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Investigating the Links between Adolescent Sleep Deprivation, Fronto-limbic connectivity and the Onset of Mental Disorders: A Review of the Literature

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Abstract

The importance of sleep for mental health has been known for some time. Although it was initially suggested that mental health conditions negatively impact sleep, it is now widely understood that this association is bidirectional. Adolescence is a period where people are at an increased risk of being sleep deprived largely due to a late shift in the circadian rhythm around puberty combined with early school start times. Combined these may lead to adolescents being at an increased risk of mental health problems. Adolescence is also a period of continued brain development with white matter maturation continuing in the frontal brain regions throughout adolescence and into early adulthood. White matter development involves myelination of axons that link areas of grey matter and is integral for communication speed and efficiency. Studies have demonstrated that sufficient sleep is required for myelination to occur. The uncinate fasciculus (UF) is one of the last white matter tracts to be myelinated with this process occurring throughout adolescence and running between the amygdala in the limbic system and the orbitofrontal (OFC) and medial prefrontal cortices (mPFC). Recent studies have shown that connectivity between the amygdala and OFC is important for an individual's ability to exert top-down executive control over amygdala based automatic emotional responses to experiences perceived as threatening. The current literature review provides an overview of these mechanisms and concludes by proposing a model of adolescent sleep deprivation leading to potential life-long mental health issues through the moderating impact of reduced UF development.

Keywords: Sleep deprivation; Mental health; Adolescence; White matter development

1. Introduction

It is now considered common knowledge amongst researchers and clinicians that a strong association exists between sleep disturbance and psychological disorders [1, 2]. In fact, sleep disturbance is listed as a symptom of many mental health disorders in the diagnostic and statistical manual of mental disorders (DSM-5) [3]. Although initially this association was believed to be largely one way with mental health disorders negatively impacting sleep onset and maintenance, this relationship is now widely accepted as being bidirectional [4].

Adolescence has been described as starting with the onset of puberty and lasting through until the person settles into an independent role in society [5]. The American Academy of Pediatrics divides adolescence into 3 sub-stages, 1) early adolescence (11-14 years), 2) mid-adolescence (15-17 years) and, 3) late adolescence (18-21 years) [6]. Sleep deprivation is a major problem for many adolescents due to a puberty related late shift in the sleep/wake cycle combined with early school start times [7]. It is also a period when many mental health conditions first emerge [8] making it a period of significant interest for mental health researchers.

Brain imaging studies conducted over the past two decades have revealed that adolescence is a period of continued brain development with a pattern of grey matter volume (GMV) reduction and white matter volume (WMV) increase [9] that progresses from the phylogenetically older posterior/inferior areas of the brain towards the evolutionarily more recent anterior areas located in the prefrontal cortex (PFC) [10]. The uncinate fasciculus (UF) is a long-range white matter tract that connects parts of the limbic system located in the temporal lobe to areas in the orbitofrontal cortex (OFC) and is one of the last white matter tracts to reach maturity

(become insulated with myelin) with development continuing throughout adolescence and into early adulthood [10, 11].

Animal studies have demonstrated that sleep duration plays an important role in the brain's ability to produce myelin [12]. It has been suggested that a well-developed UF provides the connectivity between these brain areas to allow top-down, cognitive regulation of emotions [13]. It is therefore proposed that chronic sleep deprivation may lead to reduced brain development and this could act as a moderator to the development of mental health disorders.

The aim of this literature review is to provide an overview of: 1) the association between sleep and mental health, 2) why adolescents are more likely to be sleep deprived, 3) brain development across adolescence and specifically myelination of the UF, 4) the role of the UF in relation to mental health, and 5) propose a model that suggests the association between adolescent sleep deprivation and the high emergence of mental health disorders during this period may be moderated by the structural integrity of the UF. It is envisaged that this review will act as a precursor to future longitudinal studies investigating the possible existence of significant correlations between these factors.

2. The Association Between Sleep and Mental Health

Clinicians have long reported that nearly all mood and anxiety disorders seem to occur in tandem with sleep abnormalities [1, 14]. Sleep disturbance is listed as a criterion in DSM-5 for a number of mental health conditions including anxiety and depressive disorders [3]. Studies have also demonstrated a link between sleep and mental health in adolescents [15]. In a study involving over 8000 Korean students from grades 7 – 11, Lee et al. (2012) found that chronic insufficient sleep was associated with higher scores on the Beck Scale for Suicidal Ideation (SSI)

[16]. They also found that longer weekend sleep and short weekday sleep significantly predicted higher scores on the SSI. This is of particular concern considering the common sleep pattern of many high school students which involves sleeping in on the weekends in an attempt to catch-up on lost sleep [17].

Wulff, Gatti, Wettstein, and Foster (2010) proposed a conceptual framework linking circadian rhythm disruption and psychiatric disorders. This was primarily based on 3 findings: 1) mood seems to follow a daily cycle that is regulated by circadian and homeostatic processes, 2) 90% of people with a major depressive disorder also report sleep disruption, and 3) persistent insomnia increases the chance of depression sufferers relapsing into a new episode of major depression. They proposed that mental health disorders and sleep disorders originate from the same mechanistic origin and therefore focusing on stabilizing sleep patterns may be a way of reducing mental health related symptoms and may even provide a means of early intervention for neurodegenerative diseases [18].

In an fMRI study involving 55 adolescent participants aged between 14 – 18 years (M = 16.22, SD 1.12), Tashjian, Goldenberg and Galvan (2017) found poor sleep quality was associated with greater affect related impulsivity in participants with low functional connectivity between the medial prefrontal cortex (mPFC) and default mode network but not those with high connectivity [19]. Similarly, Yoo, Gujar, Hu, Jolesz and Walker (2007) found connectivity between the amygdala and mPFC was found to be significantly reduced in the sleep deprived group suggesting that sleep deprivation may act to prevent the top-down regulation of emotional responses by the mPFC [20]. Interestingly, the sleep deprived group also demonstrated significantly greater connectivity between the amygdala and brain stem areas including the midbrain and locus coeruleus which are known to play a significant role in activating autonomic

nervous system functions such as increasing respiration and heart rate. This may suggest that sleep deprivation results in a double-edged sword of increased anxiety symptom likelihood, with reduced ability to reappraise negative emotions coupled with increased ability to activate the fight or flight response. It is possible that the increased connectivity between the amygdala and brain stem is a result of increased activation due to the inability to exert top-down control over negative emotions in the first place.

Sleep's role in memory and learning may also play a part in the development of mental health disorders. One study showed a 40% reduction in memory retention when comparing participants who underwent 36 hours of controlled sleep deprivation prior to training with those who attained adequate sleep [21]. Perhaps most importantly from a mental health perspective, the largest impact was found on the participants ability to encode positive emotional memories, while negative and neutral emotional memories were more resistant to the effects of sleep deprivation [21].

3. Sleep Deprivation during Adolescence

Sleep deprivation during adolescence is a major problem in modern society that is largely attributed to a delayed sleep phase coupled with the requirement to be up early for formal activities such as school [22, 23]. During adolescence a late shift in the circadian rhythm results in many adolescents having trouble getting to sleep early enough to allow them to achieve the 9 hours recommended by the National Sleep Foundation [22]. The link between the shift in circadian rhythm and the onset of puberty has been demonstrated in studies showing the late shift seems to be associated with puberty onset measured using the Tanner stage test [24] and also in a

study that showed the shift occurs on average one year earlier in females than males, approximately in line with known biological patterns [23].

Reduced sleep opportunity during adolescence has been shown to have an immediate impact on educational outcomes. On week nights when adolescents are generally required to wake early the next day for school, it has been reported that many may be getting as little as 6 or 7 hours or less sleep potentially leading to increased school absenteeism, sleepiness in class, inattentiveness, moodiness, and poor academic performance [25]. In a study that examined changes following a shift in school start times from 7:15am to 8:40am, the later start times were effective in allowing adolescent students to get more sleep resulting in less sleepiness at school, students being more likely to arrive at school on time and improved academic performance [26].

Sleep onset, maintenance, and duration are biologically governed by 2 separate processes, the circadian rhythm which is the approximately 24 hour biological clock, and a sleep debt process that is the result of the build-up of adenosine during waking hours [27]. The suprachiasmatic nucleus (SCN) located in the hypothalamus, helps maintain the circadian rhythm by receiving light level signals from the retina via a retino-hypothalamic tract, and then relaying messages to the pineal gland to increase melatonin production on dark and stop production when light is detected in the morning [28]. Artificial light from computer tablets and smart phones can therefore interfere with the onset of sleep. The second system, the build-up of a sleep debt, is a particular problem during adolescence due to the previously mentioned delayed sleep phase linked to puberty. In adolescent's who regularly get adequate sleep, adenosine levels build during the waking hours eventually resulting in tiredness and a desire to sleep after around 15 hours of wakefulness. After nine hours of sleep the adenosine levels have returned to baseline ready to start the cycle over again. When adequate sleep has not been attained this results in the

day starting with residual adenosine levels meaning the person already feels tired and drowsy. This is compounded as adenosine levels start building during the day and the result is adolescents who are sleep deprived all week suffering physically and mentally, possibly feeling depressed [7], not being able to concentrate at school, and sleeping in until after lunch-time on the weekends in an attempt to catch-up on their sleep debt [7, 17].

Unfortunately, this weekend attempt to catch up on sleep has been shown to be ineffective. In a study comparing reaction times between 4 groups of participants who were allowed either, no sleep for 3 days straight, 4 hours sleep per night, 6 hours sleep per night, or 8 hours of sleep per night, reaction times for the no sleep group worsened by 400% after 1 night without any sleep. The 4 hours of sleep per night group performed just as poorly after 1 night as the no sleep group. Perhaps most interestingly, the 6 hours per night group (of which many adolescents may be able to relate) recorded a 400% worsening of reaction times after 10 nights. Also concerning is that following 3 nights of recovery sleep, performance had not yet returned to baseline levels suggesting that weekend catch-up sleep by adolescence is insufficient to return to "normal" for the start of the school week [29].

It is proposed that sleep plays a vital role in brain development. This is partly based on the observation that the amount of sleep required across the life span seems to have an approximate association with known brain development patterns [30, 31]. In other words, periods of higher sleep requirements match known periods of increased brain development. Newborns typically sleep between 12 and 18 hours per day, this drops to 12 to 14 hours for 1 to 3-year old's, 10 to 11 hours for 5 to 10-year old's, around 9 hours for 11 to 17-year old's, and between 7 and 9 hours for 18 years and older [17]. This approximately parallels with what we know about brain development patterns with very high levels of synaptogenesis occurring in

newborns that gradually reduce across childhood while myelination and synaptic pruning continues throughout adolescence and tails off through early adulthood [32].

Sleep is made up of cycles of REM (rapid eye movement) and non-REM sleep. There are 3 stages of non-REM sleep (N1, N2, & N3) and 1 stage of REM sleep each sleep cycle, with each cycle lasting around 90 minutes for humans [33, 34]. The percentage of the 90 minutes spent in REM sleep increases each cycle throughout the night [34]. It has been suggested that REM sleep during very early sensitive periods might be of particular importance to brain development and that a lack of REM sleep during sensitive periods may lead to atypical synaptogenesis [35]. In animal studies involving rats and other mammals, disrupting REM sleep during periods of brain development stopped development of the cerebral cortex. Interestingly, although brain development recommenced following a return to undisrupted sleep, it never fully recovered [7, 36-38]. Li et al. (2017) found that REM sleep played a role in strengthening some newly formed dendritic spines and pruning away others. They inferred from this that overall, REM sleep plays an important role in maintaining the balance of newly formed dendritic spines.

Non-REM sleep (N1, N2, & N3) has also been identified as playing a major role in brain development during adolescence, mainly through synaptic pruning [39]. In longitudinal sleep studies of adolescents, Feinberg and colleagues (2011) found a significant decline in the delta EEG frequency of non-REM sleep that moved gradually from the posterior areas of the brain towards the anterior areas finishing at the PFC, a pattern that mirrors known brain maturation patterns. They inferred that this decline in delta frequency reflects brain development via synaptic pruning [39].

4. Adolescence: A Sensitive Period for Brain Development

A sensitive period in brain development is a period of increased neuroplasticity where the brain is best prepared to receive and benefit from environmental input or potentially be disadvantaged by lack of this input [40]. Neuroplasticity is described as the creation (synaptogenesis), stabilization, strengthening, and pruning of synapses [41]. Huttenlocher (2002) suggests there are 2 main modes of synaptogenesis: 1) a genetically controlled synapse formation that occurs without environmental input and largely occurs in brain regions responsible for basic functions such as heartbeat and breathing such as the brain stem and, 2) random formation of an abundance of synapses followed by environmental experience reflected strengthening or pruning. As the first mode is thought to be largely genetically controlled and occurs during the prenatal period, it is the latter mode that this review will focus on.

As mentioned above, brain development involves the creation of an abundance of synapses in early life through a process called synaptogenesis. This results in young children having excess of synaptic connections, around 50% more than in adulthood [42]. This is followed by a process of synaptic pruning during childhood and adolescence. Synaptic pruning has been shown to be heterogeneous between brain regions. Huttenlocher (2002) reported that at birth neurons in the occipital lobe, temporal lobe, and PFC all had around 2500 synapses per neuron. This number continues to increase and peaks at between 8-12 months in the occipital lobe, 3 months in the temporal lobe, and not until 3 years in the PFC. After reaching their peak, each area shows a gradual decline in synapse numbers, levelling off at around 12 years of age for the occipital and temporal lobes but not until the late teens for the PFC [41].

Ostby et al. (2009) found a significant level of heterogeneity across areas of the developing adolescent brain with regards to volumetric brain changes. For instance, amygdala and hippocampal volumes showed slight increases in grey matter volume (GMV) while the

cerebral cortex showed significant decreases in GMV. White matter volume (WMV) has also been shown to be changing throughout adolescence with volumes increasing in a posterior to anterior pattern [5, 15, 43]. This general pattern of reduction in GMV and increase in WMV, occurring throughout adolescence, is thought to be the combined dynamic result of both synaptic pruning and increased myelination [15, 44]. Myelination is likely to explain the majority of these volumetric changes because it impacts both GMV and WMV, that is, when unmyelinated axons become myelinated, GMV is reduced and WMV increases concurrently [44].

Sensitive periods for neural development are different than the neuroplasticity which occurs across the life span. These two types of neuroplasticity have been categorized as experience-expectant neuroplasticity and experience-dependent neuroplasticity [45]. Experience-expectant neuroplasticity refers to sensitive periods and the experiences that the brain expects to encounter during these periods to achieve development. If these experiences are not encountered during the sensitive period, future development of the impacted brain area may be significantly restricted. On the other hand, experience-dependent plasticity can occur at any stage of life and any structural brain changes that occur may be reversible following a period of underutilization. An example of this is long-term potentiation (LTP). Studies of LTP have demonstrated that repeated firing of a neuron makes that neuron more likely to fire again and that this increased likelihood of firing is long lasting, but without frequent use, the likelihood of firing eventually returns to baseline levels [46].

Initially, research on brain development was focused on sensory, motor, and language development. Because these functions have very early sensitive periods of development, it led to the since disproven suggestion that sensitive periods for brain development mainly occurred during prenatal and the very early stages of postnatal life [47]. We now know that this is because

the brain areas that develop during very early childhood are those that are associated with these functions. More recent studies suggest that adolescence may present another sensitive period for functions regulated by later developing brain areas (e.g. the PFC) [47] such as planning, attention, working memory, decision making, and inhibitory control [48].

Although the observed general pattern of adolescent brain development includes an increase in WMV and with it an increase in connectivity, this isn't the case for everyone. One study reported that 40% - 50% of 19 to 32-year-old participants showed an increase in the structural integrity of the fronto-occipital fasciculus, whereas 5 - 15% of the participants actually showed a decrease [48]. This example of within group variability may be evidence of the impact that different environmental experiences can have on brain development.

A further example of the importance of environmental input during a sensitive period has been described by Wiesel and Hubel (1965) when they reported limited recovery occurred in the vision of kittens following deprivation of vision for the first 3 months of life when compared with deprivation after 3 months of age which had little negative impact on the long-term development of sight [49]. Another example from animal studies has shown that rats exposed to stressful events during adolescence (social isolation) suffered from long-lasting negative effects including anxiety, fear behavior, and increased cortisol levels (Lukkes, Mokin, Scholl, & Forster, 2009) [50].

While further longitudinal studies with more detailed data (i.e. collected over multiple, frequent time points) is needed, overall, the current evidence of GMV reduction and WMV increase in the PFC as a result of environmental experiences during adolescence, highlights this as being a sensitive, and in many ways, the most dynamic period in terms of brain development.

5. Sleep and Myelination

The quantity and quality of sleep during adolescence have been linked to the myelination process. In animal studies involving rodents and felines, disrupting deep non-REM sleep (N3) resulted in significant impairments in the development of brain connectivity during adolescence [7] suggesting a role for non-REM sleep in the myelination process. Overall duration of sleep has also been shown to impact white matter development. Bellesi et al. (2013) reported that sleep quantity may impact the myelination process by impacting the availability of oligodendrocytes (a type of glial cell that forms myelin in the central nervous system) in the central nervous system. During sleep, oligodendrocyte precursor cell proliferation was shown to be double that occurring during waking hours [51].

In a study designed to investigate possible links between insomnia and white matter, Li et al. (2016) found reduced structural integrity of a range of white matter tracts in a study of participants who suffer with insomnia suggesting an association may exist between sleep deprivation and UF development [52]. Another finding linking reduced sleep to white matter integrity was reported by Bellesi et al. (2018), where they found that chronic sleep loss was associated with reduced myelin thickness in a sample of adolescent mice [12]. However, while these studies show that an association exists, they don’t provide evidence of causation.

Maintaining myelin has been shown to require energy, considering this, it has been proposed that chronic sleep deprivation may result in a reduction in available energy which could lead to oligodendrocytes prioritizing other cellular functions at the expense of myelin maintenance [12]. Thus, if maintaining myelin is energetically costly, then it may be that the production of myelin is also at least equally as costly. Therefore, it may be that chronic sleep deprivation during adolescence, a period when myelination is occurring in the prefrontal cortex,

could result in either axons not being myelinated, or thinner myelin sheaths being produced. From this it could be speculated that chronic sleep deprivation during adolescence might lead to reduced functional and structural connectivity in white matter tracts, in particular, late developing tracts such as the UF.

6. The Uncinate Fasciculus and Mental Health

The increase in WMV during adolescence reflects the myelination of axons. This process proceeds from the phylogenetically older posterior/inferior to the more evolutionarily recent anterior parts of the brain meaning the PFC is one of the last areas to achieve white matter maturity [10]. This suggests that frontal lobe white matter tracts such as the UF may be particularly impacted by negative environmental events that occur during adolescence and coincide with environmental impacts in this period such as sleep deprivation but also other phenomenon and experiences that occur during a similar time such as chronic stress and even substance misuse [10, 53].

White matter tracts are divided into 3 types: 1) projection tracts that link the cerebral cortex to sub-cortical structures e.g. the cortico-spinal tract, 2) commissural tracts that run between the two hemispheres linking functionally similar areas e.g. the corpus collosum, and 3) association tracts which link functionally connected areas within the same hemisphere e.g. the uncinate fasciculus. The UF links the amygdala in the limbic system with areas within the PFC (specifically the OFC) [10]. It is believed that myelination occurring during brain development is largely focused on strengthening connections between spatially separate but functionally linked areas such as the amygdala and OFC in the case of the UF [5]. Underutilized connections therefore may be lost during this period and axons running between areas of the brain that are

found to be functionally linked through frequent synchronized use will be more likely to be retained and myelinated. This suggests that adolescence may not only present an opportunity for under development, but increased development through targeted cognitive training.

It has been suggested that the information being transmitted by a white matter tract can be predicted by the functions believed to be associated with the brain areas it connects [54]. As the UF is bidirectional (information can move in both directions) and connects the amygdala with the OFC, it is suggested that it may play a role in executive (top down) control over the brains more evolutionary primitive emotional responses thought to originate in the amygdala [11, 53].

This suggestion of top down control has been demonstrated in a recent study conducted by d'Arbeloff et al. (2018). Using data from 647 healthy young adults (M = 19.63 years), they found initial evidence that the use of cognitive reappraisal techniques for the treatment of anxiety and depressive symptoms may be moderated by the structural integrity of the UF. By measuring the participants': 1) use of cognitive reappraisal as a technique for reframing negative stimuli, 2) the effectiveness of this technique on reducing anxiety and depressive symptoms, and 3) the structural integrity of the UF, they found that cognitive reappraisal was almost completely ineffective for those with impaired UF structural integrity and that performance using cognitive reappraisal improved with increased UF structural integrity [13]. Interestingly, this finding suggests that cognitive based therapies which are widely reported to be the most effective for many mental health disorders [55], may only be useful for clients with intermediate or high structural integrity of the UF . It also poses the question: should structural integrity of the UF be measured using diffusion weighted imaging prior to psychological treatment selection? (I'll save this question for my next study).

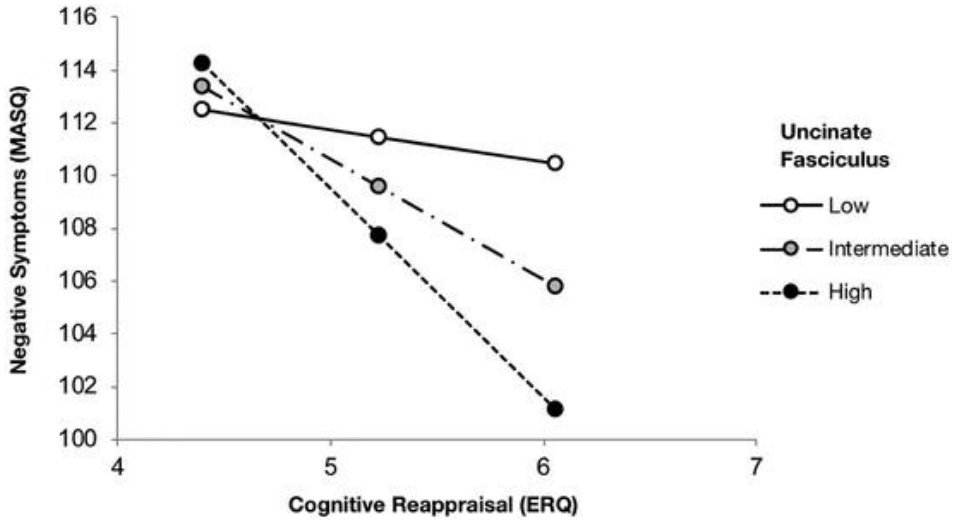

Figure 1. Structural integrity of the UF is shown to moderate the ability of cognitive reappraisal techniques for reducing negative symptoms related to mood and anxiety disorders. ERQ = Emotion Regulation Questionnaire, MASQ = Mood and Anxiety Symptoms Questionnaire, Uncinate fasciculus structural integrity. From "Microstructural Integrity of a Pathway Connecting the Prefrontal Cortex and Amygdala Moderates the Association Between Cognitive Reappraisal and Negative Emotions", by d'Arbeloff, T. C., Kim, M. J., Knodt, A. R., Radtke, S. R., Brigidi, B. D., & Hariri, A. R. (2018), *Emotions 18*(6), p. 914. Reprinted with permission from American Psychological Association publishing.

When studying white matter tract connectivity, the level of fractional anisotropy (FA) is often reported. FA values of white matter tracts can be calculated as part of diffusion tensor imaging (DTI) studies and are used to make inferences regarding fiber direction, density, axonal thickness, and myelination of white matter tracts as an overall measure of functional connectivity [56]. FA is reported as a scaled value between 0 and 1 with 0 representing no directional diffusion (isotropic) and 1 indicating strong directional diffusion (anisotropic), which is inferred as meaning strong white matter connectivity as a result of strong myelination [56].

Several studies have reported finding an association between low FA values in the UF and increased likelihood of suffering from depression and anxiety disorders [57-60]. Ho et al. (2017) found that adolescents who had experienced early life stress (ELS) and who were deemed to be highly sensitive to stress had reduced FA in the right frontal UF as well as higher levels of social anxiety [53]. These higher social anxiety levels are of increased importance when considering that early adolescents with social anxiety have been shown to be at increased risk of developing further anxiety disorders and depression in later life [61].

In a study of older participants with and without a history of depression, Taylor, MacFall, Gerig, & Krishnan (2007) found that those who had an onset of depression during adolescence or early adulthood still had lower structural integrity of the left UF in later life compared with those whose depression had a later onset [62]. This suggests that when depression emerges in adolescence, the associated structural change in the UF is long-term, providing further support for adolescence being a sensitive period for mental health disorders and UF development. Taylor and colleagues suggested that early life environmental influences and stress could be contributing factors. It seems plausible that sleep deprivation during adolescence would be one such factor.

Further evidence for the role of the UF in the development of mental health disorders comes from studies of patients with lesions to areas of the PFC who have been shown to have a higher risk of developing anxiety disorders [63]. It has been suggested that damage or underdevelopment of the ventromedial PFC results in loss of the ability to inhibit fear reactions that originate in the amygdala. In other words, a loss of top-down control is observed, similar to that witnessed as a result of reduced structural integrity of the UF which approximately connects these 2 areas.

Overall, these findings suggest that UF development during adolescence may be impacted by a variety of environmental factors, with sleep deprivation chief among them and the UF may play a pivotal role in modulating the development of anxiety disorders and depression in later life.

7. Does Chronic Sleep Deprivation During Adolescence Contribute to High Rates of Mental Health Disorders?

It has been suggested that adolescence represents a vulnerable period for the development of mental health issues due to the high number of disorders that have their onset during this period [8]. Due to the ongoing white matter development in the frontal lobe throughout adolescence and impact that environmental experiences may have on this process, it is suggested that one possible cause of this high rate of onset may be atypical development of the UF. Studies have shown an association exists between low structural integrity of the UF and mental health disorders such as major depressive disorder and anxiety disorders [58-60]. It has been suggested that the UF may moderate the development of these disorders by allowing sufficient connectivity between the PFC and amygdala to provide top down reappraisal of emotional reactions produced by the amygdala [11, 13, 53]. It has also been reported that sleep deprivation during adolescence may negatively impact development of the UF [7, 51]. It is therefore possible that chronic sleep deprivation during adolescence may contribute to the heightened emergence rates of mental health disorders observed during this period due to a reduced ability of prefrontal areas to apply top-down moderation of emotional responses originating in the limbic system. See figure 2 for proposed model.

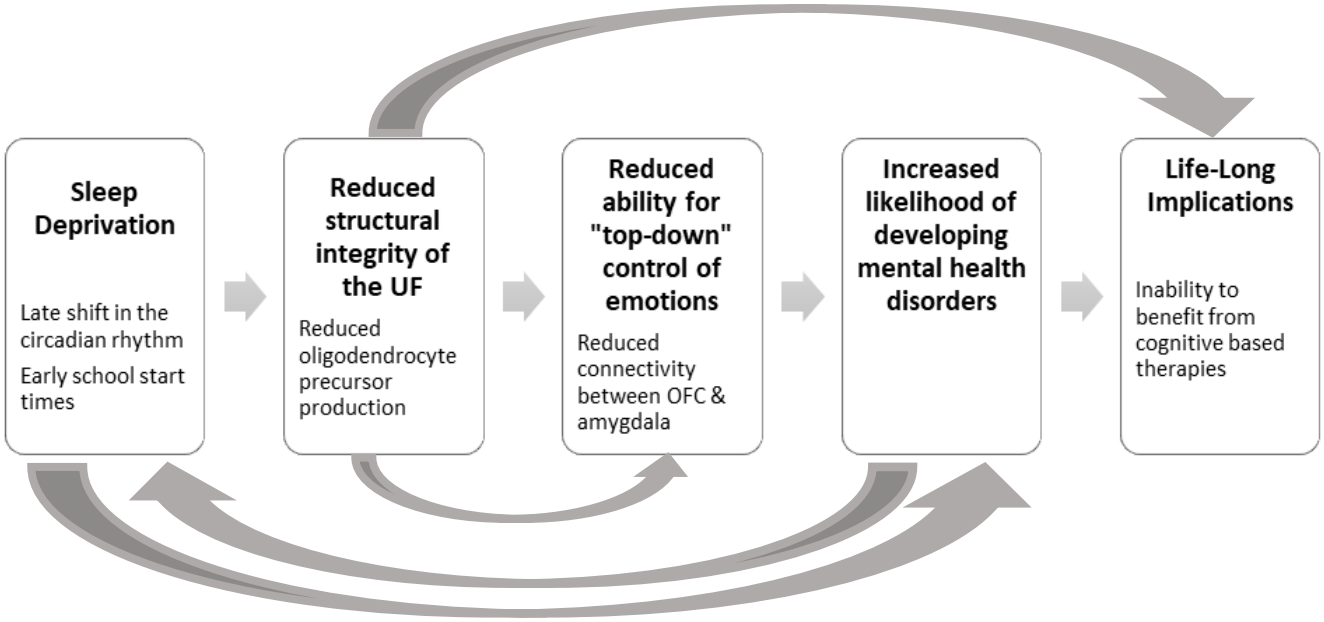

Figure 2. Proposed model showing a relationship between sleep deprivation, development of the uncinate fasciculus, "top-down" control of emotions, increased likelihood of developing mental health disorders, and the potential for life long issues. Curved arrows indicate findings from previous studies with proposed direction of impact.

Protracted brain maturation is considered beneficial as it enables neurodevelopment specialized for the environment that has been encountered during adolescence and therefore is likely to continue to be encountered throughout life. The downside is that being exposed to the stressors of modern life while the brain is still developing may result in long-term problems [64]. For instance, chronic sleep deprivation during adolescence probably wasn't an issue during the millions of years of evolution that resulted in the protracted brain developmental period we see today.

The average age of onset for mental health disorders, what is known about average brain developmental timelines, and what is known about functions of various brain regions has led to the proposal that disorders with an earlier age of emergence may involve disruptions in the earlier developing basal ganglia area, while later emerging disorders (adolescence/young adulthood) are more likely to involve disruptions to the temporal lobe (amygdala) and frontal areas such as the PFC [65]. In accordance with this suggestion, studies have consistently found that dysfunction within the basal ganglia is associated with motor and tic disorders such as Tourette's syndrome which often first appears between ages 7 and 10 [66] and atypical development of the UF and amygdala are associated with anxiety disorders and depression often first appearing during adolescence and early adulthood [57, 62].

8. Conclusion and Future Research

Once thought of as a process that occurred mainly in pre-natal and early post-natal life, brain development is now widely recognized as continuing until at least the third decade of life. This brain development generally follows a posterior to anterior trajectory with adolescence coinciding with white matter development and synaptic pruning in the PFC. It therefore stands to reason that adolescence would represent a sensitive period for functions associated with the PFC and frontal lobe white matter tracts such as the UF.

The current review has reported studies demonstrating positive correlations between sleep quality and the likelihood of developing mental disorders such as depression and anxiety, it has also reported a number of studies demonstrating positive correlations between sleep quality and connectivity between areas of the PFC and limbic system, which have been inferred to impact cognitive reappraisal abilities. Together these findings have led to the proposal of a

model (Figure 2) which suggests sleep deprivation may lead to a reduction in cognitive reappraisal ability through reduced connectivity, potentially leading to an increased likelihood of developing mental disorders and a reduced ability to benefit from popular treatment methods.

With adolescents experiencing a biological shift towards later sleep/wake times, and this clashing with early school start times, there is a possibility that large numbers of adolescents could be at risk of suffering from underdeveloped frontal white mater tracts. Together these findings make a strong case for later school start times during adolescence and further research into the impact that sleep quantity and quality has on brain development during adolescence.

Longitudinal studies of adolescents starting at 12 years of age (around the age of puberty onset) running for at least 3 years measuring structural integrity of the UF along with measures of average sleep hours per night and psychological well-being are recommended to bring together previous findings from brain development studies, sleep deprivation studies, and psychological disorder age of onset studies. This would allow correlations to be investigated between these variables. Post study follow-up with participants at 5 yearly intervals would also be very useful to gather data on mental health disorder prevalence in later life and to investigate whether reduced UF integrity during adolescence proved to be long lasting as expected or if some recovery has occurred.

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References

[1] Goldstein AN, Walker MP. The role of sleep in emotional brain function. Annu Rev Clin Psychol. 2014;10:679-708.
[2] Walker MP, van der Helm E. Overnight therapy? The role of sleep in emotional brain processing. Psychol Bull. 2009;135:731-48.
[3] APA. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing; 2013.
[4] Riemann D. Insomnia and comorbid psychiatric disorders. Sleep Med. 2007;8 Suppl 4:S15-20.
[5] Dumontheil I. Adolescent brain development. Current Opinion in Behavioral Sciences. 2016;10:39-44.
[6] Stages of Adolescence. American Academy of Pediatrics; 2012.
[7] Walker MP. Why We Sleep: The New Science of Sleep and Dreams. . UK: Penguin 2017.
[8] Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci. 2008;9:947-57.
[9] Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Ann N Y Acad Sci. 2004;1021:77-85.
[10] Olson IR, Von Der Heide RJ, Alm KH, Vyas G. Development of the uncinate fasciculus: Implications for theory and developmental disorders. Dev Cogn Neurosci. 2015;14:50-61.
[11] Von Der Heide RJ, Skipper LM, Klobusicky E, Olson IR. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain. 2013;136:1692-707.
[12] Bellesi M, Haswell JD, de Vivo L, Marshall W, Roseboom PH, Tononi G, et al. Myelin modifications after chronic sleep loss in adolescent mice. Sleep. 2018;41.
[13] d'Arbeloff TC, Kim, M. J., Knodt, A. R., Radtke, S. R., Brigidi, B. D., & Hariri, A. R. . Microstructural Integrity of a Pathway Connecting the Prefrontal Cortex and Amygdala Moderates the Association Between Cognitive Reappraisal and Negative Emotions. . Emotions. 2018;18:3.
[14] Kraepelin E. Compendium der Psychiatrie zum Gebrauch fuer Studierende und Aerzte (Abelverlag, Leipzig)1883.
[15] Tarokh L, Saletin JM, Carskadon MA. Sleep in adolescence: Physiology, cognition and mental health. Neuroscience and biobehavioral reviews. 2016;70:182-8.
[16] Lee YJ, Cho SJ, Cho IH, Kim SJ. Insufficient sleep and suicidality in adolescents. Sleep. 2012;35:455-60.
[17] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation’s sleep time duration recommendations: methodology and results summary. Sleep Health: Journal of the National Sleep Foundation. 2015;1:40-3.
[18] Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat Rev Neurosci. 2010;11:589-99.
[19] Tashjian SM, Goldenberg D, Galvan A. Neural connectivity moderates the association between sleep and impulsivity in adolescents. Dev Cogn Neurosci. 2017;27:35-44.
[20] Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep--a prefrontal amygdala disconnect. Curr Biol. 2007;17:R877-8.
[21] Walker MP, Stickgold R. Sleep, memory, and plasticity. Annu Rev Psychol. 2006;57:139-66.
[22] Crowley SJ, Acebo C, Carskadon MA. Sleep, circadian rhythms, and delayed phase in adolescence. Sleep Med. 2007;8:602-12.

[23] Hagenauer MH, Perryman JI, Lee TM, Carskadon MA. Adolescent changes in the homeostatic and circadian regulation of sleep. Dev Neurosci. 2009;31:276-84.
[24] Andrade MM, Benedito-Silva AA, Domenice S, Arnhold IJ, Menna-Barreto L. Sleep characteristics of adolescents: a longitudinal study. J Adolesc Health. 1993;14:401-6.
[25] Wolfson AR, Spaulding NL, Dandrow C, Baroni EM. Middle school start times: the importance of a good night's sleep for young adolescents. Behav Sleep Med. 2007;5:194-209.
[26] Wahlstrom KL, Owens JA. School start time effects on adolescent learning and academic performance, emotional health and behaviour. Curr Opin Psychiatry. 2017;30:485-90.
[27] Borbely AA. A two process model of sleep regulation. Hum Neurobiol. 1982;1:195-204.
[28] Klein DC, Moore, R. Y., & Reppert, S. M. . Suprachiasmatic Nucleus: The mind's clock. . Oxford, England: Oxford University Press; 1991.
[29] Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep. 2003;26:117-26.
[30] Seugnet L, Suzuki Y, Donlea JM, Gottschalk L, Shaw PJ. Sleep deprivation during early-adult development results in long-lasting learning deficits in adult Drosophila. Sleep. 2011;34:137-46.
[31] Marks GA, Shaffery JP, Oksenberg A, Speciale SG, Roffwarg HP. A functional role for REM sleep in brain maturation. Behav Brain Res. 1995;69:1-11.
[32] Hagenauer MH, Lee TM. Adolescent sleep patterns in humans and laboratory animals. Horm Behav. 2013;64:270-9.
[33] Iber C, American Academy of Sleep M. The AASM manual for the scoring of sleep and associated events : rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
[34] Hartmann E. The 90-minute sleep-dream cycle. Arch Gen Psychiatry. 1968;18:280-6.
[35] Li W, Ma L, Yang G, Gan WB. REM sleep selectively prunes and maintains new synapses in development and learning. Nat Neurosci. 2017;20:427-37.
[36] Corner MA, Mirmiran M, Bour HL, Boer GJ, van de Poll NE, van Oyen HG, et al. Does rapid-eye-movement sleep play a role in brain development? Prog Brain Res. 1980;53:347-56.
[37] Mirmiran M, van de Poll NE, Corner MA, van Oyen HG, Bour HL. Suppression of active sleep by chronic treatment with chlorimipramine during early postnatal development: effects upon adult sleep and behavior in the rat. Brain Res. 1981;204:129-46.
[38] Mirmiran M, Scholtens J, van de Poll NE, Uylings HB, van der Gugten J, Boer GJ. Effects of experimental suppression of active (REM) sleep during early development upon adult brain and behavior in the rat. Brain Res. 1983;283:277-86.
[39] Feinberg I, de Bie E, Davis NM, Campbell IG. Topographic differences in the adolescent maturation of the slow wave EEG during NREM sleep. Sleep. 2011;34:325-33.
[40] Knudsen EI. Sensitive periods in the development of the brain and behavior. J Cogn Neurosci. 2004;16:1412-25.
[41] Huttenlocher PR. Neural Plasticity: The Effects of Environment on the Development of the Cerebral Cortex. . Cambridge: Harvard University Press; 2002.
[42] Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. Brain Res. 1979;163:195-205.
[43] Ostby Y, Tamnes CK, Fjell AM, Westlye LT, Due-Tonnessen P, Walhovd KB. Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. J Neurosci. 2009;29:11772-82.
[44] Blakemore SJ. Imaging brain development: the adolescent brain. Neuroimage. 2012;61:397-406.
[45] Shatz CJ. The developing brain. Sci Am. 1992;267:60-7.
[46] Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993;361:31-9.

[47] Fuhrmann D, Knoll LJ, Blakemore SJ. Adolescence as a Sensitive Period of Brain Development. Trends Cogn Sci. 2015;19:558-66.
[48] Lebel C, Beaulieu C. Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci. 2011;31:10937-47.
[49] Wiesel TN, Hubel DH. Extent of recovery from the effects of visual deprivation in kittens. J Neurophysiol. 1965;28:1060-72.
[50] Lukkes JL, Mokin MV, Scholl JL, Forster GL. Adult rats exposed to early-life social isolation exhibit increased anxiety and conditioned fear behavior, and altered hormonal stress responses. Horm Behav. 2009;55:248-56.
[51] Bellesi M, Pfister-Genskow M, Maret S, Keles S, Tononi G, Cirelli C. Effects of sleep and wake on oligodendrocytes and their precursors. J Neurosci. 2013;33:14288-300.
[52] Li S, Tian J, Bauer A, Huang R, Wen H, Li M, et al. Reduced Integrity of Right Lateralized White Matter in Patients with Primary Insomnia: A Diffusion-Tensor Imaging Study. Radiology. 2016;280:520-8.
[53] Ho TC, King LS, Leong JK, Colich NL, Humphreys KL, Ordaz SJ, et al. Effects of sensitivity to life stress on uncinate fasciculus segments in early adolescence. Soc Cogn Affect Neurosci. 2017;12:1460-9.
[54] Passingham RE, Stephan KE, Kotter R. The anatomical basis of functional localization in the cortex. Nat Rev Neurosci. 2002;3:606-16.
[55] APS. Australian Psychological Society Evidence – based Psychological Interventions in the Treatment of Mental Disorders – Fourth Edition: Australian Psychological Society; 2018.
[56] Alger JR. The diffusion tensor imaging toolbox. J Neurosci. 2012;32:7418-28.
[57] Baur V, Hanggi J, Jancke L. Volumetric associations between uncinate fasciculus, amygdala, and trait anxiety. BMC Neurosci. 2012;13:4.
[58] Kim MJ, Whalen PJ. The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. J Neurosci. 2009;29:11614-8.
[59] Phan KL, Orlichenko A, Boyd E, Angstadt M, Coccaro EF, Liberzon I, et al. Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. Biol Psychiatry. 2009;66:691-4.
[60] Zhang A, Leow A, Ajilore O, Lamar M, Yang S, Joseph J, et al. Quantitative tract-specific measures of uncinate and cingulum in major depression using diffusion tensor imaging. Neuropsychopharmacology. 2012;37:959-67.
[61] Stein MB, Fuetsch M, Muller N, Hofler M, Lieb R, Wittchen HU. Social anxiety disorder and the risk of depression: a prospective community study of adolescents and young adults. Arch Gen Psychiatry. 2001;58:251-6.
[62] Taylor WD, MacFall JR, Gerig G, Krishnan RR. Structural integrity of the uncinate fasciculus in geriatric depression: Relationship with age of onset. Neuropsychiatr Dis Treat. 2007;3:669-74.
[63] Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci. 2011;15:85-93.
[64] Konrad K, Firk C, Uhlhaas PJ. Brain development during adolescence: neuroscientific insights into this developmental period. Dtsch Arztebl Int. 2013;110:425-31.
[65] Spear LP. The Behavioral Neuroscience of Adolescence. . New York: Norton & Co; 2010.
[66] Caligiore D, Mannella F, Arbib MA, Baldassarre G. Dysfunctions of the basal ganglia-cerebellar-thalamo-cortical system produce motor tics in Tourette syndrome. PLoS Comput Biol. 2017;13:e1005395.