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Major depressive disorder: A loss of circadian synchrony?

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Abstract

Circadian rhythms in the sleep/wake cycle, along with a range of physiological measures, are severely disrupted in individuals with major depressive disorder (MDD). Moreover, several central circadian genes have been implicated as potential genetic factors underlying the illness through candidate gene studies and some genome wide association studies. However, investigations into the molecular underpinnings of circadian disturbances in the human brain have been quite challenging. In their recent publication, Li and colleagues have used a novel approach to determine the rhythmic patterns of circadian gene expression in several regions of the human brain, and how these patterns are disrupted in MDD. Their findings demonstrate that in healthy subjects, several brain regions outside the suprachiasmatic nucleus (the master clock) exhibit diurnal gene expression patterns that are disrupted in the brains of MDD subjects. These findings will provide the foundation for future studies of gene-specific drug targets, and biomarkers for the disease.

Keywords

circadian rhythms; depression; post-mortem

Introduction

Major depressive disorder (MDD) is characterized by lengthy episodes of either depressed mood or anhedonia, along with a subset of symptoms including altered emotional, cognitive, and physiological states. Many of these symptoms involve aspects of circadian disruption (i.e. disruptions in endogenous biological rhythms). For instance, several symptoms of MDD are associated with circadian disruptions, including changes in the sleep/wake cycle [1], altered rhythms in body temperature [1], diurnal variations in mood symptom severity [2], and variations in cyclic hormones and neuro-transmitter levels [3, 4]. Furthermore, exposure to shiftwork increases the risk of developing MDD [5], and seasonal affective disorder (SAD), a subtype of MDD, is triggered by the later dawn and shorter light phase during the winter months [6, 7]. Treatments modulating the circadian cycle such as bright light therapy [8] and sleep deprivation [9] have proven to be effective in modulating mood. In addition,

most antidepressant medications alter circadian rhythms. Similar to bright light therapy, the selective serotonin reuptake inhibitor (SSRI) fluoxetine induces a phase advance in rhythms in slice culture [10], and a newly developed antidepressant, agomelatine, a melatonin receptor agonist, phase advances circadian rhythms in several physiological measures in healthy human subjects [11, 12]. Thus, increasing evidence points towards circadian abnormalities as a pathophysiological component of MDD. Understanding the precise circadian dysfunction in MDD may contribute to the development of successful treatments.

In the brain, the suprachiasmatic nucleus (SCN) of the hypothalamus is the master pacemaker, which receives light input directly from retinal ganglion cells. The SCN, in turn, coordinates rhythms throughout the brain and body [13]. Recent evidence indicates that several extra-SCN brain regions can oscillate in a circadian manner similar to the SCN, although rhythms are slightly dampened [14, 15]. Circadian rhythms in the SCN and other brain regions are generated and maintained by a cycle of gene expression in individual cells [16]. In mammals, the circadian locomotor output cycles kaput (CLOCK) protein and brain and muscle Arnt-like protein-1 (BMAL1) are central transcriptional activators of other circadian genes including the period (*Per1*, *Per2*, *Per3*) and cryptochrome (*Cry1*, *Cry2*) genes [13]. The PER and CRY proteins then inhibit their own expression by blocking CLOCK and BMAL1. While these four proteins form the central molecular loop, there are several other proteins that function as regulators either positively or negatively modulating the levels and function of the cellular circadian machinery. The heritability of MDD is approximately 37%, thus genetic factors certainly play a role in the onset of MDD [17]. An analysis of a broad circadian gene network across multiple psychiatric disorders (bipolar disorder, MDD, schizophrenia, and ADHD) in 14 GWAS studies revealed that variation within circadian genes as a collective group is higher in patients with MDD compared with controls [18]. More targeted approaches found that single nucleotide polymorphisms (SNPs) in the *Cry1* and *NPAS2* genes were associated with MDD [19], and SNPs in the *Timeless* gene were associated with depression with fatigue [20] (reviewed in [21]). While several polymorphisms in the *Clock* gene are associated with bipolar disorder, there is little evidence to indicate these polymorphisms are relevant to MDD [22]. However, the *Clock* genotype may predict therapeutic response and remission of MDD subjects [23].

While it is well established that MDD is associated with circadian rhythm disruptions and there is genetic evidence for the involvement of circadian genes in MDD, few studies have attempted to measure circadian gene expression in the brains of patients with MDD. This is due to difficulties associated with studying rhythmic gene expression in human post-mortem tissue, and includes uncertainties about time of death (TOD), length of post-mortem interval, and problems of small sample size. A limited number of human post-mortem studies have successfully approached this issue. Wu et al. [24] found that several circadian genes are rhythmically expressed in the human pineal gland. However another study was unable to replicate these findings [25]. In a recent study, Cermakian et al. [26] found cyclic circadian gene expression in the cingulate cortex and bed nucleus of the stria terminalis (BNST), and these patterns were disrupted in patients with Alzheimer's disease. Their large sample size allowed them to fit a harmonic regression model to the data points based on subjects TOD across the 24-hour day. The recent paper by Li et al. [27] used a similar technique to

examine circadian gene expression using microarray analysis in six depression-associated regions of the human post-mortem brain in control and MDD subjects. Their results provide an important foundation to begin examining the role of specific circadian genes in the pathophysiology of MDD.

Circadian gene expression in the brains of healthy controls

Because of the challenges associated with circadian analysis of human post-mortem tissue (described above), Li et al. first validated their methodology in healthy controls by demonstrating (i) that the most robust cyclic genes across the six brain regions were known circadian genes, (ii) that there is a strong between-region consistency of rhythmic patterns, and (iii) that there is a 30% overlap of extra-SCN rhythmic genes in mice. The authors selected high quality tissue from a large cohort of MDD and control subjects for whom a precise TOD was known. They selected six depression-associated brain regions including dorsolateral prefrontal cortex (DLPFC), amygdala (AMY), cerebellum (CB), nucleus accumbens (NAc), anterior cingulate cortex (AnCg), and hippocampus (HC) and ran each sample on a microarray. Data from the samples were ordered by TOD and treated as a pseudo-time series spanning one cycle (the 24-hour day) and the percentage of variance explained (PVE) was used as a goodness of fit index. Cyclic genes were determined by assessing the observed PVE with a PVE from TOD randomized datasets for each gene. Several hundred genes were determined to be cyclic in each brain region, exemplifying the robust nature of these data – a difficult feat considering an independent subjects design is highly prone to noise, and there is no way to know the physiological state of the individual at the TOD.

The analysis revealed significant expression patterns of multiple core circadian genes (e.g. *Per1*, *Per2*, *Per3*) in the DLPFC, validating their methodology (Fig. 1). Closer examination of the 922 cyclic genes in the DLPFC revealed a TOD-specific pattern of gene expression, which could serve as a basis of prediction for samples of unknown TOD (see below). In addition, the phase relationship of the three period genes (*Per1*, *Per2*, and *Per3*) was staggered in all brain regions examined: *Per1* peaked in the morning, *Per3* peaked at midday, and *Per2* peaked in the afternoon. While this relationship was known in the SCN of rodents [28], it has only now been demonstrated in other brain regions. Thus, the organization of data in the pseudo-time series allowed the detection of subtle shifts of the period genes, which may have otherwise gone unnoticed.

To examine patterns across the assessed brain regions, the authors used Fisher's metaanalysis to combine *p* values of top cyclic genes across regions. This analysis revealed *p* values smaller than those under a uniform distribution indicating strong between-region consistency of cyclic gene patterns. Furthermore, the phase and amplitude of top cyclic genes was found to be consistent across all six regions, suggesting high synchronization of circadian oscillations across brain regions in healthy subjects.

To assess whether there were expression pattern differences between chronotype, peak times were compared between the cyclic genes found in human brain and the cyclic genes reported in the nocturnal mouse prefrontal cortex [29]. Results revealed a linear relationship, but with

a phase shift of about 6.5 hours, emphasizing that extra-SCN gene oscillations are indicative of a behavioral chronotype. This finding could provide a means of characterizing chronotype in post-mortem individuals as subjects with an “evening” chronotype have higher rates of depression [30].

Disruptions in circadian gene expression are characteristic of major depressive disorder

Given the strong findings in healthy controls, the authors performed comparative analyses of a cohort of MDD subjects. Of the top 16 cyclic genes across all brain regions in control subjects, only two were significantly rhythmic in more than one brain region in MDD subjects (Fig. 1), and the amplitude of these genes was significantly decreased across all six brain regions in MDD subjects (Fig. 2C). Furthermore, combined *p* values across regions in MDD subjects were not different from uniform distribution, indicating a general desynchrony of cyclic patterns between regions, in contrast to controls.

To examine whether the altered cyclic patterns in the MDD cohort is due to disrupted rhythmicity of circadian genes or a time shift of rhythms, Li et al. [27] examined sample to sample correlations of gene expression levels between subjects with similar TOD. They found strong positive correlations in controls with similar TOD and strong negative correlations in those with opposing TOD. In MDD subjects, this pattern was weak, indicating a disruption between biological rhythms and the day/night cycle (i.e. a phase shift; Fig. 2A).

The authors then applied their TOD prediction matrix to a novel set of 60 subjects (both control and MDD). They found that predicted TOD for controls was more accurate than for MDD subjects, providing further support for a desynchronization between biological rhythms and the day/night cycle. Next, they examined correlations between in-phase genes (predicted to be positive) and out-of-phase genes (predicted to be negative). The predicted relationship held true for controls, but was clearly altered in MDD subjects indicating a disruption of cyclic gene relationships (Fig. 2B). Overall, the data suggest that MDD subjects have both a time shift of rhythms and disrupted regulation of cyclic genes.

Importantly the authors controlled for other variables that could cause disruptions, e.g. use of antidepressant drugs, drugs of abuse, and suicide. They also selected a group of “clean” MDD subjects, all of whom had committed suicide, had no history of antidepressant treatment, had negative toxicology screens, and had TOD during the day. The predicted TOD versus the actual TOD (i.e. TOD deviation) in this group was much larger (similar to their previous analysis) than the deviation in the control group, indicating that these circadian disruptions are due to the disease process rather than extraneous factors.

Circadian regulation of gene expression

Li and colleagues have used a relatively novel approach to characterize circadian gene expression patterns in the human brain and demonstrate how they are disrupted in MDD. While core circadian genes are often the focus, several recent transcriptome wide studies

demonstrated that hundreds to thousands of transcripts have cyclic patterns in various tissue types and across several mammalian species [29, 31, 32]; this indicates a need to understand how disease is associated with overall patterns in circadian gene expression. Here, the authors found several hundred transcripts that showed cyclic patterns in healthy subjects in each brain region they assessed, a novel finding in extra-SCN brain regions in human tissue. The large number of cyclic genes outside the SCN indicates strong circadian influence over genetic programming. Indeed, a recent study in mouse liver revealed that circadian modulation of RNA polymerase II (RNAPII) recruitment and initiation – along with circadian control of chromatin remodeling – occur on a genome wide scale to control transcription [33]. Thus, the mechanisms underlying circadian regulation of gene expression are quite complex; furthermore, they are pervasive throughout the genome, and possess extensive regulation extending to brain regions beyond the SCN. Future studies should examine brain region specific differences in the regulation of gene expression, particularly in MDD (see later).

In MDD subjects, circadian gene expression was disrupted in a pattern indicating that MDD subjects have an abnormal phasing of circadian gene expression, or a desynchronization between biological rhythms and day/night cycle, similar to that experienced during jet lag. While this is not a new concept [34, 35], the authors elegantly demonstrate that this desynchronization in MDD could be due to gene expression disruption in extra-SCN brain regions. Understanding the exact nature of this desynchronization in MDD subjects could be a first step in personalizing treatment to resynchronize the internal and external rhythms. In addition, it appears that subjects with MDD have abnormal phase relationships between single circadian genes in the same brain region. Critically, gene pairs that were disrupted in one brain region were not necessarily disrupted in other brain regions. The dysfunction of these specific relationships could provide clues to the precise region specific disruptions in MDD and should be a focus of future studies.

Determining brain-region specific circadian dysfunction in MDD

While the SCN is able to maintain oscillations in vitro when dissociated from other brain regions [36, 37], when other brain regions are isolated in vitro, their rhythms are quickly dampened after a few days [14, 38, 39]. Thus, it is hypothesized that the SCN serves as the master circadian pacemaker for the brain and body, coordinating rhythms in other brain regions and tissues, which then serve specific functional outputs [14, 40, 41]. Disturbances in these “subordinate” oscillators could have potent downstream effects related to the function of the region disrupted. Furthermore, features of the cellular network of the SCN make it more resistant to external disturbances [42]. For instance, in *Cry1* knockout mice, the SCN maintains rhythmicity, while all other tissues are arrhythmic [43]. Thus, it is likely that while the SCN is more resistant to genetic and environmental insults, circadian components of other brain regions are vulnerable [44]. Further studies will be important to determine which regions are vulnerable to circadian disruptions in MDD and other psychiatric disorders. A variety of tools is currently available to unravel these molecular pathways, including bioluminescent circadian reporters in both human and mouse tissues [45, 46], DREADD (designer receptors activated exclusively by designer drugs) technology [47], and novel mutant mice [48].

Conclusions and outlook

In their recent publication, Li and colleagues have shown brain region specific circadian gene expression in healthy subjects. Their findings further demonstrate that MDD subjects have both a disruption of synchrony between internal biological rhythms and external day/night rhythms, and disrupted phase relationships between individual circadian genes. The implicated genes could be candidates for the genetic disturbances underlying MDD, or could be potential biomarkers or targets for future treatments. This study also provides an extensive overview of region-specific cyclic genes. Determining which brain regions underlie circadian dysfunction in MDD will be a crucial step toward deciphering the precise mechanisms that are disrupted in MDD and their downstream consequences.

Abbreviations

MDD	major depressive disorder
SCN	suprachiasmatic nucleus
TOD	time of death

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	Control						MDD					
	DLPFC	Acg	Hip	AMY	Nac	CB	DLPFC	Acg	Hip	AMY	Nac	CB
ARNTL												
PER2												
PER3												
NR1D1												
DBP												
SFPQ												
ITIH5												
LDLR												
PER1												
INSIG1												
SLC39A14												
NFIL3												
SNTB2												
PDZRN3												
BHLHE40												
BHLHE41												

Figure 1.

The top 16 rhythmic genes in healthy controls are disrupted in MDD subjects. Genes with significant rhythms are highlighted in red ($p < 0.05$). Genes in bold were identified as rhythmic in extra-SCN tissues in the mouse [31]. DLPFC, dorsolateral prefrontal cortex; Acg, anterior cingulate cortex; HIP, Hippocampus; AMY, amygdala; Nac, nucleus accumbens; CB, cerebellum.

Figure 2.

Circadian synchrony is disrupted in major depressive disorder. Compared with controls, MDD subjects display a phase shift (**A**), disrupted synchronization of genes within a single brain region (**B**), and lower amplitude of circadian genes (**C**).