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OXIDATIVE STRESS IN SCHIZOPHRENIA AND BIPOLAR DISORDERS, RESULTS FROM A FOLLOW-UP STUDY OF TWO PROSPECTIVE STUDIES

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Background: Enhanced oxidative stress generated nucleoside damage particularly to RNA seems to contribute to accelerated aging in patients with severe mental illness and may be most pronounced in patients with schizophrenia (SCZ) but also in patients with bipolar disorder (BD) compared with healthy control individuals (HC) [1],[2]. We hypothesized that:1.

Oxidative stress generated nucleoside damage persists elevated in patients with SCZ and – to a lesser degree – in patients with BD over time compared with HC without a family history of psychiatric disorders.2. Oxidative stress generated nucleoside damage, in particular RNA damage, is positively associated with greater illness burden in patients with SCZ.

Methods: We investigated difference in oxidative stress markers between patients with SCZ, BD, and HC, followed for two years. We compared oxidative stress generated damage to DNA (8-oxodG) and RNA (8-oxoGuo) in 403 patients with schizophrenia and overweight (847 visits), 358 patients newly diagnosed with BD (627 visits), and 198 HC (359 visits). In our primary analysis we applied a linear mixed model including group (SCZ, BD, HC), time (visit 1-3) and the interaction between them as fixed effects, and an unstructured covariance pattern to account for repeated measurements on each individual study participant. We repeated the analysis threefold 1) without adjustment, 2) adjustment for sex, age and BMI, and 3) adjustment for age, sex, BMI and current smoking status (yes/no). In our secondary analysis, we investigated the association of 8-oxoGuo and 8-oxodG with illness and treatment variables in patients with SCZ (a similar analysis in patients with BD has been published previously).

Results: RNA damage levels were 1.27 fold higher (95%CI =1.20-1.33, $p_{\text{adjusted}} < 0.001$) in patients with SCZ compared with HC at baseline and 1.16 fold higher (95%CI =1.11-1.22, $p_{\text{adjusted}} < 0.001$) in patients with BD compared with HC, and the differences persisted over time. RNA damage levels were also persistently higher in SCZ compared with BD with a 1.09 fold-difference (95%CI =1.04-1.14, $p_{\text{adjusted}} < 0.001$) at baseline. DNA damage was most pronounced in patients with BD who had a 1.22 fold higher level at baseline (95%CI =1.15-1.30, $p_{\text{adjusted}} < 0.001$) compared to HC, and a 1.08 fold higher level (95%CI =1.02-1.14, $p_{\text{adjusted}} = 0.013$) compared with SCZ, while patients with SCZ had a 1.12 fold higher level (95%CI 1.05-1.21, $p_{\text{adjusted}} = 0.002$) compared with HC. However, the differences attenuated over time and were no longer statistically significant after 2 years. Increasing levels of BMI and HbA1c were associated with increased RNA damage in patients with SCZ, while no other significant associations were observed between RNA- and DNA damage and other medication, illness, and lifestyle factors. **Conclusion:** Overall, we found higher levels of RNA damage in patients with severe mental illness that persisted over time. These elevated levels were most pronounced in patients with SCZ but also present in patients with BD. Elevations in DNA damage did not persist over time. Our findings support enhanced oxidative stress generated nucleoside damage as a putative pathophysiological mechanism of accelerated aging that may mediate the higher somatic morbidity and mortality in patients with severe mental illness.

References

1.Jorgensen A, Baago IB, Rygner Z, et al. Association of Oxidative Stress-Induced Nucleic Acid Damage With Psychiatric Disorders in Adults: A Systematic Review and Meta-analysis. *JAMA psychiatry*. Aug 3 2022;doi:10.1001/jamapsychiatry.2022.0666 2.Global burden of 369 diseases and injuries in 204 countries and

territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. Oct 17 2020;396(10258):1204-1222. doi:10.1016/s0140-6736(2030925-9)

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COMPARING FAST-ACTING TREATMENTS FOR MAJOR DEPRESSIVE EPISODES: ACCELERATED REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION VS. INTRANASAL ESKETAMINE

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Background and aims Accelerated Transcranial Magnetic Stimulation (arTMS) and Intranasal Esketamine are increasingly employed as rapid-acting interventions for Major Depressive Episodes, particularly in cases showing insufficient response to standard antidepressant treatments [1,2]. Despite their growing use in clinical practice, comprehensive direct comparisons of these interventions in real-world settings remain limited [3]. This retrospective observational study aimed to evaluate and compare the clinical outcomes, specifically focusing on onset of action and durability of effects, between arTMS and Intranasal Esketamine in patients presenting with unipolar or bipolar Major Depressive Episodes with an inadequate response to prior pharmacological treatments. **Methods:** We retrospectively analyzed 37 patients treated at the Mood Disorder Unit of San Raffaele Hospital in Milan, diagnosed with unipolar or bipolar Major Depressive Episode and an inadequate response to at least one prior trial of antidepressant medication. Eighteen patients received arTMS (four sessions per day of high-frequency repetitive TMS delivered to the left dorsolateral prefrontal cortex for five consecutive days, totaling 20 sessions), and 19 patients received Intranasal Esketamine (twice weekly administrations in the first month, once weekly in the second month, bimonthly in the third month). Depression severity was assessed at baseline, one month, and three months post-treatment initiation using the Montgomery-Åsberg Depression Rating Scale (MADRS). Response was defined as a $\geq 50\%$ reduction from baseline MADRS scores, and remission was defined as a MADRS score < 10 .

Results: Of the 19 patients who initiated Intranasal Esketamine, two patients discontinued treatment after the first administration due to poor tolerability; thus, the analysis was conducted on 17 patients treated with Intranasal Esketamine and 18 patients treated with arTMS. At one month, response rates were 72% in the arTMS group and 29.4% in the Intranasal Esketamine group ($p=0.018$). Remission rates at one month were 67% for arTMS and 11.8% for Intranasal Esketamine ($p=0.002$). At three months, response rates were 83.3% in the arTMS group and 58.8% in the Intranasal Esketamine group ($p=0.146$). Remission rates at three months were 61% for arTMS and 35.3% for Intranasal Esketamine ($p=0.315$). No serious adverse events or manic switches were reported.

Conclusions: Our preliminary findings suggest that accelerated TMS may provide a more rapid onset of clinical response and remission compared to Intranasal Esketamine in patients with Major Depressive Episodes inadequately responsive to previous antidepressant treatments. However, the observed therapeutic advantage of arTMS diminished progressively over a three-month follow-up period, as clinical outcomes for patients treated with Intranasal Esketamine gradually improved. This observation aligns with existing evidence that describes a slower yet sustained antidepressant effect associated with Intranasal Esketamine [4]. These preliminary data support arTMS as a faster-acting option, while suggesting that Intranasal Esketamine may achieve comparable benefits over a longer follow-up period. Prospective, randomized controlled trials with larger sample sizes and extended follow-up periods are warranted to validate and expand upon these preliminary findings, and to confirm the comparative efficacy, durability, and safety profiles of accelerated TMS and Intranasal Esketamine.

References

[1] Sonmez AI, Camsari DD, Nandakumar AL, et al. Accelerated TMS for Depression: A systematic review and meta-analysis. *Psychiatry Res*. 2019;273:770-781. doi:10.1016/j.psychres.2018.12.041. [2] Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized

Clinical Trial. JAMA Psychiatry. 2018;75(2):139-148. doi:10.1001/jamapsychiatry.2017.3739. [3] Pettorruso M, d'Andrea G, Di Carlo F, et al. Comparing fast-acting interventions for treatment-resistant depression: An explorative study of accelerated HF-rTMS versus intranasal esketamine. Brain Stimul. 2023;16(4):1041-1043. doi:10.1016/j.brs.2023.06.003. [4] Martinotti G, Miuli A, Pettorruso M, et al. Real-world experience of esketamine use to manage treatment-resistant depression: a multicentric study on safety and effectiveness (REAL-ESK study). J Affect Disord. 2022;319:646-654. doi:10.1016/j.jad.2022.09.043.

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SELF HARM, BOREDOM AND EMOTION REGULATION: A NETWORK ANALYSIS IN A SAMPLE OF ADOLESCENTS AND YOUNG ADULTS WITH MOOD DISORDERS

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Non-suicidal self-injury (NSSI), particularly in the form of cutting, is a growing clinical concern among adolescents and young adults, especially those diagnosed with mood disorders such as Major Depressive Disorder and Bipolar Disorder. This study aims to investigate the interactions between emotional dysregulation and boredom in relation to self-injurious behaviors. The objectives were three-fold: (1) to identify the most central psychological nodes within networks comprising boredom (as measured by the Multidimensional State Boredom Scale, MSBS) and emotional dysregulation (as assessed by the Difficulties in Emotion Regulation Scale, DERS); (2) to compare the network structures between individuals with and without a history of cutting; and (3) to explore the nature of positive and negative associations within the networks to identify clinically relevant intervention targets.

A total of 127 young outpatients aged 14–25 (mean age = 16.9 ± 2.5 years) with DSM-5 diagnoses of mood disorders were recruited from the Early Intervention Service for Adolescents and Young Adults at Agostino Gemelli University Hospital, Rome. Exclusion criteria included cognitive impairment, major neurological illness, and psychotic symptoms unrelated to the primary mood disorder. All participants completed the DERS and MSBS. Statistical analysis included one-way ANOVA for univariate comparisons and network analysis using the Graphical Lasso method with Extended Bayesian Information Criterion (EBIC) regularization (gamma = 0.5) to construct sparse psychological networks. Centrality metrics (Strength, Betweenness, and Closeness) were computed to evaluate the role of each variable in the overall network structure.

Univariate results demonstrated that individuals engaging in cutting (n = 57) had significantly higher total scores on both the DERS (129.5 ± 23.2 vs. 105.6 ± 26.7; p < 0.001) and MSBS (149.7 ± 28.2 vs. 129.1 ± 34.9; p < 0.001) compared to those without cutting behaviors. Significant differences were observed in subscales related to impulse control (20.1 ± 6.2 vs. 15.3 ± 6.6; p < 0.001), emotional clarity (19.0 ± 5.0 vs. 16.4 ± 5.1; p = 0.005), and high-arousal boredom (25.1 ± 6.3 vs. 21.8 ± 7.4; p = 0.007).

Network analysis revealed that the psychological profile of individuals with cutting behaviors was characterized by denser and more conflictual connections. The DERS total score emerged as the most central node (Strength = 3.30; Betweenness = 70), with strong links to boredom dimensions such as high arousal and inattention. Specifically, significant associations were found between Impulse Control Difficulties (DERS-ICD) and High Arousal (MSBS-HA), and between Lack of Emotional Clarity (DERS-LEC) and Inattention (MSBS-IN), suggesting that emotional dysregulation interacts with boredom in ways that promote self-injurious behavior.

These findings highlight the need for a specific investigation of the underlying dimensions of self harm in order to create targeted therapeutic approaches focusing on emotion regulation skills and boredom management to reduce the risk of NSSI. Future research should replicate these findings in longitudinal designs to clarify temporal and causal mechanisms.

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BEYOND CLINICAL DATA: ASSESSING THE VALUE OF RESTING-STATE FMRI DATA FOR PREDICTION OF INDIVIDUAL DEPRESSION OUTCOMES

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Introduction & Aims: Major depressive disorder (MDD) is a highly recurrent illness, so for individualized and efficient treatment, it is critical to predict which patients are at high risk for future relapse or functional impairment. As this is currently not possible using demographic and clinical data with traditional group-level inference statistics, machine learning approaches pave a promising avenue to advance individual predictions about MDD trajectories, possibly using biomarkers. As resting-state functional connectivity (rsFC) has been associated with future relapse in MDD, this is one candidate biomarker for predictive approaches. Our central question is whether the addition of neuroimaging data brings incremental value to a clinical prognosis, beyond routinely available basic demographic and detailed clinical information.

Methods: Data from 346 patients with MDD of the Marburg-Münster Affective Disorders Cohort Study (MACS) were available. In this study, patients were assessed twice approximately two years apart with 3 Tesla magnetic-resonance imaging and clinical characterization by trained personnel. Clinical variables (containing detailed symptom profile, previous disease course, as well as environmental and psychological protective and risk factors) and rsFC measures were used to predict relapse and the level of psychosocial functioning (indicated by global assessment of functioning) after a two-year follow-up interval. Random Forest machine learning models were computed to test the incremental predictive capability of clinical or rsFC data compared to a reference model containing basic demographic and confounding variables. Furthermore, incremental predictive value of a multimodal model was tested (combining rsFC and clinical data), compared to the clinical model. To assess significance of model differences, differences of permutation test distributions were leveraged.

Results: Patients relapsed in 49% of cases and had a mean functioning level of 73.18 (±14.20) at follow-up. Clinical information significantly predicted future psychosocial functioning (21% explained variance) beyond the reference model (12% explained variance, p < 0.001). Depression relapse can be predicted by clinical information (64.64% balanced accuracy), however not significantly better than by the reference model alone (57.70% balanced accuracy, p = 0.062). Resting-state data did not yield above-chance accuracies on its own (12% explained variance and 51.72% balanced accuracy) and did not hold incremental predictive value compared to clinical variables for either outcome.

Conclusions: This analysis contributes to the current debate whether biomarkers can help overcome challenges of precision psychiatry. In a large, well-curated sample with adequate generalizability, our analyses demonstrated that baseline clinical data is fit to predict individual psychosocial functioning after two years. Yet, models containing rsFC data fall short of adding meaningful predictive value. Model complexity due to high feature numbers and limitations of rsFC data are potential sources of poor translation of MDD biomarkers. This was the first work to assess individual relapse risk and psychosocial functioning in MDD patients by using a multimodal machine learning method, including rsFC patterns. Further, approaching hierarchical comparison with permutation differences to test for significant between-model differences poses an innovative, non-parametric technique to evaluate utility of various feature modalities.

Conflict of interest

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