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Computational omics approaches to investigate the potential causal role of sleep and circadian rhythm disturbances in depression

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Abstract

Hickie et al. (2023) pose the question "Are sleep and circadian rhythm disturbances (SCRD) the cause or simply the consequence of depression or other mood disorder sub-types?" and suggest strategies to better understand the role of SCRD in depression. Here, we contribute to the discussion by highlighting state-of-the-art computational omics methods (and the data sets needed to use these methods) which have potential for improving our understanding of the role of circadian biology in mood disorders.

Introduction

It is well recognized that it is difficult to disentangle sleep dysfunction from disruption of circadian rhythms. For example, a recent review of experimental approaches designed to demonstrate independent sleep and circadian rhythm mechanisms concludes that the conceptual framework of independent mechanisms is simplistic and that the joint role of sleep and circadian rhythms serves homeostasis of essential physiological variables (Franken & Dijk, 2024). This conclusion is supported by a recent analysis of gene expression data (Jan et al. 2024). However, the knowledge that sleep disruption has a negative impact on depression through disrupting circadian physiology still leaves open the question of whether circadian disruption could be a causal driver of depression, or particular depressive subtypes, in some people. In addition, circadian phase can vary among individuals, which can lead to behavioral differences known as chronotypes that can also influence depression and mental health (Jones et al. 2019). Traditionally, circadian phase is measured by the gold standard tool Dim Light Melatonin Onset, which is defined as the start of melatonin production in the evening during dim light conditions. However, very frequent collection of blood samples over several hours can be inconvenient for participants, is labor and cost-intensive and hence leads to studies of small sample size. Moreover, such studies may be unethical for those with major depression.

Circadian rhythms are genetically governed by "clock genes," which regulate rhythmic changes throughout the whole body (Piggins, 2002). In mammals, the core clock genes are expressed in all cells and circadian oscillations have been identified in different tissue and cell types (Takahashi, 2017; Zhang et al. 2014). The primary transcriptional–translational negative feedback loop (TTFL) involves the *CLOCK* and *BMAL1* (also named *ARNTL*) genes. Their products function as a heterodimeric transcriptional activator that binds to regulatory elements containing E-box motifs of other clock genes such as *PER* (Period) and *CRY* (Cryptochrome). These proteins then translocate into the nucleus and repress their own transcription by interacting with the CLOCK-BMAL1 heterodimer. With the decline of the protein level of PER and CRY, the repression is relieved and a new rhythmic cycle starts (Takahashi, 2017). The TTFL results in thousands of clock-controlled genes showing a circadian pattern in expression level (Takahashi, 2017; Zhang et al. 2014). At the organismal level, the circadian system functions as a hierarchical network with the "central clock" located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which synchronizes clocks present in peripheral tissues. The tissue- or cell-specific internal clock can be shifted from the central clock but coordinates with it (Menet & Hardin, 2014; Yeung & Naef, 2018). Hence, clock-controlled genes show rhythmic patterns of expression in many tissues, but the times of maximum and minimum expression can vary between tissues (Zhang et al. 2014; Talamanca et al. 2023; Mure et al. 2018).

Experimental studies have demonstrated that some genes have robust circadian patterns at cellular and tissue levels (Zhang et al. 2014; Panda et al. 2002; Ruben et al. 2018; Noya et al. 2019; Weger et al. 2021) regardless of disruption to sleep, while the expression of other rhythmic genes can be disrupted when sleep desynchrony regimes are enforced. Specifically, in a study of insufficient sleep (26 participants studied in both unrestricted and restricted sleep conditions), the number of genes with a rhythmic expression profile after 7 nights of only 5 hours of sleep was

reduced from 1,855 (8.6%) to 1,481 (6.9%) (Möller-Levet et al. 2013). In a forced multi-day desynchrony study, 22 volunteers were scheduled to a 28-hour sleep–wake schedule with associated fasting–feeding and dark–dim light cycles (Archer et al. 2014). The study showed that delaying sleep by 4 hours for 3 consecutive days led to a six-fold reduction of rhythmic transcripts in the human blood transcriptome (from 6.4% to just 1%), whereas the centrally driven circadian rhythm of melatonin was unaffected. The genes (N = 39 transcripts) that remained rhythmic after sleep desynchrony are interpreted as those associated with signals from the SCN, and represent cellular, metabolic, and homeostatic blood-specific processes. In contrast, the transcripts driven by sleep alone (N = 234) or by both circadian rhythmicity and the sleep–wake cycle (N = 286) were linked with the regulation of transcription and translation which, in turn, provide powerful reinforcement of rhythmicity in peripheral tissue. In a 90-day constant bed rest protocol (20 male participants, 2 weeks baseline, 60-day bed rest, 2 weeks recovery) 91% of the transcriptome was shown to have changed compared to the baseline state with 76% of the transcriptome still affected after 10 days of recovery, with most impacted transcripts associated with mRNA translation and immune function (Archer et al. 2024). Together these results imply that decoupling of the sleep-wake cycle from circadian rhythmicity (as occurs in jetlag, shift work and likely mood disorders) results in a profound disruption of the temporal organization at the level of the transcriptome.

While the SCN is the central "pacemaker," the hypothalamus-pituitary-adrenal (HPA) axis plays a key role in controlling circadian dynamics in peripheral tissues (Li et al. 2024). The HPA regulates many other physiological processes (e.g., immune response, cell cycle, energy metabolism) including the cortisol and the stress response (Belvederi Murri et al. 2014). The extent to which peripheral and central rhythmicity are decoupled in SCRD-associated depression is unclear. Analysis of time-of-death gene expression data of 6 brain regions from major depressive disorder (MDD) (N = 34) patients and controls (N = 55) reported that gene expression rhythmicity was attenuated in MDD patients in terms of peak timing (Li et al. 2013). Emerging computational approaches applied to omics data that allow estimation of the internal body clock regardless of sample collection time are logistically attractive and could facilitate collection of larger clinical cohorts to study circadian changes under different conditions. Hence, we now review novel computational methods applied to omics data that have clear potential for advancing mechanistic understanding in circadian-associated mood disorders.

Characterizing internal circadian time using omics data and computational tools

Many computational tools have been developed to infer circadian phase from gene expression data (microarray/bulk RNA-seq). These methods provide circadian pattern metrics (i.e., period, amplitude, and phase) quantified using statistical approaches. Period refers to the time between peaks in expression (tau), amplitude is the difference between the highest and the lowest point over a cycle (sometimes divided by 2), and phase shift refers to a horizontal shift in the peaks of expression from a reference while maintaining the same period difference between peaks. Since many genes show rhythmic patterns (but with peaks at different times), rhythmic parameters can be inferred through their joint analysis. Generating predictors that can be applied to single timepoint data is an active area of research trained on data sets that have longitudinal sampling within individuals (not possible for many tissues in human), or on large cross-sectional data sets where tissue from different individuals is sampled across the 24-hour period. Data training methods are classified as supervised or unsupervised.

Supervised learning methods (e.g., molecular time-table (Ueda et al. 2004), ZeitZeiger (Hughey et al. 2016), BIO_CLOCK (Agostinelli et al. 2016)) use ground-truth data sets with known time of sampling to generate prediction models tested in other independent ground-truth data sets and then applied in data sets where sampling time was unknown. These methods identify a core set of "time-indicating genes," (e.g., 13 genes in ZeitZeiger) and train statistical models on the expression of these core genes. A limitation of supervised learning methods is the need for ground-truth samples since few data sets have samples documented with a collection "timestamp." Unsupervised machine learning methods (e.g., CYCLOPS (Anafi et al. 2017), CHIRAL (Talamanca et al. 2023)) use underlying modeling and joint analysis across multiple genes to infer circadian phase i.e., since many genes are rhythmic in their expression in a coordinated manner, the expression levels of many genes infer circadian phase more accurately than can be inferred from expression of a single gene. For example, CHIRAL uses a new mathematical method to infer circadian time applied to the Genotype-Tissue Expression (GTEx) data, which allows a comprehensive analysis of rhythmic patterns on the whole organism (since GTEx data comprise gene expression data from multiple organs from the same post-mortem donors). Briefly, the algorithm first assigns tissue internal phase (TIP) for each sample in each tissue type with a selected set of seed genes. Donor internal phase is estimated from TIPs, which assumed that each TIP is determined by the donor and the tissue. With this approach, differences across donors and tissues can be captured. Technological advances that allow generation of large data sets that can be interrogated for circadian phase, have been accompanied by an explosion in computational methods (Table 1). With adequate variation in sampling times across individuals, methods such as CYCLOPS and CHIRAL can achieve a high accuracy with a mean absolute error between 1~2 h (Talamanca et al. 2023). When new methods are presented, comparisons with standard methods are provided (and show improvements in accuracy of assignments in ground-truth data sets or computational efficiency), but independent systematic comparisons of methods across multiple data sets are now needed. Hughes et al. (2017) provide "Guidelines for genome-scale analysis of biological rhythms" and a web-based application (CircaInSilico) to generate ground-truth synthetic genome biology data to facilitate benchmarking of methods.

Both supervised and unsupervised methods need samples collected across the 24-hour period, with better prediction accuracy achieved if each time point has more samples. While such time series sample collections are achieved in sleep laboratory studies or in post-mortem (i.e., across samples the full 24-hour period is represented), samples collected in clinics or volunteer studies are likely to represent only a fraction of the 24-hour period. A new method, has been developed to predict circadian time from bulk RNA-seq without needing to collect samples in a complete time series.

Beyond using bulk tissue gene expression data to study circadian biology, chronobiology at the single-cell level will give much deeper insights into potential differences in circadian pattern

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Table 1. Computational methods to assign circadian rhythm parameters to samples based on omics data

Name	S/U[a]	Data type	Notes
Oscope (Leng et al. 2015)	U	scRNA-seq	Developed for cell-cycle detection and adapted for circadian rhythmicity
ZeitZeiger (Hughey et al. 2016)	S	microarray or bulk RNA-seq	Learns a sparse representation of the variation associated with the periodic variable in the training observations, then uses maximum likelihood to make a prediction for a test observation.
BIO_CLOCK (Agostinelli et al. 2016)	S	microarray or bulk RNA-seq	Developed alongside BIO_CYCLE for cell-cycle stage detection
CYCLOPS (Anafi et al. 2017)	U	microarray	Cyclic ordering by periodic structure.
reCAT (Liu et al. 2017)	U	scRNA-seq	Recover cell cycle along time. Can be used to analyze almost any kind of unsynchronized scRNA-seq data set to obtain a high-resolution cell-cycle time series
Tempo (Auerbach et al. 2022)	U	scRNA-seq data	Estimate circadian phase using single-cell RNA data
PLSR (Woelders et al. 2023)	S	metabolomics	Partial least squares regression. Estimates dim light melatonin onset (DLMO). Needs 2 - 3 blood samples per person.
CHIRAL (Talamanca et al. 2023)	U	bulk RNA-seq	Circular Hierarchical Reconstruction Algorithm. Developed and applied an unsupervised learning method to GTEx data to uncover tissue-specific rhythmic genes. More accurate than CYCLOPS.
CIRCUST (Larriba et al. 2023)	U	bulk RNA-seq	CIRCular-robUST. Based on circular statistics
TimeTeller (Vlachou et al. 2024)	S	bulk RNA-seq	Aims to estimate circadian clock function from a single transcriptome by modeling the multi-dimensional state of the clock. Can globally compare clocks across individuals, tissues and conditions.
COFE (Ananthasubramaniam & Venkataramanan, 2024)	U	bulk RNA-seq	Cyclic Ordering with Feature Extraction. Data-driven approach to simultaneously reconstruct the time ordering of data and identify the list of rhythmic features that contribute to the reordering.
tauFisher (Duan et al. 2024)	S	bulk RNA-seq and scRNA-seq	tauFisher claims to improve on previous methods in several ways: (1) training data does not need to be a complete time series; (2) the within-sample normalization step leads to an accurate prediction from just one sample; (3) computationally efficient; (4) predictors can be applied to data generated on any platform (5) can be applied to single-cell RNA sequencing (scRNA-seq) data, and used to investigate circadian phase heterogeneity in different cell types.

[a]Supervised (uses ground-truth data to train the model)/Unsupervised.

across different cell types. Many computational tools have been developed to infer cell-cycle state, which is a periodic biological process (Leng et al. 2015; Liu et al. 2017; Riba et al. 2022). However, circadian rhythms and the cell cycle are independent processes. Characterizing circadian rhythm using single-cell data has been rarely documented but is likely to be an area of active research as more and more single-cell gene expression data sets are generated. One published method has used scRNA-seq data applying an unsupervised Bayesian algorithm developed to estimate circadian phase with a prior knowledge of core clock genes to initialize the model (Auerbach et al. 2022). The model uses the posterior distribution of cell circadian phase to identify new rhythmic genes. This offers an opportunity to identify cell-type specific circadian patterns and ultimately cell therapies for chronobiological disorders. Disruption of circadian clocks in tumor vs non-tumor tissue in adenocarcinomas has already been demonstrated (Ananthasubramaniam & Venkataramanan 2024).

Although gene expression data are currently the most abundant, computational methods have been developed or adapted for applications to proteomic (Weger et al. 2021; Specht et al. 2023) and metabolomics (Minami et al. 2009) data. Understanding circadian rhythms in genes, proteins and metabolites targeted directly or indirectly by drugs underpins the emerging field of chronopharmacology (Li et al. 2024).

Potential for application of computational methods to infer sleep and circadian disruption in depression

Methods to infer circadian phase from a single routinely collected blood sample (the easiest tissue to access) measured for gene expression offer the possibility of cost-effective investigation of circadian parameters in people with severe mental illness compared to those without. These scalable technologies will allow generation of large data sets which are needed to draw robust conclusions. To take advantage of these new methods, key data sets need to be generated. First, post-mortem brain samples are needed to demonstrate circadian disruption in a cell type relevant to depression (e.g., excitatory neurons, inhibitory neurons, astrocytes). Second, matched post-mortem blood and brain samples are needed to demonstrate that circadian disruption is detectable in blood. If these two steps were to be established, then it would pave the way to identification of disruption of circadian functions in a subset of living patients. Investigations could be conducted longitudinally within a person comparing mental ill health episodes to periods of euthymia and good health. Since a meta-analysis of randomized clinical trials (Scott et al. 2021) has shown that improved sleep quality leads to better mental health, quantification of the changes in circadian rhythm before and after sleep improvement using omics data could provide a direct test of the causal role of circadian disruption separated from sleep

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disruption. Over the next 5-10 years we expect to see a rapid growth both in statistical and computational methods and of data sets. This emerging area of research could help provide the evidence base to address the question posed by Hickie et al. (2024).

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