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Review article

Long-term sleep disturbances in children: A cause of neuronal loss

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ABSTRACT

Short-term sleep loss is known to cause temporary difficulties in cognition, behaviour and health but the effects of persistent sleep deprivation on brain development have received little or no attention. Yet, severe sleep disorders that last for years are common in children especially when they have neurodevelopmental disabilities. There is increasing evidence that chronic sleep loss can lead to neuronal and cognitive loss in children although this is generally unrecognized by the medical profession and the public. Without the restorative functions of sleep due to total sleep deprivation, death is inevitable within a few weeks. Chronic sleep disturbances at any age deprive children of healthy environmental exposure which is a prerequisite for cognitive growth more so during critical developmental periods. Sleep loss adversely effects pineal melatonin production which causes disturbance of circadian physiology of cells, organs, neurochemicals, neuroprotective and other metabolic functions. Through various mechanisms sleep loss causes widespread deterioration of neuronal functions, memory and learning, gene expression, neurogenesis and numerous other changes which cause decline in cognition, behaviour and health. When these changes are long-standing, excessive cellular stress develops which may result in widespread neuronal loss. In this review, for the first time, recent research advances obtained from various fields of sleep medicine

Abbreviations: fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; NDD, neurodevelopmental disabilities; NREM, non-rapid eye movement; REM, rapid eye movement.

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are integrated in order to show that untreated chronic sleep disorders may lead to impaired brain development, neuronal damage and permanent loss of developmental potentials. Further research is urgently needed because these findings have major implications for the treatment of sleep disorders.

Contents

1. Introduction

Recent research activities in various fields of sleep medicine force us to view the wake–sleep states as an interrelated and orchestrated change in behavioural, cognitive, genetic, anatomical, electrical, molecular, cellular, biochemical, and endocrine functions in which the pineal melatonin plays an important role.[1] Viewing sleep as a complex, neurological process rather than an independent state promotes better understanding of sleep disorders and their adverse effects on cognition, behaviour and health. The purpose of this review is to discuss the neuronal, metabolic and other mechanisms of sleep, based on recent scientific advances; then to summarise and integrate the evidence which supports the hypothesis that in childhood chronic sleep deprivation can lead to permanent neurological damage especially during early critical developmental periods. Sleep deprivation is generally defined in sleep medicine as sufficient loss of sleep during a period of time which results in impairment of neurological and physical functions. Sleep deprivation not only depends on the quantity but also on the restorative quality and timing of sleep. Children require more sleep than adults with individual variations. Sleep deprivation can be short or long-term, partial or total. Short-term sleep deprivation could be caused by loss of a few hours of sleep. It is more difficult to define chronic or long-term partial sleep loss but in clinical practice children with neurodevelopmental disabilities frequently exhibit persistent sleep disturbances with inadequate hours of sleep for years or even lifetime. Partial and also total short-term sleep loss has been studied mainly in animals, less frequently in healthy adults but only on rare occasions in children.[2–4] Research on the permanent adverse effects of sleep loss on neurodevelopment is still minimal.[5] There are no controlled studies in children, which is not surprising as such experiments are unethical to perform, due to adverse psychological and medical consequences.

One of the anecdotal total long-term sleep deprivation experiments involved a top radio personality, Peter Tripp, who in 1959 wanted to break the world record for staying awake for the longest period of time. He succeeded in breaking the record by staying awake for 201 h but became psychotic towards the end of his ordeal. Following this event, those close to him felt that his personality had permanently changed. He lost his job, had difficulties settling and his wife divorced him.[6] Since then others have broken the world record for staying awake but all of them had serious cognitive and behavioural changes during their attempts. The long-term neurological and psychological consequences were not studied. The experiment of Peter Tripp illustrates the critical importance of sleep for survival. Indeed, complete lack of sleep in animal experiments leads to death within 3 weeks.[7,8]

In typically developing children, with exceptions, the sleep difficulties tend to be partial, short term and respond favourably to appropriate management.[9] In contrast, in children with neurodevelopmental disabilities (NDD) the prevalence rates of sleep difficulties may be as high as 75–80% and the sleep disturbances tend to last for years or even for a lifetime. While they can be helped by therapies or environmental changes they may respond less readily than typical children.[10–12] Sleep disturbances are associated with many neurological conditions, alone or in combinations, such as intellectual disability,[13] epilepsy,[14] cerebral palsy,[15] visual impairment,[16] autism,[17] attention deficit hyperactivity disorder,[18] fetal alcohol spectrum disorders[19] and brain maldevelopment.[20] Not infrequently such children only sleep for 3–4 h a night for years or for their entire lives. The number of coexisting neurological disorders and their severity proportionately predispose to disturbed sleep.[21] Untreated sleep deprivation may lead to deterioration of the already impaired brain functions as evidenced by increased difficulties in learning, memory, verbal creativity, attention, abstract reasoning and many other perceptual, cognitive and

motor functions.[22–24] Sleep problems are more common in remedial classes for children with various forms of NDD than in primary schools.[23,25] In children with obstructive sleep apnea the degree of sleep disturbance and the severity of intellectual and behavioural changes are strongly linked. For example, among first grade students with the lowest marks, there was a 6–9-fold increase in the expected prevalence of sleep apnea.[26] Thus, the possibility exists that a vicious cycle may be created which feeds back to itself as sleep disorders in children with NDD lead to increasingly impaired cognition and further deterioration of sleep.

The three most common sleep disturbances in children with NDD are difficulties falling asleep, frequent awakenings during the night and early morning arousals alone or in combinations. Although diagnostic sleep studies in the NDD population are scarce, these sleep disturbances are generally considered to be circadian rhythm sleep disorders and they tend to be associated with abnormally timed, or reduced pineal melatonin production and secretion.[27] When sleep disorders are appropriately treated, even after years of delay, caregiver reports show that there is significant improvement in intellectual function, behaviour and health.[28] However, a strong possibility still exists that the delay in treatment adversely affects the ultimate intellectual potentials of these children. Chronic sleep deprivation may occur at any age, but the adverse consequences are much more likely to occur in younger children, whose immature brains are rapidly developing in contrast to adults with mature central nervous systems.

2. Critical developmental periods

Our sensory systems respond to environmental information by transducing it to electrical activity in the brain. The vast number of neuronal groups, 'modules' or 'assemblies', also communicates by means of electrical oscillations. Because of environmental exposure during development, competition occurs between neuronal assemblies which results in the creation of neural pathways and anatomical regions responsible for later cognition and mature behaviour. The timing and duration of environmental exposure, motivation, attention to tasks and age are some of the important influencing factors. Neurodevelopment occurs in cascades as each step is built on a preceding stage. The durations of the huge number of critical periods are still unclear and they vary according to specific motor and cognitive abilities. During these critical times the synaptic activity exhibits the highest level of plasticity and connectivity which are the cellular substrate of memory formation and learning. Children's neurological circuits are particularly receptive to acquiring information. They respond quickly to genetic and environmental information but are also more susceptible to damage.[7,29] The developmental steps are accompanied by electrical, functional, structural, neurotransmitter, neuromodulator, biochemical, hormonal and other physiological changes.[29] The best example to illustrate the existence of high susceptibility to damage during critical developmental periods is fetal alcohol spectrum disorders, because even small amounts of alcohol during pregnancy may have devastating teratogenic effects on the central nervous system of the fetus in contrast to alcohol exposure in adults who have mature nervous systems.[30]

3. Electrical activity of the brain

The purpose of this section is to describe the electrical changes in sleep and relate these to brain functions, sleep disturbances and development. The global electrical activity of the brain is the summation of oscillatory frequencies between myriads of neuronal modules. In both mammals and humans, these frequencies and patterns are very different in wakefulness, drowsiness and in certain sleep stages.[31] Based on these and clinical differences, sleep patterns in the electroencephalogram (EEG) are divided into two major components: rapid eye movement (REM) and non-rapid eye movement (NREM) states and they are further divided into sub stages. Furthermore, NREM and REM sleep cyclically alternate during the night. The brain is much more active in REM than in NREM states. In REM sleep the cortical blood flow and oxygen delivery are high, especially in the brainstem and limbic regions and EEGs show intense neuronal firing in most areas of the brain. In all mammals the duration of REM sleep is much higher during early development than later in life and parallels the rate of cognitive development which indicates the need for healthy sleep.[32,33]

A healthy exposure to the environment is important because neuronal development is stimulus-dependent.[34] Contact with the environment is transduced into electrical activity which represents the critically needed exogenous stimulus. Neurons also receive endogenous stimulation provided by the intense electrical communication between neuronal assemblies especially during REM sleep.[35–38] Roffwarg and co-workers were the first to suggest that the primary purpose of REM was the promotion of brain development.[39] Exogenous and endogenous stimulation influences neurogenesis, synaptic activity, connectivity and assists in learning and memory formation. In animals, persistent REM sleep deprivation leads to increased energy expenditure, weight loss in spite of higher food intake, decreased body temperature, debilitating appearance and death.[8] Chronic REM sleep deprivation leads to increased programmed cell death (apoptosis), smaller brain size and it also limits cerebral maturation resulting from environmental enrichment.[40–42]

The development of thalamocortical and intracortical patterns of innervations between neuronal groups is also reflected in the maturation of NREM sleep and corresponds to the height of synaptic remodelling in early life.[43] In early NREM sleep spindle formation has been considered to be a marker for neuronal plasticity and consolidation of new procedural learning. Sleep spindle formation, a pattern of electrical oscillations, is often abnormal in children with NDD and with structural brain abnormalities while the increased number of spindles have been correlated with higher performance IQ.[43] However, it is now apparent that the main role of spindles is the induction and maintenance of NREM sleep.[1] Spindle activity prepares the brain for sleep globally and regionally while taking into consideration the level of previous sensory input as spindle activity is more active over areas of the cortex that have received stimulation prior to sleep.[44]

During deeper NREM sleep the spindles gradually disappear and in its deepest stages, the electrical pattern of the EEG is characterised by diffuse slowing, similar to encephalopathy due to pathological conditions which have resulted in cortical deactivation.

Recent research advances in cellular studies show that sleep is physiologically required by individual groups on neurons which is a very important observation.[45] This is even evident when the electrical oscillations of neurons are analysed in slide preparations of the brain as the recorded slow oscillatory activities are similar to the brain waves during NREM sleep.[46] However, central mechanisms are critically important for modulating and synchronizing sleep states in all regions of the brain. The radically different electrical patterns in NREM and REM sleep stages suggest different functions. NREM sleep is likely to play an important metabolic role in correcting the energy and nutritional imbalances following prolonged wakefulness while REM sleep is more important for providing a supportive role for endogenous stimulation, neurogenesis, neurological and emotional development, memory formation and learning. Clearly, there is increasing evidence from studying the electrical activity of the brain that sleep disturbances can influence neuronal development and function.

4. Homeostatic mechanisms in sleep

During early sleep research, Borbely introduced theories explaining the influence of circadian and homeostatic mechanisms on sleep.[47] He suggested that the circadian rhythm oscillators in the suprachiasmatic nuclei of the hypothalamus control the sleep–wake cycles and the homeostatic process regulates sleep need, which increases during the day and decreases during NREM sleep. It was hypothesized that the accumulation of one or more unknown substances in the brain during the waking hours were responsible for this homeostatic process. Research has since shown that prostaglandin D2, adenosine, nitric oxide, tumour-releasing factor, interleukin-1 and growth hormone releasing hormone and other substances are these homeostatic sleep-inducing factors.[45,48,49] For example, prostaglandin D2, a local hormone, and adenosine, a purine nucleoside energy regulator, accumulate in the brain during wakefulness, especially in the forebrain structures, and they promote sleep. During NREM sleep adenosine moves into the cells and serves as a fuel supply in the mitochondria. When prostaglandin D2 was continuously infused into the third ventricle of rats, it induced NREM and REM sleep in a dose-dependent manner, as judged by EEG studies and behavioural observations.[50] When adenosine was perfused into rats in another study, it produced impairment of vigilance resembling the effects of sleep deprivation.[51] With longer sleep deprivation, the accumulation of sleep regulatory substances increases and with it, the need for sleep.[45,52] During neuronal activities, the brain uses other energy sources such as glycogen, which is primarily stored in astrocytes.[53,54] Astrocytes have a role in the regulation of the pre-and post-synaptic terminals of excitatory and inhibitory synapses[55] and play an important role in the energy regulation of sleep homeostasis by releasing transmitters at receptor sites. They also have a role in cognitive decline during sleep loss.[56] Key protein levels in central synapses are high after waking and low after sleep indicating their strong homeostatic role in sleep.[57]

Sleep is not imposed on the brain by a single regulatory circuit which acts in a top-down manner. Depending on previous use, when regional neuronal groups require their own metabolic restoration, they are able to release sleep-promoting substances that may induce local NREM sleep.[45] When the homeostatic needs of local brain regions are unmet, their synaptic efficacy and connectivity are affected, which homeostatic imbalance then adversely influences the related cognitive functions, behaviours and learning. Sleep states normally require close interactions between local neuronal circuits and central mechanisms in order to avoid conflicting functions between various brain regions. As an example, after severe sleep deprivation microsleeps and lapses in attention commonly occur due to impaired interactions between central and local mechanisms.[58] In conclusion, it is again clear that temporary or persistent sleep disturbances can adversely affect brain functions both globally and locally at the cellular level.

5. Imaging studies

Neurons dynamically create oscillating electrical currents and induce corresponding magnetic fields which process requires large amount of energy. Depending on the types of functions performed during testing different regions of the brain are activated. Functional magnetic resonance imaging (fMRI) and positron emission tomography techniques detect these changes because of the underlying metabolic and hemodynamic responses. The generated electrical activity and the corresponding magnetic fields can also be studied by EEGs and magnetoencephalography (MEG) respectively. When these techniques are combined the visualization of functional activities in the brain is even more enhanced.

MRI studies in children show marked growth of the brain in the first two years of life, mainly due to grey matter development.[59] Structural and fMRI studies offer new insights into the mechanisms of sleep and the anatomical structures involved.[60,61] They are valuable tools in the understanding, diagnosis and treatment of specific sleep disorders.[62] They also shed light on how sleep deprivation can change neuroanatomical functions[58,63] and how the brain compensates for sleep loss.[5] Imaging studies have revealed decreased functional connectivity between the amygdala and medial prefrontal region following short-term sleep loss, but increased connectivity between the amygdala and autonomic activating centres in the brainstem. These findings help to explain emotional changes following sleep deprivation.[64] Imaging studies have shown reduced cerebral metabolism and also grey matter loss in cortical and subcortical structures associated with persistent obstructive sleep apnea.[64,65] Children with obstructive sleep apnea have more frequent EEG abnormalities compared to those without.[66] One may argue that the associated hypoxic episodes caused the brain damage in these children. However, in another important study adults with chronic primary insomnia and without comorbidities

were assessed by neuroimaging. Altena and colleges studied the brain volumes of 24 adults with chronic primary insomnia and 13 matched control subjects. The patients with sleep disturbances had significantly smaller grey matter volumes of the orbitofrontal and parietal cortex and a few other areas than the controls.[67] The cerebral cortex is not affected evenly by the process of sleep. In the early stages of NREM sleep the thalamus and the frontal and parietal lobes show reduced activity. In deeper NREM sleep stages the activity is further reduced in these regions and also in the basal ganglia and hippocampal structures. In contrast, the activity in REM sleep increases in the pons, limbic system and occipital regions but decreases in the parietal and prefrontal areas. Thus, fMRI confirms the existing knowledge of sleep physiology derived from other fields of sleep medicine. It shows that there is not a single superstructure for inducing sleep but a complex, widespread neurological network which operates between central and local neuronal structures.[60–62,68]

A useful way to study the neuronal mechanisms involved in sleep is to observe imaging changes in wakefulness, in sleep and following sleep deprivation. A number of fMRI studies have revealed the neuroanatomical correlates of impaired performance following sleep loss. Working memory is perhaps the most investigated cognitive function.[69] The others are verbal learning,[70] decision making, emotional responses[71] and attention.[64,72] Research into lapses of attention in individuals with sleep loss reveals interacting mechanisms in the brain that at the same time promote wakefulness and involuntary sleep.[72] Emotional events enhance memory formation by the influence of the amygdala on hippocampal structures. In sleep-deprived individuals the recollections of emotionally negative events elicit larger responses in the amygdala and occipital areas.[71] It is clear that there are individual differences in vulnerability to sleep loss. In contrast to partial sleep loss, we are not aware of human fMRI studies following severe total or chronic partial sleep deprivation. These studies are summarised in review articles.[63,73]

MEG studies also display changes in areas of the brain during wakefulness, in different sleep states or following sleep deprivation and are able to show an accurate spatio-temporal localization of specific cognitive functions.[74] MEG is based on detecting magnetic oscillations created by the electrical activity of the brain. The magnetic oscillatory activity in the range of 25–50 Hz (gamma-band frequencies) has been shown to be correlated with higher brain functions and thus the dysrhythmic sensory processing present in various neurological and psychiatric disorders can be revealed.[75–81]

The thalamocortical neuronal network has a major role in wakefulness and sleep.[1,74,82,83] During wakefulness and REM the specific gamma thalamocortical resonance is active indicating that cognitive experiences can be generated in both states. In various brain disorders the oscillatory communication between the thalamus and cortex has been reported to be disturbed and this thalamocortical dysrhythmia can also be a contributing factor to impaired sleep states.[75] Specific neurological changes in various sleep stages can be detected by MEG techniques.[84,85] While the wake state and REM sleep are similar in respect to the presence of gamma oscillations, there is an absence of any external sensory input during REM in contrast to wakefulness.[86] During deeper stages of NREM sleep, the amplitude of slow wave oscillations is higher than in wakefulness and REM sleep, but again, external environmental stimulation does not reset or change gamma oscillations. This means, as is already well known, that the external environment is for the most part excluded during REM and deep NREM sleep. Therefore, dreaming during REM is characterised by increased attentiveness to the intrinsic state but external stimuli do not influence the intrinsic activity. In conclusion, MEG brain imaging technology has a potential application in the study of all sleep disorders and sleep deprivation. Furthermore, MEG and other imaging studies have significantly increased our understanding the neurological processes involved in sleep and also changes in brain functions following short-term and chronic sleep loss.

6. Cellular stress during sleep deprivation

The most convincing evidence for permanent neuronal damage resulting from sleep loss comes from cellular studies in which animal experiments are indispensable. There is increasing evidence that even brief periods of total sleep deprivation may permanently imprint on neuronal plasticity. For example, during critical developmental periods the adverse effects of sleep loss on the visual system have been clearly shown.[87] Occlusion of one eye causes rapid remodelling of the visual cortex and its pathways. Sleep enhances neuronal plasticity while sleep loss reduces it, therefore experience-dependent (exogenous) stimulation can be modified.[88]

The effects of sleep deprivation on the neurophysiologic functions of neurons can be clarified by gene expression. Up-regulation of genes is different in wakefulness, sleep and during sleep deprivation. Microarray analysis of the mouse brain has shown that over 2000 genes are turned on or off during sleep and wakefulness and some of these genes are essential for restorative neuronal metabolisms. When certain genes are activated by sleep deprivation or abnormal sleep–wake cycles, adverse changes may occur in neuro-development and behaviour, especially in young children.[89] Since some of these genes are coded for proteins which are involved in different neuronal functions, the metabolic aspects of waking, sleep and sleep deprivation can be reliably studied by gene expression.[90–92]

During the last decade major progress has been made in the understanding of complex molecular changes following sleep deprivation which cause cellular stress.[8,90,91] Cellular stress is defined as the response of cells to adverse environmental conditions that disturb their homeostasis. During wakefulness, the brain's energy supplies progressively diminish while in NREM sleep this metabolic energy imbalance is corrected by rebuilding the diminished cellular components.[93–95] When the metabolic needs of the neurons are unmet, various degrees of cellular stress develop depending on the severity and duration of sleep of loss. Cellular stress down-regulates many so-called stress genes and up-regulates many others and the activation of these genes can lead to the production of certain proteins which are able to protect and repair cells. Interestingly this process is similar from bacteria to humans.

Under non-stressed conditions the non-productive folding of proteins in cells is prevented. During excessive stress this process may fail, the misfolded proteins begin to accumulate in aggregates and the adaptive cellular functions progressively deteriorate. Excessive cellular stress can lead to pathological changes in the mitochondria, macromolecular damage to proteins, DNA, RNA and lipids.[90,96] and to alterations of brain microRNA levels.[97] In response to significant cellular stress, the so-called unfolded protein response which is a quality control system is initiated, that degrades misfolded polypeptides, suppresses the formation of protein aggregates, and ensures the effectiveness of transcription and translation of genes in addition to a number of other complex mechanisms. This process occurs in the endoplasmic reticulum, which is a membrane network in the cytoplasm.[98,99] When the excessive stress is prolonged, and the unfolded protein response is unable to compensate, widespread neuronal death and apoptosis may occur. The wear and tear resulting from stress, the "allostatic load", is cumulative and further influences neurological functions, behaviour and health.[100–102] In addition to sleep loss, neuronal stress may have other simultaneous sources with an amplifying effect. For example, it is estimated that 5–20% of military personnel who have served in combat develop post-traumatic stress disorder. Sleep disturbances appear to be a predisposing factor but there are other simultaneous sources of stress. The continuing sleep difficulties are a consistent feature of this disorder.[103] Post-traumatic stress disorder also occurs in children with NDD but is rarely recognized.[104]

As indicated earlier, the metabolic cellular functions are controlled by a very large number of genes that are up and down regulated by the day and night changes.[98,105] Severe and long-term sleep deprivation is known to up-regulate genes in the cerebral cortex coding for immunoglobulins, energy regulating pathways, macromolecule biosynthesis and transport, stress response and inflammation.[93,94,98] Thus, sleep deprivation and resulting neuronal stress may lead to a large number of biochemical changes through various mechanisms.[91] Even short-term sleep deprivation rapidly and reversibly alters bidirectional synaptic plasticity[106] and it may result in transcriptional alterations in protein synthesis.[107] Changes also occur in the neuroendocrine[108,109] and neurotransmitter systems.[102] Interestingly, the pattern of neurobiological changes is similar to that seen in depression.[110] This is relevant in that chronic sleep deprivation may be a precursor of depression. As an example, adolescents have high rates of serious sleep disturbances associated with depression and suicidal attempts.[111] Severe restless legs syndrome predisposes to sleep disturbances and depression.[112] Post-partum depressed women are also commonly sleep-deprived.[113] However, the relationship of sleep loss to depression in these examples needs further clarification.

7. The effects of sleep deprivation on the hippocampus

The hippocampal structures play a major cognitive role and have received considerable attention with regard to sleep deprivation. They participate in learning and memory formation through reciprocal connections to various regions of the brain and also in emotional processes involving the amygdala and prefrontal cortex. The hippocampal formation is in the medial temporal lobe and includes the dentate gyrus, the hippocampus and a number of other areas that can be clearly identified at birth. During post-natal maturation of these structures, critical developmental periods exist.[114] In primates the majority of neurons are already formed pre-natally except in the granular cell layer of the dentate gyrus where more than 30% of neurons are generated post-natally, most in early life, but some even in adulthood.[115] Damage to the hippocampal structures causes profound loss of declarative memory function and cognitive deficits. Hippocampal infarction,[116] hippocampal sclerosis,[117,118] pre-natal alcohol exposure[119] and various types of early injuries to the hippocampus[120] all result in cognitive defects. During the early post-natal developments of birds, nutritional deficits have resulted in smaller hippocampal structures and fewer neurons. These birds exhibited persistent cognitive deficits despite nutritional rehabilitation.[121] Deprived rearing conditions in neonatal mice led to similar findings.[122]

Long-term sleep deprivation in animal studies has also suppressed the survival, maturation, differentiation and proliferation of neurons in the hippocampal structures.[123] Therefore, periodic severe disruption of sleep may have a permanent and cumulative effect in this anatomical region[114,124] and REM deprivation is more harmful in this process than that of NREM sleep.[125] The adverse effect of REM sleep loss in memory function has been described in numerous studies. McDermott and co-workers have shown that only 72 h of REM sleep deprivation in rats impaired their performance on hippocampus-dependent spatial learning and produced molecular and cellular alterations. A reduction in membrane excitability and synaptic plasticity diminished the performance of these rodents in learning and tasks.[126] In animals and in humans, complex task training leads to an increase in the consecutive total REM sleep time.[127] In humans, recall performance for verbal memory is greater after sleep than after wakefulness and positron emission tomography shows that in REM sleep, the brain areas are more reactive when they are exposed to certain learning tasks prior to sleep.[128] In conclusion, research indicates a detrimental role of short-term or chronic sleep loss on consolidating memory[129] and there are suggestions that such changes can be permanent.

8. Melatonin

The daily variations of light are transduced into electrical impulses by specialized retinal ganglion cells which then communicate this information to the suprachiasmatic nuclei in the hypothalamus.[130] In turn, the suprachiasmatic nuclei signal the pineal gland to down-regulate the melatonin production.[131] In the absence of light the pineal gland is relieved of the inhibitory influence of the suprachiasmatic nuclei and melatonin production occurs with its rapid release into the blood and cerebrospinal fluid. The circulating melatonin is mainly but not entirely derived from the pineal gland. Normally melatonin production begins in the evening. It is

lipid and water soluble, readily crosses all morphological barriers and can enter neuronal subcompartments where it has numerous metabolic functions. Tissues throughout the body have melatonin membrane receptors which permit localised and differentiated responses to central melatonin release.[132] Through complex but ill-defined neurological mechanisms melatonin promotes sleep onset and maintenance.[1] Sleep regulation is only one of its many functions. There is strong evidence that melatonin assists in the synchronisation of intracellular functions and in the synchronisation of circadian and circannual physiology of cells, organs, hormones, neurochemicals and other functions.[133–138] Melatonin and its by-products are protective against oxidative/nitrosative damage due to their direct free radical scavenging actions.[139,140] They ameliorate the free radical-mediated damage that is caused by neural toxins, ultraviolet light, heat stress, herbicides, metals, prescription drugs, irradiation and others.[141] Dysregulation of sleep can result in reduced melatonin production and secretion leading to increased cellular oxidative and nitrosative stress, disturbance of intracellular and extracellular metabolisms and to cognitive, behavioural and health difficulties.[27,142,143] Melatonin also influences neurogenesis and it is important in prenatal and post-natal brain and eye development.[144–147] For example, in animal studies melatonin-deficient fetuses later exhibit reduced cerebellar size,[148,149] delayed development[150,151] and abnormal neurogenesis of the hippocampal structures.[152–156] Therefore, the existing evidence suggests that chronic circadian sleep disturbance or sleep loss in various forms may lead to vast changes in health and in neuronal mechanisms.[141,143]

9. Conclusions

During the last few years, research activities have markedly increased in electrophysiology, anatomical studies, structural and functional brain imaging, cellular, molecular, and genetic, biochemical and other areas of sleep medicine. It is important for pediatric neurologists and physicians in other clinical fields to be familiar with some of these advances. NREM sleep is most important in restoring homeostatic balance following wakefulness, whereas REM sleep provides a supportive role in neurogenesis, synaptic activity, emotional and neuronal development, learning and memory formation. Sleep deprivation adversely affects cognitive functioning, behaviours and health.

The effects of persistent partial sleep difficulties on human brain development have not been adequately studied; yet chronic sleep disturbances are common, especially in children with NDD. Children with chronic sleep difficulties, more so when young, are deprived of quality environmental and endogenous brain stimulation needed for optimal neuronal development. Animal experiments unequivocally show that sleep loss even for three or four days can adversely and permanently affect neurophysiological functions and neurogenesis. Sleep deprivation, depending on the severity, leads to genetic, cellular, metabolic, electrical, neurotransmitter and other changes. Prolonged sleep loss causes cellular stress and when the defence mechanisms are no longer able to cope, permanent neuronal damage may occur. The effects of cellular stress may be cumulative throughout life. Melatonin, which has powerful neuroprotective properties, has a central role in sleep deprivation since during sleep disturbances melatonin production is often reduced and/or disturbed. The potential adverse effects of chronic sleep disorders on the brain development of children are generally unrecognized. Furthermore, it is often incorrectly thought that the sleep disturbances of children with NDD are an inevitable part of their conditions or they will eventually outgrow these difficulties, and therefore treatment is not necessary or may be ineffective. This review summarises the increasing evidence from various fields of neuroscience that chronic disturbances of sleep adversely affect brain development, especially when severe and occur during critical developmental periods. Pediatric neurologists, the scientific community and the public must be aware of these recent scientific developments. Further studies are urgently required.

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