Spatial Molecular Mapping of Depression: Divergent Neurotransmitter, Glial, and Mitochondrial Signatures

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2026 10th Scientific School Dynamics of Complex Networks and their Applications (DCNA) | 979-8-3195-2599-4/26/$31.00 ©2026 IEEE | DOI: 10.1109/DCNA72004.2026.11733433

***Abstract*—We conducted a pilot, covariate-controlled spatial correlation study to identify molecular signatures that robustly track with the MDD-vs-healthy control (HC) brain contrast, while accounting for age, sex, education, and symptom severity (MADRS). A total of 163 participants (97 HC, 66 MDD) were included. A region-wise general linear model (GLM) was applied across 166 AAL3 regions of interest (ROIs), modelling the brain measure as a function of group, age, sex, education, and MADRS. The resulting covariate-corrected group contrast map was correlated with ROI profiles from 40 publicly available molecular atlases. After controlling for covariates, 21 out of 40 markers remained significant (FDR $q < 0.05$). Negative correlations (indicating reduced marker distribution in MDD-affected regions) were strongest for opioid receptors, cholinergic terminals, serotonin transporters, NMDA receptors, D2 receptors, and glial markers. MDD-related brain changes exhibit a divergent, bidirectional molecular pattern: reduced expression of classical neuromodulatory and glial systems, coupled with increased mitochondrial metabolic markers. These findings were robust to demographic and clinical confounds. This pilot provides a spatially-resolved molecular framework for future targeted investigations.**

***Index Terms*—fMRI, functional analysis, brain networks, connectivity, major depressive disorder, molecular atlases**

I. Introduction

Major depressive disorder (MDD) is associated with widespread alterations in brain function, involving distributed networks rather than isolated brain regions. Functional neuroimaging can identify these regional patterns [1]–[3]; however, the biological and molecular systems underlying their spatial distribution remain less clear. Relating brain alterations to independently derived molecular atlases provides an opportunity to investigate whether disease-related neuroimaging patterns follow the anatomical distribution of specific neurotransmitter, cellular, and metabolic systems.

Graph-theoretical and machine-learning analyses of functional neuroimaging data have proved effective both in characterising the network reorganisation associated with MDD and in discriminating patients from healthy controls [2], [4], [5]. Comparable data-driven pipelines have been applied to other neuropsychiatric and neurological conditions, including autism spectrum disorder [6] and epilepsy [7], [8], where interpretable and contrastive learning strategies help to isolate the condition-specific components of the recorded signal. These approaches, however, operate entirely at the level of the imaging signal and remain agnostic with respect to the molecular architecture that may generate the observed spatial patterns.

The present pilot study addresses this question by examining the spatial correspondence between the functional brain differences observed between patients with MDD and healthy controls (HC) and publicly available molecular brain atlases. To reduce the influence of demographic and clinical confounding factors, the group contrast was estimated using a region-wise general linear model controlling for relevant covariates. The resulting MDD-related spatial pattern was subsequently correlated with molecular maps representing neurotransmitter systems, glial cell populations, and mitochondrial metabolism.

By integrating functional neuroimaging with molecular atlas information, this approach provides a spatially resolved framework for identifying biological systems associated with MDD-related brain alterations. The findings may also contribute to

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the development of broader nomothetic models of psychiatric disorders by providing molecularly informed network-level evidence that can be integrated with other clinical and biological dimensions [1].

II. Subjects and experimental setup

We recruited a total of 163 participants for the study, divided into two groups: 97 healthy individuals without known psychiatric conditions (the Healthy Controls, HC group) and 66 patients diagnosed with major depressive disorder (the MDD group). Each participant underwent thorough evaluations led by experienced psychiatrists, which included the administration of the Mini International Neuropsychiatric Interview [9] and the Montgomery–Åsberg Depression Rating Scale (MADRS) [10], [11]. Individuals with comorbidities, autoimmune or neurological disorders, previous head trauma, or metal implants incompatible with MRI were excluded.

MRI data were acquired using a 3T GE Discovery 750w system with the same scanning parameters reported previously [1]. The data were preprocessed in SPM12 [12], including motion correction, co-registration of structural and functional data, and normalization to the Montreal Neurological Institute (MNI) standard space. Functional connectivity was subsequently estimated from detrended mean time series extracted from nodes defined by the Automated Anatomical Labeling 3 (AAL3) atlas [13]. Comparable node-wise estimation of functional networks has previously been applied by our group to fMRI, EEG, MEG and fNIRS recordings obtained in both resting-state and task conditions [14]–[18].

III. Methods and results

We interrogated 40 publicly available molecular atlases, including 30 PET-based maps (covering neurotransmitter receptors/transporters such as MOR, MU, SERT, VAChT, D2, NMDA, NAT, GABAa, and metabolic markers) and 10 cellular maps (four glial subtypes and six mitochondrial complexes). These atlases were obtained from the JuSpace repository and prior publications [19].

Initial spatial correlations between the group contrast map and each molecular atlas were computed using JuSpace (v1.3), yielding Pearson's r and exact p-values. To account for potential confounding by demographic and clinical variables, we performed a region-wise general linear model (GLM) across 166 regions of interest (ROIs) from the AAL3 atlas. For each ROI, the imaging measure was modelled as:

$$Y_{roi} = \beta_0 + \beta_1 Age + \beta_2 Sex + \beta_3 Edu + \beta_4 MADRS + \beta_5 Group + \varepsilon \quad (1)$$

The resulting contrast vector (β_5 in Eq. (1), representing the MDD vs HC difference) was then correlated (Pearson) with the ROI profile of each molecular atlas, yielding covariate-corrected correlation coefficients and p-values.

To reduce the multiple-testing burden while retaining biologically plausible candidates, we pre-selected markers with uncorrected $p \leq 0.05$ in the initial JuSpace analysis. Within this reduced set ($k = 25$), we applied Benjamini–Hochberg false discovery rate (FDR) correction at $q \leq 0.05$ to the GLM-corrected p-values. All analyses were conducted in MATLAB (version R2023b) with SPM12 and custom scripts.

After controlling for age, sex, education (Edu), and MADRS, and applying FDR correction ($q < 0.05$) to the pre-filtered marker set (original JuSpace $p < 0.05$), 21 out of 40 markers remained significantly spatially correlated with the depression contrast map (Fig. 1). Negative correlations (indicating reduced marker distribution in MDD-affected regions) were strongest for opioid receptors (MOR, MU; r = -0.38 to -0.45, $q < 0.001$), cholinergic terminals (VAChT; r = -0.25 to -0.30, $q < 0.01$), serotonin transporters (SERT; r = -0.21 to -0.26, $q < 0.01$), NMDA receptors ($r = -0.32$, $q < 0.001$), D2 receptors ($r = -0.35$, $q < 0.001$), and glial markers (Microglia, OPC, Endothelial; r = -0.25 to -0.42, $q < 0.01$). In contrast, all six mitochondrial markers (Complex1-NADH, Complex2-SDH, Complex4-COX, RespiratoryCapacity, TissueDensity, TissueRespCapacity) showed significant positive correlations (r = 0.17 to 0.26, $q < 0.05$), indicating elevated metabolic capacity in regions with larger MDD-related differences. The groups were well matched for age (HC: 41.0 ± 11.9 years; MDD: 41.9 ± 13.1 years) but differed, as expected, on MADRS.

Visualisation of the covariate-corrected MDD vs HC contrast map (Fig. 2) revealed widespread differences predominantly involving limbic, prefrontal, temporal, and insular regions, consistent with the established neurocircuitry of depression. The correlation patterns suggest that these regions are characterised by a dual signature: reduced expression of classical neurotransmitter/glial markers alongside elevated mitochondrial indices.

IV. Conclusions

In this pilot study, we applied a covariate-controlled spatial correlation framework to map the molecular landscape of MDD-related brain alterations. Our key finding is a divergent, system-level signature: regions that distinguish MDD from HC are characterised by both decreased markers of multiple neurotransmitter and glial systems, and increased markers of mitochondrial energy metabolism.

The negative correlations converge with long-standing neurobiological hypotheses. Reduced opioid (MOR/MU) availability aligns with the dysphoria and anhedonia seen in depression, supporting the notion of an impaired endogenous opioid tone [20], [21]. The consistent negative signal for cholinergic (VAChT) and serotonergic (SERT) transporters across multiple independent PET tracers strengthens the cholinergic-serotonergic interaction hypothesis, while the NMDA and D2 findings implicate glutamatergic [22] and dopaminergic [23] circuits—key nodes in the neurobiology of mood regulation and reward. Notably, negative correlations across glial subtypes (Microglia, OPC, Endothelial) suggest that glial dysfunction, beyond neuronal systems, is spatially aligned

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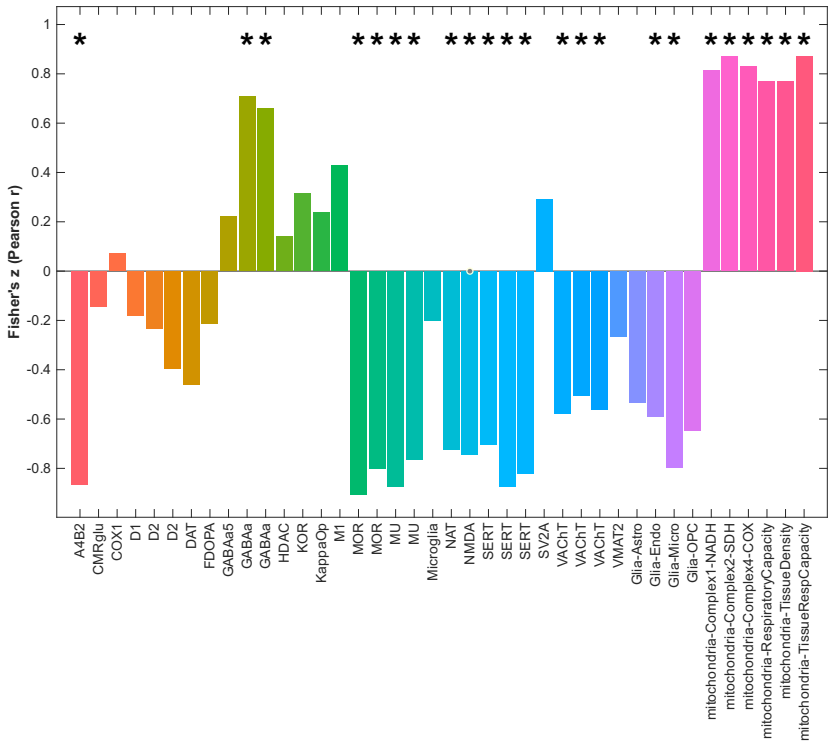


Fig. 1. Bars represent Pearson's correlation coefficients after Fisher's z transformation. Asterisks indicate correlations that remained statistically significant after FDR correction.

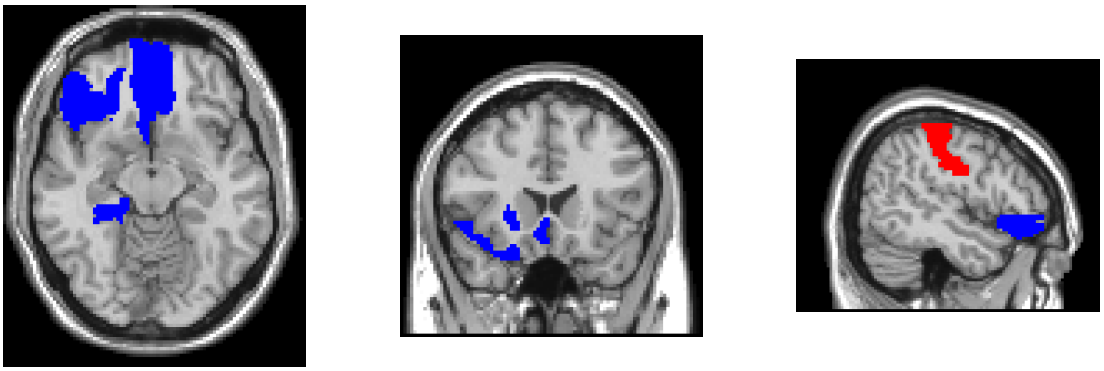


Fig. 2. Spatial correlations between the MDD-related functional brain pattern and PET or cellular molecular maps. Blue denotes reduced expression and red — elevated.

with depressive neuropathology, consistent with post-mortem evidence of reduced glial density in MDD [24], [25].

The positive correlations with mitochondrial markers are particularly novel. Increased respiratory capacity and complex activity in MDD-affected regions may reflect a compensatory metabolic response to chronic cellular stress, perhaps linked to neuroinflammation, oxidative burden, or astrocytic activation [26]. Alternatively, these could indicate a region-specific upregulation of energy demand due to altered neuronal firing or synaptic turnover. This finding, robustly surviving demographic and severity confounds, positions mitochondrial function as a potentially overlooked dimension of depression pathophysiology.

The main limitations of this pilot are its cross-sectional design, the moderate sample size, and the fact that the molecular atlases are group-level templates derived from independent healthy cohorts, so that no subject-specific molecular information is available. Combining molecular priors of this kind with interpretable and contrastive machine-learning models of functional networks [5], [6] is a natural next step towards individualised, biologically grounded markers of depression.

ACKNOWLEDGMENT

The study was funded by Russian Science Foundation (grant 26-71-10028).

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