İstanbul, Türkiye; [3] *Koç University, Graduate School of Health Sciences, İstanbul, Türkiye;* [4] *Dokuz Eylül University Institute of Health Sciences, Department of Molecular Medicine, İzmir, Türkiye;* [5] *İzmir University of Economics Faculty of Medicine, Department of Medical Biochemistry, İzmir, Türkiye;* [6] *Marmara University Faculty of Medicine, Department of Biochemistry, İstanbul, Türkiye;* [7] *Marmara University Faculty of Medicine, Department of Psychiatry, İstanbul, Türkiye;* [8] *Dokuz Eylül University Faculty of Medicine, Department of Psychiatry, İzmir, Türkiye*

Background: Bipolar disorder (BD) is a chronic psychiatric illness that is associated with premature aging and comorbidity [1]. Recent research suggests that oxidatively-induced DNA damage may play a central role in the pathophysiology of BD, as it is a shared mechanism between BD, cellular aging, and comorbidity [2]. Since BD is highly heritable, studies conducted on high-risk individuals are crucial for early detection and identifying biological risk factors [3]. Therefore, our objective was to examine oxidative DNA damage and base excision repair (BER) mechanisms in individuals with BD and their siblings compared to healthy controls (HC).
Methods: The study included 46 individuals with BD, 41 siblings of individuals with BD, and 51 HC. Liquid chromatography-tandem mass spectrometry was employed to evaluate the levels of 8-hydroxy-2'-deoxyguanosine (8-OH-dG) in urine, which were then normalized based on urine creatinine levels. The mRNA expression levels of OGG1, APE1, PARP1, and POLβ were measured through real-time-polymerase chain reaction, using cDNA obtained from blood samples.
Results: Individuals with BD and siblings of individuals with BD exhibited higher levels of 8-OH-dG compared to healthy controls. Additionally, the patient and sibling groups had lower levels of OGG1 and APE1 mRNA expression and higher levels of POLβ mRNA expression compared to healthy controls. However, there was no significant difference in these parameters between individuals with BD and siblings of individuals with BD (Table). Age, smoking status, and the number of depressive episodes had an impact on APE1 mRNA expression levels in the patient group while body mass index, smoking status, and past psychiatric history had an impact on 8-OH-dG levels in siblings.

TableComparisons among the groups

	BD (n=46)	Siblings (n=41)	HI (n=51)	Statistics*
8-OHdG / creatinine	3.20 (1.25-6.47)	3.27 (0.78 – 8.94)	2,60 (0.96 – 7.10)	BD>HC (p=0.026) Siblings>HC (p=0.006) BD vs Siblings ns.
APE1	0.34 (0.11-1.55)	0.33 (0.07-4.08)	0.83 (0.20 - 10.74)	BD<HC (p<0.001) Siblings<HC (p<0.001) BD<Siblings ns.
PARP1	0.38 (0.09 -1.42)	0.40 (0.09 -18.32)	0.40 (0.07 - 1.30)	ns
OGG1	0.15 (0.05 - 3.38)	0.15 (0.03 -1.72)	0.19 (0.07 - 0.87)	BD<HC (p=0.020) Siblings<HC (p=0.025) BD vs Siblings ns.
POLB	0.19 (0.06 - 0.55)	0.18 (0.06 - 1.03)	0.15 (0.03 - 0.61)	BD>HC (p=0.014) Siblings>HC (p=0.002) BD vs Siblings ns.

The variables were presented as median (minimum-maximum) values. All comparisons were adjusted for age, sex, body mass index and smoking status.
*Quade Non-parametric ANCOVA

Conclusions: Our study reveals, for the first time, that both individuals with BD and their full siblings exhibit elevated DNA damage and impaired base excision repair (BER) compared to healthy controls. These results suggest that abnormalities in DNA damage and repair mechanisms may be associated with familial susceptibility to BD.The identification of such abnormalities in the DNA damage and BER pathway highlights their potential as promising therapeutic targets for future research aimed at developing novel treatments for BD.

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INITIATION OF THE EUROPEAN MULTICENTRE STUDY "BIPCOM" TO UNRAVEL MEDICAL COMORBIDITIES IN BIPOLAR DISORDER

N.F. Kobayashi [1], M. Garcia-Argibay [2], O.A. Andreassen [3], M. Leboyer [4], R. Corcoy [5], K. Florian [6], B. Michael [7], A. Reif [1], G. De Girolamo [8]. [1] *Goethe University Frankfurt Medical Faculty, Department of Psychiatry- Psychosomatic Medicine and Psychotherapy, Frankfurt am Main, Germany;* [2] *Örebro University, School of medical sciences, Örebro, Sweden;* [3] *University of Oslo, NORMENT-Division of Mental Health and Addiction, Oslo, Norway;* [4] *Fondation Fondamental, Psychiatry, Créteil, France;* [5] *Institut de Recerca-Hospital de la Santa Creu I Sant Pau, Servei d'Endocrinologia i Nutrició, Barcelona, Spain;* [6] *Deutsche Gesellschaft für Bipolare Störungen GSBD e.V., n.a., Frankfurt am Main, Germany;* [7] *University Hospital Carl Gustav- Caurs Medical Faculty- Technische Universität Dresden, Department of Psychiatry and Psychotherapy, Dresden, Germany;* [8] *IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli Brescia, Unit of Epidemiological and Evaluation Psychiatry UOPEV, Brescia, Italy*

Background: Bipolar Disorder (BD) is a severe and heritable psychiatric disorder. It represents a substantial public health problem, due to its prevalence, its high degree of disability and psychiatric and somatic comorbidities, especially cardiometabolic disturbances. Such comorbidities pose a significant additive burden for patients with BD. Considering the clinical heterogeneity of these patients, a better characterization of this population is required to develop personalised treatment approaches.
Objective: BIPCOM is a multicentre study funded by the EU within the ERA-perMed Call, involving six centres from different countries (Italy, France, Germany, Norway, Spain, Sweden). The purpose of BIPCOM is to identify somatic comorbidities in BD patients to develop precision medicine approaches.
Aims: BIPCOM aims to define the prevalence rates, risk and protective factors and the natural course of somatic comorbidities of BD patients. Those data will be integrated to develop a tool to support individualized clinical decision-making in BD.
Method: BIPCOM comprises three separate clinical studies to define patient characteristics and a subsequent exploitation element. In the first study, data will be obtained from the Nordic biobanks and medical registries. In the second study, the study centres together will contribute standardized data of at least 1500 patients comprising 24 pre-specified variables (among others past and current comorbidities and treatment). Emphasis will be given to chronic somatic disorders (diabetes mellitus, metabolic syndrome, dyslipidaemia, obesity or endocrine disorders). The third study has a prospective element with in depth characterization of 400 patients including a one-year follow up with a focus on metabolic syndrome. Patients aged from 18 – 65 with a primary diagnosis of BD, who had at least one contact with mental health services in the last year will be included. A "patient schedule" will include each participant's socio-demographic, clinical and treatment-related data at baseline (T0) and at 1-year follow-up (T1). Five aspects of metabolic syndrome (MetS, waist circumference, triglyceride level, HDL level, blood pressure and fasting glucose) will be determined and subjected to clustering analysis to identify common presentation dynamics. The primary objective of this part is to identify the strongest criteria for the MetS diagnosis at T0 and/orT1 in patients with BD. Moreover, at least 20 patients per site stratified in MetS+ and MetS-, will receive in depth physical activity determinations. For this, patients will be asked to wear accelerometers for one week 3 times a year, to determine physical activity, sedentary time and circadian rhythms. With this data the association between activity and selected clinical markers will be determined. Ultimately, the data of the three studies will be integrated to aid patient care in BD by means of a clinical support tool.
Conclusions: The results of BIPCOM will provide a better understanding of the somatic comorbidities in patients with BD. Focussing especially on MetS the data will help to predict the occurrence of comorbidities to assist physicians in the

management of these patients. Ultimately, BIPCOM aims to improve comorbidity management, prevention, early detection and effective treatment of somatic disorders in patients with BD.

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DECREASED MITOCHONDRIAL COPY NUMBER IN INDIVIDUALS WITH BIPOLAR DISORDER AND THEIR UNAFFECTED SIBLINGS

I.C. Akşahin [1], H.E. Arat-Çelik [2], B. Kök-Kendirlioğlu [2], E. Çörekli-Kaymakçı [2], D. Ceylan [3]. [1] *Koc University, Graduate School of Health Sciences, Istanbul, Türkiye;* [2] *Maltepe University, Department of Psychiatry, Istanbul, Türkiye;* [3] *Koc University, Department of Psychiatry, Istanbul, Türkiye*

Background: Bipolar Disorder (BD) is a mood disorder with a high heritability rate that is associated with aging and premature mortality [1]. Increasing evidence suggests that mitochondrial DNA (mtDNA) copy number, a potential biomarker of mitochondrial function, has been linked to various age-related diseases, including BD [2]. Several studies consistently report decreased levels of mtDNA copy number in individuals with BD [2]. The most significant risk factor for BD is a positive family history of the disorder. Among first-degree relatives of individuals with BD, siblings have the highest risk of developing the disorder, with an estimated morbidity risk range of 5-10% [3]. In our study, we aimed to measure changes in mtDNA copy number in patients with BD, siblings of individuals with BD, and healthy individuals.

Methods: We recruited 36 euthymic individuals with BD, 32 healthy siblings of individuals with BD, and 41 healthy controls for our study. RNA was extracted from their peripheral blood mononuclear cells and analyzed using Reverse Transcriptase Quantitative Polymerase Chain Reaction to measure expression levels. We calculated mitochondrial copy numbers by comparing the amplifications of the mitochondrial CYTB gene to that of housekeeping nuclear DNA genes (GAPDH and β-Actin). The mitochondrial copy numbers were calculated using $2^{-\Delta\Delta CT}$ formula and reported as median (minimum-maximum) values. To compare the mitochondrial copy numbers among the study groups, we used Quade's nonparametric univariate analyses of covariance (ANCOVA) models. These models included age, sex, body mass index, smoking status, and alcohol consumption as covariates. Additionally, we conducted Spearman correlation analyses and linear regression tests to further analyze the data.

Results: There were no significant differences in age, sex, smoking status, and years of education between the study groups. However, compared to the sibling and healthy control groups, patients with BD had higher body mass indexes (p=0.007, p=0.005, respectively) and lower alcohol consumption (p=0.033). Regarding mtDNA copy numbers, there were significant differences in the siblings of individuals with BD [0.87 (0.33-3.72); p=0.031] and individuals with BD [0.81 (0.23-3.83); p=0.017] compared to the healthy control group [0.98 (0.30-2,91)]. Spearman correlation analysis revealed a positive correlation between the number of previous depressive episodes and mtDNA copy numbers (r=0.4, p=0.016). This association was confirmed by a linear regression model that included age, body mass index, smoking, and alcohol consumption as covariates (B=0.387, t=2.636, p= 0.012, CI: 0.031-0.232).

Conclusion: Our study revealed that not only individuals with BD, but also their siblings who are at risk of developing BD, have lower levels of mtDNA copy number compared to healthy controls. Furthermore, confirming a prior study [4], our findings revealed that individuals with BD and their unaffected siblings showed similar mtDNA copy numbers. The reduction of mtDNA copy number in the sibling group, which is a marker of mitochondrial dysfunction and cellular senescence, suggests that the pathophysiology of these conditions may share some environmental or genetic factors with BD.

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THE DISCOVER TRIAL – MID-STUDY LOOK AT PATIENT TRAINING AND THEIR EXPECTATIONS FROM A NEW, HOME-BASED, SELF-APPLIED TREATMENT APPROACH

L. Rubene [1], A. Sturmane [2], L. Konosonoka [2], E. Dechantsreiter [3], T. Cohen [4], N. Lerner [4], F. Padberg [3], D. Bavelier [5], F. Hummel [6], O. Bonne [7], E. Rancans [2], M. Nahum [4]. [1] *Riga Centre of Psychiatry and Narcology, Psychiatry, Riga, Latvia;* [2] *Riga Stradins University, Psychiatry and Narcology, Riga, Latvia;* [3] *LMU University Hospital, Psychiatry and Psychotherapy, Munich, Germany;* [4] *The Hebrew University of Jerusalem, School of Occupational Therapy- Faculty of Medicine, Jerusalem, Israel;* [5] *University of Geneva, Faculty of Psychology and Educational Sciences, Geneva, Switzerland;* [6] *Swiss Federal Institute of Technology, Neuro-X Institute and Brain Mind Institute, Geneva, Switzerland;* [7] *The Hebrew University of Jerusalem, Department of Psychiatry- Hadassah Medical Center-Faculty of Medicine, Jerusalem, Israel*

Background: The DiSCoVeR trial (The DiSCoVeR Project: Examining the synergistic effects of a cognitive control videogame and a self-administered non-invasive brain stimulation on alleviating depression) is a multi-site, double-blind, sham controlled, randomized controlled trial (RCT) investigating the feasibility and efficacy of an innovative, self-applied treatment approach for patients suffering from major depressive disorder (MDD) [1]. The treatment incorporates non-invasive brain stimulation, i.e. transcranial direct current stimulation (tDCS), applied over the dorsolateral prefrontal cortex, and a videogame designed to enhance cognitive control. This treatment is aimed to be self-applied at home and monitored remotely. Here we provide first insights after inclusion of half of the planned sample of the trial, comparing expected in person visits (according to the study protocol) versus actual in person visits as well as looking at the patients initial assessment of the therapy using the therapy evaluation form (CEQ) submitted after the 5th treatment session.

Methods: Before continuing to self-administer the treatment from home, patients undergo supervised training in the clinic for up to 5 sessions. At the end of the 5th session, they are asked to fill in the therapy evaluation form [2]. This questionnaire queries participants' belief about how much the therapy they are receiving will help to improve their lifestyle/functioning. Participants have to rate not only what they think but also what they feel about the level of help/improvement expected. Moreover, some questions address the current state, whereas others ask about expectations towards the end of treatment. Answers are provided on a 9-point scale when evaluating therapy success at this point in time, with 5.0 corresponding to a "Somewhat Useful" rating. Answers are provided as percentages (0-100% in 10 steps) when evaluating therapy success at end of treatment.

Results: Of the first 57 patients trained, 12 (21%) needed 5 sessions, 8 (14%) needed 4 sessions, 9 (16%) needed 3 sessions, 19 (33%) needed 2 and 8 (14%) needed 1 in person training sessions before taking the device home to continue the intervention remotely. Only 1 (2%) patient needed an extra 6th training session. 52 of the 57 completed the CEQ. Overall, when asked about the current state, patients thought that the treatment is slightly better than "somewhat useful" (5.29 points - SD±1.81, CI 4.79 to 5.79), but felt that its impact is actually a bit lower (4.96 (SD±2.19, CI 4.35 to 5.57). Concerning the end of treatment, patients expected an increase in functioning by 47% (SD±24, CI 39 to 53) and felt that they could improve by 44% (SD±24, CI 37 to 57).

Conclusions: Overall, the majority of patients needed less than 5 training sessions on site before continuing with the intervention, on their own, at home. By the end of the 5th session, patients reported to find the treatment "somewhat useful" and expected a 44-47% increase in their level of functioning by the end of treatment.

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