regard, Machine Learning (ML) could represent a turning point in the field precision psychiatry, given its capability of making single-subject level predictions.
Objectives: In the present work, we aimed at providing a biomarker-based differential diagnosis between MDD and BD. To that end, we implemented: *i)* a structural MRI-based ML model; ii) a combined ML model, trained on MRI data and Polygenic Risk Scores (PRS) for different psychiatric disorders.
Methods: 168 depressed patients (73 MDD, 95 BD) were recruited at the IRCCS San Raffaele Scientific Institute. All patients underwent T1-weighted and Diffusion Tensor Imaging scans. Voxel-Based Morphometry (VBM) measures were extracted with Computational Anatomy Toolbox 12 (CAT12). Fractional Anisotropy (FA), Axial Diffusivity (AD), Mean Diffusivity (MD), and Radial Diffusivity (RD) were extracted with Tract-Based Spatial Statistics (TBSS). PRS for MDD, BD, Schizophrenia, Attention Deficit/Hyperactivity Disorder, Anorexia Nervosa and Autism were computed for a subsample of 155 patients (67 MDD; 88 BD) through Infinium PsychArray 24 BeadChip. We trained a Multiple Kernel Learning (MKL) algorithm with voxel-wise VBM and DTI features, subsequently combining them with the extracted PRS.
Results: The neuroimaging model achieved a Balanced Accuracy (BA) of 71.65% and an Area Under the Curve (AUC) of 0.77 (85.44% sensitivity, 57.86% specificity). All the features contributed to the prediction, with AD (63%) and MD (26%) as the most predictive. Adding PRS to neuroimaging resulted in an improved performance, reaching 74.18% BA and 0.77 AUC (90.97% sensitivity, 57.38% specificity). The most predictive features of the neuroimaging-PRS model were MD (56%) and AD (27%).
Conclusions: Structural MRI discriminated between MDD and BD, and adding PRS to neuroimaging features improved the performance of the ML model. These results highlight the predictive power of structural neuroimaging for the differential diagnosis between MDD and BD, as well as prompting multimodal classifiers as a promising tool in the context of precision psychiatry.

Disclosure of Interest: None Declared

Neuroimaging

O021

Neural Associations of Preclinical Alzheimer's Disease in Individuals with Low Anxiety Scores

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Introduction: Preclinical Alzheimer's disease (AD) is characterized by subtle cognitive changes that precede the onset of clinical symptoms. Neuropsychiatric symptoms such as anxiety have been increasingly recognized for their potential role in accelerating disease progression. Although various theories have been proposed, anxiety may exacerbate cognitive decline through mechanisms involving stress-induced neurochemical dysregulation, affecting brain regions vulnerable to AD pathology.
Objectives: This study examines the neural correlates of preclinical AD in individuals with low anxiety scores, employing MRI to explore potential early biomarkers and elucidate the complex role of anxiety in the progression of AD.
Methods: A total of 172 participants from the German Center for Neurodegenerative Diseases Longitudinal Cognitive Impairment and Dementia Study (DELCODE) were categorized into three groups: Healthy Controls (HC, n=59), Subjective Cognitive Decline (SCD, n=77), and Mild Cognitive Impairment (MCI, n=36). Anxiety levels were assessed using the Geriatric Anxiety Inventory-Short Form (GAI-SF), and neural responses to novelty were examined using 3-Tesla MRI. Statistical models were adjusted for relevant covariates, including age, education and study site. The differences of the three groups were analysed by one-way ANOVA contrasts and post-hoc analyses were performed with two sample t-tests.
Results: Significant neural differences were observed across groups, particularly in the precuneus, right angular gyrus, and right cerebellum exterior ($p < 0.001$, $p = 0.001$, and $p = 0.002$ respectively). The SCD group demonstrated greater activation in the right angular gyrus compared to HC ($p = 0.008$), while the MCI group exhibited more pronounced differences L-R precuneus, right cerebellum exterior, right angular gyrus, and right middle frontal gyrus regions indicating further cognitive decline ($p< 0.001$, $p< 0.001$, $p= 0.001$, $p= 0.017$ respectively).
Conclusions: This study identifies critical brain regions, with a particular emphasis on the right angular gyrus, associated with the early stages of AD in individuals with low anxiety scores. The activation in these areas likely correlates with an early inhibition deficit at the systems level in individuals with preclinical memory impairment. However, the role of anxiety in preclinical AD is complex and variable among individuals. Anxiety may serve as an early response to subtle cognitive changes in some, while in others, it might emerge as a consequence of these changes. Moreover, the relationship between anxiety and neural alterations in AD could be bidirectional, where anxiety both influences and is influenced by the disease's progression. These findings highlight the importance of considering anxiety when identifying early biomarkers for AD and suggest that targeted interventions addressing anxiety may help slow cognitive decline.

Disclosure of Interest: None Declared

Precision Psychiatry

O022

Toward precision psychiatry using HD-EEG and normative modeling

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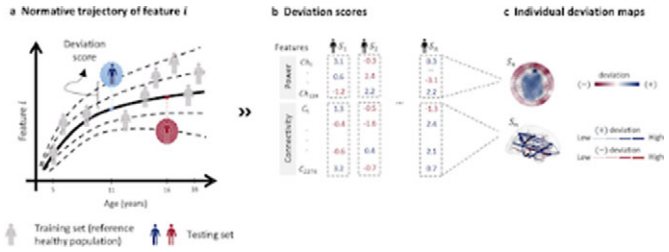
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Introduction: Electroencephalography (EEG) has been extensively studied for decades in psychiatric research. However, its integration into clinical practice as a diagnostic or prognostic tool remains unachieved. We hypothesize that a key reason for this is the underlying heterogeneity among patients, which is often overlooked in psychiatric EEG research that relies on a case-control approach.
Objectives: The main objective of this study is to quantify the electrophysiological heterogeneity of psychiatric disorders.
Methods: We combine HD-EEG with normative modeling to quantify this heterogeneity using two well-established and extensively investigated EEG characteristics—spectral power and functional connectivity—across a cohort of 1,674 patients with attention-deficit/hyperactivity disorder, autism spectrum disorder, learning disorder, or anxiety, and 560 matched controls, see figure 1.
Results: Normative models revealed that deviations from population norms among patients were highly heterogeneous and frequency-dependent. The spatial overlap of deviations among patients did not exceed 40% for spectral power and 24% for connectivity. Taking individual deviations into account significantly enhanced comparative analysis and the identification of patient-specific markers, which showed a correlation with clinical assessments.

Image 1:



Conclusions: Our study underscores the necessity of moving EEG research in psychiatry beyond the group-level approach to achieve precision psychiatry.

Disclosure of Interest: None Declared

Psychopharmacology and Pharmacoeconomics

O023

MM120 (lysergide) in a controlled clinical setting: treatment of generalized anxiety disorder without co-occurring psychotherapeutic intervention

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Introduction: Generalized anxiety disorder (GAD) is among the most common psychiatric disorders and has significant impairment on patients' daily life. Effective and well-tolerated pharmacotherapies are needed. The FDA has noted that the inclusion of psychotherapy within trials complicates assessment of psychedelic drug efficacy, although to date many psychedelic trials have included co-occurring psychotherapy.[1] Co-occurring psychotherapy confounds the evaluation of efficacy and may complicate commercial labeling. A phase 2b study of the dose response to single treatment MM120 (lysergide D-tartrate) suggests a safe, rapid, and durable dose-dependent response in participants with moderate-to-severe GAD[2] and design elements are examined herein.
Objectives: To examine the methodological use of Dosing Session Monitors (DSM) within MM120 treatment without co-occurring of psychotherapy.
Methods: This phase 2b (NCT05407064) multicenter, randomized, double-blind, placebo-controlled study enrolled adults aged 18 to 74 years diagnosed with moderate to severe GAD.[2] Two DSMs, meeting FDA recommended qualifications,[1] were assigned to a participant throughout the study duration. Prior to dosing, participants engaged in baseline study education with their DSMs. During dosing, DSMs provided assistance and comfort as needed and monitored the participant for safety. Starting at 8 hours post-dose, a pre-specified checklist to end the session was administered, although all participants were required to stay onsite a minimum of 12 hours. The follow up period for the trial was 12 weeks, and DSMs only followed up with participants at Day 2, Week 1, and Week 2 post-dose. DSM follow up focused on participant safety and did not include focus on producing post-synaptic change.
Results: In total, 198 participants were enrolled in the study. The phase 2b study demonstrated a statistically significant safe, dose-response relationship at the week 4, 8, and 12 primary and secondary endpoints.[1] Utilizing the prespecified checklist, 45% of participants receiving MM120 100µg met criteria for end of session at 8 hours post dose, with 87.5% achieving criteria at 10 hours.
Conclusions: The results demonstrate that a single treatment with MM120 produces a safe and durable clinical response without co-occurring psychotherapy. These findings indicate that MM120 treatment sessions may be safely shortened from a minimum of 12 hours to 8 hours for some participants, and psychotherapy does not appear to be essential for its safety and efficacy.

1. FDA—Center for Drug Evaluation and Research. Psychedelic drugs: considerations for clinical investigations (FDA-2023-D-1987).

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