Review

Title: Sleep spindles and cognition in depression

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Running title: Sleep spindles and depression

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Acknowledgements: We thank Sandra Dekker for figure design and drafting.

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Abstract

Sleep plays a critical role in orchestrating several cognitive functions. Sleep spindles are particularly at the forefront of studies on the consolidation of cognitive abilities, such as procedural and declarative memory. Despite that major depressive disorder (MDD) has been linked to sleep spindle alterations, their role in MDD pathogenesis and symptomatology (including memory deficits) is still scarcely investigated. Here, we first provide an overview of sleep and sleep spindle alterations in MDD and their potential effects on memory and cognition. Secondly, limited data suggest that sleep spindles deficits in severe MDD might not only lead to cognitive impairments but primarily affect memory consolidation processes during sleep. Furthermore, it seems likely that many sleep spindle related effects are masked by interacting (antidepressant) medication, selection of mixed patient groups with mild symptomatology as well as use of incomprehensive methodology in analyzing sleep. We propose a preliminary model predicting that impairments in sleep spindle related activity during sleep are mainly responsible for memory consolidation deficits in depressed patients, but that medication augmenting sleep spindle activity can enhance and restore sleep-mediated consolidation. Future studies thus need to scrutinize previous findings on sleep spindle effects in MDD.

Keywords: stage 2, spindle density, major depressive disorder, cognitive performance, memory consolidation, procedural memory, declarative memory, non-REM sleep, medication

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1. Depression and Sleep

Major depressive disorder (MDD) affects >300 million people worldwide. It has been labelled as the leading cause of disability and as a major contributor to the overall global burden of disease (World Health Organization, 2017). Lifetime prevalence of a major depressive episode has been estimated at 14.6% for high-income countries (Bromet et al., 2011). Unipolar MDD is typically characterized by a general feeling of sadness, tiredness and poor concentration as well as loss of interest or pleasure, but also by cognitive impairments (Golinkoff and Sweeney, 1989), whereas bipolar MDD also includes periods of mania. Unipolar and bipolar MDD have been suggested to exist on a dimensional spectrum of depression, instead of being categorically distinct disorders (Cassano et al., 2004).

Sleep has been extensively studied in MDD (Mendlewicz and Kerkhofs, 1991, Peterson and Benca, 2008). MDD and sleep disturbances seem to be intrinsically related (Buysse et al., 2008). Subjective sleep complaints like insomnia and hypersomnia are among the most frequently reported symptoms (Staner, 2010). Although it has become apparent that sleep disturbances are an integral part of MDD, their causal relationship remains illusive.

Illustrative of the importance of sleep in depression, one can see that changes in the sleep-wake cycle (Hickie et al., 2013) and sleep deprivation (Wu and Bunney, 1990) show an antidepressant effect in many patients, while even brief bouts of sleep can abolish this effect (Hemmeter et al., 1998). Objective changes observed in the general sleep architecture in MDD include abnormalities in latency, continuity, duration and fragmentation of sleep (Thase, 2006). Especially robust findings are increased density of rapid eye-movements (REM) during sleep, duration and decreased latency to REM sleep onsets (Luik et al., 2015; Nutt et al., 2008) with lower amounts of slow-wave sleep (SWS) and stage 2 sleep (Thase, 2006, Tsuno et al., 2005, Benca et al., 1997, but see e.g. Khan and Todd (1990) for different results in adolescents). Most current studies focus mainly on REM sleep alterations and little recent research is devoted to investigate on specific alterations in non-REM and how they contribute to the sleep-architectural changes.

2. Sleep, sleep spindles and cognitive performance

The function of sleep has been associated with a vast number of broad cognitive domains including general learning, emotional processing, memory and synaptic plasticity. Since the first targeted investigations by Jenkins and Dallenbach (1924), ample evidence has amounted to reveal specific beneficial effects of sleep on the consolidation of memory (for review see Rasch and Born, 2013). Sleep spindles are a hallmark in electrophysiological activity defining non-REM and stage 2 sleep. They consist of short (0.5–3 s) waxing and waning bursts of oscillatory activity (12–15 Hz) that consistently appear throughout non-REM sleep. The underlying mechanisms for sleep spindle generation are well understood. Sleep spindles originate from GABAergic, synchronized pacemakers in the thalamic reticular nucleus. From there they propagate through glutamatergic thalamocortical projections to widespread cortical areas. Here, they are thought to entrain and activate an intracortical circuitry to maintain the potentiation of inputs conveyed to deeper cortical layers (for a review on sleep spindles see Lüthi, 2014). Lighter stage 2 non-REM sleep is where sleep spindles can be best observed, but automatic detection algorithms can detect them nearly as frequent during deeper slow-wave sleep (SWS) periods or their intrusion into periods usually

scored as REM sleep (Silber et al., 2007). Also slower sleep spindle activity (<12 Hz) has been identified and mainly observed in frontal areas. The differential role of frontal slow sleep spindles in respect to centroparietal fast sleep spindles and potentially altered neural mechanisms still remain the focus of controversial research (Timofeev and Bazhenov, 2005, Timofeev and Chauvette, 2013).

In recent years, sleep spindles have transpired to play an active role in several cognitive functions. Diverse investigations associate sleep spindles with intelligence (Nader and Smith, 2001; Bódizs et al., 2005; Fogel and Smith, 2011; Ujma et al., 2014; Ujma et al., 2015), cortical development (Khazipov et al., 2004), regulation of arousal (Destexhe and Sejnowski, 2002) and in particular learning or better memory performances in a variety of declarative and procedural tasks (e.g. Gais et al., 2002; Morin et al., 2008; Holz et al., 2012; Schabus et al., 2004; Fogel et al., 2007; Tamminen et al., 2010; Barakat et al., 2011, but see Lustenberger et al., 2012). New mechanistic and causal investigations reveal a fine-tuned, thalamic induced hippocampo-neocortical dialog mediated by sleep spindle activity that involves the coordinated hippocampal reactivation of memory representations during the up states of slow waves (Ngo et al., 2013, Buzsáki, 2015; Staresina et al., 2015; Maingret et al., 2016; Greenberg et al., 2016; Latchoumane et al., 2017; Khodagholy et al., 2017; Wilber et al., 2017). On the systems levels, neocortical medial temporal lobe (including hippocampus) activation and connectivity are observed during sleep spindle activity (Schabus et al. 2007; Andrade et al., 2011). During sleep slow waves, the occurrence and timing of sleep spindles appears most vital for the coordination hippocampal and cortical activity to reactivate hippocampal memory representations for their integration into cortical networks (Staresina et al., 2015, Buzsáki, 2015, Ayoub et al., 2012, Takeuchi et al. 2016) as they induce synaptic plasticity (Werk et al., 2005) in cortical dendrites (Seibt et al. 2017) that likely underlie memory processing and cognitive development. These processes surrounding sleep spindle activity thus also mark ‘offline’ periods of deeper sleep in which the brain suppresses processing of environmental cues and has increased thresholds for arousal (Dang-Vu et al., 2011). Furthermore, such offline processes seem dominated by an underlying the infra-slow rhythm that is most evident during non-REM in minute-to-minute changes of sleep spindle activity (Lecci et al. 2017).

Disturbances of healthy sleep patterns, as seen also in MDD, can lead to impairments in the consolidation of memories (Djonlagic et al., 2012; Nissen et al., 2006), e.g. motor memory impairments after stage 2 sleep deprivation (Smith and MacNeill, 1994). Such and similar findings suggested an active contribution of sleep to memory function (Ellenbogen et al., 2006). Stage 2 sleep takes the largest proportion of (non-REM) sleep, increasing with age (Carskadon and Dement, 2005). As important mechanisms for active memory consolidation prevail in non-REM sleep, we must thus ask if non-REM impairments found in MDD patients bare significance to the capacity to consolidate memories. Despite these well-known MDD-related disruptions of sleep as well as of memory, the evidence is surprisingly limited when it comes to memory processing mechanisms during non-REM sleep and their contribution to memory impairments within this disorder. Some investigations on the development of MDD in relation to particularly slow-wave activity were undertaken hinting to increased SWA in depressed adolescents (Tesler et al., 2013, 2016). Similarly detailed investigations for this disorder on the role of sleep spindles are still lacking. This seems to be

particularly pressing since sleep spindle activity play an intricate role in slow waves (Contreras and Steriade, 1995, 1996, Mölle et al. 2002) and even predict their properties and occurrence (Menicucci et al., 2015). For example, slow waves are influenced by specialized neurons in the brainstem that regulate REM onset which also convey cholinergic projections to suppress sleep spindle generation in the thalamic reticular nucleus (McCarley and Massaquoi, 1992).

Part of the lack in research for sleep spindles relative in relation to slow waves might be attributed to the slow progress of methods to analyze and manipulate and discern them. Causal evidence of sleep spindle-related mechanisms stem mainly from animal investigations and basic memory tasks. Since most human findings are of correlational nature or lack a suitable animal model the role of sleep spindles in complex neurological and psychiatric human disorders remains mainly unclear. On a positive note, there is recent progress on the development of clinical methods to manipulate sleep spindles: for example, sleep spindle occurrence was boosted by amplitude modulation of white noise in the sleep spindle rhythm (Antony and Paller, 2017) and by a more selective enhancement, through non-invasive electrical brain stimulation that also improved procedural memory consolidation (Lustenberger et al., 2016). In sum, there is abundant evidence in support for a functional relationship between sleep spindles and memory consolidation; recent advances in methodology allow for a causal investigation of sleep spindles in humans for a putative link in neurological and psychiatric disorders.

3. Sleep spindles and psychiatric disorders

Although the ultimate significance of sleep spindles in general cognitive functioning remains unclear, their role in memory consolidation during sleep has lately attracted more interest for their role in manifold brain pathologies or use as a biomarker for brain disorders. As an understanding of sleep spindles thus promises insights into a broad spectrum of cognitive functions, they recently became well-characterized in large samples to use them as biogenetic markers of neuropsychiatric disease (Purcell et al., 2017). For example, sleep spindles were suggested to be a biomarker to predict several neurological and psychiatric disorders with pathological differences in cognitive decline of Parkinson's patients (Latreille et al., 2015) as well as dementia and Alzheimer's disease (Reynolds et al., 1985, Rauchs et al., 2008, Westerberg et al., 2012). In particular, several studies were published on the association of sleep spindles and psychiatric disorders such as schizophrenia (Castelnovo et al., 2016). There is evidence on the impairment of sleep spindles in schizophrenic patients that are in line with their altered brain pathophysiology (Ferrarelli et al., 2007). Both, a reduction of sleep spindle number and amplitude have further been reported in schizophrenics in which the underlying impaired thalamocortical communication and the link to concomitant memory impairments are well established (Ferrarelli et al., 2007, Ferrarelli and Tononi, 2017, Sasidharan et al., 2017, Schilling et al., 2017) and are in line with abnormal perceptions typical for schizophrenia (Vukadinovic, 2011). These findings in schizophrenia patients suggest a vital role of sleep spindles in memory consolidation processes impaired in such diseases. Indeed, it has repeatedly been shown that patients with schizophrenia show less sleep spindles and that their reductions are correlated with their deficits in sleep-dependent procedural memory consolidation (Manoach et al., 2010, Wamsley et al., 2012).

Interestingly, not only schizophrenia but also MDD entails changes in thalamic activation (Kühn and Gallinat, 2011) and a decrease of metabolism in thalamic regions (Holthoff et al., 2004). Such similarities might suggest that alterations in the widespread thalamic system, that is involved in sleep spindle generation, may also elucidate impaired mechanisms underlying MDD. Of note, the comorbidity between MDD and schizophrenia might suggest the interrelatedness on more fundamental mechanisms of both disorders and in their development. But such transitions from MDD into more severely regarded schizophrenia cases remain little investigated (Buckley et al., 2009). The contrast of many investigations of sleep spindles in schizophrenia but little in MDD is thus surprising, especially since MDD is more prevalent among the population (World Health Organization, 2017).

Several cognitive impairments accompany MDD which include attention deficits, response inhibition, executive functioning and information processing (Gotlib and Joormann, 2010; Roiser and Sahakian, 2013). But they also entail memory impairments (Burt et al., 1995). How these impairments might affect learning in general is still poorly understood. Some memory deficits were suggested to develop due to primary cognitive impairments prohibiting memory acquisition in the first place, that is, if primarily attention deficits prohibit proper encoding or if processes of post-acquisition consolidation hinder acquired memory to be consolidated (Marazziti et al., 2010). When neglecting long-term memory effects, there is good evidence that depressed patients specifically seem mainly impaired in acquisition of declarative, rather than non-declarative knowledge (Austin et al., 2001). ‘Offline’ long-term consolidation over the nighttime shows another pattern: non-declarative, procedural (e.g. finger sequence-tapping) memory consolidation has been impaired in acute MDD in an age group (>30 years) that is expected to be more sensitive to sleep disruptions, with ‘online’ learning unaffected (Dresler et al., 2010; O’Connor et al., 2005). In contrast, declarative learning (word-pair associates) was shown, as general detriment of this memory system in depressed patients suggest, to be impaired in MDD, but the overnight offline consolidation was not (Dresler et al., 2011). This demonstrates that cognitive impairments in MDD, especially in memory, cannot simply be attributed to encoding deficiencies but need to take cognitive process into account that happen offline, and thus probably primarily during sleep.

The findings of impaired memory consolidation in MDD align well with the specific contributions of hippocampal function to declarative memory consolidation during non-rapid eye movement (non-REM) sleep, but less well with procedural task-specific memories which are thought to be more influenced by REM sleep alterations (Marshall and Born, 2007). Interestingly however, procedural memory consolidation also can be independent of specific reductions of REM or deep SWS and seems more likely dependent on processes in lighter stage 2 sleep with consolidation impairments only associated with sleep spindles typical for this sleep stage (Genzel et al., 2009, Dresler et al., 2010). The reduction in hippocampal volume moderated by depression onset (Schmaal et al., 2016) and associated deficits in visual and verbal memory performance (Hickie et al., 2005) align well with the reduction in hippocampal-encoding capabilities in declarative but not procedural tasks. Nevertheless, the exact nature and contribution of MDD-related non-REM and REM sleep impairments might play in consolidation deficits, however, is still under debate (Ackermann and Rasch, 2014).

Interestingly recent evidence suggests MDD seems to also have specific impairments in episodic, rather than semantic aspects of long-term memories (Söderlund et al., 2014) which specifically rely on hippocampal function for their effective consolidation during sleep (Inostroza and Born 2013, Wang et al., 2017a) and are also positively associated with sleep spindles or spindle-band fluctuations (Weber et al., 2014, Wang et al. 2017b, Lecci et al., 2017). It thus seems tempting to speculate that hippocampal functioning during non-REM sleep also plays a major role in the consolidation of procedural or other sequence-related memories. Due to the integral part that sleep spindles play in offline memory processing, it seems likely that their impairment would also contribute to several cognitive deficits and memory deficiencies observed in MDD patients.

4. Sleep spindles and depression

There is a limited amount of studies on the topic of sleep spindles and depression (see Table I for a summary). Early sleep studies indicated decreases in sleep spindle activity in MDD patients (de Maertelaer et al., 1987, Goetz et al., 1983) confirmed also in high-risk groups (Lopez et al., 2010; Steiger et al., 2014) and those with manic-depression (Diaz-Guerrero et al., 1946). Moreover, a consistent lower amount of stage 2 NREM sleep was reported in MDD patients (Lauer et al., 1991; Mendlewicz and Kerkhofs, 1991) hinting to lower amount of sleep spindles as well. In accordance with these findings, sleep architecture differences in children at high-risk for developing MDD were found to have a reduction in low-frequency sleep spindles and slow sleep spindles in frontal and central regions, as compared to low-risk children (Sesso et al., 2017). In contrast, the study of Nishida et al. (2014) found topographical differences in both fast and slow spindles in MDD patients as compared to healthy controls with prefrontally increased slow sleep spindle amplitudes and globally stronger fast sleep spindle activity.

Several limitations are present in the few reported studies on MDD and sleep spindles. One major limitation is that the patients are often medicated with drugs that likely influence sleep architecture and sleep spindles (Wilson and Argyropoulos, 2005, Carskadon and Dement, 2005). Indeed, effects of antidepressants on REM sleep architecture have long and consistently been reported (Chen, 1979). Selective serotonin reuptake inhibitors (SSRIs) alter REM sleep but have not demonstrated any effect on non-REM aspects like spindles or slow wave activity (Rasch et al., 2009; Nicholson and Pascoe, 1988; Saletu et al., 1991; Tesler et al., 2013). In contrast, serotonin-norepinephrine-reuptake inhibitors (SNRIs, and most tricyclic antidepressants) increase (fast, >13 Hz) sleep spindle amounts and densities in non-REM as well as stage 2 sleep proportion (Rasch et al., 2009). In addition, other types of drugs prescribed to MDD patients for sleep problems and other symptoms of MDD seem to modulate sleep spindle activity as well (with some exceptions; Mocaër et al., 1987, Goetz et al., 1983). In particular GABA_A receptor modulating drugs, which are often prescribed to MDD patients, have been found to influence sleep architecture, sleep spindle activity and their topography as well (e.g. Aeschbach et al., 1994; Jobert et al., 1992a, Jobert et al., 1992b, Lancel, 1999, Feinberg et al., 2000). For example, sleep spindles are affected by benzodiazepines often increasing in sleep spindle duration and amplitude in frontal and central-posterior regions (Jobert et al., 1992b, Plante et al., 2015). In addition, often prescribed sleep hypnotics in MDD, such as zolpidem, zopiclone and benzodiazepines like

triazolam, lorazepam and even flurazepam, can increase sleep spindle activity and stage 2 sleep while decrease slow-wave activity and SWS (Lancel, 1999). Such pharmacological sleep spindle augmentations have been shown to positively impact memory hippocampus-dependent memory consolidation in a healthy sample (Mednick et al. 2013). There is also some indications that such drugs can rescue sleep-mediated procedural memory consolidation impairments in schizophrenic patients with stage 2 sleep spindle deficits (Wamsley et al., 2013), although this awaits testing in larger, more consistent patients groups. In line with this finding, Dresler and colleagues (2011) found MDD patients taking GABA_A agonists, expected to also enhance sleep spindle activity to have a less impaired procedural memory consolidation. Interestingly, there are also some hints that pharmacological suppression of general sleep spindle activity and parallel increase of slow-wave activity (via tiagabine) can impair procedural memory consolidation (Feld et al., 2013). Thus, the question arises, if some of the observed alterations in sleep physiology in MDD and potential memory consolidation effects are skewed by acute patient medication. In one prominent study, there was no difference of altered sleep spindle activity in depressed patients compared to healthy controls (Ferrarelli et al., 2007). Only one patient in this study took benzodiazepines, and no GABA_A receptor modulating drugs were taken by the other patients. Though this indicates little influence on sleep spindle activity in this study it is important to note that most of the patients in this study only had a mild or moderate diagnosis of depression and thus required only mild drug use to treat their symptoms. This study thus seems incomparable to previous reports of highly depressive patients with more severe symptoms. Therefore, interpreting findings of altered or unaltered sleep spindle alterations in medicated MDD patients still awaits future studies in patients with severe MDD, and under the consideration to exclude medication or at least the drugs that might influence sleep spindles.

Further investigations into the topographic distribution of sleep spindles came from Plante and colleagues (2013) using high-density EEG in female MDD patients of moderate severity and tested under unmedicated conditions. They reported increased frontal and parietal sleep spindle density and integrated sleep spindle activity (i.e. the absolute sleep spindle amplitudes divided by non-REM sleep duration). This seems in contrast to the decreased sleep spindle activity reported in earlier studies (de Maertelaer et al., 1987, Goetz et al., 1983) and no difference in such activity in the mixed gender group with low severity (Ferrarelli et al., 2007). Indeed, healthy women have been shown to display more sleep spindle activity than men (Huupponen et al., 2002), suggesting differential regulation by gender in sleep spindles and possibly differential effects in MDD as well. Furthermore, as MDD symptoms are also far more prevalent in females (Albert, 2015), controlling for gender seems even more critical in studies on sleep spindles and MDD.

Aging also goes along with a progressive decline of sleep spindle activity following a distinct topographical decline pattern (Nicolas et al., 2001; Martin et al., 2013; Mander et al., 2017). Age differences are thus also important for the evaluation of sleep spindle-related EEG sleep patterns in MDD patients (Lauer et al., 1991). These age-related changes in sleep spindles have recently been linked to gray matter changes in, among others, the hippocampus, which may underlie age-related deficits in overnight procedural memory consolidation (Fogel et al., 2017). One early study reports the effect of aging on sleep EEG patterns in MDD patients, but did not look into progression of sleep spindle-related activity (Ulrich, Shaw and

Kupfer, 1980). A meta study that matches potential development and decline of sleep spindle activity to the observed susceptibility and prevalence of MDD at certain ages throughout life (Jorm, 2000) is still missing. However such limitations also exist for most altered sleep activity and age-dependent alterations have yet to be matched accurately to sleep disease-specific onset patterns (Tesler et al., 2013). Thus the influence or role of age in neurological disorders, including MDD, are difficult to disentangle from normal or pathological changes in sleep architecture.

5. Sleep spindles, depression and memory

To the best of our knowledge, only one study tapped into the direct relation between sleep spindles and memory consolidation in MDD patients. Nishida and colleagues (2016) explored several sleep characteristics potentially related to impaired sleep-dependent procedural memory in MDD patients. Though Nishida and colleagues (2016) found some impairments in procedural memory in MDD patients associated with slow sleep spindle activity, they could not demonstrate a direct difference in the overnight improvements in procedural memory between patients and controls. This is in contrast to reports by Dresler and colleagues (2010; 2011) that show a clear lack in overnight procedural learning improvements in medicated patients as compared to overnight gains in the healthy control group. However, nearly all the patients in the study of Nishida and colleagues (2016) were expected to have augmented sleep spindle activity by the medication that was prescribed to typically treat sleep problems (zolpidem treatment 9 out of 11 patients, see Feinberg et al., 2000). This medication could have improved the procedural memory consolidation in most of their patients. Indeed boosts in sleep spindle activity by sleeping drugs like zolpidem (with minor direct antidepressant effects), have been linked to declarative but not procedural memory consolidation (e.g. Morgan et al., 2010, Mednick et al., 2013, Niknazar et al., 2015). Also increases in sleep spindle activity by other drugs that are very effective antidepressants like SNRIs boost procedural memory consolidation (Rasch et al. 2009). However decreases in sleep spindles with drugs like tiagabine, that are often co-prescribed in MDD patients, impaired procedural memory consolidation (Feld et al., 2013). This might be taken to speculate that medication in the depressed group of Dresler and colleagues (2010; 2012) was not sufficient to rescue the impairment in sleep spindle associated procedural memory consolidation (indeed unpublished data suggest sleep spindle activity in some of the MDD patients might to be not restored to healthy control levels). Furthermore, detailed investigation in rats using pharmacological suppression of REM sleep and the sleep spindle activity in transition to it, revealed impairments in hippocampus-dependent consolidation processes (Watts et al., 2012). This study hints towards reductions of sleep spindle activity that is close to REM sleep as a contributor in the deficits for consolidating hippocampal-dependent memories and ensuing learning deficits. It remains open if sleep spindles alone are the main determination of procedural memory consolidation or if it is also co-determined by an interactive effects of slow waves, sleep architecture changes, patients group dynamics (e.g. age) as well as medication.

6. Conclusion and model

In conclusion, the limited amount of studies on the relationship between sleep spindles and MDD (see Table I) show inconsistent results that might be explained by at least one or more of these substantial limitations: 1) insufficient replication among newer and earlier studies in unmedicated patients with high depression severity (like de Maertelaer et al., 1987, Goetz et al., 1983), 2) methodological hurdles and differences in detecting and assessing sleep spindles and related EEG activity, 3) no link to the offline memory processing impairments predicted by sleep spindle alterations. It should further be noted that discrepancies in the literature could possibly also be explained by a large amount of multiple comparisons as well as lack of control for gender, age and medication as well as socio-economic or educational differences in patients. Furthermore, the heterogeneous nature of MDD is of further concern; with the current diagnostics tools available, patients with opposite symptomatology are grouped under the same umbrella term of depression (Goldberg, 2011). This multidimensionality of MDD can most probably explain the current lack of a one-size-fits-all treatment as well as such discrepancies in the literature on sleep. To conclude, the scarceness of the literature on sleep spindles and MDD and in particular their relation to memory consolidation remains inconclusive.

Founded on these albeit limited notions, we propose a preliminary model to describe the relationship between sleep spindles, depression and memory, summarizing the current findings. Our model (Figure 1) posits that thalamo-cortical and hippocampal changes in severe cases of MDD lead to impaired intrinsic sleep spindle generation. These impairments are reflected by a general decrease in sleep stage 2 duration, lower sleep spindle activity resulting in lower numbers and density of sleep spindles and co-occurring less often together with slow waves. These sleep spindle impairments are also associated with deficits in sleep-dependent memory consolidation, specifically in procedural tasks. Consolidation of declarative memory over sleep could be less impaired perhaps due to a stronger association with slow waves than sleep spindle activity alone. However, at least part of the consolidation of memories dependent on hippocampal function is predicted to be impaired. Importantly, these impairments become worse with increased depression severity. In addition, several types of antidepressants or sleep medication increase sleep spindle activity thereby restoring some sleep detriments in patients and potentially even boosting sleep-related memory consolidation effects. Crucially, medication given to MDD patients for their symptoms that do not increase sleep spindle activity to normal levels are also not expected to restore deficits in (procedural) memory consolidation during sleep. Thus, when interpreting our model, one should not only consider the severity of the depression but also the moderating effect of medication on mood vs. sleep spindle activity as well as group dynamics in age and gender.

7. Outlook and future studies

Given the role that hampered sleep spindle activity plays in other psychiatric disorders, as well as their function in sleep-dependent memory consolidation, the elusive specificity of sleep spindles in MDD seems a worthy and promising line of research. The few studies with many limitations outlined above puts a strong emphasis on putting forward new studies to elucidate the role of sleep spindles in MDD. A possible explanation for the limited amount of earlier reports on this relationship could manifest itself in the complex and dynamic aspects of detecting sleep spindle characteristics. Conceivably, superficial sleep

spindle characteristics, such as sleep spindle count or topography might still be seemingly intact in certain patient groups, while more fine-tuned coupling mechanisms with sleep spindle activity might indeed be impaired, such as sleep spindle source, location, trajectory and interaction with other non-REM activity like slow waves or K-complexes. In addition, only recent advances make detection and examination of such complex and intricate mechanisms practically feasible for a broader sleep research field, e.g. the systematic, replicable and comprehensive detection and classification of sleep spindles together with slow waves or their co-occurrences within any of the sleep stages using automatized toolboxes (e.g. <http://www.spisop.org>).

As MDD is a complicated cognitive disorder it has likely a complex neurological and psychological causes that could be hidden in superficial investigations. Future studies should thus elucidate all those aspects by exploring the comprehensive pattern of sleep in depressed patients by highlighting the distortions of the intricate relationship of sleep spindles in relation to other activity during sleep as well as their dynamics over the course of sleep. Special attention should be given to the intricate relation of sleep spindles and hippocampal reactivations during cortical slow waves that have been demonstrated to play a central role in the active consolidation of memory, in particular the exact timing or phase-locking of sleep spindles and slow waves (Niknazar et al., 2015, Maingret et al., 2016; Greenberg et al., 2016; Latchoumane et al., 2017). Impairments in sleep spindles or other activity phase-locking to slow waves may be the next best guess to explain the patients' impairment in acquiring declarative and consolidation of procedural memory (Dresler et al., 2011). Such impairments in fine-tuned sleep activity go along with impairments in memory consolidation and may be the root in developing these MDD related impairments. Thus, a better understanding of the role of sleep spindles in MDD could give invaluable insights on MDD progression or reveal new diagnostic approaches and pharmacological and nonpharmacological therapeutic targets. Such developments have been tentatively suggested and attempted in treatment for schizophrenia (Wamsley et al., 2013). Furthermore, non-invasive brain stimulation during stage 2 NREM sleep was able to enhance sleep related declarative memory consolidation in schizophrenic patients, although sleep spindle parameters were not measured (Göder et al., 2013). In due time, such new attempts should be aimed for treating MDD and its symptoms as well.

Future studies should specifically focus on investigating the distinct relations of sleep spindle characteristics to each of the MDD symptoms. The most appropriate study to start further investigations should include tests on memory impairments and the relations to sleep, as there is ample evidence for such a relationship. However also other cognitive tasks should explore the depth and specificity of such cognitive impairments and their development over the course of MDD progression and treatment. Studies should ideally include periods where the patients are unmedicated or treated with drugs that are known to have little impact on sleep measures. Such samples might also be helpful to get a clearer picture on the role of sleep spindles in native depressive symptomatology prior to intervention and how medication might change sleep and symptoms. Sleep studies in MDD should shift their focus away from isolated investigations on either sleep spindle or slow-wave activity alone and should assess the fine-tuned coupling of sleep spindles with other sleep activity, as this leaves the best

chances to finding proxies of the observed decline in sleep functionality and cognitive abilities.

8. Summary

Despite the importance that memory and sleep has in our lives, and that the symptoms in depression reflect impairments in both, previous studies are not extensive enough to elucidate a detailed relationship and mutual influences in MDD patients. Specifically the role that alterations in sleep-spindle related activity play in the cognitive functioning and development of MDD and remain mostly unexplored. Future studies can empirically test our proposed preliminary model that is based on mixed results in limited prior studies on the topic. Our model links sleep spindles deficits to memory consolidation impairments prevalent in severe MDD patients who are not treated with medication to restore sleep spindle activity to healthy levels. This model should be tested carefully considering potentially confounding patient group dynamics, true effects of medication on sleep, and under utilization of comprehensive sleep analyses that are unbiased towards single sleep phenomena. We hope that future studies can reach consensus on sleep's role in MDD and test possible causal links to MDD progression within sleep activity to open the door for novel MDD therapies and diagnostics.

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Table I: List of publication on sleep spindles and depressive disorders.

Publication	Population [mean age ± SD yrs.]	Severity of depression	Sleep spindle findings	Other sleep EEG findings	Medication
Goetz et al., 1983	Endogenous depressed: n = 20, 6-12 yrs, gender not reported Nonendogen ous depressed: = 16, 6-12 yrs, gender not reported Controls: n = 11, 6-12 yrs, gender not reported	Severity not reported. Clinical diagnosis of MDD	Endogenous vs. control: nominally lower number and density of sleep spindles in stage 2 Nonendogeno us vs. control: nominally lower number and density of sleep spindles in stage 2	Not reported	Unmedicated
Borbély et al., 1984	Depressed: n = 9, 3 male, 31.6 ± 7.5 yrs Control: n = 9, 3 male, 31.7 ± 7.5 yrs,	Depressed: severe (minimum score of 30 on HAMD- 17) Controls: no symptoms	Depressed vs. Control: Nominal increase in sleep spindle frequency (12- 15 hz) power in patients	Depressed vs. Control: Shortened total sleep time, shorter SWS (stage 3 and 4)	Unmedicated (>2 weeks)

de Maertelaer et al., 1987	Unipolar depression: n = 8, 8 male, 42 ± 12 yrs	Unipolar depressed: very severe (37 ± 12 on HAMD-24)	Depressed vs. controls: less stage 2 sleep, decreased sleep spindle numbers and density in stage 2 sleep	Depressed vs. controls: sleep onset latency, longer REM duration, shorter REM latencies, and higher REM density	Unmedicated (>2 weeks)
	Bipolar depression: n = 11, 8 male, 41 ± 14 yrs	Bipolar depressed: very severe (33 ± 8 on HAMD-24)			
	Control: n = 9, 9 male, 35 ± 16 yrs	Control: no symptoms			

Lauer et al., 1991	Depressed: n = 74, 24 male, 39 ± 12.4 yrs	Depressed: severe (41.9% ± 10.3% of max. IMPS)	Depressed vs. controls: less stage 2 sleep; sleep spindles not assessed	Depressed vs. controls: shorter REM latency, prolonged duration of first REM period, higher REM density	Unmedicated (>1 weeks)
	Control: n = 51, 26 males, 38.3 ± 14.3 yrs	Controls: evaluated on absence of psychiatric disorders			

Ferrarelli et al., 2007	History of depression: n = 15, 8 male, 36.5 ± 11.5 yrs Control: n = 17, 12 male, 37 ± 10.1 yrs	Depressed: mild (8.7 ± 6.4 on HAMD-17) Controls: no symptoms (0.6 ± 1.1 on HAMD-17)	Depressed vs. control: no differences	Depressed vs. Control: increased sleep onset latency	Depressed: benzodiazepines (n = 1), antidepressants (n = 5), mood stabilizer (n = 1), all no antipsychotic medications Controls: unmedicated
Lopez et al., 2010	Depressed: n = 21, 11 male, 11.8 ± 2.6 yrs High-risk MDD: n = 21, 11 male, 12.8 ± 2.8 yrs Control: n = 21, 11 male, 12.2 ± 2.4 yrs	Depressed: (58.1 ± 5.8 on CDRS-R) High-risk for depression: no symptoms, (20.8 ± 1.7 on CDRS-R) Controls: no symptoms, (18.6 ± 1.8 on CDRS-R)	Depressed and High-risk vs. Control: decreased sleep spindle activity in stage 2 sleep Depressed vs. Control: Lower spindle density, more pronounced in late non-REM sleep phases	High-risk vs. Depressed and Control: higher REM density than, but less arousal and movement.	Unmedicated (>4 weeks)

Plante et al., 2013	Depressed: n = 30, 11 male, 26 ± 9.1 yrs Controls: n = 30, 11 male, 25.4 ± 8.5 yrs	Depressed: moderate, (18.6 ± 2.7 on HAMD- 17) Controls: no symptoms	Depressed vs. Control: higher frontal and parietal sleep spindle density and integrated sleep spindle activity*	Depressed vs. Control: no differences in sleep architectur e.	Unmedicated
Nishida et al. 2014	Depressed: n = 13, 9 male, 32.1 ± 10.7 yrs Control: n = 19, 17 male, 33.9 ± 6.0 yrs	Depressed: mild (11.8 ± 1.3 on HAMD- 17) Controls: no symptoms, (0.3 ± 0.1 on HAMD- 17)	Depressed vs. Control: slow sleep spindle amplitude higher prefrontally, fast sleep spindle oscillation frequency higher, increased stage 2 sleep	Depressed vs. controls: longer total sleep time, more stage 2 and stage 1 sleep. shorter SWS (and stage 4 sleep).	Depressed patients: benzodiazepine s (n = 9), SSRI (n = 3), SNRI (n = 4), trazodone (n = 3), mood stabilizer (n = 4), second- generation antipsychotic medications (n = 5) Controls: Unmedicated

Nishida et al., 2016	Depressed n = 11, 7 male, 30.0 ± 2.89 yrs	Depressed: mild (12.3 ± 1.5 on HAMD)	Depressed vs. Control: Slow frequency sleep spindle activity difference	Depressed vs. Control: more stage 2 sleep, shorter SWS (and stage 4 sleep)	Depressed: zolpidem (n = 9), SSRI (n = 3), SNRI (n = 3), trazodone (n = 3), mood stabilizer (n = 4), second- generation antipsychotic medications (n = 5)
	Controls: n = 17, 15 male, 33.76 ± 1.38 yrs	Controls: no symptoms (0.29 ± 0.14 on HAMD)			Controls: Unmedicated
Sesso et al., 2017	High-risk, healthy, but mother has MDD: n = 20, 11 male, 9.35 ± 4.03 yrs.	-	High-risk vs. Control: lower sleep spindle numbers and duration, amplitude and integrated sleep spindle activity*, lower slow sleep spindle incidence in early night	High-risk vs. Control: no sleep architectur al differences . lower slow-wave amplitude during the last hour of SWS.	Unmedicated
	Control: n = 11, 4 male, 9.82 ± 3.52 yrs.				

*integrated sleep spindle activity, calculated by integrating the absolute amplitude values of each sleep spindle divided by N2 sleep duration.

HAMD: Hamilton Rating Scale for Depression (Hamilton, 1960), reported are both the 24- and 17-point scale versions.

PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987)

IMPS: Inpatient Multidimensional Psychiatric Scale (Hiller et al., 1986)

CDRS-R: Children's Depression Rating Scale – Revised (Poznanski and Mokros, 1996, scale above 40 > indicates depression, < 28 indicates no depressive symptoms)

Figure legends:

Figure 1: Simplified model of major depressive disorder (MDD) and the role of medication on sleep spindle activity during sleep and their effect on memory consolidation. Severely depressed patients have lower sleep spindle density during non-REM sleep as compared to healthy controls. The lower sleep spindle density in depressed patients predicts impaired memory consolidation during sleep. Some types of medication that improve mood or sleep impairments in MDD patients also increase sleep spindle activity during sleep. The increased sleep spindle activity indicates enhance memory consolidation in healthy people and rescue memory impairments in depressed patients. Higher dosed medication, above the effective level, enhances memory consolidation also in depressive patients above normal levels by increasing sleep spindle activity to safe limits. Some medication treat mood but have little influence on sleep spindle and associated activity (like slow waves), thus, such medication does not rescue the impaired memory consolidation in depressive patients.

Figures

Figure 1: