Are circadian disturbances a core pathophysiological component of schizophrenia?

Running title: Circadian rhythms and schizophrenia

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Abstract

Schizophrenia is a multifactorial disorder caused by a combination of genetic variations and exposure to environmental insults. Sleep and circadian rhythm disturbances are a prominent and ubiquitous feature of many psychiatric disorders, including schizophrenia. There is growing interest in uncovering the mechanistic link between schizophrenia and circadian rhythms, which may directly impact disorder outcomes. In this review, we explore the interaction between schizophrenia and circadian rhythms from two complementary angles. First, we review evidence that sleep and circadian rhythm disturbances constitute a fundamental component of schizophrenia, as supported by both human studies and by animal models with genetic mutations related to schizophrenia. Second, we discuss the idea that circadian rhythm disruption interacts with existing risk factors for schizophrenia to promote schizophrenia-relevant behavioral and neurobiological abnormalities. Understanding the mechanistic link between schizophrenia and circadian rhythms will have implications for mitigating risk to the disorder and informing the development of circadian-based therapies.

Keywords: schizophrenia, circadian rhythm, risk factor, interaction, sleep, animal model

Introduction

Schizophrenia is a severe and chronic neurodevelopmental disorder, with a lifetime prevalence of close to 1% (Jablensky, 2000; McGrath et al., 2008). It is typically diagnosed in early adulthood with characteristic positive symptoms (i.e., delusions, hallucinations), negative symptoms (i.e., affective, avolition) and impaired cognition (i.e., learning, attention) (Tandon et al., 2013). Much attention has been given to the hypothesis that schizophrenia is a multifactorial disorder, triggered by a combination of risk factors including gene variants, as well as environmental insults that one is exposed to *in utero* and during their lifetime (van Os et al., 2008; Ayhan et al., 2016; Stilo and Murray, 2019). Risk factors for schizophrenia are believed to have a small individual impact; most likely, multiple risk factors act synergistically along the lifespan to affect disorder onset, symptoms and course of the disorder. Thus, such risk factors should be studied as an integrated system (Jablensky, 2010). The complexity of the disorder is also reflected in the limited pharmacological treatment options available. Although the antipsychotic drugs, working principally on dopamine system, are effective in controlling positive and some negative symptoms, they rarely improve cognitive and social dysfunctions that are better predictors of functional outcomes (Miyamoto et al., 2005; Kahn et al., 2015). Discovering more efficient therapeutic options may rely on exploring novel risk factors for schizophrenia and uncovering the complex mechanisms in which these risk factors interact to jointly exert their effect.

In the context of schizophrenia, a promising avenue of study is sleep and the circadian system. Indeed, disturbances in these systems are a prominent and ubiquitous feature of many psychiatric disorders, including schizophrenia (Wulff et al., 2010; Wulff et al., 2012; Jagannath et al., 2013; Monti et al., 2013; Kaskie et al., 2017; Logan and McClung, 2019). In a healthy individual, the sleep/wake cycle displays a characteristic 24-hour periodicity and is the most

documented output of the circadian (daily) system. Circadian clocks are cell autonomous, producing rhythms with a period of ~24 hours, but can also be entrained by external timing cues (Zeitgebers), such as light. The proper alignment of circadian clocks to environmental cycles is essential for organisms to anticipate and prepare for local challenges, and directly affects the fitness and longevity of many species (Evans and Davidson, 2013). In mammals, a 'master' circadian clock is located in the hypothalamic suprachiasmatic nucleus (SCN), which receives photic information directly from the retina (Hastings et al., 2018). The SCN clock is formed by many single-cell circadian oscillators that synchronize with one another to generate coordinated circadian outputs (Hastings et al., 2018). Circadian clocks are also located in most other tissues and organs. These 'peripheral' clocks can also function in an autonomous manner. However, they can be reset or synchronized by rhythmic cues that are directly or indirectly controlled by the SCN (Dibner et al., 2010; Hastings et al., 2018).

In this review, we explore the interaction between schizophrenia and circadian rhythms from two complementary angles. First, we assert that sleep and endogenous circadian rhythm disturbances are a fundamental component of schizophrenia. Second, we discuss the idea that environmental and genetic circadian rhythm disruption interacts with risk factors for schizophrenia to promote schizophrenia-relevant behavioral and neurobiological abnormalities.

Sleep and circadian disturbances constitute a fundamental component of schizophrenia

Sleep and circadian disturbances in patients with schizophrenia

Sleep disturbances in individuals with schizophrenia have been documented as early as the 19th century by Kraepelin, with 'care for sleep' being a recommended treatment (Kraepelin et al., 1919). In line with these observations, recent findings using more objective experimental tools

have confirmed that various sleep and circadian disturbances appear highly prevalent in individuals with schizophrenia (Figure 1). Indeed, up to 80% of individuals with schizophrenia exhibited difficulties with sleep (Cohrs, 2008) and sleep disturbances preceded prodromal psychotic symptoms in over 77% of patients (Tan and Ang, 2001). Sleep disturbances in subjects with schizophrenia included reduced slow-wave sleep, reduced total sleep time and efficiency, and increased rapid eye movement sleep latency that persisted after accounting for medication, social isolation and the absence of a social routine (Chouinard et al., 2004; Wulff and Joyce, 2011; Zanini et al., 2013). In individuals with schizophrenia, poorer sleep quality correlated with greater symptom severity (Korenic et al., 2019; Laskemoen et al., 2019) and patients with disturbed circadian rhythms performed worse in cognitive tests compared to patients with normal circadian rhythms (Bromundt et al., 2011). In a study measuring both actigraphy and melatonin rhythms, a substantial portion of individuals with schizophrenia had severe disruptions of the circadian sleep-wake timing. This included delayed and/or free-running sleep-wake cycles, compared to matched healthy subjects (Wulff et al., 2012). A meta-analysis of sleep parameters accessed by actigraphy reported various sleep disturbances in patients with treated and remitted schizophrenia compared to healthy controls. These included: greater total sleep time, longer time in bed, greater sleep latency, greater wake after sleep onset and reduced motor activity (Meyer et al., 2020).

Further, some reports have outlined an association between psychosis and sleep and circadian disturbances (Reeve et al., 2015; Freeman et al., 2017; Waite et al., 2019). This association was mainly studied in healthy participants, however, preliminary research showed that sleep disturbances are especially prevalent in clinical high risk (CHR) individuals for psychosis (Poe et al., 2017). Using actigraphy and sleep diaries, youth with CHR for psychosis had more fragmented diurnal rhythms and later onset of nocturnal rest than controls, and the level of these disruptions predicted psychosis symptom severity one year later (Lunsford-Avery et al., 2017).

Using wrist actimetry, older individuals with schizophrenia were found to spend more time in bed, had more fragmented sleep and were awake more during the day compared to older non-psychiatric individuals (Martin et al., 2001; Martin et al., 2005). Of note, the sparsity of research exploring aging and sleep and circadian rhythms in individuals with schizophrenia likely speaks to the challenges in conducting longitudinal studies in patients. The clinical findings summarized above suggest that sleep and circadian disturbances are likely a characteristic feature of schizophrenia, potentially involved in the development of the disorder.

With respect to the molecular markers of the circadian clock, individuals with chronic schizophrenia were found to have a loss of rhythmic mRNA expression of the clock genes *CRYPTOCHROME1 (CRY1)* and *PERIOD2 (PER2)* in skin fibroblasts cultured ex vivo and subjected to a clock synchronizing treatment (Johansson et al., 2016). In the same study, blood mononuclear cells from patients experiencing their first episode of psychosis had decreased expression of *CRY1*, *PER2* and *CLOCK,* compared to controls (Johansson et al., 2016). Further, using RNA sequencing, Seney and colleagues explored gene expression in the dorsolateral prefrontal cortex (dlPFC) of postmortem brains of subjects with schizophrenia. Using time of death data from each subject, researchers found that the set of genes with daily rhythms in subjects with schizophrenia were very distinct from those identified in the dlPFC in healthy controls, and had a different rhythmic pattern (Seney et al., 2019). Distinct cellular pathways were enriched among genes of each of these rhythmic groups. Therefore, this kind of studies might point towards the molecular underpinnings of circadian disturbances in schizophrenia.

Overall, while current evidence highlights the prevalence of sleep and circadian disturbances in individuals with schizophrenia, further studies would benefit from measuring additional biological markers of the endogenous circadian clock and peripheral clocks in individuals with schizophrenia over an extended period of time.

Targeting sleep and circadian disruptions for therapeutic intervention

In a clinical setting, sleep and circadian disruptions are seldom assessed or targeted directly for treatment in individuals with schizophrenia, despite 'sleeping better' being a desired treatment preference (Freeman et al., 2019). Luthringer and colleagues were among the first to explore the effects of the antipsychotic treatment, paliperidone ER, on sleep parameters in patients with schizophrenia. Interestingly, they found that patients showed improved sleep architecture and continuity after paliperidone ER treatment (Luthringer et al., 2007). A recent study by Mishra and colleagues explored the sleep-promoting drug ramelteon, a MT1/MT2 melatonin receptor agonist, as an add-on treatment for schizophrenia patients (Mishra et al., 2020). Compared to patients that received antipsychotics alone (haloperidol and risperidone), add-on ramelteon appeared to significantly improve sleep, as well as the severity of positive and negative symptoms. This was accompanied by increased levels of serum melatonin and aryl-alkylamine-N-acetyl-transferase (the rhythmically-expressed and rate-limiting enzyme in the melatonin synthesis pathway) and urinary melatonin (Mishra et al., 2020). Cognitive behavioral therapy for insomnia (CBT-I) is emerging as an effective sleep promoting therapy for individuals with schizophrenia who experience insomnia. CBT-I was most effective in patients with 'classic severe insomnia', denoted by short sleep duration, very poor sleep efficiency and prolonged sleep onset latency (Chiu et al., 2018), and the benefits on sleep in patients were shown to last 4 weeks post treatment (Hwang et al., 2019). Additionally, in male patients admitted to a psychiatric ward, CBT-I, in combination with controlling light/dark exposure and discussion on sleep monitoring, led to larger reductions in self-reported insomnia symptoms and earlier discharge compared to standard care alone (Sheaves et al., 2018). Future studies should conduct a more detailed assessment of the role of different antipsychotics and sleep or circadian-promoting therapies or drugs on symptom severity in

individuals with schizophrenia and related animal models. For example, one could hypothesize that promoting a proper phase relationship between the circadian system and environmental timing cues may improve schizophrenia-related symptoms by strengthening and stabilizing circadian rhythmicity.

The studies above demonstrate a high prevalence of sleep and circadian disturbances among patients with schizophrenia, which may highlight these disturbances as a core component of schizophrenia pathology. Despite this seemingly high prevalence, there is surprisingly little research targeting these disruptions for therapeutic intervention, leaving much to be discovered.

[INSERT FIGURE 1]

Animal models to study sleep and circadian disturbances in relation to schizophrenia

A number of animal models exploring genetic risk factors for schizophrenia have been used in an attempt to reproduce the sleep and circadian disruptions seen in individuals with schizophrenia (Figure 1; see Table 1 for an overview of the animal models related to schizophrenia that have been studied for sleep and circadian phenotypes). Overall, the studies provide insights on a link between schizophrenia risk genes in animal models and sleep and circadian rhythm-related phenotypes. Some of the genes mutated in the mouse models — or related genes — (including *GRM3, SNAP91, TSNARE1* and *EGR1*) were highlighted in a multi-stage schizophrenia genome-wide association study (GWAS) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Interestingly, most of the genes or proteins of interest in these mouse models have related cellular functions, namely, in neuronal communication and/or protein and vesicle trafficking.

Indeed, disrupted synaptic connectivity and function and abnormal neurotransmitter release have been suggested as key factors in the pathogenesis of schizophrenia (Frankle et al., 2003; Harrison and Weinberger, 2005). Notably, SNAP-25 is a SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) associated protein, with a role in the docking of synaptic vesicles at the presynaptic terminal membrane, resulting in fusion and neurotransmitter release (Mohrmann et al., 2010). Dysbindin-1 is a SNARE-modulating presynaptic protein, essential for synaptic homeostasis (Dickman and Davis, 2009). Dysbindin-1 has been reported to modulate *Snap-25* expression through a possible interaction with Snapin (Feng et al., 2008) and it might regulate dopamine release in the central nervous system through its actions on the SNARE complex (Kumamoto et al., 2006). Dysbindin-1 and Pallidin also have related mechanisms; they are both subunits in the BLOC-1 (the biogenesis of lysosome-related organelles complex-1) stable protein complex. It was hypothesized that they exert their effects on phenotypes via affecting BLOC-1 stability (Lee et al., 2018).

Dysfunction of vesicle trafficking and synaptic communication may contribute to the pathogenesis of schizophrenia but also to the mechanism underlying the interaction between schizophrenia and sleep and circadian rhythms. The studies presented in Table 1 are mainly descriptive reports, and future studies should aim to uncover mechanistic links between schizophrenia and the sleep and circadian systems.

The challenge of modeling schizophrenia in animal models

A limitation of studying risk factors for schizophrenia in animal models is the difficulty in faithfully recapitulating the etiological factors and behavioral phenotypes that are often heterogenous and uniquely human. It is widely accepted that the pathogenesis of schizophrenia is explained by a complex interaction between multiple interacting genetic and environmental risk

factors. Such risk factors are thought to act synergistically, affecting brain development early in life. Thus, the outcome is first seen in young adulthood. A limitation in the studies discussed in Table 1 is that most only utilized animal models with monogenic mutations, that likely only have a small impact on the pathology of schizophrenia. Studying interacting risk factors for schizophrenia as an integrated system would be more appropriate. However, this is posing various challenges, including complicated experimental designs and data analyses.

While no animal model can recapitulate the full intricacies of schizophrenia, they are nonetheless an essential hypothesis-testing preclinical tool. Animal models can be genetically or pharmacologically engineered. Moreover, they offer a high level of experimental control that is necessary when exploring mechanistic links and testing therapeutic targets. Therefore, such studies remain necessary, but should be more and more refined to try accounting for the complex nature of schizophrenia.

Distinguishing Sleep vs. Circadian Rhythm Phenotypes

Sleep/wake cycles and circadian rhythms involve interconnected yet distinct biological mechanisms. However, it is difficult to disentangle these two phenomena, especially when attempting to measure sleep and circadian phenotypes in animal models. The sleep/wake cycle is one of the most documented outputs of the circadian system. Sleep regulation involves a circadian component, whereby the SCN circadian clock controls the activity of brain sleep- and wake-promoting centers (Saper et al., 2005). Sleep regulation also involves a homeostatic component, whereby the sleep pressure (need for sleep) experienced by an individual, increases with extended wakefulness and dissipates with sleep (Borbely, 2009).

In a stable and predictable environment, the sleep/wake cycle is aligned with other circadian-regulated rhythms in the organism. However, a distinction between the two becomes

apparent when either cycle is disrupted. The studies presented in Table 1 highlight the dichotomy between the sleep/wake cycle and circadian system, as several mouse models, including *Egr3*, *DISC1* and *Grm2/3*, showed disruptions in one system and not in the other, perhaps shedding light on distinct biological mechanisms that lead to these disruptions.

Comparing Animal Models: Different Assays, Different Methods

Comparing the sleep and circadian phenotypes of various mouse models across studies is difficult due to the different assay(s) used and non-standardized experimental protocols for data collection and analysis. First, measuring sleep stages in rodent models can be done using electroencephalography (EEG) and electromyography (EMG), or general sleep can be measured less invasively through motion detection, whereby sleep is defined by a bout of immobility. Measuring circadian rhythms in rodent models can also be done in multiple ways, such as through wheel running assessment, bioluminescence recordings and by measuring other markers of the circadian clock such as body temperature and clock gene expression. Thus, the observed effects depend on the assays chosen, which needs to be considered when making comparisons between studies (Pritchett et al., 2012).

Second, experimental conditions, such as wavelength composition and intensity of light, and the type and order of light challenges, and data analysis measures are important to standardize between studies. For example, light challenges can be tested in the following order: first, a standard lighting condition of 12 hours of light and 12 hours of dark (LD), then proceed to phase shifts (delay and/or advance) and constant conditions (constant darkness [DD], constant light [LL]). LL exposure is known to induce desynchrony between the neurons of the SCN (Ohta et al., 2005), thus it is beneficial for this to be the last lighting conditions the animals are exposed to.

The goal when comparing animal models is to confidently attribute the different phenotypes observed to the different genetic mutations. This can be promoted by using a wide range of assays, standardizing variables related to the experimental conditions, using various lighting conditions and analyzing multiple measures in the data.

Genes or proteins of interest for schizophrenia linked also to sleep and circadian rhythms

While all of the animal models in Table 1 are associated with schizophrenia, a subset of the genes involved are also linked to sleep or the circadian system. Below we discuss how these models are related to sleep or circadian rhythms and the implications of this.

Briefly, *Snap-25* has a rhythmic 24-hour pattern of expression in the rodent SCN (Panda et al., 2002). Secondly, *Egr3* appears to regulate sleep homeostasis through the serotonin 2A receptor ($5\text{-HT}_{2a}R$) (Maple et al., 2015; Gronli et al., 2016). Indeed, dysfunction of the $5\text{-HT}_{2a}R$ may be involved in the pathogenesis (Hurlemann et al., 2005) and/or treatment of schizophrenia (Garay et al., 2016). *Egr3* is also implicated in the circadian system, as it is upregulated in the SCN following a nighttime light pulse (Morris et al., 1998). Lastly, glutamate is also an important neurotransmitter for conveying photic entrainment cues to the SCN (Golombek and Rosenstein, 2010), for communication between SCN hemispheres (Michel et al., 2013) and between the SCN and other brain regions (Zhang et al., 2006). As well, glutamate shows rhythmic fluctuations in the prefrontal cortex during the sleep/wake cycle (Lopez-Rodriguez et al., 2007). Group II metabotropic glutamate receptors mGLU2 and mGLU3 are encoded by the genes *Grm2* and *Grm3*, which are expressed in the SCN (Ebling, 1996), and have various effects on sleep structure (Feinberg et al., 2002).

Additionally, in a study by Dittrich et al., mice of the 129S4 strain, which have a natural deletion mutation of *Disc1,* showed altered sleep regulation compared to C57BL/6N mice (Dittrich

et al., 2017). Interestingly, introducing normal *Disc1* locus from C57BL/6N mice did not rescue the phenotype. This may highlight the involvement of additional mutations in 129S4 mice in the sleep-related pathway that may or may not involve *Disc1*.

This emphasizes that caution should be exercised when attributing causality between single mutations in mouse models and resulting phenotypes. Overall, it is possible that a gene or protein of interest involved in both schizophrenia and sleep or circadian rhythms is involved in the interaction of these factors, but in some cases, the effect could be in parallel, with no causal relationship.

Circadian disturbances may affect disorder onset and severity of schizophrenia symptoms

Negative health and behavioral consequences of circadian rhythm disruption

With the entry into a highly digital era and the high demands of the current 24-hour society, many people prioritize aligning sleep/wake times with social and work times, instead of natural circadian timing cues, such as the rising and setting of the sun (Roenneberg et al., 2019). Compelling evidence suggests that there are adverse mental and physical consequences of perturbations of our circadian biology, especially if exposure to these perturbations is chronic (Evans and Davidson, 2013). Circadian rhythm disruption has been linked to cardiovascular disease, different types of cancers, diabetes, and obesity risk (Vetter et al., 2015; Strohmaier et al., 2018; Wang et al., 2018). Chronic circadian disruption was shown to increase mortality rates in *Drosophila* (Pittendrigh and Minis, 1972) and aged mice (Davidson et al., 2006), to alter innate immune responses (Castanon-Cervantes et al., 2010), and to directly regulate mood-related behaviors and cognitive functions in mice (LeGates et al., 2012; Fisk et al., 2018). In a study by Karatsoreos and colleagues, researchers reported that housing mice in 20-hour LD cycles resulted

in a number of effects such as weight gain, a reduction of dendritic length in neurons in the brain, and decreased cognitive flexibility (Karatsoreos et al., 2011).

These observations suggest that sleep and circadian disruption lead to negative health and behavioral consequences. It is largely unknown whether sleep and circadian disruptions affect schizophrenia and if so, how? As mentioned above, reports have showed that sleep disturbances can precede prodromal psychotic symptoms in patients with schizophrenia (Tan and Ang, 2001; Chouinard et al., 2004; Wulff and Joyce, 2011; Zanini et al., 2013). However, even if a causal relationship between such disturbances and the etiology of schizophrenia is suggested, the presented results are correlations. More work would be needed to demonstrate a causal relationship between circadian disruptions and schizophrenia. Below, we describe the few studies that have attempted to address such a causal link.

[INSERT FIGURE 2]

Testing if circadian rhythm disruption is a risk factor for schizophrenia

A commonly accredited hypothesis is that schizophrenia is a multifactorial disorder where numerous risk factors interact within a genetically vulnerable individual resulting in schizophrenia illness (Davis et al., 2016). Perhaps circadian rhythm disruption increases the risk for schizophrenia and interacts with other risk factors to exacerbate schizophrenia-relevant behavioral and neurobiological abnormalities (Figure 2).

Chronotype is an individual's preferred timing of sleep and activity, which is a reflection of one's endogenous circadian clock, the social environment and age-related factors (Takahashi et al., 2018; Roenneberg et al., 2019). In general, the more extreme the chronotype (i.e. extreme morning or extreme evening preference), the greater the misalignment with conventional social

schedules (for example, work and social schedules) resulting in social jetlag (Wittmann et al., 2006). Social jetlag imposes a chronic disruption on the circadian system and late chronotypes in particular show substantial sleep debt (Roenneberg et al., 2003) and greater social jetlag than early chronotypes (Roenneberg et al., 2019). In a GWAS, Jones et al. explored the genetics of chronotype in relation to mental health disorders including schizophrenia (Jones et al., 2019). In a subset of nearly 700,000 subjects, the researchers used Mendelian randomization to infer causality between morningness (being an early chronotype) and reduced risk of schizophrenia (Jones et al., 2019). Perhaps the relationship between schizophrenia and chronotype is based on social jetlag; thus, conducting large studies on populations including individuals with schizophrenia, which would include information on chronotype and social jetlag, would be informative.

Circadian rhythm disruption as a risk factor for schizophrenia could be better studied in animal models, but such studies are scarce. To our knowledge, the only study so far that has directly tested this hypothesis is the one by Bhardwaj and colleagues (2015) using Sandy (Dysbindin-1 mutant) mice. Mice with a mutation in the *Dtnbp1* gene show behavioral abnormalities, including cognitive deficits, reminiscent of schizophrenia patients (Bhardwaj et al., 2009; Cox et al., 2009; Talbot, 2009). Sandy mice also have altered dopamine/D2 receptor signaling (Papaleo et al., 2012) and altered neuronal excitability. Schizophrenia-relevant behaviors of Sandy mice were tested once after exposure to an LD cycle, and then once more after LL exposure, a condition that alters and dampens circadian rhythmicity. LL exposure caused significant deficits in prepulse inhibition of acoustic startle response, hyperlocomotion and less anxiety-like behavior in Sandy mice compared to controls (Bhardwaj et al., 2015). It was hypothesized that circadian disturbances, due to LL exposure, may have exacerbated pre-existing connectivity impairments in the Sandy mice, and therefore unmasked behavioral deficits. Notably, 3 weeks of LD were sufficient to partially rescue the observed behavioral deficits (Bhardwaj et al., 2015).

Clearly, further research is needed to evaluate if circadian disruption is a risk factor for schizophrenia. Studies should test whether exposure to circadian disruption that desynchronizes rhythms in the SCN or in other tissues, or genetic mutations that disrupt clock function, would exacerbate schizophrenia-relevant behavioral and neurobiological abnormalities.

Conclusion

If there is a prominent link between circadian rhythms and schizophrenia, then disturbances to the circadian system could affect disorder outcomes in patients. This suggests that 'at risk' and affected individuals would benefit from limited exposure to environments that promote circadian rhythm disruption. Also, restoring circadian rhythmicity could be used as an adjunctive therapy for schizophrenia. There is a clear urgency for novel and adjunctive therapies, as the current limited treatment options are insufficient to alleviate the full range of symptoms experienced by individuals with schizophrenia. The mouse model studies suggest that the biological mechanisms that contribute to sleep disruption in the context of schizophrenia may be distinct from those responsible for altered circadian entrainment and rhythmicity, such that different treatment strategies might have to be considered to address each aspect.

Here, we argue that circadian disruption is a core pathophysiological component of schizophrenia. Circadian disruption is a consistent core feature observed in most patients. Moreover, promising preliminary evidence suggests that circadian disruption may also act an interacting risk factor for schizophrenia, affecting aspects of the disorder.

We acknowledge that sleep and circadian disruptions are not specific to schizophrenia. Indeed, a number of studies have observed sleep and circadian disruptions in various neurodevelopmental, neurodegenerative, and intellectual disorders. Perhaps this speaks to sleep

and circadian disturbances being a key psychopathological mechanism across a wide range of disorders.

The topic of sleep and circadian rhythms in schizophrenia is a burgeoning field due recent technical and methodological advances that allow this phenomenon to be studied more precisely. The majority of studies exploring the link between circadian rhythms and schizophrenia so far have mainly been correlative and descriptive in nature. There is currently a significant gap in the literature with regards to the precise mechanistic link between schizophrenia and circadian rhythms, which future research should address. Another important aspect that remains to be explored is the interaction of circadian disruption with non-genetic risk factors of schizophrenia.

Acknowledgements

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Funding

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Figure legends

Figure 1. Sleep, and circadian rhythm disturbances are comorbid with schizophrenia in human patients and related animal models. There is evidence to suggest that sleep and circadian rhythm disturbances constitute a fundamental component of schizophrenia, which we have reviewed in both human studies and in animal models that contain genetic mutations related to schizophrenia. Overall, most studies suggest disrupted rhythms in various tissues and assays in schizophrenia patients and related animal models. This disruption is usually seen as loss of circadian rhythmicity, fragmented rhythms, a decreased amplitude (A), and/or irregularity of rhythms.

Figure 2. Circadian disruption is proposed to interact with other schizophrenia risk factors to promote schizophrenia-relevant behavioral and neurobiological abnormalities. Disrupted photic input hits light-sensing retinal ganglion cells which relay the signals to the SCN. We hypothesize that because of the link between circadian rhythms and schizophrenia, disturbances to the circadian system can affect disorder outcomes and symptom severity in patients. This suggests that 'vulnerable' individuals would benefit from limiting exposure to environments that can disturb circadian rhythms, and that restoring circadian rhythmicity could be used as an adjunctive therapy for schizophrenia.

Table 1. Overview of mouse models related to schizophrenia and their known sleep and circadian phenotypes

Gene or Protein of Interest			Details of Corresponding Animal Models			
Name	Description	Link to Schizophrenia	Animal Model	Sleep Phenotype	Circadian Phenotype	Reference
Disrupted-in-schizophrenia 1 (DISC1)	*DISC1* encodes an intracellular scaffold protein, with a likely role in neurosignaling and neurodevelopment (Porteous et al., 2011)	Gene linkage and gene association studies in diverse populations (Millar et al., 2000; Hennah et al., 2003; Chubb et al., 2008)	*Drosophila,* which natively lack a *Disc1* gene, overexpressing human *DISC1*	↑Sleep time ↑Sleep bout duration	Not tested	(Sawamura et al., 2008)
			Disc1 transgenic mice that express both mouse *Disc1* and overexpress wildtype human *DISC1*	↑Wakefulness ↓Sleep time ↓Duration in NREM ↓Duration in REM (between ZT2-9) Tendency for ↓rebound of delta activity following 2-hour sleep deprivation	↓Dark (active) phase activity under LD No change in period in DD or in phase shift after a light pulse	(Jaaro-Peled et al., 2016)
			129S4 mice, which have a natural deletion mutation of *Disc1*	Altered sleep regulation compared to C57BL/6N mice; introducing *Disc1* locus from C57BL/6N does not rescue the phenotype	Not tested	(Dittrich et al., 2017)

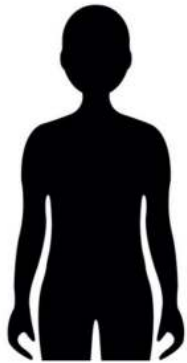|					
Early growth response 3 (Egr3)	*Egr3* gene encodes a transcription factor that plays a role in synaptic plasticity, learning and memory processes (Bozon et al., 2002; Bozon et al., 2003; Li et al., 2007; Barnes et al., 2011)	*EGR3* is regulated downstream of a cascade of genes associated with schizophrenia risk and *EGR3* was linked to schizophrenia in genetic association and gene expression studies (Mexal et al., 2005; Yamada et al., 2007; Zhang et al., 2012; Huentelman et al., 2015)	*Egr3* -/- mice have a full body knockout of *Egr3*	↓Total sleep time	↑Amplitude and ↑*Alpha* under LD/DD/LL	(Maple et al., 2018)
Group II metabotropic glutamate receptors mGlu2 and mGlu3 (Grm2/3)	Group II metabotropic glutamate receptors mGLU2 and mGLU3, encoded by the genes *Grm2* and *Grm3*, are presynaptic inhibitory autoreceptors.	Schizophrenia was associated with altered glutamate levels, and the administration of glutamate NMDA receptor antagonists in healthy subjects induced psychosis (Tsai and Coyle, 2002). The *Grm3* locus was linked to schizophrenia in genetic association studies, protein expression altered in patients in some studies (Egan et al., 2004; Harrison et al., 2008; Schizophrenia Working	*Grm2/3* -/- mice have a full body double knockout of *Grm2* and *Grm3*	↓Total sleep time ↑Fragmented sleep during light phase	↑Period in LL ↑Phase delays after a light pulse ↓Dark (active) phase activity under LD	(Pritchett et al., 2015)

		Group of the Psychiatric Genomics Consortium, 2014).			
Synaptosomal Associated Protein 25 kDa (Snap-25)	The soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex and SNARE-associated proteins (such as SNAP-25) have a role in the docking of synaptic vesicles at the presynaptic terminal membrane, resulting in fusion and neurotransmitter release.	*SNAP-25* was linked to schizophrenia in genetic association studies in certain populations, and in gene expression studies (Fatemi et al., 2001; Fanous et al., 2010).	*Snap-25* heterozygote mutants (*blind-drunk*) have a dominant missense point mutation in the SNAP-25b isoform, which increases binding characteristics of SNAP-25 to the SNARE complex and alters synaptic vesicle release (Jeans et al., 2007)	No effect of the mutation on sleep (as recorded using video tracking)	Heterogeneity of disruption: mild disruption in most mice, more disruption in others. ↑Light phase activity and ↑fragmentation under LD (no disruption in DD/LL), advanced phase of entrainment. Advanced corticosterone and vasopressin rhythms	(Oliver et al., 2012)
Dysbindin-1 (Dtnpb1)	Biogenesis of lysosome-related organelles complex-1 (BLOC-1) is a stable protein complex that consists of many subunits including Dysbindin-1 and Pallidin (Ghiani and	Genetic variants at the *Dtnbp1* locus were linked to schizophrenia in genetic association studies in certain populations (Straub et al., 2002; Schwab et al., 2003).	*Dtnpb1* mutant mice (Sandy) have a natural loss-of-function mutation in the *Dtnbp1* gene	Not tested	↑Free running period, ↑Subjective day activity, ↑Variable activity onsets under LL No disruption under LD/DD.	(Bhardwaj et al., 2015)

	Dell'Angelica, 2011; Mullin et al., 2011) Dysbindin-1 is involved in intracellular membrane trafficking and organelle biogenesis (Falcon-Perez et al., 2002).	Dysbindin-1 mRNA and protein expression were reduced in postmortem schizophrenia brain (Talbot et al., 2004; Weickert et al., 2004; Weickert et al., 2008; Tang et al., 2009).				
Pallidin	Pallidin functions exclusively as a component of the BLOC-1 complex and is necessary for promoting efficient synaptic vesicle recycling and re-formation (Ghiani and Dell'Angelica, 2011; Chen et al., 2017)	Through its activity in the BLOC-1 complex, and its interactions with BLOC-1 subunits, primarily Dysbindin-1, pallidin may play a role in neurodevelopmental disorders (Ryder and Faundez, 2009; Hartwig et al., 2018).	*Palladin* mutant mice have a non-sense mutation in the *Blos1s6* gene encoding Pallidin	↓Sleep time in the beginning of light phase ↑Fragmented sleep in LD	Heterogeneity of disruption: most mice exhibiting mild disruption, while others were dramatically disrupted. Variable activity onsets, ↓Activity under LD ↑Fragmented activity, ↓Precision and ↑Subjective day activity in DD.	(Lee et al., 2018)
SH3 and multiple ankyrin repeat domains 3 (Shank3)	SHANK3 is a scaffolding protein abundant in postsynaptic densities of excitatory synapses (Sheng and Kim, 2000).	Genetic association studies link variants in the *SHANK3* gene to autism spectrum disorder and schizophrenia (Gauthier et al., 2010; de Sena	$Shank3^{\Delta C}$ mutant mice have a deletion in exon 21 of this gene	↓Sleep time and ↓Sleep intensity in dark period of LD. Delayed sleep onset following 5-	↓Total activity in DD No disruption under LD	(Ingiosi et al., 2019)

		Cortabitarte et al., 2017)		hour sleep deprivation	↓Expression of clock genes and clock-controlled transcription factors in *Shank3^{ΔC}* mice, an effect exacerbated by sleep deprivation.	

NREM, non rapid eye movement sleep; REM, rapid eye movement sleep; LD, light-dark cycle; DD, constant darkness; LL, constant light; *Alpha*, duration of the activity phase
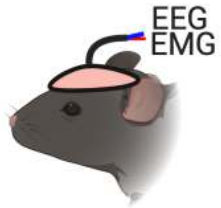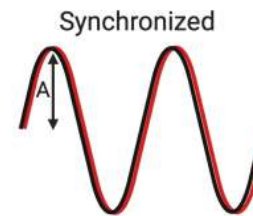
Disrupted
photic input

Shift work (night and rotating)
Jetlag (chronic)
Light at night

SCN

Earlier disease onset
Increased symptom severity

High risk individual
Diagnosed schizophrenia patient