Sleep deficiency as a driver of cellular stress and damage in neurological disorders

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SUMMARY

Neurological disorders encompass an extremely broad range of conditions, including those that present early in development and those that progress slowly or manifest with advanced age. Although these disorders have distinct underlying etiologies, the activation of shared pathways, e.g., integrated stress response (ISR) and the development of shared phenotypes (sleep deficits) may offer clues toward understanding some of the mechanistic underpinnings of neurologic dysfunction. While it is incontrovertibly complex, the relationship between sleep and persistent stress in the brain has broad implications in understanding neurological disorders from development to degeneration. The convergent nature of the ISR could be a common thread linking genetically distinct neurological disorders through the dysregulation of a core cellular homeostasis pathway.

Keywords
Sleep; Neurodevelopmental disorders; Neurodegenerative disorders; Fragile X syndrome; Autism spectrum disorder; Alzheimer’s disease; Integrated stress response; DNA damage response

Introduction

The brain is subject to unique stresses. Post-mitotic neurons are constrained in their ability to undergo cell death and replenish their population. The central neuronal network is an extremely metabolically demanding system, requiring approximately 20% of total basal oxygen consumption in adult humans, and as much as 50% in children \cite{1–3}. This demand is dependent on mitochondrial oxidative phosphorylation, which supplies much of the energy and maintains calcium and redox homeostasis to support key processes including neurogenesis, cytoskeleton assembly, signal transmission, and plasticity \cite{4–9}. Thus, the brain has a highly developed mitochondrial network, which may function to support the...
intricate synaptic networks and signal transmission necessary to sustain brain function [10]. This high metabolic load also produces high levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) as a byproduct of ATP synthesis. While the brain produces significant levels of antioxidants, stress and genetics can perturb the balance of oxidation and reduction, which along with other susceptibility features in the brain, increases the risk of persistent oxidative damage [11]. Together, these factors contribute to a brain environment that is rife with free radicals, which can lead to the accumulation of misfolded proteins and persistent DNA damage [12–15].

In post-mitotic cells such as neurons, constant repair is required since cell replacement is not an option for maintaining cellular function in the brain. Sleep likely plays a critical role during development and aging in reducing the metabolic demand of the brain [15,16] and repair of wake-induced cellular damage [17,18]. Sleep alters the translational profile of the brain to facilitate synaptic normalization and homeostasis [19–21]. Furthermore, sleep increases the clearing of metabolites accumulated during wake including misfolded proteins and proteolytic byproducts such as amyloid beta (Aβ) [22]. Wake-mediated free radicals also induce DNA lesions, which comprise a major class of DNA damage in neurons, leading to base pair modification and double-stranded DNA breakage (DSB) [13,18]. Sleep plays a direct role in repairing this DNA damage. The repair of enriched wake DSBs and gamma-irradiation induced DSBs is delayed or inhibited by sleep deprivation, with repair resuming upon the restoration of sleep [18]. In a study of overnight on-call doctors, expression of several key DNA repair genes was decreased after acute sleep deprivation [23]. Those genes include 8-oxoguanine glycosylase (OGG1), X-ray repair cross complementing 1 (XRCC1), and excision repair cross-complementing group 1 (ERCC1) in the base excision repair (BER) pathway, the primary mechanism for repairing oxidative base pair modification in neurons [24–26]. Furthermore, the study demonstrated that DNA breaks and oxidized purines were increased, and blood plasma antioxidant capacity was reduced, reflecting the role of sleep in DNA damage and repair [23].

Sleep deficiency and persistent oxidative stress leads to the accumulation of damage to proteins and DNA, which can further induce cellular stress [12–15]. Cells respond to stress through a versatile mechanism called the integrated stress response (ISR). The ISR is a signaling network found in all eukaryotic cells and is critical for cellular adaptation and homeostasis in response to external and internal stressors. Through the ISR, cells activate response programs to alleviate stress induced by misfolded proteins, DNA damage and metabolic pressure [27–30]. This includes the preferential activation of gene networks that repair and promote cell survival in the brain [31], as neurons must favor prosurvival solutions to stress. Wake is energy intensive and stressful [14,15,32,33]. Sleep provides a respite from wake and a time to activate homeostatic and repair mechanisms [18,19,22]. In fact, brain oxidation and the accumulation of DNA damage during wake play a role in triggering the induction of sleep to promote DNA repair [34–37]. Whether the ISR is functionally involved in the restorative function of sleep remains to be fully studied, however PERK signaling, a core feature of ISR activation, promotes sleep [38]. Parp1, a key factor in the initiation of DNA repair, also promotes sleep and the repair of DNA damage by inducing repair protein activity and chromosome mobility [36].
Metabolic stress and biomolecule damage is increased under conditions of sleep fragmentation [15,17,19], and inefficient and insufficient sleep are common underlying features of many neurological disorders [40–50]. Neurological disorders are highly comorbid with sleep abnormalities, suggesting that functions at the intersection of the ISR and sleep could contribute to the synaptic and behavioral deficits observed in these disorders. Despite the widely shared dysregulation of the ISR and sleep among neurological disorders, there is still little clarity on the mechanistic relationship between cellular stress and sleep dysregulation in neurological diseases. Evidence of persistent stress and stress-related damage to biomolecules along with the manifestation of sleep phenotypes is observed in neurological conditions arising by both genetic mutation and injury to the nervous system, underscoring the central nature of this relationship (Table 1). The goal of this review is to discuss our current understanding of the ISR and sleep, focusing on three neurological diseases (Alzheimer’s disease, autism spectrum disorder, and Fragile X syndrome) and propose future avenues of research to examine how these processes interact to contribute to the progression of neurological dysfunction (Fig. 1).

Alzheimer’s disease

Aging may be associated with a mild decline in mental acuity, however significant cognitive decline or memory loss is not a typical feature of healthy aging. Alzheimer’s disease (AD) is a progressive disorder, which often initially presents in older adults and worsens with age. AD is the most common cause of dementia, and the fifth leading cause of death in adults over 65 [51]. Great strides have been made in understanding the etiology and progression of AD, however our knowledge is still incomplete and our efforts to slow AD progression have yielded little success. The involvement of the ISR in neurodegeneration is widely supported and activation of the ISR has been described in both animal models [52–55] of AD as well as in brain tissue from individuals with AD [52,54–57]. An abundance of oxidative stress, ER stress, and mitochondrial dysfunction are well documented in AD. This cellular oxidative stress likely contributes to accumulation of protein and DNA damage that feeds back into ISR activation leading to persistent ISR activation in AD.

The awake brain operates at an elevated baseline of oxidative stress [3,11,58]. Elevated oxidative damage is highly implicated as a major contributor to cell death and the progression of AD. Increased oxidative stress, ER stress, and mitochondrial dysfunction are well documented in AD. The cellular stress response, which is strongly upregulated by the ISR, is likely involved in sustaining the etiology and progression of AD. BACE1 is involved in the initiation of the amyloidogenic pathway and the buildup of Aβ, which is crucial in the pathogenesis of AD. BACE1 is involved in the pathogenesis of AD, which is relevant to the pathogenesis of AD.

Reduced activity of OGG1, Uridine-DNA glycosylase (UDG), and DNA polymerase beta (POLB), key factors in the BER pathway, is observed in the brains of AD patients. Two nuclear and mitochondrial DNA damage repair pathways, the BER and the NER, are impacted in individuals with amnestic mild cognitive impairment, which represents a transitional phase between normal aging and the development of AD [63]. Both nuclear and mitochondrial DNA damage repair pathways are affected in AD, leading to a BER deficiency [65,66]. Additionally, BER function is impaired in individuals with amnestic mild cognitive impairment with advanced age, which represents a transitional phase between normal aging and the development of AD [63].
oxidative damage is apparent in this early stage of cognitive impairment, reflecting this BER deficiency [67, 68], and suggesting that BER deficiency may be an early indicator in the development of AD. This impairment is observed in both the cerebellum and inferior parietal lobule, which correspond to the least and most highly affected regions of the brain, respectively [65], indicating that BER deficiency may be a susceptibility feature of the AD brain, rather than directly contributing to neuronal cell death, which is not observed in the cerebellum.

Even in normal aging, sleep quantity and quality progressively decline with age and the association between sleep disturbances, cognitive decline, and the risk of developing dementia is widely documented. In a meta-analysis, a random effect model predicted that individuals experiencing sleep disturbances had a 1.49-fold increased risk of developing AD [69]. Common sleep problems experienced with age include insomnia, sleep fragmentation, sleep disordered breathing, disrupted circadian rhythms, and excessive daytime sleepiness, which are exacerbated with the development and progression of AD [43, 70, 71]. The role of sleep in the underlying etiology of AD is not understood, however it is likely that the progressive development of sleep abnormalities contributes to, or at least aggravates the cognitive and behavioral characteristics of AD and neurodegeneration in general.

**Autism spectrum disorder**

Autism spectrum disorder (ASD) is a behaviorally defined group of neurodevelopmental disorders (NDD) characterized by social and cognitive deficits, and is increasingly prevalent, with an estimated one in 59 children diagnosed with ASD worldwide [72]. Because ASD is currently diagnosed based only on behavioral criteria, there is no single underlying etiology, and many genetically distinct disorders are grouped together based on shared or similar cellular dysfunctions and phenotypic presentations. Studies in children with ASD increasingly implicate oxidative stress, and its deleterious effects on brain and metabolic processes, as an important feature of ASD pathophysiology. ER stress is a major contributor to ISR activation in ASD. Several genetic models of ASD have been shown to induce ER stress [73–76], however because ASD is an extremely heterogeneous disorder, any single copy number variant or genetic mutation is found in only a small fraction of ASD cases. Using a multivariate model, a recent study showed that ASD status was able to predict mRNA levels of ER stress genes including PKR-like ER kinase (PERK), activating transcription factor 4 (ATF4), activating transcription factor 6 (ATF6), X-box binding protein 1 (XBP1), C/EBP homologous protein (CHOP), and inositol-requiring enzyme 1 (IRE1). Expression of these genes were significantly upregulated in the middle frontal gyrus in individuals with ASD. Additionally, ER stress genes were positively associated with stereotyped behavior classified by the Autism Diagnostic Interview-Revised (ADI-R) [77]. Not only does protein oxidation lead to the accumulation of damaged and unfolded proteins, but mistranslated or mutated proteins are also more susceptible to oxidation, thus eliciting a cycle of damage and stress [60].

The effects of oxidative stress are potentially more damaging during early development due to low glutathione levels and an immature antioxidant system [78–80]. Thus, children are more susceptible to damage from oxidative stress at typical levels, even before considering
the elevated levels observed in children with NDD. Elevated oxidative stress has more recently become an area of interest in neurodevelopment and the development of intellectual disability disorders such as ASD. Accumulation of ROS, decreased antioxidant capacity, and damage to biomolecules have been demonstrated in the blood or postmortem brain tissue of children with ASD [81–85]. Children with ASD have an elevated concentration of 8-oxo-dG in the cerebellum and temporal cortex compared to typically developing children [81]. BTBR T+ Iprc3/J (BTBR) mice, which exhibit autism-like behavioral phenotypes, also exhibit elevated 8-oxo-dG levels in the cerebellum, which is inversely correlated with a 70–73% decrease in Oggl expression. Male BTBR mice also exhibit significantly more mitochondrial DNA damage [86]. It is important to note that BTBR mice differ genetically from their C57BL/6J controls, including single nucleotide polymorphisms between the strains in the coding and noncoding regions of Oggl. Genomic 8-oxo-dG enrichment is also observed in human post-mortem cerebellar samples, providing confidence in the translation of these results.

Abnormal sleep is a common feature of NDDs including ASD and related intellectual disability disorders [40,41,44–49]. In fact, sleep difficulties are included as a diagnostic criterion of many NDDs, and have been reported in 80% of children with intellectual disability in general [87] and 44–83% of children with ASD [44,88]. The types of sleep disturbances experienced by children with ASD are quite abundant and variable, potentially reflecting the underlying variability in etiology, however in one study, 86% of children were found to experience at least one sleep problem every day, with insomnia being the most commonly reported at 56% [89]. In addition to their prevalence, sleep problems in children with ASD also increase over time [46]. Children with ASD who are considered “poor sleepers” are more likely to have more affective problems and poorer social interactions than “good sleepers” or typically developing children [40]. These persistent sleep deficits and their correlation with behavior and social interactions suggest that sleep intervention has the potential to improve developmental outcomes of children with ASD.

**Fragile X syndrome**

Fragile X syndrome (FXS) is a neurodevelopmental disorder characterized by anxiety, social behavioral deficits, cognitive impairment, and sleep abnormalities. Individuals with FXS have an increased risk of developing attention deficit disorder (ADD) and ASD. In fact, FXS is the most common monogenic cause of inherited intellectual disability and ASD [90]. FXS is caused by the loss of fragile x mental retardation 1 (FMR1) gene expression. Its encoded protein, fragile x mental retardation protein (FMRP), has well-studied functions as a translational regulator [91], however its roles within the nucleus are much less understood. FMRP has recently been identified to have roles in gene expression and genome function, including the DNA damage response [92,93]. Individuals with FXS express important DNA repair genes at lower levels than their typically developing counterparts, including key BER factors OGG1 and XRCC1 [94]. Some of these genes, and oxidative stress itself, are also implicated in trinucleotide expansion, the most common cause of FXS in humans [95–98].

The role of the ISR in the brain in FXS is an active area of investigation. Aβ levels are elevated in the brains of FXS patients and Fmr1 KO mice, which also exhibit
elevated amyloid precursor protein (APP), thus BACE1 inhibitors have been proposed as a potential therapeutic strategy for FXS [99,100]. *Fmr1*-deficient mice exhibit elevated NADPH-oxidase activity, altered antioxidant activity, and increased oxidation of lipids and proteins. Interestingly, elevated ROS levels are developmentally dependent, detected at 4 months of age but not early (newborn and 1 mo old) or late (8 and 12 months old) in development [101,102]. FXS phenotypes and deficits at the molecular, cellular, and synaptic levels are also highly developmentally regulated [103–106]. Whether the interaction of sleep, the DNA damage response, and cellular stress plays a role in orchestrating the developmental trajectory of FXS poses an exciting question that remains to be addressed.

Sleep difficulties are a prevalent phenotype of children with FXS, and are detected very early in development, suggesting that sleep has the potential to contribute significantly to the manifestation or aggravation of other FXS phenotypes. According to a large caregiver survey, 32% of children with FXS suffer from sleep difficulties, with sleep latency and fragmented sleep being the most common difficulties [49]. Additionally, sleep problems in children with FXS were most highly reported to occur in early development, before the age of three (71% of males and 64% of females who experience sleep problems), with progressively diminishing reports of sleep problems with age (10% of males and 21% of females after the age of eleven) [49]. If sleep plays a role in the precipitation or aggravation of damage accumulation and persistent cellular stress response, these phenotypes may also exhibit a variable or developmentally dependent pattern in FXS. Consequently, this relationship presents the possibility that the alleviation of sleep deficits may have a significant impact on FXS developmental outcomes. Insufficient or poor sleep has far-reaching impacts on both physical and mental health including the development of metabolic disorders, cancer, cognition and learning deficits, and depression, which can in turn, negatively impact sleep [107–110].

**Discussion**

The relationship between sleep and activation of the ISR involves an interconnected web of bidirectional effects, which can escalate through feedback loops to drive neurological impairment. The ISR is an elaborate signaling network that integrates intrinsic and extrinsic stimuli to moderate the normal cellular stress of a functional organism. Thus, disruptions in a wide variety of pathways, which contribute to many different disorders, converge upon this central pathway. In this review, we have focused on ISR activation in the brain, which is particularly susceptible to oxidative stress. Persistent activation of the ISR in the brain has been demonstrated in neurodegenerative and neurodevelopmental disorders of diverse etiologies. We present sleep deficiency as another shared feature among these disorders, which can activate the ISR through the accumulation of unrepaired damage to biomolecules such as DNA and proteins.

Sleep deprivation induces ER stress through the unfolded protein response in the cortex [12,111,112]. Due to high metabolic demand during wake, extended wake likely leads to the depletion of ATP, inhibiting protein folding and leading the accumulation of misfolded proteins [12]. In addition to damage by ROS in the highly oxidative environment of the brain during sleep deprivation [23,113], the accumulation of aberrant proteins causes further
protein oxidation, promoting a positive feedback loop of stress and damage, which may be exacerbated by sleep deficits [12,60]. The connection between sleep and the repair of DNA damage has only been demonstrated in recent years and there is still much that remains to be understood about how sleep promotes the maintenance of a healthy genome. Current evidence supports a role for sleep in mediating the levels and activity of key repair enzymes [18,23,36] and regulating chromosome dynamics [36,37] in the repair of DNA damage. Deficiencies in sleep-mediated repair or clearance of damaged biomolecules can potentially lead to elevated levels of cellular stress, persistently activating the ISR. While the effect of sleep deprivation on oxidative stress in the brain is not uniform [113–116], dysregulation of the ISR and the accumulation of biomolecular damage may shed light on the mechanisms underlying the development of cognitive impairment observed in many neurological disorders.

Although neurological disorders are heterogenous in genetic etiology, environmental interactions, and phenotypic presentation, sleep disruption is a pervasive feature central to disorders across the spectrum [41,69,117,118]. Sleep abnormalities were once considered a side effect rather than a central phenotype in these patients, however studies of disorders with known genetic etiologies, including FXS, have offered insight into the molecular basis of sleep physiology and homeostasis in maintaining a healthy and balanced synaptic network [118–121]. Impaired sleep manifests as a variety of deleterious stresses and dysfunction at the molecular, cellular, and synaptic levels.

Pharmacological modulation of the ISR has become an area of great interest in the treatment of a variety of neurological disorders given its central role in cellular homeostasis. Beneficial effects of both inhibitors and enhancers targeting different levels of the ISR pathway have been observed, especially in neurodegenerative disorders including AD [16]. However, unexpected and undesirable side-effects are of concern when targeting the ISR in heterogeneous cell populations. Additionally, modulation of the ISR must be carefully regulated, as cells must maintain the ability to respond efficiently to other sources of normal stress stimuli. Given the relationship between sleep deficiency and cellular stress, a combinatorial approach leveraging both pharmacological and sleep intervention therapies presents a potentially more moderate and adaptable mechanism for modulating the ISR in a wide variety of neurological disorders, while also providing the many benefits of healthy sleep. While we have focused on the brain in this review, sleep deficiency, biomolecule damage, and conditions of high cellular stress pose threats to the health of all systems in the body and gaining a deeper knowledge of these processes and their relationship will be invaluable to our understanding of human health.

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## Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| Aβ           | Amyloid beta |
| AD           | Alzheimer’s disease |
| ADD          | Attention deficit disorder |
| ADI-R        | Autism Diagnostic Interview-Revised |
| APP          | Amyloid precursor protein |
| ASD          | Autism spectrum disorder |
| ATF4         | Activating transcription factor 4 |
| ATF6         | Activating transcription factor 6 |
| BACE1        | Beta-secretase 1 |
| BER          | Base excision repair |
| BTBR         | BTBR T<sup>Itpr3</sup>tf/J |
| CHOP         | C/EBP homologous protein |
| DSB          | Double-strand break |
| ERCC1        | Excision repair cross-complementing group 1 |
| FMR1         | Fragile X mental retardation 1 |
| FMRP         | Fragile X mental retardation protein |
| FXS          | Fragile X syndrome |
| IRE1         | Inositol-requiring enzyme 1 |
| ISR          | Integrated stress response |
| NDD          | Neurodevelopmental disorders |
| OGG1         | 8-oxoguanine glycosylase |
| PERK         | PKR-like ER kinase |
| POLB         | Polymerase beta |
| RNS          | Reactive nitrogen species |
| ROS          | Reactive oxygen species |
| UDG          | Uracil-DNA glycosylase |
| XBP1         | X-box binding protein 1 |
| XRCC1        | X-ray repair cross complementing 1 |
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* The most important references are denoted by an asterisk.

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Practice points

- Sleep deficits are a prevalent phenotype among neurodevelopmental and neurodegenerative disorders, and in some cases sleep phenotypes are included as a diagnostic criterion.
- The brain is a highly oxidative environment due to the high metabolic load, especially during waking activity.
- Sleep deprivation may activate the ISR through the accumulation of biomolecular damage and prolonged cellular stress.
- The expression and activity of DNA repair genes is downregulated under conditions of sleep deprivation.

Research agenda

- Further elucidate the mechanisms underlying sleep-dependent regulation of biomolecule repair.
- Examine how persistent activation of the integrated stress response in the brain may contribute to synaptic dysfunction in neurological disorders.
- Assess combinatorial approaches leveraging pharmacological and sleep intervention as an adaptable therapeutic strategy for neurological disorders.
Fig. 1.
A proposed model of the relationship between sleep and the integrated stress response (ISR), drawn from observations described in the literature. Sleep deficiency, a common phenotype among neurological disorders, may lead to persistent activation of the stress response through these pathways, driving a positive feedback loop of stress and damage in the brain.
| Neurodevelopment                      | Onset of delay | Onset of sleep difficulties | Prevalence of sleep deficits | Sleep phenotypes                                                                 | Cellular stress and damage in the brain                                                                 | Cognitive and behavioral phenotypes |
|--------------------------------------|----------------|-----------------------------|------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------|
| Autism spectrum disorder (ASD)       | 12–18 months   | 0–6 months [122]            | 86% [88]                     | Insomnia, bedtime resistance, parasomnias, sleep disordered breathing, morning rise problems, daytime sleepiness, increased sleep latency, decreased sleep efficiency, decreased REM, increased late-stage NREM [88] | ER stress, altered expression of ER stress genes, accumulation of reactive oxygen species, decreased antioxidant capacity, lipid peroxidation, increased levels of 8-oxo-dG [72–76,80–84] | Restrictive and repetitive behaviors, avoiding physical contact, communication deficits, sometimes non-verbal, social interaction deficits [123] |
| Fragile X syndrome (FXS)             | 12–16 months   | ≤3 years [50]               | 32% [50]                     | Increased sleep latency, sleep fragmentation, reduced REM duration, fewer REM bouts, disrupted NREM [50,124] | Decreased expression of DNA repair genes, elevated Aβ levels, elevated NADPH-oxidase activity, altered antioxidant activity, increased lipid and protein oxidation [93,98–101] | Cognitive impairment, hyperactivity, anxiety, social avoidance, hyper arousal to stimuli, attention deficits, increased risk of ASD [125] |
| Neurodegeneration                    |                |                             |                              |                                                                                   |                                                                                                          |                                    |
| Alzheimer's disease (AD)             | ~65 years      |                             | 45% [126]                    | Insomnia, sleep fragmentation, sleep disordered breathing, disrupted circadian rhythms, excessive daytime sleepiness, decreased REM and NREM [44,70,127,128] | Cellular oxidative stress, ER stress, mitochondrial dysfunction, upregulation of BACE1, nuclear and mitochondrial DNA oxidation, reduced activity of base excision repair proteins [53–58,60,62–67] | Sun downing (agitation/confusion beginning around dusk), dementia, memory loss, impaired communication, disorientation/confusion, poor judgement, behavioral changes, difficulty swallowing, speaking, and walking [52] |
| Parkinson's disease (PD)             | ~65–70 years   | RBD onset often precedes PD  | 90% [130]                    | REM sleep behavior disorder (RBD), daytime sleepiness, insomnia, restless leg syndrome, decreased total sleep time, decreased sleep efficiency, decreased REM and NREM, increased wake time after sleep onset, increased REM latency, sleep apnea [130] | Oxidative stress, elevated 8-oxo-G, abasic sites, and nuclear DNA strand breaks, persistent mtDNA abasic sites, impaired mitochondrial complex I, reduced ATP synthesis, increased ROS production, increased mitochondrial mutations and defective mitochondrial repair pathways, decreased GSH levels [131–133] | Problems with movement (tremor, rigidity, bradykinesia, postural instability), dementia, depression, sensory dysfunction, cognitive changes, behavioral changes, autonomic dysfunction [134] |
| Neurological injury                  |                |                              |                              | Sleep apnea, excessive daytime sleepiness, circadian rhythm misalignment, sleep-wake disturbances, fatigue, insomnia, hyperomnia, REM behavior disorder [135–138] | Oxidative stress, ER stress, elevated reactive oxygen species, neuroinflammation, disrupted brain energy metabolism, lipid peroxidation, impaired energy homeostasis, increased Aβ, BACE1, and APP [139–141] | Centralized pain, headaches, negative mood and emotional impacts, depression, anxiety, memory impairment, increased risk of neurodegenerative disease [138,142] |
| Traumatic brain injury (TBI)         |               | Risk factor and outcome     | 30–70% [135]                 | Insomnia, sleep disordered breathing, circadian rhythm dysfunctions, sleep-related movement disorders, decreased REM, prolonged REM latency, decreased NREM, reduced | Excessive ROS production, decreased ROS scavenging (decreased SODs, CATs, GPx, and glutathione), depletion of cellular energy, inflammation, DNA damage (apurinic/apyrimidinic sites, oxidative base modifications, | Depression, anxiety, impaired mobility, cognition and memory, and speaking, emotional difficulties, social isolation, fatigue [151] |
|                                    |               |                             |                              |                                                                                   |                                                                                                          |                                    |
| Stroke                              | Risk factor and outcome [143] | 20-69% (insomnia) [144] | 30-70% [135]                 | Insomnia, sleep disordered breathing, circadian rhythm dysfunctions, sleep-related movement disorders, decreased REM, prolonged REM latency, decreased NREM, reduced | Excessive ROS production, decreased ROS scavenging (decreased SODs, CATs, GPx, and glutathione), depletion of cellular energy, inflammation, DNA damage (apurinic/apyrimidinic sites, oxidative base modifications, | Depression, anxiety, impaired mobility, cognition and memory, and speaking, emotional difficulties, social isolation, fatigue [151] |
| Onset of delay | Onset of sleep difficulties | Prevalence of sleep deficits | Sleep phenotypes | Cellular stress and damage in the brain | Cognitive and behavioral phenotypes |
|---------------|-----------------------------|-----------------------------|------------------|----------------------------------------|-----------------------------------|
|               |                             |                             | total sleep time, lower sleep efficiency [145-147] | single-strand breaks, and double-strand breaks [148-150] |                                   |

Abbreviations: ROS, reactive oxygen species; REM, rapid eye movement; NREM, non-REM; RBD, REM sleep behavior disorder; ER, endoplasmic reticulum; Aβ, Amyloid beta; GSH, glutathione; BACE1, Beta-secretase 1; APP, Amyloid beta precursor protein; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase.