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SLEEP DISORDERS (P GEHRMAN, SECTION EDITOR)

An Integrated Model of Slow-Wave Activity and Neuroplasticity Impairments in Major Depressive Disorder

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Abstract

Purpose of Review In this review, we aim to integrate the most recent research highlighting alterations in sleep slow-wave activity (SWA), and impairments in neuroplasticity in major depressive disorder (MDD) into a novel model of disorder maintenance.

Recent Findings Sleep homeostasis has been shown to be impaired in MDD, with a subset of individuals also demonstrating impaired SWA. SWA is considered a marker of the homeostatic regulation of sleep, and is implicated in the downscaling of synaptic strength in the context of maintaining homeostatic plasticity. Individuals with MDD have been shown to exhibit impairments in both neural plasticity such as loss of dendritic branching, and synaptic plasticity such as decreased long-term potentiation-dependent learning and memory.

Summary Alterations in the homeostatic regulation of sleep, SWA, and synaptic plasticity in MDD suggest an underlying impairment in the modulation of synaptic strength. One candidate mechanism for this impairment is AMPA receptor trafficking.

Keywords Slow-wave activity · Major depressive disorder · Synaptic downscaling · Synaptic strength · Sleep · Mood

Introduction

Psychiatric disorders are frequently characterized by sleep disturbance including, but not limited to, difficulties falling asleep and difficulties maintaining sleep [1]. Changes in sleep have been studied extensively in major depressive disorder (MDD) because individuals with MDD frequently report difficulties with sleep that can manifest as difficulty initiating and maintaining sleep [2], but that often co-occur with daytime sleepiness and loss of energy. Numerous studies have confirmed that MDD is associated with objective changes in sleep EEG when compared to healthy controls. These changes are evident using both visually scored EEG, and methods of analysis that examine the underlying frequency structure of EEG, referred to as quantitative EEG analysis. For example, visually scored EEG changes in MDD include longer time to fall asleep (sleep onset latency), increased wake time after sleep onset, and associated increases in lighter stages of sleep including stage 1 sleep [3], changes in rapid eye-movement (REM) sleep including increased percentage of REM sleep, increased REM density (an increase in the number of actual rapid eye movements), and decreased REM latency (the time it takes to first enter REM sleep), and reduced slow-wave sleep (SWS) [4, 5]. With regard to quantitative EEG, at baseline, those with MDD show increased fast frequency EEG during sleep, including increased alpha and beta power in addition to lower amplitude delta power, or slow-wave activity (SWA), than healthy individuals, especially in the first non-REM (NREM) period [6]. It is important to note, however, that later studies investigating the regulation of SWA following a homeostatic sleep challenge such as sleep deprivation, demonstrated significant sex effects in those with MDD. For example, males with MDD were shown to have lower amplitude SWA and an altered time course across the night, while females with MDD were shown to exhibit similar [7] or higher [8] SWA amplitude in comparison to their healthy counterparts.

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As sleep changes in MDD have been well characterized, more recent research has focused on the mechanism by which these changes, and specifically changes in SWA and SWS, may be related to depression. One promising area of focus is neuroplasticity, as neuroplasticity has been posited to both be impaired in those with MDD [9] and be associated with SWA [10••]. In this review, we will discuss current theories of the role SWA plays in sleep function, in addition to presenting the most recent research demonstrating impairments in neuroplasticity in MDD. We will then integrate these lines of research into a working model to describe a possible pathway for the maintenance of mood dysfunction in MDD. We will conclude with future directions including a discussion of compelling unanswered questions.

Models of Sleep and SWA

Two-Process Model of Sleep Regulation

SWA alterations in MDD are especially salient because SWA has historically been associated with the homeostatic regulation of sleep. In 1982, Borbely proposed the Two-Process Model of Sleep Regulation [11] which postulated that there are two biological mechanisms, Process S and Process C, that regulate the sleep-wake cycle. Process C, or the circadian system, promotes alertness and is mainly controlled by light. Process S, or the homeostatic drive to sleep, increases throughout the day and decreases across the sleep period. Borbely posited that SWA could be considered a putative marker of this drive, as peak SWA in the first NREM period increases with wakefulness, representative of an accumulation of sleep pressure, and subsequently decreases exponentially during sleep, representing dissipation of the sleep drive. In fact, SWA has been shown to increase proportionally to the amount of prior wakefulness following sleep deprivation [12], and decreases subsequent to a daytime nap [13].

In the context of the two-process model and the research demonstrating slow-wave abnormalities in MDD, it has been suggested that these abnormalities reflect impaired sleep homeostasis. In fact, in the same year that the two-process model was published, Borbely and Wirz-Justice [14] also proposed the S-deficiency hypothesis of depression, which posits that individuals with depression do not build an adequate sleep drive during the course of a normal day of waking. This hypothesis is said to account for several key findings in depression, including sleep disturbances like delayed sleep onset and increased sleep fragmentation, as well as the finding that total sleep deprivation paradoxically alleviates depressive symptoms in 50% of individuals [15–17]. In order to test this hypothesis, several groups have attempted to use more objective measures to examine sleep homeostasis in depression. Goldstein and colleagues [18] examined auditory-evoked potentials (AEP), a measure of auditory processing which have been suggested to be under sleep-related homeostatic regulation due to the observation that their amplitude declines following sleep. They demonstrated that while healthy controls exhibited a significant decrease in AEP following a full night of sleep, those with MDD did not. The authors interpreted these findings as further evidence of homeostatic impairments in depression. Additionally, Plante and colleagues [19] demonstrated that low-frequency activity from the waking EEG, a marker of sleep propensity and the homeostatic drive for sleep, likewise decreased following sleep in healthy controls, and did not change in those with MDD. Taken together, while the mechanism is still not clearly understood, results from several studies provide some support for the idea that those with MDD have impaired sleep homeostasis, generally, and perhaps a deficiency of process S, more specifically.

While MDD may be characterized by impaired sleep homeostasis, an important question that remains is whether this impairment is associated with clinical outcomes. In order to study the impact of impaired sleep homeostasis, a metric known as the delta sleep ratio (DSR) was developed to assess the degree of impairment and its relationship to clinical outcomes [20]. The DSR is calculated by examining the amount of SWA in the first NREM period relative to the second NREM period. In MDD, those with lower DSR values, indicative of less dissipation of SWA from the first to the second NREM period, are more likely to develop MDD as a result of interferon treatment [21], have higher risk of relapse [20], and have less favorable therapeutic outcomes [22]. In addition to clinical treatment outcomes, a study conducted by our group investigated whether impaired sleep homeostasis, as measured by the DSR, was predictive of mood disturbance in MDD, and found that those who had lower DSR had more total mood disturbance than those who had higher DSR values [23•]. Collectively, these studies highlight the importance of the homeostatic regulation of sleep to mood functioning in MDD.

Synaptic Homeostasis Hypothesis

The Two-Process Model was one of the first theories to comprehensively postulate how and why sleep occurs, in addition to identifying SWA as an important marker of the homeostatic process. Building upon this and other advances in the understanding of neuronal transmission at the time, Tononi and Cirelli [10••] proposed the Synaptic Homeostasis Hypothesis (SHY). The SHY posits that sleep is a crucial period for the homeostatic decrease of synaptic strength that builds throughout wakefulness as a function of learning and memory, and interaction with the environment. Specifically, they first propose that over the course of waking, synaptic strength, traditionally defined as the increase in the response in the postsynaptic potential that results from a presynaptic action potential,

increases due to processes associated with long-term potentiation (LTP). Because these changes can be measured in animal models using the miniature excitatory postsynaptic currents (mEPSC), Liu and colleagues [24] measured mEPSC changes in the frontal brain areas of rodents following sleep deprivation. They demonstrated that these measures increased, providing the first direct evidence of increases in synaptic strength with continued wakefulness.

Tononi & Cirelli also suggest that initial SWA is a marker of net cortical synaptic strength, and postulate that the well-known observation that SWA increases proportionally to time spent awake [11] is a reflection of the increase in synaptic potentiation that occurs during wakefulness. Second, they propose that functional downscaling of synaptic strength takes place over the course of sleep. They contend that this downscaling of synaptic strength is a vitally important homeostatic mechanism to "prevent runaway potentiation," or an oversaturation of synaptic strength that might otherwise lead to neuronal firing instability. Although direct measures of synaptic strength are unavailable in humans, research in rodents, utilizing diverse indices of synaptic strength, including proteomics and three-dimensional electron microscopy, has demonstrated that sleep does indeed reduce synaptic strength [25, 26•]. Tononi & Cirelli also suggest that SWA dissipation is a marker of this functional downscaling of net synaptic strength. They hypothesize that the presence of the slow oscillation, characterized by the cycling of up and down states of synaptic activity, may, in and of itself, promote the downscaling of synaptic strength, suggesting that SWA may not only be a marker of the changes in net synaptic strength but may also facilitate this modulation.

The Synaptic Plasticity Model of Therapeutic Sleep Deprivation in Major Depressive Disorder

In addition to providing a framework for understanding the role of sleep, the SHY has also been applied to help explain other phenomena in the context of synaptic plasticity. For example, expanding on SHY, Wolf and colleagues [27••] have hypothesized that those with MDD exhibit deficient daytime levels of net synaptic strength during a day of typical wakefulness, and therefore fail to reach a "window of optimal associative synaptic plasticity" that is accessible to healthy individuals. They developed a model to explain the mechanism of the rapid antidepressant effects of sleep deprivation. They suggest that prolonged wakefulness functions to increase net synaptic strength in those with MDD, thereby creating a more favorable window for synaptic plasticity that previously did not exist. Because the antidepressant effects of sleep deprivation are typically reversed by recovery sleep [28], they theorize that the subsequent synaptic downscaling that takes place during recovery sleep functions to once again reduce net synaptic strength to previously deficient levels, prompting the return of symptoms.

This model may also help explain the finding that slow-wave disruption results in similar antidepressant effects. In two independent studies, SWA was selectively disrupted using an auditory stimulation paradigm conducted in real time in which tones were administered to individuals when slow waves were visually detected during sleep. Using this approach, SWA was significantly reduced without decreasing total sleep time in participants. In both studies, slow-wave disruption resulted in mood improvement. Landsness and colleagues [29] demonstrated that a 37% decrease in SWA resulted in a 10% decrease in self-reported depressive symptoms, and 27% decrease in clinician-assessed symptoms in those with MDD. Although these symptom improvements do no indicate a full antidepressant response, they are noteworthy as they occurred after only one night of SWA manipulation. Mood improvement following slow-wave disruption is not restricted to improvements in depression severity, but has also been observed with an assessment of negative affect. Using a similar slow-wave disruption paradigm to Landsness et al., Cheng and colleagues [30•] showed that those individuals with MDD who exhibited the greatest suppression of SWA showed the greatest improvement in negative affect, even when controlling for other changes in sleep architecture. Taken together, these studies suggest that reducing SWA may be beneficial in MDD, which may further imply that the presence of SWA in those with MDD may be detrimental, as has been suggested previously [31]. In the context of the Wolf model which suggests that synaptic strength is deficient in MDD, it is possible that reducing SWA may prevent synaptic downscaling from occurring during sleep, thus maintaining net synaptic strength and allowing those with MDD to access a more optimal level of synaptic plasticity during the following day. In this way, it would be possible for both sleep deprivation and slow-wave disruption to result in mood improvement via the consequent modulation of synaptic strength; sleep deprivation may allow for an increase in net synaptic strength during continued wakefulness, while slow-wave disruption may prevent a decrease in net synaptic strength during sleep.

Although the Wolf model is unable to identify the mechanism responsible for the deficiency of net synaptic strength in those with MDD or determine the neurobiological substrate associated with the changes, it does contextualize some of the most recent findings with regard to impairments in neuroplasticity in MDD.

Neuroplasticity Impairments in MDD

Behavioral evidence of learning and memory impairments in MDD has been documented for several decades [for review, see 32]. In the last 20 years, major methodological advancements

have allowed researchers to examine processes linked to neural plasticity, defined as the modifications of synapse number and strength or the remodeling of axonal and dendritic architecture [33], in MDD. From this work, it has been proposed that these cognitive deficits may be the result of impaired neural plasticity [34]. For example, using MRI, Drevets and colleagues [35] found reduced gray matter volume in those with MDD, in addition to reduced activity in the prefrontal cortex using PET. Additionally, using postmortem tissue from individuals with MDD, Stockmeier and colleagues [36] demonstrated loss of dendritic branching and spine complexity.

Impairments in synaptic plasticity, defined as cellular processes that result in lasting changes in the efficacy of neurotransmission [33], have likewise been implicated in MDD. For example, several studies have shown that serum brain-derived neurotrophic factor (BDNF), a key regulator of synaptic plasticity, is reduced in humans with MDD and that antidepressants increase BDNF expression [37, 38]. Utilizing a brain stimulation paradigm known as paired associative stimulation, Player and colleagues [39•] demonstrated that motor-evoked potentials, a marker of associative synaptic plasticity, were reduced in MDD. Whereas the downstream effects of psychotropic antidepressants have traditionally been attributed to changes in *neural plasticity*, ample recent research has implicated *rapid* antidepressant effects to increases in *synaptic plasticity* [40••, 41–43] For example, the clinical benefit of ketamine, a NMDA receptor antagonist that has been shown to produce rapid antidepressant effects, has been suggested to result from an increase in synaptic plasticity which facilitates functioning in circuits critical to mood [44]. In animal models of stress increasing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor function, which is known to increase synaptic strength, has also been shown to produce antidepressant effects [45]. Taken together, emerging evidence suggests that MDD is characterized by impairments in neuroplasticity, both at the neural and synaptic levels.

An Integrated Model of SWA and Neuroplasticity Impairments in MDD

We have seen that the Synaptic Plasticity Model of Therapeutic Sleep Deprivation in Major Depressive Disorder (27••) integrates the SHY with the most recent advances in the understanding of the impairments in neuroplasticity in MDD to propose that the disorder is characterized by deficient daytime levels of net synaptic strength that can be normalized by therapeutic sleep deprivation. What remains to be determined is the mechanism by which this deficiency is maintained. Because SWA is thought to be an index of net synaptic strength [10••], it is possible that the SWA alterations noted in MDD could reflect this underlying deficiency, and may represent promising mechanistic candidates.

As previously discussed, the homeostatic regulation of sleep has been shown to be impaired in those with MDD [7, 18, 19]. The degree of this impairment, as indexed by SWA dissipation, has also been linked to mood disturbance [23•], such that the less dissipation of SWA, indicative of more impaired homeostatic regulation, the more mood is disturbed. We have also seen that the SHY posits that SWA dissipation reflects the downscaling of net synaptic strength. Combining these lines of research, we propose that MDD is characterized by an impairment in the mechanisms that modulate synaptic strength. In this way, those with MDD would have difficulties building appropriate synaptic strength, consistent with what has been suggested by Wolf et al. [27••], in addition to exhibiting deficits in the ability to appropriately downscale synaptic strength.

Using this model as a framework, we may be able to understand several of the previously mentioned SWA findings in MDD. As previously discussed, two studies have demonstrated that reducing SWA improves mood in MDD [29, 30•]. According to the SHY, synaptic downscaling via a long-term depression (LTD)-like mechanism occurs as a result of the slow oscillations inherent to SWA. Over the course of sleep that includes SWA, net synaptic strength is reduced. The present model proposes that individuals with MDD cannot build appropriate synaptic strength as a result of impaired modulation of synaptic strength. Moreover, this model suggests that any amount of synaptic downscaling would serve to maintain a constant deficit as compared to healthy individuals. By extension, this would also suggest that reducing synaptic downscaling, via the reduction of SWA, would function to maintain a pre-sleep level of net synaptic strength thereby allowing synaptic strength to build to more appropriate levels the following day, and perhaps facilitating an improvement in mood.

This model may also explain abnormalities in SWA dynamics in MDD that have hitherto been demonstrated in males with MDD. If the modulation of synaptic strength is impaired in MDD, this impairment would naturally be associated with impairments in synaptic potentiation as an increase in synaptic strength occurs as a result of LTP. According to the SHY, initial SWA is a marker of synaptic potentiation; therefore, if synaptic potentiation were reduced this should be observable in the initial accumulation of SWA. Specifically, in those with MDD, we would expect to see a reduced amount of initial SWA. As we have seen, in males with MDD, initial SWA has been shown to be reduced in contrast to healthy males [6]. Furthermore, we would also expect that an impairment in the modulation of synaptic strength would disturb the rate of synaptic downscaling. Indeed, it has been demonstrated that males with MDD exhibit a slower time course of SWA across the sleep period [7], potentially reflecting this slower reduction of SWA. This model, however, does not account for why these impairments have only been demonstrated in males, and why there is some evidence that females with MDD show *increased* SWA. It is possible that these

discrepancies are not restricted to effects of sex, but are more generally reflective of the heterogeneity of MDD.

Lastly, this model may also elucidate the clinical benefit of ketamine. Although its effects were initially attributed to the antagonism of NMDA receptors, a recent study showed that ketamine may actually exert its effects through the activation of AMPA receptors [46•], a known mediator of LTP, and consequent increase in synaptic strength. If the modulation of synaptic strength is indeed impaired in MDD, the ability of a pharmacological agent to facilitate an increase in synaptic strength would likely result in mood improvement. Taken together, an impairment in the modulatory mechanism of synaptic strength has the potential to explain several findings in the MDD literature, in addition to providing a novel framework from which to further understand the disorder.

Potential Mechanisms

The present model postulates that individuals with depression have an impairment to the system that modulates synaptic strength. Since synaptic potentiation is facilitated by the phosphorylation and trafficking of AMPA receptors to the postsynaptic membrane following repeated cortical stimulation, a disturbance that results in the slowing of AMPA trafficking could be a prime candidate for the mechanism of this impairment. Disturbed AMPA receptor trafficking would not only prevent the appropriate buildup of AMPA receptors during waking, and therefore impede potentiation, but would also prevent appropriate downscaling of synaptic strength during sleep since the hypothesized downscaling stipulated in the SHY is based on an "LTD-type mechanism" that would require the internalization of AMPA receptors back into the cell from the postsynaptic membrane. In this way, if both accumulation and downscaling were impaired, the initial AMPA receptor deficit and subsequent mood disturbance in MDD would be maintained. Indeed, Wolf and colleagues do suggest that there is evidence that those with MDD show a reduced ability to generate cortical LTP [27••], which could be due to impaired or slowed AMPA receptor trafficking.

AMPA receptors have previously been postulated to play a role in mood disorders [for review, please see [45, 47••]. The idea of an impairment in AMPA trafficking is also consistent with the rapid antidepressant effects of sleep deprivation, slow-wave disruption, and ketamine as discussed earlier. Wolf and colleagues [27••] suggest that net synaptic strength is deficient in MDD and that sleep deprivation increases net synaptic strength to a more appropriate level which is associated with rapid antidepressant effects. As previously discussed, synaptic strength is measured in animal models using the change in mEPSC amplitude, which is suggested to be mediated via an increase in AMPA receptors on the postsynaptic neuron following LTP [48]. Wakefulness has been shown to increase LTP, so sleep deprivation in those with MDD could serve to increase the likelihood of LTP, and thus allowing for an increase in AMPA receptor density to occur despite slowed trafficking. This modulation of AMPA would then be reflected in a consequent increase in net synaptic strength, as proposed by Wolf and colleagues [27••].

Likewise, the SHY suggests that SWA facilitates a decrease in synaptic strength via an LTD-like mechanism. Any LTD-like mechanism would most likely be mediated via the endocytosis of AMPA receptors. Reducing the endocytosis of AMPA receptors by reducing SWA would therefore maintain the number of AMPA receptors on the postsynaptic neuron, thereby preserving synaptic strength. Lastly, as previously mentioned, the most recent research has shown that the mechanism of action of ketamine may be the increase in AMPA vs NMDA receptor throughput [46•]. If the ketamine-mediated antagonism of NMDA receptors increases AMPA throughput, it is possible that additional resources could be recruited to enhance AMPA trafficking due to an increase in demand, thereby overriding this impairment, and resulting in rapid mood improvements.

There is also some evidence to suggest that increasing AMPA receptor functioning may be important in the context of MDD. For example, increased AMPA functioning via AMPA potentiators has been shown to be associated with clinical improvements in MDD. Additionally, increased AMPA activation also results in increased BDNF levels which have been linked to antidepressant activity and increased neurogenesis [45]. Furthermore, some studies have also shown decreased AMPA receptor binding in the hippocampus using postmortem tissue from the brains of depressed individuals [49]; however, there are mixed results among other areas of the brain including the dorsolateral prefrontal cortex.

Although it is compelling to consider that a disturbance in the process regulating AMPA receptor trafficking could be a mechanism maintaining MDD, this idea may also be too simplistic. The trafficking of AMPA receptors into and out of the postsynaptic membrane is a complex, highly regulated process that involves several uniquely mediated steps that are specific to the direction of trafficking. It is possible, however, that a yet unidentified shared component in the process associated with AMPA receptor trafficking could be important in understanding the impairments characteristic of MDD. It is presently not possible to image AMPA receptors in vivo in humans, so this theory remains speculative. However, with the advent of new technology, including MR spectroscopy, we may be able to better estimate AMPA receptor density and activity by measuring glutamatergic transmission.

Conclusions

In summary, we propose that the modulation of synaptic strength is impaired in those with MDD. This impairment is associated with disturbed sleep homeostasis, and in some

cases, SWA abnormalities. However, there are several remaining questions that warrant future research and discussion. First, although it has been proposed that net synaptic strength is deficient in MDD, it is possible that synaptic strength in this group is actually too high, thus impairing neuroplasticity. Second, our model is based on excitatory transmission via the glutamatergic system, and although glutamate is the most abundant neurotransmitter in the brain, inhibitory cells fire approximately five times more than excitatory cells. Because of this, it will be important to know how inhibition plays a role in MDD. In fact, excitation/inhibition balance dysfunction has been implicated in autism and schizophrenia [50], and may be relevant to other psychiatric disorders, as well. Third, as the present model is an extension of both the SHY and synaptic plasticity model of therapeutic sleep deprivation, it has solely focused on the importance of SWA; however, there is significant research that has demonstrated the importance of REM sleep in MDD, including that REM alterations are consistently found in MDD, and REM has been shown to be crucial to the consolidation of emotional memory [51]. Although it is probably not the case that one type of sleep oscillation is more important than the other, the sequence of slow wave and REM may be of particular importance in the context of MDD. Fourth, as previously mentioned, although the AMPA-receptor theory is compelling, it may be too simplistic. Another candidate mechanism for the modulation of synaptic strength that merits further research and discussion are glial cells since they are (1) involved in the regulation of synaptic plasticity [52], (2) affected by sleep [53], and (3) reduced in several brain regions in individuals with MDD [54–56]. Lastly, with the advent of new technology, it is now possible to enhance slow-wave activity using a non-invasive approach. Auditory closed-loop stimulation is a process whereby auditory tones are presented when the up-state of an endogenous slow oscillation is detected which results in the enhancement of subsequent slow waves [57]. This enhancement has been shown to improve memory function and increase immune function [58]. Importantly, it will be interesting to probe how slow-wave enhancement may affect those with MDD. As slow-wave disruption has been shown to ameliorate depressive symptoms, it is possible that slow-wave enhancement could worsen symptoms. On the other hand, increasing SWA in the first NREM period may serve to modify subsequent dissipation and alter synaptic downscaling which may have opposite effects. Research using this new technology will be needed in those with MDD.

The study of SWA, as a marker of sleep homeostasis and potential mediator of the modulation of synaptic plasticity, is crucial in the context of MDD given the evidence that the disorder is characterized by impairments in neuroplasticity and alterations in sleep homeostasis and its associated processes. In this way, SWA could also provide a potential new target for treatment intervention in MDD.

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