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Neurobehavioral complications of sleep deprivation: shedding light on the emerging role of neuroactive steroids

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Abstract

Sleep deprivation (SD) is associated with a broad spectrum of cognitive and behavioral complications, including emotional lability, enhanced stress reactivity, as well as deficits in executive functions, decision making, and impulse control. These impairments, which have profound negative consequences on the health and productivity of many individuals, reflect alterations of the prefrontal cortex (PFC) and its connectivity with subcortical regions. However, the molecular underpinnings of these alterations remain elusive. Our group and others have begun examining how the neurobehavioral outcomes of SD may be influenced by neuroactive steroids, a family of molecules deeply implicated in sleep regulation and stress response. These studies have revealed that, similar to other stressors, acute SD leads to increased synthesis of the neurosteroid allopregnanolone (AP) in the PFC. Whereas this upregulation is likely aimed at counterbalancing the detrimental impact of oxidative stress induced by SD, the increase in prefrontal AP levels contributes to deficits in sensorimotor gating and impulse control, signaling a functional impairment of PFC. This scenario suggests that the synthesis of neuroactive steroids during acute SD may be enacted as a neuroprotective response in the PFC; however, such compensation may in turn set off neurobehavioral complications by interfering with the corticolimbic connections responsible for executive functions and emotional regulation.

Keywords

sleep deprivation; neurosteroids; AP; prefrontal cortex

Introduction

Sleep is an essential function for energy conservation as well as the homeostasis of multiple physiological and behavioral processes. Although most mechanisms of sleep remain

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partially elusive, the overwhelming consensus of the scientific and medical community indicates that healthy sleep habits are critical for the integrity of cognitive, metabolic, and immune functions. While the American Academy of Sleep Medicine and the National Sleep Foundation recommend that adults sleep at least 7 h per day [1,2], the increasing demand for long work shifts and “around-the-clock” work availability has led to a marked reduction of the average sleep duration in high-income countries [3,4]. Recent surveys have shown that approximately 20–30% of Americans experience occasional episodes of sleep restriction or fragmentation due to occupational demands, lifestyle choices, and behavioral disturbances [5–9]. The issue of sleep loss has become so pervasive in society that the Center for Disease Control (CDC) has recently elevated it to public health epidemic status [8]. In addition, sleep loss is a rampant problem among adolescents and college students, and often signals the excessive use of stimulants in this population [10–12]. The impact of sleep restriction is particularly harmful for high-responsibility professionals forced to lose sleep due to prolonged work shifts or emergency situations, e.g., health caregivers [13–17], military personnel [18–20], firefighters [21,22], and airline pilots [23–25]. The economic repercussions of sleep deficits are staggering [26], due to their negative influence on public safety and work productivity [27–30]. These devastating effects are known to be contributed by alterations of executive functions, a class of processes that enable the enactment of purposive, goal-directed tasks and attune cognitive and emotional responses to the environment. These effects reflect the adverse consequences of sleep loss on the prefrontal cortex (PFC) [31], a brain region that plays a key role in the orchestration of executive functions [32–35]. One of the best experimental models to study the neurochemical underpinnings of cognitive and neurobehavioral deficits induced by sleep loss is total sleep deprivation (SD), a condition of forced wakefulness lasting 24–72 h imposed to either volunteers or laboratory animals [36,37] Conversely, partial sleep deprivation entails a restriction of sleep duration to 2–6 h per night, over several nights [38, 39]. In animals, both conditions are typically achieved by exposing them to manipulations that interfere with sleep initiation, which can be inherently stressful [40]. For this and other reasons, neither procedure is fully appropriate to capture the complexity of sleep loss in the clinical setting; nevertheless, these manipulations have proven extremely useful to gain insight into the negative consequences of hyposomnia, as well as their neurobiological mechanisms. In this article, we will first discuss how SD studies in both volunteers and animal models have helped understand the nature of the neurobehavioral deficits associated with sleep loss. Then, we will overview recent preclinical evidence suggesting that neuroactive steroids - an important class of mediators that regulate sleep and stress response - may be critical in mediating and shaping the executive function deficits associated with SD. Finally, we will discuss how the implication of these steroids may offer a novel perspective to understand some of the pathophysiological links between hyposomnia and different psychopathological states, including schizophrenia and depression.

Neurobehavioral complications of sleep loss: clinical evidence

In this section, we briefly review the main cognitive and behavioral effects of sleep restriction in humans, as well as their neurological and endocrine underpinnings. A comprehensive description of the effects of sleep loss on brain and behavioral processes is beyond the scope of this article; the interested reader is referred to the references [41–45].

Cognitive consequences of SD.—Although the effects of sleep restriction are characterized by marked intra- and inter-subject variability, neuroimaging studies have shown that the PFC and its functional connections with subcortical regions (such as amygdala and hippocampus) are highly vulnerable to the harmful impact of this condition [46]. Specifically, most individuals experience a progressive intrusion of microsleep episodes, during which they lose the ability to respond to sensory stimulation for 5–30 s [47]. This situation likely translates into a gradual worsening of PFC activity and executive functions, including information processing and gating, attention, working memory, inhibitory control, cognitive flexibility, and problem solving [43, 48–52]. The escalation of wake-state instability results in prolonged reaction time, errors of omission and commission, poor short-term recall, perseveration of ineffective responses, reduced divergent thinking and poor insight into one's own actions [53–56]. Under these conditions, the execution of multitasking and flexible cognitive performances entail the recruitment of compensatory adaptive mechanisms - such as the activation of the parietal cortex and thalamus [57–63]. Although sleep is critical for learning and memory [64,65], the available evidence on the effects of SD on these functions is somewhat inconsistent. For example, different studies have shown contradictory results with respect to the impact of SD on verbal recall and reasoning ability [66–70], possibly due to differences in study design and methodology. The cognitive effects of chronic partial SD are less well-understood, but recent data support that they are akin to those induced by total SD [43, 71–75].

Affective consequences of SD.—Depressive symptoms are one of the best-documented consequences of several conditions associated with poor sleep quality and alterations in sleep architecture, including fragmented sleep, decreased slow wave sleep, shortened REM latency, and increased REM density [76, 77, 78]. Conversely, a wide body of literature has established that acute SD has mood-enhancing properties, which may reflect the involvement of the PFC (as well as its connections with the amygdala) in socio-affective reactivity [79]. Indeed, sleep-deprived individuals are hyperresponsive to both positive and negative stimuli, due to the increased activation of reward-related circuits and the amygdala [80–82]. Furthermore, they display poor self-monitoring, behavioral disinhibition, attenuated response to losses and higher propensity to engage in impulsive actions, as a result of the combination of PFC deficits and hyperactivation of the nucleus accumbens [82–84]. The negative effects of SD on mood are likely to be contributed by the loss of REM sleep. This stage modulates emotional responses to facial cues [85]; in particular, the threat stimulation theory posits that the purpose of dreams in REM sleep is to rehearse real-life challenges and prepare for appropriate responses when similar scenarios occur [86]. The activation of the mesolimbic dopaminergic system during REM sleep leads to the acquisition and consolidation of emotionally and motivationally salient information [87].

Neuroendocrine consequences of SD.—Sleep is critical for circadian rhythmicity as well as homeostatic hormonal and metabolic balances. Accordingly, SD is associated with a broad range of alterations of endocrine factors, including cortisol, growth hormone (GH), prolactin, thyroid-stimulating hormone (TSH), gonadotropin-releasing hormone (GnRH), testosterone, leptin, ghrelin, and insulin [88–93]. In keeping with these effects, SD has been shown to result in increased appetite for highly caloric food, resulting in a higher risk of

obesity and diabetes [94, 95]. In addition to these changes, SD has a complex effect on the endocrine reactivity to stress. Given that stress is defined as a condition of threatened homeostasis [79], SD inherently heightens stress sensitivity; furthermore, several studies have shown that poor sleep quality is associated with increased allostatic load [97, 98], defined as the cumulative damage of allostatic responses due to chronic stress [99, 100]. Accordingly, sleep loss is associated with the increased release of all major hormones of the hypothalamic-pituitary-adrenocortical (HPA) axis, namely corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol [101, 102]. The relationship between sleep and HPA axis regulation is complicated by the fact that, while NREM sleep is associated with a suppression of the HPA axis [103, 104], the mentation of stressful dreams during REM sleep leads to increased cortisol concentrations [105]. From this perspective, it is worth noting that CRH promotes both REM sleep [106] and wakefulness [103], and can therefore exacerbate some of the behavioral complications of SD. Several studies suggest that the 24-h urinary cortisol levels are positively correlated with the amount of REM sleep [107, 108], signifying a critical role of REM in stress response. In addition to the effects of SD on stress reactivity, several lines of evidence point to negative effects on sex hormones. Indeed, total SD has been shown to reduce the levels of progesterone in both sexes and testosterone in men [109]. Although no significant change in estradiol concentrations were found in sleep-deprived women and men [109], research in female rats has shown that REM SD during diestrus reduces the content of estrogens and increases corticosterone levels [110]. Furthermore, ovarian hormones promote recovery from SD in rats [111]. Overall, these studies suggest that SD is conducive to a wide array of endocrine disruptions, which may participate in the neurobehavioral complications of this manipulation. A critical tool to examine this hypothesis is afforded by rodent models [37, 112]. In the next section, we will outline how studies in laboratory animals have been instrumental for our current understanding of the neurobiological underpinnings of the negative impact of SD.

Neurobehavioral complications of SD: preclinical evidence

Several rodent studies have indicated that SD induces profound consequences across an ample spectrum of behavioral paradigms. Such alterations reflect changes in diverse brain neurotransmitters, including dopamine, acetylcholine, serotonin, and GABA. In particular, the dopaminergic mesocortical pathway - which projects from the ventral tegmental area (VTA) to the prefrontal cortex (PFC) - plays an essential role in a number of cognitive and emotional processes and may be directly implicated in some key behavioral consequences of SD. In keeping with this idea, Tufik and colleagues (1981) reported that SD leads to a state of supersensitivity of post-synaptic dopamine receptors in the rat brain [113]. Accordingly, SD rats respond to the administration of low doses of dopaminergic agonists with paroxysmal increases in dopamine-dependent phenotypes [113]. These modifications are not related to changes in dopamine synthesis or release [114]. The two major classes of dopamine receptors, D_1- and D_2- like, are likely both implicated in the phenotypic complications of SD. Indeed, SD-subjected rats exhibit greater dopaminergic-mediated responses upon striatal upregulation of D_2 receptors [115]; conversely, pre-treatment with the D_2 receptor antagonist haloperidol rescues SD-mediated behavioral alterations [113]. At the same time, D_1 receptors have been found to be implicated in SD-induced learning impairments in flies [116].

SD also affects serotonergic and noradrenergic signaling [117]. Unlike the effects on the dopaminergic system, binding studies showed an overall decrease of the serotonin receptors $5HT_{1A}$, $5HT_2$ and serotonin transporter (SERT) in rats subjected to SD [118]. Norepinephrine may indirectly modulate SD-mediated phenotypes by interacting with the dopamine system [119]. Furthermore, some reports suggest that these effects might be contributed by both α and β-adrenoceptors, as a reduction in β expression [120] as well as a down- and up-regulation of α1 and α2, has been found in the brain of SD rats [120].

Although these findings have been extremely useful to improve our understanding of the behavioral abnormalities associated with SD and their neurobiological basis, the translational value of most of these preclinical studies is often limited by a lack of clear correspondence between behavioral responses in animal models and human phenotypes. A novel opportunity to overcome this problem comes from the Research Domain Criteria (RDoC) initiative, a new research framework focused on dimensional and transdiagnostic approaches. The strategy outlined by the RDoC is aimed at the systematization of biological knowledge of risk factors (including information on genes, anatomical circuits and specific psychological responses) to gain insight into different domains of psychopathology [121]. The integration of cross-species tests focusing on these different dimensions enable the use of rodent models to test mechanistic hypotheses [122]. Building on this perspective, we observed that in rats, SD impairs prepulse inhibition (PPI) of the acoustic startle reflex [123]. This index, which can be studied in both rats and humans, measures how the startle response is reduced when the eliciting acoustic burst is immediately preceded by a weaker pre-stimulus. The importance of PPI in neurocognitive research comes from its value as an operational measure of sensorimotor gating, a key early-stage information-processing function that enables the formation of salience maps by filtering out irrelevant stimuli [124]. The importance of PPI in information processing is highlighted by its correlation with the efficiency and reaction time of preattentional and attentional performances, particularly in the context of complex tasks [125]; furthermore, higher PPI levels are associated with better and faster problem-solving [126]. A very exciting development of this research came in 2014, when our findings of SD-induced PPI deficits were replicated in humans [127]. Healthy volunteers subjected to 24-h SD exhibited PPI deficits in association with perceptual distortions and cognitive fragmentation. In striking analogy with our observations in rat models [123], these deficits were fully reversed after a night of normal sleep [127].

Other models of the negative consequences of SD on executive functions have been developed. For example, recent studies have shown that SD impairs the performance in the 5-choice continuous performance test (5C-CPT) in humans and rodents alike [128]. The 5C-CPT is the gold standard to assess deficits in sustained and selective attention, as well as vigilance, and has high cross-species validity [129, 130]. Another valuable example is afforded by the Iowa Gambling Task (IGT), a well-consolidated task for preference-based decision making [131]. In a rodent counterpart of this test [132], SD was recently shown to impair decision-making abilities [133].

Neurosteroids are involved in the neurobehavioral effects of SD.

Synthesis and molecular actions of neurosteroids.—The key precursor of most neurosteroids, pregnenolone, derives from the cleavage of the side chain from cholesterol, and undergoes conversion to progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD). In turn, progesterone can be reconverted to testosterone via joint actions of cytochrome P450 17A1 (CYP17A1) and 17β-hydroxysteroid dehydrogenase (17β-HSD). An alternative metabolic pathway of progesterone entails its transformation into deoxycorticosterone (DOC) by 21α-hydroxylase. Progesterone and DOC are then converted by 5α-reductase (5αR) into their metabolites 5α-dihydroprogesterone (DHP) and 5α-dihydrodeoxycorticosterone (DHDOC) [134]. In turn, the enzyme 3α-hydroxysteroid oxidoreductase (3α-HSOR) converts these steroids to allopregnanolone (AP; 3α,5α−3-hydroxypregnan-20-one) and tetrahydrodeoxycorticosterone (THDOC; 3α,5α−3,21-dihydroxypregnan-20-one) (Fig.1). Generally, the acute effects of neurosteroids are not mediated by the classical genomic steroid hormone receptors. Several classes of neurosteroids modulate brain excitability primarily by interacting with neuronal membrane receptors and ion channels, principally GABA-A receptors [135, 136]. The effects of these neurosteroids occur rapidly (within minutes), whereas steroid hormone actions via intracellular steroid receptors are usually slow in onset and elicit long-lasting effects [136]. AP and THDOC are potent allosteric modulators of GABA-A receptors and can even open GABA-A channels directly in the absence of GABA at sufficiently high concentrations [137, 138]. Additionally, 3α-androstanediol potentiates GABA-A function, albeit with lower potency than AP and THDOC [139]. In contrast with these neurosteroids, many of their 3β-hydroxyl isomers act as non-competitive GABA-A receptor modulating steroid antagonists (GAMSAs) [140]. The positive modulation of GABA-A receptors by AP and THDOC is dependent on their specific subunit composition of GABA-A receptors. For example, extrasynaptic GABA-A receptors expressing δ subunits may primarily bind to GABA only in the presence of neurosteroids [141–143]. The importance of δ subunits is underscored by evidence indicating the key role of these proteins in the physiological effects of neurosteroids [144].

Several preclinical and clinical studies suggest that the sex differences susceptibility reported in certain neuropsychiatric disorders result on dimorphic acute and chronic effects of brain and peripheral steroids. Sex differences in relation to steroid activity and imbalance have been described in several psychiatric conditions, such as depression and anxiety [145, 146], alcohol and cocaine addiction [147, 148] schizophrenia [149] and Tourette Syndrome [150], and others [151]. Of note, the majority of these sex-dependently psychiatric diseases are related to stress, GABA-A receptors and allopregnanolone [146, 148, 152–155], suggesting that, depending on sex, AP and other 5-alpha reduced neurosteroids differently modulate brain function in response to acute and chronic stress.

Role of neurosteroids in stress response regulation.—As mentioned above, neurosteroid synthesis is critical for the orchestration of stress response [156]. Indeed, neurosteroid synthesis is promoted by acute stress [157]. The mechanisms whereby stress promotes neurosteroidogenesis remain partially elusive; however, several lines of evidence suggest that a critical mechanism by which stress promotes the synthesis of AP is the

upregulation of 5αR. The expression of this enzyme in the cortex is sensitive to acute stress [158] and reduced by chronic psychosocial stress [159]. Recent evidence suggests that, in the cortex, glutamatergic pyramidal neurons may be predominantly involved in the synthesis of GABAergic neurosteroids, possibly following the activation of NMDA glutamate receptors and neuronal nitric oxide synthase (n-NOS) [160–163]. Notably, our group showed that one of the two main 5αR isoenzymes (type 2) is strategically segregated in glutamatergic pyramidal neurons in the cortex [164], suggesting a connection between these mechanisms. To the best of our knowledge, however, the mechanisms whereby NMDA receptor activation may promote 5αR synthesis or activation remain unknown to date. Irrespective of these issues, the idea that AP and similar neurosteroids reduce excitability by modulating GABA-A receptors suggest that, in pyramidal cells, these compounds may serve an autocrine function aimed at preventing excessive activation and, possibly, excitotoxicity (a typical outcome of glutamatergic stimulation). The synthesis of AP and other neurosteroids is tightly linked with HPA axis regulation. For example, brain and plasma AP levels are enhanced by CRH and ACTH [165]; in turn, neurosteroids control the activity of HPA axis, and such action is contributed by a direct control of CRH synthesis and hypothalamic release [136, 166]. Of note, the positive modulation of GABA-A receptors by AP and THDOC during stress response is likely aimed at the reduction of some of the negative psychological outcomes of acute stress, such as anxiety. While GABAergic transmission is generally silenced during acute stress [167, 168], the enhanced neurosteroid synthesis is correlated with the restoration of GABAergic functions and reduced anxiety-like behaviors [169]. Again, this background suggests that the synthesis of neurosteroids like AP and THDOC is primarily aimed at compensating for some effects of stress response and re-establishing homeostatic balances in brain regions that play a critical role in emotional and affective regulation.

Role of neurosteroids in sleep regulation and SD.—Given that AP and THDOC are potent endogenous positive modulators of GABA-A receptors, it is not surprising that these steroids elicit hypnotic- and sedative-like effects. Compared with other GABA-A receptor agonists and positive modulators, however, the sleep-promoting properties of neurosteroids may be underlain by their peculiar affinity toward extrasynaptic GABA-A receptors. In rodents, AP elicits profound changes in sleep architecture, including shorter latencies of non-rapid eye movement sleep, prolonged REM sleep duration, longer NREM episodes and higher spindle activity within the NREM phase [170]. Similarly, THDOC dose-dependently shortens sleep latency, promotes the transition between NREM and REM sleep and prolongs NREM episodes [170]. The role of AP in the regulation of sleep architecture is also supported by the fact that elevations in its brain and/or plasma levels are time-locked with modifications in wake/sleep transitions induced by administration of its precursor progesterone [171, 172]; conversely, progesterone elicits hypnotic effects [173, 174], which are likely mediated by AP and other metabolites [175, 176]. Accordingly, the hypnotic properties of progesterone are dampened by 5α-reductase inhibitors, which block the conversion of progesterone to AP [176, 178]. However, it is worth noting that, at least in postmenopausal women, some of the sleep-inducing effects of intranasal progesterone may not reflect GABA-A receptor activation [179].

Another key neurosteroid that has been implicated in sleep regulation is pregnenolone sulfate. In rats, this steroid increases the amount of REM sleep without affecting NREM and modifies sleep–wake transitions [180–182]; conversely, in humans, it increases the amount of time spent in slow wave sleep and depresses EEG sigma power, via inverse agonistic GABA-A receptor modulation [183]. Moreover, infusions of this steroids in the pedunculopontine tegmentum - one of the main brain structures involved in REM sleep generation - promote REM sleep and the propensity to fall asleep during wakefulness [182]. Although this evidence supports an important role of neurosteroids in sleep regulation, it should be noted that a recent study challenged this idea by showing that finasteride, the prototypical 5αR inhibitor, does not alter sleep spindles in men [184].

Given the involvement of neurosteroids in the physiology of sleep and stress response, our group hypothesized their implication in the mechanisms of SD. To test this hypothesis, we recently measured the expression and activity of 5αR, as well as neuroactive steroid levels, in the PFC and other regions of sleep-deprived rats [185]. Our results showed that the PPI deficits induced by SD were underpinned by changes in corticolimbic expression of the two main 5αR isoenzymes. We detected that, after 72 h of SD, both 5αR1 and 5αR2 were upregulated in the PFC, but only the content of the latter was inversely correlated with PPI levels. In addition, we found a significant enhancement of AP in this region. To verify whether the behavioral complications induced by SD were underpinned by the enhancement in 5αR and AP levels, we tested the effects of the 5αR inhibitor finasteride on the behavioral changes induced by SD. The prototypical 5αR inhibitor finasteride countered both the PPI deficits and risk-taking behaviors induced by SD, while injections of AP exacerbated such defects [185]. Interestingly, we also found that low doses of progesterone had an effect similar to that of finasteride, possibly pointing to the importance of a balance between progesterone and its product AP within the PFC to maintain the integrity of executive functions [185]. Ongoing studies in our laboratories are evaluating how changes in AP may interfere with the function of the PFC. A potentially important molecular link to understand how AP and other neurosteroids may impair executive functions involves the dopaminergic system. Indeed, our group has documented that both pharmacological and genetic inactivation of 5αR type 1 interferes with the function of D_1-like receptors on the regulation of sensorimotor gating [186– 189], in an AP-sensitive fashion [189]. Notably, preliminary data in our laboratories have shown that D_1-like receptor antagonists reverse the gating deficits induced by SD in a fashion similar to the 5αR inhibitor finasteride. While the mechanisms whereby AP may contribute to the signaling of dopamine receptors remains unclear, several reports have pointed to the cross-talk of D_1 and GABA-A receptors in the PFC [190–192]. Notably, D1 receptors are the most abundant class in the PFC [193,194], and their activation may cooperate with GABAergic functions to reduce glutamate release in this region [195]. This observation is particularly important given that the reduction of glutamatergic signaling and the reduction in NMDA receptor activation, is known to produce many of the impairments in executive functions observed after SD, including perceptual, attentional and working memory deficits [196–198]. From this perspective, it is also interesting to note that our previous research showed that D_1 receptor activation potentiates the gating-disrupting effects of NMDA glutamate receptors [199].

Are neurosteroids involved in the link between sleep problems and gating disorders?—One of the major current limitations to establishing a dependable platform for translational neuropsychiatric research lies in the descriptive, qualitative nature of the DSM-5 classification criteria. Because of the exclusive reliance on symptoms in the diagnostic process, most psychiatric disorders are likely to encompass converging, yet diverse, pathophysiological conditions sharing some clinical phenotypes. For example, a recent genetic study has shown that the diagnostic classification of schizophrenia outlined in the DSM IV encompasses at least eight distinct clinical disorders, reflective of separate biological mechanisms [200]. The RDoC matrix offers a complementary phenomenological approach to demarcate the boundaries and define the overlaps across different psychopathological conditions, by integrating many information levels, such as genomics, biological underpinnings and behavioral components of normal and abnormal functioning [121].

A telling example of this strategy, which may apply to the outcomes of SD, is offered by PPI. This sensorimotor gating index has recently been integrated in the sensorimotor function RDoC domain, within the sub-construct Inhibition and Termination. The loss of PPI has been documented across multiple, diverse neuropsychiatric disorders, including schizophrenia, schizotypal personality disorder, bipolar disorders, obsessive compulsive disorder (OCD), Tourette's Syndrome (TS), and post-traumatic stress disorder (PTSD) [201–203]. In keeping with the phenotypic perspective of RDoC, these otherwise highly heterogeneous conditions have been grouped under a common rubric of *gating disorders* [204]. This frame of reference may help gain novel insight into the mechanisms whereby SD triggers and/or exacerbates a wide array of distinct clinical entities. Indeed, all gating disorders have been shown to be accompanied by sleep disturbances and sensitive to their negative impact. For example, the risk of sleep disturbances in schizophrenia or bipolar disorder is almost twice as high as that reported in healthy controls, with insomnia as the most frequently reported sleep disturbance across groups [205]. Sleep disturbances are highly prevalent in bipolar disorder, and often consequent to a reduced need for sleep in mania [206, 207]. Sleep disruption is a triggering factor for manic/hypomanic episodes in some vulnerable patients [208, 209], or an exacerbating factor for depression in others [210, 211]. Sleep problems are also a hallmark of schizophrenia [212–215], with delays in falling asleep, difficulties in maintaining sleep, reduced total sleep time, several night time awakenings, nightmares, and non-restorative sleep [216]. Similar to bipolar patients, reduced need for sleep occurs particularly during episodes of psychotic exacerbation and before the first symptomatic signs of relapse as well as in patients with high risk for psychosis [217]. Further underscoring the relevance of sleep loss in psychosis and mania, recent research has shown that acute SD may serve as a proxy paradigm to study these conditions [218]. Indeed, acute SD results in psychotomimetic states, with perceptual distortions, anhedonia and cognitive disorganization [127, 218]; furthermore, SD leads to a rapid elevation of mood and exacerbation of manic symptoms [208]. Sleep loss is also associated with greater severity symptoms in TS [219, 220], OCD [221, 222], and PTSD [223]. Taken together, this evidence suggests that sleep problems may provide a relevant target for transdiagnostic treatment in patients affected by gating disorders.

As highlighted above, our findings suggest that neurosteroids may contribute to the link between SD and gating disorders. In line with this idea, we and others have pointed to the involvement of these molecules in the pathophysiology of schizophrenia [152, 186–188, 224–229], TS [230–232], and PTSD [233]. Future studies will be needed to fully evaluate the integration of neurosteroids with other pathogenic factors in these disorders.

The function of AP in SD: a double-edged sword?

As outlined in the previous sections, our recent results have delineated a critical role of AP and progesterone in the executive complications of SD; some of these alterations may have important repercussions on the pathogenesis of gating disorders. The mechanisms that lead to the increased 5αR expression and AP synthesis in the PFC of SD-exposed subjects remain unknown. It should be noted that the negative role of AP on executive functions is in apparent contrast with the beneficial effects of this neurosteroid on anxiety-like behaviors and oxidative stress. Indeed, previous reports have documented that AP injections significantly improve anxiety-like behaviors and attenuate lipid peroxidation and nitrite levels, by activating GABA-A receptors [234]. AP has also been shown to reduce oxidative stress in cells [235–237]. In fact, positive modulation of GABA-A receptors by neurosteroids helps maintain neuronal redox homeostasis by increasing mitochondrial respiration and ATP generation [238]. These data collectively suggest that the upregulation of 5αR and AP levels may provide a compensatory response to SD; however, the price of this neuroprotective reaction may lead to subtle PFC deficits, possibly facilitating the intrusion of microsleep episodes and sleep attacks. Ultimately, the robust enhancement in AP synthesis may activate GABA-A receptors within the pyramidal cells of the PFC, opposing their activation, causing connectivity deficits and ultimately resulting in deficits of information processing and executive functions (Fig. 2).

This idea underscores that the negative cognitive consequences of SD may arise from the attempt of the brain to counteract the neurotoxic effect of sleep loss through compensatory mechanisms. In general, whereas neurosteroids promote neuronal adaptation to stress, they may also hinder the execution of multitasking performance and reduce cognitive flexibility. It should be noted that, while the upregulation of 5αR and AP in acute SD may represent an appropriate response to withstand the bioenergetic challenges of this condition, it is likely that chronic sleep restriction may elicit opposite outcomes. Accordingly, chronic stress has been shown to reduce both 5αR and AP in the PFC of rodents [239]. Future research will be needed to understand how neurosteroids support the pathophysiology and complications of sleep disturbances and stress coping, as well as their relations with gating disorders. This direction may pave the way for the identification of neurosteroid targets in the therapy of sleep problems and gating disorders as well as the identification of the role of 5αR in other executive tasks, such as 5C-CPT and IGT.

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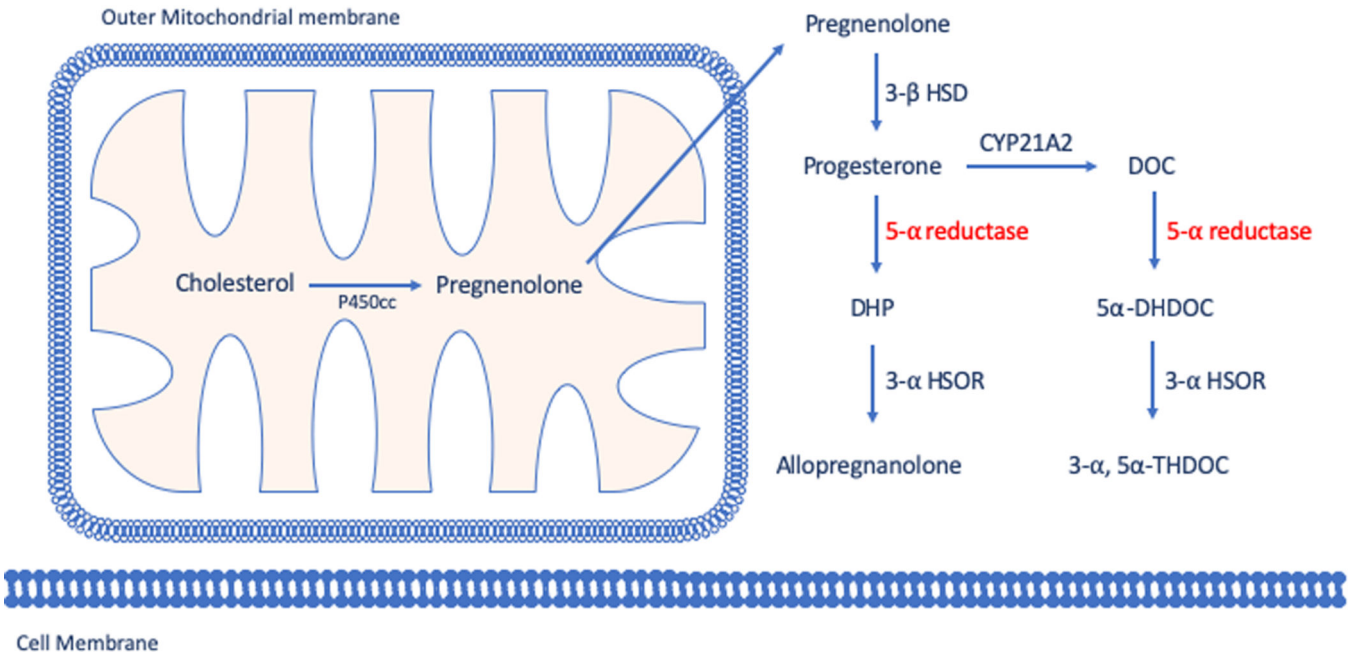

Figure 1. Simplified schematization of neurosteroids biosynthesis by 5-alpha reductase pathway.
For a complete steroid synthesis pathway including other neurosteroids, see Frau and Bortolato 2018.

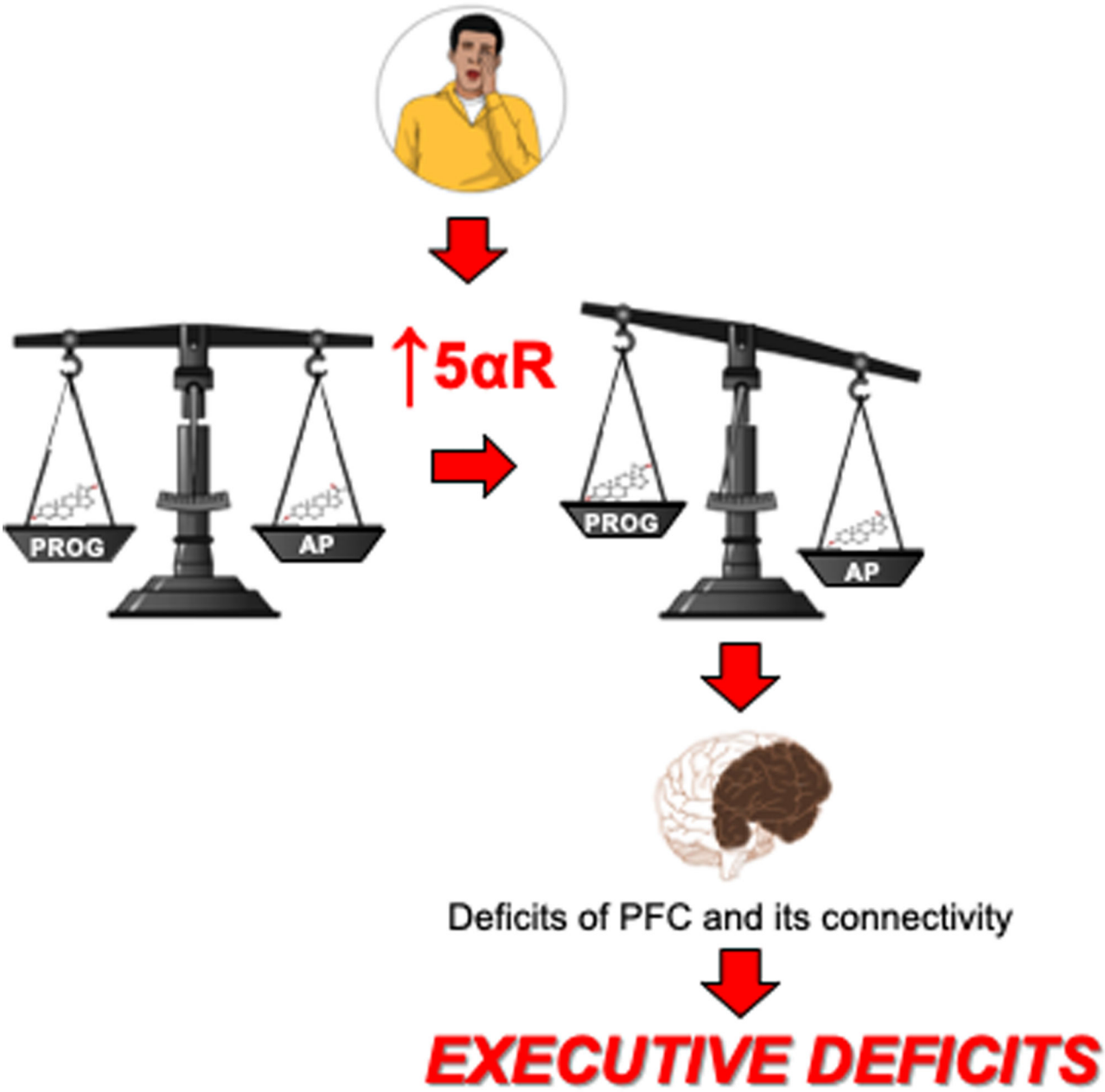

Figure 2. Diagram of the hypothesized role of neurosteroids in the neurobehavioral complications induced by sleep deprivation.

Similar to other stressors, acute sleep deprivation leads to increased expression of 5-alpha reductase and synthesis of the neurosteroid allopregnanolone in the PFC. Whereas this upregulation is likely aimed at counterbalancing the detrimental impact of oxidative stress induced by sleep deprivation, such compensatory mechanism may in turn set off neurobehavioral complications by interfering with the corticolimbic connections responsible for executive functions and emotional regulation. Enzymes: CYP21A2: Steroid 21-hydroxylase; 3β-HSD; 3β-hydroxysteroid dehydrogenase; 3α-HSOR: 3α-hydroxysteroid

oxidoreductase. Steroids: DOC, deoxycorticosterone; 5α-DHDOC, 5α-dihydro deoxycorticosterone; 3α,5α-THDOC, 3α,5α-tetrahydrodeoxycorticosterone, DHP, 5α-dihydroprogesterone. See text for further details.