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Circadian rhythms in auditory hallucinations and psychosis

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Abstract

Circadian rhythms are imprinted in all organisms and influence virtually all aspects of physiology and behavior in adaptation to the 24-h day–night cycle. This recognition of a circadian timekeeping system permeating essentially all healthy functioning of body and mind quickly leads to the realization that, in turn, human ailments should be probed for the degree to which they are rooted in or marked by disruptions and dysregulations of circadian clock functions in the human body. In this review, we will focus on psychosis as a key mental illness and foremost one of its cardinal symptoms: auditory hallucinations. We will discuss recent empirical evidence and conceptual advances probing the potential role of circadian disruption in auditory hallucinations. Moreover, a dysbalance in excitation and inhibition within cortical networks, which in turn drive a disinhibition of dopaminergic signaling, will be highlighted as central physiological mechanism. Finally, we will propose two avenues for experimentally intervening on the circadian influences to potentially alleviate hallucinations in psychotic disorders.

KEYWORDS

audition, circadian clock, dopamine, E/I balance, hallucinations, psychosis

1 | BACKGROUND

Auditory hallucinations are a cardinal symptom of psychotic disorders, affecting more than two-thirds of patients with a diagnosis of schizophrenia.[1,2] Hallucinations thus constitute one of the main diagnostic positive symptoms of schizophrenia spectrum disorders in the two major classification systems, in distinction of the usually longer-lasting and potentially more debilitating negative symptoms, such as cognitive decline, anhedonia, or flat affect.[3] However, auditory hallucinations are not pathognomonic for psychotic disorders, as they present with significant frequency (recent estimates ranging from 45% to 60%) in the context of a number of other mental disorders such as mood, dissociative, personality, and post-traumatic stress disorders, and may also affect approximately a third of patients with neurodegenerative disorders such as Parkinson's disease.[4] Due to their typically negative (e.g., derogatory or threatening) content, hallucinations in psychosis cause significant distress.[2] Moreover, their presence is associated with increased risk for unfavorable outcomes such as more severe psychopathology, suicide, violence, low functioning, and neurocognitive deficits[2]—irrespective of diagnosis.[4]

Strikingly, the experience of auditory verbal hallucinations (AVH), that is, "hearing voices," is also not uncommon in the general population, with a lifetime prevalence of approximately 10%.[5,6] The phenomenology

of hallucinations is very similar across diagnoses as well as in comparisons of clinical and non-clinical populations[7,8] suggesting that they occur across a continuum. Likewise, neuroimaging studies exploring neural correlates of AVH experiences revealed a similar engagement of brain networks across diagnoses or between clinical and non-clinical populations.[9] However, differences between hallucinators with and without need for care have been observed across various neurobiological and cognitive dimensions.[7,8] It seems therefore likely that the final clinical manifestation including severity, diagnostic category, distress, and need for care results from the interaction between a common neurophysiological substrate and other factors such as environmental risk factors (e.g., trauma),[7,8] cognitive mechanisms (e.g., cognitive appraisal of voices, reasoning biases; emotional factors), but also biological factors such as neurotransmitter activity[10] or brain network organization.[11] Altogether, this raises the question what common neurophysiological factor mediates auditory hallucinations along such a continuum. One such biological factor, often overlooked in the literature and the main focus of this review, is circadian abnormalities.

We hypothesize that circadian disruptions drive a dysbalance of the excitation-to-inhibition (E:I) ratio within cortical networks and a dopamine (DA) dysfunction both causing a shift in sensory processing which in turn lead to auditory hallucinations. To explore this putative role of circadian rhythms, we will begin by reviewing the overall link between circadian disruption and psychotic disorders and introduce dopamine as a central mediator for circadian misalignment. Next, we will move into the auditory domain, which we will first approach by examining the evidence of auditory clocks. We will then discuss the pathophysiology of auditory hallucinations and recent empirical evidence and conceptual advances probing the potential role of circadian disruption in auditory hallucinations and, specifically, introduce E:I dysbalance and dopamine dysfunction as central physiological mechanisms and identify recent evidence of a circadian rhythmicity. Finally, we will propose two avenues for experimentally intervening on the circadian influences to potentially alleviate hallucinations in psychotic disorders.

2 | CIRCADIAN DISRUPTION AND PSYCHOTIC DISORDERS

2.1 | Circadian disruption: Definition and effects on health

The interplay between circadian rhythms and behavior is instrumental for our health. A disruption thereof has been linked to cognitive and physical impairments or disorders.

The easiest recognizable form of disruption within this framework is a shift in the sleep/wake cycle to the environmental day/night cycle, which mainly result in sleep problems and daytime sleepiness.[12] A common cause for such a misalignment arises from jet lag when individuals travel across multiple time zones. The lag in synchronization between internal circadian rhythms and the current zeitgebers both photic and non-photic (e.g., feeding times) result in disturbed sleep, daytime fatigue, hormone profiles, and changes in mood. While this misalignment is usually transient and dissipates with time, a minority of people, for example, patients diagnosed with bipolar disorder, may develop problems with re-alignment requiring much longer time scales up to months.[12] An alternative cause for circadian disruption is shift work, an inevitable development driven by the access to light during the night. Accordingly, long-term shift workers exhibit increased risk for cancer.[13] Night shift workers, with a prevalence of 15%–20% in industrial societies, also suffer from elevated incidence of cardiovascular and metabolic disorders and exhibit an increased prevalence of behavioral health and psychiatric disorders compared to their day-shift counterparts.[14,15]

2.2 | Circadian disruption and psychosis

Sleep disturbances and abnormal sleep–wake cycles may precede and exacerbate psychotic experiences, for example, a night of sleep deprivation in healthy participants results in significant increases in anxiety, depression, and paranoia.[16,17] Sleep is not only regulated by the circadian phase, but a reciprocal influence has been shown as well, for example, sleep deprivation altering the phase of circadian rhythms.[18] Of note, these mutual influences are not easy to distinguish. Nevertheless, circadian abnormalities are hence not only a common characteristic of inflammatory or neurodegenerative diseases; circadian disruptions such as circadian misalignment of melatonin secretion from night-time into day-time are encountered in the majority of patients with psychotic disorders.[19,20] The prevalence of sleep and circadian rhythm disruption in patients with schizophrenia lies around 80% and has thus been described as a hallmark of the disorder.[21] These patients report a broad range of disturbances: sleep onset latency, difficulties to maintain sleep, circadian advances/delays, bidian (48 h) sleep/wake cycles, and highly irregular and fragmented sleep patterns.[19] In a similar vein, the endorsement of sleep problems was associated with an increased risk for reporting at least one psychotic symptom (even if corrected for anxiety and depression) in the general population.[22] Furthermore, it was found that difficulties falling asleep and early morning awakenings were

associated with significantly higher risk of one or more reported psychotic experiences in the general population.[23] Altogether these disturbances are strongly associated with negative clinical outcomes, including relapse, poorer coping, higher distress, increased frequency of depression and even complete suicide.[19] However, circadian disruption phenotypes in patients with psychotic disorders are very heterogeneous,[24] and the nature of the relationship between circadian abnormalities and psychotic symptoms remains unclear. More specifically, it is unknown which specific mechanisms link circadian disruption or shifts in circadian rhythmicity to the altered perceptions and beliefs that are at the heart of psychosis, and whether circadian disruption acts as a direct mediator of state symptomatology, or rather represents a distal vulnerability factor interacting with other genetic and environmental factors to eventually lead to the emergence of psychotic disorders—or both.[25]

2.3 | Pathophysiology of circadian misalignment in psychosis: The role of dopamine

What is the etiological mechanism contributing to circadian misalignment in psychosis? One widely accepted notion is dysfunction of neurotransmitter systems as glutamate and especially dopamine, which has been associated as an underlying mediator of psychosis.[26] Dopaminergic neurons in the ventral tegmental area (VTA) or substantia nigra pars compacta (SN) are, albeit not directly, regulated by the suprachiasmatic nucleus (SCN)—the master pacemaker governing circadian rhythms. Intriguingly, dopamine levels can in turn feedback and influence SCN activity.[27,28] There is also evidence for a modulatory role of dopamine in peripheral clocks such as the striatal clock.[29] Furthermore, dopamine regulates circadian rhythms via hormone production and as it affects the release of prolactin or melatonin in the pituitary and pineal gland, respectively.[30,31]

Importantly, the link between dopamine and sleep–wake systems is bidirectional. Dopamine signaling has diurnal rhythms, which are directly regulated by the circadian clock.[32] Moreover, dopamine is modulated by melatonin, with melatonin specifically exerting an inhibitory effect on the dopaminergic system.[33,34] Consequently, disruption in dopamine signaling will affect circadian rhythms and vice versa.

The bidirectional involvement of dopamine in the regulation of sleep and circadian rhythms implies that alterations in dopamine signaling, such as they occur in schizophrenia (see below, section 3.3), would lead to disruptions to sleep and circadian rhythms. Indeed, pharmacological elevation of dopamine transmission led to disrupted sleep and fragmented rest/activity rhythms.[35,36] Thus, dysregulation of the dopaminergic system may be a key mechanism underlying the circadian disruption prevalent in schizophrenia. On the other hand, the fact that dopamine is also under the control of the circadian clock and exhibits sleep-dependent changes makes it likely that, in turn, circadian disruption may lead to a dysregulation of dopamine signaling. For example, sleep deprivation has been shown to cause an increase in dopaminergic activity.[37,38] Altogether, dopamine is an important modulator of the circadian system and therefore constitutes a common mechanism underlying both sleep and circadian regulation on one hand and psychotic symptoms such as auditory hallucinations on the other.

3 | THE ROLE OF CIRCADIAN DISRUPTION IN THE EMERGENCE OF AUDITORY HALLUCINATIONS

3.1 | Circadian clocks in audition

Given that circadian rhythms have been found in various organs such as the heart, stomach, or liver, the question arises how the auditory system itself is modulated by the circadian timekeeping system as well. Indeed, experiments in mice revealed that the cochlea and inferior colliculus express core clock genes, that is, *Per1*, *Per2*, *Bmal1*, and *Rev-Erbα*.[39,40] Using real-time bioluminescence on an organotypic cochlea slice of transgenic mice, which express a PER2::LUCIFERASE fusion protein, revealed that cochlea PER2 expression oscillates in a rhythm synchronous to the SCN. In line with previous evidence from other peripheral tissue like the liver,[41] these oscillations persisted for about a week in culture and thus corroborate a robust and self-sustained clock within the cochlea.[39]

But how does this auditory clockwork affect auditory function? Evidence on the circadian regulation of the auditory system is sparse, and existing studies were primarily performed in rodents and focused on diurnal patterns of hearing sensitivity[42] (Figure 1). Acoustic startle response (ASR, a motor or eye reflex upon an unexpected salient acoustic stimulus) in mice was found to be greater in the morning than in the evening indicating a higher hearing sensitivity during the resting phase. A modulatory role of PER2 was shown in *Per2* knockout, which exhibit a diminish ASR in contrast to healthy wildtype mice (Russell et al., 2021). In humans, an overall identical pattern in ASR was found, that is, a greater ASR response in the evening.[43] Intriguingly, sensitivity to noise trauma follows a 24-h rhythm but inverted variation.[44] Comparing the recovery to noise exposure in mice during the day and night

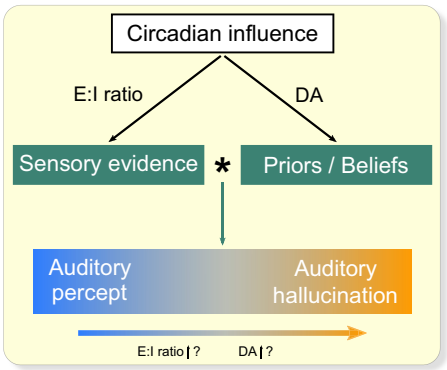

FIGURE 1 Circadian influence on auditory percept and hallucinations. An auditory percept is formed from a balanced integration of incoming sensory input and existing priors/beliefs. However, how does an auditory hallucination emerge and what role do circadian influences play? It is hypothesized that a circadian disruption affects this integration process, putatively due to a shifted processing of sensory evidence caused by a shift in excitation-to-inhibition (E:I) ratio in auditory cortices or a change in perceptual bias driven by dopamine (DA) signaling toward prior expectations ultimately leading to an auditory percept in the absence of sensory input—an auditory hallucination.

revealed a complete recovery during the day, whereas loss of hair cells and thus permanent damage was caused during the night, suggesting a vulnerability of the auditory system at night.

Despite the established evidence for auditory clocks, the central question remains to what extent these clocks play a role in the occurrence and maintenance of auditory hallucinations. The best evidence for auditory clocks localizes to the auditory periphery (i.e., the inner ear and ascending pathways in the brain stem; for a recent review, see[45]). This leaves us with a notable gap of knowledge between these markedly peripheral clock mechanisms thus far identified on the one hand and the perceptually strikingly complex, often verbal nature of auditory hallucinations, on the other, clearly pointing to relevant cortical auditory contributions. (Note that the processes involved in perceiving verbal auditory hallucinations such as speech recognition, pitch perception, and emotional judgment of complex sound all point to auditory cortical contributions.[46]) To this end, we will next review the concept of auditory hallucinations in more depth and discuss potential, centrally located mechanisms that may be susceptible to circadian rhythms and circadian disruption.

3.2 | Auditory hallucinations: Definitions and pathophysiology

A hallucination is defined as a percept without a corresponding sensory event in the outside, physical world that causes this percept.[47] By this strict definition, a series of seemingly unrelated perceptual phenomena can be subsumed also as hallucinations: Earworms (i.e., the often unwanted, intrusive internal "replay" of melody fragments[48]) or tinnitus (i.e., the often distressing percept of a ringing or buzzing tone in lieu of an acoustic signal causing it)[49] (see below).

Auditory hallucinations as a key symptom of psychosis are, first, for most verbal. That is, the patient perceives an (often identifiable, discriminable) human voice. Furthermore, a suggested taxonomy of auditory hallucinations in psychosis furthers the dimensions of language complexity, self-other misattribution, and spatial location (inside vs. outside the head[50]). Second, there will be no sense of intent for auditory hallucinations: the patient usually does not intend to listen to these voices and cannot help but doing so. Accordingly, the voices are for most be perceived as intrusive or unwanted, as they elude the listener's voluntary control (for a detailed account of the phenomenology of auditory hallucinations as a "transdiagnostic" feature see[51]).

In the emerging field of computational psychiatry, the occurrence of hallucinations has been approached fruitfully from a vantage points on how the mind gathers and integrates information and forms beliefs. We here exhibit this framework in at least some detail, as it will prove useful when linking the pathophysiology of hallucinatory percepts back to disturbances of the circadian system of the patient.

First, prominent computational–psychiatry accounts emphasize the dysregulation of feedforward/feedback loops in sensation and perception as an explanation for the emergence of hallucination: The Bayesian predictive coding account.[52,53] This has been formalized within a framework of Bayesian perception, reflected in a misalignment of prior predictions and incoming sensory evidence ("prediction error," in technical terms). The suggested key pathology here is thought to lie in the synaptic gain, as it would align well with the suggested multiplicative changes in the precision with which the psychotic brain encodes both, perceptual prior expectations, and actual sensory evidence. As the next section will elaborate, many of the demonstrated pathophysiologies in psychotic disorders center on changes to synaptic gain, such as in dopaminergic and *N*-methyl-D-aspartate (NMDA) receptor function.

In the auditory domain, the much-studied auditory mismatch negativity response (MMN) is as a marker for sensory evidence accumulation. Compelling evidence has been collected suggesting a reductiwon of MMN in psychosis,[54] and that it responds to pharmacological NMDA-receptor-affine interventions (see e.g.,[55]). Also, the strikingly high confidence with which hallucination-prone individuals

hold ambiguous auditory percepts is commensurate with the Bayesian Perception framework,[56] in that overly strong prior expectations can come to dominate a relatively weakened representation of sensory evidence. This ties in well also with recent findings in psychotic and non-psychotic hallucinators (Powers et al., 2017) and in optogenetically manipulated mice[57] (see next section for a detailed discussion of the dopaminergic origin of these findings)—both studies have yielded high-confidence false alarms in a perceptually ambiguous, auditory detection paradigms as a viable laboratory operationalization of auditory hallucinations.

Second and closely related to changes in afferent "bottom-up" prediction error versus efferent "top-down" predictions, a relative neurophysiological dysbalance of Excitatory-to-inhibitory (E:I) drive in given neural populations has been proposed in empirical studies in human and non-human model systems.[58–61] Accordingly, the conjecture arises that local changes to the E:I balance in the central auditory pathway are associated with a different weighing of sensory evidence[62,63] and that a relative hyperexcitability, as previously described as a general pathophysiological phenomenon in psychosis,[64] might promote the emergence of auditory hallucinations.

Notably, the often debilitating chronic condition of tinnitus, which can be framed as a non-verbal variant of an auditory hallucination "phantom perception" of sound, has not only been modeled also as a relative disturbance of E:I balance.[65] Second, in close analogy to psychotic hallucinations, tinnitus is currently thought of as a disturbance in a Bayesian perception, namely a relative shift in precision of perceptual priors and sensory evidence, presumably throughout the multiple stages of the afferent and efferent auditory pathways.[49,66] Until now, there is only preliminary evidence that also the subjective percepts of tinnitus might be related to individual circadian rhythms,[67] which is to be expected if it shares core common pathophysiological principles with the emergence of auditory verbal hallucinations.

3.3 | Dopamine and E:I balance as mediators of auditory hallucinations

The introduction of chlorpromazine in 1950 and the description of its effect in treating psychotic states paved the way for a huge body of research that amounted to the formulation of the dopamine hypothesis, which since then has emerged as the most prominent and enduring neurobiological model of schizophrenia and psychosis in general. In its initial version, the dopamine hypothesis postulates that psychotic symptoms such as delusions and hallucinations arise from a hyperdopaminergic state in the brain and that antipsychotic drugs exert their effect by counteracting this state.[68] In a similar vein, administration of dopamine stimulants in healthy participants induces psychotic symptoms.[69,70] Although the dopamine hypothesis has undergone several refinements over the years, its major premise has remained unchanged.[71] In fact, all currently licensed antipsychotic drugs have as common denominator their ability to block dopamine D2 receptors,[71] even though they may have several effects on other neurotransmitters as well.[72]

In unraveling the relation between dopamine and auditory hallucinations, it is essential to note that, on the one hand, dopaminergic function in striatal regions is increased in schizophrenia and correlates with symptom severity.[76,77] On the other hand, the discrimination of auditory information relies on projections from the auditory cortex to subcortical striatal networks.[78] Critically, recent work reported that the rate of hallucination-like perceptions in mice, measured by the aforementioned high confidence false alarms within an auditory discrimination task, was predicted by striatal dopamine levels. Moreover, optogenetic stimulation of dopamine release and blocking of dopamine receptors by haloperidol administration led to an increase and reduction in auditory hallucinations, respectively[57] (Figure 2A). Altogether this evidence corroborates the notion of a mediating role of striatal dopamine on the emergence of positive symptoms and auditory hallucinations in particular.

Considering this established contribution of dopamine, the question arises what in turn causes the hyperdopaminergic brain state. Neuroimaging studies observed increased activation of the thalamus and hippocampus during hallucinations, which may directly influence auditory processing but also in the striatum indicative of a widespread dysfunction of neural networks.[79] More importantly, striatal dopamine release is mainly innervated via projections from the frontal cortex.[71,80] This ties to the previously described concept of a dysbalance in excitation and inhibition within cortical networks, more specifically a lower inhibition in frontal networks leading to an amplified innervation of dopaminergic neurons in the striatum.[81] Empirical evidence in support of this concept has been provided by administration of ketamine intervention in mice, leading to an increased synthesis of striatal dopamine—an effect that could be counteracted by activating inhibitory signals within cortical networks.[82] Of note, ketamine intake is associated with both positive and negative symptoms in healthy individuals as well as patients with schizophrenia.[83]

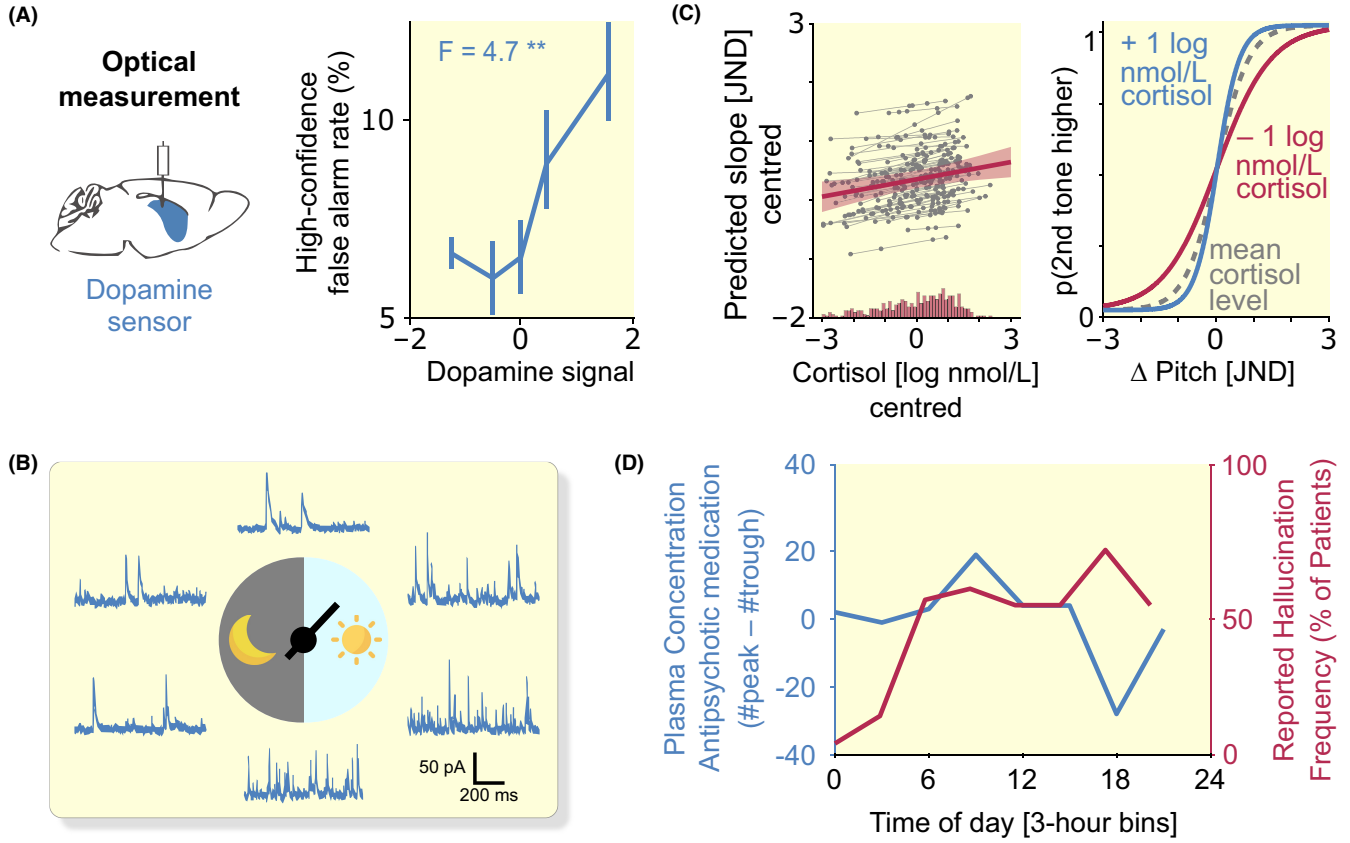

FIGURE 2 Collective evidence from dopamine and E:I balance to circadian rhythmicity in auditory perception and hallucinations. (A) Optical measurement of striatal dopamine revealed positive relation between dopamine levels and high-confidence false alarms on an auditory discrimination task as a measure of auditory hallucinations (adapted with permission from[57]). (B) Tracking of spontaneous inhibitory postsynaptic currents in mice revealed a modulation in activity across the day-night cycles, with highest inhibition during the day, that is, when mice are asleep (data adapted with permission from[73]). (C) Performance on an auditory discrimination task, assessed by the slope of the psychometric curve (the steeper the better the performance) in healthy individuals covaried with cortisol levels (adapted with permission[74]). (D) Reported hallucinations in patients with schizophrenia fluctuated over the course of a day, which highest occurrences in the evening (orange line). In addition, antipsychotic drug concentration (derived by the differences in number peaks and troughs observed across participants, blue line) showed an anti-phasic pattern, maximal about 12 h earlier (data aggregated and smoothed based on Tables 2 and 4 in[75]).

3.4 | Current evidence on the circadian rhythmicity of auditory hallucinations

The final question remained unanswered is if auditory hallucinations are under a circadian influence. However, studies examining this aspect are rare or in fact allow only indirect inferences. Tracking spontaneous inhibitory postsynaptic currents in (nocturnal) mice across 24 h revealed an inhibitory signal almost twice as high as during the light phase when mice are asleep in comparison to the dark phase[73] (Figure 2B) suggesting a circadian modulation of E:I balance. In contrast, performance on an auditory pitch discrimination task of healthy individuals covaried with cortisol levels[74] (Figure 2C), a central endocrine marker under circadian regulation.[84] Considering these findings suggests that auditory hallucinations may be under circadian influence as well.

To date, only sparse evidence is available from patients with schizophrenia where the occurrence of auditory hallucinations was directly related to antipsychotic drug concentration during the course of a day. Strikingly, the study revealed that auditory hallucinations were not only reported most frequently in the evening but also lasted the longest during this time of day.[75] Intriguingly, as can be synthesized from this study (see Figure 2D), small plasmatic fluctuations in antipsychotic drug concentration appear to exhibit an anti-phasic pattern relative to the circadian peaks and troughs of reported auditory hallucinations. This highlights the potentially critical, unstudied role that circadian dynamics may play in the emergence and treatment of psychosis.

4 | OUTLOOK: HOW TO INTERVENE ON CIRCADIAN DISRUPTIONS IN PSYCHOSIS?

Recapitulating the collected evidence, circadian disruption paralleled by an E:I dysbalance within cortical networks and an aberrant dopamine signaling poses a mechanistically plausible pathway toward the experience of psychotic symptoms, as shown here specifically for auditory hallucinations. Thus, the question arises how this insight can be utilized in treating positive symptoms in psychosis. Albeit rather speculative, we see two approaches lying close at hand (Figure 3).

The first approach relates specifically to the previously discussed anti-phasic pattern between antipsychotic drug concentrations and auditory hallucinations in patients with schizophrenia.[75] Although conventional dosing schedules target a stable concentration of antipsychotics, the concept of chrono-pharmacology suggests an administration of antipsychotics adapted to individual rhythms of positive symptoms such that peak levels of antipsychotic drugs coincide with time periods during which auditory hallucination are worst (Figure 3, bottom right). As an ideal outcome, total dosage might be reduced on the long run if a better match with individual circadian chronotype[85] could be achieved, at least in the initial phase before a stable plateau of antipsychotic medication is attained. Notably, to date only one study demonstrated the anti-phasic pattern between antipsychotic drug and auditory hallucination; thus, the proposed chrono-pharmacological avenue warrants further work. Such future studies should move from a systematic assessment of chronotype and emergence of auditory hallucinations in clinical and healthy populations toward the essential question if chronobiologically informed therapeutic regimes can help mitigate psychotic symptom severity.

Furthermore, both circadian disruptions in general and psychotic disorders specifically go hand in hand with abnormal sleep patterns and vice versa. Considering the intertwined relation between sleep and circadian systems, a stabilization of sleep patterns is an obvious target in managing symptom burden in patients with psychotic disorders. Similarly, non-invasive brain stimulation techniques, such as auditory stimulation, may provide an accessible tool to facilitate sleep, that is, accelerate sleep onset or facilitate sleep depths.[86,87] More intriguingly and specifically considering the proposed central role of cortical E:I ratio on auditory hallucinations, a recent study observed a modulation of E:I balance across a period sleep.[88] Utilizing

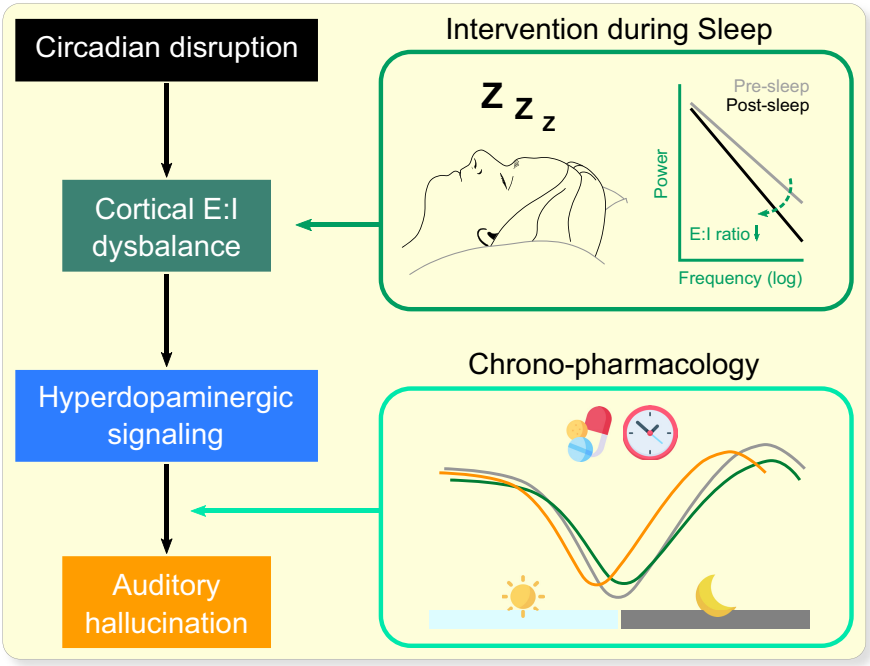

FIGURE 3 Intervention on circadian disruption in psychosis. Recent empirical insights and conceptual advances suggest that key mechanisms leading to auditory hallucinations during circadian disruption are an E:I dysbalance within cortical networks which in turn exerts an excitatory drive of striatal dopamine levels. Considering this cascade, one potential interventions may be a manipulation of oscillatory brain activity during sleep to modulate cortical E:I balance. Furthermore, following a chrono-pharmacological approach, dosage and administration timing of antipsychotic drugs could be individually adapted to the circadian rhythmicity of psychotic symptom occurrence.

the power-spectral slope (i.e., the 1/f exponent) as an approximation for E:I ratio in human neurophysiological data,[58,89] it can be shown that a homeostatic regulation of the spectral slope toward more negative values is indicative of a net increase in inhibition (Figure 3, top right). Thus, sleep represents an intriguing window of opportunity to intervene in order to counteract any trait- or state-like E:I dysbalances and, consequently, the likelihood of psychotic symptoms to emerge. However, on the one hand, the ramifications between sleep and circadian disruption are difficult to set apart; thus, a disentangling, for example, via forced desynchrony approaches,[90] can provide a critical understanding of the distinct sleep and circadian role on auditory hallucinations. On the other hand, the discoveries linking sleep and E:I balance have only been made recently and are highly understudied. Thus, our understanding requires future work to address fundamental questions: How do overnight changes in E:I ratio translate into changes in sensory evidence accumulation and the proneness to auditory hallucinations? Most critically, the feasibility of sleep interventions on homeostatic E:I regulation and, consequently, on auditory perception remains to be demonstrated.

5 | CONCLUSION

Our synthesis of the literature demonstrates that our knowledge on the implications of circadian disruption on auditory hallucinations is only beginning to form, despite the consensus on the importance of circadian rhythms on human mental health. We here highlight a putative mechanistic link of disrupted circadian rhythms to aberrant auditory perception in psychosis, via dysregulations in dopamine signaling and a dysbalance of E:I dynamics. Furthermore, we propose two putative approaches to ameliorate positive symptoms in psychosis via targeted chronobiological interventions. Future work will need to explore these new avenues toward accessible treatments, synergistically counteracting circadian disruption and improving psychotic symptoms.

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