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Sleep Disturbance in Tourette's Disorder: Potential Underlying Mechanisms

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Abstract

Purpose of review: Sleep disturbance is common in TD. However, our understanding of the pathophysiological mechanisms involved is preliminary. This review summarizes findings from neuroimaging, genetic, and animal studies to elucidate potential underlying mechanisms of sleep disruption in TD.

Recent findings: Preliminary neuroimaging research indicates increased activity in the premotor cortex, and decreased activity in the prefrontal cortex is associated with NREM sleep in TD. Striatal dopamine exhibits a circadian rhythm; and is influenced by the suprachiasmatic nucleus via multiple molecular mechanisms. Conversely, dopamine receptors regulate circadian function and striatal expression of circadian genes. The association of TD with restless legs syndrome and periodic limb movements indicates shared pathophysiology, including iron deficiency, and variants in the *BTDB9* gene. A mutations in the *L-Histidine Decarboxylase* gene in TD, suggests the involvement of the histaminergic system, implicated in arousal, in TD.

Summary: These biological markers have implications for application of novel, targeted interventions, including noninvasive neuromodulation, iron supplementation, histamine receptor antagonists, and circadian-based therapies for tic symptoms and/or sleep and circadian rhythms in TD.

Keywords

sleep disturbance; Tourette's disorder; neuroimaging

Introduction

Tourette's disorder (TD) and other persistent tic disorders (PTD) are neurological conditions involving the involuntary expression of repeated, stereotyped, movements and/or

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vocalizations present for beyond one year [1]. Up to 1.4 million individuals in the US are affected by PTDs [2] with males disproportionality affected [3]. Initial tics typically present between 4 and 8 years of age, with symptoms reaching a precipice during prepuberty. As many as two-thirds of children experience substantial improvement in symptoms by adulthood, but many individuals continue to express tic symptoms at clinically significant levels throughout adulthood [4]. TD adversely impacts functioning in social, emotional, occupational, academic, and physical domains [5]. Psychiatric comorbidities are present in as many as 86% of individuals with TD, with attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) being the most common, followed by mood disorders, anxiety disorders, and disruptive behavior disorders [6]. Sleep disturbance also commonly co-occurs with TD [7].

Sleep Disruption in Tourette's Disorder

Sleep disorders and disruption present at rates as high as 80% in individuals with TD [7]. Sleep disturbance increases with advancing age in individuals with TD [8], and females with TD appear more susceptible to sleep disruption and reduced sleep sufficiency relative to males [9,10]. Individuals with TD exhibit increased rates of insomnia relative to the general population [11]. Parasomnias, including sleep walking, nocturnal enuresis, night terrors, and nightmares are also common, with children somewhat more susceptible than adults [12,13]. Sleep-related movements disorders, including restless legs syndrome (RLS), periodic limb movements, and nocturnal bruxism also frequently present in TD [13–16]. Daytime sleepiness, too, is relatively common in TD [15].

As documented in polysomnography studies, sleep problems in TD are characterized by longer sleep onset latency, increased nighttime awakenings and movements during sleep, and reduced sleep duration and sleep efficiency [7]. Sleep architecture findings are inconsistent [7]. There is support for reduced slow wave sleep (i.e., non-rapid eye movement sleep [NREM] N3) in TD [17,18], but studies have found the inverse pattern [19,20]. The reasons for this discrepancy are unclear. However, one contributing factor may be the small sample sizes across studies. Additionally, it is possible that differences in psychiatric comorbidity contributed to this discrepancy - although this cannot be assessed as comorbidity information was not reported in all studies.

Similarly, studies have shown both decreased rapid eye movement (R) [19,21] and increased R sleep [22]. This difference may be accounted for by use of a 1-night PSG protocol [19] and home cassette electroencephalography [21] in the studies finding decreased R compared to use of a two-night PSG protocol in the study finding increased R [22]. Additionally, differences in comorbidity across the three studies may have contributed to inconsistent findings. In the two studies finding decreased R, comorbid ADHD and OCD were present in one study [21], and comorbidity was not reported on in the other [19]. In contrast, in the study finding increased R, participants were free of psychiatric disorders [22]. However, it is of note that Kirov et al. [22] noted that increased REM has been observed in psychiatric disorders and may compensate for lowered REM efficiency, although they did not believe this to explain the increased REM finding in this particular study [22]. Increased NREM N1 [18] and decreased N2 sleep [23] have also been shown, which may be related to

psychotropic medication use in the first study [18] and an unmedicated sample in the other [23] along with differences in psychiatric presentation. A home sleep apnea test, used to evaluate motor activity during sleep in adults with TD relative to controls, showed increased motor activity during sleep in adults with TD [24]. The few available studies indicate increased sleep onset latency, reduced sleep efficiency, and increased sleep fragmentation per wrist-worn measurement in adults with TD relative to controls [13], and no significant association between total sleep time, and sleep efficiency with tic symptom severity in youth with TD in an uncontrolled study [25].

Sleep disruption is associated with a number of clinical factors that are commonly associated with TD. Stimulant medication for ADHD, along with tic medication, such as antipsychotics and alpha adrenergic 2-agonists (e.g., clonidine, guanfacine), can disrupt sleep, though adverse sleep effects of tic medications have not been evident from existing analyses [26–28,12]. Further, alpha-2-adrenergic agonists, particularly clonidine, have also been associated with improved sleep in individuals with neurodevelopmental disorders [29], although there has been no controlled testing in TD. Co-occurring ADHD and anxiety are frequently related to sleep disturbance [12,15,30], with OCD and depression also associated in individuals with TD [9,13].

Tics are present during sleep in as many as 100% of individuals with TD, and can occur across all sleep stages, though at reduced frequency, intensity, and complexity [7]. Several studies have shown an association between tic severity and sleep disruption [9,18,31]; however, findings are mixed [13,15,23,25] and the importance of this association is not yet clear. Higher tic severity could disrupt the settling process required for optimal sleep onset and maintenance [13], and sleep loss could also contribute to heightened tic severity [32]. In addition, it is possible that neural processes leave individuals with TD susceptible to emergence of both tics and sleep disruption – although this has yet to be investigated [13,33]. Such knowledge of neural mechanisms and other biomarkers implicated in sleep patterns within TD may enhance understanding of the underlying pathophysiology of TD more broadly, and aid in identification of novel, targeted interventions for sleep and TD. As such, this review will summarize the evidence base regarding mechanistic links between sleep disturbance and TD.

Neural Mechanisms Underlying Sleep and Circadian Rhythms in Tourette's Disorder

Our understanding of the neural mechanisms implicated in sleep in TD is presently preliminary (Table 1). TD is broadly characterized by deficits in communication within cortico-basal ganglia-thalamo-cortical circuitry, with excess postsynaptic dopamine frequently implicated [34,35]. Findings from waking positron emission tomography (PET) imaging studies in TD have primarily shown increased glucose metabolism in lateral premotor, primary motor, and supplementary motor cortical areas, and the cerebellum; and decreased glucose metabolism in the thalamus and the basal ganglia – particularly the ventral striatum – relative to controls [36–38]. To date, only one study has evaluated neural activity during sleep in TD. This study used [^{15}O]H_2O PET imaging during N2 sleep as a relatively quiescent state with respect to tic symptoms relative to wake [39]. Results showed the waking tic state was associated with increased blood flow, an index of neural

activation, in the cerebellum, thalamus, putamen, globus pallidus, insula, anterior cingulate, and supplementary motor area relative to NREM sleep in TD. Findings also demonstrated increased blood flow in bilateral premotor cortex and decreased blood flow in the left inferior frontal gyrus and superior temporal gyrus during NREM sleep in TD relative to controls [39]. These findings are aligned with years of neuroimaging research implicating the premotor cortex and prefrontal cortex, which are involved in motor planning, execution, and inhibition, in the pathophysiology of TD. A meta-analysis of functional imaging studies (13 fMRI, 1 H_2O PET) showed that despite differences in neural activity across numerous brain regions in individuals with TD and controls, premotor and prefrontal regions were most consistently associated with tic symptoms [40]. Activation of the inferior frontal gyrus, in particular, has been associated with tic inhibition [41]. Findings from the single NREM sleep study showed decreased blood flow in a number of subcortical regions, including the bilateral putamen and claustrum, left cerebellum, and left insula during NREM sleep in TD relative to controls [39]. Prior research has shown increased activation in the putamen, insula, and cerebellum just prior to tic generation [42], and the insula has been linked to premonitory urges to tic [43]. Additionally, a few aforementioned brain regions involved in NREM sleep in TD are also implicated in insomnia. For example, insomnia is associated with smaller reductions in glucose metabolism (measure of neural activation) from wake to NREM sleep in brain regions related with arousal (hypothalamus, thalamus, reticular activating system), and cognitive and emotional processing (medial prefrontal cortex, insula, amygdala, hippocampus, and anterior cingulate cortex) [44]. Further, insomnia has been associated with reduced functional connectivity of the amygdala with the insula, thalamus, striatum, suggesting dysfunction in emotional processing; and increased connectivity of the amygdala with the premotor cortex and sensory motor cortex, suggesting an adaptive sensory response to perceived threat [45]. Taken together, these findings suggest overlap in neural markers associated with TD and insomnia.

While these findings are informative, the researchers imaged NREM sleep solely as a purported baseline “resting state” to support their goal of evaluating neural activity of TD during wake. In addition, as H_2O PET and other standard functional imaging approaches involve the syncing of neural activation with image acquisition in time, it is necessary for subjects to sleep in the scanner and for the head to remain in a stationary position. Further, subjects had underwent sleep restriction the night prior to the PET scan to promote falling asleep in the scanner while undergoing polysomnography (PSG). This may have introduced a confound, as sleep deprivation is known to affect multiple brain regions implicated in TD (see section below). An alternative approach employing [^{18}F]Fluorodeoxyglucose positron emission tomography ([^{18}F]FDG PET) as part of a three-night in-lab PSG protocol to correct for first night effects of PSG (i.e., vigilance-inducing effects of a new environment) on sleep has been introduced to provide a more naturalistic environment (a bedroom) for imaging of neural correlates of sleep [46]. In the protocol, PSG is used to align the timing of [^{18}F]FDG injection and uptake with NREM sleep, followed by image acquisition in the scanner while alert. Repetition of this procedure coinciding with the wake state allows for comparison of neural correlates of sleep and wake [46]. Further investigation of neural activity during sleep in TD, in addition to its association with tic occurrence/severity and sleep disruption would be informative.

There is also an animal study that points to mechanisms underlying tic persistence during sleep in TD. In a rat model of TD, infusion of the $GABA_A$ antagonist bicuculline into the motor regions of the striatum results in tic-like behaviors. In a comparison of tic-like behaviors across three states (wake, transition from wake to sleep, and sleep) using this model, tic frequency and intensity were significantly decreased during sleep relative to wake. During the transition from sleep to wake, tics persisted at a similar frequency but reduced intensity relative to wake. The authors surmised that the tic reduction observed despite persistent infusion of bicuculline in the motor regions of the striatum suggests the presence of neural mechanisms that override the effects of the striatum on tic expression. During wake, each tic occurrence was associated with a single local field potential (LFP) spike, as recorded via extracellular electrophysiological signals in the striatal regions. However, this association decreased during the transition period from wake to sleep and was no longer present during sleep, despite continuous LFP spike occurrence across all three states [47]. Maximal striatal neural activity preceded changes in LFP spikes, but this activity decreased during sleep. Taken together, these findings suggest that while LFP spikes are related to tic expression during wake, their continued activity during sleep is not associated with tic expression during sleep. Thus, the reduction in maximal striatal neural activity during sleep may serve to block or significantly reduce tic expression during this period. This suggests a potential mechanism by which tics are inhibited during sleep in humans [47].

Sleep loss and tiredness are commonly cited antecedents to waking tic exacerbation [32]. Though the effects of sleep disturbances on the brain have been investigated, the neural mechanisms underlying the link between sleep disturbances and tics have not. For example, in healthy humans, sleep deprivation has been associated with decreased waking neural activity in the thalamus, basal ganglia, cerebellum, prefrontal cortex, frontal cortex, and posterior parietal cortex, striatum, and cerebellum, which are regions that have been implicated in TD pathophysiology [48,49]. Controlled investigations are needed to evaluate the effects of sleep deprivation or restriction on waking tic release and tic suppression through functional imaging studies. In addition, the role of sleep-loss induced stress and anxiety in waking tic symptoms should also be examined in order to understand the complex interplay between comorbid symptomatology, sleep, and tics [32].

Neural processes underlying circadian rhythms and TD may also be linked [50]. The circadian rhythm, generated by a master clock in the suprachiasmatic nuclei (SCN) in the hypothalamus, partly regulates the sleep-wake cycle in addition to regulating release of hormones (melatonin, cortisol), core body temperature, and subcortical neural activity [51,52]. In vivo real-time monitoring of electrical activity in the dorsal striatum of freely moving mice has demonstrated that the striatum exhibits robust diurnal and circadian rhythms in activity [53]. These rhythms are dependent upon the SCN, as lesions of this structure caused the loss of rhythmicity measured in the striatum. In addition, the SCN is purported to exert control over rhythmic activity of dopamine in the striatum through the substantia nigra and ventral tegmental area. The substantia nigra and ventral tegmental area are surmised to be indirectly influenced by the SCN though several pathways, including the lateral habenula, orexinergic system, and medial preoptic nucleus in the hypothalamus [54]. Basal dopamine (DA) levels or tone within the striatum are known to exhibit a daily

rhythm with peaks during activity [55,56]. These studies have found that the transcription of monoamine oxidase A is under clock control [55] and that daily variation in the function of the dopamine transporter (DAT) is responsible for the rhythms [56]. Furthermore, there is evidence for SCN-independent rhythms in circadian clock gene expression in the substantia nigra [57] but these cells do not appear to exhibit rhythms in electrical activity [58]. Also, in rat models of TD, striatal dopamine expression exhibits a circadian rhythm [59] The control of rhythms in dopamine in the striatum is multi-faceted and involves multiple structures and molecular mechanisms [60]. It is likely that these rhythms in dopamine in the striatum contribute to the circuits underlying TD and other tic disorders.

Dopamine is dysregulated in TD and this neurotransmitter is known to be a potent regulator of circadian function and clock gene expression. D1 receptors are present within the central clock (SCN) and regulate clock gene expression (e.g. [61]). Functionally, there is evidence for a circuit originating in the midbrain that sends a direct dopamine input to the SCN which regulates the effects of light [62]. In the striatum, there is also evidence that dopamine regulates clock gene expression [63]. Further, a D2/D3 receptor agonist, quinpirole, was associated with decreased overall expression of *mClock* and *mPer1* genes. It was also associated with time of day-dependent alterations in neuronal expression of mPer1 protein levels in the mouse striatum, decreasing expression in the day and increasing expression in the night [63]. A D1 receptor agonist, SKF38393, stimulated expression of all clock genes assessed [63]. There is also evidence that signaling mediated by the dopamine D2 receptor (D2R) enhances the transcriptional capacity of the CLOCK:BMAL1 complex [64] and that chronic activation of dopamine receptors can re-program rhythms in clock gene expression in the striatum [65]. Other work has also suggested a direct relationship between extracellular dopamine levels and the rhythm of expression of the clock protein PERIOD2 (PER2) in the dorsal striatum of rats [66]. Together, these findings show dopamine receptors regulate striatal expression of circadian genes.

Clinically, tic severity is associated with greater evening chronotype (i.e., rest-activity preferences or patterns that are delayed in timing; [50]) in adults with TD per cross-sectional survey data [13], and adults with TD report significantly greater eveningness but not greater objective circadian phase delay relative to controls [67]. Overall, the role of circadian disruption in TD is still unclear; for example, timing of peak tic occurrence could lead to rhythm malentrainment or perhaps neural mechanisms and/or genetic susceptibilities could predispose individuals to both circadian disruption and tic symptoms. Nevertheless, crosstalk between the SCN and dopamine suggests the utility of circadian interventions for disorders involving dopaminergic dysfunction, such as TD [54].

Pathophysiological Links between Tourette's Disorder and Sleep Disorders

The co-occurrence of sleep disorders with TD suggests potential overlapping biomarkers; understanding such overlap can provide insight into the underlying pathophysiology of PTDs. For example, RLS – a common but underdiagnosed sleep-related movement disorder, characterized by uncomfortable sensations and urges to move the legs that increase when the body is at rest and peak in severity during the evening [68] – presents in individuals with PTDs at rates ranging from 1.6% to 59% [69,70]. One study showed 10% of 144 individuals

with PTDs and 23% of their parents exhibited RLS [14]. TD and RLS exhibit overlap in clinical characteristics as, similarly to TD, individuals with RLS experience uncomfortable sensory symptoms characterized by internal tension and temporarily relieved by engagement in movement, and suppression of movement leads to increased discomfort and urges [68]. This overlapping phenomenology suggests a shared underlying pathophysiology between RLS and TD.

One theory posits that the comorbidity of TD, RLS, and ADHD in addition to the presence of iron deficiency in each of these conditions suggests they are related and linked by a common pathophysiology [71,72]. This iron hypothesis postulates that the differential impact of iron deficiency on dopaminergic function in these conditions contributes to their distinct clinical presentations. Despite differences in the role of dopamine in these conditions, iron supplementation may be associated with improved symptoms across these conditions [71]. Indeed, use of iron supplementation in RLS is supported by meta-analysis and clinical guidelines [73,74]. In TD, case review data indicate a trend toward improved tic severity with iron supplementation, but controlled trials are needed to investigate its efficacy [75]. Further, a family history of RLS noted in individuals with TD suggests shared heritability [14,76]. Indeed, variants in the *BTBD9* gene, associated with susceptibility for RLS and periodic limb movements during sleep, have been implicated in TD, especially in individuals free of comorbid OCD [77].

Further, genetic studies point to involvement of the histaminergic system in TD. Histaminergic neurons originate in the tuberomammilary nucleus (TMN) which is in the hypothalamus and broadly releases histamine (HA) throughout the central nervous system. The release is controlled with a diurnal rhythm with high neural activity in the TMN and subsequent HA release peaking during the day in humans. The post-synaptic effect of HA is largely excitatory and thus HA is considered one of the main transmitters that control arousal [78]. In a family with high TD occurrence, a mutation in the *L-Histidine Decarboxylase* (*HDC*) gene was present in all affected family members across two generations, suggesting involvement of the histaminergic system in TD [79]. Further, dopamine D2/D3 receptor binding in the basal ganglia was altered in both the aforementioned affected family members and mice with the *HDC* mutation, suggesting that deficits in the histaminergic system may play a role in dopaminergic dysfunction [80]. These findings have implications for the use of histamine (H3) receptor antagonists, which are currently used to promote wakefulness in narcolepsy and daytime sleepiness, for individuals with PTDs with or without daytime sleepiness [81,82]. However, per case report, an H3 receptor antagonist, Pitolisant, was associated with improved daytime alertness, but no reduction in tics [83]. In a placebo-controlled investigation of an H3 receptor antagonist, AZD5213, 2 mg of the medication was associated with small, significant tic worsening relative to placebo, and 0.5 mg was associated with no significant differences in tic severity relative to placebo (NCT01904773).

Sleep and Circadian Interventions and Clinical Implications for Tourette's Disorder

There is a paucity of research evaluating the effects of sleep and circadian interventions in TD and no formal clinical recommendations to guide evaluation and management of sleep

problems in TD. With respect to treatment recommendations for TD, behavior therapy (i.e., Comprehensive Behavioral Intervention for Tics; CBIT) [84] is the first line intervention per American Academy of Neurology guidelines [85]. CBIT encompasses habit reversal training, involving increasing awareness of tics, and premonitory urges or other precursors to tics, and implementation of a competing response to block tic occurrence. Function-based assessment and intervention to target contextual variables that exacerbate tics and minimize their impact [84]. Relaxation training and behavioral rewards are additional treatment components [84]. CBIT has demonstrated efficacy for tics in children [86] and adults [87], but respective treatment response rates (52% and 38%) [86,87] suggest more tailored intervention may be beneficial. Alpha-2-adrenergic agonists (e.g., guanfacine, clonidine) are deemed first-line among pharmacotherapies due to their relatively mild side effect (e.g., sedation) profile [85], but have limited benefit in children with tics without comorbid ADHD [88]. Typical (e.g., haloperidol, pimozide) and atypical (e.g., risperidone, ziprasidone, aripiprazole) antipsychotic medications are frequently used, however, side effects (e.g., weight gain, metabolic syndrome, cognitive dulling, tremor) can limit their tolerability [28]. Further, a number of children with TD feel TD symptoms are not well-managed by with pharmacotherapy [89], and that co-occurring psychiatric conditions predominate relative to TD in terms of functional challenges [90]. Thus, there is a need for tailored treatments geared toward the full range of clinical challenges associated with TD.

As sleep problems are a common challenge in TD, evaluation of poor or insufficient sleep as a potential tic-exacerbating factor is of value during clinical assessment and would align with existing functional assessment approaches [84,91]. In the event that poor sleep is associated with increased tic occurrence, clinical evaluation may cover the degree of persistence and triggers of poor sleep and screen for common sleep disorders as relevant. Should poor sleep hygiene, life stressors, and/or co-occurring psychiatric disorders (ADHD, anxiety) be drivers of impaired sleep, these would be meaningful targets for tailored interventions (e.g., sleep hygiene, stress management, cognitive-behavioral and mindfulness-based sleep interventions, relaxation training, parent training) [92–94]. Conversely assessment of the degree to which tics disrupt the settling process required for sleep is an important consideration. Should tics interfere with sleep onset, an evening dose of tic medication (e.g., clonidine) or evening implementation of habit reversal training (i.e., competing responses) may help shorten sleep onset latency. Additionally, mindfulness-based stress reduction for tics [95], entailing present-focused moment awareness of premonitory urges to tic and their rising and falling nature, while focusing on breathing may be beneficial. This method emphasizes allowing the premonitory urge to dissipate independently without engaging in the tic or reducing the urge to tic by other means [95]. This intervention also promotes mindful awareness of contextual factors associated with tic exacerbation and attenuation [95].

Due to the prevalence of insomnia in TD, interventions for insomnia warrant investigation in this clinical population. Clinical guidelines recommend Cognitive behavioral therapy for insomnia (CBT-I) as a first-line intervention for insomnia in adults [96]. However, neither the effects of CBT-I, nor other behavioral sleep interventions (e.g., sleep extension) have been investigated in TD. Hypnotic medications are also frequently used to treat insomnia, but are associated with adverse side effects (e.g., drowsiness, parasomnias, memory loss,

tolerance, dependence) [97]. As previously mentioned, a number of prescription medications are used off-label to treat sleep disturbance, particularly in children [29]. Clonidine, already used to treat tics, may be promising for addressing sleep disturbance in TD [98]. Over-the-counter sleep aids, particularly melatonin, have risen in prevalence and dose used [99,100]. Survey data indicate 27.1% of adults with PTDs [67] and 14% of parents of children with TD [101] endorse melatonin use. Per parent report, child melatonin use was associated with improved sleep, and improved motor and vocal tics symptoms [101]. Research has shown that melatonin is associated with improved sleep onset latency and total sleep time in children with neurodevelopmental disorders [102], and has also been associated with improvements in daytime behavior in individuals with autism and ADHD [103], with minimal side effects. Melatonin (MT1) receptors have been found in the striatum of mice and humans [104], providing another mechanism by which melatonin may be clinically useful. However, there are no published reports of trials evaluating the effects of melatonin in individuals with TD.

Treatments tailored to the underlying biology of sleep may also have utility in TD. For example, noninvasive neuromodulatory interventions targeting brain regions implicated in sleep in TD may reduce sleep disturbance. One such intervention presently under investigation for sleep disturbance in TD is frontal cerebral thermal therapy, involving circulation of cool fluid via a forehead-worn temperature-regulating device during sleep [105]. This intervention has been shown to target neural mechanisms underlying insomnia, and has been associated with reductions in whole brain, frontal, and cingulate glucose metabolism [106], and reduced sleep onset latency relative to sham treatment in adults with insomnia [105]. As prior findings have shown increased cerebral blood flow in the premotor area during NREM sleep in TD relative to controls [39], frontal cerebral thermal therapy may have neurobiological relevance for reducing sleep disturbance and tic symptoms in TD. Repetitive transcranial magnetic stimulation (rTMS), entailing extracranial application of magnetic fields supplying an electric current to stimulate intracranial neural regions [107], also warrants empirical investigation to establish the degree to which it may improve sleep disruption in TD. rTMS can increase or decrease neural activity, pending its high or low frequency, respectively [108]. In TD, rTMS has been applied to premotor and motor regions with the goal of tic reduction, with positive effects found for the supplementary motor area [109]. However, its effects on sleep disruption in TD have yet to be investigated. Nevertheless, rTMS has been successfully applied in individuals with sleep disorders. Findings have shown positive sleep effects for the application of rTMS over the dorsolateral prefrontal cortex in individuals with primary insomnia [110].

Delayed circadian timing is another potential therapeutic target, although evidence to date supports subjective, rather than objective delays in circadian timing in TD [67]. Light is the strongest circadian entraining agent, producing circadian phase advances with morning light exposure (when administered subsequent to the core body temperature minimum), and circadian phase delays with evening exposure (when administered before the core body temperature minimum) [111]. As such, light therapy, involving use of a “light box” or wearable device, commonly emitting white or ‘blue’ (short-wavelength) light to the retina at 2500 to 10,000 lux, has been employed to shift circadian phase in an array of sleep, psychiatric, and neurological disorders [112,113]. It also improves mood and wakefulness

[114], and has been associated with reductions in severity of core symptoms of psychiatric and neurological disorders, including common comorbidities of TD, namely ADHD and OCD [115,116].

A few preliminary studies have evaluated the effects of light therapy in TD. Per case summary, six weeks of light therapy at 10,000 lux used to boost mood was associated with tic reduction from 10-to-20 tics per hour to less than or equal to one tic per hour in a 52-year-old woman with persistent vocal tic disorder, with tic resurgence upon stopping use and tic reduction upon reinitiation [117]. Additionally, morning light therapy at 2500 lux in two 15-year-old males was associated with small decreases in tic severity as assessed after one week of treatment, relative to sham control administered six weeks later [118]. In a pilot study evaluating the effects of short-wavelength, morning light therapy administered via a wearable device in adults (n = 14) with TD, findings showed a significant objective circadian phase advance by approximately 45 minutes, and small, significant reductions in tic severity and tic-related impairment. There was also a significant association between circadian phase advancement and reduction in tic-related impairment following light therapy. Further, significant reductions in anxiety and daytime sleepiness were observed, with minimal side effects [67]. There were no significant reductions in actigraphy sleep variables or self-reported sleep disturbance, depression, stress, or disability [13]. Though promising, these findings are limited by the lack of a controlled design and a heterogeneous sample with respect to circadian timing. Therefore, sham-controlled investigation of the effects of light therapy on circadian phase and tic symptoms in individuals with TD with co-occurring delayed circadian timing is needed. Future research should also seek to determine whether morning light therapy influences dopaminergic expression in TD.

Conclusions

Sleep disturbance is prevalent in TD, with insomnia, parasomnias, and sleep-related movement disorders being common. Sleep disturbance is more common in women and older individuals with TD, and exacerbated by a number of clinical factors. Prominently, ADHD, anxiety, and stimulant medication are associated with increased sleep disturbance, but also depression, OCD, and occasionally, tic severity. Objective evidence supports the presence of sleep deficits in TD, although the impact on sleep architecture patterns has been inconsistent. Research identifying mechanisms implicated in the association between sleep and TD is in its infancy, but nascent findings point to several promising leads.

Preliminary findings suggest sleep in TD is marked by increased neural activity within the premotor cortex and reduced activity in the prefrontal cortex. Future research should seek to understand the influence of co-occurring psychiatric symptoms and sex effects on these neural mechanisms; longitudinal imaging studies could inform our understanding of long-term trajectories of neural mechanisms underlying sleep in TD, given the higher prevalence of sleep disturbances in adults with TD compared to children with TD. Research is also needed to understand the effects of sleep loss, which is a known tic-exacerbating factor, on waking neural function. Further, the potential mediating role of aversive emotions (e.g., anxiety), known to exacerbate sleep disturbance and ticcing, in the association between neural function and sleep could inform the development of

comprehensive pathophysiological models of sleep disturbance in TD. Preliminary clinical research suggests a pattern of subjective, but not objective, delays in circadian timing in TD, with basic research implicating bidirectional links between circadian and dopaminergic systems in this association. These links have implications for treatment decisions, such as medication timing Further, key mechanisms link TD to specific sleep disorders, with iron deficiency underlying TD and RLS, variants in the *BTBD9* gene linking TD to RLS and periodic limb movements, and genes associated with orexin/hypocretin and histaminergic systems connecting TD to narcolepsy and daytime sleepiness.

These mechanistic links have implications for a range of novel, targeted interventions, including noninvasive neuromodulation, iron supplementation, histamine receptor antagonists, and circadian-based therapies for tic symptoms and/or sleep and circadian rhythms in TD. However, to date, controlled investigations of iron supplementation are still needed and H3 receptor antagonists have not produced significant tic reduction. These studies have primarily focused on treating tic symptoms, but it would be informative for future trials to evaluate the efficacy of these medications for both tics and specific sleep disorder symptoms (e.g., restless legs syndrome, daytime sleepiness) in individuals with TD. Controlled investigations of interventions targeting sleep are lacking. Preliminary research evaluating the effects of a circadian-based intervention, morning light therapy, appear promising for advancing circadian phase and reducing tic symptoms, but require further investigation in sham-controlled trials. Controlled studies of melatonin are also needed to examine its effects on sleep and/or circadian rhythms in TD. And certainly, behavioral sleep interventions should be evaluated for their efficacy in addressing sleep disturbance and tic symptoms in TD.

Statements and Declarations

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Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

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Table 1

Mechanisms of Sleep Disturbance in TD

	Clinical Findings	Possible Pathophysiological Mechanisms
Insomnia	Insomnia prevalent in 32.2% of children with TD vs. 13.7% in controls [11] "Difficulty getting to sleep at night" in 30.6% of children with TD vs. 9.0% of controls [15] "Trouble getting to sleep" in 44.7% of children with TD vs. 14.9% of controls [119] *Actigraphy:* Longer sleep onset latency, lower sleep efficiency, and greater sleep fragmentation in adults with TD relative to controls [67] *PSG:* Longer sleep onset latency, increased wake after sleep onset, reduced sleep efficiency, and reduced NREM N3 in TD vs. controls [18,23,120]	Drawing on sleep imaging data in TD, increased blood flow in the premotor cortex, and decreased blood flow in the prefrontal cortex (left inferior frontal gyrus), and left insula during NREM sleep in TD compared to controls [39] are relevant potential mechanisms of insomnia [44,45] in TD. The thalamus, implicated in both TD [40] and insomnia [44], is also a possible mechanism of insomnia in TD.
Parasomnias	*Sleep walking*: 40.5% of children with TD vs. 14.9% of controls [119]; 17% of children with TD vs. 1.7% and 3.5% of learning disability and seizure disorder comparison groups, respectively [121]; 17% of children with TD vs. 4% of controls [122]; Higher rate in children (23.5%) vs. adults (8.5%) with TD [123] *Night terrors:* 15.8% of children with TD vs. 1.7% and 3.8% in learning disability and seizure disorder comparison groups, respectively [124]; "waking up screaming in the night" in 13.9% of children with TD and 4.9% of controls [15]; 48.9% of children with TD vs. 21.2% of controls [119] *Nocturnal Enuresis:* 7% of children with TD vs. 2% of controls [122] *Sleep talking:* 30.0% of children with mild-moderate TD vs. 13.1% of controls [15]; 45.6% of children with TD vs. 22.8% in controls [26] *Nightmares:* 15% of children with mild-moderate TD vs. 2.3% in controls [15]; "Unpleasant dreams" in 15% of children with TD vs. 4.4% of controls [26]	No TD studies regarding mechanism
Movement disorders of sleep	*RLS:* Present in 10% of child and adult probands with TD and 23% of their parents [14] *PLMD:* "Unusual movements during sleep" in 22.2% of children with TD vs 5.6% of controls [15] *Nocturnal bruxism:* 19.4% of children with TD vs 4.1% of controls [15]; 35% of children with TD vs. 15% of controls [122] *PSG:* Increased movement index during sleep in mixed sample of adolescents and adults relative to controls [18]	Family history of RLS in those with TD suggests shared heritability [14,76] Variants in *BTDB9* gene, associated with susceptibility for RLS and PLMD, are linked to TD [77] *Iron hypothesis:* TD, RLS, and ADHD share iron deficiency [72,125]
Tics During Sleep; Sleep in TD	*Subjective-Report:* Tics occurred during sleep in 13.8–31.8% individuals with TD per self- or parent/partner-report [13,126,127] *PSG*: Tics occurred during sleep in 100% of adolescents and adults with TD [18]; Tics presented during all sleep stages, especially N1, N2, and R [18]	A reduction in maximal striatal neural activity may block or reduce tic expression during sleep per animal model [47] Increased blood flow in bilateral premotor cortex, and decreased blood flow in left inferior frontal gyrus and superior temporal gyrus during NREM sleep in TD relative to controls [39] Decreased blood flow in subcortical regions (bilateral putamen and claustrum, left cerebellum, and left insula) during NREM sleep in TD relative to controls [39]
Daytime Sleepiness	19.4% of children with TD vs. 5.6% in controls [15] Falling asleep at school in 12.5% of children with severe TD and 5.6% in TD overall vs. 0.4% in controls [15]	Mutation in *L-Histidine Decarboxylase* (*HDC*) gene present in all family members with TD across two generations, implicating the histaminergic system (involved in regulation of arousal) in TD [78,79] Dopamine D2/D3 receptor binding in basal ganglia altered in family members with TD and mice with *HDC* mutation, suggesting histaminergic system deficits may play a role in dopaminergic dysfunction [80] Histamine (H3) receptor antagonist, Pitolisant, reduced daytime sleepiness but not tics in case report [83]
Delayed Circadian Timing	Greater eveningness preference in adults with TD relative to controls [67] Evening chronotype correlated with higher vocal tic severity and total tic severity in adults with TD [13]	Striatal dopamine expression (dysregulated in TD) exhibits a circadian rhythm in rat models of TD [59] Striatal dopamine is influenced by the SCN through multiple molecular mechanisms [54] Dopamine is a potent regulator of circadian function and striatal expression of clock genes [61,63]

Note. TD = Tourette's disorder; NREM = non-rapid eye movement sleep; RLS = restless legs syndrome; PLMD = periodic limb movement disorder; PSG = polysomnography; SCN = suprachiasmatic nucleus. Statistically significant clinical findings are reported for case-control comparisons and correlations.