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A double dissociation of memory impairments in major depression

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ABSTRACT

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

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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), 17 received SNRIs (Duloxetine, Venlafaxine), 7 received other antidperessants (Mirtazapine, Sulpiride), 3 received lithium and 7 received $GABA_A$ 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 biographical and clinical data see Table 1. Exclusion criteria for all subjects were ambidexterity, assessed by a score between −50 and +50 in the Edinburgh Handedness Inventory (Oldfield, 1971), professional typing skills, musical skills on manually playable instruments like piano, shift work and transmeridian flights in the last 3 months. All subjects gave written informed consent and the study was approved by the local ethics committee.

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 (Plihal 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. Polysmonography 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.

	Patients		Controls	Patients (both tasks)		Controls (both tasks)
n (females)	37 (20)	$p > 0.6$	31 (17)	27 (15)	$p > 0.6$	22 (12)
Age, y	48.3 ± 8.6	$p > 0.8$	48.1 ± 10.4	48.9 ± 9.0	$p > 0.2$	46.1 ± 9.2
Age range, y	30–62		30–65	30–61		30–62
BDI	27.8 ± 9.1		2.3 ± 2.5	28.1 ± 9.7		2.5 ± 2.8
HAMD	24.5 ± 6.0		–	23.7 ± 5.8		–
Episodes	3.1 ± 2.2		–	3.0 ± 2.0		–
Age at onset, y	38.1 ± 11.4		–	38.8 ± 12.0		–
Duration, m	120.1 ± 124.2		–	117.6 ± 125.1		–
Current episode, m	10.1 ± 11.7		–	9.7 ± 9.1		–

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.