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The influence of sleep disturbance on psychosis in vulnerable individuals, modulated by the dopaminergic system

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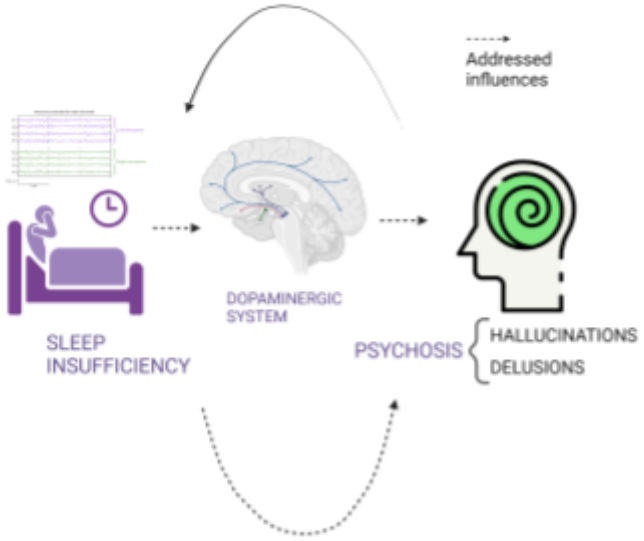
Summary

The current review explores the influence of sleep disturbances on the emergence of psychotic episodes through modulation of the dopaminergic neurotransmitter system. While substantial research has examined sleep disturbances as a consequence of psychosis, this review investigates how sleep disturbances may contribute to the development of psychosis, a primary group of symptoms found in schizophrenia. Dopamine antagonists, currently used as antipsychotic treatments, provide insights into the relationship between sleep disturbances and psychosis. On the other hand, dopamine agonists such as amphetamine reveal important insight into the endogenous sensitization theory and supersensitivity theory of psychosis. Alterations in dopamine release of D1/D2 dopamine receptors in the striatum have been found in both disturbed sleep and psychosis. Research into schizophrenia reveals strong correlations between altered sleep architecture and duration in schizophrenic patients and an increased risk of psychosis onset in those experiencing sleep problems. Genes of the phosphodiesterase family have been associated with both psychosis and sleep disturbances through their effects on dopamine expression in the medium spiny projection neurons of the striatum. Moreover, the expression of genes involved in sleep-wake regulation is influenced by dopamine. The reviewed literature indicates a relationship between hyperdopaminergia, sleep disturbances (such as insomnia or sleep fragmentation), and psychosis. However, it appears that sleep disturbances alone are insufficient to cause psychosis or schizophrenia. Instead, this phenomenon is influenced by a complex interplay of genetic and environmental factors.



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1. Introduction

Schizophrenia is a severe mental disorder characterized in the DSM-V by fundamental disturbances in thinking, perception and emotions (American Psychiatric Association, 2013). The life expectancy of schizophrenic patients is generally reduced by 10 years caused by suicide (Sher & Kahn, 2019). Even though schizophrenia affects less than 1% of people worldwide, the burden of the disease is one of the most costly (Sher & Kahn, 2019).

The three primary symptom groups of schizophrenia are psychotic, negative and cognitive symptoms . Psychotic symptoms (positive symptoms) include hallucinations, delusions and thought disorder, with most research focusing on the first category (Owen et al., 2016). With the change of diagnosis criteria for mental disorders it became more clear that acute psychosis can be a one-time occurance and part of more differential diagnosis rather than only schizophrenia. Antipsychotic treatment for acute psychosis is currently the same as for chronic psychosis and is categorized into two types: typical (e.g. haloperidol) and atypical (e.g. clozapine, risperidone,

olanzapine). Both types block the dopamine D2 receptor, but differ among the degree of receptor occupancy (Bruijnzeel et al., 2014). Three drugs—asenapine, olanzapine, and clozapine—are likely to demonstrate significant D1 receptor antagonism at doses used for treating psychosis. D1 receptors are the major postsynaptic dopamine receptor subtype present in the prefrontal cortex while a combination of both D1 and D2 receptors is present in the motor striatum and the nucleus accumbens (Stahl, 2017). However, a broad range of non-dopaminergic targets are affected by the administration of antipsychotic drugs, such as serotonergic, muscarinic, histaminergic, and adrenergic receptors.

Typical antipsychotic drugs often lead to extrapyramidal side effects, such as dyskinesias (involuntary movements in the face, neck, trunk, pelvis), parkinsonism, akinesia (inability to move muscles and limbs), catalepsy (severe muscle rigidity), akathisia (inability to remain still) and neuroleptic malignant syndrome (idiosyncratic reaction characterized by fever, altered mental status, and autonomic dysfunction). Other side effects include sedation, and anticholinergic reactions (Blair & Dauner, 1992). Atypical antipsychotic drugs based on clozapine may still lead to these side effects to different extents, along with metabolic and endocrine side effects (Ågren, 2021; Bruijnzeel et al., 2014).

Apart from schizophrenia, the use of antipsychotics is used for a broad range of disorders such as bipolar disorder, tic disorder, agitation, and sleeping problems. More recently, antipsychotic treatment has reached patients suffering from anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), major depression, personality disorders, disruptive disorders, and dementia (Hálfdánarson et al., 2017). With a positive trend in use between 2005 and 2014 in Central and Eastern Europe and an increase in incidence of depressive symptoms, it is important to find alternatives or improvements to antipsychotic treatment (Hálfdánarson et al., 2017).

Additionally, between 30% and 80% of patients with schizophrenia report sleep disturbances, which have been associated with psychosis for a long time. Such sleep disturbances are shorter sleep time, lower sleep quality and nightmares, and can lead to sleep disorders (e.g. insomnia,

nightmare disorders, sleep apnea) that were less investigated in association with psychosis (Reeve et al., 2019). Currently, it is widely accepted that sleep is regulated by two processes:(1) process S, and (2) process C. (1) Process S refers to the homeostatic pressure accumulated during awakening duration and that decreases with sleeping. (2) Process C refers to the circadian process that is regulated by the suprachiasmatic nucleus, also known as the circadian pacemaker. The architecture of sleep consists of cycles through different stages, including non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, each playing a crucial role in restorative processes and cognitive functions. NREM sleep includes three stages of increasing depth, while REM sleep is associated with vivid dreaming and brain activity similar to wakefulness, with a typical sleep cycle repeating every 90 minutes (Chokroverty, 2010).
The ability to sleep is affected by motivational and cognitive factors and research suggests that this process could be regulated by the mesolimbic pathway. This pathway entails projections from ventral tegmental area (VTA) dopamine neurons to the nucleus accumbens (NAc). The alteration of sleep architecture and quality can lead to disruptions in the dopaminergic receptor expression or activity causing a susceptibility to psychosis in vulnerable individuals. These disruptions can alter the circadian rhythm which in turn will also influence the nocturnal activity levels by causing sleep disturbance (Figure 1).

Figure 1. The interplay between sleep, circadian rhythm and psychosis (Yates, 2016)

People with ultra-high risk of psychosis can offer insight into the genesis of the disorder, which is why this review includes research targeting this group. Diagnosis includes three criteria: attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms and genetic risk. Increased vulnerability of individuals at high risk of psychosis is attributed to mainly environmental factors such as prenatal/perinatal factors, childhood and adolescent factors, affective dysregulation and sociodemographic factors (Fusar-Poli et al., 2017). However, genetic predisposition for circadian abnormality, sleep disturbance, dopamine alterations, increased activity levels and psychosis are interconnected and all influence the profile of early psychosis (Figure 1) (Yates, 2016).

A comprehensive review of the influence of sleep disturbances on the emergence of psychosis is needed to synthesize available evidence and to guide future academic and clinical research. This review focused on data derived from clinical studies and animal models including studies focused on patients that experienced the initial onset of psychosis. Here, it is sought to address two main research questions: 1) What is the influence of sleep disturbance on psychosis and 2) What is the role of dopamine in sleep disturbance and psychosis?

2. Dopamine and psychosis

The dopamine hypothesis has been one of the leading hypotheses involving the cause of psychosis in schizophrenic patients since the 1960s (Howes & Kapur, 2009).
The hypothesis states that overactive dopaminergic pathways are responsible for what is described as positive symptoms of schizophrenia, such as psychosis. The premise of this hypothesis is set by the discovery of the antidopaminergic effect of multiple antipsychotics in the brain, by Philip Seeman (*P. Seeman et al., 1987*).

2.1 Psychoactive substances and stress as models of psychosis

Psychoactive drugs can influence the risk of psychosis. Drugs like ketamine, amphetamine and cocaine increase the activity of the dopaminergic system. Psychoactive drugs targeting other systems can indirectly affect the dopaminergic system by enhancing dopamine release through secondary mechanisms, to levels comparable to those observed in schizophrenia. Commonly, the administration of amphetamines, dopamine agonists, lead to psychotic episodes in healthy people, which is why administration of amphetamine is a common model of psychosis (Howes & Kapur, 2009).

The data show that amphetamine and cocaine produce identical dopamine elevations both in the nucleus accumbens and dorsomedial striatum, whereas non-psychedelic substances such as nicotine increases dopamine in the nucleus accumbens only (Danielsson et al., 2021). This is suggesting that the manner in which dopamine is increased in different brain areas might be important to the triggering of psychosis.

Other studies also found higher concentrations of endogenous dopamine in response to stress in patients with psychosis and patients at clinical high risk of psychosis compared to healthy individuals. PET scans detected higher dopaminergic activity in the associative striatum and sensorimotor striatum but not in the limbic striatum. Stress was induced on the three groups with the MIST test, in which the participants are submitted to solving arithmetic problems under time pressure (Mizrahi et al., 2012). These findings challenge the notion that in schizophrenia, alterations in subcortical dopamine transmission (either by amphetamine or stress) are most prominently localized to the ventral (limbic), rather than dorsal striatum (sensorimotor and associative). However, other studies disproved this hypothesis, yielding no significant increase in ventral or dorsal striatal dopamine tracer binding in subjects after executing a stressful task compared to the control (Bloomfield et al., n.d.). Despite the contradictions, most studies show a high dopaminergic activity in the striatum of patients suffering from psychosis. Further research is needed to elucidate the particular contributions of each striatal region.

A possible explanation for these results can be the sensitization hypothesis in which a higher response is expected if exposed to stressful stimuli. These results highlight the importance when considering relapse after stopping antipsychotic treatment, as stress alone could be a trigger (Jm & Mj, 1997; Myin-Germeys & van Os, 2007).

2.2 Endogenous sensitization to dopamine

The “endogenous sensitization” theory of psychosis states that overexposure to dopamine can lead to sensitization through increased behavioral and neurochemical responses and consequently to psychosis. This effect was studied by Weidenaur et al. by using dopaminergic stimulation of amphetamine in the prefrontal cortex, known for establishing reciprocal regulatory connections with subcortical dopamine neurons. The experiments performed on healthy subjects and untreated first episode psychosis patients showed a larger release of dopamine in patients with first-episode psychosis than in healthy volunteers using PET scans. The PET tracers targeted the D2/3 dopamine receptors. Moreover, after long-term treatment with amphetamines the healthy subjects reached the same level of dopamine release as the first episode psychosis patients (Weidenauer et al., 2020). These results bring experimental proof that the pathogenic substrate underlying psychosis in schizophrenia after treatment can be a state of “endogenous sensitization” in subcortical dopamine systems.

However, a different study showed elevated serum levels of dopamine in drug-free patients and antipsychotic-treated schizophrenic patients compared to healthy subjects, but no difference between the antipsychotic treated patients and drug-free patients. The results were sex-independent. Serum concentration of dopamine was preferred against blood dopamine concentration, as generally dopamine concentrations in blood are low and considered a pitfall (Rao et al., 1993). This study confirmed the overactivity of dopaminergic neurons in patients suffering from psychosis. Interestingly, the elevated dopamine can be found in the serum of both patients with and without medication. According to the endogenous sensitization theory there should be a change in dopamine levels based on the blockage of dopaminergic receptors. These contradicting results might be explained by the behavioral sensitivity model further discussed.

2.3 Effects of antipsychotic treatment

Supersensitivity in psychosis typically refers to the heightened responsiveness of dopamine receptors in the brain. An animal study showed that dopamine supersensitivity after long-term antipsychotic treatment could stem from loss of D2 receptor-dependent inhibitory postsynaptic currents in D2 receptor-expressing medium spiny neurons (MSN). This activity was found in the nucleus accumbens core, a brain structure with high dopamine release in mice. Chronic antipsychotic treatment (14 days), treatment discontinuation (14 days treatment + 7 days withdrawal), and the expression of dopamine supersensitivity (14 days treatment + 7 days withdrawal + a single cocaine injection.) all led to increased activity in nucleus accumbens core D2-MSNs. This suggests that hyperexcitation of D2-MSNs following antipsychotic treatment could result from a lack of modulatory dopaminergic input, which is reduced after chronic antipsychotic treatment, rendering D2-MSNs hyperexcitable through incoming excitatory transmission (Kruyer et al., 2021).

Based on the premise that D2 receptor upregulation in the striatum of mice is observed after administration of antipsychotics, another research investigated the same effects in humans by positron emission tomography (PET). The first study examining the relationship between long-term antipsychotic treatment and D2 dopamine receptors through in vivo neuroimaging shows that the number of D2 dopamine receptors increased after treatment with both typical and atypical antipsychotics in humans.The left striatum, right striatum and cerebellum of patients showed an upregulation of 37% compared to the drug-free control. Interestingly, the highest receptor upregulation (98%) developed severe dyskinesia after changing treatment to antipsychotics with low D2 affinity (Silvestri et al., 2000). The study shows that long-term typical and atypical antipsychotic dopamine depletion specifically targets the D2 dopamine

receptors and that the upregulation of such receptors could be a factor for extrapyramidal side effects of antipsychotic treatment such as dyskinesia. A reason behind the receptor upregulation might be the sensitization of the striatum to dopamine.

Notably, approximately a third of patients with schizophrenia present resistance to antipsychotic treatment. A clinical study shows that resistance is associated with an elevation in glutamatergic response in the anterior cingulate cortex and a normal dopaminergic response in the striatum of schizophrenic patients (Demjaha et al., 2014). However, treatment-responsive patients show an elevated striatal dopamine level in accordance with the previous research by Silvestri et al. Overall, elevated levels of dopamine in the striatum are part of the profile of psychosis possibly due to an endogenous sensitization, confirming the dopamine theory of psychosis. The high levels of dopamine could be triggered by a genetic predisposition, as the effects were observed in both treatment-naive patients and antipsychotic using patients. Antipsychotic medication was demonstrated to intervene in the dopaminergic system, mainly D2 dopamine receptors, leading to supersensitivity in the striatum. In addition, a stronger behavioral response and increased dopamine release after amphetamine administration or exposure to stress have been observed in patients with psychosis.

Dopamine alterations were detected in different brain areas such as the striatum and the nucleus accumbens. However, other neurotransmitters such as glutamate are involved in neurochemical reactions involved in psychosis. Psychosis could therefore be the result of the interplay between these neurotransmitters and their simultaneous activity in one or more of the aforementioned brain regions.

3. Dopamine and sleep disturbance

Dopamine plays an important role in motivational behaviors driven by the mesolimbic dopamine pathway that connects the ventral tegmental area (VTA) and the nucleus accumbens,

dopamine release getting triggered especially by reward anticipation(Bromberg-Martin et al., 2010). Recent studies have looked into the connection between these brain areas and the sleep/wake cycle.

Dopamine levels measured during homeostatic conditions in freely moving rats in both the medial prefrontal cortex and nucleus accumbens showed that there are fluctuations of dopamine during the sleep-wake cycle. In the nucleus accumbens, dopamine levels were higher during both waking and REM sleep compared to slow wave sleep. In the medial prefrontal cortex, dopamine levels were highest during waking, lowest during slow wave sleep, and intermediate during REM sleep (Léna et al., 2005). One potential mechanism that causes changes to occur is the activity of afferent neurons at the level of dopamine cell bodies in the ventral tegmental area or dopamine terminals in limbic areas. Alternatively, changes in dopamine release could result from alterations in afferents at the level of dopamine terminals in the nucleus accumbens and medial prefrontal cortex. These findings suggest that changes in dopaminergic activity occur across the sleep-wake cycle. As REM sleep showed high dopamine levels in the nucleus accumbens and REM dream-states resemble a psychosis-like state, these manifestations can be considered cognitive and neurochemical similarities with a psychosis.

3.1 Sleep architecture after dopaminergic inhibition

An animal study showed the effect of REM sleep deprivation (RSD) on the dopamine D2 receptor in the dorsal and ventral striatum. Blockage of D2 dopamine receptors with haloperidol (D2 antagonist and a typical antipsychotic) showed a dramatic reduction of REM sleep RSD in rats, compared to the saline, non-sleep deprived rats. In addition, D2 receptors were down-regulated after RSD and up-regulated during the rebound period (a period of 48 h after RSD), contrasting with D1 down-regulation during rebound. The study suggests that D2

dopamine receptors are involved in sleep regulation and consequently REM/slow wave sleep balance. The up-regulation of the D2 receptors could be due to a supersensitivity in the striatum caused by RSD, but future studies could investigate the neural mechanism behind this (Lima et al., 2008). Since haloperidol is a typical antipsychotic drug this study shows that clinical treatment could lead to alterations in the sleep-wake cycle of patients with psychosis. Moreover, since REM sleep is crucial for emotional processing (Miller & Gehrman, 2019), alterations caused by changes in dopamine could worsen the symptoms of psychosis.

Another study in rats showed that dopamine D1 receptor antagonist significantly reduces sleep latency and dopamine D1 receptor agonist increases sleep latency after REM sleep deprivation. Moreover, haloperidol, both a D1 and D2 receptor blocker, also reduces sleep latency. L-sulpiride, a selective dopamine D2 receptor blocker, was ineffective, which suggests that only the D1 receptor is involved in this process. The study concluded that dopaminergic control, particularly via D1 receptors, plays a significant role in modulating sleep latency following REM sleep deprivation (Fratta et al. , 1987). These results suggest that not only does REM sleep deprivation influence the dopamine system through the D1 dopamine receptors, but inhibition of the dopaminergic effect through D1 can also lead to sleep disturbance. Therefore, excitement and insomnia following REM sleep deprivation could be related to the hyperactivity of the dopaminergic system and therefore a combination of dopamine dysfunction and REM sleep deprivation can lead to further worsening of sleep quality.

Narcoleptic canines (a genetic model for excessive sleepiness) displayed increased dopamine release in the striatal extracellular fluid after injection with modafinil and amphetamine. In addition, these two compounds did not display the wakefulness effects in the dopamine transporter knock-out (DAT KO) mice. However, DAT KO mice showed normal sleep/wake activity patterns but different sleep architecture, such as shorter REM time and sleep fragmentation. Mice lacking both DAT alleles exhibited a 3 fold increase in wakefulness and NREM sleep was reduced relative to wild-type. This result implies that the dopamine

transporter might be at the bases of the wake-promoting effect of modafinil and amphetamine and that human variants of DAT gene locus could display a vulnerability to sleep-wake disorders. (Wisor et al., 2001). As amphetamine administration is a valuable model for psychosis, the alterations in sleep architecture promoted by amphetamine administration suggest there could be associations with the sleep alterations found in psychosis.
In rats, selective destruction of dopamine neurons in the substantia nigra pars compacta led to an increase of 33.7% in wakefulness (or sleep-reduction) over a 24-h period. Loss of substantia nigra pars compacta DA neurons also led to sleep-wake fragmentation. Conversely, optogenetic stimulation of the neuronal dopamine terminals increased total sleep with 66% compared to the control (Qiu et al., 2016). Lesions of the dorsal striatum can cause sleep disturbance through the dopaminergic system in contrast to the ventral striatum (nucleus accumbens). These findings suggest that dopamine secretion in the substantia nigra has a sleepiness effect and that its destruction can lead to severe awakening.

3.2 Dopamine system after sleep deprivation

Sleep deprivation (SD) shows increased stress accompanied by behavioral changes such as a constant period of wakefulness (30-35 min), characterized by increased motor activity, exploratory behavior, increased alertness and reactivity towards environmental stimuli. An animal study showed that blocking dopamine receptors in the limbic system antagonizes these effects. Dopamine D1 receptors showed increased binding capacity after sleep deprivation that resulted in reduced hypermotility and reduced sleep latency. On the contrary, no change was observed with D2 antagonists. This activity was only found to be affected in the limbic system and not in the striatum (Fadda et al., 1992). These findings suggest that there is an active role of the limbic dopamine in wakefulness through the D1 dopamine receptors and in the behavioral

consequences of sleep deprivation such as hypermotility. Notably, hypermotility is associated with the behavioral consequences of psychosis (Sacchetti et al., 2018).
In Drosophila, acute sleep deprivation can cause cognitive impairments due to deficitary dopamine signaling. Sleep deprivation impacted dopamine pathways, evidenced by elevated transcript levels of dopamine D2 receptors and dopamine D1. Notably, inhibiting signaling through the D1 receptor in sleep-deprived animals during their critical developmental period prevented later impairments in adult learning (Seugnet et al., 2011). These findings show that sleep deprivation has an influence on the dopamine pathway through the D1 and D2 receptors, which were previously identified to play a role in rodent sleep deprivation as well.

3.3 Circadian clock alterations

Genetic studies provide additional important insight. A mechanism that modulates the interaction between D2 receptors and sleep disturbance could be the down regulation of the CLOCK:BMAL1 system (genes involved in the regulation of sleep and circadian cycle). Experiments show that D2 signaling enhances the transcriptional activity of CLOCK:BMAL1 complex in mice. In addition, clock gene expression and light responsiveness are altered in the retinas of D2 knockout mice. Thereby, dopamine is a likely mediator of light signaling to the retinal circadian clock (Yujnovsky et al., 2006). Therefore, disruptions in dopamine signaling could lead to sleep disturbances based on the alteration of the circadian clock.

The findings collectively highlight the crucial role of dopamine in regulating the sleep-wake cycle, sleep architecture, and circadian rhythms. Disruptions in dopaminergic activity, whether through pharmacological intervention, genetic modifications, or sleep deprivation, significantly impact sleep patterns and may contribute to sleep-related disorders and symptoms of psychosis.

Understanding these mechanisms provides insights into potential therapeutic approaches for managing sleep disturbances and psychosis.

4. The influence of sleep disturbance on psychosis

Drawing the line between sleep disturbance as a cause or consequence of psychosis has been proven difficult in research . Despite this, the following clinical and animal studies unraveled significant findings.

One clinical study looked at youth at clinical high risk (CHR) for schizophrenia that can be assessed based on prodromal symptoms. Prodromal symptoms are symptoms that precede the onset of psychosis and could deliver insight into potential triggers of psychosis. The study on CHR performed with EEG showed a significant correlation between the diagnosis and severity of the prodromal symptoms and sleep dysfunction, and more wakefulness after sleep onset compared to the healthy control group. Differences in high frequency gamma waves (25-40 Hz) that manifest predominantly during awakening in cortical areas were hypothesized to be increased in power during sleep for CHR compared to the control group. Confirming the hypothesis, CHR individuals had higher NREM sleep EEG gamma power, covering the frontal/prefrontal, parietal, and occipital regions, relative to the control group. The increased wakefulness after sleep presented by CHR could be a cause of the increased gamma power that was also detected in the N3 phase (deepest stage that is the least likely to be affected by wakefulness) of NREM (Mayeli et al., 2021). These results suggest that patients at clinical high risk of psychosis have an altered sleep architecture. In addition, the brain activity during NREM of the CHR resembles the awakening state of health patients.A shortcoming of the study is that REM sleep, which shares electrophysiological, pharmacological, and neurochemical features with psychosis, was not reported.

However, a recent study in cats found that gamma power in the 30–45 Hz range was relatively high under the effect of ketamine (NMDA receptor blocker) similar to quiet wakefulness and REM sleep. The strength of functional connections between cortical areas decreased significantly under ketamine administration, similar to what is observed during REM sleep. This decrease indicates a disruption in the functional interactions between cortical regions, which could be linked to cognitive features shared by dreaming and psychosis. This suggests that ketamine administration induces alterations in gamma power comparable to those during REM sleep. The cats were assessed with polysomnographic recordings after sub-anaesthetic ketamine administration (model of psychosis). The authors speculate that the occurrence of cognitive features, such as hallucinogenic imagery, shared by dreaming and psychosis are due to a decreased activity in the dorsolateral prefrontal brain. As dopamine release in the nucleus accumbens is the highest during REM sleep (Se et al., 2019), the dopamine pathway could be one of the shared chemical features of REM and psychosis.

A meta analysis across 65 randomized controlled trials comprising 72 interventions and 8608 participants, revealed small significant improvement in positive psychosis after treatment with Eszopiclone (medication used for treatment of insomnia) or cognitive behavioral therapy for insomnia. This suggests that successful improvement of sleep quality leads to better mental health overall but it is premature to state that the methods used can improve psychotic symptoms because only 5 primary studies were included based on positive symptoms (Scott et al., 2021).

A cross-sectional and longitudinal study used two large nationally representative data sets from the British Psychiatric Morbidity Surveys to identify associations between insomnia and hallucinations. Accounting for confounding variables such as paranoia, depression and anxiety the research showed that mild sleep problems were associated with 2–3 times greater odds of reporting hallucinations, whilst chronic insomnia was associated with four times greater odds.

The study followed-up with investigating the variables and data suggests that insomnia might not only be a consequence of psychosis but also an influence (Sheaves et al., 2016).

A genome-wide association study from 2024 showed a correlation between sleep-related phenotypes and schizophrenia modulated by genes through in humans. The study looked into five sleep related phenotypes but this review will limit the results to insomnia, long sleep duration and sleep duration as they serve for the purpose of identifying a correlation with sleep and not other patterns of the circadian cycle. In this study reduced sleep efficiency was linked to the expression of the PDE11 gene, which catalyzes the hydrolysis of cAMP and cGMP in the cerebellum and the hippocampus. FINEMAP41 (a selection tool using summary data from genome-wide association studies) was used to identify credible sets of likely causal single nucleotide polymorphism(Crinion et al., 2024). In a previous study testing the association between the phosphodiesterase (PDE) protein superfamily and psychosis, PDE inhibitors were used as treatment for schizophrenia on animal models. It was hypothesized that the inhibitory effects of papaverine on PDE10A, a cyclic nucleotide phosphodiesterase, can lead to a novel potential treatment to schizophrenia. The drug reduced catalepsy, which is a symptom associated with antipsychotic treatment(Siuciak et al., 2006). These studies together suggest that the PDE dysregulation can link sleep efficiency to psychotic symptoms. Further studies should investigate if changes in PDE caused by sleep disruptions could show similar results to those found by in vivo inhibition.

These findings collectively illustrate the complex interplay between sleep disturbances and psychosis. Sleep dysfunction, especially in those at clinical high risk for schizophrenia, shows altered brain activity that mirrors wakefulness, suggesting it may contribute to psychotic symptoms. Animal studies further support the link between REM sleep-like brain activity and psychosis. Interventions improving sleep can modestly benefit psychotic symptoms, though more robust evidence is needed. Insomnia is both a consequence and a potential contributor to

psychosis, and genetic studies highlight the role of specific genes in mediating these effects. Further research is essential to untangle the causal relationships and explore targeted treatments.

5. Discussion

Until now, research has shown that neuropsychiatric disorders, including schizophrenia, are accompanied by sleep disturbances such as insomnia and alterations in sleep architecture. Thus, this review aimed to determine if sleep disturbances influence the emergence of psychotic episodes in vulnerable individuals. Thereby, finding the connection between these two systems can lead to a preventive approach in the treatment of psychosis. One of the proposed modulatory pathways is the dopaminergic system. The reviewed literature offers insight into the implications of dopamine in psychosis and sleep disturbance.

Significant improvements in psychosis were attributed to sleep quality improvement (higher sleep efficiency) which can be a future addition to the psychotherapeutic treatment (Scott et al., 2021). Data from healthy individuals and patient groups indicate that sleep disruption raises dopamine activity, heightening the risk of psychosis. Additionally, elevated dopamine levels can disrupt sleep, potentially creating a positive feedback loop in psychosis where poor sleep and high dopamine levels reinforce each other, leading to an increased risk of psychosis. Antipsychotics, which primarily reduce dopamine levels through D2 dopamine receptor antagonism, may help normalize this pattern.

Clinical high risk groups show higher gamma power during NREM and more wakefulness after onset of sleep, as well as increasing severity of prodromal symptoms of psychosis correlated with the severity of sleep dysfunction. The same increase in gamma waves was confirmed and additionally associated with REM sleep in cats after a ketamine sensitization. Ketamine was used as a modeling agent of psychosis in this study (Castro-Zaballa et al., 2019). Ketamine is an

NMDA blocker, which inhibits the binding of glutamate. Additionally, patients that show resistance to antipsychotics have a higher response in glutamate. Thus, the effects of glutamatergic blockage suggest that an interplay between dopamine and glutamate is the basis of the observed sleep architecture changes (Marc Cantillon et al., 2017). These changes in gamma power suggest that psychosis resembles an awakening state of the brain.

In section 4, the phosphodiesterase gene (PDE) family is linked to sleep duration, sleep efficiency and psychosis. PDE10A inhibitors led to reduced striatal function and side effects specific to antipsychotic treatment, like catalepsy. Specific within the brain, the mRNA and proteins expressed by PDE10A are predominantly expressed in the medium spiny projection neurons (MSN) of the striatum. The MSNs are important for processing cognitive and motor functions from the cortex and the dopaminergic system as shown by the high activity of D2-MSN after antipsychotic treatment in section 2.3. Therefore MSNs might be the morphological connection between PDE and psychosis through dopamine (Xu et al., 2002).

In addition, literature shows that sleep deprivation induces behavioral changes characterized by increased motor activity and alertness, which are accompanied by alterations in dopaminergic neurotransmission (3.2). Notably, dopamine D1 receptor antagonists have been shown to reduce hypermotility and sleep latency after sleep deprivation, while D1 receptor agonists prolong sleep latency and D2 receptors showed no effect. These findings underscore that particularly D1 receptors modulate sleep behavior related to dopamine blockers used as antipsychotic treatment, which is surprising as most research shows a strong relationship between high density D2 dopamine receptors and psychosis.

Additionally, dopamine transporter knockout mice exhibit altered sleep architecture, implicating the dopamine transporter in regulating wakefulness. Furthermore, dopamine D2 receptors play a role in regulating REM sleep, with D2 receptor inhibition leading to decreased REM sleep and upregulation of D2 receptors observed after REM sleep deprivation. These results suggest a complex interplay between dopaminergic neurotransmission and REM sleep regulation, highlighting the importance of D2 receptor activation in maintaining normal REM sleep patterns. D2 receptor has been found to be upregulated in patients experiencing psychosis (2.3), therefore D2 supersensitivity could also lead to REM disturbance.

Existing research used rat models to study the relationship between dopamine and sleep disturbance, but no current animal model is viable for psychosis (Xu et al., 2002).

While animal models for sleep disturbances are usually feasible using techniques like classic single platform for REM sleep deprivation, behavioral models for psychosis are still lacking. The reviewed literature used the ketamine and amphetamine animal models. However, psychotic disorders involve genetic, environmental, and neurobiological factors. Single-agent models like ketamine or amphetamine may oversimplify the complexity of the problem. As previously discussed, the neurobiological and cognitive features shared between REM and psychosis could make REM sleep in mice a suitable animal model (Mizrahi et al., 2012).

Overall, research indicates that sleep disturbances, influenced by dopaminergics system, elevate the risk of psychosis, forming a feedback loop particularly relevant in schizophrenia. Improving sleep quality shows promise in decreasing psychotic symptoms, and animal models for sleep disturbances, especially REM sleep, could enhance the understanding and treatment of psychosis.

6. Conclusions

In order to fill in the research gap that separates causality from consequence, further studies could use the available knowledge in order to integrate the three elements discussed in this paper: sleep disturbance, psychosis and dopamine.

In summary, the interaction between dopamine, sleep and psychosis is a process with significant implications for the neurological function and the pathophysiology of sleep disorders and psychiatric conditions. Further research underlying dopaminergic modulation of sleep behavior may offer novel therapeutic targets for sleep-related disorders and schizophrenia. It is possible that targeting sleep disturbances would be a less invasive approach than antipsychotic treatment. On the other hand, targeting sleep disturbances along antipsychotic treatment could be a valuable therapeutic direction. Additionally, integrating findings from animal models and clinical studies and developing the current research methods is crucial for advancing our understanding of the environmental factors leading to schizophrenia.

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References

1. Ågren, R. (2021). Worldwide antipsychotic drug search intensities: Pharmacoepidemological estimations based on Google Trends data. *Scientific Reports*, *11*, 13136. https://doi.org/10.1038/s41598-021-92204-0
2. Blair, D. T., & Dauner, A. (1992). Extrapyramidal symptoms are serious side-effects of antipsychotic and other drugs. *The Nurse Practitioner*, *17*(11), 56, 62–64, 67. https://doi.org/10.1097/00006205-199211000-00018
3. Blockage of dopaminergic D2 receptors produces decrease of REM but not of slow wave sleep in rats after REM sleep deprivation. (2008). *Behavioural Brain Research*, *188*(2), 406–411. https://doi.org/10.1016/j.bbr.2007.11.025
4. Bloomfield, M. A., McCutcheon, R. A., Kempton, M., Freeman, T. P., & Howes, O. (n.d.). The effects of psychosocial stress on dopaminergic function and the acute stress response. *eLife*, *8*, e46797. https://doi.org/10.7554/eLife.46797
5. Bromberg-Martin, E. S., Matsumoto, M., & Hikosaka, O. (2010). Dopamine in motivational control: Rewarding, aversive, and alerting. *Neuron*, *68*(5), 815–834. https://doi.org/10.1016/j.neuron.2010.11.022
6. Bruijnzeel, D., Suryadevara, U., & Tandon, R. (2014). Antipsychotic treatment of schizophrenia: An update. *Asian Journal of Psychiatry*, *11*, 3–7. https://doi.org/10.1016/j.ajp.2014.08.002
7. Chokroverty, S. (2010). Overview of sleep & sleep disorders. *Indian Journal of Medical Research*, *131*(2), 126.
8. Crinion, S., Morris, D. W., & Lopez, L. M. (2024). Neuropsychiatric disorders, chronotype and sleep: A narrative review of GWAS findings and the application of Mendelian randomization to investigate causal relationships. *Genes, Brain, and*

Behavior, *23*(1), e12885. https://doi.org/10.1111/gbb.12885

9. Demjaha, A., Egerton, A., Murray, R. M., Kapur, S., Howes, O. D., Stone, J. M., & McGuire, P. K. (2014). Antipsychotic Treatment Resistance in Schizophrenia Associated with Elevated Glutamate Levels but Normal Dopamine Function. *Biological Psychiatry*, *75*(5), e11–e13. https://doi.org/10.1016/j.biopsych.2013.06.011
10. Dopamine D1 and opioid receptor binding changes in the limbic system of sleep deprived rats. (1992). *Neurochemistry International*, *20*, 153–156. https://doi.org/10.1016/0197-0186(92)90229-K
11. *Dopamine receptors and the dopamine hypothesis of schizophrenia*. (n.d.). https://doi.org/10.1002/syn.890010203
12. Fratta, W., Collu, M., Martellotta, M. C., Pichiri, M., Muntoni, F., & Gessa, G. L. (1987). Stress-induced insomnia: Opioid-dopamine interactions. *European Journal of Pharmacology*, *142*(3), 437–440. https://doi.org/10.1016/0014-2999(87)90084-7
13. Fusar-Poli, P., Tantardini, M., Simone, S. D., Ramella-Cravaro, V., Oliver, D., Kingdon, J., Kotlicka-Antczak, M., Valmaggia, L., Lee, J., Millan, M. J., Galderisi, S., Balottin, U., Ricca, V., & McGuire, P. (2017). Deconstructing Vulnerability for Psychosis: Meta-Analysis of Environmental Risk Factors for Psychosis in Subjects at Ultra High-Risk. *European Psychiatry*, *40*, 65–75. https://doi.org/10.1016/j.eurpsy.2016.09.003
14. Hálfdánarson, Ó., Zoëga, H., Aagaard, L., Bernardo, M., Brandt, L., Fusté, A. C., Furu, K., Garuolienė, K., Hoffmann, F., Huybrechts, K. F., Kalverdijk, L. J., Kawakami, K., Kieler, H., Kinoshita, T., Litchfield, M., López, S. C., Machado-Alba, J. E., Machado-Duque, M. E., Mahesri, M., … Bachmann, C. J. (2017). International trends in antipsychotic use: A study in 16 countries, 2005–2014. *European Neuropsychopharmacology*, *27*(10), 1064–1076. https://doi.org/10.1016/j.euroneuro.2017.07.001

15. Howes, O. D., & Kapur, S. (2009). The Dopamine Hypothesis of Schizophrenia: Version III—The Final Common Pathway. *Schizophrenia Bulletin*, *35*(3), 549–562. https://doi.org/10.1093/schbul/sbp006
16. Léna, I., Parrot, S., Deschaux, O., Muffat-Joly, S., Sauvinet, V., Renaud, B., Suaud-Chagny, M.-F., & Gottesmann, C. (2005). Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep–wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. *Journal of Neuroscience Research*, *81*(6), 891–899. https://doi.org/10.1002/jnr.20602
17. Marc Cantillon, Cantillon, M., Arul Prakash, Prakash, A., Ajay Alexander, Alexander, A., R. M. J. Ings, Ings, R., Dennis Sweitzer, Sweitzer, D., Laxminarayan Bhat, & Bhat, L. (2017). Dopamine serotonin stabilizer RP5063: A randomized, double-blind, placebo-controlled multicenter trial of safety and efficacy in exacerbation of schizophrenia or schizoaffective disorder. *Schizophrenia Research*, *189*, 126–133. https://doi.org/10.1016/j.schres.2017.01.043
18. Miller, K. E., & Gehrman, P. R. (2019). REM Sleep: What Is It Good For? *Current Biology: CB*, *29*(16), R806–R807. https://doi.org/10.1016/j.cub.2019.06.074
19. Mizrahi, R., Addington, J., Rusjan, P. M., Suridjan, I., Ng, A., Boileau, I., Pruessner, J. C., Remington, G., Houle, S., & Wilson, A. A. (2012). Increased Stress-Induced Dopamine Release in Psychosis. *Biological Psychiatry*, *71*(6), 561–567. https://doi.org/10.1016/j.biopsych.2011.10.009
20. Reeve, S., Sheaves, B., & Freeman, D. (2019). Sleep Disorders in Early Psychosis: Incidence, Severity, and Association With Clinical Symptoms. *Schizophrenia Bulletin*, *45*(2), 287–295. https://doi.org/10.1093/schbul/sby129
21. Sacchetti, E., Valsecchi, P., Tamussi, E., Paulli, L., Morigi, R., & Vita, A. (2018). Psychomotor agitation in subjects hospitalized for an acute exacerbation of Schizophrenia. *Psychiatry Research*, *270*, 357–364.

https://doi.org/10.1016/j.psychres.2018.09.058

22. Scott, A. J., Webb, T. L., Martyn-St James, M., Rowse, G., & Weich, S. (2021). Improving sleep quality leads to better mental health: A meta-analysis of randomised controlled trials. *Sleep Medicine Reviews*, *60*, 101556. https://doi.org/10.1016/j.smrv.2021.101556
23. Se, J., Vt, van H., Dr, M., P, M.-V., S, S., A, van der S., Hs, D., J, E., D, K., J, T., Rn, B., M, H., Ks, R., Ma, T., H, Y., Sa, S., Y, J., Jw, H., Rm, F., … Ar, W. (2019). Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nature Communications*, *10*(1). https://doi.org/10.1038/s41467-019-09576-1
24. Seugnet, L., Suzuki, Y., Donlea, J. M., Gottschalk, L., & Shaw, P. J. (2011). Sleep Deprivation During Early-Adult Development Results in Long-Lasting Learning Deficits in Adult Drosophila. *Sleep*, *34*(2), 137–146. https://doi.org/10.1093/sleep/34.2.137
25. Sheaves, B., Bebbington, P. E., Goodwin, G. M., Harrison, P. J., Espie, C. A., Foster, R. G., & Freeman, D. (2016). Insomnia and hallucinations in the general population: Findings from the 2000 and 2007 British Psychiatric Morbidity Surveys. *Psychiatry Research*, *241*, 141–146. https://doi.org/10.1016/j.psychres.2016.03.055
26. Sher, L., & Kahn, R. S. (2019). Suicide in Schizophrenia: An Educational Overview. *Medicina*, *55*(7), 361. https://doi.org/10.3390/medicina55070361
27. Silvestri, S., Seeman, M. V., Negrete, J.-C., Houle, S., Shammi, C. M., Remington, G. J., Kapur, S., Zipursky, R. B., Wilson, A. A., Christensen, B. K., & Seeman, P. (2000). Increased dopamine D2 receptor binding after long-term treatment with antipsychotics in humans: A clinical PET study. *Psychopharmacology*, *152*(2), 174–180. https://doi.org/10.1007/s002130000532
28. Siuciak, J. A., Chapin, D. S., Harms, J. F., Lebel, L. A., McCarthy, S. A., Chambers, L., Shrikhande, A., Wong, S., Menniti, F. S., & Schmidt, C. J. (2006). Inhibition of the striatum-enriched phosphodiesterase PDE10A: A novel approach to the treatment of psychosis. *Neuropharmacology*, *51*(2), 386–396.

https://doi.org/10.1016/j.neuropharm.2006.04.013

29. Stahl, S. M. (2017). Drugs for psychosis and mood: Unique actions at D3, D2, and D1 dopamine receptor subtypes. *CNS Spectrums*, *22*(5), 375–384. https://doi.org/10.1017/S1092852917000608
30. Wisor, J. P., Nishino, S., Sora, I., Uhl, G. H., Mignot, E., & Edgar, D. M. (2001). Dopaminergic Role in Stimulant-Induced Wakefulness. *The Journal of Neuroscience*, *21*(5), 1787–1794. https://doi.org/10.1523/JNEUROSCI.21-05-01787.2001
31. Xu, R., Hranilovic, D., Fetsko, L. A., Bucan, M., & Wang, Y. (2002). Dopamine D2S and D2L receptors may differentially contribute to the actions of antipsychotic and psychotic agents in mice. *Molecular Psychiatry*, *7*(10), 1075–1082. https://doi.org/10.1038/sj.mp.4001145
32. Yates, N. J. (2016). Schizophrenia: The role of sleep and circadian rhythms in regulating dopamine and psychosis. *Reviews in the Neurosciences*, *27*(7), 669–687. https://doi.org/10.1515/revneuro-2016-0030
33. Yujnovsky, I., Hirayama, J., Doi, M., Borrelli, E., & Sassone-Corsi, P. (2006). Signaling mediated by the dopamine D2 receptor potentiates circadian regulation by CLOCK:BMAL1. *Proceedings of the National Academy of Sciences*, *103*(16), 6386–6391. https://doi.org/10.1073/pnas.0510691103

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