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Medial prefrontal-hippocampal connectivity and motor memory consolidation in depression and schizophrenia

Memory consolidation and PFC-HPC connectivity

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Abstract

Background: Overnight memory consolidation is disturbed in both depression and schizophrenia, creating an ideal situation to investigate the mechanisms underlying sleep-related consolidation and to distinguish disease specific processes from common elements in their pathophysiology.

Methods: We investigated patients with depression and schizophrenia as well as healthy controls (each n=16) under a motor memory consolidation protocol with fMRI and polysomnography.

Results: Significantly less overnight improvement in a sequential finger tapping task associated with the degree of hippocampal-prefrontal-cortex functional connectivity during the task was identified as a common deficit in both patient groups. A task-related overnight decrease in activation of the basal ganglia was observed in controls and schizophrenia; in contrast patients with depression showed an increase. During the task schizophrenic patients additionally recruited adjacent cortical areas in comparison to controls, which showed a decrease in fMRI activation overnight and were related to disease severity. Effective connectivity analyses revealed that the hippocampus was functionally connected to the motor-task-network, and the cerebellum decoupled from this network overnight.

Conclusion: While both patient groups showed similar deficits in consolidation associated with HPC-PFC connectivity, other activity patterns more specific for disease pathology differ.

Introduction

In the last few decades increasing evidence has arisen supporting the notion of memory consolidation processes occurring during sleep (1;2). In particular, sleep appears to make the neural representations of motor memories more efficient. After sleep, healthy subjects mostly show a decrease in brain activation in some areas of the motor network (MN) (3;4); different studies show slightly different results most likely due to the wide spread usage of more lenient statistical thresholds and correction methods. Further, the hippocampus (HPC) has been shown to be especially involved in motor sequence learning (5;6). Since the HPC has been implicated to “drive” systems memory consolidation by distributing new memories into existing networks via the prefrontal cortex (PFC), it has been proposed that the HPC involvement in the motor-sequence task could predict sleep related improvement during the following night (6;7;1;8;2).

Cognitive impairment, a characteristic of both depression and schizophrenia, presents an important social and economic issue. Schizophrenia and depression seem to show some general overlapping pathophysiology such as hippocampal-prefrontal connectivity abnormalities, as well as disease specific mechanisms (9). Further, both diseases seem to affect sleep and memory; sleep-related memory consolidation – especially of the sequential finger tapping task – has been found to be disturbed in medicated depression and schizophrenia (10;11;12;13;14;15). It remains unclear however which neural mechanisms exactly underlie these deficits, and if disturbed sleep actually plays a role.

The common factor of affected overnight memory consolidation in two different patient groups creates an ideal situation to investigate the mechanisms behind motor

memory consolidation and common disease pathophysiology. In this study we investigated the neural mechanism associated with decreased memory consolidation in medicated depression (DEP) and schizophrenia (SCZ) using behavioural measurements, sleep monitoring and functional magnetic resonance imaging (fMRI). First we aimed to replicate the overnight decrease in brain activation during the sequential finger tapping task in controls (CON) and the behavioural deficit in consolidation in patients. We further investigated neural correlates related to the behavioural impairment and hypothesized that the HPC, as an important structure involved in learning, would firstly be connected to the MN and critical for overnight consolidation, and secondly show dysfunctional coupling in both patient groups as a common disease mechanism and associated with performance levels.

Methods

Participants

All participants underwent a 4-day study period (see figure 1A). Patients were recruited from the clinic of the Max Planck Institute of Psychiatry, Munich, Germany. Recruitment criteria for patients: right-handedness assessed via Edinburgh Handedness Inventory and a clinical diagnosis of a schizophrenia/schizoaffective disorder or an acute depressive episode within major depressive disorder based on DSM-IV and ICD-10 criteria. Only medicated patients were included since up until now deficits in sleep-related memory consolidation have only been shown in patients receiving medication (14;13). Exclusion criteria for both patient groups were a major co-morbid disorder such as substance abuse disorder or advanced cognitive impairment, e.g. dementia. All patients (16 DEP, 16 SCZ) were on medication with e.g. antidepressants and neuroleptics (see suppl. materials p. 2). After screening psychiatric, physical, or sleep disorders with semi-structured interviews and physical examination, sixteen healthy controls were included in the experiment and paid for their participation. All participants completed the questionnaires to assess psychiatric symptoms (Beck Depression Index BDI, Symptom Severity Scale SCL-90), morning-evening preference (morningness eveningness questionnaire M_EQ) and sleep quality (Pittsburgh sleep quality index PSQI) during the study period. The ethics committee of the Ludwig Maximilian University, Faculty of Medicine, Munich, Germany, approved the study. The experiments were performed after written informed consent of each subject was provided.

Motor Learning Task

To investigate procedural motor memory, we employed a sequential-finger-tapping task (3;4), during which the subjects repeatedly tap with their left hand the five element sequence (4-1-3-2-4) as quickly and accurately as possible during trials of 30 s (see figure 1A and suppl. material p. 4). To measure sleep related consolidation we used absolute change in correctly tapped sequences; end-training performance outside the scanner (trials 6-8) was used as baseline and subtracted by the retest performance outside the scanner. During fMRI scans, a 'paced' and a 'fast' version of the task was used. During the paced sequence, a white dot continuously ran underneath the sequence, and subjects were instructed to tap the sequence at the pace of the dot. The speed was set at 5 sequences /30 sec. During the fast version, the participants could freely tap whilst under the instruction to perform as quickly and accurately as possible. Adherence to protocol was assessed online. We chose both options to assess cerebral activity for identical tapping speed as well as for the subject's maximal performance. During the paced-version the subjects tapped at the same speed during both days, consolidation effects should be stronger; during the fast-version the subjects are encouraged to perform at their best-possible level, which should drive them to reach their limits and thus group differences should be more pronounced. In general, paced and fast results largely overlapped, therefore consolidation effects are presented in the paced version and group effects in the fast version. For detailed results and discussion on fast vs. paced version of the task please refer to supplementary materials p.4, 24, and 25.

Polysomnography:

Polysomnographic data was recorded during two subsequent nights in the sleep laboratory, stored and analyzed with a digital recorder (Comlab 32 Digital Sleep Lab, Brainlab V 3.3 Software, Schwarzer GmbH, Munich, Germany). According to the American Association of Sleep Medicine (AASM) guidelines (16), we recorded scalp EEG from the F3, F4, O3, O4, C3, and C4 derivations, each referenced against the contralateral mastoid (filtered from 0.5 to 70 Hz), and further an electrooculogram (EOG) and a mental/submental electromyogram (EMG), with a sampling rate of 250 Hz.

Sleep data analysis

For sleep data analysis, independent professionals, blind to condition and group, scored the sleep stages using standard criteria from AASM (16). Additionally, the EEG of the experimental nights underwent a spectral-analysis via fast-fourier-transformation using in-house software. After removal of artifacts the EEG from C4 (contra-lateral to the tipping hand) was digitally filtered from 0.53 to 30 Hz (24 dB/octave). Power spectra (in μV^2) were derived from overlapping 2 s time windows (shifted for 1 s) and averaged per epoch of 30 s. Spectral power in several frequency bands (summed power values) was calculated for slow oscillations (0.53 – 1 Hz), delta (0.53 – 4 Hz), theta (4.5 – 8 Hz), alpha (8.5 – 12 Hz), sigma (12.5 – 16 Hz), and beta (16.5 – 20 Hz) frequency range. An automated and validated algorithms detected sleep spindles and REM density (described in supplementary materials p.5).

All demographic, behavioral, and sleep comparisons were performed with SPSS and alpha was set as $p < 0.05$. For more details regarding data analysis and statistical procedures please see supplementary materials p. 4-6.

FMRI

FMRI was performed at 3T (Discovery MR750, GE Healthcare, Waukesha, WI, USA) using a 12-channel head coil, covering the whole brain with 34 slices, AC–PC aligned, echo-planar imaging (EPI) sequence, flip angle 90° , 64×64 in-plane matrix, in-plane FOV 24 cm, 3 mm slice thickness, 1 mm slice spacing, repetition time (2.5 s, echo time (TE) 30 ms. Additionally, multi-slice 2D spoiled gradient echo imaging (flip angle 55° , TR 1 s, and bandwidth 125 kHz) with two TEs (1.4 and 3.9 ms) was acquired for B0 mapping using the same image geometry.

FMRI analysis was done with Matlab2012b and SPM8 software (www.fil.ion.ucl.ac.uk/spm). All functional images underwent the usual preprocessing steps. Subject, group and condition effects were estimated using a general linear model (GLM) (8). After fixed-effect analysis individual contrast images (tapping>pause) were included in a flexible factorial model with the factors subject, group (CON, DEP, SCZ), day (day 1, day 2) and considering day×group interaction. The contrast weights and factors were set according to (11). All results were collected at uncorrected $p < 0.005$ and then corrected on the cluster level to control for multiple comparisons. Contrasts of individual groups are presented whole brain FWE corrected $p < 0.05$ (see e.g. fig 1B red, suppl. fig 6A). This was done both for activity analysis and to assess functional connectivity during the task with a psychophysiological-interaction (PPI) analysis with a spheroid volume of interest (VOI)

located in the right hippocampal subiculum (HPC; MNI coordinates 26, -30, -12) (7). The resting state analysis with the same VOI as the PPI was evaluated with a threshold of $p < 0.05$ FWE voxel corrected for multiple comparisons, except for individual groups, which were $p < 1 \times 10^{-7}$ whole brain FWE corrected for multiple comparisons (e.g. see fig. 1B, blue).

A more detailed description of the fMRI analysis is presented in the suppl. materials p.7ff.

Results

Behaviour and Sleep

Patient groups showed significantly higher scores in the PSQI, BDI and SCL in comparison to CON (PSQI $F_{2, 45} = 4.75$, $p < 0.01$, BDI $F_{2, 45} = 17.01$, $p < 0.001$, SCL $F_{2, 45} = 9.08$, $p < 0.001$), but no demographic differences were found (see suppl. table 1). However, age showed marginal significance (DEP > SCZ) so the main results of the MRI analysis were recalculated with age as regressor of no interest with no noticeable change in results. Sleep parameters did not show any significant effect of group, day (learning vs. non-learning) or group × day interaction and spindle parameters did not correlate with change in learning performance (see suppl. table 3 and suppl. fig 4 for more sleep data analysis). Replicating previous results, CON showed a significant difference in absolute tapping performance improvement overnight in comparison to patient groups ($F_{2, 45} = 4.127$, $p < 0.03$, CON vs. DEP $T_{30} = 2.067$, $p < 0.05$; CON vs. SCZ $T_{30} = 2.690$, $p < 0.02$; see fig. 1D), while there was no significant difference in baseline performance on day 1 ($F_{2, 45} = 1.61$, $p > 0.2$, see suppl. fig 3).

Task fMRI Activity and Connectivity

Consolidation Effects

PPI-analysis revealed that in controls the HPC was functionally connected to the default mode network (DMN e.g. precuneus, high parietal and medial PFC) and to temporal lobe as well as the MN (pre/post-central gyri, basal ganglia, cerebellum) during the task (fig.1.B, suppl. table 14). Resting state functional connectivity

analysis with the same volume of interest showed that the HPC-MN connectivity (basal ganglia and cerebellum) was task specific (fig 1.B, suppl. table 15). Over all groups the cerebellum was less connected to the HPC during the second tapping session compared to the first (fig.1.C, suppl. tab.10).

Further, activity analysis showed that over all groups, a decreased activation of parietal areas and post-central gyrus was seen overnight (fig. 1.C, suppl. tab. 8). In controls, additionally a decrease in the basal ganglia (striatum and left pallidum) was observed (fig 1.C, suppl. tab. 8).

To investigate which HPC connectivity is important for overnight memory consolidation, we performed a one sample t-test with the connectivity maps during fast-tapping and change in performance as regressor. HPC-PFC connectivity on day 1 predicted the overnight change in motor performance in the regression analysis (fig. 1.D, suppl. tab. 9).

In comparison to controls, both patient groups showed decreased activation of task relevant areas during tapping (suppl. fig. 6.B) as well as a generally decreased HPC connectivity to all areas, especially PFC (see suppl. fig.7B, suppl. table 11, 12).

Depression

DEP presented with less of a task induced deactivation of the default mode network (DMN, suppl. fig. 6.B and more pronounced in paced see suppl. fig 7.A) relative to CON (DEP>CON). Further regarding consolidation, DEP showed an overnight increase in those sub-cortical regions, which had previously been shown in CON to become more efficient overnight. This became apparent in the interaction between

DEP and CON and day, in the basal ganglia and PFC, DEP showed an increase, while CON underwent a decrease overnight (fig 2.A, suppl. tab. 6).

Schizophrenia

In contrast, SCZ in comparison to CON and DEP recruited additionally a variety of areas including mainly adjacent pre- and postcentral gyri (fig. 2.B). These adjacent areas then underwent an overnight decrease in activation and were present in the interaction between DEP and SCZ and day (fig. 2.A and B, suppl. tab. 5). We confirmed that these regions represent a disease specific mechanism of schizophrenia by including the activity maps of SCZ in a one-sample t-test with the values from the SCL-90 symptom scale, revealing a significant correlation on day 2 with these areas (see fig 2.B).

Figure 1 and 2 please about here

Discussion

This study investigated the neural correlates of decreased overnight motor memory consolidation in psychiatric patients to elicit the mechanism behind this consolidation. fMRI analyses suggest that behavioural deficits of patients with depression (DEP) and schizophrenia (SCZ) are caused by decreased hippocampal-prefrontal (HPC-PFC) connectivity, which we could show relates to overnight memory consolidation. Although both patient groups show similar behavioural and HPC-PFC deficits, other neural mechanisms activated differed during task execution and seem to be disease specific. DEP showed increased activation of subcortical regions overnight, while SCZ recruited adjacent cortical areas in relation to controls, which then underwent overnight decrease in activation and were related to disease severity with SCL values correlating positively with activity. A model of the findings from this study can be seen in figure 3.

Figure 3 please about here

Initially we could replicate the behavioural findings (13;14) that medicated SCZ and DEP show decreased overnight motor memory consolidation. In general, studies have shown that DEP and SCZ suffer from a wide variety of cognitive deficits from basic sensory and perception functions, information processing to episodic and declarative memory deficits (22;23).

Overnight consolidation

Overnight memory consolidation presented four main effects on the neural correlates of the task: 1, across all subjects the activation of high parietal areas known to be

part of the frontoparietal network, important for attention and memory processes, e.g. working memory (24), decreased overnight. This may indicate that the task execution became more automatic. 2, in controls the basal ganglia showed a decrease in activation overnight, possibly implying that the task representation becomes more efficient through consolidation, which has been shown previously (4;3). 3, functionally the cerebellum decouples from the HPC and thus in this case seemingly the motor network (MN) overnight, in corroboration to the theory that initially during learning both networks, cortico-cerebellar and cortico-striatal, are important for all motor memory, whereas in time motor-sequence-memory becomes independent of cortico-cerebellar and more dependent on cortico-striatal network (25). 4, HPC-PFC connectivity during learning predicted the change in motor-performance overnight in our study and thus is indicated to be one mechanism behind overnight memory consolidation.

The HPC-PFC connectivity has previously been shown to be important for integration of newly learned information from the HPC-episodic form into existing neural networks/schemas in the cortex (26;20;27). It has been proposed that exactly this “updating” of schemas and thus systems memory-consolidation, is one of the functions of sleep (1;28). Originally it was thought that procedural memory is HPC-independent. However, more recently it could be shown that the HPC is activated during motor sequence tasks (6;5). We can add to this by showing to our knowledge for the first time that the HPC is indeed functionally connected to the MN during the task and takes part in consolidation via the HPC-PFC connection. Schemas have been shown to be important for motor learning in general (29;30) and this specific motor task (10); this is most likely due to the pre-establishment of cortical neural-

networks adaptable to the specific task and thus enabling faster systems consolidation.

Overlapping elements in depression and schizophrenia

In this task the HPC-PFC connectivity seemed to be the deficit creating impaired sleep related consolidation and thus confirmed as a common element in the pathophysiology of both depression and schizophrenia (9). The HPC was less connected to the PFC in both patient groups in comparison to controls (see suppl. fig 7B) at the same time the HPC-PFC connectivity predicted in the regression analysis the deficits in performance (see fig 1D). HPC-PFC connectivity changes have also been seen previously in DEP (31;32) as well as SCZ (33;34;35;36;37); in both diseases during rest as well as tasks, in white matter analysis (32;38) and even in a mouse model for schizophrenia (39). Recent electrophysiological data from an animal model of schizophrenia suggests that fragmented NREM sleep and impaired slow-wave propagation culminates in deficient ripple-spindle coordination and disrupted spike timing, and that this is due to deficits in hippocampal-cortical connectivity, which would indicate that sleep spindles are an indirect “marker” for deficits in connectivity (40).

Disease specific findings: Schizophrenia

In addition to the deficit in common with DEP, SCZ displayed disease specific mechanisms. SCZ recruited additional areas (in particular the pre- and post-central cortex) during the task, and those areas did indeed show consolidation effects with

decreased task-related activity overnight and were related to symptom severity. SCZ seemed to only decrease activation of the additionally recruited areas to a final level set by disease severity. A previous study has shown a thalamic over-connectivity of the same cortical areas (sensory-motor cortex), which predicted symptoms (41). They further reported a thalamic under-connectivity with prefrontal-striatal-cerebellar regions relative to controls (41). On day 1 disease severity correlated positively with left insula activity, which has been shown previously by others (42). Schizophrenia has been described as a disease with a sub-cortical not cortical memory profile (43) with striatal (44) as well as frontal (45) dysfunctions. Thus SCZ seemed to display a more cortical and not sub-cortical mechanism, in contrast to DEP who exhibited sub-cortical up-regulation.

Disease specific findings: Depression

In contrast to CON and SCZ, DEP showed an increase in activation overnight during task execution. The interaction analysis between DEP and the other groups revealed a significant effect, with increasing activation of basal ganglia and frontal regions overnight in DEP and decreasing activation in CON and SCZ, pointing towards subcortical mechanisms being activated in DEP. Increased activation of the cerebellum during a motor sequence task as well as superior temporal gyrus during sequence learning has been observed in DEP previously (46). In our study DEP also displayed a decreased deactivation in DMN during the task, reflecting a typical disease specific finding. The DMN – consisting of precuneus, high parietal areas, PFC and HPC – is usually more activated during rest than during task completion and has been implicated to play a role in general memory, reminiscing, mind-

wandering, and similar functions (47;48). In patients with depression, a hyperconnectivity between the DMN and the cognitive-control-network via the dorsal nexus has been found, resulting in increased DMN activation in patients (49;50). This increased connectivity has been suggested to have a causal and/or maintenance role in depressive symptomatology and to predict treatment outcome (49;50). Patients often suffer from rumination and persistent thoughts, which has been associated with disturbed activation of the mPFC and disconnection to the cognitive-control-network (49;50).

Hippocampal Connectivity

Using histology and functional connectivity analysis, the HPC has been previously associated with two distinct brain networks. One involves the parahippocampal cortex, lateral and posterior parietal cortex, posterior cingulate and PFC. The other network includes the peri- and entorhinal cortices and lateral temporal cortex extending into the temporal pole (51;20). The dentate gyrus, CA3 and subiculum are present in both networks and are implied to be the ultimate level of integration of information, making them ideal areas to capture both networks as in this study. Using a subiculum seed, we found the HPC to be connected to the MN and the DMN during the task, while during rest the HPC was functionally connected to the DMN, pre/post-central gyri, and occipital and temporal cortex. It has been proposed that the HPC with its ideal processing capacities is an automatic recording system, which then drives the consolidation of new information by integration via the HPC-PFC connection into existing neural networks (1;26). This could explain the connectivity between the HPC and the MN during the task with the HPC-DMN connection for

general memory (47;48). Although, the HPC has been shown to be especially involved in motor sequence learning (6;5) and proposed that its' involvement in the motor-sequence task could predict sleep related improvement during the following night, we are the first to provide direct evidence for the importance of the HPC-PFC in motor memory consolidation. The patients showed decreased HPC-MN and critically HPC-PFC connectivity during the task, suggested here to determine the behavioural deficits. In contrast, during rest the patients showed decreased connectivity with the second HPC-network (pre/post central gyri, temporal cortex), which in healthy subjects has been associated with mentalizing and processing language and emotional cues (51). It is possible that patients showed decreased flexibility in network-switching and thus failed to reconnect the HPC to the second HPC-network during rest. In SCZ a decreased connectivity of the HPC and the temporal lobe has been shown previously (52).

Sleep and Memory Consolidation

Recently it has been proposed that hippocampal sharp wave ripples together with slow oscillations and sleep spindles act in concert to create an optimal milieu for memory-replay and systems memory integration (2;1;28). During sharp wave ripples memory-replay in the HPC and PFC can be recorded (53;54;55). Furthermore, sleep spindles have sometimes but not always been shown to increase after and correlate with learning (56;57). In fact studies in both patients with depression (M. Dresler et al., unpublished data) and with schizophrenia (14) have also shown a correlation between spindles measures and consolidation. Schizophrenic patients show changed coherence of spindles, which may be linked to white matter changes and

memory deficits (58), and a mouse model of schizophrenia shows impaired hippocampal ripple-associated replay (59). In the present study we did not find any changes of sleep stages or features induced by learning or differences between the groups. Only by including both DEP and CON and not SCZ did we find a significant correlation between spindle density and memory consolidation (see suppl. figure 4). One possible explanation is the number of participants since others only found such a correlation with increased patient numbers (14;15;13) and many have reported no such finding (60;61). However in this study, while the relationship between memory consolidation and spindles was positive in DEP and CON, it appeared negative in SCZ. In general, correlations with sleep features and cognitive makers seem unreliable and even studies with very large sample sizes cannot always confirm relationships previously reported (Ackermann, Hartmann et al., personal communication, Ujma, et al in Rev). Further, more recent research indicated that the sequence of sleep spindles together with the slow oscillations and sharp wave ripples may represent a “marker” for HPC-PFC connectivity in a rat model of schizophrenia (40) and considering only spindles that follow slow oscillations seem to have a higher predictive value for memory consolidation in SCZ than all spindles together (U. Bartsch, E. Wamsley, D. Manoach and M. Jones, personal communication). This could indicate that correlations between spindles and overnight consolidation may reflect the change in HPC-PFC connectivity seen during encoding and subsequent sleep affecting overnight consolidation and spindles. Perhaps by solely including those spindles preceded by a slow oscillation we would have found a significant relationship for SCZ as well. It is important to keep in mind that while the overnight enhancement in performance seen in healthy controls has been shown to depend on sleep, the deficit in overnight consolidation for both patient

groups has actually never been shown to be sleep-related. Hence, it is possible that patients show more degradation of performance during the day instead of consolidation deficits in sleep.

One caveat of this study is the medication status of the patients. More detailed discussions regarding medication effects and paced vs. fast can be found on the supplementary materials p. 24ff.

Conclusion

In summary, by combining data from healthy controls and patients with impaired overnight memory consolidation, we could show that the HPC is functionally connected to the MN during a motor task and that the HPC-PFC connectivity seems to be crucial for overnight memory consolidation. Deficits in overnight motor memory consolidation in medicated patients with depression and schizophrenia is indicated to rely on decreased HPC-PFC connectivity during the task, which seems to be a common pathophysiology. While both patient groups showed similar deficits in consolidation associated with HPC-PFC connectivity, other activity patterns being more specific for disease pathology differ. In depression there is an up-regulation of subcortical regions; whereas schizophrenia patients recruit adjacent cortical areas, mainly pre/post central gyri, which then decrease activation overnight and are related to symptom severity.

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Figure 1A shows the study design. Healthy controls (CON, green), patients with depression (DEP, blue) and patients with schizophrenia (SCZ, red, all n=16) spent 3 nights in our sleep laboratory. After an adaptation and an additional baseline night with polysomnography (baseline, B-night) the subjects performed eight tapping trials (see methods) at the computer outside the scanner, then performed six tapping trials in both the paced version of the task and the fast version each with simultaneous fMRI acquisition followed by 6 min of rest acquisition. Each trial length was 30 sec and the subjects repeated the 5-element sequence. During the paced condition, subjects tapped in a predetermined speed (5 sequences/30 s), while during the fast condition speed was self-paced, but whilst asking the subject to tap as fast as possible. The following night the subjects again slept with polysomnography in the sleep lab (learning, L-night) and were retested the next morning with six trials at the computer outside the scanner, then each with six tapping trials for the paced version of the task and the fast version each with simultaneous fMRI acquisition.

1B HPC connectivity analysis: For visual comparison the areas connected to the HPC during the task (red) and rest functional connectivity (blue) in controls are shown in overlay. The DMN is connected both during the task and rest. Additionally during the task the cerebellum and basal ganglia and during rest additionally the temporal lobe, occipital areas and pre/post-central cortex are recruited. This shows that the MN is functionally connected to the HPC during the task.

1C Overnight changes in activity and connectivity: All groups show a decoupling of the cerebellum from the HPC in the PPI analysis overnight (left) and decrease ($1 > 2$) in activity in parietal areas during tapping (middle), while CON additionally show a decrease in the basal ganglia in the activity analysis (right). See supplementary tables 8 and 10.

1D To evaluate which HPC-connection was critical for overnight consolidation and thus the behavioural effect of decreased consolidation in patients, we modelled the HPC-connectivity maps of day 1 with the change in tapping performance and found that HPC-PFC connectivity predicted the performance change overnight.

DEP=Depression, SCZ=Schizophrenia, CON=Controls, 1=first day, 2=second day, 1.C-D: DEP=blue, SCZ=red, CON=green, P=paced, F=fast; See supplementary table 9, 14, 15.

Figure 2A Depression: In the interaction with CON and day, DEP show an overnight increase in activation of the basal ganglia as well as the prefrontal cortex during the task. In contrast, the interaction analysis for DEP with SCZ and day reveals that SCZ show decreased activation on day 2 in areas which were previously hyperactive on day 1 as compared to CON (see fig. 2B), whereas DEP show a slight increase in recruitment of these areas. On the bottom of panel the BOLD signal from day 1 and day 2 for DEP, SCZ and CON is presented.

Figure 2B Schizophrenia: The left panel depicts task-specific activations seen in CON (red), the adjacent cortical areas SCZ recruit additionally (blue, see also suppl. fig. 6) and the areas which undergo consolidation and decrease overnight in SCZ (green, see also fig. 2A) during the task execution. There is a noticeable overlap between blue and green areas. The panel on the right shows those brain areas, which activity on day 2 correlated with symptom severity (SCL-90 scores). Again the same cortical areas are seen as in the previous analysis, showing that increased activation in these areas is a disease specific finding.

DEP=Depression, SCZ=Schizophrenia, CON=Controls, 1=first day, 2=second day, 2 A: DEP=blue, SCZ=red, CON=green, P=Paced; See supplementary table 4-7.

Figure 3 Models: 3.A shows the model for the overnight consolidation effects (green). In general the HPC is functionally connected to the MN as well as the DMN during the task. After consolidation an decreased activation of parietal areas is seen perhaps due to less attention needed for task performance and the MN becomes more efficient. This is seen in a decreased activation of the BG and a decoupling of the CB from the HPC-MN network. The HPC-PFC connection seems to be critical for consolidation, network-integration and thus overnight change in performance. Panel 3.B shows the model of the overnight changes in patients. Since the critical HPC-PFC connection is impaired in both SCZ and DEP and HPC-MN connectivity as well as MN activation is affected in both patient groups, different mechanisms are activated. SCZ additionally recruit adjacent cortical areas, which then decrease activation overnight, while DEP increasingly recruit subcortical areas (BG) overnight. Additionally DEP show a general increased activation of the DMN during the task. MC=motor cortex and associated areas, CB=cerebellum, BG=basal ganglia, HPC=hippocampus, PFC=prefrontal cortex, DMN=default-mode regions, MN=motor network, DEP=depression (blue), SCZ=schizophrenia (red), CON=controls

Reference List

1. Genzel L, Kroes MCW, Dresler M, Battaglia FP (2014): Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? *Trends in Neurosciences* 37:10-19.
2. Diekelmann S, Born J (2010): The memory function of sleep. *Nat Rev Neurosci* 11:114-126.
3. Fischer S, Nitschke MF, Melchert UH, Erdmann C, Born J (2005): Motor memory consolidation in sleep shapes more effective neuronal representations. *J Neurosci* 25:11248-11255.
4. Walker MP, Stickgold R, Alsop D, Gaab N, Schlaug G (2005): Sleep-dependent motor memory plasticity in the human brain. *Neuroscience* 133:911-917.
5. Schendan HE, Searl MM, Melrose RJ, Stern CE (2003): An fMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron* 37:1013-1025.
6. Albouy G, Sterpenich V, Balteau E, Vandewalle G, Desseilles M, Dang-Vu T, *et al* (2008): Both the Hippocampus and Striatum Are Involved in Consolidation of Motor Sequence Memory. *Neuron* 58:261-272.
7. Albouy Gv, King BR, Maquet P, Doyon J (2013): Hippocampus and striatum: Dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation. *Hippocampus* :n/a.
8. Genzel L, Dresler M (2012): Sleep - more local and complex than previously thought? *Frontiers in Neurology* 3.
9. Godsil BP, Kiss JP, Spedding M, Jay TM (2013): The hippocampal–prefrontal pathway: The weak link in psychiatric disorders? *Eur Neuropsychopharmacol* 23:1165-1181.
10. Genzel L, Ali E, Dresler M, Steiger A, Tesfaye M (2011): Sleep-dependent memory consolidation of a new task is inhibited in psychiatric patients. *J Psychiatr Res* 45:555-560.
11. Dresler M, Genzel L, Kluge M, Schüssler P, Weber F, Rosenhagen M, *et al* (2010): Off-line memory consolidation impairments in multiple sclerosis patients receiving high-dose corticosteroid treatment mirror consolidation impairments in depression. *Psychoneuroendocrinology* 35:1194-1202.
12. Dresler M, Kluge M, Genzel L, Schüssler P, Steiger A (2010): Impaired off-line memory consolidation in depression. *Eur Neuropsychopharmacol* 20:553-561.
13. Dresler M, Kluge M, Pawlowski M, Schüssler P, Steiger A, Genzel L (2011): A double dissociation of memory impairments in major depression. *J Psychiatr Res* 45:1593-1599.
14. Wamsley EJ, Tucker MA, Shinn AK, Ono KE, McKinley SK, Ely AV, *et al* (2012): Reduced Sleep Spindles and Spindle Coherence in Schizophrenia: Mechanisms of Impaired Memory Consolidation? *Biol Psychiatry* 71:154-161.

15. Manoach DS, Thakkar KN, Stroynowski E, Ely A, McKinley SK, Wamsley E, *et al* (2010): Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. *J Psychiatr Res* 44:112-120.
16. Iber C, Ancoli-Israel S, Chesson Jr AL, Quan SF (2007): *Das AASM-Manual zum Scoring von Schlaf und assoziierten Ereignissen*, 1 ed. Westchester,IL: American Academy of Sleep Medicine.
17. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ (1994): Statistical parametric maps in functional imaging: A general linear approach. *Hum Brain Mapp* 2:189-210.
18. Glascher J, Gitelman D (2008): Contrast weights in flexible factorial design with multiple groups of subjects.
19. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997): Psychophysiological and Modulatory Interactions in Neuroimaging. *NeuroImage* 6:218-229.
20. Lavenex P, Amaral DG (2000): Hippocampal-neocortical interaction: A hierarchy of associativity. *Hippocampus* 10:420-430.
21. He BJ, Zempel JM, Snyder AZ, Raichle ME (2010): The Temporal Structures and Functional Significance of Scale-free Brain Activity. *Neuron* 66:353-369.
22. Clark L, Chamberlain SR, Sahakian BJ (2009): Neurocognitive Mechanisms in Depression: Implications for Treatment. *Annu Rev Neurosci* 32:57-74.
23. Dickinson D, Harvey PD (2009): Systemic Hypotheses for Generalized Cognitive Deficits in Schizophrenia: A New Take on An Old Problem. *Schizophrenia Bulletin* 35:403-414.
24. Cabeza R, Ciaramelli E, Moscovitch M (2012): Cognitive contributions of the ventral parietal cortex: an integrative theoretical account. *Trends Cogn Sci* 16:338-352.
25. Doyon J, Benali H (2005): Reorganization and plasticity in the adult brain during learning of motor skills. *Curr Opin Neurobiol* 15:161-167.
26. Tse D, Takeuchi T, Takekuma M, Kajii Y, Okuno H, Tohyama C, *et al* (2011): Schema-Dependent Gene Activation and Memory Encoding in Neocortex. *Science* 333:891-895.
27. Nieuwenhuis ILC, Takashima A (2011): The role of the ventromedial prefrontal cortex in memory consolidation. *Behav Brain Res* 218:325-334.
28. Lewis PA, Durrant SJ (2011): Overlapping memory replay during sleep builds cognitive schemata. *Trends Cogn Sci* 15:343-351.
29. Genzel L, Quack A, Jaeger E, Konrad B, Steiger A, Dresler M (2012): Complex motor sequence skills profit from sleep. *Neuropsychobiology* 66:237-243.
30. Magill R (2007): *Motor learning and control*, 9 ed. New York: McGraw-Hill.
31. Cao X, Liu Z, Xu C, Li J, Gao Q, Sun N, *et al* (2012): Disrupted resting-state functional connectivity of the hippocampus in medication-naive patients with major depressive disorder. *Journal of Affective Disorders* 127:194-203.

32. Steffens D, Taylor W, Denney K, Bergman S, Wang L (2011): Structural Integrity of the Uncinate Fasciculus and Resting State Functional Connectivity of the Ventral Prefrontal Cortex in Late Life Depression. *PLoS ONE* 6:e22697.
33. Benetti S, Mechelli A, Picchioni M, Broome M, Williams S, McGuire P (2009): Functional integration between the posterior hippocampus and prefrontal cortex is impaired in both first episode schizophrenia and the at risk mental state. *Brain* 132:2426-2436.
34. Boyer P, Phillips JL, Rousseau FL, Ilivitsky S (2007): Hippocampal abnormalities and memory deficits: New evidence of a strong pathophysiological link in schizophrenia. *Brain Research Reviews* 54:92-112.
35. Wolf RC, Vasic N, Sambataro F, Hoese A, Frasch K, Schmid M, *et al* (2009): Temporally anticorrelated brain networks during working memory performance reveal aberrant prefrontal and hippocampal connectivity in patients with schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 33:1464-1473.
36. Lesh TA, Niendam TA, Minzenberg MJ, Carter CS (2011): Cognitive Control Deficits in Schizophrenia: Mechanisms and Meaning. *Neuropsychopharmacology* 36:316-338.
37. Hanlon FM, Houck JM, Pyeatt CJ, Lundy SL, Euler MJ, Weisend MP, *et al* (2011): Bilateral hippocampal dysfunction in schizophrenia. *NeuroImage* 58:1158-1168.
38. Qiu A, Tuan TA, Woon PS, Abdul-Rahman MF, Graham S, Sim K (2010): Hippocampal-cortical structural connectivity disruptions in schizophrenia: An integrated perspective from hippocampal shape, cortical thickness, and integrity of white matter bundles. *NeuroImage* 52:1181-1189.
39. Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA (2010): Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. *Nature* 464:763-767.
40. Phillips K, Bartsch U, McCarthy A, Edgar D, Tricklebank M, Wafford K, *et al* (2012): Decoupling of Sleep-Dependent Cortical and Hippocampal Interactions in a Neurodevelopmental Model of Schizophrenia. *Neuron* 76:526-533.
41. Anticevic A, Cole MW, Repovs G, Murray JD, Brumbaugh MS, Winkler AM, *et al* (2013): Characterizing Thalamo-Cortical Disturbances in Schizophrenia and Bipolar Illness. *Cereb Cortex* .
42. Wylie KP, Tregellas JR (2010): The role of the insula in schizophrenia. *Schizophrenia Research* 123:93-104.
43. Paulson J, Heaton R, Sadek J, Perry W, Delis D, Braff D, *et al* (1995): The nature of learning and memory impairments in schizophrenia. *Journal of International Neuropsychological Society* 1:88-99.
44. Brandt GN, Bonelli RM (2008): Structural neuroimaging of the basal ganglia in schizophrenic patients: a review. *WMW Wiener Medizinische Wochenschrift* 158:84-90.
45. Ragland J, Laird A, Ranganath C, Blumenfeld R, Gonzales S, Glahn DC (2009): Prefrontal Activation Deficits During Episodic Memory in Schizophrenia. *Am J Psychiatry* 166:863-874.

46. Naismith SL, Lagopoulos J, Ward PB, Davey CG, Little C, Hickie IB (2010): Fronto-striatal correlates of impaired implicit sequence learning in major depression: An fMRI study. *Journal of Affective Disorders* 125:256-261.
47. Greicius MD, Supekar K, Menon V, Dougherty RF (2009): Resting-State Functional Connectivity Reflects Structural Connectivity in the Default Mode Network. *Cereb Cortex* 19:72-78.
48. Vincent JL, Snyder AZ, Fox MD, Shannon BJ, Andrews JR, Raichle ME, *et al* (2006): Coherent spontaneous activity identifies a hippocampal-parietal memory network. *Journal of Neurophysiology* 96:3517-3531.
49. Pizzagalli DA (2011): Frontocingulate Dysfunction in Depression: Toward Biomarkers of Treatment Response. *Neuropsychopharmacology* 36:183-206.
50. Sheline YI, Price JL, Yan Z, Mintun MA (2010): Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci* 107:11020-11025.
51. Kahn I, Andrews-Hanna JR, Vincent JL, Snyder AZ, Buckner RL (2008): Distinct Cortical Anatomy Linked to Subregions of the Medial Temporal Lobe Revealed by Intrinsic Functional Connectivity. *Journal of Neurophysiology* 100:129-139.
52. Crossley NA, Mechelli A, Fusar-Poli P, Broome MR, Matthiasson P, Johns LC, *et al* (2009): Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. *Hum Brain Mapp* 30:4129-4137.
53. Peyrache A, Khamassi M, Benchenane K, Wiener SI, Battaglia FP (2009): Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. *Nat Neurosci* 12:919-926.
54. Wilson M, McNaughton B (1994): Reactivation of hippocampal ensemble memories during sleep. *Science* 265:676-679.
55. Girardeau G, Zugaro M (2011): Hippocampal ripples and memory consolidation. *Curr Opin Neurobiol* 21:452-459.
56. Genzel L, Kiefer T, Renner L, Wehrle R, Kluge M, Grözinger M, *et al* (2012): Sex and modulatory menstrual cycle effects on sleep related memory consolidation. *Psychoneuroendocrinology* 37:987-989.
57. Gais S, Mölle M, Helms K, Born J (2002): Learning-dependent increases in sleep spindle density. *J Neurosci* 22:6830-6834.
58. Ferrarelli F, Peterson MJ, Sarasso S, Riedner BA, Murphy M, Benca RM, *et al* (2010): Thalamic dysfunction in schizophrenia suggested by whole-night deficits in slow and fast spindles. *Am J Psychiatry* 167:1339-1348.
59. Suh J, Foster D, Davoudi H, Wilson M, Tonegawa S (2013): Impaired Hippocampal Ripple-Associated Replay in a Mouse Model of Schizophrenia. *Neuron* 80:484-493.

60. Poulin J, Daoust AM, Forest G, Stip E, Godbout R (2003): Sleep architecture and its clinical correlates in first episode and neuroleptic-naïve patients with Schizophrenia. *Schizophr Res* 62:147-153
61. Van Cauter E, Linkowski P, Kerkhofs M, HUBain P, L'Hermite-Baleriaux M, Leclercq R, *et al* (1991): Circadian and sleep-related endocrine rhythms in schizophrenia. *Arch Gen Psychiatry* 48:348-356