Journal of Affective Disorders 210 (2017) 14–18

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

CLOCK gene variants associated with the discrepancy between subjective and objective severity in bipolar depression

Masahiro Suzuki[a,b,*], Sara Dallaspezia[a], Clara Locatelli[a], Cristina Lorenzi[a], Makoto Uchiyama[b], Cristina Colombo[a], Francesco Benedetti[a]

[a] Department of Clinical Neurosciences, Scientific Institute and University Vita-Salute San Raffaele, Milan, Italy
[b] Department of Psychiatry, Nihon University School of Medicine, Tokyo, Japan

ARTICLE INFO

Keywords:
Depression
Bipolar disorder
CLOCK
Clinical rating scales
Cognitive distortion

ABSTRACT

Background: The discrepancy between subjective and objective severity of depressive syndromes has been proposed as a predictor of treatment outcome and suicidal risk in depression, and is associated with depressive cognitive distortions. A recent study reported that evening-type depressed patients showed higher depressive cognitions than morning-type patients. Therefore, it can be hypothesized that genetic factors affecting evening preference, such as carrying of the *CLOCK* rs1801260*C allele, may influence the discrepancy.

Method: We tested this hypothesis in 132 patients affected by a major depressive episode in the course of bipolar disorder. The severity of depression was evaluated using self-rated (Beck Depression Inventory: BDI) and observer-rated (Hamilton Depression Rating Scale: HDRS) measures. The BDI-HDRS discrepancy score was calculated and the effects of the rs1801260 polymorphism on this score and on depressive cognitive distortions, as measured on the Cognitions Questionnaire, were examined.

Results: The rs1801260*C carriers showed higher BDI-HDRS discrepancy scores than T/T homozygotes. Mediation analysis using bootstrapping procedures revealed that the dimension of depressive cognition "hopelessness" fully mediates the association between the rs1801260 polymorphism and the BDI-HDRS discrepancy.

Limitations: Many gene polymorphisms other than *CLOCK* rs1801260 may also influence the BDI-HDRS discrepancy and depressive cognitive distortions.

Conclusion: Our current results suggest that factors affecting the biological clock can influence the "non-clock" psychopathological features of mood disorders.

1. Introduction

The Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), an observer-rated scale, and the Beck Depression Inventory (BDI) (Beck et al., 1961), a self-report inventory, are the most commonly used rating scales to measure depression severity and treatment response. Both scales have good reliability and validity (Rush et al., 2008), but discrepant scores on these two scales are often observed (Moller and von Zerssen, 1995; Richter et al., 1998), with many patients under- or over-reporting depressive symptoms on self-ratings relative to observer-ratings. Patients who overrate their depression severity in comparison with the clinicians' ratings exhibit poor response to antidepressant treatments, including pharmacotherapy (Dunlop et al., 2011; Rane et al., 2010) and chronotherapeutics (Suzuki et al., 2016). Furthermore, a discrepancy between subjective and objective severity is associated with vulnerability to suicide in patients with mild depression (Tsujii et al., 2014). From these findings, a discrepancy between the BDI and HDRS results (BDI-HDRS discrepancy) can be proposed as a viable predictor of treatment outcome and suicidal risk for daily clinical practice.

To date, a number of demographic and clinical factors have been reported to be associated with a discrepancy between the subjective and objective severity of depression. Younger age and higher educational attainment are predictive of higher self-ratings of depression relative to observer-ratings (Enns et al., 2000). Patients who over-report the severity of their depression show personality traits of low extraversion (Enns et al., 2000; Schneibel et al., 2012), low agreeableness (Corruble et al., 1999; Enns et al., 2000), low openness to experience (Duberstein and Heisel, 2007), low self-esteem (Domken et al., 1994) and high neuroticism (Enns et al., 2000; Paykel and Prusoff, 1973; Schneibel et al., 2012). In addition, we recently reported that the BDI-HDRS discrepancy is associated with worse antidepres-

* Corresponding author at: Department of Psychiatry, Nihon University School of Medicine, 30-1 Oyaguchi-Kamicho, Itabashi-ku, Tokyo 173-8610, Japan.
E-mail address: suzuki.masahiro94@nihon-u.ac.jp (M. Suzuki).

http://dx.doi.org/10.1016/j.jad.2016.12.007
Received 15 July 2016; Received in revised form 21 October 2016; Accepted 13 December 2016
Available online 13 December 2016
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sant response and cognitive distortions (Suzuki et al., 2016), including systematic errors in the perception and processing of information (Beck, 2011). In regard to biological factors, a near-infrared spectroscopy study reported that lower prefrontal cortex activation during a verbal fluency task was associated with the BDI-HDRS discrepancy (Akashi et al., 2015). However, the effect of genetic factors on this discrepancy has not been previously studied.

A single nucleotide polymorphism (SNP) in the 3'-flanking region of the *CLOCK* gene (3111 T/C; rs1801260) has been suggested to influence sleep and activity in healthy humans. Studies reported that the rs1801260*C allele associated with evening preference (Katzenberg et al., 1998; Mishima et al., 2005), although negative findings were also reported (Pedrazzoli et al., 2007; Robilliard et al., 2002). In depressed patients with bipolar disorder, compared with T/T homozygotes, carriers of the rs1801260*C allele showed higher activity levels in the evening, delayed sleep onset (mean, 79 min later) and a reduced amount of sleep during the night (mean, 75 min less) (Benedetti et al., 2007b). Furthermore, the rs1801260*C allele was associated with a higher rate of recurrence of bipolar disorder (Benedetti et al., 2003; Serretti et al., 2003). The functional implications of rs1801260 have been confirmed by transfecting a mammalian cell line (mouse embryonic fibroblasts isolated from Clock−/− knockout mice) with pcDNA plasmids containing the human *CLOCK* gene with either the T or C SNP at position 3111; the *CLOCK* 3111*C variant resulted in higher *CLOCK* mRNA levels than the *CLOCK* 3111*T variant, consequently also modifying the expression of other circadian genes of the molecular machinery of the biological clock (Ozburn et al., 2016).

Recently, Muller et al. (Muller et al., 2016) investigated the relationship between diurnal preference and symptom patterns in clinically depressed individuals; they found an association between a tendency of “eveningness” and higher cognitive depressive symptoms (e.g., pessimism, guilt, suicidal thoughts and worthlessness). It is thought that the item content of the BDI and the HDRS differ considerably, with the BDI weighing depressive cognitions and the HDRS weighing somatic/vegetative symptoms (Bagby et al., 2004; Uher et al., 2008). Therefore, it can be hypothesized that genetic factors affecting evening preference, such as carrying of the rs1801260*C allele, may influence the BDI-HDRS discrepancy. Here, we tested this hypothesis in a homogenous sample of patients affected by a major depressive episode in the course of bipolar disorder. Based on our previous finding that the BDI-HDRS discrepancy was related to cognitive distortion (Suzuki et al., 2016), we also studied whether depressive cognitive distortions mediate the association between the rs1801260 polymorphism and the BDI-HDRS discrepancy.

2. Methods

2.1. Patients

We studied 132 inpatients who were consecutively admitted to the mood disorder unit of San Raffaele Hospital in Milano and who met the criteria for a major depressive episode without psychotic features in the course of bipolar disorder type I (DSM-IV criteria, SCID-I interview) (First et al., 1995). Patients were recruited between December 2006 and May 2015. All patients were Caucasian of Italian descent. The inclusion criterion was a HDRS score (Hamilton, 1960) of ≥18 at baseline. The exclusion criteria were other axis I diagnoses, mental retardation in axis II diagnoses, pregnancy, history of epilepsy, major medical or neurologic disorders, treatment with long-acting neuroleptic drugs in the last 3 months before admission and history of drug or alcohol dependency or abuse within the last 6 months. After a complete description of the study was given to the subjects, their written informed consent for participation was obtained. This study was approved by the local ethical committee (ASL Citta’ di Milano).

2.2. Data collection

Severity of depression was rated with the 21-item version of the HDRS and the 13-item version of the BDI. HDRS was rated by doctors in charge. The BDI-HDRS discrepancy score was calculated by the following formula: (BDI total score on day 0) /(39, maximum score of the BDI) ×100 - (HDRS total score on day 0) /(63, maximum score of the HDRS) ×100 (Suzuki et al., 2016). Using this formula, subjective severity and objective severity are equally weighted and each severity is shown on a scale of 100. Hence, the range of scores for the BDI-HDRS discrepancy is −100 to 100.

The depressive cognitive distortion was rated using the Cognitions Questionnaire (CQ) (Fennell and Campbell, 1984). The CQ is a 40-item self-rating scale that assesses specific dimensions of negative thinking in relation to a number of hypothetical events. The questionnaire comprises five dimensions, which are applied to the consequences of hypothetical situations: emotional impact, causal attribution, generalization across time, generalization across situations and perceived uncontrollability. It also gives a total score of cognitive distortion and enables the identification of specific cognitive distortions in response to positive, negative and neutral events. The score for each dimension ranges from 0 to 16 and the total CQ score ranges from 0 to 80, with a higher score indicating a higher cognitive distortion.

Genotyping of *CLOCK* rs1801260 was performed by personnel blind to clinical data. Genomic DNA was extracted from leucocytes by NaCl precipitation. Polymerase chain reaction (PCR) was performed with the following primers: 5’-TCC AGC AGT TTC ATG AGA TGC-3’ and 5’-GAG GTC ATT TCA TAG CTG AGC-3’. The PCR reaction was carried out in a 10-mcl volume containing 150 ng of genomic DNA, 1 mcM of each primer, 200 mnM of each dNTP, 1× PCR Gold Buffer (Perkin Elmer, Milano, Italy), 0.025 U/mcl of AmpliTaq Gold Polymerase (Perkin Elmer) and 1.5 mM $MgCl_2$. DNA was heated at 95 °C for 5 min, then five cycles were performed with the following steps: 95 °C for 30 s, 58 °C for 30 s and 72 °C for 1 min. This profile was followed by another 30 cycles of 95 °C for 30 s, 57 °C for 30 s and 72 °C for 10 min. The reaction ended with an extension step at 72 °C for 10 min. Amplified fragments were analyzed using denaturing gradient gel electrophoresis through a 30–60% denaturant gradient in a 7% acrylamide gel run at 60 °C and 150 V overnight.

2.3. Statistics

Since previous studies showed that subjects with C/C had similar characteristics to those with T/C (Benedetti et al., 2007a, 2007b; Katzenberg et al., 1998; Serretti et al., 2003, 2005), carriers of the C allele (*C) were pooled together in view of the low numbers of C/C homozygotes. Demographic and clinical variables in rs1801260*C carriers and T/T homozygotes were compared using a *t*-test for continuous variables and a chi-square test for categorical variables.

The dimensions of depressive cognitive distortions, which showed a significant association with the rs1801260 polymorphism, were then tested to determine whether they mediate the relationship between the rs1801260 polymorphism and the BDI-HDRS discrepancy. To test mediation, we first confirmed that the models met the criteria for mediation using a regression analysis (Baron and Kenny, 1986): (1) the independent variable is significantly related to the dependent variable; (2) the independent variable is significantly related to the proposed mediator; and (3) the proposed mediator is significantly related to the dependent variable when controlling for the effects of the independent variable. Subsequently, we evaluated the mediational effects using the bootstrap method (Preacher and Hayes, 2008). The bootstrap percentile confidence interval was defined using the values that marked the upper and lower 2.5% of the bootstrap distribution based on 10,000 replications. Statistical significance was set at $p < 0.05$. All analyses were conducted using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), and for the mediation analyses, the PROCESS macro was

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