Journal of Psychiatric Research 47 (2013) 252–258

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Brain-derived neurotrophic factor val66met genotype and early life stress effects upon bipolar course

Shefali Miller [a,b,*], Joachim Hallmayer [a], Po W. Wang [a], Shelley J. Hill [a], Sheri L. Johnson [c], Terence A. Ketter [a]

[a] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, USA
[b] Sierra Pacific Mental Illness Research Education and Clinical Centers, Palo Alto VA Health Care System, Palo Alto, CA, USA
[c] Department of Psychology, University of California-Berkeley, Berkeley, CA, USA

ARTICLE INFO

Article history:
Received 28 June 2012
Received in revised form
12 October 2012
Accepted 24 October 2012

Keywords:
Bipolar disorder
Brain-derived neurotrophic factor
Childhood abuse
Early life stress
Illness course
Gene-environment interaction

ABSTRACT

Background: Gene–environment interactions may contribute to bipolar disorder (BD) clinical course variability. We examined effects of brain-derived neurotrophic factor (BDNF) val66met genotype and early life stress (ELS) upon illness severity and chronicity in adult BD patients.
Methods: 80 patients (43 BD I, 33 BD II, 4 BD not otherwise specified, mean ± SD age 46.4 ± 14.0 years, 63.7% female) receiving open evidence-based and measurement-based care in the Stanford Bipolar Disorders Clinic for at least 12 months underwent BDNF val66met genotyping and completed the Childhood Trauma Questionnaire. BDNF met allele carrier genotype and history of childhood sexual and physical abuse were evaluated in relation to mean prior-year Clinical Global Impressions-Bipolar Version-Overall Severity of Illness (MPY-CGI-BP-OS) score and clinical and demographic characteristics.
Results: BDNF met allele carriers (but not non-met allele carriers) with compared to without childhood sexual abuse had 21% higher MPY-CGI-BP-OS scores (3.5 ± 0.7 versus 2.9 ± 0.7, respectively, $t = -2.4$, df = 28, $p = 0.025$) and 35% earlier BD onset age (14.6 ± 5.7 versus 22.8 ± 7.9 years, respectively, $t = 3.0$, df = 27, $p = 0.006$). Regression analysis, however, was non-significant for a BDNF-childhood sexual abuse interaction.
Limitations: small sample of predominantly female Caucasian insured outpatients taking complex medication regimens; only one gene polymorphism considered.
Conclusions: Between group comparisons suggested BDNF met allele carrier genotype might amplify negative effects of ELS upon BD illness severity/chronicity, although with regression analysis, there was not a significant gene-environment interaction. Further studies with larger samples are warranted to assess whether BDNF met allele carriers with ELS are at risk for more severe/chronic BD illness course.
Published by Elsevier Ltd.

1. Introduction

Bipolar disorder (BD) is a serious psychiatric illness affecting up to 4% of the population, characterized by recurrent debilitating episodes of depression and mood elevation (Merikangas et al., 2007). BD illness severity varies widely across affected individuals, ranging from relatively milder (fewer lifetime mood episodes with longer periods of interepisode affective and functional recovery) to more severe (more chronic course with more frequent severe episodes and at most brief partial interepisode improvement) (Suppes et al., 2000). Early identification of individuals prone to chronic severe illness trajectories may permit earlier more robust interventions (such as, perhaps, second-generation antipsychotics) for such individuals to minimize the longer-term neurobiological and functional sequelae of recurrent mood episodes (Post, 1992).

Unfortunately, to date, tools for predicting outcome in BD patients have been limited (Treuer and Tohen, 2010), highlighting the need for further research to identify biomarkers and integrate them with clinical indicators to predict illness severity and chronicity. Both biological (e.g. genes) and environmental (e.g. early life stress, ELS) factors may contribute to bipolar illness severity and chronicity. For instance, familial clustering of aspects of bipolar illness course (e.g. age at onset, episode frequency, and suicidality) suggests a heritable component to more severe and chronic course (Craddock and Sklar, 2009). Similarly, ELS (i.e. childhood physical

* Corresponding author. 401 Quarry Road, Stanford, CA 94305-5723, USA. Tel.: +1 650 725 8203; fax: +1 650 724 9900.
E-mail addresses: shefalis@stanford.edu, shefalimiller1@gmail.com (S. Miller).

0022-3956/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jpsychires.2012.10.015

and sexual abuse) has been associated with earlier BD onset age, higher cycling frequency, suicidality (Garno et al., 2005; Leverich et al., 2002), and greater prospective percent time ill (Leverich et al., 2002).

While both genes and environment thus appear to influence the course of BD, emerging evidence suggests that they act synergistically, with specific genetic factors rendering individuals more or less vulnerable to environmental stress (Caspi et al., 2010). To date, however, effects of gene-environment (G × E) interactions on BD outcomes have been relatively unexplored. Elucidating such interaction effects could facilitate early identification of individuals most at risk for severe, chronic bipolar illness course, and who are thus important candidates for earlier and more robust interventions to reduce episode recurrence and enhance functioning and quality of life.

A genetic factor of particular interest with respect to mood disorders is the functional polymorphism in the brain-derived neurotrophic factor (BDNF) gene, BDNF val66met, involving a valine-to-methionine substitution at the 66th codon. BDNF is a nerve growth factor important for neuronal survival (Ghosh et al., 1994), with evidence supporting its involvement in hippocampal long-term potentiation (Lu and Chow, 1999). In vitro expression of the BDNF met allele in hippocampal neurons results in impaired activity-dependent secretion of BDNF (Egan et al., 2003). In humans, BDNF met allele carrier genotype has been associated with hippocampal-dependent memory impairments (Egan et al., 2003; Hariri et al., 2003) and decreased hippocampal volumes (Bueller et al., 2006; Pezawas et al., 2004).

Despite its demonstrated associations with impaired neuronal development and functioning, BDNF met allele carrier genotype alone has not been clearly associated with increased risk of mood symptoms or syndromal mood disorders (Groves, 2007; Post, 2007); however, emerging data do support G × E interaction effects such that BDNF met allele carriers, when exposed to ELS, may experience greater affective disturbance. Specifically, a G × E interaction between BDNF met allele carrier genotype and ELS has been associated with violent suicide attempts (Perroud et al., 2008; Pregelj et al., 2011) and predisposes individuals in non-clinical samples to depressive symptomatology (Aguilera et al., 2009; Gatt et al., 2009; Juhasz et al., 2011; Wichers et al., 2008) and biomarkers associated with mood disorders, such as increased salivary cortisol and abnormal hippocampal, amygdala, and prefrontal cortex volumes (Casey et al., 2009; Gatt et al., 2009; Gerritsen et al., 2012).

We therefore conducted a pilot study examining whether the impact of childhood sexual or physical abuse on bipolar illness course is moderated by BDNF val66met genotype, such that BDNF met allele carriers compared to non-met allele carriers are more vulnerable to the negative affective sequelae of ELS.

2. Methods

2.1. Patients

This study was approved by the Stanford University Administrative Panel on Human Subjects, and patients provided verbal and written informed consent prior to participation. 80 outpatients 18 years of age and older, meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) criteria for bipolar I disorder (BD I), bipolar II disorder (BD II), or bipolar disorder not otherwise specified (BD NOS), who had been followed in the clinic for at least 12 months were recruited from the Stanford Bipolar Disorders Clinic. Patients were excluded if they had a current primary Axis I disorder other than BD, or met DSM-IV-TR criteria for current manic or mixed episodes, or had current psychotic symptoms (delusions or hallucinations), as such clinical states could impair ability to complete study assessments.

2.2. Diagnostic and clinical assessments

Bipolar Disorders Clinic patients were initially assessed with the Systematic Treatment Enhancement for Bipolar Disorders (STEP-BD) Affective Disorders Evaluation (ADE) (Sachs et al., 2003) and monitored longitudinally for at least 12 months with the STEP-BD Clinical Monitoring Form (CMF) (Sachs et al., 2002). The ADE and CMF contain modified versions of the Structured Clinical Interview for DSM-IV Diagnosis (SCID) (First et al., 1997) mood disorders module. BD diagnoses ascertained by a Bipolar Disorders Clinic psychiatrist-administered ADE were confirmed by a Bipolar Disorders Clinic research coordinator-administered Mini-International Neuropsychiatric Interview-Plus (MINI-PLUS) (Sheehan et al., 1998). Administration of the ADE also entailed assessment of demographic information and clinical characteristics such as lifetime psychiatric comorbidities and history of psychosis, psychiatric hospitalization, or rapid cycling. For each clinic visit, a Clinical Global Impressions Bipolar Version-Overall Severity of Illness (CGI-BP-OS) (Spearing et al., 1997) score was determined based on the number and severity of depressive and/or mood elevation symptoms, in a standardized fashion. The CGI-BP-OS is an integrative measure that accounts for not only syndromal but also subsyndromal mood elevation and depressive symptoms, and ranges from 1 (normal, not at all ill) to 7 (extremely ill). CGI-BP-OS scores from the 12 months preceding study enrollment were averaged to yield the mean-prior-year (MPY-CGI-BP-OS) score, the primary metric of bipolar illness severity and chronicity utilized in the study.

2.3. DNA extraction and BDNF val66met genotyping

DNA was obtained from peripheral venous blood or saliva. All genotyping assays were conducted within the laboratory of Dr. Joachim Hallmayer at Stanford by the same technician blinded to CTQ, MPY-CGI-BP-OS, and all other clinical data. BDNF val66met genotyping was conducted as per the laboratory's standard protocol, utilizing the following primers for G196A in the BDNF gene: forward 5′-ATC CGA GGA CAA GGT GGC-3′ and reverse 5′-CCT CAT GGA CAT GTT TGC AG-3′. This generated 300 bp of polymerized chain reaction (PCR) products, subsequently digested by Pml I (New England Biolabs, Ipswich, MA) to yield either allele A (met; undigested, 300 bp) or allele G (val; digested to 180 bp + 120 bp bands), which were visualized on 7% polyacrylamide gel using a 50 bp marker. Patients were classified as either BDNF met allele carriers (val/met or met/met genotype, U.S. population combined prevalence approximately 27.1%) or BDNF non-met allele carriers (val/val genotype, U.S. population prevalence approximately 68.4%), as the prevalence of BDNF met/met homozygotes in our study was expected to be low (U.S. population prevalence approximately 4.5%) (Shimizu et al., 2004).

2.4. Early life stress assessment

At the time of study enrollment, patients completed the Childhood Trauma Questionnaire (CTQ), a validated self-report assessment of childhood trauma exposure (Bernstein et al., 2003). The CTQ contains 28 items and is divided into five subscales: physical abuse, emotional abuse, physical neglect, emotional neglect, and sexual abuse. CTQ subscales are scored continuously as well as categorically ("none", "low", "moderate", or "severe" levels of abuse), with categories based on cutoff scores defined by the CTQ