Multimodal MRI analysis of brain structure and function in schizophrenic cohorts

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***Abstract*—Schizophrenia, a profound psychiatric challenge affecting the global population, remains a focus of intensive research. In this ongoing project, we initiate the development of a comprehensive pipeline for the analysis of magnetic resonance imaging (MRI) scans, aiming to unravel the complex dynamics associated with High-Risk Mental States (HRMS) and First Episode of Psychosis (FEP). The project spans a longitudinal cohort study, providing a 2-year prognostic trajectory evaluation for individuals in HRMS and those experiencing FEP.**

The neuroimaging component plays a pivotal role in understanding the intricate mind-brain interaction. MRI sessions, incorporating structural and functional scans, commenced with an initial dataset of 10 patients. The preprocessing of T1 scans involves segmentation and skull stripping, laying the foundation for subsequent analyses. Functional MRI (fMRI) scans, focusing on the cingulate gyrus associated with psychosis, offer dynamic insights into neural processes.

Our current analysis, albeit with a limited dataset, sets the groundwork for future investigations. Both structural (T1) and functional (fMRI) MRI results are inconclusive at this early stage due to the small dataset. The ongoing exploration of functional activation patterns in the cingulate gyrus provides valuable early insights. The pipeline's developmental phase anticipates an expanded dataset over the next year and a half, promising a more comprehensive understanding of schizophrenia's neuroimaging correlates.

This project underscores the evolving nature of psychiatric research, acknowledging the ongoing journey toward a deeper comprehension of schizophrenia's complexities. As the dataset grows and the pipeline refines, our efforts aim to contribute significantly to the broader understanding of this debilitating disorder.

1. Introduction

Mental illness & Schizophrenia

Mental illness is a vast and multifaceted category encompassing various conditions that profoundly affect cognitive, emotional, and behavioral well-being. The impact of mental illness extends beyond the individual, creating challenges for families, communities, and global public health systems. These conditions disrupt an individual's thinking, mood, and daily functioning, creating a pervasive and complex challenge for societies worldwide.

Globally, mental illness has emerged as a significant public health concern, affecting millions of individuals across diverse demographics. The World Health Organization (WHO) emphasizes the widespread prevalence and far-reaching consequences of mental health disorders, underscoring the urgent need for comprehensive research and effective interventions. Within this landscape, schizophrenia stands as a particularly severe mental disorder, disrupting thought processes, perceptions, and emotions. The global prevalence of schizophrenia emphasizes its critical role in mental health research, with implications for diagnosis, treatment, and prevention [1].

Within the spectrum of mental health disorders, certain individuals are at a heightened risk of transitioning from a high-risk profile to experiencing a first psychotic episode. The identification of these high-risk factors is crucial for early intervention and the development of targeted preventive care strategies. Factors contributing to this vulnerability include genetic predisposition, environmental influences, and neurodevelopmental markers [2].

This research project addresses the pressing need for improved protocols in identifying individuals at high risk of developing psychosis. By concentrating on early detection, the protocol aims to provide timely and targeted preventive care for these vulnerable populations. This includes interventions that extend beyond the traditional scope of mental health care, incorporating psychoeducation, community support, and pharmacological interventions [3].

The mind-brain interaction

The mind-brain interaction forms the intricate foundation of our understanding of mental health. This relationship is bidirectional, suggesting that changes in brain function can influence mental processes, and vice versa. For instance, psychological stress can impact neural activity, while neurochemical imbalances can significantly influence mood and cognition [4].

Navigating the vast terrain of consciousness studies involves confronting the explanatory gap, which comprises the "easy" and "hard" problems of consciousness. While the "easy" problems focus on understanding specific cognitive functions, the "hard" problem delves into the intricate complexities of subjective experiences. To bridge this gap, a comprehensive exploration is essential, seeking to unveil how physical brain processes correlate with the intricate tapestry of human consciousness [5].

Defining the mind requires navigating a spectrum of philosophical models that shape our understanding of its relationship with the brain. Traditionally, many researchers have leaned towards materialistic and functionalistic views, but this project adopts an open perspective to explore the intricate nature of the mind-brain interaction.

Several philosophical models define the brain as a product, conceptualizing the mind as the local byproduct of individual brain activity. Identity theories [6, 7], functionalism [8, 9], connectionism [10, 11], biological naturalism [12, 13], computational theory of mind [14, 15], emergentism [16, 17], and materialism [18, 19] all align with this view, emphasizing the uniqueness of the mind as it emerges from individual brain processes.

On the contrary, alternative philosophical models posit the mind as a universal field or property, suggesting an interaction with the brain that goes beyond causation. Substance dualism [20, 21], property dualism [22, 23], idealism [24, 25], and panpsychism [26, 27] represent these views, proposing a more expansive and interconnected relationship between the mind and the brain, where the mind is considered a universal force or property influencing consciousness.

In the realm of consciousness studies, these contrasting perspectives open doors to diverse hypotheses and approaches. By acknowledging the multiplicity of viewpoints, this project aims to contribute to a more nuanced and comprehensive understanding of the mind-brain interaction. This openness invites exploration beyond conventional materialistic and functionalistic frameworks, fostering an environment where diverse philosophical models can inform and enrich our understanding of consciousness and mental processes.

Bridging the gap

In the pursuit of unraveling the intricate relationship between the mind and the brain, neuroscience employs a diverse array of tools and methodologies, each contributing to a more profound understanding of the mind-brain interaction. One pivotal avenue involves uncovering abnormal neurochemical processes associated with mental illness. Delving into the intricate mechanisms underlying these conditions, researchers investigate neurotransmitters such as dopamine and glutamate, providing valuable insights into the neurochemical basis of mental health disorders [28].

Artificial intelligence (AI) and image processing algorithms stand out as indispensable tools in deciphering the complexities of neuroimaging data. These advancements enable the extraction of meaningful patterns and correlations from vast datasets, offering unprecedented insights into the mind-brain relationship. The refinement of neuroimaging techniques, facilitated by sophisticated algorithms, enhances the accuracy and efficiency of data interpretation, pushing the boundaries of our understanding [29].

Beyond the traditionally implied materialistic and functionalistic models in research, this project explores new philosophical frameworks, recognizing their paramount importance. Alternative perspectives broaden our understanding of the mind-brain interaction, challenging traditional paradigms and fostering fresh insights. This intellectual exploration opens avenues for innovative approaches and hypotheses, contributing to a richer understanding of consciousness and mental processes [30].

Central to this research project is a specific emphasis on finding reliable biomarkers, a key tool in bridging the explanatory gap between neurochemical processes and mental health disorders. Concentrating on this aspect, the study aims to identify correlations that establish a robust foundation for providing preventive care strategies tailored to individuals at high risk of developing psychosis [31].

2. Study Design

Schizophrenia, a heterogeneous psychiatric disorder with diverse clinical and biological manifestations, stands as a major cause of disability among young individuals. Identifying those in High-Risk Mental States of developing psychosis (HRMS) emerges as a crucial strategy to enhance prognosis and functionality in this disorder. Despite being an emerging field, few studies address the characteristics and risk factors of these individuals in their transition to psychosis.

The objective of this project is to establish a longitudinal cohort of individuals aged 16 to 35, comprising three subgroups: 1) individuals with HRMS; 2) individuals with a diagnosis of first-episode psychosis (FEP); and 3) healthy controls. The 2-year prognosis evaluation will encompass measuring the transition to psychosis and the onset of other psychiatric disorders in the HRMS group, and the stability of diagnosis and socio-occupational functioning in the FEP group. The secondary objective will explore the impact of specific predictors (clinical, neuropsychological, and neuroimaging) on this prognosis, enhancing the ability to predict outcomes and implement preventive interventions in psychosis.

Participants with HRMS and FEP will undergo 3-tesla magnetic resonance imaging sessions at the study's initiation and during the third visit (2 years of follow-up). Healthy controls will undergo this test at the study's outset. These sessions will utilize standardized scanning sequences, including T1 and T2 structural images, H-MRS in the anterior cingulate cortex and left hippocampus, and resting-state functional magnetic resonance imaging (rs-fMRI).

Data collection will utilize standardized scanning sequences previously employed in European multicenter studies such as PSYSCAN, OPTiMiSE, and EU-GEI, minimizing variation between recruitment sites. Structural image parameters will be based on those from the Alzheimer's Disease Neuroimaging Initiative (ADNI), specifically developed for multicenter studies. The sequence will include a FLAIR scan, classified as a clinical examination, performed at HUB or OSATEK based on availability. Magnetic resonance data will be transferred to OSATEK via a secure server, ensuring efficient data flow and compliance with privacy laws, guaranteeing central quality control and audit.

For this preliminary phase of the project, we worked with a dataset comprising a total of 10 subjects, categorized into three groups: 4 control subjects, 2 individuals in High-Risk Mental States (EMA), and 4 individuals experiencing a First Episode of Psychosis (PSI).

The neuroimaging component of the study involved two distinct MRI modalities: T1 scans and functional MRI (fMRI)

scans. T1 scans provide detailed structural information about the brain, allowing for the assessment of anatomical features. The parameters for the T1 scans were as follows: Field of View (FOV) of 248x256x208, voxel resolution of 1x1x1, a response time of 2300 ms, and an echo time of 2.98 ms.

Functional MRI (fMRI) scans, on the other hand, focus on capturing dynamic changes in brain activity associated with specific tasks or at rest. The parameters for the fMRI scans were: Field of View (FOV) of 88x88x60, voxel resolution of 2.5x2.5x2.5, a response time of 1500 ms, and an echo time of 33 ms. These fMRI scans provide insights into the functional connectivity and activation patterns within the brain, with a specific focus on regions associated with psychosis, such as the cingulate gyrus.

While the dataset is currently limited to 10 subjects, comprising controls, individuals in High-Risk Mental States (EMA), and those with a First Episode of Psychosis (PSI), this serves as an initial exploration. As the project progresses, the dataset is expected to expand, providing a more comprehensive foundation for subsequent analyses and a deeper understanding of the neuroimaging correlates of schizophrenia.

3. Preprocessing

3.1. Structural data

The T1 data underwent a comprehensive preprocessing pipeline utilizing SPM12, integrating segmentation, bias correction, and spatial normalization into a unified model—an extension of the unified segmentation algorithm, "New Segment" in SPM8. This sophisticated process classified the data into distinct tissue types, including white matter, grey matter, CSF, bone, soft tissue, and air/background. The iterative algorithm addressed the circularity in traditional segmentation methods, employing a generative model with parameters for image intensity non-uniformity, such as FWHM of the bias, bias regularization, and a cleanup procedure.

This integrated model, detailed in the Unified Segmentation paper [32], represents an evolution of the older algorithm, introducing improvements like nuanced mixing proportions, an enhanced registration model, multi-spectral data integration, and an extended set of tissue probability maps. Despite ongoing development of toolbox options and pending seamless integration into SPM8, this approach has proven effective. Many researchers historically relied on older SPM versions for optimized voxel-based morphometry (VBM), emphasizing spatial normalization, tissue segmentation, and smoothing before statistical tests. The aim was to align brain images with standard space, mitigating confounding effects from non-brain structural variability.

The unified model overcomes the historical circularity challenge, where registration required initial tissue classification and vice versa. By consolidating both components into a single generative model, it includes parameters addressing image intensity non-uniformity. The iterative estimation of model parameters alternates among classification, bias correction, and registration steps, providing a superior alternative to serial applications of each component.

The data were classified into different tissue types based on tissue probability maps. The number of Gaussians used to represent the intensity distribution for each tissue class was flexible, acknowledging the non-Gaussian nature of tissue intensity distributions. The unified segmentation algorithm also allowed for the consideration of multiple channels, enabling the integration of information from scans with different contrasts.

The preprocessing pipeline included the consideration of warping options and parameters, such as MRF cleanup, to enhance the accuracy of subsequent analyses. Affine regularization ensured robust initial alignment, and the procedure included the derivation of a fudge factor based on smoothness, allowing for improved model accuracy.

Deformation fields, both forward and inverse, could be saved for further analysis. The preprocessing pipeline also considered voxel sizes and bounding box specifications for the written normalized or imported images.

In summary, the T1 preprocessing pipeline was a sophisticated and integrated approach that aimed to enhance the accuracy of subsequent analyses by addressing bias, improving tissue classification, and achieving spatial normalization. The unified segmentation algorithm in SPM12 allowed for a comprehensive and iterative process that considered multiple parameters to optimize the results.

In the preprocessing section, we present three figures, each consisting of four images, to illustrate the results of the structural data preprocessing for control (Fig. 1), EMA (Fig. 2), and PSI (Fig. 3) groups.

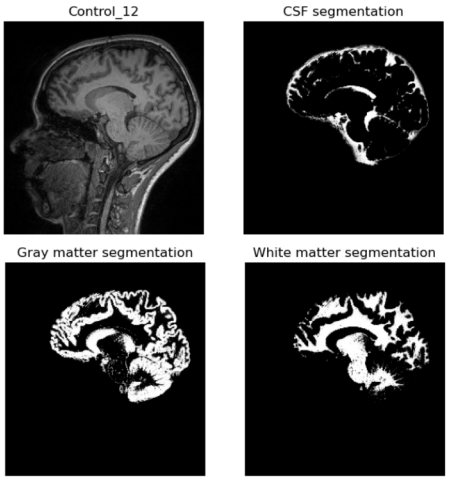

Fig. 1: The figure displays the original T1-weighted image of one subject of the control group, the cerebrospinal fluid (CSF) segmented mask, the segmented gray matter mask and the segmented white matter mask.

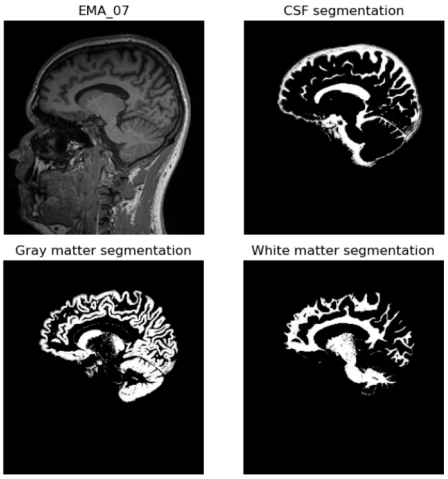

Fig. 2: The figure displays the original T1-weighted image of one subject of the EMA group, the cerebrospinal fluid (CSF) segmented mask, the segmented gray matter mask and the segmented white matter mask.

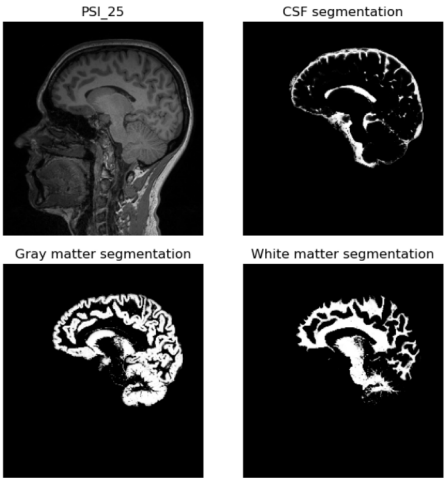

Fig. 3: The figure displays the original T1-weighted image of one subject of the PSI group, the cerebrospinal fluid (CSF) segmented mask, the segmented gray matter mask and the segmented white matter mask.

3.2. Functional data

Functional and anatomical data were preprocessed using a flexible preprocessing pipeline [33] including realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation and MNI-space normalization, and smoothing. Functional data were realigned using SPM realign & unwarp procedure [34], where all scans were coregistered to a reference image (first scan of the first session) using a least squares approach and a 6 parameter (rigid body) transformation [35], and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of the functional data was corrected following SPM slice-timing correction (STC) procedure [36, 37], using sinc temporal interpolation to resample each slice BOLD timeseries to a common mid-acquisition time. Potential outlier scans were identified using ART [38] as acquisitions with framewise displacement above 0.5 mm or global BOLD signal changes above 3 standard deviations [39, 40], and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 2.5 mm isotropic voxels following a direct normalization procedure [32, 41] using SPM unified segmentation and normalization algorithm [42, 43] with the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 8 mm full width half maximum (FWHM).

Two figures are presented below to visually represent the impact of the preprocessing pipeline on the functional. The first figure (Fig. 4) provides insight into the initial state of the functional images, emphasizing any variations or artifacts present in the raw data. The second figure (Fig. 5) highlights the effectiveness of the preprocessing pipeline in enhancing the quality and consistency of the functional data. By juxtaposing the preprocessed and raw data, these figures serve as valuable tools for assessing the impact of the preprocessing steps on the functional images across the cohort of ten subjects.

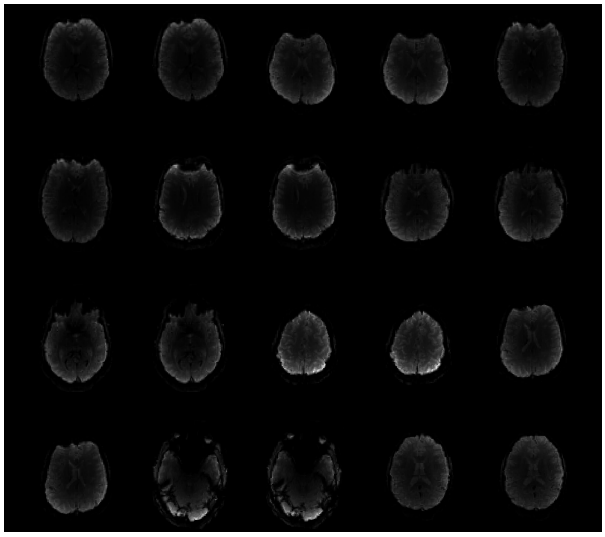

Fig. 4: The figure captures the first and last volume of each subject's functional data before undergoing preprocessing.

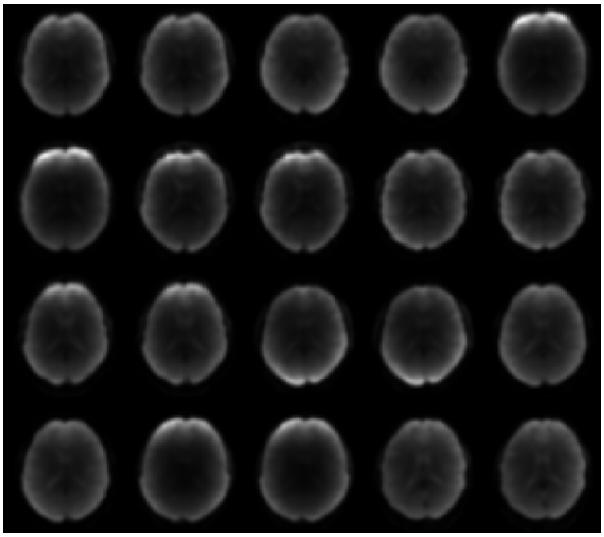

Fig. 5: The figure captures the first and last volume of each subject's functional data after undergoing preprocessing.

In addition, functional data were denoised using a standard denoising pipeline [43] including the regression of potential confounding effects characterized by white matter timeseries (10 CompCor noise components), CSF timeseries (5 CompCor noise components), motion parameters and their first order derivatives (12 factors) [44] , outlier scans (below 63 factors) [39], session effects and their first order derivatives (2 factors), and linear trends (2 factors) within each functional run, followed by high-pass frequency filtering of the BOLD timeseries [45] above 0.01 Hz. CompCor [46, 47] noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 199.8 to 257.1 (average 242.6) across all subjects [40].

4. Analysis

4.1. Structural data

In the analysis of structural data, our study delved into a comprehensive examination of various parameters derived from the segmented tissue images obtained through meticulous preprocessing. These parameters play a pivotal role in unraveling crucial insights into the neuroanatomical characteristics of our subjects and are instrumental in understanding potential variations associated with the studied groups. The computed parameters include brain volume, gray matter volume, gray matter ratio (expressed as the ratio of gray matter volume to brain volume), white matter volume, white matter ratio (calculated as the ratio of white matter volume to brain volume), and cerebrospinal fluid volume. Each of these parameters serves as a valuable metric for investigating structural alterations and abnormalities, offering a nuanced perspective on brain morphology and composition.

- Brain Volume: The brain volume, representing the total space occupied by the entire brain, is a foundational metric crucial for structural assessments. This parameter allows for direct comparisons of overall brain size across different subjects, forming the basis for various analyses in neuroimaging studies.

- White Matter Volume: White matter volume encompasses the space occupied by nerve fibers and myelinated axons within the brain's white matter regions. Exploring white matter volume is crucial for understanding neural connectivity and integrity, shedding light on the intricate communication networks within the brain.

- White Matter Ratio: The white matter ratio, defined as the proportion of white matter volume relative to the total brain volume, quantifies the contribution of white matter to overall brain size. This parameter is essential for evaluating neural connectivity, offering valuable insights into how white matter relates to the structural composition of the entire brain.

- Gray Matter Volume: Gray matter volume refers to the space occupied by neuronal cell bodies, dendrites, and synaptic connections within the brain's gray matter regions. Analyzing gray matter volume provides valuable insights into the density and distribution of neural elements, contributing significantly to our understanding of neuroanatomy and variations across individuals.

- Gray Matter Ratio: The gray matter ratio, calculated as the proportion of gray matter volume relative to the total brain volume, offers a quantitative measure of the concentration of gray matter. This parameter is instrumental in assessing neural density in relation to the overall size of the brain, providing a nuanced perspective on brain composition.

- Cerebrospinal Fluid Volume: Cerebrospinal fluid volume represents the space occupied by cerebrospinal fluid, encompassing fluid-filled regions within the brain. Analyzing CSF volume provides critical information about the overall composition and fluid dynamics within the central nervous system. This parameter contributes to a comprehensive understanding of brain structure, particularly in relation to the distribution and dynamics of cerebrospinal fluid.

4.2. Functional data

In our pursuit to understand the neural underpinnings of schizophrenia, the cingulate gyrus took center stage as a focal point of investigation. While numerous brain regions and neural pathways offer valuable insights into the complexities of schizophrenia, practical considerations, including the constraints of time and resources, prompted a strategic focus on the cingulate gyrus for this particular study.

The cingulate gyrus holds immense relevance in the schizophrenia research landscape due to its integral role in mediating emotional regulation, cognitive functions, and attentional processes [48, 49]. This brain region's intricate connectivity with various neural networks positions it as a key player in the manifestation of symptoms associated with schizophrenia [50]. Understanding the nuanced alterations within the cingulate gyrus may unlock valuable insights into the disorder's underlying mechanisms.

The decision to concentrate on the cingulate gyrus does not diminish the importance of other brain regions or pathways implicated in schizophrenia. Rather, it reflects a pragmatic approach to conduct an in-depth exploration within a manageable scope. This focused investigation allows for a more detailed and comprehensive analysis of the cingulate gyrus, laying the foundation for future studies that can expand the examination to encompass additional regions of interest.

By acknowledging the limitations of a focused investigation, we aim to contribute valuable data on the cingulate gyrus's role in schizophrenia while recognizing the broader landscape of potential neural contributors to the disorder. This strategic focus serves as a stepping stone for more extensive explorations, providing a foundation for future research endeavors to delve into the rich tapestry of interconnected brain regions implicated in schizophrenia.

4.2.1. First-level analysis: Seed-based connectivity maps (SBC) and ROI-to-ROI connectivity matrices (RRC) were estimated characterizing the patterns of functional connectivity with atlas.AC (Cingulate Gyrus, anterior division), and atlas.PC (Cingulate Gyrus, posterior division). Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients from a weighted general linear model (weighted-GLM [51]), defined separately for each pair of seed and target areas, modeling the association between their BOLD signal timeseries.

4.2.2. Group-level analyses: Group-level analyses were performed using a General Linear Model (GLM [52]). For each individual voxel a separate GLM was estimated, with first-level connectivity measures at this voxel as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable), and groups or other subject-level identifiers as independent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory [53, 54]. Results were thresholded using a combination of a cluster-forming $p<0.001$ voxel-level threshold, and a familywise corrected p-FDR<0.05 cluster-size threshold [55].

5. Results

Our exploration into the neural correlates of schizophrenia encompasses both structural and functional dimensions, providing insights into the disorder's complex nature. It's essential to acknowledge the study's limitations, notably the modest dataset size, which influences result robustness. Structural analyses involved a detailed preprocessing pipeline, revealing parameters like brain volume and tissue ratios. Meanwhile, functional investigations focused on the cingulate gyrus, recognizing the complexities of connectivity analysis. Despite limitations, our findings offer initial glimpses into schizophrenia's neural aspects, laying the groundwork for future, more extensive studies.

5.1. Structural data

Our initial hypothesis posited that individuals in the EMA and PSI groups would exhibit lower brain, white matter, and gray matter volumes, potentially accompanied by a higher cerebrospinal fluid (CSF) volume. However, given the inherent limitations of our small dataset, it is crucial to interpret the results with caution. While we cannot definitively confirm these trends, preliminary observations suggest a notable alignment of mean values with our initial expectations.

In comparing the mean values across groups, it becomes apparent that the control group tends to exhibit higher brain, white matter, and gray matter volumes, while demonstrating a lower CSF volume. These trends, although suggestive, underscore the need for a larger sample size and more comprehensive investigations to draw definitive conclusions regarding structural differences associated with schizophrenia and related psychotic disorders. The following graphs present a visual representation of these trends in brain (Fig. 6), white matter (Fig. 10, 11), gray matter (Fig. 8, 9), and CSF (Fig. 7) volumes among the study groups.

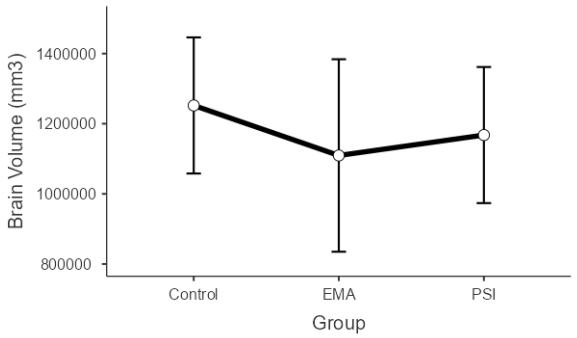

Fig. 6: The figure shows the mean values (white circle) and the variance range of the brain volume for each group.

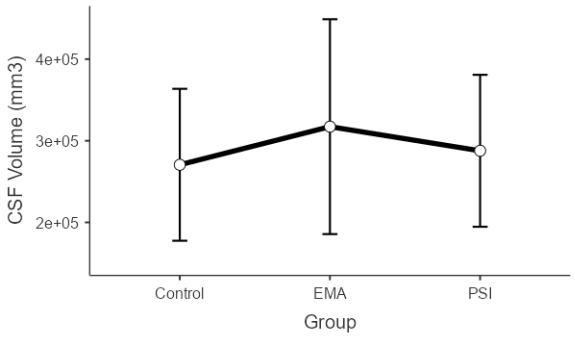

Fig. 7: The figure shows the mean values (white circle) and the variance range of the CSF volume for each group.

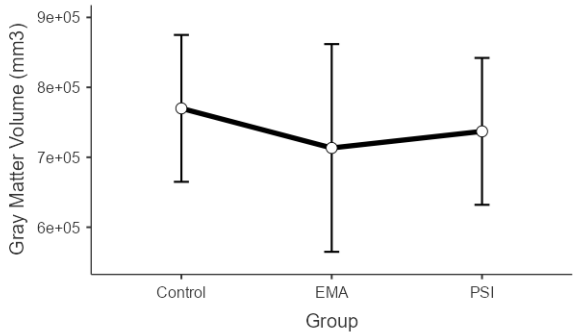

Fig. 8: The figure shows the mean values (white circle) and the variance range of the gray matter volume for each group.

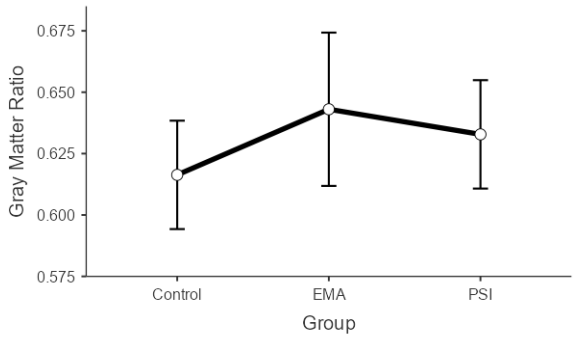

Fig. 9: The figure shows the mean values (white circle) and the variance range of the gray matter ratio for each group.

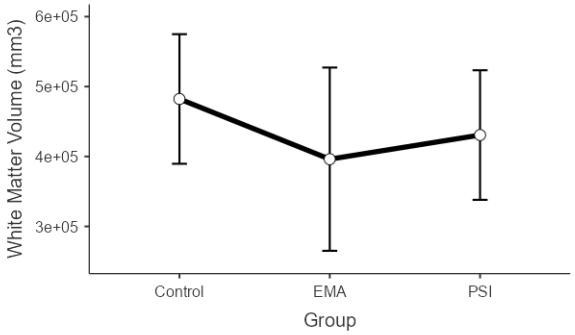

Fig. 10: The figure shows the mean values (white circle) and the variance range of the white matter volume for each group.

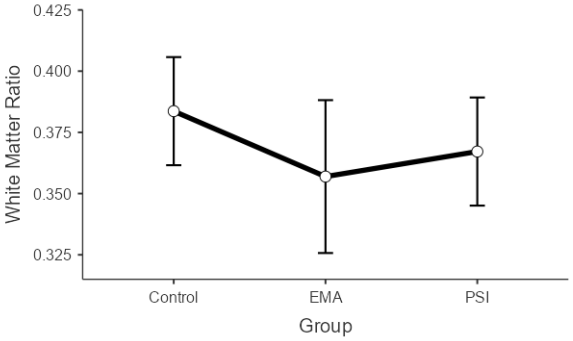

Fig. 11: The figure shows the mean values (white circle) and the variance range of the white matter ratio for each group.

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5.2. *Functional data*

In examining the functional dynamics associated with schizophrenia and related psychotic disorders, we present the 1st-level and 2nd-level results. These outcomes offer insights into the patterns of functional connectivity within the cingulate gyrus, contributing to our understanding of neural alterations linked to these psychiatric conditions. The 1st-level results explore seed-based connectivity maps (SBC) and ROI-to-ROI connectivity matrices (RRC), while the 2nd-level results, employing a General Linear Model (GLM), provide a collective perspective across subjects.

5.2.1. First-level results: In the 1st-level functional connectivity analysis, we present multi-slice images capturing distinct axial planes of the brain, focusing on the posterior division of the cingulate gyrus. The color overlays on these images depict the patterns of connectivity, with warm colors indicating positive connectivity and cool colors representing negative connectivity. This visualization method provides a comprehensive view of how different brain regions interact in three individual subjects: one from the control group (Fig. 12), one from the EMA group (Fig. 13), and one from the PSI group (Fig. 14).

Positive connectivity, reflected in warm colors, signifies regions of the brain where the Blood Oxygen Level Dependent (BOLD) signal fluctuations are positively correlated, indicating synchronized activity between those regions. In contrast, negative connectivity, represented by cool colors, suggests regions with negatively correlated BOLD signal fluctuations, indicating an inverse relationship in activity.

The connectivity values range from 1 to -1, where 0 to 1 corresponds to warm colors, indicating positive connectivity, and 0 to -1 corresponds to cool colors, indicating negative connectivity. Notably, these results showcase the activity in the posterior division of the cingulate gyrus across the three groups during resting-state conditions.

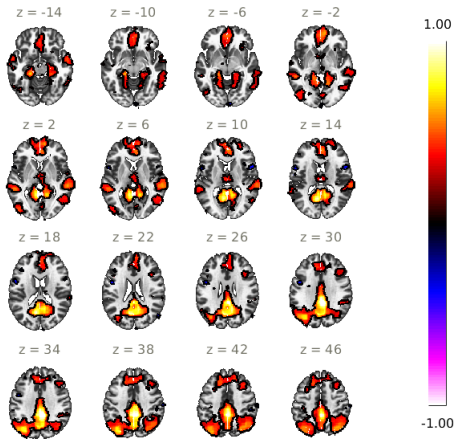

Fig. 12: The figure shows 16 brain slices from a control subject. They are overlayed with the connectivity data.

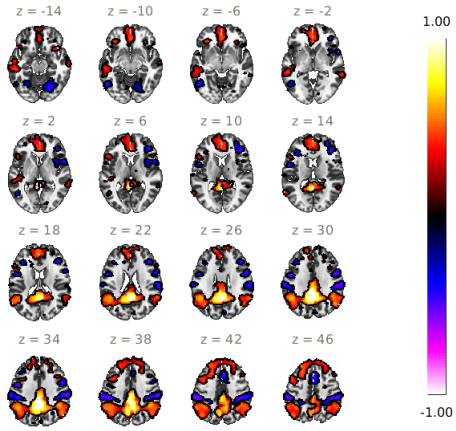

Fig. 13: The figure shows 16 brain slices from an EMA subject. They are overlayed with the connectivity data.

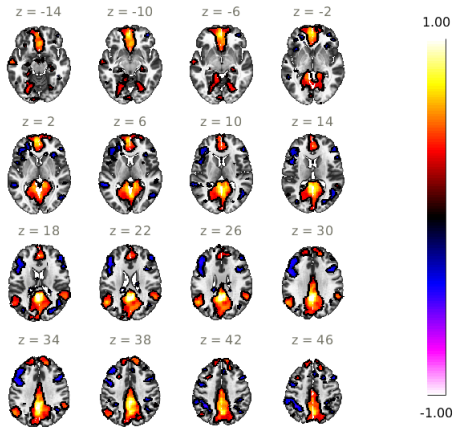

Fig. 14: The figure shows 16 brain slices from a PSI subject. They are overlayed with the connectivity data.

5.2.2. Group-level results: In the 2nd-level functional connectivity analysis, we delve into the intricate patterns of positive and negative connectivity within the cingulate gyrus. Two multi-slice images capture axial views of the brain, offering insights into the group-level differences in connectivity. The first image focuses on the control group (Fig. 15), while the second image combines data from both EMA and PSI groups (Fig. 16).

The connectivity range in the control group's image spans from 310.89 to -98.37, illustrating variability in connectivity strength across this small sample. Notably, the second image, representing patients (EMA and PSI groups combined), demonstrates a narrower range, from 47.44 to -13.28. The narrower range in the second image suggests a potentially more confined range of connectivity values in the cingulate gyrus for patients compared to controls.

However, upon observing the activation areas of both images, it becomes evident that the activation area in the second image is broader than in the first one. This could imply two possibilities: either the activation area of the cingulate gyrus

in patients is larger, or the increased variance in connectivity within the patient group, possibly influenced by the larger sample size, is contributing to the observed difference.

Given the limited dataset, drawing definitive conclusions requires caution. However, these preliminary 2nd-level results provide a foundation for future investigations with larger cohorts. Further exploration, potentially incorporating additional neuroimaging data, is essential for a more nuanced understanding of functional connectivity alterations in the cingulate gyrus associated with schizophrenia spectrum disorders.

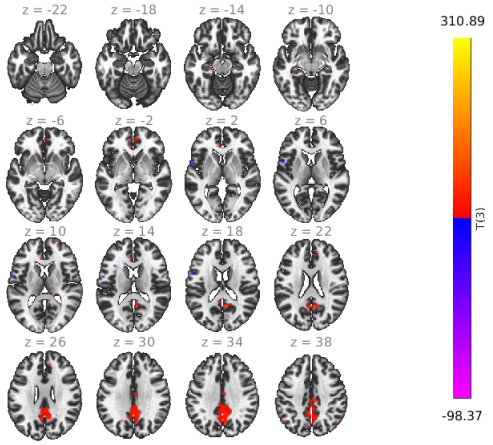

Fig. 15: The figure shows 16 brain slices overlayed with the results of the GLM in the control group.

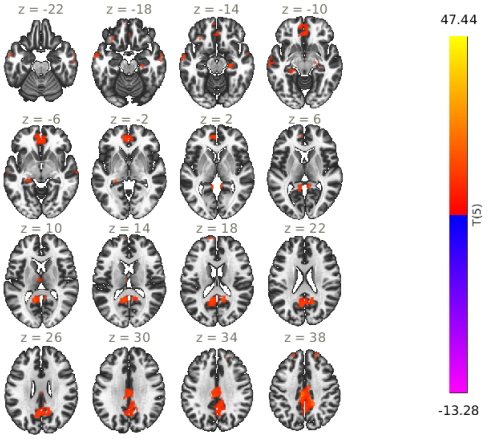

Fig. 16: The figure shows 16 brain slices overlayed with the results of the GLM in the patients group (EMA and PSI).

6. Discussion

In the discussion section, we acknowledge the inherent limitations imposed by the small dataset size, which restricts the conclusiveness of our findings. This limitation serves as a critical factor in interpreting the results and underscores the need for future research with larger cohorts.

Despite the constraints posed by the dataset size, the developed pipeline stands out for its emphasis on generalizability, scalability, and replicability. The unified segmentation algorithm, incorporating segmentation, bias correction, and spatial normalization within a single model, offers a comprehensive and efficient approach. This integrated model, an extension of the unified segmentation algorithm known as "New Segment" in SPM8, presents a robust foundation for preprocessing T1 data. The iterative algorithm, addressing circularity challenges in traditional segmentation methods, enhances accuracy and sets the stage for more nuanced analyses.

While our initial focus on the cingulate gyrus in the functional analysis yielded intriguing insights, the discussion underscores the need for caution in drawing definitive conclusions. The discussion emphasizes the potential for more profound results with an expanded dataset size and more in-depth analyses. Scaling up the dataset and incorporating additional neuroimaging data could unveil novel insights into the neural underpinnings of schizophrenia spectrum disorders.

The scalable and replicable nature of the pipeline positions this research as a valuable stepping stone for future investigations. It serves as a solid foundation upon which subsequent studies can build, allowing for a more comprehensive exploration of the intricate neural mechanisms associated with schizophrenia. As the dataset grows and analysis becomes more sophisticated, the potential for meaningful contributions to the understanding of this complex disorder increases.

References

[1] W. H. Organization, "Mental health: Strengthening our response," 2019, retrieved from https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response.

[2] T. D. Cannon, K. Cadenhead, B. Cornblatt, S. W. Woods, J. Addington, E. Walker, and R. Heinssen, "Prediction of psychosis in youth at high clinical risk: A multisite longitudinal study in north america," *Archives of General Psychiatry*, vol. 65, no. 1, p. 28–37, 2008.

[3] P. Fusar-Poli, S. Borgwardt, A. Bechdolf, J. Addington, A. Riecher-Rössler, F. Schultze-Lutter, and A. R. Yung, "The psychosis high-risk state: A comprehensive state-of-the-art review," *JAMA Psychiatry*, vol. 70, no. 1, p. 107–120, 2013.

[4] J. LeDoux, *Synaptic Self: How Our Brains Become Who We Are*. Penguin, 2002.

[5] D. J. Chalmers, "Facing up to the problem of consciousness," *Journal of Consciousness Studies*, vol. 2, no. 3, pp. 200–219, 1995.

[6] U. T. Place, "Is consciousness a brain process?" *Philosophy of Mind: Classical and Contemporary Readings*, 1956.

[7] J. J. C. Smart, "Sensations and brain processes," *Philosophical Review*, vol. 68, no. 2, pp. 141–156, 1959.

[8] H. Putnam, "Minds and machines," in *Dimensions of Mind*, 1960.

[9] N. Block, "Troubles with functionalism," in *Readings in Philosophy of Psychology*, N. Block, Ed., 1980.

[10] D. E. Rumelhart, J. L. McClelland, and the PDP Research Group, *Parallel Distributed Processing: Explorations in the Microstructure of Cognition*. MIT Press, 1986.

[11] P. S. Churchland and T. J. Sejnowski, *The Computational Brain*. MIT Press, 1992.

[12] F. Crick and C. Koch, "Towards a neurobiological theory of consciousness," *Seminars in the Neurosciences*, vol. 2, no. 4, pp. 263–275, 1990.

[13] P. S. Churchland, *Neurophilosophy: Toward a Unified Science of the Mind-Brain*. MIT Press, 1986.

[14] J. A. Fodor, *The Language of Thought*. Harvard University Press, 1975.

[15] Z. W. Pylyshyn, *Computation and Cognition: Toward a Foundation for Cognitive Science*. MIT Press, 1984.

[16] J. Kim, "Making sense of emergence," *Philosophical Studies*, vol. 95, no. 1-2, pp. 3–36, 1999.

[17] M. A. Bedau, *Emergence: Contemporary Readings in Philosophy and Science*. MIT Press, 2008.

[18] D. Papineau, *Thinking about Consciousness*. Oxford University Press, 2002.

[19] P. M. Churchland, *A Neurocomputational Perspective: The Nature of Mind and the Structure of Science*. MIT Press, 1989.

[20] R. Swinburne, *Mind, Brain, and Free Will*. Oxford University Press, 2010.

[21] R. Descartes, *Meditations on First Philosophy*. Hackett Publishing Company, 1641.

[22] D. J. Chalmers, *The Conscious Mind: In Search of a Fundamental Theory*. Oxford University Press, 1996.

[23] K. R. Popper and J. C. Eccles, *The Self and Its Brain: An Argument for Interactionism*. Routledge, 1977.

[24] G. Berkeley, *A Treatise Concerning the Principles of Human Knowledge*. Hackett Publishing Company, 1710.

[25] B. Russell, *The Problems of Philosophy*. Oxford University Press, 1912.

[26] G. Strawson, *Panpsychism: Contemporary Perspectives*. Oxford University Press, 2006.

[27] D. Skrbina, *Panpsychism in the West*. MIT Press, 2007.

[28] O. D. Howes and S. Kapur, "The dopamine hypothesis of schizophrenia: Version iii—the final common pathway," *Schizophrenia Bulletin*, vol. 35, no. 3, p. 549–562, 2009.

[29] R. C. Craddock, S. Jbabdi, C. G. Yan, J. T. Vogelstein, F. X. Castellanos, A. Di Martino, and M. P. Milham, "Imaging human connectomes at the macroscale," *Nature Methods*, vol. 10, no. 6, p. 524–539, 2013.

[30] D. C. Dennett, *Consciousness explained*. Little, Brown, 1991.

[31] O. Sporns, "The human connectome: A complex network," *Annals of the New York Academy of Sciences*, vol. 1224, no. 1, p. 109–125, 2011.

[32] J. Ashburner and K. Friston, "Unified segmentation," *NeuroImage*, vol. 26, pp. 839–851, 2005.

[33] A. Nieto-Castanon, "fmri minimal preprocessing pipeline," in *Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN*. Hilbert Press, 2020, pp. 3–16.

[34] J. L. Andersson, C. Hutton, J. Ashburner, R. Turner, and K. J. Friston, "Modeling geometric deformations in epi time series," *Neuroimage*, vol. 13, no. 5, pp. 903–919, 2001.

[35] K. J. Friston, J. Ashburner, C. D. Frith, J. B. Poline, J. D. Heather, and R. S. Frackowiak, "Spatial registration and normalization of images," *Human Brain Mapping*, vol. 3, no. 3, pp. 165–189, 1995.

[36] R. N. A. Henson, C. Buechel, O. Josephs, and K. J. Friston, "The slice-timing problem in event-related fmri," *NeuroImage*, vol. 9, p. 125, 1999.

[37] R. Sladky, K. J. Friston, J. Tröstl, R. Cunnington, E. Moser, and C. Windischberger, "Slice-timing effects and their correction in functional mri," *Neuroimage*, vol. 58, no. 2, pp. 588–594, 2011.

[38] S. Whitfield-Gabrieli, A. Nieto-Castanon, and S. Ghosh, *Artifact Detection Tools (ART)*, Cambridge, MA, 2011, release Version, 7(19), 11.

[39] J. D. Power, A. Mitra, T. O. Laumann, A. Z. Snyder, B. L. Schlaggar, and S. E. Petersen, "Methods to detect, characterize, and remove motion artifact in resting state fmri," *Neuroimage*, vol. 84, pp. 320–341, 2014.

[40] A. Nieto-Castanon, "Preparing fmri data for statistical analysis," in *fMRI Techniques and Protocols*, M. Filippi, Ed. Springer, submitted, doi:10.48550/arXiv.2210.13564.

[41] V. D. Calhoun, T. D. Wager, A. Krishnan, K. S. Rosch, K. E. Seymour, M. B. Nebel, S. H. Mostofsky, P. Nyalakanai, and K. Kiehl, "The impact of t1 versus epi spatial normalization templates for fmri data analyses," vol. 38, no. 11, pp. 5331–5342, 2017.

[42] J. Ashburner, "A fast diffeomorphic image registration algorithm," *Neuroimage*, vol. 38, no. 1, pp. 95–113, 2007.

[43] A. Nieto-Castanon, "fmri denoising pipeline," in *Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN*. Hilbert Press, 2020, pp. 17–25.

[44] K. J. Friston, S. Williams, R. Howard, R. S. Frackowiak, and R. Turner, "Movement-related effects in fmri time-series," *Magnetic Resonance in Medicine*, vol. 35, no. 3, pp. 346–355, 1996.

[45] M. N. Hallquist, K. Hwang, and B. Luna, "The nuisance of nuisance regression: Spectral misspecification in a common approach to resting-state fmri preprocessing reintroduces noise and obscures functional connectivity," *Neuroimage*, vol. 82, pp. 208–225, 2013.

[46] Y. Behzadi, K. Restom, J. Liau, and T. T. Liu, "A component based noise correction method (compcor) for bold and perfusion based fmri," *Neuroimage*, vol. 37, no. 1, pp. 90–101, 2007.

[47] X. J. Chai, A. Nieto-Castanon, D. Ongur, and S. Whitfield-Gabrieli, "Anticorrelations in resting state networks without global signal regression," *Neuroimage*, vol. 59, no. 2, pp. 1420–1428, 2012.

[48] G. Bush, P. Luu, and M. I. Posner, "Cognitive and emotional influences in anterior cingulate cortex," *Trends in Cognitive Sciences*, vol. 4, no. 6, pp. 215–222, 2000.

[49] C. S. Carter, T. S. Braver, D. M. Barch, M. M. Botvinick, D. Noll, and J. D. Cohen, "Conflict and cognition: On the relative dominance of the dorsal anterior cingulate cortex and prefrontal cortex," *Psychological Science*, vol. 12, no. 6, pp. 467–473, 2001.

[50] S. A. Meda, A. Gill, M. C. Stevens, R. P. Lorenzoni, D. C. Glahn, V. D. Calhoun, J. A. Sweeney, C. A. Tamminga, M. S. Keshavan, G. Thaker *et al.*, "Large scale brain networks in non-psychotic siblings of individuals with schizophrenia," *Frontiers in Human Neuroscience*, vol. 6, p. 129, 2012.

[51] A. Nieto-Castanon, "Functional connectivity measures," in *Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN*. Hilbert Press, 2020, pp. 26–62.

[52] ——, "General linear model," in *Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN*. Hilbert Press, 2020, pp. 63–82.

[53] K. J. Worsley, S. Marrett, P. Neelin, A. C. Vandal, K. J. Friston, and A. C. Evans, "A unified statistical approach for determining significant signals in images of cerebral activation," *Human Brain Mapping*, vol. 4, no. 1, pp. 58–73, 1996.

[54] A. Nieto-Castanon, "Cluster-level inferences," in *Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN*. Hilbert Press, 2020, pp. 83–104.

[55] J. Chumbley, K. Worsley, G. Flandin, and K. Friston, "Topological fdr for neuroimaging," *Neuroimage*, vol. 49, no. 4, pp. 3057–3064, 2010.