We furthermore found intersubject correlations to be larger in hippocampus and vmPFC when a consistent schema was present, indicating more consistent processing of novel information for this group. These results add support to the systems consolidation theory and to the view that the vmPFC takes over the integrative

function of the hippocampus in systems consolidation in time. These data moreover support the use of more ecologically valid ways of investigating both online and offline mnemonic processes. In sum, data presented here suggest a more context-dependent, active, and permanent nature of systems consolidation than was thus far assumed, leading to a more consistent view on how novel information can be efficiently incorporated into existing cortical networks.

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