Brain MRI Alterations in Systemic Lupus Erythematous patients with and without neurocognitive events

First author/s (?)1, Sebastiano Vacca2, Luca Saba3

2University of Cagliari, School of Medicine and Surgery, Cagliari, Italy

3Department of Radiology, Azienda Ospedaliero-Universitaria (A.O.U.), di Cagliari—Polo di Monserrato, Cagliari, Italy.

Corresponding Author: ?

**Abstract**

Systemic lupus erythematosus (SLE) is a complex autoimmune disease known for its diverse clinical manifestations, including neuropsychiatric involvement (NPSLE), which significantly impacts patient quality of life and can lead to mortality. This study conducted a comprehensive analysis of the relationships between brain magnetic resonance imaging (MRI) findings, neuropsychiatric events, and laboratory values in SLE patients, shedding light on potential biomarkers and diagnostic indicators for NPSLE.

Using a diverse dataset of 27 SLE patients, this study employed advanced MRI analysis through the VolBrain platform to quantitatively assess brain structural attributes. The analysis revealed significant differences in brain regions, particularly the occipital cortex, cerebellum, and grey matter structures, between NPSLE and non-NPSLE patients. Furthermore, correlations between MRI findings and laboratory values, including complement levels and anti-dsDNA antibodies, were explored.

The study unveiled intriguing associations between MRI features and NPSLE manifestations. For instance, mood abnormalities, seizures, and cerebrovascular events showed significant correlations with specific brain regions, emphasizing the importance of considering structural attributes in understanding these neuropsychiatric symptoms. Additionally, the study found that higher disease activity scores (SLEDAI) were associated with certain brain regions' volume alterations.

Incorporating ordinary least square (OLS) regression analysis, the study highlighted the predictive potential of MRI features, with Calc right volume % emerging as a significant predictor of SLEDAI scores.

This comprehensive approach underscores the intricate interplay between brain structural attributes and NPSLE events, offering valuable insights into potential biomarkers and diagnostic indicators. Nevertheless, further research is needed to validate and expand upon these initial findings, potentially leading to enhanced diagnostic and therapeutic strategies for neurocognitive and psychiatric disorders in SLE patients.

**Abbreviations**

Ang - Angular Gyrus

aPL - Antiphospholipid Antibody

C3 - Complement Component 3

C4 - Complement Component 4

CO - Cerebral Cortex

Cun - Cuneus

FuG - Fusiform Gyrus

GRe - Gyrus Rectus

IC - Intracranial Cavity

ICC - Intracranial Cavity Volume

MPrG - Medial Precentral Gyrus

MRI - Magnetic Resonance Imaging

MTG - Middle Temporal Gyrus

NP - Neuropsychiatric

NPSLE - Neuropsychiatric Systemic Lupus Erythematosus

OCP - Occipital Cortex

OpIFG - Opercular Part of the Inferior Frontal Gyrus

PHG - Parahippocampal Gyrus

SCA - Subcallosal Area

SLE - Systemic Lupus Erythematosus

SLEDAI - Systemic Lupus Erythematosus Disease Activity Index

SLICC/ACR-DI - Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index

SMG - Supramarginal Gyrus

STG - Superior Temporal Gyrus

TMP - Temporal Pole

WMH - White Matter Hyperintensities

# **Introduction**

Systemic lupus erythematosus (SLE), commonly referred to as lupus, is a complex autoimmune disease, characterized by a dysregulated immune system that leads to chronic inflammation and the potential for multiorgan involvement [1-3]. Being a major connectivitis, lupus primarily affects the musculoskeletal system and skin, but it can also manifest as neuropsychiatric events [4,5], causing significant mortality and morbidity, as they account for up to 19% of death in patients with SLE [6], while impairing patients' quality of life. The etiology of neuropsychiatric lupus (NPSLE) remains poorly understood, and the identification of reliable biomarkers would be crucial for early diagnosis, prognosis, and therapeutic intervention.

Advances in medical imaging techniques, particularly magnetic resonance imaging (MRI) of the brain, have provided valuable insights into the structural and functional alterations associated with NPSLE [7,8]. MRI allows for non-invasive visualization of brain structures and facilitates the detection of abnormalities that may contribute to the development of neuropsychiatric symptoms in lupus patients. Despite the efforts in imaging advancements, and the findings of some articles, there is still little consensus on the association of MRI measurements and the clinical side of NPSLE.

The diversity of neuropsychiatric manifestations in lupus presents significant diagnostic challenges. These manifestations can range from mild cognitive dysfunction to severe psychiatric disorders, including psychosis, mood disorders, and cerebrovascular events [9,10]. These symptoms often overlap with other psychiatric conditions, making accurate diagnosis and appropriate management essential. Laboratory investigations, including autoantibody profiles and serologic markers, play a crucial role in the diagnosis and monitoring of lupus. However, their association with brain MRI findings and neuropsychiatric events remains insufficiently explored.

In this paper, we present a comprehensive analysis of the correlations between brain MRI findings, neuropsychiatric events, and laboratory values in lupus erythematosus patients. This comprehensive approach holds promise for unraveling the underlying pathophysiological processes and may contribute to the development of personalized treatment strategies for NPSLE, providing clinicians and researchers with a deeper understanding of the complex interplay between the brain, immune system, and neuropsychiatric manifestations in lupus. Ultimately, this knowledge may pave the way for improved diagnostic and therapeutic approaches, leading to enhanced patient outcomes and a better quality of life for individuals living with NPSLE.

# **Methodology**

## Patients and study design

## Clinical and immunological data

Demographics, classic atherogenic risk variables (such as hypertension, hyperlipidaemia, and smoking), and basic laboratory data were evaluated for patients and controls. Regarding SLE duration, activity, damage, conventional serology, autoantibodies, and therapy, patients were classified. The SLE Disease Activity Index (SLEDAI) [11] was employed to evaluate the state of the disease in nine organ systems, including the central nervous system, vascular, renal, musculoskeletal, serosal, cutaneous, immunologic, constitutional, and hematologic. To evaluate accumulated damage in multiple organs, the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI) [12] was utilised.

Complement (C3, and C4) levels and the presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin), anti-DNA, anti-Ro, anti-La, anti-Sm, anti-DWEYS, and anti-RNP antibodies within ? of the onset of the neuropsychiatric signs were included in the immunological data.

Furthermore, therapeutic information was acquired, including whether the patients were under any anticoagulant and antiplatelet agent, the mg equivalent of their prednisone dosage, antimalarial therapy, immunosuppressants, and any biological drug.

The presence of NPSLE was assessed through the confirmation of the occurrence of a neurological event, such as mood abnormality, seizures, psychosis, or a cerebrovascular event.

## Neuroradiological data

## Volumetric Analysis

volBrain ([https://​​VolBrain​​.upv​​.es](https://volbrain.upv.es/)) [13] is an internet-based system designed to aid researchers in the automated analysis of volumetric brain data obtained from MRI scans, eliminating the need for any specialized infrastructure. This system computes the intracranial cavity volume (ICC), which encompasses the combined volume of white matter, grey matter, and cerebrospinal fluid, while also providing volume measurements for various macroscopic regions such as the cerebral hemispheres, cerebellum, and brainstem, all while ensuring anonymity. The vol2Brain pipeline’s is capable of accurately and efficiently dividing the brain into 135 separate regions, with the option of giving measurements at various anatomical scales, including brain tissues and lobes, Additionally, measurements of cortical thickness for each lobe and cortical structure are provided, and the results are summarised automatically in a report.

## Statistical Analysis

To compare continuous and categorical variables between groups, respectively, the Student's t test or Wilcoxon rank-sum test (for normally or non-normally distributed data, respectively) and Fisher's exact test were employed. Analysis of covariance (ANCOVA) was used to correct for variables.

Furthermore, a correlation analysis, using either Pearson’s coefficient or Spearmann’s coefficient (for normally or non-normally distributed data, respectively), was conducted on every variable. The most correlated MRI features with every clinical and immunological variable were partially correlated with the neurological events, accounting for prednisone, SLEDAI, NPSLE, age and sex as partial correlations. Moreover, the neurological events were partially correlated with MRI variables, accounting for prednisone, SLEDAI, age and sex.

Ordinary Least Square (OLS) Regression Analysis was conducted on every clinical and immunological continuous feature, considered as the target variable, using the most correlated MRI features as the predictor variables.

A p-value of < 0.05 was considered as statistically significant. All statistical analyses were conducted on Python version 3.9.

# **Results**

## Patients Characteristics

27 patients with a diagnosis of SLE were included in the study, of which 24 were females and 3 males. The average age was 43 years, with a mean disease duration of 94 months (Table 1). On average, their SLEDAI-2K score was 8.29, while their SLICC-DI and PGA were 0.96 and 1.04, respectively. The 14 patients who suffered a neuropsychiatric (NP) event had, on average, a SLEDAI-2K of 10.5, while those who did not suffered the NP event of 5.9. On the same note, the NPSLE patients had higher PGA and SLICC-DI, as well as, on average, a higher dsDNA titre. Every patient but one, was on a steroid regimen, in particular prednisnone, while 8 were taking an anticoagulant, 19 Hydroxychloroquine, 23 an immunosuppressive agent, and 9 a biological drug. Complement levels of all participants were within the upper limit of normal range.

## Volumetric Analysis

Volumetric differences between various groups were tested. In particular, differences in MRI scans of SLE patients were analysed by grouping them based on different clinical and immunological data. Regarding NPSLE and non NPSLE patients, many brain regions and their characteristics were found to be different, and the 5 most statistically significant lower in the NPSLE group were: CO Total volume % (p-value = 0.0031), OCP total thickness norm (p = 0.0031), OCP left thickness norm (p = 0.0042), Ang right thickness mm (p = 0.0042), OCP total thickness mm (p = 0.0057) (Table 2).

Regarding the SLEDAI-2K score, after the Wilcoxon Test, the MRI features that resulted as significantly between two groups, one with a score below 4 and the other above it, based on studies such as Yee et al. , were several: PHG total thickness greater in higher SLEDAI (p = 0.0063), as well as both its right and left thickness taken singularly were greater the higher the SLEDAI (p<0.02), and Calc right volume %, greater with higher SLEDAI scores.

The SLICC-DI analysis, where the patients were divided based on the presence of organ damage or not (SLICC-DI of at least 1, and 0, respectively), revealed how the OpIFG total and right volume % differed the most between groups (p = 0.0031 and 0.0076, respectively), with the damaged group having the smaller volume; another region was the right MPoG (volume % p = 0.0088, volume cm3 p-value = 0.0153).

When comparing patients who tested positive for dsDNa antibodies, regions that results lower in volume or more asymmetrical in the positive group, included: CO right volume % (p = 0.0169), Insular total volume % (p = 0.0478), Insular right volume % (p = 0.0169), OpIFG thickness asymmetry (p = 0.0169), Brainstem volume % (p = 0.0203), Hippocampus volume asymmetry (p = 0.0203), FuG thickness asymmetry (p = 0.0203).

In patients with below the normal lower limit C3 levels, left and total PCu thickness were significantly lower than in patients in the normal range (p < 0.001), while IOG volume resulted higher than the normal-range group (p < 0.001).

4 patients were diagnosed with Antiphospholipid antibody (aPL) Syndrome and were shown to have diminished thickness in: AIns left thickness mm (p = 0.0017), ACgG right thickness mm (p = 0.0017), MTG total volume % (p-value = 0.0017), as well as more Abnormal Appearing White Matter volume cm3 (p = 0.006332).

## Correlation Analysis

Regarding the partial correlation analysis (Table 3), the most correlated MRI features with NP-SLE were: SCA thickness asymmetry (r = 0.45, p = 0.02957), Amygdala right volume % (r = 0.43, p = 0.04282), Temporal thickness asymmetry (r = 0.47, p = 0.02452), TMP thickness asymmetry (r = 0.52, p = 0.01122). Both SCA and TMP thickness asymmetry were positively correlated with the presence of a CVA event after partial correlation (r = 0.71, p = 0.00014 and r = 0.69, p = 0.00023, respectively).

On the other hand, the partial correlation analysis of the neurocognitive events (Table 4) revealed a very strong positive partial correlation (0.997544) between depression and Intracranial Cavity (IC) volume %, TMP thickness asymmetry (0.840671) and Inf. Lateral Ventricle left volume cm3 (0.821521). Similarly, a strong positive partial correlation (0.994986) between Seizures and the Intracranial Cavity (IC) volume % was found. The analysis demonstrates a strong negative partial correlation (-0.975061) between Psychosis and Intracranial Cavity (IC) volume % as well.

Calc total volume % was amongst the most correlated with SLEDAI, even after partial correlation (r = 0.41730, p = 0.04758), and was inversely correlated with the presence of seizures (r = -0.47, p = 0.01358). Two highly correlated features. still after the adjusted analysis, were IOG volume asymmetry % (r = 0.49211, p = 0.01707) and the 4th ventricle total volume (r = 0.58, p = 0.00410).

For the SLICCDI correlation, OpIFG total and right volume % and right MPoG volume, were amidst the most highly correlated with the score as well, but neither proved to be associated with a NP event. On the other hand, SMG total volume % was lower in patients with SLICC of at least 1 (p-value = 0.0133) and was also associated with the depressive episode (r = 0.49, p = 0.01741) after the adjustments.

None of the statistically correlated MRI features between dsDNA positive and negative patients survived the partial correlation, but the presence of seizures was associated with the AnG left thickness mm (r = -0.48, p = 0.01049).

Amidst the highly correlated features with the diagnosis of the aPL Syndrome, Lateral Ventricle right volume % (r = 0.58, p = 0.00397), Abnormal Appearing White Matter volume cm3 (r = 0.55, p = 0.00835) were the most relevant even after the adjusted correlation. When tested against the NP event, we obtained the following results: event\_CVA vs Abnormal Appearing White Matter volume cm3: r = 0.44, p = 0.04167; Event\_Mood abnormalities (depressive) vs Abnormal Appearing White Matter volume cm3: r = -0.44, p = 0.04095.

When computing the correlation with C3 levels as the target, the MRI features with the highest negative coefficients, after the adjusted analysis, were: Calc right volume % (r = -0.54, p = 0.00752), Calc total volume cm3 (r = -0.49, p = 0.02058), IOG total volume cm3 (r = -0.45, p = 0.03774), SOG right volume cm3 (r = -0.59, p = 0.00396), TTG volume asymmetry (r = -0.57, p = 0.00587). Only Calc total volume cm3 was significantly correlated with a NP event, with seizures (r = -0.48, p = 0.01049).

* 1. OLS Regression

The OLS Regression Analysis (Table 5) conducted on the continuous variables as the target ones, yielded a R-Squared of 0,725 and an Adjusted R-Squared of 0,553 for the SLEDAI score, and a R-Squared of 0,715 and an Adjusted R-Squared of 0,537 for the SLICC-DI score. For SLEDAI, the overall model's significance, as measured by the F-statistic (F = 4.212, p = 0.00535; F = 4.012, p = 0.00678), indicates that at least one of the predictor variables has a statistically significant effect on SLEDAI-2k and SLICCDI respectively.

1. **Discussion**

The current study investigates the intriguing correlation between laboratory values, specifically antibodies, and brain MRI findings in patients with SLE, as well as the incidence of neuropsychiatric events experienced by a subset of these patients in relation to their brain MRI results.

The most common neuropsychiatric manifestations in our study population were mood abnormalities, in particular depression, seizure, psychosis, as well as cerebrovascular disease, accordingly to the meta-analysis by Untermann et al. [14], where the most common neurologic syndromes were headache, mood abnormalities with depression, cognitive disfunction, seizures and cerebrovascular disease.

Thanks to the use of the VolBrain online platform, our study is one of the most complete to-date as far as localizing and quantifying brain MRI changes in patients with SLE, with and without NP involvement.

Few studies have investigated brain MRI lesion load in NP-SLE patients and their differences with controls or non NPSLE patients; amongst these, a retrospective study, involving 76 SLE patients and 26 controls, by Roldan et al. [15] demonstrated how patients had significantly higher whole-brain and right and left hemisphere brain lesion loads than controls (all p≤0.02); additionally there was a strong relationship between neurocognitive z-scores in all categories and whole brain and hemisphere lesion load. Lastly, these associations increased when glucocorticoid medication and the SLE disease activity index were considered. Another retrospective study, by Sarbu et al. [16], which included 108 NPSLE patients, provided the relationship between brain MRI alterations and NPSLE cognitive and immunological features, as in 59.3% of cases, brain abnormalities were discovered. Cerebrovascular syndrome and microbleeds were associated with Large Vessel Disease (p = 0.001), cognitive impairment with White Matter Hyperintensities (p = 0.045), and myelopathy with inflammatory-like lesions (p = 0.020). Low C4 and CH50 levels were associated with inflammatory-like lesions (p = 0.019), and lupus anticoagulant levels were associated with WMH (p = 0.018), microbleeds (p = 0.002), and atrophy (p = 0.008).

In our study, the comparison of NPSLE and non NPSLE patients, yielded as one of the most statistically different areas the OCP, both its total thickness and the left hemispheric one, indicating a possible biomarker for distinguishing the two groups, even when the NP event is not clear. In particular, the total thickness of the OCP and of the right AnG, together with the total volume % of the CO, were smaller in the NPSLE group compared to the non NPSLE. We found a statistically significant positive connection between the diagnosis of NPSLE and SCA thickness asymmetry indicating that those with NPSLE have more asymmetry in their SCA thickness. Every single other MRI feature proved to be statistically significant after the adjusted correlation, further bolstering their relationship. The same regions were then tested against the NP events, and both TMP and SCA thickness asymmetry were associated with the CVA event (p<0.05). We discovered that mood abnormalities (depressive) exhibited a significant positive partial correlation with NP-SLE (r = 0.44, p = 0.03427), as well as seizures (r = 0.43, p = 0.03994). This shows that, even after controlling for these factors, the presence of NP-SLE is associated with a greater chance of suffering from seizures and depressive mood abnormalities.

OCP volume, on the other hand, proved to differ between patients tested positive for Anti-DWEYS antibodies and those who did not, both in its total and left volume. Alongside OCP, the volume of the Cerebellar Vermal Lobule VIII-X was quite different, supporting the findings by Mártensson et al. [17], whereby investigating volumetric differences between 29 controls, 41 NPSLE and non 28 NPSLE patients in a cross-sectional study, the demonstrated how SLE, and in particular NPSLE, patients had a lower cerebellar grey matter density, especially at the level of the Cerebellar Vermal Lobule VIII and VII. To further explore this finding, we computed the correlation and partial correlation of the Cerebellar Vermal Lobule VIII-X with Anti-DWEYS and the NP events. The correlation turned out significant (r = -0.55, p = 0.00267), even though when adjusted the p-value turned out slightly above the significant threshold (r = -0.40, p = 0.057). When tested against the NP event, the partial correlation with the depressive disorder stood out (r = -0.44, p = 0.03543). In the Mártensson’s paper [17], the author reported a weak correlation with delayed psychomotor speed between patients and controls (p = 0.05, r = 0.21); our findings go along with this result, as it is well-known how psychomotor retardation is one of major depressive disorder main finding, as proven by several studies [18-20] including a systematic review by Bennabi et al. [22], who pointed out how it might be correlated with the disease severity.

The literature is lacking on any correlation between SLE activity scores and MRI brain imaging lesions. A retrospective study including 325 patients by Checa et al. [22] was amongst the few that investigated this. Their logistic regression analysis did not conclude any relevant finding on the association between SLEDAI and MRI lesions, but they proved how SLICCDI is associated with a higher risk of ischemic changes, both lacunar infarcts in various regions, as the white matter (OR 1.43 (1.07–1.90)) and cerebellum (OR 1.79 (1.33–2.41)), and large vessels infarcts (OR 2.07 (1.23–3.50)). In our analysis, we dug deeper into this matter, and discovered how PHG and Calc were the two regions who most stood out for the relationship with the score. In particular, Calc total volume was directly correlated with high SLEDAI scores, even after adjusting for confounders. Even more interesting was its moderate association with the presence of seizures, who proved to be above the significance threshold. On the other hand, SLICCDI seemed to reflect mostly on OpIFG volume and thickness asymmetry, and not as much on white matter and cerebellum as in Checa et al.

Amongst the immunological factors, anti-dsDNA is one of the most relevant when it comes to SLE and its disease activity, as it increases the more severe the disease gets [23-25]. In the same Checa et al. [22] study, there was no evidence of increased risk of ischemic changes on brain MRI; on the other hand, Petri et al. [26] analyzed brain MRI of 97 SLE patients, founding evidence of increased presence of focal lesions in patients with abnormal dsDNA (p = 0.05). In our analysis several MRI features correlated with dsDNA levels, but none was below the threshold of statistical significance after the partial correlation. On the other hand, patients who tested positive had lower Insular, Hippocampal and Brainstem volumes, corroborating the hypothesis that their presence can lead to brain damage.

Strictly related to dsDNA and SLE activity levels is the complement system. It is well-known how if on one hand dsDNA increase during SLE active phase, the complement, due to its activation, is depleted, bringing C3 and C4 levels down [27-30]. In our analysis, every patient had C4 levels in the normal range, but that was not the case for C3. In patients with lower C3 levels, indicating a more active and possibly serious disease, PCu left and total thickness was significantly lower, while Calc right and total volume were inversely correlated with C3 levels, but directly associated with the presence of seizures (p<0.05). The reflection of active NPSLE, and so of low complement levels, has been researched by Bawazit et al. [31] in a retrospective study with 49 NPSLE patients, where they investigated NPSLE and complement association with white matter lesions. However, in their study C3 did not have a statistically significant relationship with white matter lesion (p = 0.589), similar to our analysis, where only certain cortical areas where amidst the one significantly related with C3 levels.

Antiphospholipid Syndrome (APS) has been recognized having a severe neurologic impact [32-34], and its impact on brain MRI has been quantified, as by Kaichi et al. [35], who proved that patients with APS and SLE had a higher prevalence of abnormal MR findings (73% vs. 53%), such as large territorial infarcts (p = 0.01), lacunar ones (p = 0.01), or with cortical localization (p = 0.01), than SLE patients without APS. Our findings confirm the moderate association between APS and cerebrovascular events (r = 0.47, p = 0.01), which reflected on White Matter Abnormalities above all, who was correlated with those same events (r = 0.44, p = 0.04167), as well as depressive episodes.

For the cerebrovascular event, it is well known the association with WMH, as pointed out in this review by Nikskd et al. [36]. In our study, we observed significant positive correlations between CVA events and WMH, but we at the same time we were able to prove their relationship with grey matter features as well, such as SCA thickness asymmetry and TMP thickness asymmetry, and GRe right thickness, emphasizing the potential significance of these structural attributes in predicting or understanding CVA.

Regarding the other NP events, one of the few studies who investigated their association with WMH or Grey Matter Hyperintensities, has been conducted by Arinuma et al. [37] where 53 NPSLE patients underwent brain MRI, and the frequency of brain lesions, present in 25 of them, for different NP events was assessed. Majority of the events were associated with White Matter Hyperintensities and Grey Matter atrophy, with marked severity in almost half of them. Events such as psychosis and mood disorders were rarely associated with MRI abnormalities in this paper, while we found that depressive episodes were positively correlated with features like MPrG volume asymmetry (p = 0.0006), and negative correlations were observed with features related to the cerebellar vermal lobules (p = 0.004) and OCP thickness (p = 0.002); instead, insular (p = 0.0003), and frontal volumes (p = 0.001) were negatively correlated with psychotic events, indicating that in these patients their volumes were smaller, and STG (p = 0.004) and Cun (p = 0.01) thickness asymmetry was directly correlated with movement disorders, contrary to FO right volume (p = 0.014) who was lower in patients with such disorder.

There have been aa handful of studies to develop ML models to differentiate between SLE and controls, or SLE and NPSLE [38, 39], and a few have tried to predict SLEDAI and SLICCDI based on clinical information [40-43], but none was built on top of MRI features. To conclude our analysis, an OLS Regression model was utilised to further assess MRI and clinical variables association. Notably, Calc right volume % has a positive coefficient of 63.0838 with a significant p-value of 0.035, suggesting that an increase in Calc right volume % is associated with higher SLEDAI-2k scores. IOG volume asymmetry and SCA left thickness mm both have coefficients with p-values slightly above the typical significance threshold of 0.05 (p = 0.061 and 0.151, respectively). MPoG right volume % (p = 0.01) was negatively associated (-68.4273) with SLICCDI, indicating a decrease in its volume for higher scores.

1. **Conclusion**

In conclusion, these findings underscore the complex interplay between brain structural attributes and NP events, providing valuable insights into potential biomarkers or indicators for these conditions. However, further research is warranted to validate and extend these preliminary observations, potentially paving the way for improved diagnostic and therapeutic strategies in the realm of neurocognitive and psychiatric disorders.