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UNSUPERVISED NEUROBIOLOGICALLY-DRIVEN STRATIFICATION OF CLINICAL HETEROGENEITY IN TREATMENT-RESISTANT DEPRESSION

F. Colombo [1,2], F. Calesella [1,2], B. Bravi [1,2], L. Fortaner-Uyà [1,2], C. Monopoli [2], M. Carminati [1,3], R. Zanardi [3], I. Bollettini [2], S. Poletti [1,2], F. Benedetti [1,2], B. Vai [1,2]. [1] *University Vita-Salute San Raffaele, Department of Psychology, Milan, Italy;* [2] *IRCCS San Raffaele Scientific Institute, Psychiatry and Clinical Psychobiology Unit- Division of Neuroscience, Milan, Italy;* [3] *IRCCS San Raffaele Scientific Institute, Mood Disorders Unit, Milan, Italy*

Background: Major depressive disorder (MDD) is an heterogeneous psychiatric condition embracing various and coexisting symptoms, with 30% of patients not adequately responding to treatments [1]. Despite increasing efforts in discovering MDD biomarkers, their prognostic value is still puzzling due to the weak consistency between clinical outcomes and the underlying neurobiology [2]. Stratifying patients based on neurobiological data could help in unveiling disease subtypes and tailoring personalised treatments.

Aims: Using an unsupervised machine learning approach, we aim to define biologically-driven MDD clusters based on multimodal structural neuroimaging data. The identified clusters are then clinically profiled for treatment-resistant depression (TRD), depressive symptomatology, and childhood trauma.

Methods: T1-weighted and diffusion tensor images were acquired from 102 MDD patients. TRD was defined as a failure to respond to at least two antidepressant treatments [3]. In 64 patients, depressive symptomatology was rated on the Beck Depression Inventory–Short Form (BDI-SF), and composite scores for different domains (Negative Self-Esteem, Anergy, and Dysphoria) were derived [4]. Childhood trauma was evaluated with the Childhood Trauma Questionnaire (CTQ). Clustering analyses were performed using a stability-based relative clustering approach within a cross-validation framework [5], considering extracted tract-based fractional anisotropy (TBSS, FSL), cortical thickness, and regional measures of grey matter volumes (CAT12) as input features. Gaussian mixture model was implemented for clustering, and support vector machine was trained to learn and predict clusters' labels through a 10x2 repeated cross-validation. By iterating over a number of clusters from 2 to 5, the best clustering solution that minimised the stability (i.e., prediction error) was identified. Statistical significance was assessed by 10000 simulations from a single null Gaussian distribution. A parallel grid search was implemented for hyperparameter tuning. Confounding effects of age, sex and total intracranial volume were controlled in cross-validation. The clinical relevance of the discovered clusters was explored with a MANOVA, considering clusters' labels as fixed factors and BDI-SF and CTQ domains as dependent variables. Linear discriminant analysis (LDA) was performed to assess their discriminative power. The proportion of TRD patients between clusters was investigated with Chi-square test.

Results: The stability-based clustering approach identified 2 clusters with normalised stability=0.316 ($p<10e-9$), which were significantly different for TRD ($\chi2(1)=7.00$, $p=0.008$). One cluster showed a mixed profile of TRD (high-TRD, n=59), whereas a high proportion of treatment-responsive patients was observed in the other (low-TRD, n=43). The MANOVA showed a significant between-clusters difference (Wilks' lambda=0.68, $F(9,50)=2.64$, $p=0.014$). LDA revealed that Anergy (b=0.545), CTQ minimization/denial (b=0.398) and emotional neglects (b=0.199) subscales were associated with the high-TRD cluster, while Dysphoria (b=-0.210), Negative Self-Esteem (b=-0.183), and CTQ physical neglect (b=-0.104) were associated with the low-TRD cluster.

Conclusions: With a stability-based clustering approach, we demonstrated that structural neuroimaging can uncover depression subtypes indicative of clinically meaningful insights. The high-TRD cluster is associated with energy-related depressive symptomatology and minimization of childhood trauma, whereas the low-TRD subtype is characterised by cognitive and affective depressive symptomatology. A multimodal stratification can help in understanding the pathophysiological mechanisms of MDD and improve personalised healthcare in a precision psychiatry perspective.

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POSTPARTUM HORMONAL CONTRACEPTIVE USE AND RISK OF DEPRESSION

S.V. Larsen [1,2], A.P. Mikkelsen [3,4], B. Ozenne [1,5], X. Liu [6], K.B. Madsen [6], T. Munk-Olsen [6,7], Ø. Lidegaard [2,4], V.G. Frokjaer [1,8]. [1] *Copenhagen University Hospital - Rigshospitalet, Neurobiology Research Unit, Copenhagen, Denmark;* [2] *University of Copenhagen, Department of Clinical Medicine, Copenhagen, Denmark;* [3] *Copenhagen University Hospital - Herlev and Gentofte Hospital, Department of Gynaecology and Obstetrics, Herlev, Denmark;* [4] *Juliane Marie Centre - Copenhagen University Hospital - Rigshospitalet, Department of Gynaecology and Obstetrics, Copenhagen, Denmark;* [5] *Section of Biostatistics - University of Copenhagen, Department of Public Health, Copenhagen, Denmark;* [6] *Aarhus University, NCRR – The National Centre for Register-based Research, Aarhus, Denmark;* [7] *University of Southern Denmark, Department of Clinical Research, Odense, Denmark;* [8] *Mental Health Services in the Capital Region of Denmark, Psychiatric Center Copenhagen, Copenhagen, Denmark*

Background: Hormonal contraceptive (HC) use has been associated with depressive episodes [1]. However, it is unclear whether this relationship also holds true in the postpartum period [2], a time period of abrupt hormonal changes where women are already at heightened risk of depression [3]. Advance of such knowledge could aid in optimizing contraceptive counselling strategies for postpartum women.

Aim: To determine if HC initiation after delivery is associated with depression in the postpartum period.

Methods: This population-based cohort study was based on Danish national health registry data. All women living in Denmark who gave birth for the first time between 1997 and 2017 were eligible for inclusion (n=528,405). Women were excluded if they had a depressive episode within 24 months prior to delivery, had a multiple birth or stillbirth, or had a diagnosis with breast cancer or a liver tumour at the time of delivery. HC use was treated as a time-varying exposure such that women transitioned from non-exposed to exposed on the day they filled a HC prescription and remained exposed for the rest of the follow-up period. We report adjusted hazard ratios (HRs) using Cox regression comparing the incidence of depression in the postpartum period among users and non-users, where depression was defined as initiation of antidepressant medication or receiving a hospital depression diagnosis within 12 months after delivery. Covariates included calendar year, maternal age, education level, civil status, medical indications for HC use, previous psychiatric disorder, familial psychiatric history, pre-gestational and gestational diabetes, pre-eclampsia and eclampsia, preterm birth, instrument-assisted delivery, and fertility treatment.

Results: Our analysis included 475,635 first-time mothers, of which 196,780 (41%) initiated HC before the end of follow-up (mean [SD] age; 27.5 [4.3] years for users vs. 29.5 [4.8] years for non-users). During follow-up, 2,899 users vs. 5,121 non-users were registered with incident depression in the postpartum period, resulting in an incidence rate of 24 vs. 15 per 1,000 person years, respectively. HC use was associated with depression in the postpartum period, with a HR of 1.52 (95% CI, 1.44-1.59), compared to no use. For combined oral contraceptive use, the HR was 1.71 (95% CI, 1.61-1.80); for combined non-oral contraceptive use (Patch and vaginal ring) 1.93 (95% CI, 1.60-2.33); for progesterone-only pill use 1.05 (95% CI, 0.96-1.15); and for progesterone-only non-