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Supporting information

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Appendix S1. Treatment dropout.

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Increased plasma levels of 8-oxoguanine DNA glycosylase-1 in bipolar disorder

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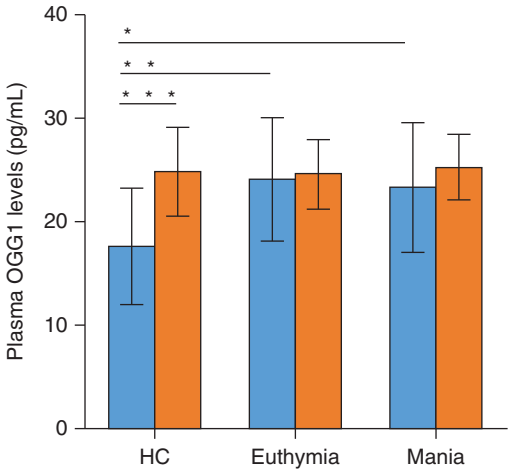

Fig.1 Plasma levels of 8-Oxoguanine DNA glycosylase-1 (OGG1) among the study groups: A two-way analysis of covariance revealed a significant interaction effect of bipolar disorder (BD) diagnosis and sex on the levels of OGG1 ($F = 6.609$, d.f. = 1, $P = 0.012$). Omnibus F-test showed that the BD diagnosis had a significant impact on the levels of OGG1 in women ($P < 0.001$), but no significant impact in men ($P = 0.917$). An independent samples t-test showed that healthy control (HC) women had significantly lower levels of OGG1 than HC men ($P < 0.001$). Analysis of variance and post-hoc Bonferroni analysis revealed significantly elevated levels of OGG1 in both euthymic and manic women in comparison to HC women ($P = 0.001$ and $P = 0.018$, respectively). OGG1 levels did not differ between manic and euthymic states either among women or men. ***$P < 0.001$; **$P = 0.001$; *$P = 0.018$). (■) Women. (■) Men.

Bipolar disorder (BD) is a chronic and severe mental illness. Evidence shows accelerated oxidation-induced DNA damage in BD as indicated by increased levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), the most prevalent DNA base damage product.[1] The base excision repair (BER) is the major repair mechanism for oxidation-induced DNA damage. It is responsible for recognizing and removing oxidized DNA base lesions by activation of DNA glycosylases.[2] A DNA glycosylase in the initial steps of the BER pathway, 8-Oxoguanine DNA glycosylase-1 (OGG1), is specialized for excision of 8-OH-guanine lesions.[2] Previous studies have indicated decreased expression of the *OGG1* gene in BD.[3,4] We aimed to investigate oxidation-induced DNA damage together with BER activity in BD. The impact of sex and mood state on the DNA damage and repair process was also explored as both variables are known to be associated with susceptibility for DNA damage and repair mechanisms.[5,6]

Forty-eight patients with DSM-IV BD type I (28 euthymic, 20 manic; 43 medicated) and 49 healthy controls (HC) were included in the study. Individuals were excluded from the study if they had: any Axis I psychiatric diagnosis (other than BD); acute infection; any neurological disorders; history of head trauma or brain surgery; any chronic medical condition; any substance use disorder (except for tobacco use); pregnancy; or current breastfeeding. Each participant provided a 10-mL blood sample between 09.00 and 10.00 hours. Absolute levels of 8-OHdG and OGG1 protein were assessed in plasma samples using enzyme-linked immunosorbent assays according to the manufacturer's instructions (catalogue no: E-EL-0028; catalogue no: E-EL-H1939; Elabscience, Wuhan, China). Statistical analyses were completed using SPSS 25.0 (IBM, Armonk, NY, USA). Group differences with regard to clinical features, and plasma levels of 8-OHdG and OGG1 were tested using independent samples t, χ^2, and analysis of variance tests. Linear regression models were used to identify the impacts of clinical variables on dependent variables. A two-way analysis of covariance was applied to test the interactions among clinical variables and OGG1 levels. The Omnibus F-test was used to identify the main effects of BD diagnosis and sex on OGG1 levels.

The patient and HC groups did not differ with regard to age, sex, or body mass index (Table S1). The number of smokers was higher in the patient group compared to the HC group ($\chi^2 = 8.838$, $P = 0.003$). Levels of 8-OHdG did not differ either between patients (4.07 ± 1.83 pg/mL) and HC (4.20 ± 1.53 pg/mL; $t = 0.599$, d.f. = 76, $P = 0.551$) or between euthymic and manic states ($P = 0.783$; Fig. S1). Plasma levels of OGG1 were significantly higher in BD patients (24.26 ± 5.07 pg/mL) compared to those in HC (20.43 ± 6.23 pg/mL; $t = 3.215$, d.f. = 91, $P = 0.002$; Fig. 1). Both the euthymic (24.36 ± 5.04 pg/mL) and manic (24.15 ± 5.23 pg/mL) BD groups had significantly higher plasma levels of OGG1 in comparison to HC (20.43 ± 6.23 pg/mL; $F = 5.134$, d.f. = 2, $P = 0.008$; post-hoc euthymic patients vs HC: $P = 0.047$; manic patients vs HC: $P = 0.019$); however, OGG1 levels did not differ between the manic and euthymic states ($P = 0.836$; Fig. 1).

A linear regression analysis that included age, sex, body mass index, smoking status, and BD diagnosis showed significant impacts of BD diagnosis ($P = 0.002$) and sex ($P < 0.001$) on the levels of OGG1. A two-way analysis of covariance revealed a significant interaction effect of BD diagnosis and sex on the levels of OGG1 ($F = 7.997$, d.f. = 1, $P = 0.006$). Omnibus F-test confirmed that the BD diagnosis had a significant impact on the levels of OGG1 only in women ($P < 0.001$), but not in men ($P = 0.968$). Both euthymic and manic women showed significantly elevated levels of OGG1 in comparison to HC women (Fig. 1). In the patient group, the linear regression analyses including age, sex, body mass index, smoking status, and medications did not show any significant impact of the variables on OGG1 levels.

Unchanged levels of 8-OHdG may not indicate absence of DNA damage as we have previously shown increases in other DNA base lesion markers in euthymic BD.[4] The increased protein levels of OGG1 are in contrast to the previously reported lower gene expression of OGG1 in BD.[3,4] However, previous studies investigated the intracellular expression levels of mRNA of OGG1 in leukocytes, whereas we analyzed extracellular protein levels of OGG1. The protein expression does not necessarily reflect mRNA levels due to differentially regulated transcription and translation processes.[7] More importantly, the plasma protein levels may include the OGG1 proteins released from various types of tissues in the body, so plasma levels may imply globally increased OGG1 levels.[8]

The significant effect of female sex on the OGG1 levels in the BD group is in line with previously reported female susceptibility to DNA oxidation/damage in mood disorders and under psychological and environmental stressors (e.g., smoking, radiation).[5,9,10] Our findings could be

suggestive of a defective DNA repair process as an associated mechanism to the increased DNA damage with a higher susceptibility of women with BD. Further investigations involving brain tissue as well as peripheral samples, and using other measurements (e.g., immune blotting, chromatography) with consideration of the medication and sex effect to validate our findings are needed.

Disclosure statement

None of the authors declare any conflicts of interest.

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Supporting information

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Figure S1. Plasma levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in study groups: (A) Plasma levels of 8-OHdG did not show significant difference between patients with bipolar disorder (BD) and the healthy control (HC) group ($F = 0.231$, d.f. = 76, $P = 0.551$). (B) The 8-OHdG levels did not differ among euthymic and manic states of illness either.

Table S1. Clinical features of the study groups

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