

1 Section A: Full List of LLM Questions Used in LITR

To support the design of the LLM-Instructed Topological Reconstruction (LITR) module, we developed a set of grounded inquiries aimed at deepening the understanding of each Region of Concern (ROC) included in the brain graph. These questions serve as the foundation for integrating neuroanatomical, cognitive, and pathological knowledge into both node features and graph structure, enabling a more interpretable and biologically plausible model.

The following ten questions were systematically applied to each brain region (ROI) for Major Depressive Disorder, guiding literature retrieval, knowledge-informed graph construction, and semantic embedding generation. Below, we present a representative example using the Precentral_L region to illustrate both the questions and the corresponding LLM-generated answers:

- **Q1:**Please describe in detail the anatomical location of the ROC_name_data within the AAL template.

A:Anatomical Location of the Precentral_L. The Precentral_L is located in the frontal lobe of the brain, specifically in the left hemisphere. It is situated just anterior to the central sulcus (also known as the Rolandic fissure) and is bordered posteriorly by the postcentral gyrus, which is involved in somatosensory processing. The precentral gyrus is often referred to as the primary motor cortex, which is essential for the planning and execution of voluntary movements.

- **Q2:**What are the primary cognitive and neurological functions associated with the ROC_name_data?

A:Primary Functions of the Precentral_L. The primary function of the Precentral_L is motor control. It is responsible for the execution of voluntary movements, particularly those on the contralateral side of the body (right side in this case). The precentral gyrus is organized somatotopically, meaning that different areas correspond to different body parts, with the lower extremities represented medially and the face represented laterally. In addition to motor functions, it also plays a role in motor learning and coordination.

- **Q3:**What is the broader significance of the ROC_name_data in neuroscience research?

A:Significance of the Precentral_L in Neuroscience. In neuroscience, the Precentral_L is significant for several reasons:- **Motor Function**: It is critical for understanding the neural basis of motor control and coordination.- **Neuroplasticity**: It serves as a model for studying neuroplasticity, as it can adapt and reorganize in response to injury or learning.- **Clinical Relevance**: Given its role in motor functions, it is often examined in conditions like stroke, traumatic brain injury, and neurodegenerative diseases.

- **Q4:**What functional or structural abnormalities are typically observed in the ROC_name_data among patients with Major Depressive Disorder?

A:Functional or Structural Abnormalities in MDD. Research has identified several functional and structural abnormalities in the Precentral_L in patients with Major Depressive Disorder:- **Structural Changes**: Some studies have reported reduced gray matter volume in the Precentral_L among individuals with MDD.- **Functional Alterations**: Functional MRI studies often show altered activation patterns in the Precentral_L during tasks involving motor control or emotional processing, indicating potential disruptions in motor function and emotional regulation.

- **Q5:**How can the graph-theoretical properties of the ROC_name_data contribute to modeling dynamic brain networks in depression?

A:Graph Theory Attributes and Dynamic Network Models. Graph theory attributes of the Precentral_L can indeed be utilized to construct dynamic network models for depression. By analyzing the connectivity patterns and network properties of the Precentral_L with other brain regions, researchers can better understand how motor control and emotional regulation interact in the context of MDD. This approach can help identify biomarkers for the disorder and enhance our understanding of its neurobiological underpinnings.

- **Q6:**To what extent does the ROC_name_data contribute to classification performance in MDD prediction models?

A:Importance in Classification Models for MDD. The Precentral_L can play a significant role in classification models for Major Depressive Disorder. Its involvement in motor functions and emotional regulation may contribute to distinguishing between depressed and non-depressed individuals.

Features derived from imaging data related to the Precentral_L can improve the accuracy of machine learning models aimed at predicting MDD.

- **Q7:**What are the current controversies or conflicting findings regarding the role of the ROC_name_data in MDD research?

A:Controversial Points in MDD Research. Controversial points regarding the Precentral_L in MDD research include:- **Inconsistent Findings**: While some studies report atrophy or functional abnormalities, others find no significant differences, leading to debates about the reliability of these findings.- **Causality vs. Correlation**: The relationship between abnormalities in the Precentral_L and the onset or severity of MDD remains unclear, with ongoing discussions about whether these changes are a cause or consequence of the disorder.

- **Q8:**Do abnormalities in the ROC_name_data tend to reverse with symptom remission during the course of Major Depressive Disorder?

A:Reversal of Abnormalities with Symptom Remission. There is evidence suggesting that some abnormalities in the Precentral_L may reverse with symptom remission during the course of Major Depressive Disorder. Longitudinal studies have shown that successful treatment (e.g., psychotherapy, pharmacotherapy) can lead to normalization of function and structure in this region, although individual responses can vary.

- **Q9:**Which other brain regions exhibit strong structural or functional associations with the ROC_name_data?

A:Strong Associations with Other Brain Regions. The Precentral_L exhibits strong associations with several other brain regions, including:- **Postcentral Gyrus**: For somatosensory processing.- **Supplementary Motor Area**: Involved in planning and coordinating movements.- **Basal Ganglia**: Important for motor control and reward processing.- **Anterior Cingulate Cortex**: Related to emotional regulation and decision-making.

- **Q10:**Are abnormalities in the ROC_name_data consistently observed across multimodal imaging data (e.g., sMRI, fMRI, DTI) in MDD studies?

A:Consistency Across sMRI/fMRI/DTI Multimodal Data. There is some consistency in the abnormalities of the Precentral_L observed across different modalities such as structural MRI (sMRI), functional MRI (fMRI), and diffusion tensor imaging (DTI). While findings may vary depending on the specific methodology and population studied, multiple studies have reported similar patterns of structural and functional alterations in the Precentral_L in MDD, supporting the idea that this region plays a crucial role in the disorder.This comprehensive overview highlights the significance of the Precentral_L in the context of Major Depressive”

By combining language-informed priors with data-driven brain signals, LITR enhances both the structural and functional fidelity of the resulting graph, providing a biologically grounded foundation for accurate and interpretation.

2 Section B: Top 10 Brain Regions and Literature Support

To enhance the transparency and interpretability of our model, we present the top-10 most influential brain regions identified through gradient-based attribution. For each of these regions, the Literature-Augmented Semantic Aggregation (LASA) module automatically retrieves the top-5 most relevant publications based on semantic weight, reflecting the significance of these studies in shaping the final graph representation. The selected literature provides valuable insight into the role of each brain region in Major Depressive Disorder, including their structural and functional characteristics, as well as their relationship with depression. These associations are not just based on anatomical and functional data but are derived from cross-modal attention scores, which quantify the relevance of each publication to the brain region in question.

Table 1,2,3 and 4 show key brain regions and their first five literature references. We take the brain region *PCUN.R*(Table 1)as an example to highlight the important value of each paper in depression research.

The Precuneus Right (*PCUN.R*) is involved in high-level cognitive functions such as self-reflection, memory retrieval, and the integration of sensory information. Research indicates that this region is often implicated in depressive symptomatology, particularly through its role in the default mode network (DMN). The LASA module identified the following key papers:

Brain Region	Weight	Title
PCUN.R	0.28	Yao C, Wang P, **ao Y, et al. Increased individual variability in functional connectivity of the default mode network and its genetic correlates in major depressive disorder[J]. Scientific Reports, 2025, 15(1): 8853.
	0.27	Tao Y, Zhou Y, Li W, et al. Altered default mode network and glymphatic function in insomnia with depression: A multimodal MRI study[J]. Sleep Medicine, 2025, 131: 106482.
	0.22	Zhu Y, Huang T, Li R, et al. Distinct resting-state effective connectivity of large-scale networks in first-episode and recurrent major depression disorder: evidence from the REST-meta-MDD consortium[J]. Frontiers in Neuroscience, 2023, 17: 1308551.
	0.14	Hu X, Cheng B, Tang Y, et al. Gray matter volume and corresponding covariance connectivity are biomarkers for major depressive disorder[J]. Brain Research, 2024, 1837: 148986.
	0.09	Camilleri J A, Hoffstaedter F, Zavorotny M, et al. Electroconvulsive therapy modulates grey matter increase in a hub of an affect processing network[J]. NeuroImage: Clinical, 2020, 25: 102114.

Table 1: Summary of research literature for brain region *PCUN.R* in major depressive disorder. Each brain region spans five associated publications.

- Weight: 0.28. Yao C, Wang P, **ao Y, et al. Increased individual variability in functional connectivity of the default mode network and its genetic correlates in major depressive disorder[J]. Scientific Reports, 2025, 15(1): 8853.
This paper explores how connectivity variability in the DMN, with a focus on the precuneus, is associated with genetic predispositions to MDD.
- Weight: 0.27. Tao Y, Zhou Y, Li W, et al. Altered default mode network and glymphatic function in insomnia with depression: A multimodal MRI study[J]. Sleep Medicine, 2025, 131: 106482.
This study examines the overlap between altered DMN function and glymphatic dysfunction in patients with both insomnia and MDD.
- Weight: 0.22. Zhu Y, Huang T, Li R, et al. Distinct resting-state effective connectivity of large-scale networks in first-episode and recurrent major depression disorder: evidence from the REST-meta-MDD consortium[J]. Frontiers in Neuroscience, 2023, 17: 1308551.
This research highlights how altered connectivity patterns in the precuneus differ between first-episode and recurrent depression.
- Weight: 0.14. Hu X, Cheng B, Tang Y, et al. Gray matter volume and corresponding covariance connectivity are biomarkers for major depressive disorder[J]. Brain Research, 2024, 1837: 148986.
This paper investigates structural changes in the precuneus and their relationship to cognitive decline in MDD patients.
- Weight: 0.09. Camilleri J A, Hoffstaedter F, Zavorotny M, et al. Electroconvulsive therapy modulates grey matter increase in a hub of an affect processing network[J]. NeuroImage: Clinical, 2020, 25: 102114.
This study presents findings on how ECT affects the precuneus as part of its modulation of brain network connectivity.

By automating the retrieval of the top-5 most relevant publications for each brain region using the LASA module, we can better understand how these regions contribute to the complex neurobiological mechanisms of MDD. Each of the identified studies not only strengthens the scientific basis of our model but also enhances the interpretability of the brain regions involved. This approach, which incorporates semantic attribution and graph-based modeling, provides a more biologically grounded foundation for understanding and diagnosing MDD, facilitating the development of more effective and targeted treatments.

Brain Region	Weight	Title
OLF.R	0.45	Herrmann T, Koepfel C, Linn J, et al. Olfactory brain activations in patients with major depressive disorder[J]. Scientific reports, 2023, 13(1): 10072.
	0.17	Yuan T F, Slotnick B M. Roles of olfactory system dysfunction in depression[J]. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2014, 54: 26-30.
	0.14	Zhang C, Liang J, Yan H, et al. Neuroimaging changes in pre-treatment and post-treatment patients with bipolar disorder and their relationship with genetic characteristics[J]. Journal of Affective Disorders, 2025: 119572.
	0.13	Andres-Rodriguez L, Borrás X, Feliu-Soler A, et al. Peripheral immune aberrations in fibromyalgia: A systematic review, meta-analysis and meta-regression[J]. Brain, behavior, and immunity, 2020, 87: 881-889.
	0.11	Camilleri J A, Hoffstaedter F, Zavorotny M, et al. Electroconvulsive therapy modulates grey matter increase in a hub of an affect processing network[J]. NeuroImage: Clinical, 2020, 25: 102114.
SMA.L	0.55	Ren W, Wang M, Wang Q, et al. Altered functional connectivity in patients with post-stroke fatigue: A resting-state fMRI study[J]. Journal of Affective Disorders, 2024, 350: 468-475.
	0.24	Chopra A, Singal P, Kodya S. Impact of deep transcranial magnetic stimulation on insomnia outcomes in patients with treatment-resistant depression: a retrospective study[J]. Journal of Clinical Sleep Medicine, 2024, 20(5): 813-815.
	0.11	Di Cerbo A. Convergences and divergences in the ICD-11 vs. DSM-5 classification of mood disorders[J]. Turk Psikiyatri Dergisi, 2021, 32(4): 293.
	0.06	Bennie J A, De Cocker K, Biddle S J H, et al. Joint and dose-dependent associations between aerobic and muscle-strengthening activity with depression: A cross-sectional study of 1.48 million adults between 2011 and 2017[J]. Depression and anxiety, 2020, 37(2): 166-178.
	0.04	Park E H, Jung M H. The impact of major depressive disorder on adaptive function: A retrospective observational study[J]. Medicine, 2019, 98(52): e18515.
CRBL45.L	0.50	Zhang R, Zhou X, Yuan D, et al. Associations between cerebellum and major psychiatric disorders: a bidirectional Mendelian randomization study[J]. European Archives of Psychiatry and Clinical Neuroscience, 2025: 1-11.
	0.19	Chen S, Zhang X, Lin S, et al. Connectome architecture modulates the gray matter atrophy in major depression disorder patients with diverse suicidal ideations[J]. Brain imaging and behavior, 2024, 18(2): 378-386.
	0.15	V. Farahani F, Fafrowicz M, Karwowski W, et al. Identifying diurnal variability of brain connectivity patterns using graph theory[J]. Brain Sciences, 2021, 11(1): 111.
	0.09	Miao H, Zhong S, Liu X, et al. Childhood trauma history is linked to abnormal brain metabolism of non-medicated adult patients with major depressive disorder[J]. Journal of affective disorders, 2022, 302: 101-109.
	0.07	Gadotti V M, Zamponi G W. Anxiolytic effects of the flavonoid luteolin in a mouse model of acute colitis[J]. Molecular brain, 2019, 12(1): 114.

Table 2: Summary of research literature for brain regions *OLF.R*, *SMA.L*, *CRBL45.L* in major depressive disorder. Each brain region spans five associated publications.

Brain Region	Weight	Title
PCG.L	0.50	Sun J, Chen L, He J, et al. Altered brain function in first-episode and recurrent depression: a resting-state functional magnetic resonance imaging study[J]. <i>Frontiers in Neuroscience</i> , 2022, 16: 876121.
	0.19	Uyar B, Donmezdil S. Comparison of healthcare workers and non-healthcare workers in terms of obsessive-compulsive and depressive symptoms during COVID-19 pandemic: a longitudinal case-controlled study[J]. <i>Frontiers in Public Health</i> , 2023, 11: 1283317.
	0.15	Bai M, Yu H, Chen C, et al. Pigment epithelium-derived factor may induce antidepressant phenotypes in mice by the prefrontal cortex[J]. <i>Neuroscience Letters</i> , 2022, 771: 136423.
	0.09	Camilleri J A, Hoffstaedter F, Zavorotny M, et al. Electroconvulsive therapy modulates grey matter increase in a hub of an affect processing network[J]. <i>NeuroImage: Clinical</i> , 2020, 25: 102114.
	0.07	Husain S F, Tang T B, Yu R, et al. Cortical haemodynamic response measured by functional near infrared spectroscopy during a verbal fluency task in patients with major depression and borderline personality disorder[J]. <i>EBioMedicine</i> , 2020, 51.
PoCG.R	0.33	Uyar B, Donmezdil S. Comparison of healthcare workers and non-healthcare workers in terms of obsessive-compulsive and depressive symptoms during COVID-19 pandemic: a longitudinal case-controlled study[J]. <i>Frontiers in Public Health</i> , 2023, 11: 1283317.
	0.28	Camilleri J A, Hoffstaedter F, Zavorotny M, et al. Electroconvulsive therapy modulates grey matter increase in a hub of an affect processing network[J]. <i>NeuroImage: Clinical</i> , 2020, 25: 102114.
	0.15	Husain S F, Tang T B, Yu R, et al. Cortical haemodynamic response measured by functional near infrared spectroscopy during a verbal fluency task in patients with major depression and borderline personality disorder[J]. <i>EBioMedicine</i> , 2020, 51.
	0.15	Whitfield-Gabrieli S, Wendelken C, Nieto-Castañón A, et al. Association of intrinsic brain architecture with changes in attentional and mood symptoms during development[J]. <i>JAMA psychiatry</i> , 2020, 77(4): 378-386.
	0.09	Park E H, Jung M H. The impact of major depressive disorder on adaptive function: A retrospective observational study[J]. <i>Medicine</i> , 2019, 98(52): e18515.
PHG.L	0.41	Rolls E T, Cheng W, Gilson M, et al. Effective connectivity in depression[J]. <i>Biological Psychiatry: Cognitive Neuroscience and Neuroimaging</i> , 2018, 3(2): 187-197.
	0.19	Yang Y, Bai R, Liu S, et al. Abnormal brain functional networks in systemic lupus erythematosus: a graph theory, network-based statistic and machine learning study[J]. <i>Brain Communications</i> , 2025, 7(2): fcaf130.
	0.15	Qiu H, Li X, Luo Q, et al. Alterations in patients with major depressive disorder before and after electroconvulsive therapy measured by fractional amplitude of low-frequency fluctuations (fALFF)[J]. <i>Journal of affective disorders</i> , 2019, 244: 92-99.
	0.14	Pilisi R, Tényi T, Büki A, et al. The role of repetitive transcranial magnetic stimulation in the treatment of mental disorders, especially in treatment-resistant major depressive disorder[J]. <i>Orvosi Hetilap</i> , 2020, 161(1): 3-10.
	0.12	Andres-Rodriguez L, Borrás X, Feliu-Soler A, et al. Peripheral immune aberrations in fibromyalgia: A systematic review, meta-analysis and meta-regression[J]. <i>Brain, behavior, and immunity</i> , 2020, 87: 881-889.

Table 3: Summary of research literature for brain regions *PCG.L*, *PoCG.R*, *PHG.L* in major depressive disorder. Each brain region spans five associated publications.

Brain Region	Weight	Title
CRBL3.R	0.72	Alalade E, Denny K, Potter G, et al. Altered cerebellar-cerebral functional connectivity in geriatric depression[J]. PloS one, 2011, 6(5): e20035.
	0.14	Chen S, Zhang X, Lin S, et al. Connectome architecture modulates the gray matter atrophy in major depression disorder patients with diverse suicidal ideations[J]. Brain imaging and behavior, 2024, 18(2): 378-386.
	0.05	Miao H, Zhong S, Liu X, et al. Childhood trauma history is linked to abnormal brain metabolism of non-medicated adult patients with major depressive disorder[J]. Journal of affective disorders, 2022, 302: 101-109.
	0.05	Miao H, Zhong S, Liu X, et al. Childhood trauma history is linked to abnormal brain metabolism of non-medicated adult patients with major depressive disorder[J]. Journal of affective disorders, 2022, 302: 101-109.
	0.03	Amitai M, Taler M, Ben-Baruch R, et al. Increased circulatory IL-6 during 8-week fluoxetine treatment is a risk factor for suicidal behaviors in youth[J]. Brain, behavior, and immunity, 2020, 87: 301-308.
IOG.L	0.31	Liu Y, Dong K, Sun L. Divergent spatiotemporal signatures characterize impaired facial emotional recognition in major depressive disorder: An event-related microstate study[J]. Journal of Affective Disorders, 2025, 381: 281-290.
	0.29	Hou Z, Chen Y, Sun Y, et al. Sleep duration and insomnia with comorbid depression and anxiety symptoms in Chinese adults: A cross-sectional study[J]. Nature and Science of Sleep, 2023: 1079-1091.
	0.14	Husain S F, Tang T B, Yu R, et al. Cortical haemodynamic response measured by functional near infrared spectroscopy during a verbal fluency task in patients with major depression and borderline personality disorder[J]. EBioMedicine, 2020, 51.
	0.13	Botsford J, Schulze L, Bohländer J, et al. Interpersonal trust: development and validation of a self-report inventory and clinical application in patients with borderline personality disorder[J]. Journal of personality disorders, 2021, 35(3): 447-468.
	0.13	Rasing S P A, Stikkelbroek Y A J, Boddien D H M. Is digital treatment the holy grail? Literature review on computerized and blended treatment for depressive disorders in youth[J]. International Journal of Environmental Research and Public Health, 2020, 17(1): 153.
CRBL45.R	0.38	Zhang R, Zhou X, Yuan D, et al. Associations between cerebellum and major psychiatric disorders: a bidirectional Mendelian randomization study[J]. European Archives of Psychiatry and Clinical Neuroscience, 2025: 1-11.
	0.18	Chen S, Zhang X, Lin S, et al. Connectome architecture modulates the gray matter atrophy in major depression disorder patients with diverse suicidal ideations[J]. Brain imaging and behavior, 2024, 18(2): 378-386.
	0.16	Miao H, Zhong S, Liu X, et al. Childhood trauma history is linked to abnormal brain metabolism of non-medicated adult patients with major depressive disorder[J]. Journal of affective disorders, 2022, 302: 101-109.
	0.15	Keszler G, Molnár Z, Rónai Z, et al. Association between anxiety and non-coding genetic variants of the galanin neuropeptide[J]. PLoS One, 2019, 14(12): e0226228.
	0.14	Gadotti V M, Zamponi G W. Anxiolytic effects of the flavonoid luteolin in a mouse model of acute colitis[J]. Molecular brain, 2019, 12(1): 114.

Table 4: Summary of research literature for brain regions *CRBL3.R*, *IOG.L*, *CRBL45.R* in major depressive disorder. Each brain region spans five associated publications.