Received: 28 February 2017 | Accepted: 24 August 2017
DOI: 10.1002/ajmg.b.32599

REVIEW ARTICLE

WILEY American Journal of Medical Genetics Part B Neuropsychiatric Genetics

The role of *CLOCK* gene in psychiatric disorders: Evidence from human and animal research

Jaqueline B. Schuch[1] | Julia P. Genro[2] | Clarissa R. Bastos[3] | Gabriele Ghisleni[3] | Luciana Tovo-Rodrigues[4]

[1] Laboratory of Immunosenescence, Graduate Program in Biomedical Gerontology, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil

[2] Graduate Program in Bioscience, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil

[3] Laboratory of Clinical Neuroscience, Graduate Program in Health and Behavior, Universidade Católica de Pelotas, Pelotas, Rio Grande do Sul, Brazil

[4] Graduate Program in Epidemiology, Universidade Federal de Pelotas, Pelotas, Rio Grande do Sul, Brazil

Correspondence
Luciana Tovo-Rodrigues, PhD, Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas (UFPel), Rua Marechal Deodoro, 1160 – 3° andar, Bairro Centro – Pelotas, RS, Brasil, Cep: 96020-220.
Email: luciana.tovo@gmail.com

Funding information
Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES); Brazilian National Council for Scientific and Technological Development (CNPq)

The circadian clock system drives daily rhythms in physiology, metabolism, and behavior in mammals. Molecular mechanisms of this system consist of multiple clock genes, with Circadian Locomotor Output Cycles Kaput (*CLOCK*) as a core member that plays an important role in a wide range of behaviors. Alterations in the *CLOCK* gene are associated with common psychiatric disorders as well as with circadian disturbances comorbidities. This review addresses animal, molecular, and genetic studies evaluating the role of the *CLOCK* gene on many psychiatric conditions, namely autism spectrum disorder, schizophrenia, attention-deficit/hyperactivity disorder, major depressive disorder, bipolar disorder, anxiety disorder, and substance use disorder. Many animal experiments focusing on the effects of the *Clock* gene in behavior related to psychiatric conditions have shown consistent biological plausibility and promising findings. In humans, genetic and gene expression studies regarding disorder susceptibility, sleep disturbances related comorbidities, and response to pharmacological treatment, in general, are in agreement with animal studies. However, the number of controversial results is high. Literature suggests that the *CLOCK* gene exerts important influence on these conditions, and influences the susceptibility to phenotypes of psychiatric disorders.

KEYWORDS
circadian rhythm, clock genes, dopaminergic system, mood disorders, sleep

1 | INTRODUCTION

The endogenous circadian timing system controls daily rhythms in physiology, metabolism, and behavior in mammals. Dysregulations of circadian rhythmicity, usually manifested in alterations of the sleep-wake cycle, are often observed as comorbid symptoms in psychiatric disorders. However, a causative role in these disorders has already been suggested (Karatsoreos, 2014; Kissling et al., 2008).

The endogenous circadian rhythm is regulated by the master pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which coordinates clock rhythms in other brain regions and peripheral organs in a process that is aligned with external environmental stimuli (Buhr & Takahashi, 2013; Okamura, Yamaguchi, & Yagita, 2002; Reppert & Weaver, 2002). The molecular mechanism of the circadian clock system involves transcription-translation negative-feedback loops of multiple circadian genes, as well as post-transcriptional and post-translational modification and degradation of clock proteins (Buhr & Takahashi, 2013; Ko & Takahashi, 2006; Okamura et al., 2002; Reppert & Weaver, 2002).

1.1 | *CLOCK* gene: Function and expression

The human Circadian Locomotor Output Cycles Kaput (*CLOCK*) gene, placed at chr4q12 and 119 kb long, is one of the most important genes

of the endogenous master clock system. Its main function relies on the transcription activation of downstream core clock genes and the promotion of rhythmic chromatin opening, also regulating DNA accessibility of other transcription factors (Doi, Hirayama, & Sassone-Corsi, 2006; Hirayama et al., 2007). It encodes a protein of 846 amino acids, which acts both as a transcription factor as well as an acetyltransferase. CLOCK H3 and H4 histone acetylation plays a pivotal role in the modulation of chromatin structure (Doi et al., 2006). Briefly, in the maintenance of the core circadian rhythm, CLOCK protein is able to form a heterodimer with BMAL1 (encoded by Aryl Hydrocarbon Receptor Nuclear Translocator, *ARNTL*), and this heterodimer binds to E-box enhancer elements upstream of Period (*PER1*, *PER2*, *PER3*) and Cryptochrome (*CRY1*, *CRY2*) genes, activating their transcription. PER and CRY proteins heterodimerize and repress their own transcription by interacting with CLOCK/BMAL1 complexes. The synchronized expression of circadian genes is essential for the organization of the 24-hr cycle (Buhr & Takahashi, 2013; Ko & Takahashi, 2006; Okamura et al., 2002; Reppert & Weaver, 2002). A natural significant age-dependent rhythmicity was already observed in the expression of several genes in the human prefrontal cortex, including *PER1* and *PER2* (Chen et al., 2016).

Contrary to its function in rhythmic transcription regulation of the clock-controlled genes, expression of mammal *CLOCK* is described to be nearly constitutive in the SCN (von Gall, Noton, Lee, & Weaver, 2003) and, for humans, constitutive expression has also been observed in peripheral tissues, such as the oral mucosa, skin, and blood (Balmforth et al., 2007; Bjarnason et al., 2001; Chen et al., 2016). The simultaneous *Clock* co-expression in the blood, hippocampus, and prefrontal cortex in rats suggests its expression in blood may be a good marker of its availability in the brain (Witt et al., 2013). Interestingly, a large range of inter-individual variation in the expression of *CLOCK* mRNA levels was observed in human blood cells at the population level (Balmforth et al., 2007), suggesting a variety of expression modulation in the general population. Moreover, a hypomethylation of *CLOCK* promoter as well as a higher *CLOCK* expression in blood cells of nightshift workers have been observed, (Bhatti et al., 2015; Bracci et al., 2014; Zhu et al., 2011), demonstrating an association between circadian modulation and CLOCK regulation and reinforcing the link between circadian rhythm and epigenetics.

1.2 | Animal models for *CLOCK* gene

Animal models have been used to aid in understanding the effects of different genes and proteins on phenotypes. Two main mutations of *Clock* have been used with this purposed: *Clock* semidominant allele and knockout, which present substantial differences in terms of phenotype.

*Clock*Δ19 is a specific semidominant mutation originally identified in an N-ethyl-N-nitrosourea mutagenesis screen, characterized by the skip of exon 19 in the *Clock* gene (King, Vitaterna et al., 1997; King, Zhao et al., 1997; Vitaterna et al., 1994). The mutant protein lacks the transactivation domain, and consequently, binds to Bmal1 forming a nonfunctional heterodimer that prevents the occurrence of typical transcription-inducing actions of this heterodimer (Vitaterna et al., 1994). *Clock*Δ19/Δ19 mice display a long circadian period that becomes arrhythmic with prolonged exposure to constant darkness (King, Vitaterna et al., 1997; King, Zhao et al., 1997; Vitaterna et al., 1994, 2006). *Clock*Δ19 mice display an increase in cocaine reward and in the excitability of dopamine neurons in the midbrain ventral tegmental area (VTA), a key brain reward region that has been implicated in many psychiatric disorders. At the molecular level, the mutation is associated with increased expression and phosphorylation of tyrosine hydroxylase (the rate-limiting enzyme in dopamine synthesis), as well as changes in several genes known to regulate dopamine activity in the VTA (McClung et al., 2005). This mutation is also linked to alterations in circadian phenotype, altered sleep patterns, hyperactivity, mania-like and depressive-like behaviors, obesity, metabolic alterations, and increased reward value for cocaine (McClung et al., 2005; Naylor et al., 2000; Roybal et al., 2007; Rudic et al., 2004; Turek et al., 2005).

The *Clock* knockout (KO) is a traditional homologous recombination mutation (DeBruyne et al., 2006), in which mice continue to express a robust circadian rhythm in locomotor activity, although they also present altered responses to light. At the molecular and biochemical extents, null mutant animals present several alterations in clock genes expression in both SCN and liver. However, the molecular feedback loops of clock rhythm maintain its normal function, suggesting a molecular compensation mechanism (DeBruyne et al., 2006). In fact, *NPAS2*, a paralog gene of *CLOCK* (Hogenesch et al., 1997; Zhou et al., 1997), is able to dimerize with BMAL1 (Reick, Garcia, Dudley, & McKnight, 2001) and functionally substitute for CLOCK in the SCN and in the peripheral tissue (DeBruyne, Weaver, & Reppert, 2007; Landgraf, Wang, & Diemer, 2016).

1.3 | The role of CLOCK in the central nervous system

Several behavioral and molecular studies suggest an important role of Clock in neuronal function, mainly in the dopaminergic outputs regulation, a pathway that is linked to the etiology of many psychiatric disorders. Tyrosine hydroxylase (TH), cholecystokinin (CCK), and many other regulators of dopaminergic transmission are under transcriptional control of the CLOCK protein (Arey et al., 2014; Sidor et al., 2015). Moreover, expression *of* dopamine beta hydroxylase *(Dbh)* and monoamine oxidase *(Mao)* zebrafish genes has been shown to be significantly enhanced when co-transfected with *Clock1a/2* and *Bmal1b* (Huang et al., 2015). Other neurotransmitter signaling systems have also been found to be altered following *Clock* gene disruption, including the glutamatergic (McClung et al., 2005; Ozburn et al., 2013) and GABAergic systems (McClung et al., 2005). Clock also regulates the expression of neurogenic transcription factors, affecting the differentiation of mouse adult neural stem/precursor cells (Kimiwada et al., 2009).

In addition, the CLOCK acetylation function seems to regulate cortisol signaling responses, through reduction in the binding of glucocorticoid receptor (NR3C1) to glucocorticoid response elements,

as well as transcription repression of several glucocorticoid-responsive genes related to hypothalamic–pituitary–adrenal axis (Nader, Chrousos, & Kino, 2009). Zhang, Lahens, Ballance, Hughes, and Hogenesch (2014) have recently shown that 43% of all protein coding genes in the mammalian body display circadian rhythm expression, largely in an organ-specific manner. In the central nervous system, the proportion of circadian genes was approximately 4%, suggesting that a greater number of genes may be regulated by *CLOCK* and other core circadian genes in this tissue. In fact, in a chromatin immunoprecipitation with massively parallel DNA sequencing (ChIP-Seq) experiment using mice striatal tissue, 6,458 unique DNA binding sites for *Clock* could be identified (Ozburn et al., 2015).

1.4 | *CLOCK* gene variability in human populations and genetic association studies

The genomic variability of *CLOCK* gene (common polymorphisms, i.e., Minor Allele Frequency [MAF] ≥ 1%), according to the 1000 Genomes Project Consortium (2015) phase 3 (Sudmant et al., 2015), comprises 406 SNPs for African, 271 for European, 278 for Asian, and 277 for American continental populations. The rs1801260 (3111T/C) variant is the most studied one, located at 3′-untranslated region (3′-UTR), which is a region very important for mRNA stability, expression, and function. Recently, data from mouse embryonic fibroblasts transfected with 3111T/C constructs showed that the C-allele of rs1801260 results in significantly increased *Clock* and *Per2* mRNA expression over 24 hr (Ozburn et al., 2016). A higher expression of *CLOCK* in presence of the C allele has also been observed in experiments with different human cell lines (Shi et al., 2016). This SNP is placed in an interaction site with miRNA-182 (Ozburn et al., 2016; Saus et al., 2010), which could explain the functional results.

The rs1801260 (3111T/C) variant has already been associated with evening preference in European and Japanese populations (Katzenberg et al., 1998; Mishima, Tozawa, Satoh, Saitoh, & Mishima, 2005) and an association with delayed sleep phase syndrome (DSPS) has been suggested (Iwase et al., 2002). In interaction with the G-protein b3 subunit gene (*GNB3*), it was suggested to have a diurnal preference modulation effect (Lee, Paik, Kang, Lim, & Kim, 2007). Other polymorphisms in the *CLOCK* gene have also pointed to an association with sleep duration (Allebrandt et al., 2010). However, a number of studies report failure to replicate these associations (Chang, Buch, Bradstreet, Klements, & Duffy, 2011; Choub et al., 2011; Pedrazzoli et al., 2007; Robilliard et al., 2002), including recent genome-wide association studies on chronotypes and sleep traits (Hu et al., 2016; Jones et al., 2016; Lane et al., 2016). It is well recognized, however, that true positive SNPs may not achieve association with a trait/function at the level of genome-wide significance (Purcell et al., 2009).

The function of *CLOCK* as a transcription factor and as a histone acetyltransferase, as demonstrated in animal models and in vitro functional experiments, implies that genetic and epigenetic variations in the gene could contribute to physiological changes, which might lead to alterations in susceptibility to psychiatric disorders. Disturbances of the circadian clock system may be a key factor in explaining the high level of sleep disturbances comorbid with common psychiatric conditions. In this review, we collate data from a considerable number of studies and discuss findings from animal and molecular studies that examine the influence of the *CLOCK* gene on diverse aspects of main psychiatric disorders.

2 | AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a neurodevelopmental disease associated with deficits in social interaction and communication. Sleep problems are considered one of the most common clinical symptoms among affected children (Cotton & Richdale, 2006; Ming, Gordon, Kang, & Wagner, 2008), and circadian disruption has also been suggested as an endophenotype of ASD (Sacco et al., 2010). However, only a few genetic studies have focused on the role of clock genes in ASD etiology or sleep problems in children with ASD. A genome-wide expression study identified many circadian-related genes that are expressed differently in lymphoblastic cell lines from individuals with ASD compared to controls. For instance, a decreased expression of the *CLOCK* gene was observed in individuals with ASD (Hu et al., 2009). Two other studies assessed a possible influence of the *CLOCK* gene in ASD. Nicholas et al. (2007) evaluated 11 clock-related genes in a sample mainly comprised of Caucasian individuals. Four *CLOCK* gene polymorphisms were included in the analyses (rs1801260, rs6811520, rs2272073, SNP4 G/A), but no associations were detected. A recent study screened for mutations in clock-related genes in Japanese individuals with ASD and controls. Many genetic variants were found exclusively in ASD patients with sleep disorder, including rs3762836 (p.H542R) located at the *CLOCK* gene locus (Yang et al., 2016). Other genetic variations that were detected were not related to this specific gene.

Taking the findings mentioned above into consideration, the relation between *CLOCK* gene and ASD remains uncertain. It is not clear whether the observed effect in studies is related to ASD per se or to sleep-related phenotypes in ASD. Further studies should consider this issue in their design, in an attempt to clarify the meaning of the observed association. In addition, it has been suggested that clock-related genes could modulate synaptic proteins. In this sense, evidences indicate that abnormal circadian rhythms and melatonin synthesis might affect neuronal transmission, including modifications in neurotransmitter levels (Bourgeron, 2007). The scarcity of studies as well as the biological plausibility of an association between clock-related genes and autism indicates the necessity of more studies in this field.

3 | ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder (ADHD) is a common, childhood-onset, chronic neuropsychiatric disorder characterized by developmentally inappropriate inattentiveness, increased impulsivity,

and hyperactivity (American Psychiatric Association, 2013). Aside from these core symptoms, sleep disturbances are found to be highly comorbid with ADHD. ADHD is associated with more eveningness/later chronotypes and with a phase delay of circadian phase markers, such as dim light melatonin onset and delayed sleep onset (Coogan & McGowan, 2017). It is unclear whether sleep and circadian problems are secondary effects of ADHD or whether they play a causative role in ADHD (Kissling et al., 2008). The biological plausibility for a role of the *CLOCK* gene in ADHD is related to the dopaminergic system impairment observed in*Clock*Δ19 mutant mice (Huang et al., 2015; Parekh, Ozburn, & Mcclung, 2015), which is of central importance in current etiological understanding of ADHD.

Behavioral analyses demonstrated that rodents treated with methylphenidate and atomoxetine, the two main drugs used in medical treatment for ADHD, caused changes in both circadian and diurnal rhythms (Algahim et al., 2009; Antle et al., 2012; O'Keeffe, Thome, & Coogan, 2012). In mice, treatment with atomoxetine during daytime also led to alteration in *Clock* gene expression, dependent on lighting conditions. Daytime treatment led to a decrease of *Clock* expression, while atomoxetine treatment during nighttime did not lead to any changes in expression (O'Keeffe et al., 2012). Baird, Coogan, Kaufling, Barrot, and Thome (2013) investigated the effects of methylphenidate and atomoxetine administration on *Clock* gene expression in different brain regions of mice. Both drugs led to specific circadian clockwork modulations depending on the analyzed neuroanatomical structure. There was no statistical main effect of treatment neither significant time-treatment interaction effect on *Clock* expression. However, the treatment with both methylphenidate and atomoxetine led to an alteration of the *Clock* expression acrophase, indicated by an expression peak occurring earlier in response to light, in the dorsomedial hypothalamus and the caudate putamen. These results suggest that therapeutic properties and/or adverse side effects of these drugs could involve modulation of the circadian clock, including the *Clock* gene. In humans, evidence also suggest that methylphenidate may exacerbate symptoms related to sleep and circadian rhythm disruption (Corkum, Panton, Ironside, MacPherson, & Williams, 2007; Galland, Tripp, & Taylor, 2010; Ironside, Davidson, & Corkum, 2010; Sangal et al., 2006; Schwartz et al., 2004).

Only a few genetic association studies, using candidate gene approach, focused on the role of *CLOCK* gene polymorphisms on ADHD. Kissling et al. (2008) investigated rs1801260 in male adults with ADHD of European origin, and found that T-carriers showed higher number of ADHD-related symptoms. The same association was also observed considering as outcome the patients' self-reported ADHD symptoms in childhood. Similar results were observed in studies using a family-based approach, as in two clinical samples of ADHD from the United Kingdom and Taiwan. An increased transmission of T allele of rs18011260 from parents to children and adolescents was shown in the combined data, as well as within the Taiwanese data set alone (Xu et al., 2010). Using a case-control approach, Cao, Cui, Tang, and Chang (2012) also observed an association between rs18011260 and ADHD in a sample of children with Han Chinese origin. However, the detected risk allele in this sample, in contrast to the studies reviewed so far, was the C allele. The same study reported that 56.6% of the sampled children with ADHD had sleep disturbances, a phenotype that was also associated with the presence of C allele, concluding that individuals carrying a C allele were more susceptible to ADHD as well as to ADHD-related sleep disturbances (Cao et al., 2012). Finally, Jeong et al. (2014) conducted a population-based study in healthy Korean adults, in which diurnal preference and ADHD-related symptoms were assessed. Five SNPs in the *CLOCK* gene (rs3805148, rs12504300, rs4864542, rs12649507, rs1801260) were evaluated. An association of the number of ADHD-related symptoms with rs1801260 in male subjects was observed. Moreover, inattention symptoms were associated with rs3805148, rs12504300, rs4864542, and rs12649507 in a haplotype-wise analysis. On the other hand, there was no association between diurnal preference and the *CLOCK* gene. No statistical significant effect of diurnal preference as a mediator variable was observed as well, suggesting that the association between *CLOCK* and ADHD-related features was not mediated by the degree of evening preference (Jeong et al., 2014).

In conclusion, although there are only few studies evaluating the link between ADHD and *CLOCK*, and while a publication bias cannot be ruled out, the variant rs18011260 has been found to play an important role in ADHD, pointing to the need for more studies in the field. Although animal studies suggest that ADHD drug treatments are able to modulate or impact the expression of circadian genes, the causality between sleep condition and ADHD should be the focus of further studies.

4 | MOOD DISORDERS

Disruptions of circadian rhythms appear to be both a symptom and an anticipating feature of major depressive disorder (MDD) and bipolar disorder (BD) (Boland & Alloy, 2013; Boyce & Barriball, 2010). Many patients with mood disorders (50–85%) show sleep disturbances and other circadian alterations related to appetite, social interactions, blood pressure, and hormone levels (Ford & Cooper-Patrick, 2001; Rumble, White, & Benca, 2015).

Several preclinical studies, using different approaches, have pointed to a role of circadian genes in mood-related behaviors (Kronfeld-Schor & Einat, 2012). *Clock*Δ19 mutant mice show increased exploratory activity, hyperactivity, reduced anxiety and depressive-related behavior, decreased sleep, and rapid mood cycling with a profound manic-like phenotype during the daytime and a period of euthymia at night (Roybal et al., 2007; Sidor et al., 2015; van Enkhuizen, Minassian, & Young, 2013). Behavioral abnormalities described above coincide with abnormal daytime spikes of dopaminergic activity and increased firing rates of dopaminergic neurons in the VTA, and with increased tyrosine hydroxylase levels and dopamine synthesis in the nucleus accumbens (NAc), suggesting a mechanistic connection between circadian gene disruption and anticipation of manic episodes in BD (Coque et al., 2011; Sidor et al., 2015). Furthermore, *Clock*Δ19 mutant mice show biochemical, morphological, and neurophysiological changes in NAc microcircuits that can be

ameliorated by lithium treatment, suggesting that dysfunctional NAc phase signaling may contribute to the mania-like behavioral manifestations that result from diminished circadian gene function (Dzirasa et al., 2010). In addition, *Clock*Δ19 mutant mice treated with lithium (Coque et al., 2011; Roybal et al., 2007) and inhibitors of glycogen synthase kinase-3ß (Kozikowski et al., 2011) showed similar effects related to the reversion of behavioral abnormalities. Similarly, the induction of functional Clock protein expression via viral-mediated gene transfer specifically in the VTA has also been shown to rescue behavioral changes of *Clock*Δ19 mutant mice (Roybal et al., 2007).

Male knockdown mice of *Clock* specifically in the VTA present a phenotype similar to *Clock*Δ19 mice, exhibiting hyperactivity and reduced anxiety-related behavior. However, a substantial increase in depressive-like behavior was also observed in these mice (Mukherjee et al., 2010). Furthermore, chronic mild stress in an animal model for depressive-like behavior led to anhedonic behavior associated with disturbed diurnal oscillation in circadian gene expression in the basolateral amygdala, in which a higher *Clock* expression was observed during the morning (Savalli, Diao, Schulz, Todtova, & Pollak, 2015). Nevertheless, other studies showed that chronic unpredictable stress inhibited Clock protein expression in the SCN during the light period. Also, in the hippocampus, a peak of Clock protein expression was shifted from the dark to light period, showing that Clock protein plays an important role in long-lasting, depressive-like, stress-induced behavior (Jiang et al., 2013). Logan et al. (2015) observed that chronic unpredictable stress altered diurnal rhythms of *Clock* expression and other circadian genes, in the SCN and in the NAc. More recently, Calabrese, Savino, Papp, Molteni, and Riva (2016) demonstrated that chronic mild stress reduces Clock protein levels in the prefrontal cortex. Altogether, these studies demonstrated that chronic stress can lead to a disruption in the circadian system, especially affecting Clock expression.

Furthermore, in a mouse model of seasonal affective disorder, melatonin treatment showed antidepressant-like effects, leading to increased *Clock* mRNA levels in the SCN and also increased mRNA levels of the serotoninergic system in the dorsal raphe nucleus, thus pointing to a relation between antidepressant effects and *Clock* regulation (Nagy et al., 2015). The effect of fluoxetine, a classical antidepressant, was tested in mice selectively bred for high anxiety and depression-like behavior, showing that treated mice have longer circadian periods with no differences in hippocampal *Clock* gene expression compared to normal mice (Schaufler et al., 2016).

In genetic association studies focusing on *CLOCK* and BD, MDD, and related phenotypes, rs1801260 is the most frequently tested polymorphism. Studies focused on comorbid circadian symptoms and severity symptoms in patients, and explored the disorders' etiology, using healthy controls.

In patients with BD, the presence of the rs1801260C allele was associated with higher lifetime recurrence rates of illness episodes, increased occurrence of insomnia (both lifetime occurrence and during depressive episodes), worse response to treatment of sleep disturbances (Benedetti et al., 2007), number and recurrence of manic episodes (Benedetti et al., 2003), evening preference (Lee et al., 2010), and appetite disturbances in female patients with BD (Maciukiewicz et al., 2014). In addition, three SNPs within or near the *CLOCK* gene (rs534654, rs6850524, rs4340844) were significantly associated with BD, early insomnia (rs534654), middle insomnia (rs534654, rs6850524, rs4340844), late insomnia (rs534654, rs4340844), and rapid cycling (rs534654) in these patients (Shi et al., 2008). Several haplotypes consisting of six SNPs (rs534654, rs2412648, rs6850524, rs11735267, rs7660668, rs4340844) at the *CLOCK* gene region also showed nominal association with BD and late insomnia (Shi et al., 2008). Six SNPs (rs3805148, rs3736544, rs12504300, rs4864542, rs12648271, rs6850524) in a single 75 kb linkage block in the *CLOCK* gene showed an association with BD (Kripke, Nievergelt, Joo, Shekhtman, & Kelsoe, 2009), most consistently found for rs3805148 and rs12504300. However, in this same study, rs1801260 was not associated with BD (Kripke et al., 2009). A family-based association study in a Latin population showed only a nominal association of *CLOCK* (rs17777927) with BD (Gonzalez et al., 2015). Haplotype analysis found no association between BD and nine additional markers in the same linkage disequilibrium block as *CLOCK* rs17777927 SNP (rs10462028, rs1801260, rs3805148, rs3736544, rs11932595, rs4340844, rs4864542, rs2070062, rs13132420) (Gonzalez et al., 2015).

The effect of gene-gene interactions on BD-related traits has also been explored. A multi-locus interaction among rs6442925 (*BHLHB2*), rs1534891 (*CSNK1E*), and rs534654 (*CLOCK*) was associated with BD (Shi et al., 2008). Also, an interaction between *CLOCK* (rs11824092) and *ARNTL* (rs11932595) genes was associated with sleep disturbances in BD (Maciukiewicz et al., 2014). Similarly, interactions between *PER3* (rs2640909) and *CLOCK* (rs119325595) genes seem to play a role in sleep quality, sleep duration, habitual sleep efficiency, and subjective sleep quality (Dmitrzak-Węglarz et al., 2016).

Considering affective disorders in general, the CC genotype of rs1801260 has been shown to be associated with higher recurrence of initial, middle, and early insomnia in patients with MDD and BD, and a similar trend toward a decreased need for sleep was observed only in individuals with BD (Serretti et al., 2003). On the other hand, the presence of at least one T allele in the same locus is associated with higher global seasonality scores, and higher body weight and appetite compared to CC genotypes (Kim et al., 2015). A recent study investigated the relation of nine SNPs in the *CLOCK* gene (rs1801260, rs3805148, rs6849474, rs11932595, rs12648271, rs6850524, rs12649507, rs4340844, rs534654) and chronotypes and sleep disturbances in patients with bipolar and unipolar depression (Dmitrzak-Węglarz et al., 2016). The results show an association between rs12648271 and chronotype in the control group, and between rs3805148 and sleep duration in patients with depression. Depressed patients with BD carrying the rs1801260C allele showed higher impairments of white matter integrity, visible in myelination, orientation coherence, and microtubular axonal structure of fibers, which are all potential structural biomarkers for the disorder (Bollettini et al., 2016). The C variant in patients with depression along with BD lead to higher discrepancy between the subjective and objective severity of depression (Suzuki et al., 2017). In line with these studies,

the *CLOCK* gene, might regulate non-clock functions such as information processing and decision making. In this context, patients with bipolar and unipolar depression who carried the C allele showed an increase in their activity levels during the second part of the day, shorter latencies of responses to emotional stimuli in neuropsychological performance tasks, and blood oxygen-level dependent (BOLD) neural responses in a moral valence decision task (Benedetti et al., 2008).

Considering MDD diagnosis, circadian gene expression measured in peripheral blood leukocytes shows that older adults with a previous history of MDD have higher *CLOCK* mRNA levels compared to non-depressed participants (Gouin et al., 2010). Regarding genetic association studies, the rs1801260C allele has shown a significant protective effect in a male patient subset with MDD (Shi et al., 2016). In terms of CLOCK post-transcriptional regulation, the T allele of rs76481776 on miRNA-182, which leads to an overexpression of the mature form of miRNA-182 and consequently a significant reduction in *CLOCK* gene expression, has been associated with late insomnia in patients with MDD (Saus et al., 2010).

Some studies have focused on treatment with lithium, a mood stabilizer able to affect circadian rhythms and the expression of the *CLOCK* gene. In this context, McCarthy et al. (2011) evaluated lithium responses in patients with BD according to 16 variants in seven circadian clock genes, and found no association between treatment response and three SNPs in the *CLOCK* gene (rs1801260, rs3736544, rs34897046). Moreover, fibroblast cell lines from patients with BD, treated with lithium in vitro, showed functional cellular clock and longer period, and lower sensibility to lithium modulation compared to cell lines from controls (McCarthy et al., 2013). However, the same study showed no relative contribution of the *CLOCK* gene to these cellular alterations in response to lithium. The rs1801260C allele has been shown to be associated with higher insomnia in individuals with MDD under fluvoxamine or paroxetine treatment (Serretti et al., 2005). The TT genotype has been found to correlate with relapse within 6 months after recovery in patients with MDD on antidepressant treatment (Serretti et al., 2004). Haplotype analysis (rs3736544, rs1801260, rs3749474) indicated that the GTT haplotype was associated with higher remission rates in MDD patients treated with fluvoxamine (Kishi et al., 2009a).

Nevertheless, several other studies did not support previously reported associations of BD and MDD (Bailer et al., 2005; Byrne et al., 2014; Calati, Gaspar-Barba, Yukler, & Serretti, 2010; Crisafulli et al., 2013; Desan et al., 2000; Etain et al., 2014; Kishi et al., 2009b, 2011; Mansour et al., 2009; Nievergelt et al., 2006). Other negative findings involve investigations of treatment response (Geoffroy et al., 2016; Rybakowski, Dmitrzak-Weglarz, Kliwicki, & Hauser, 2014b), seasonal variations in mood (Geoffroy et al., 2015; Johansson et al., 2003; Paik et al., 2007), and chronotypes (Etain et al., 2014). Also, sleep disturbances (insomnia, daytime sleepiness, sleep quality) were not associated with rs1801260 in untreated patients with MDD (Antypa et al., 2012; Serretti et al., 2010). Moreover, nine SNPs in *CLOCK* gene (rs1801260, rs3805148, rs6849474, rs11932595, rs12648271, rs6850524, rs12649507, rs4340844, rs534654) were evaluated in relation to temperamental dimensions (depressive, cychothymic, hyperthymic, irritable, and anxious) in BD patients and no association was observed (Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al., 2014).

In summary, these findings emphasize the importance of the *CLOCK* gene in regulation of mood disorders, although the data are still controversial regarding clinical findings. Several clinical studies failed to report an association between mood disorder diagnosis or associated symptoms and *CLOCK* gene SNPs. Lack of gender-stratified analyses or population-specific studies are amongst the possible reasons for the inconsistent finding.

5 | SCHIZOPHRENIA

There is evidence pointing to strong links between disrupted circadian clocks and schizophrenia (reviewed in Karatsoreos, 2014). Sleep disturbance is a critical aspect of symptomatology and pathophysiology of schizophrenia regardless of medication status or clinical phase of illness. Reduced sleep quality with decreased total sleep time and sleep efficiency has already been observed in individuals with schizophrenia (Kamath, Virdi, & Winokur, 2015). Genome-wide association studies (GWAS) evaluating chronotype, sleep duration, and disturbance traits revealed an interesting genomic correlation between schizophrenia and sleep traits (i.e., sleep duration, oversleeping, and chronotype (Jones et al., 2016; Lane et al., 2016, 2017).

Johansson, Owe-Larsson, Hetta, and Lundkvist (2016) assessed circadian expression of *CLOCK* and seven other clock genes in fibroblast cultures and in mononuclear cells of blood sampled from individuals with first onset psychosis, who later developed schizophrenia. Lower levels of *CLOCK* mRNA expression were observed in individuals with schizophrenia compared to controls, but only in blood cells. No difference was detected regarding *CLOCK* gene expression in fibroblast cultures. These findings strongly suggest that the molecular clock machinery is altered in schizophrenia, possibly due to the disease and not due to epigenetic effects caused by long-term drug treatments, since the expression alteration was observed previously to any treatment enrollment.

Some polymorphisms in the *CLOCK* gene were investigated with regard to schizophrenia. The C allele of rs1801260 was associated with risk for schizophrenia in Japanese (Takao, Tachikawa, Kawanishi, Mizukami, & Asada, 2007) and Han Chinese patients (Zhang et al., 2011). However, Kishi et al. (2009a) failed to replicate this finding in a larger Japanese sample, evaluating six different SNPs (rs11939815, rs11931061, rs11133385, rs3736544, rs1801260, rs3749474). Negative results were also observed by Mansour et al. (2009), when they evaluated 10 SNPs in the *CLOCK* gene.

An exploratory study was conducted by Saleem, Anand, Jain, and Brahmachari (2001), who aimed to investigate the putative polymorphic property of CAG repeats that encode a portion of the C terminal region of the CLOCK protein. However, no variation in the length of the CAG-repeat stretch was observed in patients with schizophrenia of Indian origin.

Many reports were conducted to evaluate the comorbid traits strongly related to circadian cycles in schizophrenia or side effects of treatment for schizophrenia. An association between rs1801260 and clozapine-induced diurnal sleepiness was detected in individuals with major psychosis, primarily schizophrenia, treated with clozapine monotherapy for 6 months (Lattuada et al., 2004). The C allele and CC genotype were associated with higher daytime sleepiness, regardless of clozapine plasma levels, suggesting that C carriers would be more susceptible to a clozapine hypersomnolence side-effect (Lattuada et al., 2004). On the other hand, the polymorphisms rs11939815, rs11133385, rs3736544, rs1801260, and rs3749474 were not associated with schizophrenia or with clinical improvement, in a Korean sample treated with antipsychotics (Crisafulli et al., 2012).

Patients under clozapine treatment frequently report sialorrhea as an inconvenient side effect, believed to be related to the circadian rhythm (Solismaa et al., 2014). Solismaa et al. (2014) evaluated four *CLOCK* gene SNPs in Finnish patients and controls; however, no association was detected in a case-control analysis nor considering sialorrhea as a comorbidity in patients with schizophrenia. Regarding restless legs syndrome, which is more common during the night, it was found in a sample of Korean patients with schizophrenia that the T allele of rs2412646 confers a risk to develop this sleep disorder. No statistically significant association was observed considering rs1801260, while haplotype analysis revealed a significant influence of the T–T haplotype (rs1801260–rs2412646) in schizophrenic patients with restless legs syndrome (Jung et al., 2014).

In conclusion, results regarding the etiology of schizophrenia are inconclusive. However, candidate gene studies as well as expression studies suggest a role of *CLOCK* in the etiology of the disorder and in circadian rhythm-related features that occur as side-effects of treatment for schizophrenia.

6 | SUBSTANCE USE DISORDER

Substance use disorder comprises abuse and dependence of substances, including alcohol, tobacco, nicotine, and opioids. This disorder represents a significant health problem, associated with impaired control, social impairments, and other disabilities (American Psychiatric Association, 2013). Disruptions in sleep cycle, activity cycles, blood pressure, and body temperature rhythms are related to drug addiction (Jones, Knutson, & Haines, 2003; Wasielewski & Holloway, 2001). It has also been suggested that clock genes could regulate the reward system through dopamine neurotransmission, which is directly associated with addiction (McClung et al., 2005; Spencer et al., 2012).

Evidence from animal models has demonstrated an interesting link between addiction, circadian rhythms, and clock genes (Hirsh, 2001). In this regard, *Drosophila* types with mutations in circadian genes, such as *Clock*, were associated with lower cocaine sensitization (Andretic, Chaney, & Hirsh, 1999), but not with ethanol tolerance (Pohl et al., 2013). Similarly, mice lacking the *Clock* gene showed abnormalities in cocaine-induced locomotor sensitization (McClung et al., 2005). Studies have also shown that impairments in *Clock* functions lead to an increased vulnerability for cocaine use and increased cocaine reward (McClung et al., 2005; Ozburn, Larson, Self, & Mcclung, 2012). Furthermore, mice with the *ClockΔ19* mutation have been associated with an increase in the reward value for cocaine (Roybal et al., 2007) and an increase in alcohol intake and preference, with an augmented response to the sedative effects of alcohol (Ozburn et al., 2013). Despite these findings, the same pattern observed for cocaine and alcohol may not occur for other substances; mice with the same mutation in the *Clock* gene (*ClockΔ19*) did not present modifications in rhythmic behavior induced by methamphetamine (Mohawk, Baer, & Menaker, 2009), and exhibited a similar response to nicotine compared to wild-type (WT) controls (Bernardi & Spanagel, 2013).

In an attempt to assess the effect of the administration of different drugs on the circadian rhythm, several studies using animal models have been performed. In general, in rats and mice, alcohol intake has been associated with changes in the pattern of the circadian period and higher locomotor activity (Rosenwasser et al., 2005; Seggio, Fixaris, Reed, Logan, & Rosenwasser, 2009), whereas chronic morphine administration was observed to change the circadian rhythm during the withdrawal period (Glaser, Reyes-Vázquez, Prieto-Gómez, Burau, & Dafny, 2012). Cocaine self-administration was correlated with the regulation of circadian-related gene expression; specifically, *Clock* mRNA levels were upregulated in response to cocaine treatment (Lynch, Girgenti, Breslin, Newton, & Taylor, 2008). Moreover, Uz et al. (2005) demonstrated an increased expression of *Clock* in the caudate-putamen after cocaine administration. Nevertheless, Falcon, Ozburn, Mukherjee, Roybal, and McClung (2013) did not detect changes in the expression levels of *Clock* after cocaine administration, although other circadian-related gene expression seemed to be affected.

In addition, human gene expression and genetic studies also suggest a link between *CLOCK* expression and drug abuse. Lower mRNA levels of *CLOCK* were observed in alcohol-dependent male subjects compared to controls (Huang et al., 2010). The difference remained present even after the first week of treatment. On the other hand, Ando et al. (2010) did not observe a correlation between expression levels of *CLOCK* and alcohol intake in Japanese men. Yang et al. (2012) assessed comorbid dependence on multiple substances, including cocaine, opioid, and alcohol dependence in both European and Afro-American families. A genome-wide significant linkage signal was observed on chromosome 4, in close proximity to the *CLOCK* gene. Furthermore, Sjöholm et al. (2010) and Kovanen et al. (2010) evaluated the influence of SNPs in the *CLOCK* gene on alcohol use disorder in the Finnish population. The T allele of rs2412648 was nominally associated with alcohol dependence (Kovanen et al., 2010), and the G allele of rs11240 was associated with alcohol use disorder combined with depression (Sjöholm et al., 2010). However, other SNPs (rs3805151, rs2412646) were not related to alcohol use (Kovanen et al., 2010; Sjöholm et al., 2010). Polymorphisms in the *CLOCK* gene have also been evaluated in European-American and Afro-American samples. No association with these polymorphisms was detected for cocaine dependence (rs1801260, Malison, Kranzler, Yang, & Gelernter, 2006) or alcohol and coffee consumption (rs70965446,

TABLE 1 *CLOCK* gene expression studies conducted in human and mice

	Specie	Cell line/tissue	Treatment or design	Approach	Results	Reference
ASD	Human	Lymphoblastic cell lines	ASD patients vs controls	Genome-wide expression	Reduced *CLOCK* expression in ASD patients	Hu et al. (2009)
ADHD	Mice	Brain	Treatment with atomoxetine	Candidate-gene	Reduced *Clock* expression under daytime treatment	O'Keeffe et al. (2012)
	Mice	Brain	Methylphenidate and atomoxetine administration	Candidate-gene	Alteration of *Clock* expression acrophase in the dorsomedial hypothalamus and caudate putamen	Baird et al. (2013)
MDD	Human	Peripheral blood leukocytes	MDD patients vs control	Candidate-gene	Older adults with previous history of MDD presented higher *CLOCK* mRNA levels compared to non-depressed participants	Gouin et al. (2010)
	Mice	Brain	Chronic mild stress	Candidate-gene	Increased Clock protein expression in the morning observed in anhedonic group in basolateral amygdala	Savalli et al. (2015)
	Mice	Brain	Chronic mild stress	Candidate-gene	Reduced Clock level in prefrontal cortex.	Calabrese et al. (2016)
	Mice	Brain	Chronic unpredictable stress	Candidate-gene	Reduced Clock level in the SCN and peak phase shift of Clock in the hippocampus	Jiang et al. (2013)
	Mice	Brain	Melatonin treatment in a mouse model of seasonal affective disorder	Candidate-gene	Increased *Clock* mRNA level in the suprachiasmatic nucleus in response to treatment	Nagy et al. (2015)
	Mice	Brain	Fluoxetine treatment in selectively bred for high anxiety and depression-like behavior	Candidate-gene	Not associated	Schaufler et al. (2016)
BD	Human	Skin fibroblast cells lines	Cells from patients with BD treated with lithium in vitro	Genome-wide expression	Not associated	McCarthy et al. (2013)
	Mice	Brain	Optogenetic stimulation paradigm	Candidate-gene	Increased Clock mRNA expression in ventral tegmental area in ClockΔ19 mutant mice across the light-dark cycle	Sidor et al. (2015)
	Mice	Brain	Viral-mediated gene transfer	Candidate-gene	CLOCK overexpression in the VTA of ClockΔ19 mutant mice was sufficient to normalize the hyperactivity and levels of anxiety	Roybal et al. (2007)
	Human	Lymphoblastoid cell lines	Cells from patients with BD treated with lithium in vitro	Genome-wide expression	Not associated	Geoffroy et al. (2017)
SCZ	Human	Fibroblast cultures	SCZ patients vs controls	Candidate-gene	Not associated	Johansson et al. (2016)
	Human	PBMC collected at first onset psychosis	SCZ patients vs controls	Candidate-gene	Lower *CLOCK* mRNA expression levels in SCZ patients	Johansson et al. (2016)
SUD	Rat	Dorsal striatum	Cocaine self-administration	Microarray analysis	Upregulation of *Clock* mRNA levels	Lynch et al. (2008)

(Continues)

TABLE 1 (Continued)

	Specie	Cell line/tissue	Treatment or design	Approach	Results	Reference
	Mice	Brain	Cocaine administration	Candidate-gene	Increased expression of *Clock* in the caudate-putamen	Uz et al. (2005)
	Mice	Brain	Cocaine administration	Candidate-gene	Not associated	Falcon et al. (2013)
	Human	PBMC	Male alcohol dependents	Candidate-gene	Lower *CLOCK* mRNA levels in alcohol dependents compared to controls	Huang et al. (2010)
	Human	PBMC	Alcohol consumption	Candidate-gene	Not associated	Ando et al. (2010)
ANX	Mice	Brain	Younger mice (between 3 and 5 weeks of age) exposed to dim light at night	Candidate-gene	Mice had increased *Clock* gene expression in the hypothalamus	Cissé et al. (2016)

ASD, autism spectrum disorder; ADHD, attention deficit/hyperactivity disorder; MDD, major depressive disorder; BD, bipolar disorder; SCZ, schizophrenia; SUD, substance use disorder; ANX, anxiety disorder; PBMC, Peripheral blood mononuclear cells.

rs1801260; Gamble et al., 2011). Moreover, two studies evaluated the influence of rs1801260 on personality traits in healthy Japanese subjects (Otowa et al., 2011; Tsuchimine, Yasui-Furukori, Kaneda, & Kaneko, 2013), and found the C allele to be associated with higher reward dependence scores (Tsuchimine et al., 2013). Altogether, these findings demonstrate a relevant influence of the *CLOCK* gene on use of different substances and on phenotype-related substance dependence.

7 | ANXIETY DISORDERS

Anxiety is a usual response to stress; however, when anxiety becomes excessive and uncontrollable and is accompanied by disturbances in sleep, concentration, and social and occupational functioning it starts to interfere with daily normal activities. Nevertheless, the role of circadian clock-related genes in anxiety disorders has rarely been explored (Sipilä et al., 2010), and only a few preclinical studies investigated the influence of the *Clock* gene on anxiety traits.

In mice, the rhythms of the *Clock* gene are first driven mainly in gestational period by external lighting environment and continue to develop after weaning, when the SCN represent the first tissue to stabilize in the adult phase of rhythmic *Clock* gene expression typically by 2 weeks of age (Christ, Korf, & von Gall, 2012). Some studies have suggested that the environmental lighting conditions experienced in early life can play an important role in affective behavior (Borniger, McHenry, Abi Salloum, & Nelson, 2014; Toki et al., 2007). Recently, young mice (between 3 and 5 weeks of age) exposed to dim light at night showed increasing anxiety-like behavior in the open field with increasing age (Cissé, Peng, & Nelson, 2016). Furthermore, these mice showed increased levels of *Clock* gene expression in the hypothalamus compared to dark-night exposed counterparts. In the same study, adolescent mice also showed freezing responses to a fearful stimulus (foot shock) (Cissé et al., 2016).

Additionally, animals with the *ClockΔ19* allele mutation showed reduced anxiety-like behavior (Roybal et al., 2007), and spent more time in open spaces while showing higher locomotor activity (Dzirasa et al., 2011; Lamont, Legault-Coutu, Cermakian, & Boivin, 2007; Roybal et al., 2007). Also, it was demonstrated that mice raised by *Clock* mutant mothers develop anxiety-like behavior in adulthood (Koizumi, Kurabayashi, Watanabe, & Sanada, 2013). However, Easton, Arbuzova, and Turek (2003) did not observe any change in anxiety behavior in *ClockΔ19* mutant animals after conducting open field tests.

ClockΔ19 mutant mice treated with lithium, or after a viral-mediated *Clock* gene transfer directly in the VTA, show behavioral responses similar to WT animals and increased dopaminergic activity (Roybal et al., 2007). In vitro experiments with slice preparations from VTA of *ClockΔ19* mutant mice show increased dopamine cell firing and decreased intracellular levels of dopamine that were restored near to WT levels by chronic lithium treatment (Coque et al.,

TABLE 2 Molecular and allele frequency characterization of most reported polymorphisms in *CLOCK* gene in association studies

SNP ID	Allele[a]	Location	AFR	EUR	EAS	SAS	AMR	Positive results	Negative results
rs6850524	G	Intron 1	0.32	0.58	0.67	0.66	0.65	MD—Shi et al. (2008)	SCZ—Mansour et al. (2009), Solismaa et al. (2014)
									MD—Dmitrzak-Węglarz et al. (2016), Maciukiewicz et al. (2014), Kripke et al. (2009), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014)
									ANX—Sipilä et al. (2010)
rs12649507	G	Intron 1	0.83	0.70	0.43	0.59	0.58		ADHD—Jeong et al. (2014)
									MD—Dmitrzak-Węglarz et al. (2016), Maciukiewicz et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014)
rs12648271	G	Intron 2	0.97	0.75	0.43	0.62	0.60		MD—Dmitrzak-Węglarz et al. (2016), Maciukiewicz et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Kripke et al. (2009)
rs11939815	G	Intron 2	0.32	0.65	0.67	0.82	0.69	SCZ— Kishi et al. (2009a)	SCZ—Crisafulli et al. (2012)
									MD—Crisafulli et al. (2013), Kishi et al. (2009b)
rs4340844	A	Intron 10	0.83	0.66	0.43	0.56	0.55	MD—Shi et al. (2008)	MD—Dmitrzak-Węglarz et al. (2016), Gonzalez et al. (2015), Maciukiewicz et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014)
rs11133385	G	Intron 10	0.83	0.70	0.43	0.59	0.58	SCZ—Kishi et al. (2009a)	SCZ—Crisafulli et al. (2012)
									MD—Crisafulli et al. (2013), Kishi et al. (2009b)
rs11932595	A	Intron 12	0.62	0.58	0.90	0.56	0.68		SCZ—Mansour et al. (2009)
									MD—Dmitrzak-Węglarz et al. (2016), Gonzalez et al. (2015), Maciukiewicz et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014)
									ANX—Sipilä et al. (2010)
rs2412648	T	Intron 14	0.84	0.70	0.43	0.59	0.58	SUD—Kovanen et al. (2010)	MD—Etain et al. (2014), Shi et al. (2008)
									SUD—Sjöholm et al. (2010)
rs6849474	G	Intron 16	0.84	0.70	0.43	0.59	0.58		MD—Dmitrzak-Węglarz et al. (2016), Maciukiewicz et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014)
rs3736544	G	Exon 21 p.588N	0.75	0.65	0.67	0.82	0.71	SCZ—Kishi et al. (2009a)	SCZ—Crisafulli et al. (2012), Mansour et al. (2009)
								MD—Kishi et al (2009a)	MD—Crisafulli et al. (2013), Gonzalez et al. (2015), Kishi et al (2009b, 2011), Kripke et al. (2009), McCarthy et al. (2011)

(Continues)

TABLE 2 (Continued)

SNP ID	Allele[a]	Location	AFR	EUR	EAS	SAS	AMR	Positive results	Negative results
rs3805148	A	Intron 22	0.83	0.66	0.43	0.56	0.55	MD—Dmitrzak-Węglarz et al. (2016), Kripke et al. (2009)	ADHD—Jeong et al. (2014)
									MD—Gonzalez et al. (2015), Maciukiewicz et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014)
rs1801260	A	3′ UTR	0.85	0.69	0.90	0.62	0.76	ADHD—Cao et al. (2012), Jeong et al. (2014), Kissling et al. (2008), Xu et al. (2010)	ASD—Nicholas et al. (2007)
								SCZ—Jung et al. (2014), Kishi et al. (2009a), Lattuada et al. (2004), Takao et al. (2007), Zhang et al. (2011)	SCZ—Crisafulli et al. (2012), Mansour et al. (2009), Solismaa et al. (2014)
								MD—Antypa et al. (2012), Benedetti et al. (2003, 2007, 2008), Bollettini et al. (2016), Kim et al. (2015), Kishi et al (2009a), Lee et al. (2010), Maciukiewicz et al. (2014), Serretti et al. (2003, 2004, 2005), Shi et al. (2016), Suzuki et al. (2017)	MD—Bailer et al. (2005), Crisafulli et al. (2013), Dmitrzak-Węglarz et al. (2016), Gonzalez et al. (2015), Johansson et al. (2003), Kishi et al (2009b), Kishi et al. (2011), McCarthy et al. (2011), McCarthy et al. (2013), Paik et al. (2007), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Serretti et al. (2010), Nievergelt et al. (2006)
								SUD—Tsuchimine et al. (2012)	SUD—Gamble et al. (2011), Malison et al. (2006), Otowa et al. (2011)
									ANX—Sipilä et al. (2010)
rs3749474	C	3′ UTR	0.83	0.66	0.43	0.56	0.55	SCZ—Kishi et al. (2009a)	SCZ—Crisafulli et al. (2012), Solismaa et al. (2014)
								MD—Kishi et al. (2009a)	MD—Crisafulli et al. (2013), Kishi et al. (2009b), Kishi et al. (2011)
									ANX—Sipilä et al. (2010)
rs534654	G	Downstream 3,848 bp	0.80	0.81	0.98	0.96	0.80	MD—Shi et al. (2008)	MD—Dmitrzak-Węglarz et al. (2016), Etain et al. (2014), Maciukiewicz et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014), Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, et al. (2014)

Table includes SNPs reported in four or more genetic association studies. The allele depicted in the table does not necessarily correspond to the risk one in the association studies. Molecular and allele frequency information were retrieved from 1000 Genomes Project Consortium (2015) (Phase 3). Strand reference: forward; genome assembly reference: GHRC38; reference Isoform: NM_001267843.

[a]Ancestral allele. ASD, autism spectrum disorder; ADHD, attention deficit/hyperactivity disorder; SCZ, schizophrenia; SUD, substance use disorder; MD, Mood disorders; ANX, anxiety disorders; AFR, African population; AMR, American population; EAS, East Asian population; EUR, European population, SAS: South Asian population.

2011). Interestingly, a selective reduction in VTA cell firing using the Herpes simplex virus (HSV) vector containing the Kir2.1 potassium channel subunit (HSV-Kir2.1 virus) in *Clock*Δ19 mice was enough to reverse the increased exploratory behavior and anxiety-related abnormalities in these animals (Coque et al., 2011). Furthermore, a knockdown of *Clock* gene expression using interference RNA in the VTA corroborates with the hyperactivity, the anxiolytic effects, as well as the increased dopamine cell firing seen in *Clock*Δ19 mice (Mukherjee et al., 2010).

Altogether, these findings demonstrate that the CLOCK gene could be related to anxiety regulation, although no clear mechanism has been proposed. Nevertheless, the evidence suggests an important role in mood disorders, the dopaminergic system, and specific brain regions, and points to a need for more studies on anxiety traits.

8 | CONCLUSION

Apart from circadian timing, clock genes may also be involved in a number of other biological and behavioral processes. Here, we comprehensively reviewed literature findings of molecular and genetic data for the *CLOCK* gene with regard to main psychiatric disorders.

The notable role of the *CLOCK* gene in psychiatric disorders is clearly demonstrated by animal studies. Studies on expression and function of this gene in humans and animals are in accordance with preclinical findings (Table 1). Mood disorders are the main evaluated phenotype. The majority of the studies were conducted based on a candidate-gene or a small set of candidate-genes approach, using mice exposed to several treatments. Most of them observed differences in gene or protein expression, suggesting that *CLOCK* plays a role in psychiatric disorders.

A large amount of candidate gene studies corroborate with these findings, although the number of inconsistent results is high (Table 2). A large number of polymorphisms have already been evaluated along the *CLOCK* gene. The most analyzed polymorphism was rs1801260. It showed the highest proportion of positive results among the analyzed polymorphisms considering the published data so far. The functional role of this variant in *CLOCK* gene regulation (Ozburn et al., 2016; Shi et al., 2016) could explain it, supporting the hypothesis of functional role of *CLOCK* on psychiatric disorders. Although the hypothesis of genetic association based on functional variants is compelling, the direction of the association among the studies has inconsistencies. Controversial findings regarding the association status observed across clinical studies might be due to many different aspects, discussed above.

Most of the studies have a small sample size, with a few reaching a sample size of 500 cases and controls (Supplementary Table S1). The lack of statistical power may be an important limitation for the studies included in this review, since it is dependent on the sample size and also on the effect size (usually small for common genetic variants associated with complex diseases). Another potential source of inconsistencies across results might be due to the heterogeneity among the outcomes as well as the instrument used to assess them. Many studies tested the associations between *CLOCK* polymorphisms and psychiatric disorders, others with sleep or circadian-related comorbidities, while others considered as outcome the response to specific treatment (Supplementary Table S1). The assessment of symptoms and diagnoses of psychiatric disorders also showed some divergence among studies, although most of the studies used DSM-IV criteria. The same occurs concerning circadian rhythm and sleep-related assessment, which was measured through different questionnaires (Supplementary Table S1). In this sense, a comparison among the observed results is limited.

Heterogeneity was also observed concerning the statistical analyses, mainly concerning the genetic model assumed (additive, dominant), and the adjustment for confounders. Most of the psychiatric disorders included in this review present sex differences, and a stratification of analyses by sex was already suggested by Shi et al. (2016). In this sense, sex differences in glucocorticoid levels may influence the expression of *CLOCK*, thereby, leading to sex-dependent effects on clock-influenced gene expression pathways. This scenario could influence the susceptibility to MDD in a gender-specific manner, and also be related to other psychiatric disorders. Until now, few genetic studies have considered stratification by sex, which can be a putative explanation for inconsistencies among studies.

Regarding genetic background differences across populations, many SNPs of circadian system were observed to have MAFs correlated with environmental variables (Dall'Ara et al., 2016; Forni et al., 2014). Forni et al. (2014) showed a highly significant correlation between photoperiodic amplitude and allele frequency of a *CLOCK* SNP in worldwide populations, suggesting a large heterogeneity in MAF for SNPs in *CLOCK* locus among populations. The frequencies of ancestral allele of the most studied polymorphisms in psychiatric disorders, according to The 1000 Genomes Project Consortium (2015) (phase 3) information, are shown in Table 2. Although methodological issues cannot be ruled out, the difference in MAFs among populations can also be a reasonable explanation for the mixed results collated in this review including those inconsistencies related to the direction of association observed for rs1801260 (Table 2 and Supplementary Table). In fact, ethnic variation has already been proposed to have implications for the interpretation of results in circadian rhythm association studies (Barbosa, Pedrazzoli, Koike, & Tufik, 2010). None of the largest published GWASs on sleep related traits or chronotype have found the *CLOCK* gene amongst the genome wide significant loci (Hu et al., 2016; Jones et al., 2016; Lane et al., 2016). Psychiatric Genomics Consortium (PGC) GWASs have also not found genome-wide significant associations of the *CLOCK* gene with any major disorder (Ripke et al., 2011, 2013; Sklar et al., 2011). Nonetheless, such studies have only been conducted in European populations so far. Substantial differences in allele frequencies among populations might have an important impact on the genome-wide studies regarding *CLOCK* gene findings as well.

Moreover, the role of environment factors cannot be excluded as a reasonable explanation for the inconsistencies observed among genetic studies. As pointed out by Landgraf, McCarthy, and Welsh

(2014), the circadian clock and the stress response systems are closely related, being the stress response a possible common mechanism in which circadian clock genes could affect psychiatric disorders. Additionally, psychiatric disorders such as ADHD, SCZ, BD, and MDD are often accompanied by metabolic dysfunction symptoms, such as obesity (Barandas, Landgraf, McCarthy, & Welsh, 2015), which, in turn, have already been associated with *CLOCK* gene (Valladares, Obregón, & Chaput, 2015). Although most of the studies relate the association of *CLOCK* and psychiatric disorders by linking both through sleep patterns, it is also noteworthy that *CLOCK* has been associated with several metabolic processes in animal and human studies (Barandas et al., 2015; Turek et al., 2005). However, to the best of our knowledge, only a few genetic association studies focused on metabolic comorbidities. Further studies exploring the role of *CLOCK* in metabolic mechanisms are needed to clarify this link.

Finally, the influence of *CLOCK* gene in psychiatric disorders might also emerge from a complex relation involving several clock genes. McCarthy et al. (2012) findings support the hypothesis that variation within clock gene network contributes to BD susceptibility and is also related to others psychiatric disorders, such as ADHD, MDD, and SCZ. While none of the individual clock genes have been strongly implicated by GWAS, collectively they are associated with BD-spectrum illnesses at a higher rate than it would be expected by chance (McCarthy, Nievergelt, Kelsoe, & Welsh, 2012). This finding suggests that modest associations detected in GWAS could represent authentic effects that are too weak to achieve genome-wide significance. Results from expression data also support the hypothesis that a large complex set of circadian genes are involved in psychiatric disorder. For instance, in humans, gene expression data using high-quality postmortem brains showed that cyclic patterns were weaker in the brains of patients with MDD due to shifted peak timing and potentially disrupted phase relation between individual circadian genes (Li et al., 2013). On the other hand, a clear involvement of circadian genes in psychiatric disorders etiology is not a consensus. Byrne et al. (2014) suggested that genes encoding components of the molecular clock are not good candidates for BD, SCZ or MDD susceptibility, using a gene-based analysis (Ripke et al., 2011, 2013; Sklar et al., 2011). An update of this analysis, based on more recent PGC published data, however, would be helpful to improve the current understanding of the role of *CLOCK* gene in psychiatric disorders. It would be especially interesting for SCZ giving the recent findings showing genome correlations between this disorder and sleep related traits and chronotype (Lane et al., 2016, 2017).

In conclusion, animal studies point to a biological plausibility of the *CLOCK* gene being a causative factor in major psychiatric disorders. While expression and genetic association studies, in general, are in agreement with this assumption, the number of controversial results is high. Despite the large number of candidate gene studies that have identified polymorphisms associated with mood and other psychiatric disorders, this review therefore suggests that the effect of common variants in the *CLOCK* gene is likely to be small, as it has been observed for other common variants in other genes and complex phenotypes. Finally, further studies, especially those based on genome-wide approaches, are needed to clarify the role of *CLOCK* in psychiatric disorders and their circadian alteration comorbidities.

ACKNOWLEDGMENTS

This work was financially supported by the funding agencies CAPES and CNPq.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ORCID

Luciana Tovo-Rodrigues http://orcid.org/0000-0002-8732-6059

REFERENCES

1000 Genomes Project Consortium. (2015). A global reference for human genetic variation. *Nature*, *526*, 68–74.

Algahim, M. F., Yang, P. B., Wilcox, V. T., Burau, K. D., Swann, A. C., & Dafny, N. (2009). Prolonged methylphenidate treatment alters the behavioral diurnal activity pattern of adult male Sprague-Dawley rats. *Pharmacology Biochemistry & Behavior*, *92*, 93–99.

Allebrandt, K. V., Teder-Laving, M., Akyol, M., Pichler, I., Müller-Myhsok, B., Pramstaller, P., … Roenneberg, T. (2010). CLOCK gene variants associate with sleep duration in two independent populations. *Biological Psychiatry*, *67*, 1040–1047.

American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders (DSM-5).

Ando, H., Ushijima, K., Kumazaki, M., Eto, T., Takamura, T., Irie, S., … Fujimura, A. (2010). Associations of metabolic parameter and ethanol. *Chronobiology International*, *27*, 194–203.

Andretic, R., Chaney, S., & Hirsh, J. (1999). Requirement of circadian genes for cocaine sensitization in drosophila. *Science (80-.)*, *285*, 1066–1068.

Antle, M. C., van Diepen, H. C., Deboer, T., Pedram, P., Pereira, R. R., & Meijer, J. H. (2012). Methylphenidate modifies the motion of the circadian clock. *Neuropsychopharmacology*, *37*, 2446–2455.

Antypa, N., Mandelli, L., Nearchou, F. A., Vaiopoulos, C., Stefanis, C. N., Serretti, A., & Stefanis, N. C. (2012). The 3111T/C polymorphism interacts with stressful life events to influence patterns of sleep in females. *Chronobiology International*, *29*, 891–897.

Arey, R. N., Enwright, J. F., Spencer, S. M., Falcon, E., Ozburn, A. R., Ghose, S., … McClung, C. A. (2014). An important role for cholecystokinin, a CLOCK target gene, in the development and treatment of manic-like behaviors. *Molecular Psychiatry*, *19*, 342–350.

Bailer, U., Wiesegger, G., Leisch, F., Fuchs, K., Leitner, I., Letmaier, M., … Aschauer, H. N. (2005). No association of clock gene T3111C polymorphism and affective disorders. *European Neuropsychopharmacology*, *15*, 51–55.

Baird, A. L., Coogan, A. N., Kaufling, J., Barrot, M., & Thome, J. (2013). Daily methylphenidate and atomoxetine treatment impacts on clock gene protein expression in the mouse brain. *Brain Research*, *1513*, 61–71.

Balmforth, A. J., Grant, P. J., Scott, E. M., Wheatcroft, S. B., Kearney, M. T., Staels, B., & Marx, N. (2007). Inter-subject differences in constitutive expression levels of the clock gene in man. *Diabetes and Vascular Disease Research*, *4*, 39–43.

Barandas, R., Landgraf, D., McCarthy, M. J., & Welsh, D. K. (2015). Circadian clocks as modulators of metabolic comorbidity in psychiatric disorders. *Current Psychiatry Reports*, *17*, 98.

Barbosa, A. A., Pedrazzoli, M., Koike, B. D. V., & Tufik, S. (2010). Do Caucasian and Asian clocks tick differently? *Brazilian Journal of Medical and Biological Research*, *43*, 96–99.

Benedetti, F., Radaelli, D., Bernasconi, A., Dallaspezia, S., Falini, A., Scotti, G., … Smeraldi, E. (2008). Clock genes beyond the clock: CLOCK genotype biases neural correlates of moral valence decision in depressed patients. *Genes, Brain, and Behavior*, *7*, 20–25.

Benedetti, F., Serretti, A., Colombo, C., Barbini, B., Lorenzi, C., Campori, E., & Smeraldi, E. (2003). Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *123B*, 23–26.

Benedetti, F., Dallaspezia, S., Fulgosi, M. C., Lorenzi, C., Serretti, A., Barbini, B., … Smeraldi, E. (2007). Actimetric evidence that clock 3111 T/C SNP influences sleep and activity patterns in patients affected by bipolar depression. *American Journal of Medical Genetics Part B, Neuropsychiatric Genetics*, *144B*, 631–635.

Bernardi, R. E., & Spanagel, R. (2013). The ClockΔ19 mutation in mice fails to alter the primary and secondary reinforcing properties of nicotine. *Drug and Alcohol Dependence*, *133*, 733–739.

Bhatti, P., Zhang, Y., Song, X., Makar, K. W., Sather, C. L., Kelsey, K. T., … Wang, P. (2015). Nightshift work and genome-wide DNA methylation. *Chronobiology International*, *32*, 103–112.

Bjarnason, G. A., Jordan, R. C., Wood, P. A., Li, Q., Lincoln, D. W., Sothern, R. B., … Ben-David, Y. (2001). Circadian expression of clock genes in human oral mucosa and skin: Association with specific cell-cycle phases. *The American Journal of Pathology*, *158*, 1793–1801.

Boland, E. M., & Alloy, L. B. (2013). Sleep disturbance and cognitive deficits in bipolar disorder: Toward an integrated examination of disorder maintenance and functional impairment. *Clinical Psychology Review*, *33*, 33–44.

Bollettini, I., Melloni, E. M. T., Aggio, V., Poletti, S., Lorenzi, C., Pirovano, A., … Benedetti, F. (2016). Clock genes associate with white matter integrity in depressed bipolar patients. *Chronobiology International*, *34*, 1–13.

Borniger, J. C., McHenry, Z. D., Abi Salloum, B. A., & Nelson, R. J. (2014). Exposure to dim light at night during early development increases adult anxiety-like responses. *Physiology & Behavior*, *133*, 99–106.

Bourgeron, T. (2007). The possible interplay of synaptic and clock genes in autism spectrum disorders. *Cold Spring Harbor Symposia on Quantitative Biology*, *72*, 645–654.

Boyce, P., & Barriball, E. (2010). Circadian rhythms and depression. *Australian Family Physician*, *39*, 307–301.

Bracci, M., Manzella, N., Copertaro, A., Staffolani, S., Strafella, E., Barbaresi, M., … Santarelli, L. (2014). Rotating-shift nurses after a day off: Peripheral clock gene expression, urinary melatonin, and serum 17-β-estradiol levels. *Scandinavian Journal of Work, Environment and Health*, *40*, 295–304.

Buhr, E. D., & Takahashi, J. S. (2013). Molecular components of the mammalian circadian clock. In: A. Kramer, M. Merrow (Eds.), *Circadian clocks. Handbook of experimental pharmacology*, vol 217. Berlin, Heidelberg: Springer.

Byrne, E. M., Heath, A. C., Madden, P. A. F. F., Pergadia, M. L., Hickie, I. B., Montgomery, G. W., … Wray, N. R. (2014). Testing the role of circadian genes in conferring risk for psychiatric disorders. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *165*, 254–260.

Calabrese, F., Savino, E., Papp, M., Molteni, R., & Riva, M. A. (2016). Chronic mild stress-induced alterations of clock gene expression in rat prefrontal cortex: Modulatory effects of prolonged lurasidone treatment. *Pharmacological Research*, *104*, 140–150.

Calati, R., Gaspar-Barba, E., Yukler, A., & Serretti, A. (2010). T3111C clock single nucleotide polymorphism and mood disorders: A meta-analysis. *Chronobiology International*, *27*, 706–721.

Cao, Y.-L., Cui, Q.-T., Tang, C.-H., & Chang, X. (2012). Association of CLOCK gene T3111C polymorphism with attention deficit hyperactivity disorder and related sleep disturbances in children. *Zhongguo Dang Dai Er Ke Za Zhi*, *14*, 285–288.

Chang, A.-M., Buch, A. M., Bradstreet, D. S., Klements, D. J., & Duffy, J. F. (2011). Human diurnal preference and circadian rhythmicity are not associated with the *CLOCK* 3111C/T gene polymorphism. *Journal of Biological Rhythms*, *26*, 276–279.

Chen, C.-Y., Logan, R. W., Ma, T., Lewis, D. A., Tseng, G. C., Sibille, E., & McClung, C. A. (2016). Effects of aging on circadian patterns of gene expression in the human prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *113*, 206–211.

Choub, A., Mancuso, M., Coppedè, F., LoGerfo, A., Orsucci, D., Petrozzi, L., … Murri, L. (2011). Clock T3111C and Per2 C111G SNPs do not influence circadian rhythmicity in healthy Italian population. *Neurological Sciences*, *32*, 89–93.

Christ, E., Korf, H.-W., & von Gall, C. (2012). Chapter 6—When does it start ticking? Ontogenetic development of the mammalian circadian system. *Progress in Brain Research*, *199*, 105–118.

Cissé, Y. M., Peng, J., & Nelson, R. J. (2016). Dim light at night prior to adolescence increases adult anxiety-like behaviors. *Chronobiology International*, *33*, 1473–1480.

Coogan, A. N., & McGowan, N. M. (2017). A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. *Attention Deficit and Hyperactivity Disorders*, *9*, 129–147.

Coque, L., Mukherjee, S., Cao, J.-L., Spencer, S., Marvin, M., Falcon, E., … McClung, C. A. (2011). Specific role of VTA dopamine neuronal firing rates and morphology in the reversal of anxiety-related, but not depression-related behavior in the clockΔ19 mouse model of mania. *Neuropsychopharmacology*, *36*, 1478–1488.

Corkum, P., Panton, R., Ironside, S., MacPherson, M., & Williams, T. (2007). Acute impact of immediate release methylphenidate administered three times a day on sleep in children with attention-deficit/hyperactivity disorder. *Journal of Pediatric Psychology*, *33*, 368–379.

Cotton, S., & Richdale, A. (2006). Brief report: Parental descriptions of sleep problems in children with autism, Down syndrome, and Prader-Willi syndrome. *Research in Developmental Disabilities*, *27*, 151–161.

Crisafulli, C., Chiesa, A., Han, C., Lee, S.-J., Balzarro, B., Andrisano, C., … Serretti, A. (2013). Case-control association study of 36 single-nucleotide polymorphisms within 10 candidate genes for major depression and bipolar disorder. *Psychiatry Research*, *209*, 121–123.

Crisafulli, C., Chiesa, A., Han, C., Lee, S.-J., Park, M. H., Balzarro, B., … Serretti, A. (2012). Case-control association study for 10 genes in patients with schizophrenia: Influence of 5HTR1A variation rs10042486 on schizophrenia and response to antipsychotics. *European Archives of Psychiatry and Clinical Neuroscience*, *262*, 199–205.

Dall'Ara, I., Ghirotto, S., Ingusci, S., Bagarolo, G., Bertolucci, C., & Barbujani, G. (2016). Demographic history and adaptation account for clock gene diversity in humans. *Heredity (Edinb)*, *117*, 165–172.

DeBruyne, J. P., Noton, E., Lambert, C. M., Maywood, E. S., Weaver, D. R., & Reppert, S. M. (2006). A clock shock: Mouse CLOCK is not required for circadian oscillator function. *Neuron*, *50*, 465–477.

DeBruyne, J. P., Weaver, D. R., & Reppert, S. M. (2007). CLOCK and NPAS2 have overlapping roles in the suprachiasmatic circadian clock. *Nature Neuroscience*, *10*, 543–545.

Desan, P. H., Oren, D. A., Malison, R., Price, L. H., Rosenbaum, J., Smoller, J., … Gelernter, J. (2000). Genetic polymorphism at the CLOCK gene locus and major depression. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *96*, 418–421.

Dmitrzak-Węglarz, M., Pawlak, J., Wiłkość, M., Miechowicz, I., Maciukiewicz, M., Ciarkowska, W., … Hauser, J. (2016). Chronotype and sleep quality as a subphenotype in association studies of clock genes in mood disorders. *Acta Neurobiologiae Experimentalis*, *76*, 32–42.

Doi, M., Hirayama, J., & Sassone-Corsi, P. (2006). Circadian regulator CLOCK is a histone acetyltransferase. *Cell*, *125*, 497–508.

Dzirasa, K., Coque, L., Sidor, M. M., Kumar, S., Dancy, E. A., Takahashi, J. S., … Nicolelis, M. A. L. (2010). Lithium ameliorates nucleus accumbens phase-signaling dysfunction in a genetic mouse model of mania. *The Journal of Neuroscience*, *30*, 16314–16323.

Dzirasa, K., McGarity, D. L., Bhattacharya, A., Kumar, S., Takahashi, J. S., Dunson, D., … Nicolelis, M. A. L. (2011). Impaired limbic gamma oscillatory synchrony during anxiety-related behavior in a genetic mouse model of bipolar mania. *The Journal of Neuroscience*, *31*, 6449–6456.

Easton, A., Arbuzova, J., & Turek, F. W. (2003). The circadian Clock mutation increases exploratory activity and escape-seeking behavior. *Genes, Brain, and Behavior*, *2*, 11–19.

Etain, B., Jamain, S., Milhiet, V., Lajnef, M., Boudebesse, C., Dumaine, A., … Bellivier, F. (2014). Association between circadian genes, bipolar disorders and chronotypes. *Chronobiology International*, *31*, 807–814.

Falcon, E., Ozburn, A., Mukherjee, S., Roybal, K., & McClung, C. A. (2013). Differential regulation of the period genes in striatal regions following cocaine exposure. *PLoS ONE*, *8*, e66438.

Ford, D. E., & Cooper-Patrick, L. (2001). Sleep disturbances and mood disorders: An epidemiologic perspective. *Depression and Anxiety*, *14*, 3–6.

Forni, D., Pozzoli, U., Cagliani, R., Tresoldi, C., Menozzi, G., Riva, S., … Sironi, M. (2014). Genetic adaptation of the human circadian clock to day-length latitudinal variations and relevance for affective disorders. *Genome Biology*, *15*, 499.

Galland, B. C., Tripp, E. G., & Taylor, B. J. (2010). The sleep of children with attention deficit hyperactivity disorder on and off methylphenidate: A matched case-control study. *Journal of Sleep Research*, *19*, 366–373.

Gamble, K. L., Motsinger-Reif, A. A., Hida, A., Borsetti, H. M., Servick, S. V., Ciarleglio, C. M., … Johnson, C. H. (2011). Shift work in nurses: Contribution of phenotypes and genotypes to adaptation. *PLoS ONE*, *6*, e18395.

Geoffroy, P. A., Etain, B., Lajnef, M., Zerdazi, E.-H., Brichant-Petitjean, C., Heilbronner, U., … Bellivier, F. (2016). Circadian genes and lithium response in bipolar disorders: Associations with PPARGC1A (PGC-1α) and RORA. *Genes, Brain, and Behavior*, *15*, 660–668.

Geoffroy, P. A., Lajnef, M., Bellivier, F., Jamain, S., Gard, S., Kahn, J.-P., … Etain, B. (2015). Genetic association study of circadian genes with seasonal pattern in bipolar disorders. *Scientific Reports*, *5*, 10232.

Glaser, A. M., Reyes-Vázquez, C., Prieto-Gómez, B., Burau, K., & Dafny, N. (2012). Morphine administration and abrupt cessation alter the behavioral diurnal activity pattern. *Pharmacology Biochemistry & Behavior*, *101*, 544–552.

Gonzalez, R., Gonzalez, S., Villa, E., Ramirez, M., Zavala, J., Armas, R., … Escamilla, M. (2015). Identification of circadian gene variants in bipolar disorder in Latino populations. *Journal of Affective Disorders*, *186*, 367–375.

Gouin, J.-P., Connors, J., Kiecolt-Glaser, J. K., Glaser, R., Malarkey, W. B., Atkinson, C., … Quan, N. (2010). Altered expression of circadian rhythm genes among individuals with a history of depression. *Journal of Affective Disorders*, *126*, 161–166.

Hirayama, J., Sahar, S., Grimaldi, B., Tamaru, T., Takamatsu, K., Nakahata, Y., & Sassone-Corsi, P. (2007). CLOCK-mediated acetylation of BMAL1 controls circadian function. *Nature*, *450*, 1086–1090.

Hirsh, J. (2001). Time flies like an arrow. Fruit flies like crack? *Pharmacogenomics Journal*, *1*, 97–100.

Hogenesch, J. B., Chan, W. K., Jackiw, V. H., Brown, R. C., Gu, Y. Z., Pray-Grant, M., … Bradfield, C. A. (1997). Characterization of a subset of the basic-helix-loop-helix-PAS superfamily that interacts with components of the dioxin signaling pathway. *The Journal of Biological Chemistry*, *272*, 8581–8593.

Hu, V. W., Sarachana, T., Kim, K. S., Nguyen, A., Kulkarni, S., Steinberg, E., … Lee, N. H. (2009). Gene expression profiling differentiates autism case-controls and phenotypic variants of autism spectrum disorders: Evidence for circadian rhythm dysfunction in severe autism. *Autism Research*, *2*, 78–97.

Hu, Y., Shmygelska, A., Tran, D., Eriksson, N., Tung, J. Y., & Hinds, D. A. (2016). GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person. *Nature Communications*, *7*, 10448.

Huang, J., Zhong, Z., Wang, M., Chen, X., Tan, Y., Zhang, S., … Wang, H. (2015). Circadian modulation of dopamine levels and dopaminergic neuron development contributes to attention deficiency and hyperactive behavior. *The Journal of Neuroscience*, *35*, 2572–2587.

Huang, M.-C., Ho, C.-W., Chen, C.-H., Liu, S.-C., Chen, C.-C., & Leu, S.-J. (2010). Reduced expression of circadian clock genes in male alcoholic patients. *Alcoholism, Clinical and Experimental Research*, *34*, 1899–1904.

Ironside, S., Davidson, F., & Corkum, P. (2010). Circadian motor activity affected by stimulant medication in children with attention-deficit/hyperactivity disorder. *Journal of Sleep Research*, *19*, 546–551.

Iwase, T., Kajimura, N., Uchiyama, M., Ebisawa, T., Yoshimura, K., Kamei, Y., … Yamauchi, T. (2002). Mutation screening of the human Clock gene in circadian rhythm sleep disorders. *Psychiatry Research*, *109*, 121–128.

Jeong, S. H., Yu, J.-C., Lee, C. H., Choi, K.-S., Choi, J.-E., Kim, S. H., & Joo, E.-J. (2014). Human CLOCK gene-associated attention deficit hyperactivity disorder-related features in healthy adults: Quantitative association study using Wender Utah Rating Scale. *European Archives of Psychiatry and Clinical Neuroscience*, *264*, 71–81.

Jiang, W.-G., Li, S.-X., Liu, J.-F., Sun, Y., Zhou, S.-J., Zhu, W.-L., … Lu, L. (2013). Hippocampal CLOCK protein participates in the persistence of depressive-like behavior induced by chronic unpredictable stress. *Psychopharmacology*, *227*, 79–92.

Johansson, A.-S., Owe-Larsson, B., Hetta, J., & Lundkvist, G. B. (2016). Altered circadian clock gene expression in patients with schizophrenia. *Schizophrenia Research*, *174*, 17–23.

Johansson, C., Willeit, M., Smedh, C., Ekholm, J., Paunio, T., Kieseppä, T., … Partonen, T. (2003). Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology*, *28*, 734–739.

Jones, E. M., Knutson, D., & Haines, D. (2003). Common problems in patients recovering from chemical dependency. *American Family Physician*, *68*, 1971–1978.

Jones, S. E., Tyrrell, J., Wood, A. R., Beaumont, R. N., Ruth, K. S., Tuke, M. A., … Weedon, M. N. (2016). Genome-wide association analyses in 128,266 individuals identifies new morningness and sleep duration loci. *PLoS Genetics*, *12*, e1006125.

Jung, J.- S., Lee, H.-J., Cho, C.-H., Kang, S.-G., Yoon, H.-K., Park, Y.-M., … Kim, L. (2014). Association between restless legs syndrome and CLOCK and NPAS2 gene polymorphisms in schizophrenia. *Chronobiology International*, *31*, 838–844.

Kamath, J., Virdi, S., & Winokur, A. (2015). Sleep disturbances in schizophrenia. *Psychiatric Clinics of North America*, *38*, 777–792.

Karatsoreos, I. N. (2014). Links between circadian rhythms and psychiatric disease. *Frontiers in Behavioral Neuroscience*, *8*, 162.

Katzenberg, D., Young, T., Finn, L., Lin, L., King, D. P., Takahashi, J. S., & Mignot, E. (1998). A CLOCK polymorphism associated with human diurnal preference. *Sleep*, *21*, 569–576.

Kim, H.-I., Lee, H.-J., Cho, C.-H., Kang, S.-G., Yoon, H.-K., Park, Y.-M., … Kim, L. (2015). Chronobiology International Association of CLOCK, ARNTL, and NPAS2 gene polymorphisms and seasonal variations in mood and behavior Association of CLOCK, ARNTL, and NPAS2 gene polymorphisms and seasonal variations in mood and behavior. *Chronobiology International*, *32*, 785–791.

Kimiwada, T., Sakurai, M., Ohashi, H., Aoki, S., Tominaga, T., & Wada, K. (2009). Clock genes regulate neurogenic transcription factors, including NeuroD1, and the neuronal differentiation of adult neural stem/progenitor cells. *Neurochemistry International*, *54*, 277–285.

King, D. P., Vitaterna, M. H., Chang, A. M., Dove, W. F., Pinto, L. H., Turek, F. W., & Takahashi, J. S. (1997). The mouse Clock mutation behaves as an antimorph and maps within the W19H deletion, distal of Kit. *Genetics*, *146*, 1049–1060.

King, D. P., Zhao, Y., Sangoram, A. M., Wilsbacher, L. D., Tanaka, M., Antoch, M. P., … Takahashi, J. S. (1997). Positional cloning of the mouse circadian clock gene. *Cell*, *89*, 641–653.

Kishi, T., Kitajima, T., Ikeda, M., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., … Iwata, N. (2009a). Association study of clock gene (CLOCK) and schizophrenia and mood disorders in the Japanese population. *European Archives of Psychiatry and Clinical Neuroscience*, *259*, 293–297.

Kishi, T., Kitajima, T., Ikeda, M., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., … Iwata, N. (2009b). CLOCK may predict the response to fluvoxamine treatment in Japanese major depressive disorder patients. *Neuromolecular Medicine*, *11*, 53–57.

Kishi, T., Yoshimura, R., Fukuo, Y., Kitajima, T., Okochi, T., Matsunaga, S., … Iwata, N. (2011). The CLOCK gene and mood disorders: A case-control study and meta-analysis. *Chronobiology International*, *28*, 825–833.

Kissling, C., Retz, W., Wiemann, S., Coogan, A. N., Clement, R. M., Hünnerkopf, R., … Thome, J. (2008). A polymorphism at the 3′-untranslated region of theCLOCK gene is associated with adult attention-deficit hyperactivity disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147B*, 333–338.

Ko, C. H., & Takahashi, J. S. (2006). Molecular components of the mammalian circadian clock. *Human Molecular Genetics*, *15*, R271–R277.

Koizumi, H., Kurabayashi, N., Watanabe, Y., & Sanada, K. (2013). Increased anxiety in offspring reared by circadian Clock mutant mice. *PLoS ONE*, *8*, e66021.

Kovanen, L., Saarikoski, S. T., Haukka, J., Pirkola, S., Aromaa, A., Lönnqvist, J., & Partonen, T. (2010). Circadian clock gene polymorphisms in alcohol use disorders and alcohol consumption. *Alcohol Alcoholism*, *45*, 303–311.

Kozikowski, A. P., Gunosewoyo, H., Guo, S., Gaisina, I. N., Walter, R. L., Ketcherside, A., … Caldarone, B. (2011). Identification of a glycogen synthase kinase-3β inhibitor that attenuates hyperactivity in CLOCK mutant mice. *ChemMedChem*, *6*, 1593–1602.

Kripke, D. F., Nievergelt, C. M., Joo, E., Shekhtman, T., & Kelsoe, J. R. (2009). Circadian polymorphisms associated with affective disorders. *Journal of Circadian Rhythms*, *7*, 2.

Kronfeld-Schor, N., & Einat, H. (2012). Circadian rhythms and depression: Human psychopathology and animal models. *Neuropharmacology*, *62*, 101–114.

Lamont, E. W., Legault-Coutu, D., Cermakian, N., & Boivin, D. B. (2007). The role of circadian clock genes in mental disorders. *Dialogues in Clinical Neuroscience*, *9*, 333–342.

Landgraf, D., McCarthy, M. J., & Welsh, D. K. (2014). Circadian clock and stress interactions in the molecular biology of psychiatric disorders. *Current Psychiatry Reports*, *16*, 483.

Landgraf, D., Wang, L. L., Diemer, T., & Welsh, D. K. (2016). NPAS2 compensates for loss of CLOCK in peripheral circadian oscillators. *PLoS Genetics*, *12*, e1005882.

Lane, J. M., Liang, J., Vlasac, I., Anderson, S. G., Bechtold, D. A., Bowden, J., … Saxena, R. (2017). Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. *Nature Genetics*, *49*, 274–281.

Lane, J. M., Vlasac, I., Anderson, S. G., Kyle, S. D., Dixon, W. G., Bechtold, D. A., … Saxena, R. (2016). Genome-wide association analysis identifies novel loci for chronotype in 100,420 individuals from the UK Biobank. *Nature Communications*, *7*, 10889.

Lattuada, E., Cavallaro, R., Benedetti, F., Cocchi, F., Lorenzi, C., & Smeraldi, E. (2004). Genetic dissection of drug effects in clinical practice: CLOCK gene and clozapine-induced diurnal sleepiness. *Neuroscience Letters*, *367*, 152–155.

Lee, H.-J., Paik, J.-W., Kang, S.-G., Lim, S.-W., & Kim, L. (2007). Allelic variants interaction of CLOCK gene and G-protein beta3 subunit gene with diurnal preference. *Chronobiology International*, *24*, 589–597.

Lee, K. Y., Song, J. Y., Kim, S. H., Kim, S. C., Joo, E. J., Ahn, Y. M., & Kim, Y. S. (2010). Association between CLOCK 3111T/C and preferred circadian phase in Korean patients with bipolar disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*, 1196–1201.

Li, J. Z., Bunney, B. G., Meng, F., Hagenauer, M. H., Walsh, D. M., Vawter, M. P., … Bunney, W. E. (2013). Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 9950–9955.

Logan, R. W., Edgar, N., Gillman, A. G., Hoffman, D., Zhu, X., & McClung, C. A. (2015). Chronic stress induces brain region specific alterations of molecular rhythms in mice that correlate with depression-like behavior. *Biological Psychiatry*, *78*, 249–258.

Lynch, W. J., Girgenti, M. J., Breslin, F. J., Newton, S. S., & Taylor, R. (2008). Gene profiling the response to repeated cocaine self-administration in dorsal striatum: A focus on circadian genes. *Brain*, *1213*, 166–177.

Maciukiewicz, M., Dmitrzak-Weglarz, M., Pawlak, J., Leszczynska-Rodziewicz, A., Zaremba, D., Skibinska, M., & Hauser, J. (2014). Analysis of genetic association and epistasis interactions between circadian clock genes and symptom dimensions of bipolar affective disorder. *Chronobiology International*, *31*, 770–778.

Malison, R. T., Kranzler, H. R., Yang, B. Z., & Gelernter, J. (2006). Human clock, PER1 and PER2 polymorphisms: Lack of association with cocaine dependence susceptibility and cocaine-induced paranoia. *Psychiatric Genetics*, *16*, 245–249.

Mansour, H. A., Talkowski, M. E., Wood, J., Chowdari, K. V., McClain, L., Prasad, K., … Nimgaonkar, V. L. (2009). Association study of 21 circadian genes with bipolar I disorder, schizoaffective disorder, and schizophrenia. *Bipolar Disorders*, *11*, 701–710.

McCarthy, M. J., Nievergelt, C. M., Shekhtman, T., Kripke, D. F., Welsh, D. K., & Kelsoe, J. R. (2011). Functional genetic variation in the Rev-Erbα pathway and lithium response in the treatment of bipolar disorder. *Genes, Brain, and Behavior*, *10*, 852–861.

McCarthy, M. J., Nievergelt, C. M., Kelsoe, J. R., & Welsh, D. K. (2012). A survey of genomic studies supports association of circadian clock genes with bipolar disorder spectrum illnesses and lithium response. *PLoS ONE*, *7*, e32091.

McCarthy, M. J., Wei, H., Marnoy, Z., Darvish, R. M., McPhie, D. L., Cohen, B. M., & Welsh, D. K. (2013). Genetic and clinical factors predict lithium's effects on PER2 gene expression rhythms in cells from bipolar disorder patients. *Translational Psychiatry*, *3*, e318.

McClung, C., Sidiropoulou, K., Vitaterna, M., Takahashi, J. S., White, F. J., Cooper, D. C., & Nestler, E. J. (2005). Regulation of dopaminergic transmission and cocaine reward by the Clock gene. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 9377–9381.

Ming, X., Gordon, E., Kang, N., & Wagner, G. C. (2008). Use of clonidine in children with autism spectrum disorders. *Brain and Development*, *30*, 454–460.

Mishima, K., Tozawa, T., Satoh, K., Saitoh, H., & Mishima, Y. (2005). The 3111T/C polymorphism of hClock is associated with evening preference and delayed sleep timing in a Japanese population sample. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *133B*, 101–104.

Mohawk, J. A., Baer, M. L., & Menaker, M. (2009). The methamphetamine-sensitive circadian oscillator does not employ canonical clock genes. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 3519–3524.

Mukherjee, S., Coque, L., Cao, J.-L., Kumar, J., Chakravarty, S., Asaithamby, A., … McClung, C. A. (2010). Knockdown of Clock in the ventral tegmental area through RNA interference results in a mixed state of mania and depression-like behavior. *Biological Psychiatry*, *68*, 503–511.

Nader, N., Chrousos, G. P., & Kino, T. (2009). Circadian rhythm transcription factor CLOCK regulates the transcriptional activity of the glucocorticoid receptor by acetylating its hinge region lysine cluster: Potential physiological implications. *FASEB Journal*, *23*, 1572–1583.

Nagy, A. D., Iwamoto, A., Kawai, M., Goda, R., Matsuo, H., Otsuka, T., … Yasuo, S. (2015). Melatonin adjusts the expression pattern of clock genes in the suprachiasmatic nucleus and induces antidepressant-like effect in a mouse model of seasonal affective disorder. *Chronobiology International*, *32*, 447–457.

Naylor, E., Bergmann, B. M., Krauski, K., Zee, P. C., Takahashi, J. S., Vitaterna, M. H., & Turek, F. W. (2000). The circadian clock mutation alters sleep homeostasis in the mouse. *The Journal of Neuroscience*, *20*, 8138–8143.

Nicholas, B., Rudrasingham, V., Nash, S., Kirov, G., Owen, M. J., & Wimpory, D. C. (2007). Association of Per1 and Npas2 with autistic disorder: Support for the clock genes/social timing hypothesis. *Molecular Psychiatry*, *12*, 581–592.

Nievergelt, C. M., Kripke, D. F., Barrett, T. B., Burg, E., Remick, R. A., Sadovnick, A. D., … Kelsoe, J. R. (2006). Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *141B*, 234–241.

O'Keeffe, S. M., Thome, J., & Coogan, A. N. (2012). The noradrenaline reuptake inhibitor atomoxetine phase-shifts the circadian clock in mice. *Neuroscience*, *201*, 219–230.

Okamura, H., Yamaguchi, S., & Yagita, K. (2002). Molecular machinery of the circadian clock in mammals. *Cell and Tissue Research*, *309*, 47–56.

Otowa, T., Tochigi, M., Umekage, T., Ebisawa, T., Kasai, K., Kato, N., & Sasaki, T. (2011). No association between CLOCK gene 3111C/T polymorphism and personality traits in healthy Japanese subjects. *Psychiatry and Clinical Neurosciences*, *65*, 604.

Ozburn, A. R., Falcon, E., Mukherjee, S., Gillman, A., Arey, R., Spencer, S., & McClung, C. A. (2013). The role of clock in ethanol-related behaviors. *Neuropsychopharmacology*, *38*, 2393–2400.

Ozburn, A. R., Falcon, E., Twaddle, A., Nugent, A. L., Gillman, A. G., Spencer, S. M., … McClung, C. A. (2015). Direct regulation of diurnal Drd3 expression and cocaine reward by NPAS2. *Biological Psychiatry*, *77*, 425–433.

Ozburn, A. R., Larson, E. B., Self, D. W., & Mcclung, C. A. (2012). Cocaine self-administration behaviors in ClockΔ19 mice. *Psychopharmacology*, *223*, 169–177.

Ozburn, A. R., Purohit, K., Parekh, P. K., Kaplan, G. N., Falcon, E., Mukherjee, S., … McClung, C. A. (2016). Functional implications of the CLOCK 3111T/C single-nucleotide polymorphism. *Frontiers in Psychiatry*, *7*, 67.

Paik, J. W., Lee, H. J., Kang, S. G., Lim, S. W., Lee, M. S., & Kim, L. (2007). CLOCK gene 3111C/T polymorphism is not associated with seasonal variations in mood and behavior in Korean college students. *Psychiatry and Clinical Neurosciences*, *61*, 124–126.

Parekh, P. K., Ozburn, A. R., & Mcclung, C. A. (2015). Circadian clock genes: Effects on dopamine, reward and addiction. *Alcohol*, *49*, 341–349.

Pedrazzoli, M., Louzada, F. M., Pereira, D. S., Benedito-Silva, A. A., Lopez, A. R., Martynhak, B. J., … Tufik, S. (2007). Clock polymorphisms and circadian rhythms phenotypes in a sample of the Brazilian population. *Chronobiology International*, *24*, 1–8.

Pohl, J. B., Ghezzi, A., Lew, L. K., Robles, R. B., Cormack, L., & Atkinson, N. S. (2013). Circadian genes differentially affect tolerance to ethanol in drosophila. *Alcoholism, Clinical and Experimental Research*, *37*, 1862–1871.

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., … Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, *460*, 748–752.

Reick, M., Garcia, J. A., Dudley, C., & McKnight, S. L. (2001). NPAS2: An analog of clock operative in the mammalian forebrain. *Science*, *293*, 506–509.

Reppert, S. M., & Weaver, D. R. (2002). Coordination of circadian timing in mammals. *Nature*, *418*, 935–941.

Ripke, S., Sanders, A. R., Kendler, K. S., Levinson, D. F., Sklar, P., Holmans, P. A., … Gejman, P. V. (2011). Genome-wide association study identifies five new schizophrenia loci. *Nature Genetics*, *43*, 969–976.

Ripke, S., Wray, N. R., Lewis, C. M., Hamilton, S. P., Weissman, M. M., Breen, G., … Sullivan, P. F. (2013). A mega-analysis of genome-wide association studies for major depressive disorder. *Molecular Psychiatry*, *18*, 497–511.

Robilliard, D. L., Archer, S. N., Arendt, J., Lockley, S. W., Hack, L. M., English, J., … Von Schantz, M. (2002). The 3111 Clock gene polymorphism is not associated with sleep and circadian rhythmicity in phenotypically characterized human subjects. *Journal of Sleep Research*, *11*, 305–312.

Rosenwasser, A. M., Fecteau, M. E., Logan, R. W., Reed, J. D., Cotter, S. J. N., & Seggio, J. A. (2005). Circadian activity rhythms in selectively bred ethanol-preferring and nonpreferring rats. *Alcohol*, *36*, 69–81.

Roybal, K., Theobold, D., Graham, A., DiNieri, J. A., Russo, S. J., Krishnan, V., … McClung, C. A. (2007). Mania-like behavior induced by disruption of CLOCK. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 6406–6411.

Rudic, R. D., McNamara, P., Curtis, A.-M., Boston, R. C., Panda, S., Hogenesch, J. B., & Fitzgerald, G. A. (2004). BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. *PLoS Biology*, *2*, e377.

Rumble, M. E., White, K. H., & Benca, R. M. (2015). Sleep disturbances in mood disorders. *Psychiatric Clinics of North America*, *38*, 743–759.

Rybakowski, J. K., Dmitrzak-Weglarz, M., Dembinska-Krajewska, D., Hauser, J., Akiskal, K. K., & Akiskal, H. H. (2014). Polymorphism of circadian clock genes and temperamental dimensions of the TEMPS-A in bipolar disorder. *Journal of Affective Disorders*, *159*, 80–84.

Rybakowski, J. K., Dmitrzak-Weglarz, M., Kliwicki, S., & Hauser, J. (2014). Polymorphism of circadian clock genes and prophylactic lithium response. *Bipolar Disorders*, *16*, 151–158.

Sacco, R., Curatolo, P., Manzi, B., Militerni, R., Bravaccio, C., Frolli, A., … Persico, A. M. (2010). Principal pathogenetic components and biological endophenotypes in autism spectrum disorders. *Autism Research*, *3*, 237–252.

Saleem, Q., Anand, A., Jain, S., & Brahmachari, S. K. (2001). The polyglutamine motif is highly conserved at the Clock locus in various organisms and is not polymorphic in humans. *Human Genetics*, *109*, 136–142.

Sangal, R. B., Owens, J., Allen, A. J., Sutton, V., Schuh, K., & Kelsey, D. (2006). Effects of atomoxetine and methylphenidate on sleep in children with ADHD. *Sleep*, *29*, 1573–1585.

Saus, E., Soria, V., Escaramís, G., Vivarelli, F., Crespo, J. M., Kagerbauer, B., … Estivill, X. (2010). Genetic variants and abnormal processing of pre-miR-182, a circadian clock modulator, in major depression patients with late insomnia. *Human Molecular Genetics*, *19*, 4017–4025.

Savalli, G., Diao, W., Schulz, S., Todtova, K., & Pollak, D. D. (2015). Diurnal oscillation of amygdala clock gene expression and loss of synchrony in a mouse model of depression. *International Journal of Neuropsychopharmacology*, *18*, pyu095.

Schaufler, J., Ronovsky, M., Savalli, G., Cabatic, M., Sartori, S. B., Singewald, N., & Pollak, D. D. (2016). Fluoxetine normalizes disrupted light-induced entrainment, fragmented ultradian rhythms and altered hippocampal clock gene expression in an animal model of high trait anxiety- and depression-related behavior. *Annals of Medicine*, *48*, 17–27.

Schwartz, G., Amor, L. B., Grizenko, N., Lageix, P., Baron, C., Boivin, D. B., & Joober, R. (2004). Actigraphic monitoring during sleep of children with ADHD on methylphenidate and placebo. *Journal of the American Academy of Child & Adolescent Psychiatry*, *43*, 1276–1282.

Seggio, J. A., Fixaris, M. C., Reed, J. D., Logan, R. W., & Rosenwasser, A. M. (2009). Chronic ethanol intake alters circadian phase shifting and free-running period in mice. *Journal of Biological Rhythms*, *24*, 304–312.

Serretti, A., Benedetti, F., Mandelli, L., Lorenzi, C., Pirovano, A., Colombo, C., & Smeraldi, E. (2003). Genetic dissection of psychopathological symptoms: Insomnia in mood disorders and CLOCK gene polymorphism. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *121B*, 35–38.

Serretti, A., Cusin, C., Benedetti, F., Mandelli, L., Pirovano, A., Zanardi, R., … Smeraldi, E. (2005). Insomnia improvement during antidepressant treatment and CLOCK gene polymorphism. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *137B*, 36–39.

Serretti, A., Gaspar-Barba, E., Calati, R., Cruz-Fuentes, C. S., Gomez-Sanchez, A., Perez-Molina, A., & De Ronchi, D. (2010). 3111T/C CLOCK gene polymorphism is not associated with sleep disturbances in untreated depressed patients. *Chronobiology International*, *27*, 265–277.

Serretti, A., Zanardi, R., Franchini, L., Artioli, P., Dotoli, D., Pirovano, A., & Smeraldi, E. (2004). Pharmacogenetics of selective serotonin reuptake inhibitor response: A 6-month follow-up. *Pharmacogenetics*, 607–613.

Shi, J., Wittke-Thompson, J. K., Badner, J. A., Hattori, E., Potash, J. B., Willour, V. L., … Liu, C. (2008). Clock genes may influence bipolar disorder susceptibility and dysfunctional circadian rhythm. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147*, 1047–1055.

Shi, S., White, M. J., Borsetti, H. M., Pendergast, J. S., Hida, A., Ciarleglio, C. M., … Johnson, C. H. (2016). Molecular analyses of circadian gene variants reveal sex-dependent links between depression and clocks. *Translational Psychiatry*, *6*, e748.

Sidor, M. M., Spencer, S. M., Dzirasa, K., Parekh, P. K., Tye, K. M., Warden, M. R., … McClung, C. A. (2015). Daytime spikes in dopaminergic activity drive rapid mood-cycling in mice. *Molecular Psychiatry*, *5*, 1–14.

Sipilä, T., Kananen, L., Greco, D., Donner, J., Silander, K., Terwilliger, J. D., … Hovatta, I. (2010). An association analysis of circadian genes in anxiety disorders. *Biological Psychiatry*, *67*, 1163–1170.

Sjöholm, L. K., Kovanen, L., Saarikoski, S. T., Schalling, M., Lavebratt, C., & Partonen, T. (2010). CLOCK is suggested to associate with comorbid alcohol use and depressive disorders. *Journal of Circadian Rhythms*, *8*, 1.

Sklar, P., Ripke, S., Scott, L. J., Andreassen, O. A., Cichon, S., Craddock, N., … Purcell, S. M. (2011). Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nature Genetics*, *43*, 977–983.

Solismaa, A., Kampman, O., Seppälä, N., Viikki, M., Mäkelä, K.-M., Mononen, N., … Leinonen, E. (2014). Polymorphism in alpha 2A adrenergic receptor gene is associated with sialorrhea in schizophrenia patients on clozapine treatment. *Human Psychopharmacology Clinical and Experimental*, *29*, 336–341.

Spencer, S., Torres-Altoro, M. I., Falcon, E., Arey, R., Marvin, M., Goldberg, M., … McClung, C. A. (2012). A mutation in CLOCK leads to altered dopamine receptor function. *Journal of Neurochemistry*, *123*, 124–134.

Sudmant, P. H., Rausch, T., Gardner, E. J., Handsaker, R. E., Abyzov, A., Huddleston, J., … Korbel, J. O. (2015). An integrated map of structural variation in 2,504 human genomes. *Nature*, *526*, 75–81.

Suzuki, M., Dallaspezia, S., Locatelli, C., Lorenzi, C., Uchiyama, M., Colombo, C., & Benedetti, F. (2017). CLOCK gene variants associated with the discrepancy between subjective and objective severity in bipolar depression. *Journal of Affective Disorders*, *210*, 14–18.

Takao, T., Tachikawa, H., Kawanishi, Y., Mizukami, K., & Asada, T. (2007). CLOCK gene T3111C polymorphism is associated with Japanese schizophrenics: A preliminary study. *European Neuropsychopharmacology*, *17*, 273–276.

Toki, S., Morinobu, S., Imanaka, A., Yamamoto, S., Yamawaki, S., & Honma, K. I. (2007). Importance of early lighting conditions in maternal care by dam as well as anxiety and memory later in life of offspring. *The European Journal of Neuroscience*, *25*, 815–829.

Tsuchimine, S., Yasui-Furukori, N., Kaneda, A., & Kaneko, S. (2013). The CLOCK C3111T polymorphism is associated with reward dependence in healthy Japanese subjects. *Neuropsychobiology*, *67*, 1–5.

Turek, F. W., Joshu, C., Kohsaka, A., Lin, E., Ivanova, G., McDearmon, E., … Bass, J. (2005). Obesity and metabolic syndrome in circadian clock mutant mice. *Science (80-.)*, *308*, 1043–1045.

Uz, T., Ahmed, R., Akhisaroglu, M., Kurtuncu, M., Imbesi, M., Dirim Arslan, A., & Manev, H. (2005). Effect of fluoxetine and cocaine on the expression of clock genes in the mouse hippocampus and striatum. *Neuroscience*, *134*, 1309–1316.

Valladares, M., Obregón, A. M., & Chaput, J.-P. (2015). Association between genetic variants of the clock gene and obesity and sleep duration. *Journal of Physiology and Biochemistry*, *71*, 855–860.

van Enkhuizen, J., Minassian, A., & Young, J. W. (2013). Further evidence for Clock Δ19 mice as a model for bipolar disorder mania using cross-species tests of exploration and sensorimotor gating. *Behavioural Brain Research*, *249*, 44–54.

Vitaterna, M. H., King, D. P., Chang, A. M., Kornhauser, J. M., Lowrey, P. L., McDonald, J. D., … Takahashi, J. S. (1994). Mutagenesis and mapping of a mouse gene, Clock, essential for circadian behavior. *Science (80-.)*, *264*, 719–725.

Vitaterna, M. H., Ko, C. H., Chang, A.-M., Buhr, E. D., Fruechte, E. M., Schook, A., … Takahashi, J. S. (2006). The mouse Clock mutation reduces circadian pacemaker amplitude and enhances efficacy of resetting stimuli and phase-response curve amplitude. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 9327–9332.

von Gall, C., Noton, E., Lee, C., & Weaver, D. R. (2003). Light does not degrade the constitutively expressed BMAL1 protein in the mouse suprachiasmatic nucleus. *The European Journal of Neuroscience*, *18*, 125–133.

Wasielewski, J. A., & Holloway, F. A. (2001). Alcohol's interactions with circadian rhythms. A focus on body temperature. *Alcohol Research Health*, *25*, 94–100.

Witt, S. H., Sommer, W. H., Hansson, A. C., Sticht, C., Rietschel, M., & Witt, C. C. (2013). Comparison of gene expression profiles in the blood, hippocampus and prefrontal cortex of rats. *Silico Pharmacology*, *1*, 15.

Xu, X., Breen, G., Chen, C.-K., Huang, Y.-S., Wu, Y.-Y., & Asherson, P. (2010). Association study between a polymorphism at the 3′-untranslated region of CLOCK gene and attention deficit hyperactivity disorder. *Behavioral and Brain Functions*, *6*, 48.

Yang, B.-Z., Han, S., Kranzler, H. R., Farrer, L. A., Elston, R. C., & Gelernter, J. (2012). Autosomal linkage scan for loci predisposing to comorbid dependence on multiple substances. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *0*, 361–369.

Yang, Z., Matsumoto, A., Nakayama, K., Jimbo, E. F., Kojima, K., Nagata, K., … Yamagata, T. (2016). Circadian-relevant genes are highly polymorphic in autism spectrum disorder patients. *Brain and Development*, *38*, 91–99.

Zhang, J., Liao, G., Liu, C., Sun, L., Liu, Y., Wang, Y., … Wang, Z. (2011). The association of CLOCK gene T3111C polymorphism and hPER3 gene 54-nucleotide repeat polymorphism with Chinese Han people schizophrenics. *Molecular Biology Reports*, *38*, 349–354.

Zhang, R., Lahens, N. F., Ballance, H. I., Hughes, M. E., & Hogenesch, J. B. (2014). A circadian gene expression atlas in mammals: Implications for biology and medicine. *Proceedings of the National Academy of Sciences of the United States of America*, *111*, 16219–16224.

Zhou, Y. D., Barnard, M., Tian, H., Li, X., Ring, H. Z., Francke, U., … McKnight, S. L. (1997). Molecular characterization of two mammalian bHLH-PAS domain proteins selectively expressed in the central nervous system. *Proceedings of the National Academy of Sciences of the United States of America*, *94*, 713–718.

Zhu, Y., Stevens, R. G., Hoffman, A. E., Tjonneland, A., Vogel, U. B., Zheng, T., & Hansen, J. (2011). Epigenetic impact of long-term shiftwork: Pilot evidence from circadian genes and whole-genome methylation analysis. *Chronobiology International*, *28*, 852–861.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Schuch JB, Genro JP, Bastos CR, Ghisleni G, Tovo-Rodrigues L. The role of *CLOCK* gene in psychiatric disorders: Evidence from human and animal research. *Am J Med Genet Part B*. 2017;1–18. https://doi.org/10.1002/ajmg.b.32599