A double dissociation of memory impairments in major depression

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A B S T R A C T

Sleep benefits the consolidation of both declarative and nondeclarative memories, however the question if these two memory systems profit from sleep in more or less similar ways is still under debate. Studying the on-line and off-line consolidation of declarative and nondeclarative memory tasks in depressed patients and healthy controls, we here present a clear double dissociation between memory systems and consolidation phases, suggesting radically different ways how sleep benefits memory consolidation. 37 medicated inpatients with an acute episode of major depression and 31 healthy controls were assessed using a nondeclarative (sequential finger tapping) memory task before and after a night with polysomnography, 27 of the depressed and 22 of the control subjects additionally performed a declarative (paired associates) task. Although depressed patients and control subjects did not differ in practice-dependent learning of the nondeclarative motor task in the wake state, healthy subjects showed overnight improvements in tapping performance of 11.4%, while the patients’ performance decreased overnight by 11.5%. This pattern was reversed for the declarative task: While patients learned 33.5% less word pairs than controls in the wake state, overnight changes did not differ between the two groups. These results suggest a double dissociation of memory consolidation processes in major depression: Off-line memory consolidation in major depression is impaired for nondeclarative, but not declarative tasks. The same tasks in the wake state show a reversed pattern, with performance in declarative but not nondeclarative tasks being impaired in major depression.

1. Introduction

Memory is differentiated into multiple processes and subsystems. Major distinctions include the differentiation between encoding, consolidation and recall on the one hand and between declarative and nondeclarative memory on the other. A growing body of evidence supports a role of sleep in the consolidation of both declarative memory and nondeclarative procedural skills (Walker and Stickgold, 2006), however the question if these two memory systems profit from sleep in more or less similar ways is still under debate. Specifically, slow wave sleep (SWS) seems to be related to declarative memory consolidation (Gais and Born, 2004), while rapid eye movement (REM) sleep (Plihal and Born, 1997; Smith, 1996) and sleep stage 2 (Walker and Stickgold, 2006) have been associated with nondeclarative memory consolidation. Particularly off-line gains in nondeclarative procedural skills are thought to crucially rely on sleep, while their stabilization might also occur during wakefulness (Walker and Stickgold, 2006). In patients with major depression (MD), most studies demonstrate deficits in declarative memory, but intact nondeclarative memory (Austin et al., 2001). However, considering the well documented changes of sleep-electroencephalogram (EEG) in depression (Armitage, 2007; Kupfer, 1995) and during antidepressant pharmacotherapy (Steiger and Kimura, 2010), the sleep-related consolidation of nondeclarative memories in medicated depression has been proposed to be a crucial topic in the sleep-memory consolidation debate (Vertes, 2004). Neither REM-suppressing medication nor manual REM sleep or SWS deprivation impair declarative or nondeclarative memory consolidation in healthy subjects (Rasch et al., 2009; Genzel et al., 2009). However, while off-line components of nondeclarative memory turn out to be impaired in MD (Dresler et al., 2010a), the relationship between sleep and both declarative and nondeclarative off-line memory consolidation in MD still has to be clarified. In the light of diminished SWS in depression and suppressed REM sleep during antidepressant pharmacotherapy, we tested the hypothesis that medicated patients with an acute episode of MD would show impairments in the sleep-related consolidation of both declarative and nondeclarative memory. In line with the literature, we
expected declarative learning to be impaired but nondeclarative learning to be preserved in the encoding session.

2. Methods

2.1. Participants

37 inpatients (48.3 ± 8.6 years, 20 female) with an acute episode of unipolar MD and without psychiatric or non-psychiatric comorbidity at the end of their first week of hospitalization were included in this study. Diagnosis was established in semi-standardized interviews by two independent senior psychiatrists according to ICD-10. Clinical status was further assessed with the 21 items version of the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck et al., 1961). In line with our former study (Dresler et al., 2010a,b) inclusion criteria were set at a score of at least 18 in the HAMD and the BDI. All patients were medicated: 14 patients received tricyclics ( Amitriptyline, Clomipramine, Doxepin, Trimipramine), 15 received SSRIs (Citalopram, Escitalopram, Sertraline), 7 received SNRIs (Amitriptyline, Clomipramine, Doxepin, Trimipramine), 15 received the BDI. All patients were medicated: 14 patients received tricyclics ( Amitriptyline, Clomipramine, Doxepin, Trimipramine), 15 received SSRIs (Citalopram, Escitalopram, Sertraline), 7 received other antidepressants (Mirtazapine, Sulpiride), 3 received lithium and 7 received GABAergic agonists (Lorazepam and Zopiclone). 31 healthy control subjects (48.1 ± 10.4 years, 17 female) recruited by internet and newspaper advertisements served as a control group. In semi-standardized interviews the participants reported no history of psychiatric illness, no stressful life event in the last year, no medication use and no non-psychiatric comorbidity. Clinical status was further assessed with the BDI, exclusion criterion was a score above 7. For illness, no stressful life event in the last year, no medication use and interviews the participants reported no history of psychiatric

2.2. Procedures

Subjects were tested on two consecutive days between 08:00 and 11:00 h. For nondeclarative learning, a sequential finger tapping task (Walker et al., 2002) was used. The subjects were required on the first day to repeatedly tap a sequence of 5 numbers (4-1-3-2-4) during 12 periods of 30 s, interrupted by a 20 s pause each, as often and correctly as possible with their non-dominant hand on a special 4-keys computer keyboard (training session). During tapping trials, the number-sequence was displayed in white on a black background in the middle of the screen to minimize working memory load. Each key press produced a dot below the tapped number, forming a row left to right. Once the five dots of a sequence were completed, each subsequent key press removed a dot from left to right. When the dots had all been removed, further key presses added them again. Each trial was automatically scored for the number of correctly tapped sequences, thus assessing both speed and accuracy of motor performance. In the 20 s pause between the trials, the displayed sequence was darkened and the dots were replaced with the word “Pause”. Five seconds before the pause ended, an acoustic countdown signaled the upcoming start of the next trial. Changes of motor performance were measured in a three trial test session 24 h later, after a night of normal sleep.

For declarative learning, 27 of the depressed patients (48.9 ± 9.0 years, 15 female) and 22 of the healthy controls (46.1 ± 9.2 years, 12 female) were assessed using a paired associates task (Plilhal and Born, 1997). 44 semantically related word pairs (e.g. animal-dog) were presented for 5 s each with a 100 ms interstimulus interval. Four word pairs (two at the beginning and two at the end) were excluded from the response phase to account for primacy/recency effects. Immediately following the presentation, the subjects were shown the first word of each of the remaining 40 word pairs and asked to type in the word that completes the pair. After each response was entered the correct answer was displayed for 2 s. The common version of this task repeats learning trials until 60% of the presented words are recalled correctly. However, a pilot study showed that this version is not applicable to depressed patients, since several patients were not able to perform to the criterion even after 60 min. Hence, we used the version of Tucker et al. (2006), in which subjects performed just one learning trial. At retest, subjects were shown the same 40 target words and were asked to type in the word that completes the word pair. Declarative memory testing was introduced at a later point in the study, i.e. none of the subjects were excluded from one of the tests for individual reasons and there were no significant differences between the task groups regarding age or depression severity.

The subjects slept two nights from 23:00 (lights off) to 07:00 (lights on) in the sleep laboratory of the Max Planck Institute of Psychiatry, Munich. The first night served as an adaptation night. Polysomography was recorded, stored and analyzed with a digital recorder (Comlab 32 Digital Sleep Lab, Brainlab V 3.3 Software, Schwarzer GmbH, Munich, Germany). For scalp EEG we recorded from C3 and C4 leads (filtered from 0.5 to 70 Hz), electrooculogram (EOG), and mental/submental electromyogram (EMG), with a sampling rate of 250 Hz.

2.3. Data analysis

Based on the number of correct sequences tapped per 30 s trial and therefore reflecting both the speed and accuracy of motor performance, the main outcome measures for nondeclarative learning were practice-dependent changes on day 1 and overnight

Table 1

Biographical data of all patients and controls and of subgroups assessed with the declarative task in addition to the nondeclarative task, given as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>Patients (both tasks)</th>
<th>Controls (both tasks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (females)</td>
<td>37 (20)</td>
<td>31 (17)</td>
<td>27 (15)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.3 ± 8.6</td>
<td>p &gt; 0.6</td>
<td>48.1 ± 10.4</td>
<td>p &gt; 0.6</td>
</tr>
<tr>
<td>Age range, y</td>
<td>30–62</td>
<td>p &gt; 0.8</td>
<td>30–65</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>BDI</td>
<td>27.8 ± 9.1</td>
<td>2.3 ± 2.5</td>
<td>28.1 ± 9.7</td>
<td>2.5 ± 2.8</td>
</tr>
<tr>
<td>HAMD</td>
<td>24.5 ± 6.0</td>
<td>–</td>
<td>23.7 ± 5.8</td>
<td>–</td>
</tr>
<tr>
<td>Episodes</td>
<td>3.1 ± 2.2</td>
<td>–</td>
<td>3.0 ± 2.0</td>
<td>–</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>38.1 ± 11.4</td>
<td>–</td>
<td>38.8 ± 12.0</td>
<td>–</td>
</tr>
<tr>
<td>Duration, m</td>
<td>120.1 ± 124.2</td>
<td>–</td>
<td>117.6 ± 125.1</td>
<td>–</td>
</tr>
<tr>
<td>Current episode, m</td>
<td>10.1 ± 11.7</td>
<td>–</td>
<td>9.7 ± 9.1</td>
<td>–</td>
</tr>
</tbody>
</table>

BDI: Beck Depression Inventory Score; HAMD: Hamilton Depression Inventory Score; Episodes: Number of episodes including the current; Duration: Duration of illness since first episode; Current episode: Duration of current episode; p-values are given for differences between the groups regarding age and gender distribution.
changes from day 1 to day 2. Tapping performance at the end of the training session on day 1 was compared with performance at the beginning of that session (practice-dependent learning) and with performance of the next session on day 2 (off-line consolidation). Practice-dependent learning was calculated as the percent increase in correct sequences typed from the first trial to the average of the last three trials on day 1. Overnight changes were calculated as the percent increase or decrease from the average of the last three trials of day 1 to the average of the three trials of day 2. For declarative learning, the main outcome measures were memory performance on day 1 and overnight changes from day 1 to day 2. Performance was measured as the number of correctly completed word pairs, while overnight changes were calculated as the percent increase or decrease from the number of correctly completed word pairs on day 1 to the number of correctly completed word pairs on day 2. For sleep data analysis independent professional experts scored the sleep stages using standard criteria (Rechtschaffen and Kales, 1968).

For statistical analysis (using SPSS 16) we partitioned the variables in 3 sets and performed for each of them a multivariate analysis of variance (MANOVA), one for declarative memory data (remembered word pairs on day 1, overnight changes), one for nondeclarative memory data (baseline motor performance, training gains on day 1, overnight changes) and one for sleep data (S2, SWS, REM, Wake, TST). The only influential factor in the MANOVAs was diagnosis. For variable sets that revealed a significant factor effect, we conducted further univariate F-tests to identify those variables on which the factor effect was significant. Exploratively we tested gender differences via a MANOVA with the two independent variables gender and depression and with the two dependent variables nondeclarative and declarative overnight changes.

Since the possible effect of REM-suppressing drugs on nondeclarative memory consolidation in MD has been proposed as a litmus test for the sleep-memory consolidation hypothesis (Vertes, 2004), we compared both time spent in REM sleep and nondeclarative overnight changes between 25 patients receiving at least one REM-suppressing antidepressant like amitriptyline, citalopram, duloxetine, or venlafaxine (Kluge et al., 2007; Wilson and Argyropoulos, 2005) and 6 patients receiving only antidepressants that do not suppress or even enhance REM sleep like mirtazapine or trimipramine (Wilson and Argyropoulos, 2005; Schmid et al., 2005; Sonntag et al., 1996) with simple t-tests. 6 patients receiving both REM-suppressing and REM-enhancing medication were not included in the analysis. In addition, since sleep stage 2 was proposed to subserve nondeclarative memory consolidation (Walker and Stickgold, 2006) while being promoted by GABA_A agonists (Lancel and Steiger, 1999), we compared both time spent in S2 and nondeclarative overnight changes between 7 patients with and 30 patients without GABA_A agonistic medication (benzodiazepines and non-benzodiazepine hypnotics) with simple t-tests.

Pearson product–Moment correlation coefficients were used to describe the relationship between memory consolidation and sleep variables, clinical depression scores, and number of depressive episodes. All tests were calculated with an alpha of 0.05. All group differences are given as mean ± SD.

3. Results

3.1. Memory data

The MANOVA for declarative memory data revealed a significant effect of depression (F_{2,46} = 6.4, p < 0.001). Subsequent F-tests revealed that patients remembered significantly less word pairs than controls in the encoding session on day 1 (13.8 ± 6.1 vs. 20.6 ± 8.4 correctly remembered word pairs; F_{1,47} = 11.4, p < 0.001), but did not differ in overnight changes (6.1 ± 32.3% increase vs. 3.3 ± 16.3% decrease in correctly remembered word pairs; F_{1,47} = 1.5, p > 0.2). Also for nondeclarative memory data the MANOVA revealed a highly significant effect of depression (F_{1,64} = 14.2, p < 0.001). F-tests revealed that patients showed a significantly lower baseline motor performance on day 1 (4.2 ± 3.0 vs. 7.1 ± 3.8 correctly tapped sequences per 30 s; F_{1,66} = 12.1, p < 0.001) and a significantly worse procedural memory consolidation overnight (11.2 ± 17.2% decrease vs. 11.3 ± 15.6% increase in correctly tapped sequences; F_{1,66} = 31.4, p < 0.001), while training gains in the encoding session on day 1 did not differ between the groups (184.7 ± 109.8% vs. 166.0 ± 152.3% increase in correctly tapped sequences; F_{1,66} = .3, p > 0.5). For memory data see Figs. 1 and 2 and Table 2.

3.2. Sleep data

The MANOVA for sleep data revealed a significant effect of depression (F_{5,62} = 6.4, p < 0.001). Subsequent F-tests revealed that patients spent significantly more time in S2 (234.1 ± 57.6 vs. 205.3 ± 42.7 min; F_{1,66} = 11.4, p < 0.001) and significant less time in
Table 2
Memory data, given as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Nondeclarative task</th>
<th>Declarative task</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Training</td>
<td>Consolidation</td>
</tr>
<tr>
<td>Patients</td>
<td>4.2 ± 3.0</td>
<td>185 ± 110%</td>
</tr>
<tr>
<td>Controls</td>
<td>7.1 ± 3.8</td>
<td>166 ± 152%</td>
</tr>
<tr>
<td>Statistics</td>
<td>F = 12.1 p &lt; 0.001</td>
<td>F = 3.14</td>
</tr>
</tbody>
</table>

Baseline: Number of correctly tapped sequences in the first trial; Training: Increase from first tapping trial to the mean of the last three trials on day 1; Nondeclarative consolidation: Increase/decrease from the mean of the last three trials on day 1 to the mean of the three trials on day 2; Encoding: Number of correctly remembered word pairs; Declarative consolidation: Increase/decrease from the number of correctly remembered word pairs on day 1 to the number of correctly remembered word pairs on day 1.

Table 3
Sleep data, given as mean minutes ± SD.

<table>
<thead>
<tr>
<th></th>
<th>S2</th>
<th>SWS</th>
<th>REM</th>
<th>Wake</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>234.1 ± 57.6</td>
<td>60.1 ± 44.8</td>
<td>62.1 ± 36.8</td>
<td>53.0 ± 36.0</td>
<td>423.5 ± 35.6</td>
</tr>
<tr>
<td>Controls</td>
<td>205.3 ± 42.8</td>
<td>81.5 ± 37.0</td>
<td>89.8 ± 22.8</td>
<td>67.5 ± 38.4</td>
<td>412.0 ± 37.5</td>
</tr>
<tr>
<td>Statistics</td>
<td>F = 5.3 p &lt; 0.05</td>
<td>F = 4.5</td>
<td>F = 13.2</td>
<td>F = 1.9</td>
<td>F = 1.7</td>
</tr>
</tbody>
</table>

S2: Time spent in sleep stage 2; SWS: Time spent in slow wave sleep; REM: Time spent in REM sleep; Wake: Time spent awake; TST: Total sleep time.

both SWS (60.1 ± 44.8 vs. 81.5 ± 37.0 min; F₁,₆₆ = 11.4, p < 0.001) and REM sleep (62.1 ± 36.8 vs. 89.8 ± 22.8 min; F₁,₆₆ = 11.4, p < 0.001) than controls. The groups did not differ in TST (423.5 ± 35.6 vs. 412.0 ± 37.5 min; F₁,₆₆ = 1.7, p > 0.2) or time spent awake (55.0 ± 36.0 vs. 67.5 ± 38.4 min; F₁,₆₆ = 1.9, p > 0.1) (Table 3).

3.3. Gender and medication effects

The gender x diagnosis MANOVA revealed a significant effect (F₂,₄₂ = 9.8, p < 0.001), which however was exclusively caused by the already known effect of depression on nondeclarative memory consolidation. We found no gender effect or gender x diagnosis interaction, neither for nondeclarative (gender: F₁,₄₁ = 4.4, p > 0.5; gender x diagnosis: F₁,₄₁ = 1, p > 0.7) nor declarative (gender: F₁,₄₁ = 1, p > 0.7; gender x diagnosis: F₁,₄₁ = 1.3, p > 0.2) memory consolidation.

Patients receiving REM-suppressing drugs experienced significantly less REM sleep than patients without such medication (49.1 ± 29.6 vs. 109.3 ± 27.9 min; t = −4.5, p < 0.001), but did not differ in nondeclarative memory consolidation (12.1 ± 18.2% vs. 10.5 ± 13.4% overnight decrease; t = 2, p > 0.8). Patients receiving GABA agonists experienced significantly more S2 (278.4 ± 62.0 vs. 223.8 ± 52.3 min; t = −2.4, p < 0.05) and significantly better nondeclarative memory consolidation (1.3 ± 12.2% overnight increase vs. 1.4 ± 17.0% overnight decrease; t = −2.2, p < 0.05) than patients without such medication. Of note, three patients treated with lithium showed markedly worse overall performance and sleep-related consolidation of nondeclarative memory in comparison with the majority of lithium-free patients (5.2 ± 1.2 vs. 8.5 ± 4.5 correctly tapped sequences; 23.3 ± 15% vs. 10.1 ± 17% overnight decrease), which is in line with a recent meta-analysis reporting impairments in psychomotor performance due to lithium treatment (Wingo et al., 2009). We did not find any differences regarding sleep-related declarative memory consolidation, age, or depression severity between any of the medication groups.

3.4. Correlations

The comparable nondeclarative memory consolidation of patients with and without REM-suppressing drugs was reflected by a lack of correlation between time spent in REM sleep and nondeclarative memory consolidation in the patients group (r = 0.04, p > 0.8). In addition, we found no significant correlations between declarative or nondeclarative memory consolidation and any of the other sleep data, neither in the patient group nor in the control group. We also did not find any correlations between declarative or nondeclarative memory consolidation and the HAMD or BDI scores, the duration of the current depressive episode or the number of depressive episodes. However we observed a difference between recurrent depressive episodes vs. first episode patients: The former experienced significantly worse sleep-related nondeclarative memory consolidation, even when age is taken into account as a covariate (15.3 ± 14.9% vs. 0.0 ± 18.6% overnight decrease, p < 0.05). Surprisingly, we found a strong negative correlation of r = −0.6 (p < 0.01, Bonferroni corrected) between age and nondeclarative memory consolidation in the control group, but not in the patient group (r = 0.03, p > 0.8). Declarative memory consolidation did not correlate with age in both groups. For all correlation data see Table 4.

4. Discussion

Sleep vitally contributes to the consolidation of both declarative and nondeclarative skills (Walker and Stickgold, 2006). However in major depression and during antidepressant pharmacotherapy, changes of sleep EEG are well documented (Armitage, 2007; Kuper, 1995; Steiger and Kimura, 2010). In patients with MD, most studies demonstrate deficits in declarative memory, but intact nondeclarative memory (Austin et al., 2001). Here we show that this mismatch is complemented by a reversed pattern in the sleep-related aspects of memory consolidation, resulting in a double dissociation: Depressed patients show preserved on-line nondeclarative learning and offline declarative memory consolidation, while experiencing strong impairments in on-line declarative learning and off-line nondeclarative memory consolidation compared to healthy controls. Interestingly, patients with recurrent episodes of depression were more strongly impaired in their sleep-related consolidation of nondeclarative memory than first episode patients. As expected from psychomotor retardation in depression, baseline motor performance was lower in depressed patients (Sobin and Sackeim, 1997).
4.1. Memory function in depression

Differential memory function in MD has been studied under several perspectives. Traditionally, the differentiation between declarative and nondeclarative memory is thought to be identical with that between explicit and implicit memory (Müller et al., 1998). However, in recent years this equalization was questioned (Robertson et al., 2004a), since nondeclarative skills can be acquired intentionally (explicit learning like in the sequential finger tapping task used here) as well as unintentionally (implicit learning like in the serial reaction time task, (Nissen and Bullemer, 1987)). When this differentiation is accounted for, implicit nondeclarative learning was shown to be impaired in MD (Naismith 1987)). When this differentiation is accounted for, implicit nondeclarative learning is impaired in MD. Another approach differentiates between effortful and automatic memory processes (Hasher and Zacks, 1979). A failure of effort demanding processes was proposed as a possible explanation for the patterns of memory impairments seen in MD (Roy-Byrne et al., 1986). Indeed, numerous studies demonstrate that memory impairments in MD are related to the degree of effortfulness of the tasks applied (Hartlage et al., 1993). The declarative paired associate learning task used in our study requires sustained attention over several minutes and can therefore be considered as a prototypical effortful task. In contrast, sequential finger tapping is a highly repetitive task, with the required motor movements becoming automatic very quickly. Our results showing impaired declarative and preserved nondeclarative on-line learning thus confirm the literature on selective impairments of effortful memory processes in MD, however they expand it in showing that regarding the off-line components of memory consolidation the pattern of impairment is reversed.

4.2. Sleep

Depressed patients spent significantly less time in SWS and REM sleep and significantly more time in sleep stage 2 than controls, while TST and time spent awake did not differ between the groups. These results mainly confirm the literature: The most pronounced sleep alterations associated both with depression and antidepressant medication regard changes in SWS and REM sleep: SWS is diminished, REM latencies are shortened, and REM density is elevated in drug-free patients with MD (Armitage, 2007; Kupfer, 1995; Steiger and Kimura, 2010). While many antidepressants suppress REM sleep, their effect on SWS is quite diverse (Wilson and Argyropoulos, 2005; Steiger and Kimura, 2010).

In the initial acquisition of nondeclarative motor skills, performance asymptotically improves with continued practice. This initial fast learning component is followed by a slow learning component, which seems to depend critically on sleep (Karni et al., 1995; Walker et al., 2003). Classically, both REM sleep and sleep stage 2 have been proposed to subserve nondeclarative memory consolidation (Pil pellets and Born, 1997; Walker et al., 2002). At first glance, our results support the role of REM sleep rather than S2 in nondeclarative memory consolidation: Depressed patients show marked impairments in the consolidation of a nondeclarative motor task, while spending more time in S2 and less time in REM sleep than healthy controls. However, several recent studies conflict with a major role of REM sleep in the off-line consolidation of motor skills (Genzel et al., 2009; Hornung et al., 2007; Rasch et al., 2009). On second sight, also our data do not confirm a major role of REM sleep in the observed impairments in nondeclarative memory consolidation: Despite ample variance, time in REM sleep did not correlate with nondeclarative memory consolidation at all in the patients group. In addition, patients receiving REM-suppressing medication did not differ from patients without REM-suppressors in nondeclarative memory consolidation, despite experiencing less than half REM time. In contrast, patients receiving GABA_A agonists spent significantly more time in S2 and experienced significantly better nondeclarative memory consolidation than patients without such medication. Hence, it is tempting to speculate that S2 indeed has had a major role in memory consolidation in our study, which, however, was superimposed by a general consolidation impairing effect of depression. However, S2 did not correlate significantly with memory consolidation in the patient group in the control group, rendering this speculation rather unlikely.

SWS is proposed to subserve declarative memory consolidation (Born et al., 2006; Pil pellets and Born, 1997). Surprisingly, despite experiencing 25% less SWS than controls, depressed patients showed nominally even better declarative memory consolidation than controls, however this difference was not significant.

4.3. Neural mechanisms

While the hippocampal formation underlies declarative learning (Eichenbaum, 2000), cortico-striatal and cortico-cerebellar circuits are involved in the acquisition of nondeclarative motor skills (Doyon et al., 2009). Hippocampal volume reductions are well documented in depression (Bremner et al., 2000; Campbell et al., 2004), and are associated with memory loss (Sheline et al., 2002). Hippocampal impairments are probably caused by hypothalamic-pituitary-adrenal (HPA) axis hyperactivity (Brown, 2009), which in turn is one of the most prominent

Table 4
Correlations between memory data and sleep, age and depression scores (Bonferroni correction in parenthesis).

<table>
<thead>
<tr>
<th>Patients</th>
<th>S2</th>
<th>SWS</th>
<th>REM</th>
<th>Wake</th>
<th>TST</th>
<th>Age</th>
<th>BDI</th>
<th>HAMD</th>
<th>Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declarative</td>
<td>$r = -0.36$</td>
<td>$r = 0.14$</td>
<td>$r = -0.07$</td>
<td>$r = 0.44$</td>
<td>$r = 0.44$</td>
<td>$r = -0.02$</td>
<td>$r = -0.09$</td>
<td>$r = -0.10$</td>
<td>$r = -0.26$</td>
</tr>
<tr>
<td></td>
<td>$p &gt; 0.4$</td>
<td>$p &gt; 0.4$</td>
<td>$p &gt; 0.7$</td>
<td>$p &lt; 0.05$</td>
<td>$p &lt; 0.05$</td>
<td>$p &gt; 0.9$</td>
<td>$p &gt; 0.6$</td>
<td>$p &gt; 0.6$</td>
<td>$p &gt; 0.1$</td>
</tr>
<tr>
<td>Nondeclarative</td>
<td>$r = 0.14$</td>
<td>$r = 0.12$</td>
<td>$r = -0.04$</td>
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<td>$r = 0.01$</td>
<td>$r = 0.12$</td>
<td>$r = 0.27$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p &gt; 0.4$</td>
<td>$p &gt; 0.4$</td>
<td>$p &gt; 0.8$</td>
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<td>$p &gt; 0.5$</td>
<td>$p &gt; 0.1$</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Controls</th>
<th>S2</th>
<th>SWS</th>
<th>REM</th>
<th>Wake</th>
<th>TST</th>
<th>Age</th>
<th>BDI</th>
<th>HAMD</th>
<th>Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declarative</td>
<td>$r = -0.07$</td>
<td>$r = 0.32$</td>
<td>$r = -0.24$</td>
<td>$r = -0.07$</td>
<td>$r = 0.09$</td>
<td>$r = 0.08$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p &gt; 0.7$</td>
<td>$p &lt; 0.1$</td>
<td>$p &gt; 0.2$</td>
<td>$p &lt; 0.7$</td>
<td>$p &gt; 0.6$</td>
<td>$p &gt; 0.7$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondeclarative</td>
<td>$r = 0.07$</td>
<td>$r = -0.25$</td>
<td>$r = -0.25$</td>
<td>$r = -0.33$</td>
<td>$r = 0.32$</td>
<td>$r = -0.60$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.6$</td>
<td>$p &gt; 0.1$</td>
<td>$p &gt; 0.1$</td>
<td>$p &lt; 0.05$</td>
<td>$p &lt; 0.05$</td>
<td>$p &lt; 0.001$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S2: Time spent in sleep stage 2; SWS: Time spent in slow wave sleep; REM: Time spent in REM sleep; Wake: Time spent awake; TST: Total sleep time; BDI: Beck Depression Inventory; HAMD: Hamilton Depression Rating Scale; Episodes: number of depressive episodes.
neurobiological findings in depression (Holsboer, 2000). While glucocorticoids have been suggested to impair mainly declarative memory consolidation by perturbing hippocampal neural networks (Born and Fehm, 1998; Brenner et al., 2004), some studies show hippocampal contributions also to nondeclarative motor learning (Schendan et al., 2003), especially to overnight gains in sequential motor skills (Albouy et al., 2008). Considering the role of HPA hormones in sleep-related memory consolidation (Wagner and Born, 2008), the marked changes in nocturnal HPA hormone secretion in depression (Linkowski, 2003; Steiger, 2007), and the impact of HPA hormones on sleep regulation (Steiger, 2007), hormonal dysregulation in depression might also influence memory consolidation via its effects on sleep. In a recent study we have shown that high-dose glucocorticoid therapy in patients with multiple sclerosis impairs nondeclarative memory consolidation similarly to the impairments seen in depressed patients (Dresler et al., 2010b).

The cerebellum is thought to be mainly active during the fast learning phase of nondeclarative motor skills, while this activity decreases with practice and may become undetectable when the task is well learned. In contrast, the striatum is significantly more activated when subjects have reached asymptotic performance and therefore is probably more critical for the long-term storage of well-learned motor skills (Doyon et al., 2003). Hence, the sleep-related consolidation of motor sequences has been associated with functional plasticity in the cortico-striatal system (Doyon and Benali, 2005). However, gray matter volume reductions in depression are reported also for the striatum (Bonelli et al., 2006), which is also prone to HPA hyperactivity (Metz, 2007). Since both the hippocampus and the striatum are on the one hand impaired in depression, and on the other hand involved in slow learning processes of nondeclarative motor skills, impaired off-line memory consolidation of a finger tapping task in depression is not surprising.

4.4. Effects of medication

Considering the variety of drugs used in this study and the very diverse effects of different antidepressants on cognitive functions (Amado-Boccara et al., 1995) and sleep (Wilson and Argyropoulos, 2005), we restricted an analysis of medication effects on two drug types with comparatively clear effects on sleep: REM-suppressing antidepressants and GABA A agonists.

REM sleep has been proposed as a major factor in the off-line consolidation of nondeclarative memory (Plihal and Born, 1997; Smith, 1996). The possible effect of REM-suppressing drugs on memory consolidation in MD therefore has been proposed as a litmus test for the sleep-memory consolidation hypothesis (Vertes, 2004). However, neither manual nor pharmacological REM sleep suppression impairs memory consolidation in healthy subjects (Genzel et al., 2009; Rasch et al., 2009). Here we confirm our earlier finding that also in MD, REM-suppressing medication does not impair nondeclarative memory consolidation (Dresler et al., 2010a).

Besides REM sleep, sleep stage 2 has been proposed to facilitate nondeclarative memory consolidation (Walker and Stickgold, 2006). GABA A agonists are known to promote S2, partly to the cost of REM sleep and SWS (Lancel and Steiger, 1999). Their effect on memory depends on the time of intake: GABA A agonists taken before the acquisition phase impair learning and result in anterograde memory deficits. In contrast, they produce retrograde memory facilitation if taken after acquisition, possibly due to less interference in the sedated phase (Wistedt, 2004). Our finding that patients receiving GABA A agonists show markedly less consolidation impairments than patients without such medication confirms this effect of retrograde memory facilitation. However, since patients with and without GABA A agonists also significantly differed in their amount of S2, possible effects of S2 cannot be disentangled from more direct medication effects.

4.5. Effects of age

The off-line consolidation of procedural skills is known to be impaired in older compared to younger subjects (Brown et al., 2009). In addition, aging is related to a decrease in sleep quality (Bixler et al., 1984; Bliwise, 1993), which in turn may lead to age-related impairments in sleep-related procedural memory consolidation (Spencer et al., 2007). However, we found a strong negative correlation between nondeclarative memory consolidation and age only for the healthy subjects. The virtual absence of any age effect in MD patients is highly surprising in the light of our former study showing strong synergistic effects of age and depression on off-line memory consolidation (Dresler et al., 2010a). However, in that study the most striking effect was the difference between patients above and below the age of 30 years, the latter showing no memory impairments at all. The reported age effect therefore may be due to a qualitative age threshold rather than a continuous worsening of memory consolidation with age. Indeed a reanalysis of our former data of the 30+ years MD patients group revealed a quite low correlation between age and off-line memory consolidation of r = −0.27, which failed to be significant (p > 0.1). In our present study we assessed only patients above the age of 30 years, thereby possibly missing any effects of an age threshold.

4.6. Conclusion and future directions

In conclusion, our results suggest a double dissociation of memory impairments in MD: Declarative on-line learning and nondeclarative off-line memory consolidation are impaired in MD, while nondeclarative on-line learning and declarative off-line memory consolidation do not show any deficits. This pattern suggests that sleep benefits declarative and nondeclarative memory consolidation in radically different ways.

A major limitation of our study is that the patients received a very diverse medication. This makes it difficult to disentangle the medication effects on baseline performance and overnight changes in the declarative and nondeclarative memory tasks from depression effects per se. Hence, studies with unmedicated patients are needed to address these problems. Another limitation is that we did not assess educational status or intelligence, which might influence memory tasks. In addition to the assessment of these factors, nocturnal hormone secretion should be assessed and manipulated in future studies to validate suggestions about HPA hormone playing a potential role in the consolidation impairments found in MD (Dresler et al., 2010b).

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Contributors

MD, MK and AS designed the study; MD and LG performed the experiments; MD performed the analysis and wrote the first draft of the manuscript; all authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare they have no actual or potential competing financial interest.