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Research report

Altered expression of circadian rhythm genes among individuals with a history of depression

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ABSTRACT

Background: Depression has been associated with several circadian rhythm perturbations, suggesting a disruption of the circadian clock system in affective disorders. The interaction of several circadian clock genes generates these daily circadian rhythms.
Methods: This cross-sectional study evaluated whether circadian gene expression differed between individuals with a history of depression and participants without a similar history. The participants were 60 healthy older adults. Half of the participants had a history of depression. Real-time quantitative polymerase chain reaction was used to measure the circadian gene *Clock*, *BMAL1*, *Period1*, and *Period2* messenger RNA levels in peripheral blood leukocytes.
Results: Individuals with a history of depression had higher *Clock*, *Period1*, and *Bmal1* mRNA levels, compared to non-depressed participants.
Limitations: Although circadian gene expression fluctuates throughout the day, clock gene mRNA levels were evaluated only in the morning.
Conclusions: These results suggest that disruptions of the molecular mechanisms underlying the circadian clock system may be associated with depression.

1. Introduction

Depression has been associated with several circadian rhythm perturbations (Wirz-Justice, 2006). Insomnia and a shorter REM stage latency after sleep onset are frequently observed among depressed patients (Kupfer and Foster, 1972; Riemann et al., 2001). Depression has also been related to greater nocturnal elevation in body temperature (Rausch et al., 2003). Moreover, depressed patients display an earlier morning cortisol spike and have higher overall cortisol output than non-depressed patients (Yehuda et al., 1996). Furthermore, some studies have reported lower blood concentrations of melatonin, and delayed melatonin release in depressed patients, compared to controls (Parry and Newton, 2001). Collectively, these results suggest a disruption of the circadian clock system related to major depression (Monteleone and Maj, 2008).

The suprachiasmatic nucleus (SCN) of the hypothalamus is the internal clock entraining several physiological systems to a

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cycle of about 24 h (Hastings, 1997). The interaction of several circadian clock genes is thought to be responsible for the circadian fluctuation in protein expression (Zheng and Sehgal, 2008). These circadian genes have been found not only in the SCN, but also in several central and peripheral tissues such as extra-SCN brain regions, eye, heart, kidney, lung, liver, skeletal muscle, oral mucosa, and peripheral blood leukocytes (PBLs), indicating the presence of peripheral circadian oscillators throughout the body (Buijs and Kalsbeek, 2001).

Altered circadian gene expression may represent a vulnerability factor associated with increased risk for depression (Mendlewicz, 2009; Turek, 2007). The generation of circadian rhythms is instantiated by the transcriptional and translational feedback loops of several clock genes (Shearman et al., 2000). Perturbations in one or several of these genes may disrupt the circadian fluctuation in mRNA and protein expression and possibly also increase risk for depression (Turek, 2007; Zheng and Sehgal, 2008).

Clock gene polymorphisms have been associated with increased risk of recurrence of bipolar depression (Benedetti et al., 2003), but this result has not been replicated in all studies (Desan et al., 2000; Johansson et al., 2003). However, several other circadian gene polymorphisms have been related to risk for affective illness. Furthermore, the interaction of several clock gene polymorphisms may be necessary to disrupt circadian gene function (Kripke et al., 2009; Lavebratt et al., 2009). Indeed, the interaction of 3 clock gene polymorphisms predicted bipolar affective disorder (Shi et al., 2008). The current study therefore evaluated differences in four circadian gene mRNAs expressed in PBLs of individuals with and without a history of depression.

2. Methods

2.1. Participants

Participants were part of a larger study of caregiving stress and health. The 60 participants were recruited via notices placed in community and university newspapers, senior citizen centers, the Alzheimer's Disease Association, and from neurologists' referrals. Caregivers ($n=25$) were providing at least 5 h of care per week for a family member with a progressive dementia. Noncaregiving controls ($n=35$) were demographically similar to caregivers but without caregiving responsibilities. Subjects with immunologically-related health problems (e.g. cancer or recent surgeries), or those taking medications with broad immunological consequences, were excluded from the study. From the larger sample, participants were included in the present study if they had their blood drawn between 9 and 11 AM, were between the ages of 45 and 85, had a history of depression, or were demographically similar to a participant with a history of depression. Participants were studied between September 2007 and February 2008. The Ohio State University Biomedical Research Review Committee approved the project; all subjects gave written informed consent prior to participation.

2.2. Measures

Diagnostic Interview for Genetic Studies (DIGS (Nurnberger et al., 1994)). This semi-structured interview provided data on both current and lifetime history of affective disorders using DSM-IV criteria. Participants were classified as having had a history of depression if they had a past or current diagnosis of major depressive disorder, dysthymia, or major depressive disorder not otherwise specified. Interviews were administered by well-trained graduate psychology or nursing students who were supervised by a clinical psychologist with extensive experience with structured interviews.

The Center for Epidemiological Studies Depression Scale (CES-D) assessed the severity of depressive symptoms (Basco et al., 1997; Radloff, 1977). Studies have shown acceptable test–retest reliability and excellent construct validity (Basco et al., 1997). Widely used, the CES-D has distinguished depressed from non-depressed participants in community and clinical samples (Basco et al., 1997).

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), a self-rated questionnaire, provided data on sleep quality and disturbances over a one-month interval. The PSQI has good diagnostic sensitivity and specificity in distinguishing poor and good sleepers (Buysse et al., 1989).

Health-related data were collected to assess the possibility that relationships between depression and circadian gene expression might reflect the contribution of other variables. Health questions from the Older Adults Resources Survey (OARS) (Fillenbaum and Smyer, 1981) assessed underlying diseases. Assessment of health-related behaviors included body mass index (BMI), smoking status, medication use, and alcohol intake (Kiecolt-Glaser and Glaser, 1988). Two questions assessed exercise (Washburn et al., 1987).

2.3. Determination of mRNA levels

All blood samples were drawn between 9 AM and 11 AM to control for diurnal variation in circadian gene expression. Peripheral blood leukocytes were isolated from heparinized blood samples using an accuspin (Sigma) and Histopaque-1077 (Sigma) separation solution. RNA was isolated from human PBLs using Trizol Reagent (Invitrogen). RNA concentration was determined in a nanodrop spectrophotometer. Complementary DNA was produced by reverse transcription using Superscript III Reverse Transcriptase (Invitrogen) and random hexamers. The messenger RNA (mRNA) levels of 4 circadian genes were determined by real-time quantitative polymerase chain reaction using the Power Sybr Green method (Applied Biosystems). The primer pairs were: CCAGAGGCCCCTAACTCCTC/TGGTCTGCCATTGGATGATCT for *brain and muscle Arnt-like protein 1* (*Bmal1*), CAGTGCTCCTGTTCC-TGCA TC/CCCGCCAACTGCAGAATCT for *Period1*, ACTGC-CAAAATCTTACTCTGC/AGCAAGGCTCAACAAATCATC for *Period2*, TTGGCAAAATGTCATGAGCAC/TTGCCCCTTAGTCAGGAACCT, and for *Clock*. The results for the circadian genes were normalized against the housekeeping gene, G3PDH, Glyceraldehyde 3 Phosphate Dehydrogenase.

2.4. Statistical analysis

Analysis of variance and chi-square tests assessed group differences in age, sex, caregiving status, health, and self-reported depressive symptoms and sleep disturbances. Circadian gene variables had non-normal, highly skewed distributions that were not normalized even after data transformation.

Spearman's Rho correlations evaluated the relationships among the four circadian genes and depressive symptoms and mood disturbances. Given the non-normal distributions of the gene variables, the nonparametric Mann–Whitney *U* test was used to examine group differences in circadian gene expression among individuals with and without a history of depression. A logistic regression model evaluated whether circadian gene expression was associated with history of depression over and above differences in sex, age, caregiving status, and health and assessed the unique contribution of each circadian gene. Logistic regression models were fitted with the circadian gene mRNA levels as predictors and history of depression as a dependent variable. Statistical significance was evaluated using 2-sided tests at the .05 level of significance.

3. Results

3.1. Sociodemographic and clinical characteristics of study participants

Participants' mean age was 71.02 (SD = 10.11). The sample was comprised of 46 women and 14 men. Fifty-four participants were Caucasian and 6 were African-American. About one-third of the sample had a high school education and 68.3% of the participants were college graduate. Twenty-five participants were caring for a relative with dementia.

Thirty participants had a lifetime history of depression, and 30 were never clinically depressed. Among the 30 participants with a history of depression, 16 had a diagnosis of a single major depressive episode, 13 had recurrent major depressive episodes, and 1 had a diagnosis of depressive disorder not otherwise specified. Among the 30 participants with a history of depression, 4 were currently clinically depressed. No participant had dysthymia, bipolar disorder, or seasonal affective disorder. Individuals with a history of depression did not significantly differ from participants without a history of depression on age, $F(1,59) = .01$, $p = .91$, sex, $\chi^2\ (1) = 1.49$, $p = .22$, and caregiving status, $\chi^2\ (1) = 1.71$, $p = .19$.

3.2. History of depression and circadian gene mRNA expression

The Mann–Whitney *U* test revealed that there was a significant difference between individuals with and without a history of depression in circadian gene mRNA expression. Individuals with a history of depression had greater *Clock* ($U = 320.00$, $z = -1.92$, $p = .05$), *Period 1* ($U = 292.50$, $z = -2.33$, $p = .02$), and *Bmal1* ($U = 308.00$, $z = -2.1$, $p = .04$). However, *Period2* ($U = 419.00$, $z = -.46$, $p = .65$) mRNA expression did not significantly differ between individuals with and without a history of depression. Figs. 1–3 depict the relationships between *Clock*, *Period1*, and *Bmal1* mRNA expression and history of depression.

When the four circadian gene variables were entered simultaneously in a logistic regression model, only the *Clock* mRNA level was an independent predictor of history of depression, $z = 3.77$, $p = .05$, while *Period1*, $z = .71$, $p = .41$, *Period2*, $z = .06$, $p = .80$, and *Bmal1*, $z = 1.48$, $p = .23$ did not uniquely predict history of depression. The association between *Clock* mRNA levels and history of depression persisted even after adjusting for differences in age, sex and caregiving status.

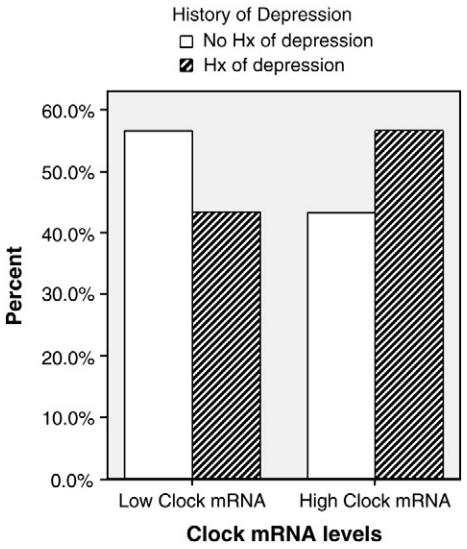

Fig. 1. The graph depicts the proportion of individuals having high- and low-Clock mRNA expression as a function of their history of depression status. For illustration purposes, the Clock mRNA expression variable was dichotomized using a median split.

3.3. History of depression, current depression and insomnia symptoms, and circadian gene expression

Adjusting for caregiving status, individuals with a history of depression did not have greater current depressive symptomatology than participants without such history, $F\ (3,57) = .25$, $p = .62$. However, individuals with a history of depression reported greater sleep disturbances, compared to participants without a history of affective illness, $F\ (3,57) = 7.44$, $p = .008$. No significant Spearman's rho correlations were found between

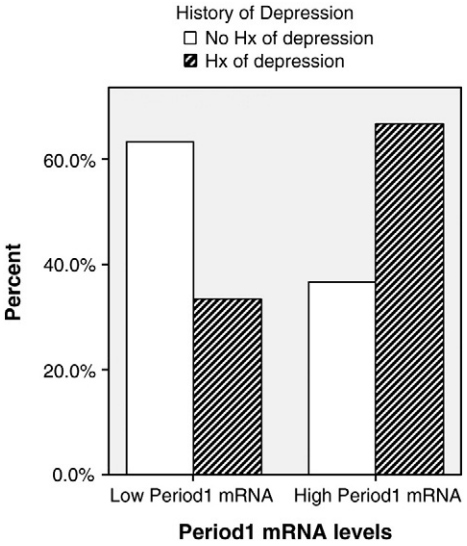

Fig. 2. The graph depicts the proportion of individuals having high- and low-Period1 mRNA expression as a function of their history of depression status. For illustration purposes, the Period 1 mRNA expression variable was dichotomized using a median split.

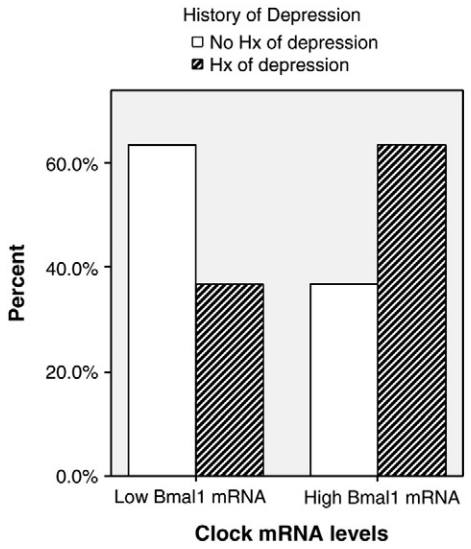

Fig. 3. The graph depicts the proportion of individuals having high- and low-Bmal1 mRNA expression as a function of their history of depression status. For illustration purposes, the Bmal1 mRNA expression variable was dichotomized using a median split.

circadian gene expression and depressive and insomnia symptoms, all *ps*>.12.

3.4. Potentially confounding health variables

Differences in health and health behaviors between participants with and without a history of depression were evaluated as potential confounding variables. When body mass index, alcohol and tobacco use, smoking status, amount of exercise in the past week, and number of self-reported medical conditions were added to the logistic regression model, Clock mRNA expression was still an independent predictor of history of depression, $z=3.91$, $p=.05$.

The most common medications taken by participants were statins ($N=24$), non-steroidal anti-inflammatory drugs ($N=23$), diuretics ($N=14$), angiotensin II receptor antagonists ($N=17$), beta-blockers ($N=17$), antidepressants ($N=13$), thyroid supplements ($N=13$), calcium-channel blockers ($N=13$), and sedative/anti-anxiety medications ($N=6$). Individuals with a history of depression were more likely to use non-steroidal anti-inflammatory drugs, $\chi^2=5.71$, $p=.02$, compared to participants without a history of affective illness. Furthermore, antidepressant medication has been associated with altered circadian gene expression in animal models (Uz et al., 2005; Ogden et al., 2004). When antidepressant, anti-anxiety, and non-steroidal anti-inflammatory drugs were entered in the model, *Clock* mRNA expression remained an independent predictor of history of depression, $z=3.89$, $p=.05$.

4. Discussion

Individuals with a history of depression displayed a different pattern of circadian gene expression than individuals without a history of unipolar affective disorder. Specifically, the presence of a history of depression was associated with higher *Clock*, *Bmal1*, and *Period1* mRNA expression. When the circadian gene variables were analyzed as a set, only *Clock* mRNA levels independently predicted history of depression.

This over-expression of circadian genes mRNA may represent a biomarker of vulnerability to unipolar affective disorder. The current findings parallel the data showing that Clock gene polymorphism was related to the number of lifetime episodes of depression (Benedetti et al., 2003). However, other human genetics studies have failed to establish an association between Clock gene polymorphisms and depression (Desan et al., 2000; Johansson et al., 2003). Several studies have reported associations between different circadian clock gene polymorphisms and mood disorders (Lavebratt et al., 2009; Soria et al.). However no specific clock genes have been reliably related to depression (Kripke et al., 2009). The lack of consistent findings may be due to the fact that the circadian clock system comprises several genes forming redundant transcriptional and translational feedback loops (Zheng and Sehgal, 2008). Therefore, the redundant processes inherent to this system might mitigate the effect of one polymorphism on circadian gene function. Furthermore, the intercellular coupling of circadian oscillatory may compensate for the impact of one component of the circadian clock gene system (Benca et al., 2009). Indeed, several polymorphisms might be necessary to actually disrupt the functioning of the circadian clock genes system (Shi et al., 2008). In the current study, we assessed disruption of the circadian clock system at another levels of analysis, namely mRNA expression. The fact that we found an over-expression of both positive and negative regulators of the circadian clock system at the mRNA levels reinforces the idea of a link between disruptions of the molecular circadian oscillators and depression.

Several authors have proposed that disorganization of the circadian clock system at the molecular level may be directly related to affective disturbances (Bunney and Potkin, 2008; Bunney and Bunney, 2000; McClung, 2007; Mendlewicz, 2009; Monteleone and Maj, 2008; Turek, 2007). Moreover, altered circadian gene expression may also indirectly influence vulnerability to depression by impacting the occurrence of depression risk factors such as sleep disturbances (Jackson et al., 2003; Turek, 2007). For example, the C variant of the clock gene polymorphism has been associated with insomnia symptoms in individuals with recurrent major depression (Benedetti et al., 2003; Serretti et al., 2005). In accord with this theory, individuals with a history of depression reported more sleep disturbances than non-depressed controls. However, sleep disturbances per se were not associated with circadian gene expression. Alternatively, some theorists have suggested that depression may induce sensitization processes and epigenetic changes that lead to long term alterations in gene expression (Anisman et al., 2008).

One of the limitations of this study is that circadian genes' mRNA expression was assessed in PBLs. It is unclear whether peripheral expression of circadian genes reflects the functioning of the master clock, the SCN of the hypothalamus. There is some evidence that mood disturbances affect the functioning of the central circadian clock system. Chronic administration of fluoxetine impacted *Clock*, *Bmal1*, and *Npas2* mRNA expression in the mouse hippocampus (Uz et al., 2005). Furthermore, the mood stabilizer, valproate, decreased the expression of *CK1δ* and *Cry2* in the amygdala (Ogden et al., 2004). The efficacy of

these drugs in the treatment of affective disorders suggests a possible central disorganization of the circadian clock system among patients with mood disorders. Our results raise the possibility that this disorganization of circadian oscillators extends to peripheral tissues as well.

The potential clinical implications of the present findings are the possibility of identifying individuals at risk of developing depression based on the functioning of their circadian clock gene system. These individuals may be particularly responsive to chronobiological treatments of depression such as sleep deprivation, light therapy, interpersonal and social rhythm therapy or agomelatine treatment, a melatonergic antidepressant drug. Furthermore, the treatment of insomnia symptoms among depressed patients is associated with improved depression outcomes (Manber et al., 2008). Targeting disturbances of circadian rhythms may then be especially important among individuals presenting altered circadian gene expression.

The present sample included only individuals with a history of unipolar depression. Replication with individuals diagnosed with bipolar disorder and seasonal affective disorder is warranted, given that these two disorders have been associated with dysregulation of the circadian gene system (McClung, 2007). Moreover, circadian gene expression fluctuates throughout the day. In the current study, circadian gene expression was evaluated in the morning between 9 and 11 AM. It would be of interest to compare circadian gene expression between individuals with and without a history of depression during a 24-hour period in a controlled environment in which exposure to light and social zeitgebers will be systematically regulated.

In summary, this study suggests that individuals with a history of depression had altered expression of circadian genes in PBLs, compared to participants without a history of affective illness. This suggests a disruption of peripheral circadian oscillators among depression-prone individuals. Prospective, longitudinal studies are needed to explore whether individuals presenting altered circadian gene expression are at increased risk for mood disorders or whether persistent sleep disturbances lead to disruption of the circadian clock gene function and increased risk for depression.

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Conflict of interest

Dr. Beversdorf reported speaking for Novartis, Eisai, and Pfizer within the past year on topics unrelated to the content of this manuscript. None of the other authors reported biomedical financial interests or potential conflicts of interest.

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