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Structural and Functional Brain Alterations in Multiple Sclerosis Patients Using Magnetic Resonance Imaging

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Thesis Approval

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Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is substantially my own work and has not been submitted for any other degree at the Arab American University or any other institution.

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Dedication

In the name of Allah, the Most Gracious, the Most Merciful.
I offer my deepest gratitude to him for his infinite blessings, guidance, and strength that have sustained me throughout this journey.

To the soul of my beloved father, your memory continues to inspire me, and your absence is profoundly felt; may Allah grant you eternal peace and mercy. To my dear mother and family, whose unwavering love, prayers, and sacrifices have been a constant source of strength and resilience. To my husband and son, for their boundless patience, encouragement, and unwavering support that carried me through every challenge.

Finally, I would like to express my sincere gratitude and thanks to my research supervisors, who played a major role in completing this research.

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Abstract

Introduction

Multiple sclerosis (MS) is a neurodegenerative disease that identified by the demyelination process and axonal damage, which badly affects the brain function and connectivity. Resting-state functional magnetic resonance imaging (rs-fMRI) is an effective tool that profounds useful insights into alterations in brain activity and connectivity within MS patients. Core resting-state networks (RSNs)—such as the Default Mode Network (DMN), Central Executive Network (CEN), and Salience Network (SN)—play crucial roles in cognitive and motor processes. Examining disruptions within these networks in MS can enhance the understanding of the disease's underlying mechanisms and aid in identifying potential biomarkers for its progression.

Purpose

This study aims to explore alterations in brain activity and functional connectivity within resting-state networks in MS patients compared to healthy controls, by focusing on three key measures of (rs-fMRI): amplitude of low-frequency fluctuations (ALFF) to assess spontaneous neural activity, degree centrality (DC) to evaluate global connectivity, and regional homogeneity (ReHo) to examine local connectivity across the brain.

Methods

Resting-state fMRI and structural (T1-3D ISO) data were collected from 20 MS patients and 20 age-matched healthy controls (HCs) using a 1.5 T Philips scanner. The DPABI toolbox was used to compute brain activity and connectivity, degree centrality (global connectivity), and regional homogeneity (local connectivity) after applying the preprocessing pipeline, which included mainly slice timing correction, realignment, nuisance

covariates regression, and temporal filtering between 0.01 and 0.08 Hz. The activity and connectivity matrices were extracted from RSNs, including 18 brain regions.

Result

The results showed a significant reduction in ReHo and DC among MS patients, especially in regions of the CEN and SN, indicating impaired local and global connectivity. Conversely, ALFF was found to be elevated in certain CEN regions in MS patients, which may reflect compensatory hyperactivity in response to network disruptions. Notably, the salience network exhibited consistent reductions across all three measures, suggesting widespread functional impairment in brain regions responsible for integrating and prioritizing stimuli.

Conclusion

These findings highlight the utility of rs-fMRI in detecting subtle but meaningful changes in brain function that are not always apparent through structural imaging. The study contributes to a growing body of evidence supporting the role of triple-network dysfunction in MS and reinforces the potential of functional imaging markers in the early diagnosis, clinical monitoring, and personalized treatment planning for patients with MS.

Keywords: Multiple Sclerosis, Resting-State fMRI measurements, Triple-Network Model, Brain Activity, Functional Connectivity.

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List of Definitions of Abbreviations

Abbreviations	Title
ALFF	Amplitude of Low-Frequency Fluctuations
ACC	Anterior Cingulate Cortex
AInsula	Anterior Insula
BOLD	Blood Oxygen Level-Dependent
CNS	Central Nervous System
CEN	Central Executive Network
CSF	Cerebrospinal Fluid
CIS	Clinical Isolated Syndrome
DMN	Default Mode Network
DIS	Dissemination in Space
DIT	Dissemination in Time
DC	Degree Centrality
DTI	Diffusion Tensor Imaging
EPI	Echo-Planar Imaging
EDSS	Expanded Disability Status Scale
fMRI	Functional Magnetic Resonance Imaging
FC	Functional Connectivity
FLAIR	Fluid-Attenuated Inversion Recovery
fALFF	Fractional Amplitude of Low Frequency Fluctuations
FOV	Field of View
FFT	Fast Fourier Transform
HCs	Healthy Controls
IPL	Inferior Parietal Lobule
LP	Lateral Parietal Cortex
LPFC	Lateral Prefrontal Cortex

MS	Multiple Sclerosis
MRI	Magnetic Resonance Imaging
MTI	Magnetization Transfer Imaging
MRS	Magnetic Resonance Spectroscopy
MPFC	Medial Prefrontal Cortex
PCC	Posterior Cingulate Cortex
PPC	Posterior Parietal Cortex
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
RS	Resting-State
rs-fMRI	Resting-State Functional Magnetic Resonance Imaging
RSA	Regional Spontaneous Activity
ReHo	Regional Homogeneity
ROI	Region of Interest
RPFC	Rostral Prefrontal Cortex
RRMS	Relapsing-Remitting Multiple Sclerosis
SN	Salience Network
SNR	Signal-to-Noise Ratio
SMG	Supramarginal Gyrus
SPMS	Secondary Progressive Multiple Sclerosis
tb-fMRI	Task-Based fMRI

Chapter One: Introduction

1.1 Background

Multiple sclerosis (MS) is a chronic, idiopathic autoimmune disease that affects the central nervous system (CNS). It is characterized by inflammation, demyelination, and axonal degeneration, leading to significant but not yet fully understood functional changes in the brain that are closely associated with clinical deficits. The disease occurs when the immune system mistakenly attacks the myelin sheath — the protective covering of nerve fibers — resulting in recurrent focal demyelinating lesions in the white matter of the brain and spinal cord. These lesions interrupt the normal transmission of electrical impulses along neurons, giving rise to a range of neurological symptoms, including motor impairments, cognitive dysfunction, and psychiatric disturbances (Papiri et al., 2023).

The onset and progression of symptoms in MS are often complex and unpredictable, shaped by sudden episodes of tissue damage and repair, the brain's capacity for neuroplastic reorganization, and the chronic nature of the disease. While substantial progress has been made in managing acute relapses, the underlying mechanisms of neuroplasticity and long-term disease progression in MS remain inadequately understood. Although the exact etiology of MS is still unclear, it is widely accepted that the disease results from a multifactorial interaction between genetic susceptibility and environmental factors, ultimately triggering an aberrant immune response (Ghasemi et al., 2017).

Multiple sclerosis is a global health concern with an increasing prevalence. It is estimated that more than 2.8 million people around the globe have MS (Walton et al., 2020). Women are two to three times more likely than men to be diagnosed with the disease, although the reason for this gender disparity remains unclear (Forouhari et al., 2021; Murúa et al., 2021).

Magnetic Resonance Imaging (MRI) has been widely used to investigate the pathophysiological mechanisms of various brain and spinal cord disorders. Over the past few decades, MRI has become indispensable in the diagnosis, monitoring, and treatment of MS,

as well as in elucidating its natural history and underlying mechanisms. Furthermore, it serves as a critical outcome measure in clinical trials (Hemond et al., 2018).

Functional magnetic resonance imaging (fMRI) provides valuable insights into brain function that complement the anatomical data obtained from structural MRI, making it a critical tool in both neuroscience research and clinical practice. In the context of MS, fMRI aims to deepen the understanding of disease pathology and progression. Research using fMRI has identified several cerebral physiological processes that appear to be disrupted in individuals with MS (Marshall et al., 2014; Rocca et al., 2022). Among the various fMRI techniques, resting-state fMRI (rs-fMRI) offers several advantages, including simplified signal acquisition, minimal patient effort, and consistent identification of functional brain regions across diverse patient populations (Smitha et al., 2017).

Exploring both functional connectivity (FC) and regional spontaneous brain activity (RSA) by capturing the spontaneous fluctuation in the blood oxygen level-dependent (BOLD) during resting-state (RS) conditions appears to be a promising strategy for gaining deeper insights into alterations in brain activity and connectivity in MS patients (Smitha et al., 2017). As the prevalence of MS continues to rise, there is an increasing need to comprehensively map the brain's functional networks and understand how MS pathology disrupts functional integration, eventually supporting predictions of functional network collapse in parallel with the progression of clinical symptoms.

Among the numerous stable resting-state networks (rsNWs) identified to date, three core networks stand out due to their functional significance and synchronized activity: the default mode network (DMN), the salience network (SN), and the central executive network (CEN). Collectively referred to as the triple network model, these interrelated systems are considered fundamental neurocognitive networks involved in a broad spectrum of cognitive processes (Menon, 2011; Wu et al., 2016).

To investigate the functional roles of these brain networks across various cognitive domains, it's important to outline their key characteristics. The first network DMN is typically classified as a task-negative network due to its prominent activity during rest and its association with self-referential processing and mind-wandering (Lin et al., 2017). The second network, CEN, is recognized as a task-positive network that plays a role in higher-level cognitive functions, attention control, working memory tasks, goal-oriented actions, and decision-making (Li et al., 2018; Sbaihat et al., 2022). Conversely, the SN serves as the third brain network. It is responsible for identifying, filtering, and combining key internal factors (e.g., autonomic signals) and external stimuli (such as emotional content) that impact behavioral responses. Furthermore, it plays a vital role in the functional and dynamic transition between the two previously mentioned brain networks (DMN and CEN), facilitating transitions between task-oriented and task-free cognitive states (Goulden et al., 2014; Menon et al., 2010; Sbaihat et al., 2021).

The coordination among the networks in the triple network model plays an important role in maintaining cognitive function and regulating behavior. In individuals with MS, disruptions in the connectivity and interaction among these networks have been linked to cognitive impairments, including deficits in attention, memory, and executive functioning. Notably, these disruptions can occur even in the absence of clear structural brain damage, indicating that altered triple network dynamics may serve as an early and sensitive marker of cognitive decline and disease progression in MS. Therefore, understanding the normal patterns of connectivity and interaction between these networks is essential for identifying changes that are specifically related to MS pathology (Bonavita et al., 2017; Carotenuto et al., 2020).

Resting-state fMRI measurements can precisely map the physiological impacts of neuronal activity, including gray matter atrophy, white matter microstructural abnormalities, and reduced resting-state connectivity within motor and cognitive networks in patients with MS (Du et al., 2019). These four measurements are amplitude of low-frequency fluctuations (ALFF), fractional ALFF (fALFF), regional homogeneity (ReHo), and degree centrality (DC). ALFF and fALFF are applied to evaluate RSA. ALFF reflects the strength of this

activity, while fALFF indicates the proportion of low-frequency fluctuations within the total frequency range. ReHo is used to examine local FC, and DC is used to assess global FC. Since ReHo and DC capture different aspects of brain synchronization—local versus distant—they complement each other. Combined with ALFF and fALFF, these parameters provide a comprehensive view of rsNWs dynamics, revealing patterns of spontaneous activity, regional temporal coherence, and functional connectivity (Sbaihat et al., 2022; Yin et al., 2018).

This study takes a different approach from many earlier studies that concentrated on specific brain regions or single networks. It simultaneously examines alterations across the triple brain networks by utilizing various rs-fMRI metrics, providing a more thorough understanding of functional brain disruptions in MS. Also, there is no previous fMRI studies have been conducted in Palestine focusing on MS patients.

1.2. Problem statement

Multiple sclerosis is a long-term neurological condition that impacts the CNS, causing a wide range of symptoms, including cognitive impairments and motor dysfunction. Emerging evidence suggests that alterations in brain activity and functional connectivity may play a key role in the progression and symptomatology of the disease.

This study investigates differences in brain activity and functional connectivity between MS patients and healthy controls (HCs) using ALFF, DC, and ReHo measures. The study seeks to identify functional alterations linked to MS that could improve understanding of cognitive decline and act as possible indicators for diagnostic purposes.

1.3 Aim and Objectives

This study aims to investigate the differences in RSA and FC within the triple network model between individuals with MS and HCs using rs-fMRI data. This aim will be addressed through the following objectives:

1. The study will compare brain activity in both groups using ALFF, evaluate global connectivity through DC, and examine local connectivity using ReHo.

2. The study also identifies significant alterations in MS patients that may serve as biomarkers for disease progression and cognitive dysfunction, and to understand the neural mechanisms underlying the disease.

1.4 Research Hypothesis

It's hypothesized that individuals with MS will exhibit significant alterations in brain activity and FC compared to HCs. Specifically, it's expected that patients with MS will show altered brain activity, as measured by ALFF, decreased global connectivity as indicated by DC, and reduced local connectivity as assessed by ReHo. These alterations may be associated with symptom severity and cognitive dysfunction. Furthermore, distinct patterns of connectivity changes may serve as potential biomarkers for disease progression and clinical outcomes in MS.

1.5 Research Question

How do patterns of brain activity and Functional connectivity differ between individuals diagnosed with MS and neurologically healthy controls?

1.6 Significance of the Study

This study holds substantial potential for deepening the understanding of the neural mechanisms underlying MS. By examining differences in RSA and FC between MS patients and HCs, it will elucidate how MS affects brain function at both global and local levels. Identifying specific patterns of altered connectivity could provide valuable biomarkers for monitoring disease progression, enabling earlier diagnosis and more targeted therapeutic interventions. Additionally, clarifying the relationship between connectivity alterations and cognitive or motor impairments may lead to improved strategies for managing MS-related symptoms and enhancing the clinical care and quality of life for patients. It could contribute to the development of more personalized treatment approaches for MS, improving clinical care and outcomes for those affected by the disease.

Chapter Two: Theoretical Frameworks and Previous Studies

2.1 Introduction

This study is dedicated to assessing the brain alterations of MS patients using MRI. This chapter covers the related literature and presents the theoretical framework of MS, along with a comprehensive explanation of the imaging system using structural and functional MRI, and its effect on the brain's triple network.

The theoretical part includes important details for a deep understanding of the main topic, starting with a precise explanation of MS, beginning with its definition, causes, types, and how it is diagnosed, including imaging techniques, followed by an overview of the triple brain model and its relation with resting-state fMRI.

2.2 Theory

2.2.1 Multiple Sclerosis Characteristics and Etiology

Multiple sclerosis occurs when the immune system erroneously attacks and harms the myelin, the protective covering of nerve fibers, leading to demyelination and damage to the axons. MS is characterized by recurrent episodes of focal demyelination, or lesions in the white matter of the brain and spinal cord. This damage impairs the conduction of electrical signals along the nerves (Forouhari et al., 2021; McGinley et al., 2021).

The precise cause of MS remains unclear. However, it is widely considered a complex condition with multiple factors contributing to its development. First, genetic susceptibility increases the risk of MS, as certain genes affect the immune response and the likelihood of autoimmune diseases. Second, environmental factors, such as location, lifestyle, and number of infections, have also been found to be associated with MS, especially past infection with Epstein-Barr virus (EBV). People residing farther from the equator face a higher risk of developing MS, likely due to reduced sunlight exposure and lower vitamin D levels. Additionally, lifestyle factors such as smoking and adolescent obesity contribute to increased

risk. The interplay between inherited genetic factors and environmental conditions compromises the immune system's tolerance, ultimately triggering an attack on the myelin (Bjornevik et al., 2023; Ghasemi et al., 2017; Murúa et al., 2021).

2.2.2 Symptoms and Primary Subtypes of MS

The demyelination process in MS results in a broad spectrum of symptoms, which can vary in severity and differ significantly from person to person. It is determined by which regions of the CNS are affected. Common early signs include visual issues like optic neuritis, characterized by one-sided vision loss and pain when moving the eye. Sensory changes, such as numbness, tingling, or paresthesia, frequently occur in the limbs or face. Motor symptoms are also prevalent and can involve muscle weakness, spasticity, and coordination or balance problems, leading to difficulties with walking (Brola et al., 2014; Izquierdo et al., 2019).

Cognitive and neuropsychiatric symptoms are increasingly recognized as significant aspects of MS patients. These can include memory issues, shorter attention spans, and diminished executive functioning. Fatigue is a prominent symptom, often described as excessive relative to activity levels and not alleviated by rest. Autonomic dysfunction may manifest as bladder and bowel problems, including urgency, incontinence, or constipation (DeMeo et al., 2021; Silveira et al., 2019).

Multiple sclerosis manifests in various forms, with the most prevalent phenotypes as shown in the table Table 2.1. Clinically isolated syndrome (CIS) represents the initial presentation in approximately 80% of MS cases. It is characterized by a sudden neurological episode involving one or more areas of the CNS and may progress to relapsing-remitting MS (RRMS). Over a 20-year period, the risk of converting from CIS to RRMS is about 21% in individuals with a normal initial MRI, whereas it rises to 82% in those with one or more silent white matter lesions (Doshi et al., 2016).

In the RRMS, patients typically experience substantial recovery after each relapse. The initial stages of MS, marked by demyelination, are thought to result from an inflammatory

response in which autoreactive lymphocytes cross the blood–brain barrier (BBB). Disability accumulates over time, and each relapse may result in incomplete recovery. As many as 80% of individuals with RRMS progress to secondary progressive MS (SPMS) within 10 to 15 years following their diagnosis. which is characterized by a gradual decline in neurologic function, sometimes accompanied by small remissions, plateaus, and relapses (Doshi et al., 2016).

Around 15% of patients are diagnosed with primary progressive MS (PPMS), which is marked by a steady and continuous worsening of disability from the initial symptoms, without clear episodes of relapses or remissions. In contrast, primary relapsing MS (PRMS) is marked by a consistent increase in disability and relapses from the beginning of the disease (Doshi et al., 2017; Ghasemi et al., 2017; Lublin et al., 2014). Figure 2.2 illustrates the MS disease course.

Table 2.1**:** Types of MS. Source: Atlas of MS 2013 (Browne et al., 2014).

Type of MS	**Definition**	**Percentage of MS patients worldwide**
Relapsing-Remitting	Relapses, periods in which symptoms increase, followed by remitting, periods in which symptoms decrease or disappear	85% of MS patients
Secondary Progressive	Progressive loss of functions associated with progressive axonal damage occurs without remission periods after initial relapsing-remitting	80% of RR patients develop secondary progressive MS
Primary Progressive	Progressive disability from disease onset without remission	10% of MS patients
Progressive Relapsing	Increase in disability and relapses from the beginning of the disease	5% of MS patients

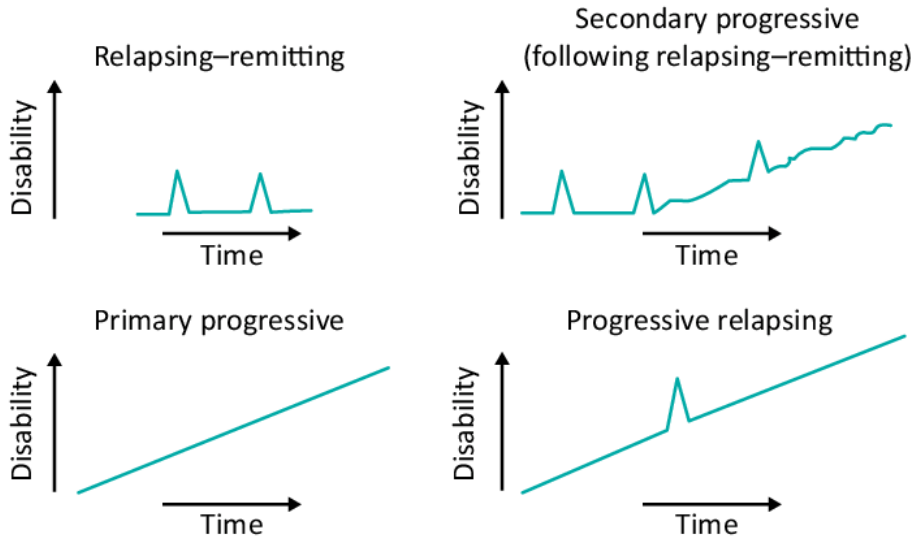

Figure 2.1: MS disease course (Ford, 2020).

2.2.3 Diagnosis of MS

The diagnosis of MS is based on the McDonald diagnostic criteria, a set of guidelines designed to assist neurologists in diagnosing the disease. It primarily depends on clinical assessment, laboratory testing, and MRI. The clinical evaluation conducted by a neurologist involves a physical examination, cognitive assessment, clinical rating scales, and classification of the subtype of MS. Laboratory tests are typically performed to eliminate other possible diseases. Lumbar Puncture (LP) is also performed to check oligoclonal bands in CSF, while MRI is utilized to evaluate pathology in the brain and spinal cord (Ghasemi et al., 2017).

The diagnosis of MS depends on fulfilling the criteria for both Dissemination in Space (DIS) and Dissemination in Time (DIT) (Polman et al., 2011). DIT can be verified either through clinical evidence of two relapses affecting multiple regions of the CNS (clinical DIS) at different times or by MRI findings. Characteristic locations for these lesions in the CNS are juxtacortical/ cortical, periventricular, and infratentorial brain and spinal cord (Hemond et al., 2018).

2.2.4 Overview of Structural MRI in Detecting MS

Structural MRI plays a critical role in the diagnosis and ongoing assessment of MS, with demyelinating lesions being a key characteristic of the disease, which can be identified using structural MRI methods. Important MRI sequences such as T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) are crucial for detecting these lesions, especially within the white matter of the brain and spinal cord. On T2 and FLAIR images, these lesions appear as hyperintense (bright) areas, and their identification is critical for fulfilling the McDonald criteria, which require evidence of lesions to confirm DIT and DIS (Hemond et al., 2018; Thompson et al., 2018).

Magnetic resonance imaging is crucial not only for the initial diagnosis but also for the ongoing tracking of disease progression and assessing treatment effectiveness. Serial MRI scans allow clinicians to identify the appearance of new lesions or the growth of existing ones. Furthermore, structural MRI aids in distinguishing between active lesions, typically indicated by gadolinium enhancement on T1-weighted sequences, and chronic non-enhancing lesions. This distinction is critical for accurately assessing disease activity and tracking disease progression over time (Kaunzner et al., 2017; Tomassini et al., 2020).

Moreover, MRI is crucial for distinguishing MS from other neurological disorders exhibiting overlapping symptoms, such as neuromyelitis optica and certain cerebrovascular conditions, making it a valuable tool in differential diagnosis. The unique features of the lesions observed on MRI facilitate accurate differentiation between MS and other neurological conditions, ensuring that patients receive the most appropriate treatment (Brownlee et al., 2017; Wildner et al., 2020).

Consequently, MRI is now commonly regarded as a fundamental tool for diagnosing the disease and monitoring its progression, largely due to its noninvasive, reliable, and reproducible nature (Filippi et al., 2012). This efficacy is attributed to MRI's remarkable capacity to detect localized white matter damage and asymptomatic lesions, offering highly detailed, high-resolution images of the CNS in patients that were previously unattainable (Sahraian et al., 2010).

2.2.5 Conventional MRI Sequences

A. T2-weighted imaging

Identifying MS lesions using T2-weighted MRI is the classic approach for visualizing MS plaques in patients because of its high sensitivity to alterations in tissue water content, which reflects a hallmark of MS pathology, demyelination and inflammation, as shown in Figure 2.2. Consequently, these sequences facilitate the clear visualization of lesions as bright (hyperintense) areas against the darker background of the normal tissue. Typical lesions are generally small, round, or oval, and may occur throughout the CNS wherever myelin exists. T2-weighted imaging is also essential to distinguish between various types of lesions, such as active inflammatory and chronic lesions (Fujita et al., 2021; Hemond et al., 2018). Distinctive features become clearer when lesion morphology, location, and signal properties are analyzed through complementary MRI sequences (Filippi et al., 2012).

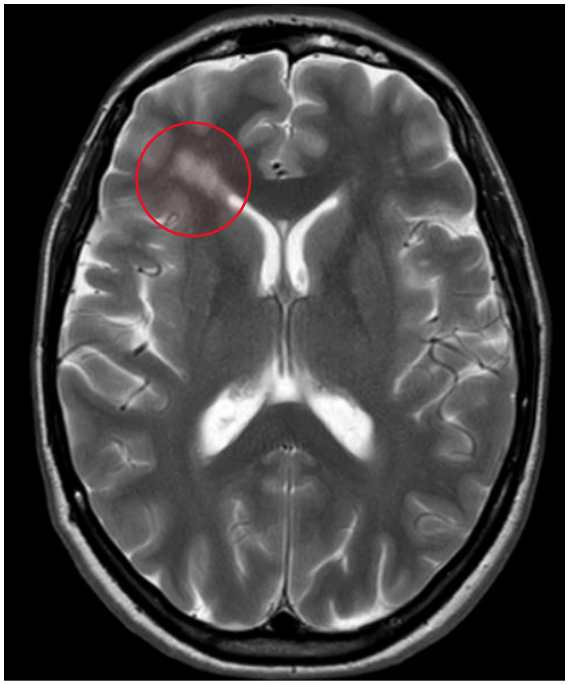

Figure 2.2: Axial T2-Weighted image for MS lesion (Jenin Governmental Hospital).

B. FLAIR imaging

Fluid-attenuation inversion recovery imaging is a T2-weighted MRI method specifically designed to enhance the visualization of lesions adjacent to CSF, as illustrated in Figure 2.3. This technique applies an inversion pulse before the standard T2 sequence, with the inversion time precisely set to suppress the CSF signal. This makes lesions like those associated with MS stand out more clearly against the now-dark CSF. While FLAIR provides superior contrast for these lesions, it does so with a decrease in signal-to-noise ratio (SNR) and increased scan duration relative to conventional T2-weighted MRI.

The three-dimensional FLAIR MRI sequence plays a crucial role in diagnosing and monitoring MS. Since it is not affected by flow artifacts, it's highly effective at identifying the characteristic white matter lesions of the disease, which appear as hyperintense (bright) areas on the images. This sequence is particularly good at revealing lesions in the periventricular, juxtacortical, and infratentorial regions of the brain.

It is particularly useful in distinguishing between active and chronic lesions in MS. The number, size, and distribution of lesions visible on 3D FLAIR can provide valuable insights into the total disease impact in individuals with MS, which is essential for monitoring disease progression and treatment effectiveness (Rovira et al., 2015; Tillema et al., 2013).

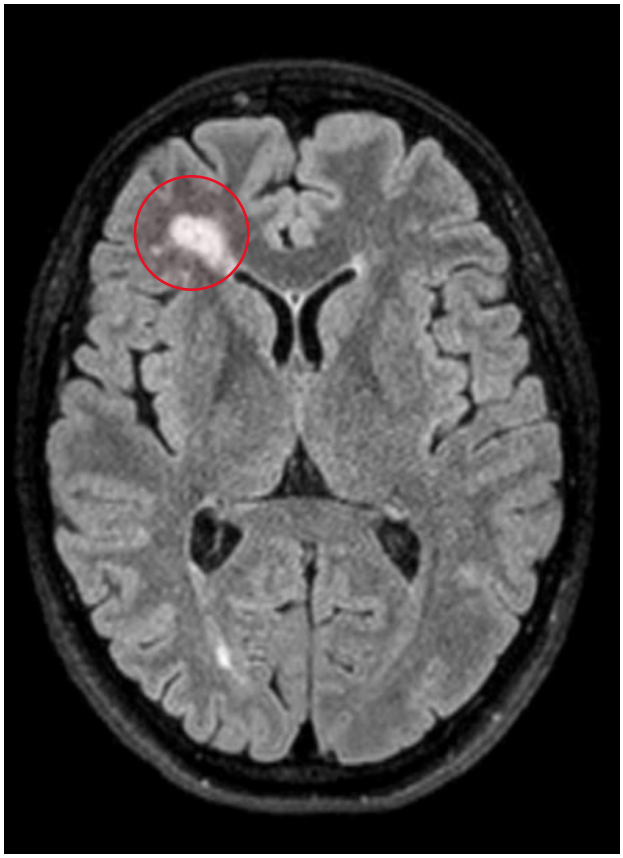

Figure 2.3: Axial FLAIR image for MS lesion (Jenin Governmental Hospital).

C. T1-weighted imaging

Imaging of the brain and spinal cord via MRI mainly utilizes 2D imaging methods. These 2D scans typically have slice thicknesses of 3mm or greater, and an additional sagittal scan is often necessary for reliable detection of lesions in the corpus callosum. A significant exception is the use of 3D T1-weighted scans, which are employed to measure brain volume and cortical thickness, as shown in Figure 2.4.

The 3D T1-weighted MRI sequence offers high-resolution, three-dimensional anatomical detail about the brain and spinal cord. Many contemporary approaches to processing MRI scans include an essential preprocessing step that involves reslicing the input scans to achieve isotropic resolutions of 1mm or smaller. Consequently, scans already near this resolution experience less interpolation blurring compared to those with thicker slices, like the standard 2D T1-SE scans. For this reason, 3D T1-weighted scans with high tissue

contrast and isotropic resolutions of 1mm or better are preferred for MRI volumetry in MS (Hu et al., 2019).

This sequence is particularly useful for several reasons. It can depict the presence and location of MS lesions. These lesions often appear as focal areas of decreased signal intensity compared to the surrounding normal brain tissue due to inflammation and increased water content. Additionally, 3D T1-weighted images can quantify progressive brain atrophy associated with MS, offering valuable information on disease progression and the effectiveness of treatment interventions (Nederpelt et al., 2023).

Moreover, these scans should be performed before gadolinium (Gd) contrast administration, as the enhancement of blood vessels can disrupt volumetric measurements. The sequence can reveal areas of disrupted BBB, indicative of active, inflammatory lesions, which helps understand disease activity and guide treatment decisions. Furthermore, the high spatial resolution of 3D T1-weighted images allows for detailed analysis of the structure and brain morphology, which can be useful in identifying specific patterns or characteristics associated with MS subtypes (Battaglini et al., 2017; Kaunzner et al., 2017; Traboulsee et al., 2016; Wattjes et al., 2015).

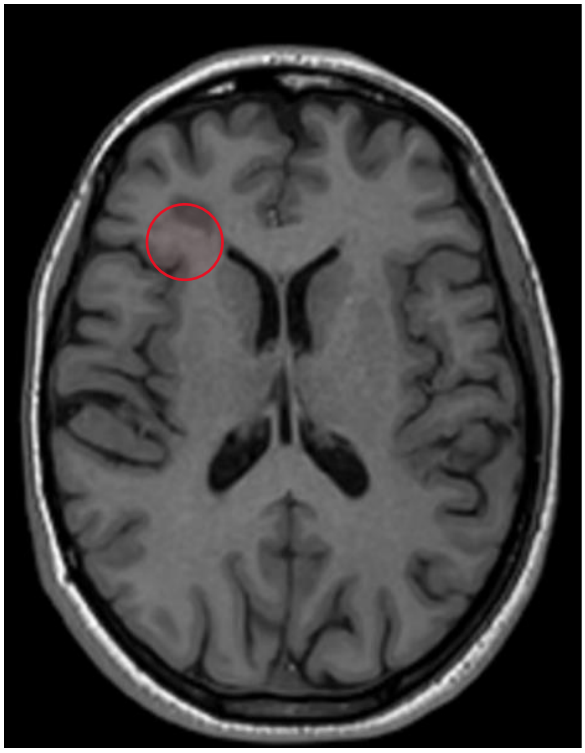

Figure 2.4: Axial T1-Weighted image shows black holes for MS lesion (Jenin Governmental Hospital).

2.2.6. Limitations of Using Structural MRI

While conventional MRI has its benefits, it falls short in terms of pathological specificity and sensitivity (Hemond et al., 2018). Nevertheless, it does not fully capture the full spectrum of brain changes owing to several limitations, notably in detecting grey matter lesions. Conventional T1- and T2-weighted sequences often fail to detect early cortical lesions or widespread grey matter degeneration. This is particularly concerning since grey matter atrophy, most prominent in areas including the thalamus and basal ganglia, strongly correlates with cognitive decline and disability progression. Cortical thinning in areas like the frontal and temporal lobes, a critical indicator of neurodegeneration, is frequently overlooked, despite its clinical significance. This limitation hinders the identification of patients at risk of rapid functional deterioration (Rovira et al., 2015; Filippi et al., 2011).

The main concern is the imprecision in identifying the underlying pathological processes. Structural MRI cannot differentiate between inflammation, demyelination,

remyelination, or neurodegeneration within lesions. For example, T2 hyperintense lesions may reflect edema, gliosis, or axonal loss, while gadolinium-enhancing lesions indicate BBB disruption without providing insight into long-term outcomes. This diagnosis impedes the ability to predict disability progression or to tailor treatments to specific pathological mechanisms (Fox et al., 2011).

Moreover, the well-documented MRI-clinical paradox underscores the weak correlation between standard MRI metrics (such as T2 lesion volume) and clinical symptoms. Patients with similar lesion loads often exhibit markedly different levels of disability, underscoring the limited utility of structural MRI in predicting functional outcomes. Metrics such as cortical atrophy or thalamic volume loss, which are more predictive of cognitive deficits, are seldom evaluated in clinical settings (Collorone et al., 2021; Fox et al., 2011).

To overcome the limitations of traditional structural MRI, various advanced MRI techniques have emerged. These modalities allow for the detection of subtle pathological alterations and the enhancement of knowledge regarding imaging biomarkers associated with disease progression, cognitive deterioration, and treatment outcomes in MS. By offering deeper insights into the underlying neuropathological processes, these techniques aid in earlier diagnosis and contribute to the creation of personalized treatment plans. Prominent techniques encompass Magnetization Transfer Imaging (MTI), Diffusion Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS), and Functional MRI (fMRI).

2.2.7. The Triple Brain Networks Model

As a key concept in neuroscience, the triple network model focuses on the dynamic relationships between three fundamental brain networks involved in managing cognitive and emotional processes. These primary networks consist of the DMN, the CEN, and the SN. Collectively, they regulate a wide range of mental functions, spanning from internal reflections to external problem-solving, and allow attention to be shifted as needed (Wang et al., 2020; Zhang et al., 2025).

The DMN is primarily active when the person is not focused on the outside world, such as during rest, daydreaming, or introspection. It is involved in self-focused thinking and mind-wandering, and processing autobiographical memories. Key areas of the DMN include the Posterior Cingulate Cortex (PCC), which aids in self-reflection and recalling memories, Medial Prefrontal Cortex (MPFC), which facilitates self-referential thought, and the Lateral Parietal Cortex (LP), which is associated with recalling episodic memories, processing autobiographical information, and making future decisions (Chen et al., 2013; Lu et al., 2024; Sestieri et al., 2011).

The CEN facilitates higher-order cognitive functions, including decision-making, problem-solving, and working memory. It aids in concentrating on external tasks, handling intricate information, and making choices. The CEN is generally activated during activities that demand attention and focus, including planning, reasoning, and multitasking. Important regions of the CEN consist of the Lateral Prefrontal Cortex (LPFC), which plays a role in working memory and cognitive control, and the Posterior Parietal Cortex (PPC), which assists with spatial working memory. When the CEN is engaged, the DMN is usually suppressed, allowing the brain to concentrate on the external world rather than internal thoughts (Chen et al., 2013; Ridder et al., 2022).

The SN plays a vital function in detecting important environmental stimuli and facilitates the brain's transition between the DMN and the CEN. It filters sensory, emotional, and cognitive information, allowing for adaptive shifts in attention based on external conditions. The SN activates in response to new or attention-grabbing stimuli, whether they are emotional, sensory, or task-related. Additionally, this network is vital for signaling when a transition is necessary from inward-focused, self-referential processing (DMN) to outward-directed, goal-oriented activity (CEN). Regions such as the anterior insula and anterior cingulate cortex (ACC) are crucial components of the SN, playing a role in assessing emotional significance and integrating physical sensations (Green et al., 2016; Seeley, 2019).

2.2.8 Overview of Functional MRI (fMRI) in Detecting MS

Functional MRI is a non-invasive imaging method used to assess brain activity by monitoring BOLD changes, which has demonstrated utility in MS by revealing evidence of neuroplasticity. It aids in evaluating how the brain adapts to damage by identifying distinct neural activation patterns, particularly during cognitive or motor activities. Unlike conventional MRI, which depicts structural abnormalities, fMRI provides insights into functional changes and neuroplastic adaptations, even in structurally normal areas (Mahmoudi et al., 2025).

Resting-state fMRI has shown altered brain connectivity and reduced network efficiency, both of which are linked to cognitive impairment in individuals with MS. In contrast, task-based fMRI (tb-fMRI) reveals abnormal brain activation during targeted cognitive or motor tasks, offering a better understanding of compensatory mechanisms. Combined, these fMRI methods serve as important tools for tracking disease progression, assessing cognitive dysfunction, and evaluating the outcomes of rehabilitation interventions in MS (Mahmoudi et al., 2025; Rocca et al., 2022).

Since the 1990s, when temporal correlations in BOLD signal fluctuations were first identified during rest, without the need for active tasks (Biswal et al., 1995). The rs-fMRI has been increasingly utilized to map regional brain connectivity based on the coherence of spontaneous BOLD signal fluctuations. This technique represents a promising approach for identifying potential biomarkers of brain-related disorders. An increasing number of studies suggest that the brain is structured into dynamic, intrinsic functional networks active during rest (Kampaite et al., 2024). Moreover, the association between MS and disrupted brain connectivity is widely recognized. As such, patterns and structures derived from RSA and FC are being considered as potential neurophysiological indicators for detecting gray matter degeneration and white matter disruptions, and altered connectivity within motor and cognitive networks in individuals with MS (Huang et al., 2020).

The rs-fMRI evaluates functional connectivity in the human brain by examining the temporal correlation of low-frequency fluctuations, usually within the 0.01 to 0.08 or 0.1 Hz

range, in the BOLD signal. These changes correspond to synchronized patterns of spontaneous neuronal signaling and uninstructed cognitive operations (Sbaihat et al., 2021).

Because participants are not required to engage in particular tasks during rs-fMRI, the outcomes are unaffected by task demands such as effort, motivation, or cognitive ability. This makes FC measurements largely objective. Additionally, rs-fMRI is generally well tolerated, even by individuals with severe symptoms, as it requires only a short scan duration. Some researchers suggest that a scanning time of approximately 6 minutes is sufficient to obtain reliable data (Dijk et al., 2010). While others advocate for longer sessions, around 12 minutes, to enhance data quality (Park et al., 2020).

By analyzing both localized brain activity and extensive functional connectivity, rs-fMRI can uncover network-level alterations in the brain that structural scans cannot detect. In the case of MS, regions that seem structurally intact might still exhibit disrupted connectivity or changes in regional activity, providing a more profound understanding of the disease's functional consequences. Despite its broad potential, it is important to recognize that rs-fMRI measurements can be affected by even subtle head movements, physiological factors such as breathing and heart rate variability, and technical limitations of MRI hardware, such as gradient heating during scans (Maknojia et al., 2019).

2.2.9 Overview of Resting-State fMRI Measurements

The rs-fMRI employs several key metrics to evaluate RSA and FC, such as amplitude of low-frequency fluctuations (ALFF), fractional ALFF (fALFF), regional homogeneity (ReHo), and degree centrality (DC).

A. Amplitude of Low-Frequency Fluctuations

Amplitude of low-frequency fluctuations is among the earliest and most widely used measures in rs-fMRI for assessing regional brain activity. It quantifies the strength of spontaneous BOLD signal fluctuations occurring within a low-frequency band, usually between 0.01 and 0.1 Hz. These low-frequency variations are believed to reflect spontaneous

neural activity and intrinsic physiological processes, particularly those related to baseline or default brain function (Yue et al., 2023).

Increased ALFF values indicate enhanced spontaneous activity in a brain area, while decreased ALFF values suggest diminished resting-state activity. In clinical research, including those studies on MS, ALFF can identify hypoactive or hyperactive brain regions. For instance, decreased ALFF in sensorimotor areas may correspond to motor impairments, whereas increased ALFF in prefrontal or parietal regions could indicate a compensatory mechanism as a reaction to network disruption integrity (Golestani et al., 2017).

B. Fractional ALFF

Fractional ALFF is an advancement of the traditional ALFF measurement. While ALFF measures the absolute amplitude of low-frequency brain activity.

It quantifies the ratio of power within the low-frequency band (typically 0.01–0.1 Hz) to the overall power across the entire BOLD signal frequency range. This normalization helps reduce the impact of non-neuronal noise, such as cardiac and respiratory signals, which generally occur at higher frequencies. By emphasizing this relative measure, fALFF offers a more specific and reliable indication of spontaneous neuronal activity. In the context of MS, fALFF has proven valuable for detecting subtle alterations in cortical regions affected by diffuse, small-scale damage (Wang et al., 2016). Empirical findings have shown both elevated and reduced fALFF values in patients with MS, reflecting regional variations in brain function that may result from either dysfunction or compensatory neuroplastic responses (Du et al., 2019).

C. Regional Homogeneity

Regional homogeneity assesses the coordination of neural activity within a specific brain area. It measures how closely the BOLD signal time series of a specific voxel matches those of its adjacent voxels, typically the 26 adjacent voxels in three-dimensional space. Higher ReHo values signify a greater level of synchronized neural activity, suggesting intact and efficient local processing. In contrast, lower ReHo values imply reduced synchronization, which may reflect disrupted or disorganized local function. ReHo is

particularly effective for detecting region-specific functional abnormalities and has shown utility in identifying subtle changes in individuals with MS. For example, decreased ReHo in the motor cortex has been associated with impaired motor function, while alterations in ReHo in prefrontal regions may be linked to cognitive dysfunction (Golestani et al., 2017).

D. Degree Centrality

Degree centrality is a concept from graph theory used to assess how extensively a particular brain region (or node) is functionally connected to the rest of the brain. It does this by counting the number of meaningful connections, or "edges," between a given voxel or region and all other areas in the brain. Regions with high DC are considered functional "hubs," playing a key role in coordinating activity across different brain systems. Conversely, regions with low DC exhibit fewer connections and are thus more functionally isolated (Mei et al., 2024).

In MS, alterations in DC indicate disruptions in the brain's intrinsic functional architecture, which are associated with neuroinflammation and neurodegeneration typical of the disease (Liu et al., 2023). The study shows that MS patients often display both increases and decreases in DC across different brain networks, reflecting a complex interplay of maladaptive and compensatory changes. For instance, reduced DC is commonly observed in the salience network and cingulate cortex, correlating with longer disease duration and increased disability. Conversely, increased DC in regions like the superior temporal gyrus and cerebellum may indicate a compensatory form of hyperconnectivity (Luo et al., 2017).

2.2.10 The Relation Between rs-fMRI Measurements and Triple Brain Network

The connection between rs-fMRI findings and the triple brain network model has emerged as a central focus in neuroscience, especially for understanding changes in FC and RSA in individuals with MS. This association is especially relevant when examining interactions within and between core intrinsic brain networks, including the DMN, the CEN and the SN, along with other networks related to cognitive and motor function. Alterations in these networks are increasingly recognized as markers of disease progression and are closely linked to clinical symptoms (Meng et al., 2022).

In MS, numerous studies have reported disrupted connectivity patterns within the DMN. In early disease stages, connectivity is often elevated, likely reflecting compensatory mechanisms, whereas in later stages, reduced connectivity suggests a decline in network function. Given the DMN's involvement in self-referential processing and memory, such disruptions have been associated with cognitive impairments, particularly in memory performance and information processing speed (Rocca et al., 2018; Sacco et al., 2013).

The CEN is crucial for working memory and cognitive control, and undergoes notable changes. Decreased functional connectivity within this network is associated with diminished executive functions, including impaired attention and planning. The SN, which facilitates the detection of salient stimuli and mediates switching between the DMN and CEN, is similarly affected. Disruptions in the SN impair the brain's ability to allocate attention and shift between internal and external focus, contributing to cognitive decline (Rocca et al., 2018).

Changes in FC within these networks are strongly associated with structural brain damage. Decreased FC in sensorimotor and cognitive networks is linked to a higher T2 lesion burden, whereas increased FC in visual and sensory areas may reflect maladaptive neural plasticity. Dynamic resting-state fMRI studies show that patients with progressive MS experience fluctuating network activity, which may underlie variability in clinical presentation (Droby et al., 2020; Rocca et al., 2018)

In conclusion, rs-fMRI metrics indicate that triple-network dysfunction in MS involves widespread disconnection (as indicated by DC), localized dysregulation (as measured by ReHo), and aberrant spontaneous activity (as reflected by ALFF and fALFF). Mapping these metrics onto the DMN, CEN, and SN offers a comprehensive view of how MS affects the brain's functional organization. These disruptions often align with specific cognitive impairments and fatigue (Luo et al., 2020; Sbaihat et al., 2022).

2.3 Previous Studies

Liang et al. (2025) used multilevel resting-state fMRI features and machine learning techniques to distinguish between MS and neuromyelitis optica spectrum disorder (NMOSD). Their research identified distinct functional connectivity patterns within key brain networks. Specifically, NMOSD patients showed increased connectivity in the DMN and SN, but decreased connectivity in the CEN. These findings indicate a disruption and reorganization of the triple network system, which is important for cognitive control, internal thought, and attention. The study demonstrates the value of rs-fMRI metrics in classifying diseases and highlights the relevance of the triple network model in understanding the neuropathological differences between MS and NMOSD (Liang et al., 2025).

Sbaihat et al. (2022) investigated the consistency of spontaneous neural activity and functional connectivity within key resting-state networks by utilizing ultrahigh-field 7-Tesla resting-state functional MRI (rs-fMRI). Participants completed two separate scanning sessions on a 7-Tesla MRI machine. The study focused on examining the stability of important resting-state parameters, including ALFF, ReHo, and DC, across multiple resting-state networks. The findings demonstrated high test-retest reliability for most of these metrics, particularly in the DMN, dorsal attention network (DAN), and sensorimotor network. These results support the use of ultrahigh-field 7T rs-fMRI as a dependable and reproducible tool for assessing intrinsic brain activity (Sbaihat et al., 2022).

Riazi et al. (2022) proposed a new method for analyzing dynamic brain connectivity in MS patients through resting-state fMRI. Utilizing spectral independent component analysis (ICA) and graph theory, they identified unique connectivity states and noted that MS patients displayed altered temporal characteristics, including shorter dwell times in certain states compared to HCs. These results indicate that dynamic connectivity metrics may act as sensitive biomarkers for identifying functional disruptions in MS (Riazi et al., 2022).

Rocca et al. (2022) presented an extensive review of fMRI research investigating functional brain changes in MS. They noted that in the early stages of MS, increased functional activation might indicate compensatory mechanisms, while in later stages, decreased network efficiency and impaired long-range connectivity are associated with

cognitive decline. The review also stressed the increasing importance of dynamic functional connectivity analysis and the potential of advanced methods like artificial intelligence and multimodal imaging to reveal mechanisms of neural adaptation and disease progression in MS (Rocca et al., 2022).

Wang et al. (2020) examined dynamic functional network connectivity in unmedicated patients with bipolar disorder and major depressive disorder using the triple-network model (DMN, SN, CEN). They discovered that both groups spent more time in states characterized by reduced connectivity between networks and exhibited decreased variability in crucial network interactions. These disruptions in dynamic brain connectivity provide insight into the differences in mood disorders and highlight the significance of investigating brain network dynamics in psychiatric research (Wang et al., 2020).

Zhou et al. (2016) investigated the changes in brain entropy, which reflects the complexity of spontaneous brain activity, in patients with RRMS. Through resting-state fMRI, they discovered that individuals with RRMS exhibited notable variations in brain entropy in several areas, correlating with clinical disability. These results suggest that brain entropy could serve as a non-invasive functional biomarker for evaluating the effects of the disease in MS (Zhou et al., 2016).

Weiler et al. (2014) utilized rs-fMRI to examine spontaneous brain activity, measured by ALFF, and functional connectivity within the DMN in individuals with mild Alzheimer's disease (AD), amnestic mild cognitive impairment (aMCI), and healthy controls. Their results showed reduced ALFF in the PCC of AD patients, along with altered connectivity patterns in the frontal and parietal areas of the DMN. The observed decrease in ALFF reflected localized neural disruptions, whereas changes in functional connectivity were more strongly linked to cognitive impairment, indicating its potential as a sensitive marker for detecting early neurodegenerative processes (Weiler et al., 2014).

Rocca et al. (2014) performed a multicenter fMRI study to investigate the neural correlates of cognitive dysfunction in MS. Their results showed that MS patients with

cognitive impairment had altered functional connectivity in important brain networks, especially within the DMN and frontoparietal regions. These disruptions were linked to deficits in attention, memory, and executive functions, emphasizing the impact of network-level dysfunction on cognitive decline in MS. The study highlights the value of resting-state fMRI in identifying biomarkers for cognitive impairment in these patients (Rocca et al., 2014).

In conclusion, despite the growing interest in rs-fMRI studies related to MS, several shortcomings persist. Many studies concentrate on individual networks or specific imaging metrics, which hinders a comprehensive understanding of brain dysfunction. Moreover, the triple-network model has not been extensively investigated in MS using integrated metrics like ALFF, ReHo, and DC. To date, no research has applied this model to MS patients in Palestine, highlighting both a regional and methodological gap. This study aims to fill these gaps by examining various resting-state measures within the triple-network framework, seeking to provide new insights into functional changes associated with MS.

Chapter Three: Methodology

This chapter outlines the methodological framework employed in this research. It describes the research design, study environment, target population, sampling strategies, and data collection methods to achieve the research objectives. In addition, it explains the instruments used for data collection, the procedures for data analysis, and the strategies implemented to ensure the validity and reliability of the findings. Ethical considerations observed throughout the study are also discussed. The selected methods were carefully designed to maintain scientific rigor and to generate accurate, reliable, and meaningful results.

3.1 Study Design and Settings

The research employed a quantitative, case-control design. After securing approval from the Institutional Review Board (IRB) at Arab American University Palestine (AAUP) (see Appendix A), the study was conducted at the MRI department of Jenin Governmental Hospital, after gathering the testing patients, including patients diagnosed with MS at the neurology clinic. Before data collection, participants received a detailed explanation of the study procedures and were asked to sign a written informed consent form, ensuring their voluntary participation.

3.2 Study Population and Instrument

This study included 20 patients diagnosed with MS, including 16 with RRMS and 4 with PPMS. The average disease duration among the MS patients was 5.6 years, and their ages ranged from 21 to 49 years, with a mean age of 36.1 years. A control group of 20 healthy individuals, matched for age and gender, was also included. These healthy controls had no history of psychiatric or neurological disorders. Their ages ranged from 22 to 38 years, with a mean age of 34.1 years. All participants from both groups underwent brain imaging using a 1.5 Tesla Philips MRI scanner at Jenin Governmental Hospital in Jenin, Palestine. This sample size was chosen due to practical factors such as scanner availability and time constraints of the IRP period, consistent with other exploratory fMRI studies in neurological

populations. Although the smaller participant count may reduce statistical power, the study design is adequate for examining initial trends in brain activity and connectivity.

3.3 Sample Inclusion Criteria

Participants were eligible for inclusion if they had a confirmed diagnosis of MS by a neurologist and were referred for an MRI scan as part of their clinical evaluation. Additional requirements included being between 18 and 50 years of age and the ability to provide written informed consent. These criteria ensured a relevant and cooperative study sample.

3.4 Sample Exclusion Criteria

Exclusion from the study applied to individuals with metallic implants or medical devices that could interfere with MRI imaging or pose safety concerns. Those who were unable to remain still during the scan or who declined to provide informed consent were also excluded. These measures were taken to ensure participant safety and the quality of the collected imaging data.

3.5 Ethical Considerations

Ethical integrity was a fundamental aspect of this study. Prior to data collection, ethical approval was secured from the university's Research Ethics Committee under the reference number (R-2024/A/41/N) (Appendix A) to ensure adherence to institutional and national regulations. Participants were thoroughly informed about the study's objectives and procedures and gave their written informed consent (refer to Appendix B). Participation was voluntary, and individuals could withdraw at any time without consequence. To protect privacy, no identifying personal data, such as names, addresses, or ID numbers, was collected, and all data were stored securely. Confidentiality was maintained throughout, and data handling procedures adhered strictly to applicable data protection regulations. Participants were treated with respect and care, and efforts were made to minimize any potential risk or discomfort.

3.6 Experimental Design

The study design in this study attended to have 20 subjects from each group, allowing for comparison and finding potential alterations in functional connectivity and brain activity Figure 3.1.

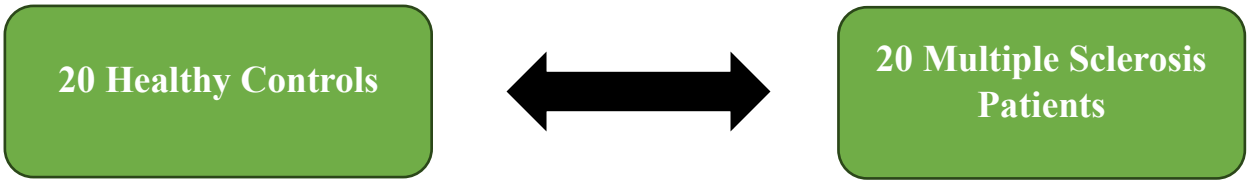

Figure 3.1: The experimental design of the study, including two sessions for healthy controls and multiple sclerosis patients.

3.7 Magnetic Resonance Data Acquisition

The MR data were collected using a 1.5 T Philips scanner, employing the echo-planar imaging (EPI) sequence to acquire the fMRI data. 180 volumes were acquired resting state. The MR parameters were as follows in Table 3.1.

Table 3.1: The EPI sequence parameters.

Repetition Time (TR)	Echo Time (TE)	Flip Angle (FA)	Field of View (FOV)	Matrix Size	Slice Thickness	Number of Slices	Voxel Size
3000 ms	50 ms	90˚	128 × 128 mm	30 × 30	4 mm	30	1.4 × 1.4 × 4 mm^3

To acquire structural images, the T1-3D isotropic (T1-3D ISO) sequence was used. The MR parameters are listed in Table 3.2.

Table 3.2: shows the T1-3D-ISO sequence parameters.

Repetition Time (TR)	Echo Time (TE)	Flip Angle (FA)	Field of View (FOV)	Matrix Size	Slice Thickness	Number of Slices	Voxel Size
25 ms	4.6 ms	30˚	256 × 256 mm	64 × 64	1 mm	155	$1\times1\times1mm^3$

While 1.5T systems are widely available and clinically useful, they present certain limitations compared to higher field strengths such as 3T or 7 T. Specifically, 1.5T scanners offer lower signal-to-noise ratio (SNR), reduced spatial resolution, and less sensitivity to BOLD signal changes. These factors may limit the ability to detect subtle structural abnormalities or weak functional connectivity patterns, which could influence the sensitivity of our findings.

3.8 Triple-Network ROIs

The triple-network model included 18 ROIs, selected based on the CONN toolbox atlas (Whitfield-Gabrieli & Nieto-Castanon, 2012) , and grouped into three networks: DMN, CEN, and SN. Figure 3.2, Panels A–C.

The masks for the DMN and CEN each consisted of four regions of ROIs, while the SN mask encompassed seven ROIs. Specifically, the DMN included the medial prefrontal cortex, bilateral lateral parietal, and the posterior cingulate cortex. The CEN was composed of the right and left lateral prefrontal cortex along with the right and left Posterior parietal cortex. For the SN, the ROIs consisted of the anterior cingulate cortex, bilateral anterior insula, bilateral rostral prefrontal cortices, and bilateral supramarginal gyrus. Additionally, the analysis considered the overall triple brain networks.

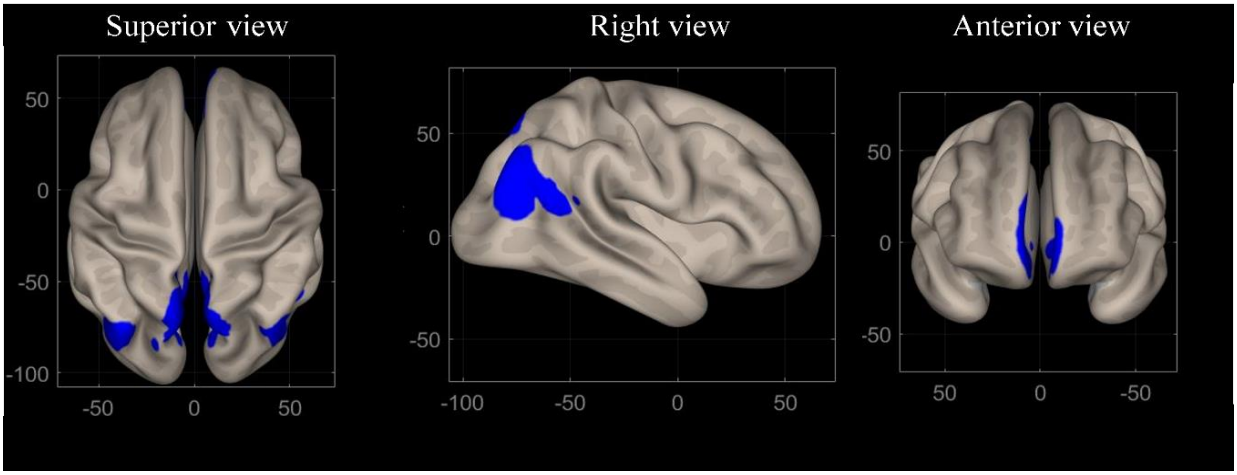

Figure 3.2. A: Description of the default mode network region.

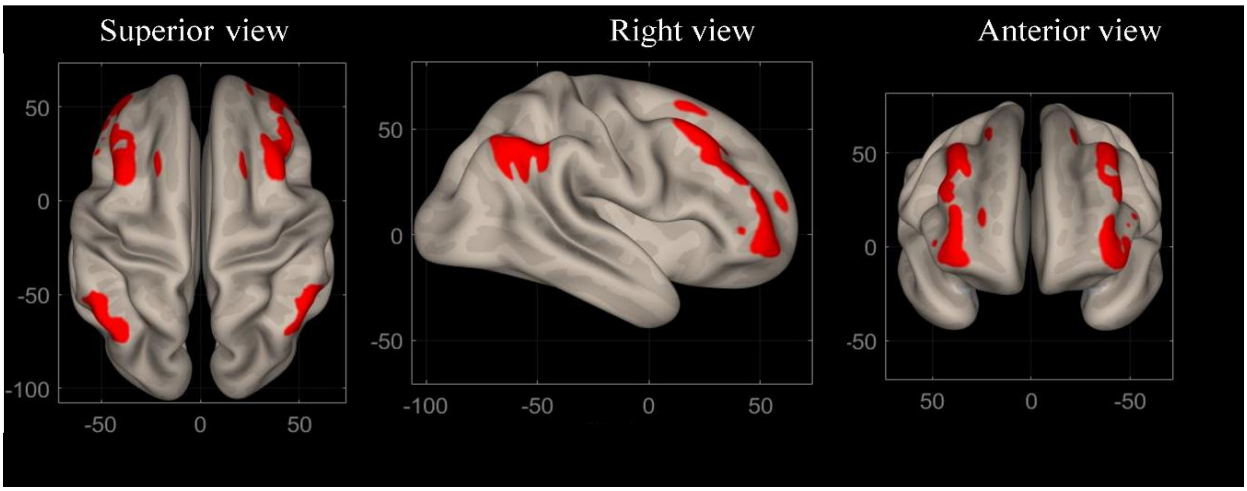

Figure 3.2. B: Description of the central executive network region.

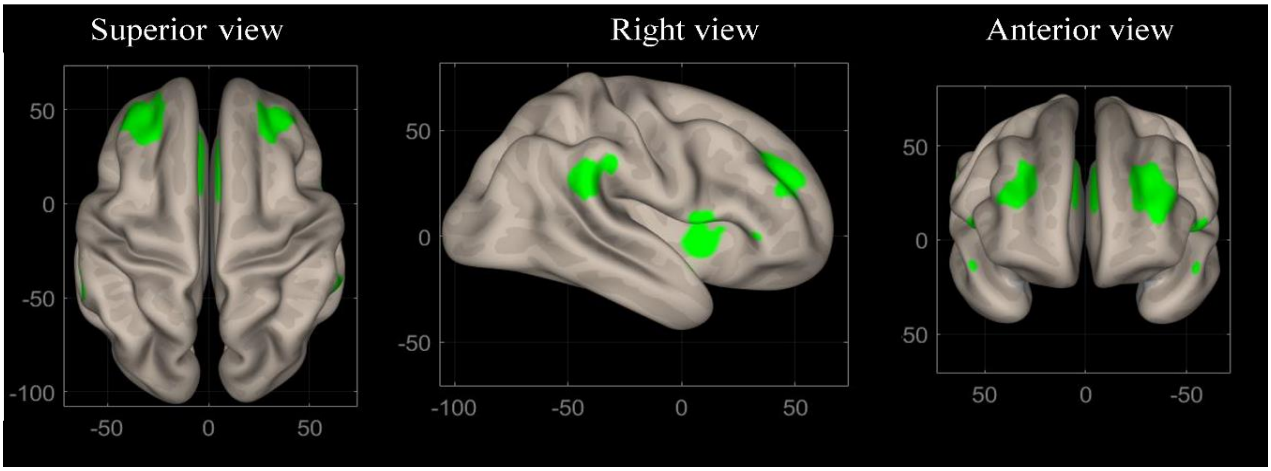

Figure 3.2. C: Description of the salience network region.

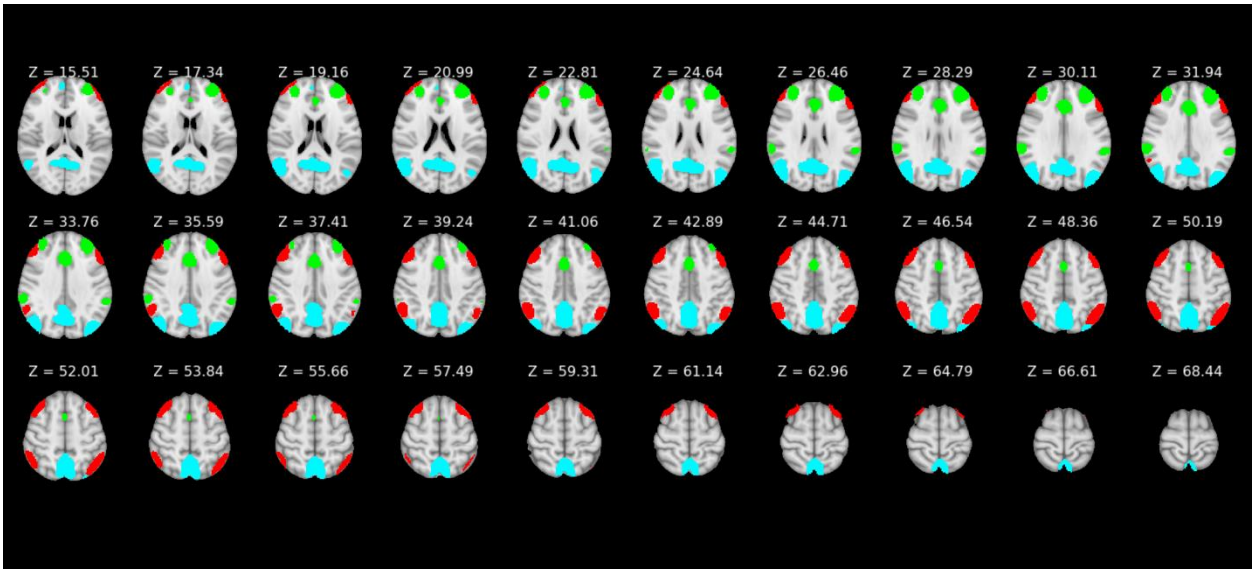

Figure 3.3: Description of three brain networks across a sectional view of the brain, the red color reflecting the Central executive network, the green color reflecting Salience network, and the bright blue reflecting the Default mode network.

3.9 fMRI Data Analysis

The fMRI data preprocessing for both the HCs and MS groups was performed using the Data Processing & Analysis for Brain Imaging (DPABI) toolbox (Yan et al., 2016). In combination with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/), this was done in conjunction with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) within the MATLAB environment, version 2024a (The MathWorks, Inc., Natick, MA, USA). The preprocessing workflow involved

several steps: discarding the first ten volumes to allow for signal stabilization, correcting for slice timing differences, performing realignment along with field map correction, and co-registering high-resolution T1-weighted images with the functional scans. The registered T1-weighted images were then segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). To reduce nuisance effects, the Friston 24-parameter model was used to regress out head motion from the realigned data. Furthermore, signals originating from WM and CSF were also removed to lessen physiological noise.

Because motion can substantially impact the FC results, the Friston 24-parameter model, along with framewise displacement, were used to evaluate head movement at the individual subject level. Participants with head movement exceeding 3 mm in translation or 3° in rotation were excluded from further analysis. Additionally, standard masks for the whole brain, white matter, grey matter, and CSF were created from the segmented structural images and applied before calculating the fMRI metrics.

The ALFF was calculated by initially converting the BOLD signal time series into the frequency domain using a Fast Fourier Transform (FFT), followed by obtaining the power spectrum. The ALFF value for each voxel was then determined by summing the amplitudes within the low-frequency range of 0.01–0.1 Hz (Zang et al., 2007; Zuo et al., 2010).

Subsequently, temporal filtering in the range of 0.01 to 0.1 Hz was applied to the time series of all voxels in the preprocessed fMRI data to compute functional connectivity metrics such as DC and ReHo. For DC calculation, Pearson's correlation coefficients were computed between the time series of each voxel and those of all other grey matter voxels in the brain. The resulting correlation vector was binarized using a threshold of $r > 0.25$ ($p \leq 0.001$), and the number of significantly correlated voxels was summed to obtain the DC value for each voxel (Takeuchi et al., 2015).

Regional homogeneity was calculated by measuring the synchronization of a voxel's time series with those of its 26 closest neighboring voxels within the grey matter, using Kendall's coefficient of concordance (KCC) as the similarity metric (Zang et al., 2004).

All fMRI metrics were normalized using Z-score standardization, which involved subtracting the global mean from each voxel's value and dividing by the standard deviation of the entire brain. Finally, spatial smoothing was applied with a full width at half maximum (FWHM) of 3 mm^3.

3.10 ROI-based FC Analysis

All predefined brain regions were used to compute the ROI based connectivity analysis; The functional connectivity among the ROIs within the triple networks was assessed by extracting the mean BOLD signal time series from each ROI. Pearson's correlation coefficients were then calculated between the mean time series of every ROI pair, generating two 18 × 18 connectivity matrices for each participant. To enhance the normality of the correlation values, Fisher's r-to-z transformation was applied to all connectivity matrices.

3.11 Statistical Analysis

All fMRI metrics utilized in this study—ALFF, DC, and ReHo—were extracted from voxels located within the 18 ROIs that make up the triple networks, for all participants across both groups. These extracted values were then used to conduct voxel-wise statistical analysis. A two-sample t-test assuming equal variances was employed to evaluate differences in brain activity and connectivity between the MS and HC groups. Prior to conducting the parametric analysis, data normality was verified using the Kolmogorov-Smirnov test.

Chapter Four: Results

In this chapter, the study's findings will be presented, which focus on the research question and objective discussed in previous chapters. The results are structured around major themes and categories identified through data analysis. Each section offers a thorough summary of the collected data and relevant tables and figures as needed.

4.1 fMRI Parameters

The resulting fMRI parameters demonstrated different quantities of the RSA and the local/global FC for both groups. Figures 4.1 through 4.6 show the averaged activity and connectivity maps across the HCs and MS groups. Each figure displays averaged brain activity across multiple orientations (right and left lateral, right and left medial, superior, inferior, anterior, and posterior), with color-coded intensity indicating the strength of the respective metric. Table 4.1 summarizes the mean and standard deviation values across key networks.

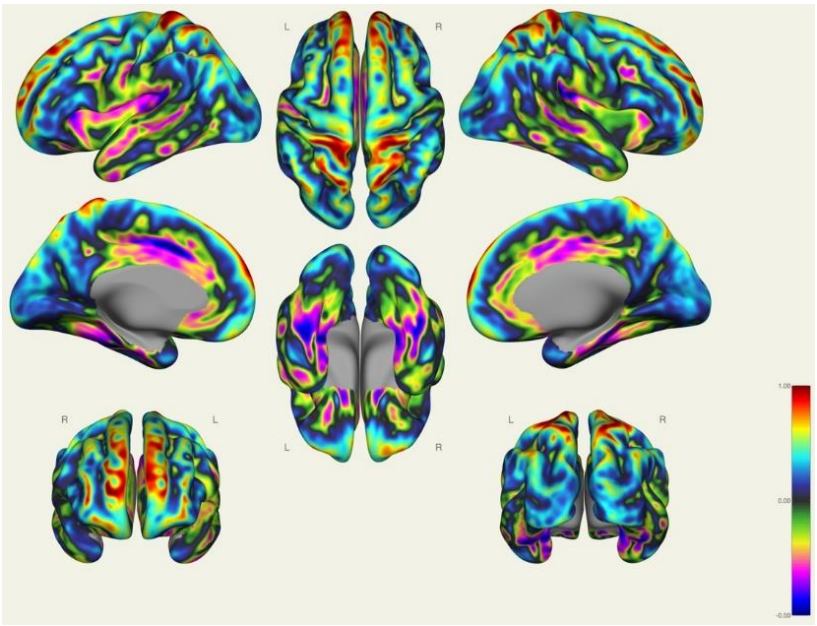

Figure 4.1: The averaged degree centrality metrics of 20 patients with multiple sclerosis (mean age: 36.1 ± 8.3 years). Bar color reflects the global connectivity strength. The red color reflects the highest global connectivity; the blue reflects the lowest.

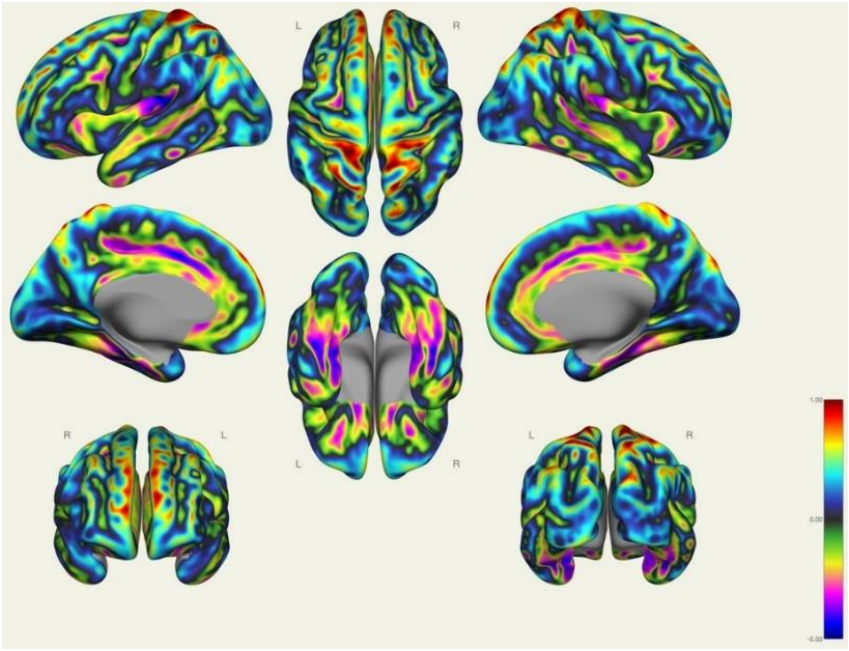

Figure 4.2: The averaged degree centrality metrics of 20 healthy control subjects (mean age: 34.1 ± 7.2 years). Bar color reflects the global connectivity strength.

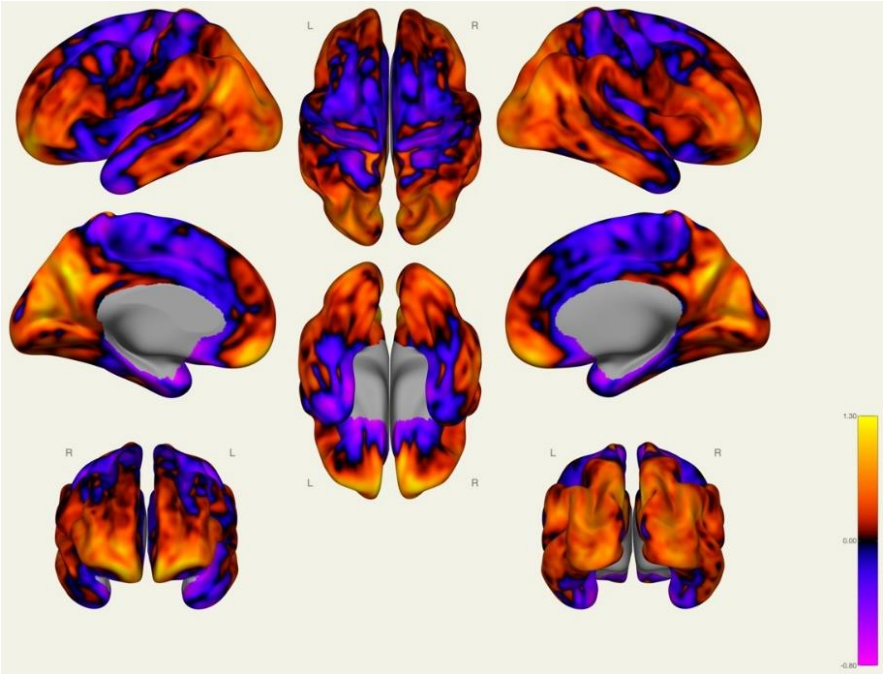

Figure 4.3: The averaged regional homogeneity values in 20 patients with multiple sclerosis (mean age: 36.1 ± 8.3 years. The yellow color reflects the highest regional connectivity strength, and pink reflects the lowest.

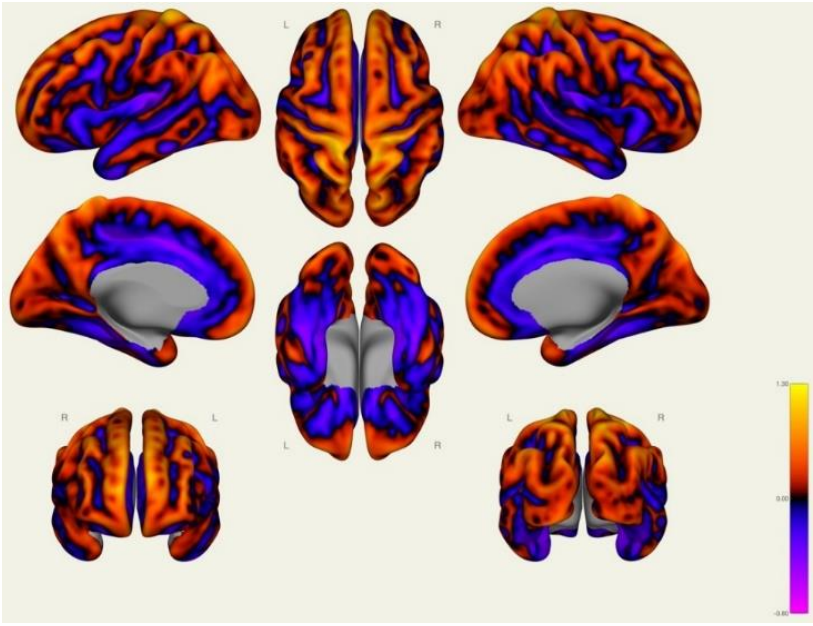

Figure 4.4: The averaged regional homogeneity values in 20 healthy control subjects (mean age: 36.1 ± 8.3 years). Bar color reflects the regional connectivity strength.

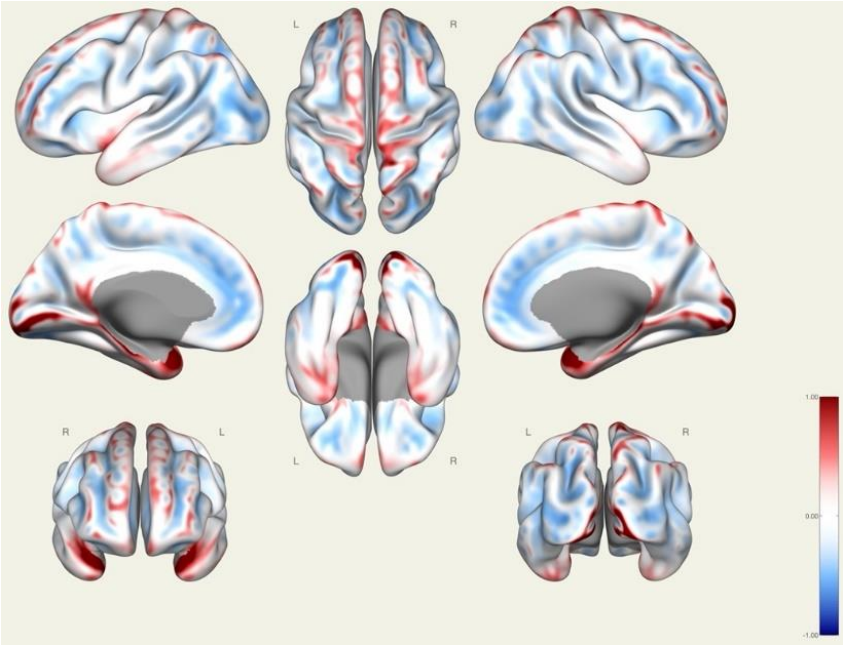

Figure 4.5: The averaged amplitude of low-frequency fluctuation (ALFF) values in 20 patients with multiple sclerosis (mean age: 36.1 ± 8.3 years). The red color reflects the highest regional brain activity, while the blue reflects the lowest.

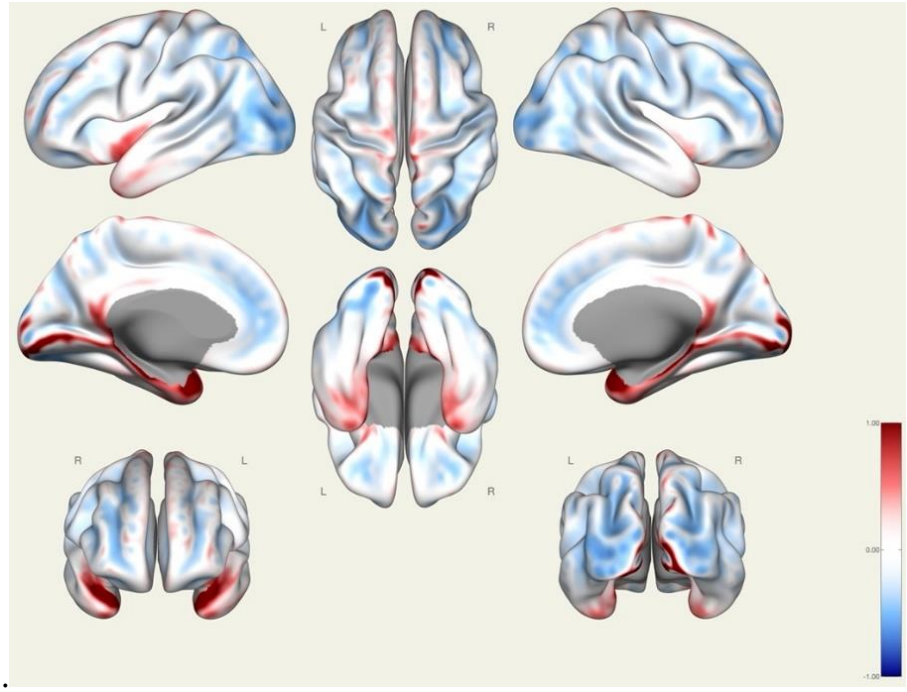

Figure 4.6: The averaged amplitude of low-frequency fluctuation (ALFF) values in 20 healthy control subjects (mean age: 36.1 ± 8.3 years). Bar color reflects the regional brain activity.

Table 4.1 The extracted values of the DC, ReHo, and ALFF.

Healthy Control						
ROIS	**DC**		**ReHo**		**ALFF**	
	Mean	Std	Mean	Std	Mean	Std
Central executive network	0.565	0.181	0.482	0.174	0.105	0.152
Default Mode network	0.365	0.198	0.614	0.132	-0.025	0.105
Salience network	0.184	0.145	0.194	0.157	-0.087	0.129
Default Mode (MPFC)	0.358	0.308	0.514	0.294	-0.041	0.181
Default Mode. Left (LP)	0.461	0.282	0.700	0.230	-0.176	0.136
Default Mode. Right (LP)	0.359	0.234	0.621	0.178	-0.168	0.133
Default Mode (PCC)	0.348	0.213	0.620	0.195	0.050	0.129
Salience (ACC)	-0.044	0.201	0.076	0.222	-0.105	0.193
Salience AInsula (L)	0.080	0.298	0.132	0.270	0.166	0.234
Salience AInsula (R)	0.079	0.273	0.183	0.273	0.024	0.223
Salience. Left (PFC)	0.368	0.281	0.245	0.217	-0.085	0.169
Salience. Right (PFC)	0.291	0.289	0.234	0.202	-0.237	0.166
Salience. Left (SMG)	0.246	0.261	0.407	0.295	-0.136	0.136
Salience. Right (SMG)	0.322	0.294	0.278	0.298	-0.227	0.140
Fronto Parietal. Left (PPC)	0.501	0.300	0.434	0.305	-0.046	0.196

Fronto Parietal. Right (LPFC)	0.608	0.253	0.501	0.144	0.156	0.201
Fronto Parietal. Right (PPC)	0.558	0.354	0.473	0.382	-0.070	0.196
Language. Left IFG	0.073	0.258	0.305	0.280	0.008	0.195
Group Average	**0.318**	**0.257**	**0.390**	**0.236**	**-0.050**	**0.167**
Multiple Sclerosis						
ROIS	**DC**		**ReHo**		**ALFF**	
	Mean	**Std**	**Mean**	**Std**	**Mean**	**Std**
Central executive network	0.543	0.177	0.327	0.166	0.258	0.244
Default Mode network	0.309	0.201	0.526	0.204	-0.027	0.113
Salience network	0.139	0.139	0.118	0.128	-0.123	0.122
Default Mode (MPFC)	0.326	0.389	0.422	0.353	-0.063	0.197
Default Mode. Left (LP)	0.431	0.327	0.587	0.302	-0.034	0.178
Default Mode. Right (LP)	0.281	0.283	0.633	0.304	-0.110	0.179
Default Mode (PCC)	0.285	0.180	0.512	0.195	0.007	0.150
Salience (ACC)	-0.119	0.122	-0.058	0.169	-0.210	0.110
Salience. AInsula (L)	-0.031	0.274	0.118	0.222	0.025	0.215
Salience. AInsula (R)	0.039	0.386	0.240	0.285	-0.131	0.142
Salience. Left (RPFC)	0.364	0.269	0.153	0.230	-0.031	0.243
Salience. Right (RPFC)	0.396	0.306	0.195	0.279	-0.154	0.259
Salience. Left (SMG)	0.092	0.328	0.332	0.343	-0.213	0.161
Salience. Right (SMG)	0.100	0.256	0.133	0.312	-0.257	0.127
Fronto-Parietal. Left (PPC)	0.516	0.399	0.268	0.301	0.157	0.311
Fronto-Parietal. Right (LPFC)	0.675	0.250	0.368	0.210	0.378	0.330
Fronto-Parietal. Right (PPC)	0.411	0.280	0.250	0.284	0.041	0.243
Language. Left (IFG)	0.128	0.285	0.354	0.327	-0.023	0.155
Group average	**0.271**	**0.269**	**0.304**	**0.256**	**-0.028**	**0.193**

The table displays the quantitative findings for three important rs-fMRI metrics—DC, ReHo, and ALFF. These metrics were extracted from various ROIs within the triple network model and other functionally significant areas. The results are shown as group means and standard deviations for both HCs and patients with MS.

Overall, HC participants exhibited higher DC and ReHo values, particularly within the SN and CEN, suggesting stronger global and local connectivity. In contrast, ALFF values were generally elevated in MS patients, particularly in frontal-parietal regions, possibly reflecting compensatory increases in spontaneous neural activity.

4.1.1 Central Executive Network

In the CEN, MS patients showed reduced local connectivity, with ReHo values significantly lower than those of HCs (0.327 ± 0.166 vs. 0.482 ± 0.174). Key areas such as the right lateral prefrontal cortex (LPFC) and right posterior parietal cortex (PPC) exhibited notable decreases in ReHo.

Degree centrality values were also slightly reduced in MS patients (0.543 ± 0.177) compared to HCs (0.565 ± 0.181). In contrast, ALFF values were significantly higher in MS patients, particularly in the right LPFC (0.378 ± 0.330) for MS patients and (0.156 ± 0.26)for HCs, and left PPC (0.157 ± 0.311) in MS patients to (-0.046 ± 0.196) for HCs, suggesting elevated spontaneous activity possibly reflecting neural compensation (Du et al., 2019).

4.1.2 Default Mode Network

The DMN showed moderate reductions in connectivity among MS patients. Group-level DC values were lower in MS (0.309 ± 0.201) compared to HCs (0.365 ± 0.198), and ReHo also declined (0.526 ± 0.204 in MS vs. 0.614 ± 0.132 in HCs). ALFF values in this network were generally low or negative for both groups. However, MS patients exhibited slightly less negative ALFF values, particularly in the left lateral parietal cortex, indicating possible disruptions in default-mode deactivation during rest (Aguilar et al., 2022; Won et al., 2021).

4.1.3 Salience Network

The SN demonstrated consistent reductions across all three metrics in MS patients, DC: Decreased from 0.184 ± 0.145 (HCs) to 0.139 ± 0.139 (MS). while ReHo: Dropped from 0.194 ± 0.157 to 0.118 ± 0.128, with a notable decline in the anterior cingulate cortex (ACC). In ALFF: More negative in MS (-0.123 ± 0.122) vs. HCs (-0.087 ± 0.129), with significant decreases in the ACC and left anterior insula. These findings suggest substantial impairment in regions involved in detecting and integrating salient stimuli.

4.1.4 Group-Level Summary

When analyzing the whole-brain averages across all ROIs, a consistent pattern of functional disruption was observed in the MS group. Both DC and ReHo were lower in MS patients compared to HCs, indicating widespread impairments in both global and local connectivity. These reductions suggest compromised network integration and diminished regional synchronization, which may contribute to the cognitive and behavioral difficulties seen in MS.

Conversely, the ALFF exhibited a slight overall increase in the MS group. Although this increase was not uniform across all regions, heightened ALFF in specific areas, such as those within the CEN, may indicate region-specific compensatory mechanisms. These findings support the idea that the MS brain might attempt to preserve function by increasing spontaneous neural activity in regions experiencing connectivity loss.

Overall, the group-level results highlight a dual phenomenon in MS: a breakdown in functional connectivity alongside localized increases in intrinsic neural activity, potentially as an adaptive response. This complex interaction may reflect the brain's efforts to compensate for structural damage and sustain cognitive performance.

4.2 Degree Centrality Result

A notable DC was found in the right supramarginal gyrus (SMG) of MS patients compared to healthy controls ($p = 0.007$), as shown in Figure 4.7. The right SMG is an important node within the salience network, playing a role in attentional reorienting, empathy, and social cognition. This decline in global connectivity indicates a disruption in the brain's capacity to integrate important sensory and cognitive information, which may contribute to the attentional and cognitive deficits frequently seen in MS patients (Lashkari et al., 2021).

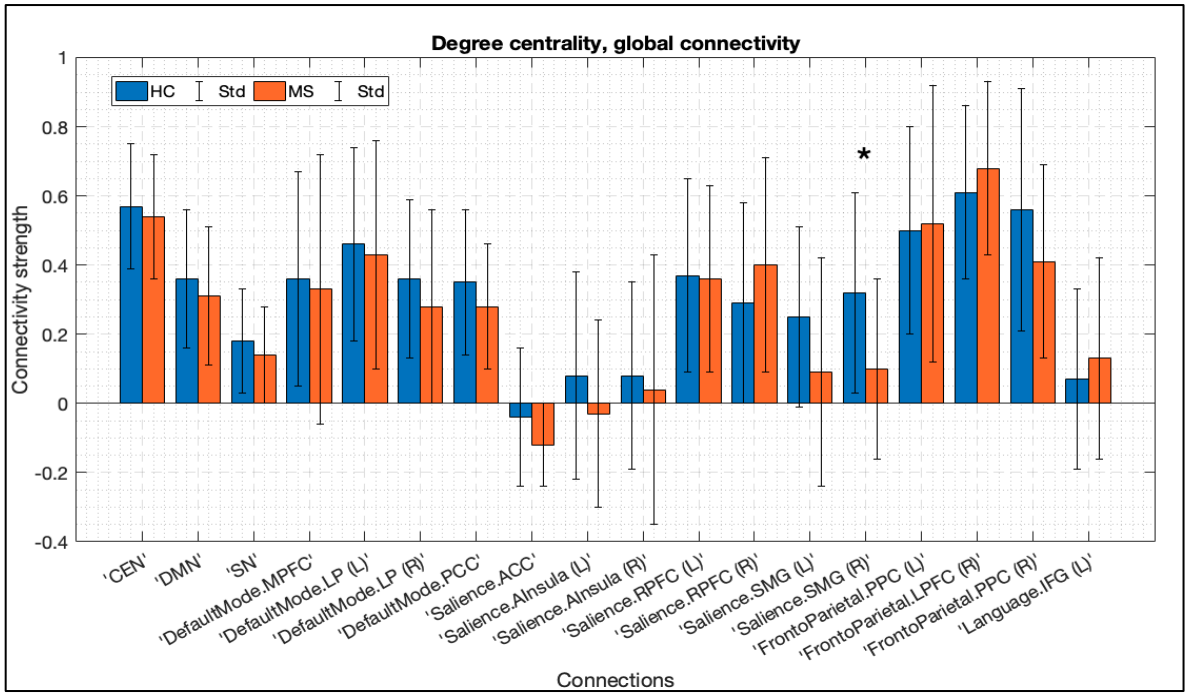

Figure 4.7: The global connectivity strength of DC values in MS patients compared to HCs.

4.3 Regional Homogeneity Results

Significant reductions in ReHo in the right LPFC ($p = 0.04$) and right PPC ($p = 0.026$) within the CEN, as well as in the ACC ($p = 0.026$) within the SN, Figure 4.8. These regions are associated with executive control and emotional regulation, and reduced local synchronization may underlie MS-related cognitive deficits.

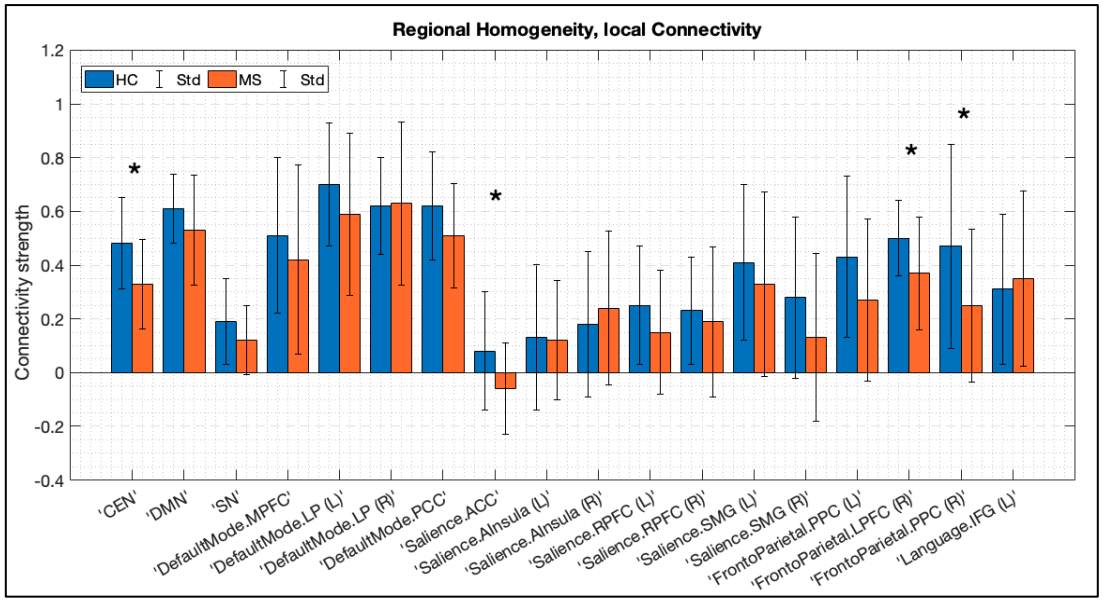

Figure 4.8: The local connectivity strength of ReHO values in MS patients compared to HCs.

4.4 Amplitude of Low-Frequency Fluctuations Results

Increased ALFF values were noted in the right LPFC (p = 0.01) and left PPC (p = 0.017) in the CEN of MS patients. In the DMN, a significant increase in ALFF was also noted in the left lateral parietal cortex (p = 0.004), as shown in Figure 4.9, suggesting compensatory hyperactivity. Conversely, reduced ALFF was found in the ACC (p = 0.049) and left anterior insula (p = 0.01), supporting the idea of network dysfunction in salience detection and switching.

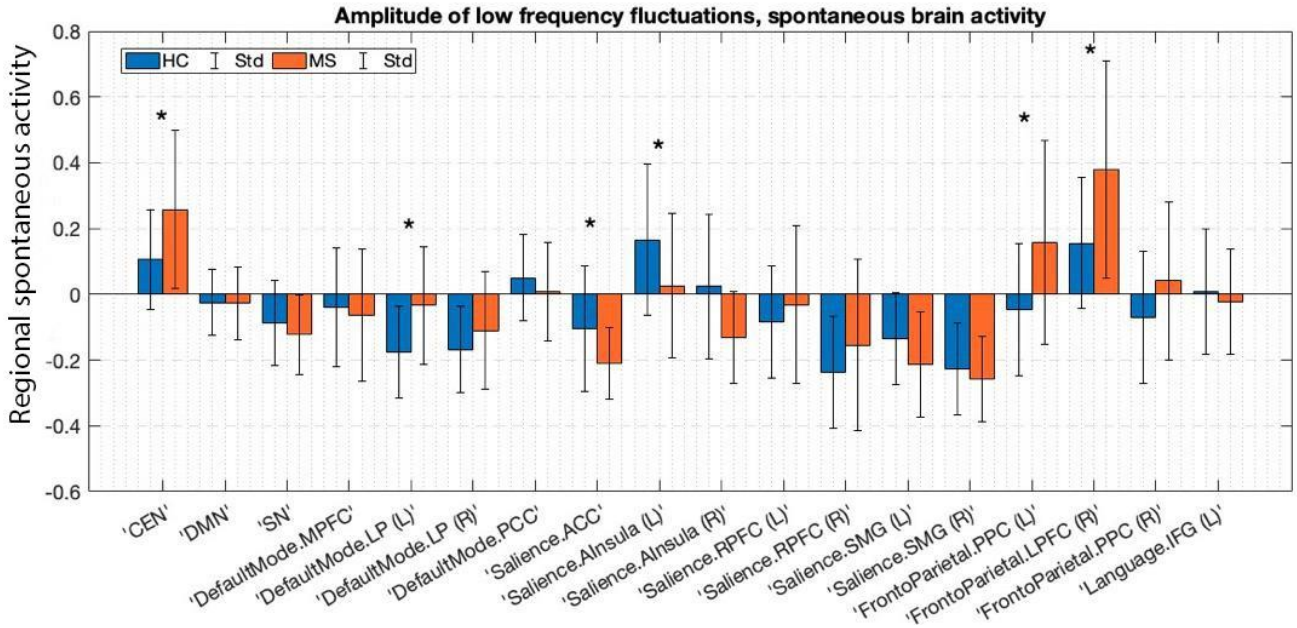

Figure 4.9: The spontaneous brain activity of ALFF values in MS patients compared to HCs.

4.5 ROI-based Connectivity Analysis

The results of the ROI based analyses have been computed after extracting the pre-processed BOLD signal, as shown in Figure 4.10 from each ROI and running correlations in Figure 4.11 after averaging all functional connectivity across 20 HC. And then the same computation for the MS patients, Figure 4.12. A significant reduction in connectivity strength was observed between the DMN and SN in MS patients ($p = 0.02$), indicating impaired inter-network communication.

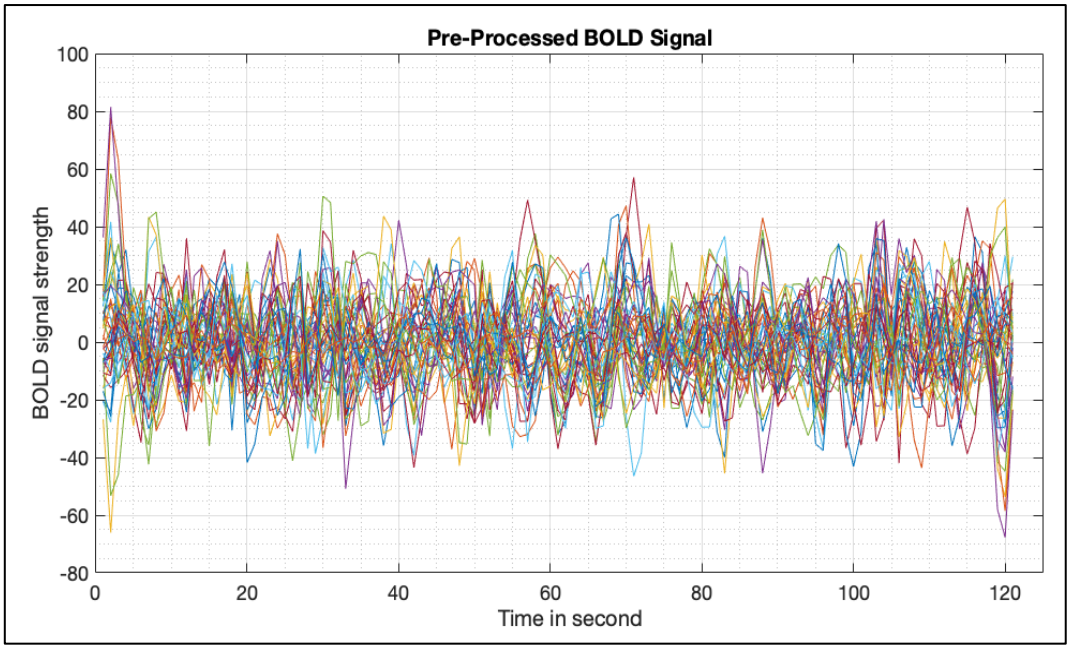

Figure 4.10: The pre-processed BOLD signal extracted from a single healthy control subject.

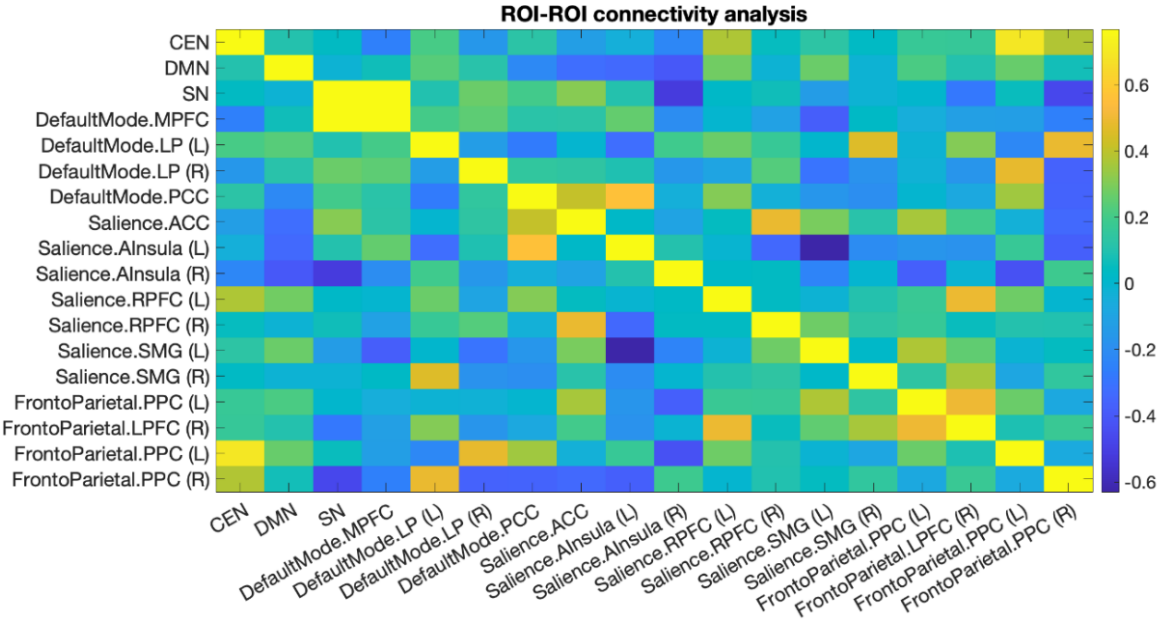

Figure 4.11: The functional connectivity across 20 HCs across 18 ROIs and the connectivity strength in several ROI-to-ROI brain regions.

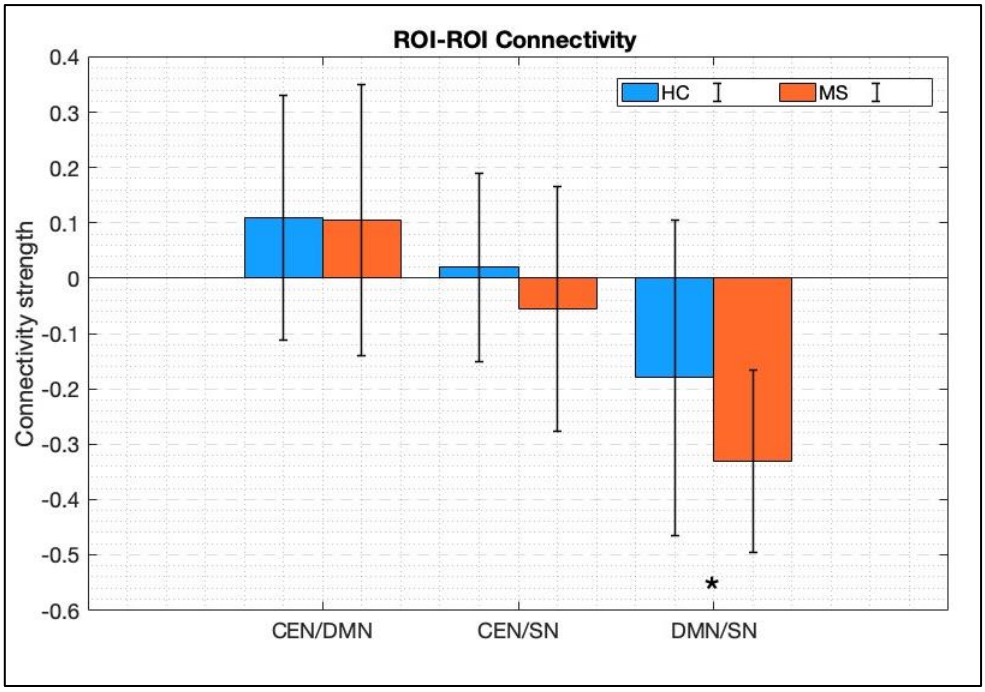

Figure 4.12: The connectivity strength of ROIs between the networks in MS patients compared to HCs.

In summary, the results reveal a pattern of disrupted FC and altered RSA in MS, particularly within the SN and CEN. These alterations may underlie many of the cognitive and emotional symptoms observed in MS patients.

Chapter Five: Discussion and Conclusion

This chapter discusses the structural and functional brain changes between MS patients and HCs. To explore alterations in brain function associated with MS, three analytical metrics—ALFF, DC, and ReHO—are employed in the triple brain networks.

By comparing these measurements in both groups, the study aims to uncover notable differences in brain function and network structure linked to MS. These findings could help shed light on how the disease affects the brain and potentially reveal biomarkers for tracking MS progression and cognitive decline. Gaining insight into these changes may support the development of better diagnostic tools and treatments for individuals with MS.

5.1 Discussion

The findings showed significant alterations of triple brain networks in MS patients compared to HCs, indicated by notable differences in ALFF, DC, and ReHo values across various brain regions. According to these results, patients with MS have distinctive patterns of intrinsic brain activity that are correlated with the triple network's functional dynamics.

5.1.1 Amplitude of Low-Frequency Fluctuations Analysis

In the current study, the results have shown an alteration (both increased and decreased) of ALFF values in MS patients compared to HCs. These alterations indicate disturbances in the brain's natural neuronal activity, probably resulting from demyelination and axonal injury. An increase of ALFF values may indicate a compensatory neuroplastic response, where certain brain areas enhance spontaneous activity to sustain functional output despite disruption in local or global networks. This increased low-frequency oscillatory activity may indicate the CNS's adaptive attempts to redistribute cognitive or sensorimotor resources, particularly in areas less impacted by structural damage (Due et al., 2019; Yan et al., 2022).

On the other hand, a reduction in ALFF values may indicate decreased spontaneous neural activity in areas where structural damage surpasses the brain's ability to reorganize

functionally (Zhe et al., 2023). This could suggest a breakdown in local circuit integrity or a failure of compensatory mechanisms, often linked to advanced or progressive stages of MS. Lower ALFF may also reflect hypoactivation or functional disengagement of certain brain regions that struggle to support cognitive or motor functions effectively (Dobryakova et al., 2023; Laura et al., 2018; Tomassini et al., 2012).

A. Increased ALFF Values

In the results, there are increased ALFF values in the CEN, particularly in the right lateral prefrontal cortex (LPFC) and the left posterior parietal cortex (PPC), which are regions involved in working memory and cognitive control (Dixon, 2015; Whybird et al., 2021). This finding aligns with previous studies (Dobryakova et al., 2022; Sulpizio et al., 2021) that reported increased activity in these regions, suggesting a possible compensatory mechanism in response to cognitive impairment in MS patients.

The observed increase in activity in the left lateral parietal cortex, a region that partially overlaps with the inferior parietal lobule (IPL). While direct evidence from previous MS studies focusing specifically on this area is limited, some research (Rocca et al., 2022) has reported increased activation in the angular gyrus, a key component of the IPL and an important hub within the DMN. This anatomical and functional overlap highlights the potential relevance of our findings and supports the hypothesis that altered activity in this region may reflect compensatory mechanisms in response to MS-related neural disruption. Given its central role within the DMN, this region warrants further investigation in future studies.

B. Decreased ALFF Values

There is a significant reduction in ALFF values in the anterior cingulate cortex (ACC) and the left anterior insula (AInsula) in MS patients compared to healthy controls. These regions are core components of the SN, which is crucial for detecting, filtering, and integrating cognitively, emotionally, and sensorily relevant stimuli to guide behavior and facilitate dynamic switching between the DMN and CEN (Li et al., 2024). The reduced spontaneous neural activity in these regions, highlighted by lower ALFF, indicates a

disruption in the intrinsic functional integrity of the SN in MS. These changes may hinder patients' ability to process important information effectively, which could lead to frequent cognitive and emotional symptoms associated with MS, such as attention deficits, diminished cognitive flexibility, and emotional instability.

These results align with previous research highlighting functional disruptions within the ACC in MS patients (Lashkari et al., 2021; Liu et al., 2016; Plata-Bello et al., 2018; Yan et al., 2022) , while Rahnemayan et al. (2025) reported decreased activity in the insula, which affects emotional awareness (Rahnemayan et al., 2025).

5.1.2 Degree Centrality Analysis

Changes in DC in MS patients reflect significant alterations in the brain's functional architecture, primarily driven by underlying pathological processes such as demyelination, axonal loss, and neurodegeneration (Groppa et al., 2021). A decrease in DC values suggests fewer functional connections within a brain region, often pointing to functional disconnection or damage in critical hubs responsible for processing and integrating information (Carotenuto et al., 2022). Conversely, an increase in DC values in some areas may reflect compensatory mechanisms, where these regions boost their connectivity to meet cognitive or functional demands despite widespread damage (Zhou et al., 2014). For instance, increased DC in DMN may indicate a complicated interplay between compensatory strategies to address functional disconnection in other areas and potential overactivity that could contribute to certain cognitive symptoms (Meijer et al., 2017). Overall, variations in DC are seen as indicators of both neurofunctional disruption and adaptive reorganization, emphasizing the complex relationship between damage and compensation in the MS brain.

A. Decreased DC Values

In this study, there is a decrease in global connectivity (DC value) in the right supramarginal gyrus (SMG) of the SN, which is responsible for empathy and social cognition (Silani et al., 2013). This finding is corroborated by Lashkari et al. (2021), who noted reduced FC in the SMG. Although their study employed seed-based analysis and did not evaluate global metrics such as degree centrality, the regional disconnection they identified is consistent with our findings. Their integration of fMRI and DTI further underscores both functional and structural deficits in the related parietal areas (Lashkari et al., 2021).

5.1.3 Regional Homogeneity Analysis

Changes in local connectivity within the triple brain network in MS patients reflect disrupted local synchronization of neural activity, suggesting a breakdown in the functional integration of large-scale networks essential for cognitive and behavioral functions. These findings emphasize the significance of local connectivity alterations as both indicators and possible contributors to the clinical symptoms of MS (Zhu et al., 2020).

A. Decreased ReHo Values

The result shows a decreased local connectivity of the ACC of the SN, which is responsible for combining emotional and cognitive processes to affect behavior and decision-making (Schimmelpfennig et al., 2023). Lashkari et al. (2021) and Hulst et al. (2011) have reported the same result (Hulst et al., 2012; Lashkari et al., 2021).

Also, there is a decrease in ReHo values in the CEN, especially within the right posterior parietal cortex (PPC), which plays an essential role in maintaining sustained attention to spatial locations, including staying alert and directing focus (Sengupta et al., 2024); and the right lateral prefrontal cortex (LPFC), which is responsible for working memory and cognitive control (Dixon, 2015).

This reduction in ReHO values in the LPFC in MS patients compared to HCs indicates impaired local functional connectivity in that area. This observation corresponds with the findings of Zhu et al. (2020), who similarly noted decreased ReHo in the LPFC of MS patients, underscoring the prefrontal cortex's susceptibility to disease-related changes in intrinsic brain activity (Zhu et al., 2020). Nevertheless, not all research has produced comparable results. For example, Cui et al. (2017) found an increase in ReHo in the prefrontal cortex of MS patients (Cui et al., 2017).

The differences in findings could be attributed to variations in MS subtypes, disease duration, or methodological factors, such as preprocessing techniques or ReHo calculation methods. In this study, the majority of patients had RRMS, while a smaller group had PPMS. The observed ReHo reductions may mainly reflect early dysfunction in RRMS, with possible contributions from network degradation in PPMS. However, limited PPMS cases prevented subtype-specific analysis (Zhu et al., 2020). In general, compensatory mechanisms in the earlier or less severe stages of the disease might result in localized increases in ReHo, while more advanced stages could be linked to declines due to neural degradation (Hawellek et al., 2011).

5.1.4 Region of Interest-Based Analysis

The ROI-based analysis revealed a significant reduction in connectivity strength between the DMN and SN in MS patients compared to HCs. This disruption in inter-network communication is clinically relevant, as it may underlie common cognitive symptoms in MS, such as fatigue, attention deficits, and impaired executive function. The SN is essential for identifying and prioritizing relevant stimuli, while the DMN is involved in self-referential thought and task disengagement. According to Menon’s triple network model (2011), the SN functions as a dynamic regulator, switching between the DMN and the CEN to support cognitive flexibility and the allocation of attention. Consequently, disrupted connectivity between the SN and DMN may hinder effective distribution of cognitive resources, contributing to mental fatigue and attentional difficulties, common symptoms experienced by individuals with MS (Menon, 2011).

These findings back the research hypothesis, suggesting that MS patients show changes in FC potentially related to cognitive issues. Additionally, the disruptions observed align with previous studies (Rocca et al., 2022) that highlight how impaired dynamics of the triple network—especially involving the SN and DMN—are linked to reduced network efficiency and cognitive decline in MS. Thus, the results lend empirical support to the triple-network disruption framework outlined in the study, underscoring its significance for comprehending functional brain changes and clinical symptoms in MS. Also, supporting the idea of a gradual "network collapse" as the disease progresses (Schoonheim et al., 2015).

5.2 Conclusion

This study investigated functional brain alterations in patients with MS compared to HCs using rs-fMRI. By employing three complementary neuroimaging metrics—ALFF, DC, and ReHo- the study examined intrinsic brain activity and connectivity within the DMN, CEN, and SN, collectively referred to as the triple-network model.

The results revealed significant alterations in ALFF, indicating disrupted spontaneous neural activity in MS patients. In addition, both ReHo and DC were reduced, particularly within the SN and CEN, reflecting impaired local synchronization and diminished global connectivity. Interestingly, increased ALFF was observed in specific regions of the CEN, potentially representing compensatory hyperactivity in response to reduced network efficiency. Such patterns help clarify many common cognitive and behavioral symptoms in MS patients.

Additionally, the ROI-based analysis within the triple networks offered focused insights into the specific regions most impacted by the disease. Among the three networks, the SN exhibited the most consistent and widespread reductions across all three measures, suggesting profound functional impairment in regions associated with attentional control and the dynamic switching of cognitive resources. This triple-network dysfunction—especially pronounced in the SN—may contribute to hallmark MS symptoms such as cognitive fatigue, executive dysfunction, and reduced cognitive flexibility.

These findings highlight the value of rs-fMRI as a sensitive tool for detecting subtle, functionally significant brain changes not readily captured by conventional structural MRI. Functionally based biomarkers derived from rs-fMRI may enhance early diagnosis, track disease progression, and inform personalized therapeutic strategies in MS care.

5.3 Recommendations

Based on the results of this study, several recommendations are made to guide future research. First, rs-fMRI should be recognized as a valuable tool for routine clinical evaluations, as it can detect subtle functional brain changes even when structural alterations are not visible it is strongly recommended to combine structural and functional MRI in diagnostic and monitoring protocols, as this multimodal approach offers a more comprehensive view of MS-related brain changes, enhancing diagnostic accuracy and therapeutic planning.

Second, longitudinal studies are strongly encouraged to monitor alterations in brain activity and connectivity over time in MS patients. These studies would provide valuable insights into the progression of functional changes and the brain's ability to adapt through neuroplasticity.

Third, future research should utilize higher-field MRI scanners, such as 3T or 7T, which offer better spatial and temporal resolution compared to the 1.5T scanner used in this study. These advanced imaging techniques could help identify more subtle or early-stage functional changes that are vital for diagnosis and monitoring.

Finally, future studies should involve larger and more diverse patient populations to improve the statistical power and generalizability of results across various MS subtypes, age groups, and disease stages.

5.4 Strength of the Study

This study presents several notable strengths that enhance its scientific value and clinical relevance. Firstly, as far as we know, it is among the first studies in Palestine to investigate functional brain alterations in MS patients using rs-fMRI, contributing valuable regional data to the global understanding of MS and laying the groundwork for future neuroimaging research in the local context. Secondly, the adoption of the triple-network model provides a comprehensive framework for evaluating the functional disruptions associated with MS. Another key strength lies in the use of three complementary fMRI measures, which collectively capture spontaneous neural activity, local synchronization, and global connectivity, offering a multidimensional perspective on brain function.

Moreover, the inclusion of a matched control group, along with strict preprocessing protocols and ROI-based statistical analyses, enhances the study's methodological rigor and reliability. Finally, the study's results hold meaningful clinical implications, highlighting the potential of rs-fMRI as a sensitive tool for early diagnosis, monitoring of disease progression, and informing personalized treatment strategies in MS care.

5.5 Limitations of the Study

This study offers valuable insights into brain functional changes in individuals with MS using rs-fMRI. However, several limitations should be considered. First, the relatively small sample size regarding the time duration of ethical approval (n=20 for both MS patients and healthy controls) may limit the statistical power of the analysis and reduce the generalizability of the results to the broader MS population. A larger and more diverse sample would be beneficial in confirming these findings and ensuring they are representative across different MS subtypes and clinical profiles.

Second, the study was conducted using a 1.5 Tesla MRI scanner, which, while clinically accessible, offers lower spatial and temporal resolution compared to higher-field systems such as 3T or 7T MRI. This may have limited the sensitivity for detecting subtle

changes in brain connectivity and spontaneous activity. Furthermore, the lack of clinical correlation is a limitation; while imaging metrics were analyzed, no correlation was made with clinical variables such as the expanded disability status scale (EDSS), due to the absence of an available database.

Finally, rs-fMRI is particularly susceptible to motion artifacts because of the additional time added to the original image protocol, as well as physiological noise, including fluctuations due to cardiac and respiratory cycles, which may influence BOLD signal measurements. Although preprocessing techniques were applied to minimize these effects, some residual noise may still affect the results.

5.6 Future Work

Future studies should aim to build on the current findings by addressing both methodological and clinical research gaps. Longitudinal studies are particularly important to track changes in FC and RSA over the course of disease progression and treatment. This would provide insight into the temporal dynamics of neurodegeneration and potential compensatory mechanisms in MS. Additionally, future work should incorporate higher-field MRI scanners (e.g., 3T or 7T), which offer improved spatial and temporal resolution and may enhance the detection of subtle or early-stage functional changes that were not captured with the 1.5T system used in this study. Combining rs-fMRI with advanced multimodal imaging techniques, such as DTI or MTI, could provide a more comprehensive view of structural–functional interactions in MS. It is also recommended to integrate imaging findings with clinical measures, cognitive performance scores, and biological markers to improve the translation of neuroimaging data into clinical decision-making. Expanding the sample size and including diverse MS subtypes, age groups, and disease stages will further improve the generalizability and clinical applicability of future research.

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Appendices

Appendix A: IRB Approval

Arab American University
Institutional Review Board - Ramallah

الجامعة العربية الأمريكية
مجلس اخلاقيات البحث العلمي – رام الله

IRB Approval Letter

Study Title: "Structural Changes Detection in the Central Nervous System of Multiple Sclerosis Patients Based on Magnetic Resonance Imaging".

Submitted by: Beesan Wasfi Izzat Mostafa

Date received: 25th February 2024

Date reviewed: 29th February 2024

Date approved: 3rd March 2024

Your Study titled **"Structural Changes Detection in the Central Nervous System of Multiple Sclerosis Patients Based on Magnetic Resonance Imaging"** with the code number **"R-2024/A/41/N"** was reviewed by the Arab American University Institutional Review Board - Ramallah and it was approved on the 3rd of March 2024.

الجامعة العربية الأمريكية - فلسطين
مجلس اخلاقيات البحث العلمي - رام الله
IRB-R
ARAB AMERICAN UNIVERSITY-PALESTINE
INSTITUTIONAL REVIEW BOARD - RAMALLAH

Sajed Ghawadra, PhD
IRB-R Chairman
Arab American University of Palestine

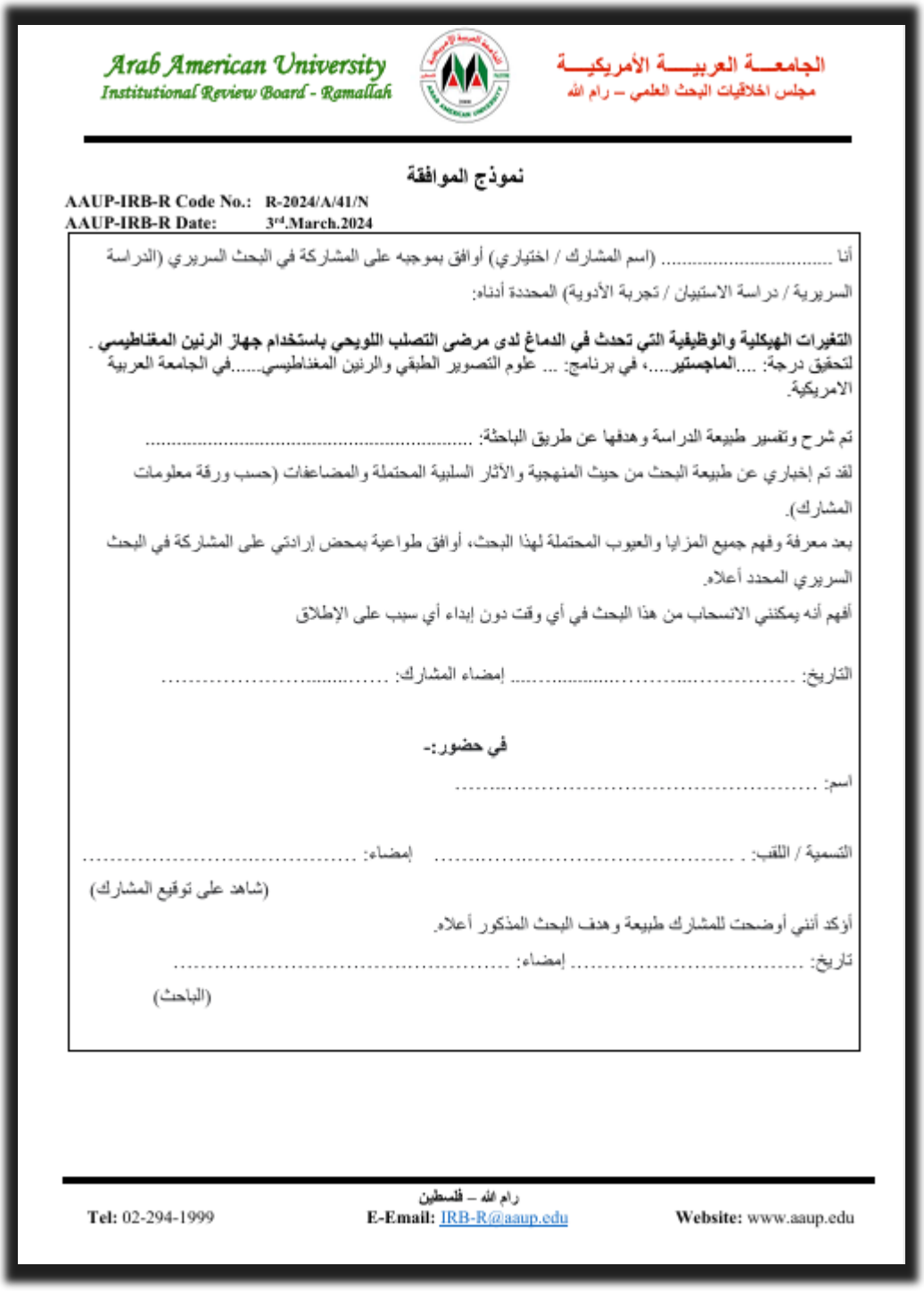
General Conditions:

1. Valid for 6 months from the date of approval.
2. It is important to inform the IRB-R with any modification of the approved study protocol.
3. The Bord appreciates a copy of the research when accomplished.

رام الله – فلسطين

Tel: 02-294-1999 **E-Email:** IRB-R@aaup.edu **Website:** www.aaup.edu

Appendix B: Consent Form



Arab American University
Institutional Review Board - Ramallah

الجامعـــة العربيـــة الأمريكيـــة
مجلس اخلاقيات البحث العلمي – رام الله

نموذج الموافقة

AAUP-IRB-R Code No.: R-2024/A/41/N
AAUP-IRB-R Date: 3rd.March.2024

أنا ..... (اسم المشارك / اختياري) أوافق بموجبه على المشاركة في البحث السريري (الدراسة السريرية / دراسة الاستبيان / تجربة الأدوية) المحددة أدناه:

التغيرات الهيكلية والوظيفية التي تحدث في الدماغ لدى مرضى التصلب اللويحي باستخدام جهاز الرنين المغناطيسي .
لتحقيق درجة: ....**الماجستير**.....، في برنامج: ... علوم التصوير الطبقي والرنين المغناطيسي.....في الجامعة العربية الامريكية.

تم شرح وتفسير طبيعة الدراسة وهدفها عن طريق الباحثة: .....

لقد تم إخباري عن طبيعة البحث من حيث المنهجية والآثار السلبية المحتملة والمضاعفات (حسب ورقة معلومات المشارك).

بعد معرفة وفهم جميع المزايا والعيوب المحتملة لهذا البحث، أوافق طواعية بمحض إرادتي على المشاركة في البحث السريري المحدد أعلاه.

أفهم أنه يمكنني الانسحاب من هذا البحث في أي وقت دون إبداء أي سبب على الإطلاق

التاريخ: ..... إمضاء المشارك: .....

في حضور:-

اسم: .....

التسمية / اللقب: ..... إمضاء: .....

(شاهد على توقيع المشارك)

أؤكد أنني أوضحت للمشارك طبيعة وهدف البحث المذكور أعلاه.

تاريخ: ..... إمضاء: .....

(الباحث)

رام الله – فلسطين
Tel: 02-294-1999 **E-Email:** IRB-R@aaup.edu **Website:** www.aaup.edu

التغيرات الهيكلية والوظيفية التي تحدث في الدماغ لدى مرضى التصلب اللويحي باستخدام جهاز التصوير بالرنين المغناطيسي

بيسان وصفي عزات مصطفى

لجنة الإشراف:

د. عبد الناصر عاصي

د. حسن صبيحات

د. أحمد أبو عرة

د. علي أبو عرة

ملخص

مقدمة

التصلب اللويحي هو حالة تنكسية عصبية تؤدي إلى إزالة الميالين وتلف (MS) التصلب المتعدد المحاور العصبية، مما يؤثر على وظائف الدماغ وترابطه. يوفر التصوير بالرنين المغناطيسي الوظيفي (rs–fMRI) رؤى مهمة حول التغيرات في نشاط الدماغ وترابطه لدى مرضى في حالة الراحة , بما في ذلك شبكة الوضع الافتراضي(RSNs)التصلب المتعدد. تُعد شبكات حالة الراحة الرئيسي ، أساسية للوظائف الإدراكية (SN) ، وشبكة البروز (CEN) ، والشبكة التنفيذية المركزية(DMN) والحركية. قد يساعد البحث في الاضطرابات داخل هذه الشبكات في التصلب المتعدد على توضيح .آليات المرض وتحديد المؤشرات الحيوية المحتملة لتطوره

الهدف

تهدف هذه الدراسة إلى استكشاف التغيرات في نشاط الدماغ والاتصال الوظيفي داخل شبكات حالة الراحة لدى مرضى التصلب المتعدد مقارنة بالضوابط الصحية، من خلال التركيز على ثلاثة مقاييس رئيسية لـ (rs–fMRI) : سعة التقلبات منخفضة التردد لتقييم النشاط العصبي التلقائي، ومركزية الدرجة لتقييم الاتصال العالمي، والتجانس الإقليمي لفحص الاتصال المحلي عبر الدماغ.

الطرق

جُمعت بيانات التصوير بالرنين المغناطيسي الوظيفي في حالة الراحة والبيانات البنيوية (T1-3D ISO) من 20 مريضًا بالتصلب المتعدد (MS) و20 من الأصحاء (HCs) المطابقين لأعمارهم، باستخدام جهاز فيليبس بقوة 1.5 تيسلا. استُخدمت مجموعة أدوات DPABI لحساب نشاط الدماغ والاتصال، ومركزية الدرجة (الاتصال العالمي)، والتجانس الإقليمي (الاتصال المحلي) بعد تطبيق خط المعالجة المسبقة، بما في ذلك بشكل رئيسي تصحيح توقيت الشريحة، وإعادة المحاذاة، وانحدار المتغيرات المصاحبة المزعجة، والتصفية الزمنية بين 0.01 و0.08 هرتز. استُخرجت مصفوفات النشاط والاتصال من الشبكات العصبية الشبكية (RSNs)، بما في ذلك 18 منطقة دماغية.

النتيجة

أظهرت النتائج انخفاضًا ملحوظًا في ReHo وDC لدى مرضى التصلب المتعدد، وخاصةً في مناطق CEN وSN، مما يشير إلى ضعف في الاتصال المحلي والعالمي. في المقابل، وُجد ارتفاع في ALFF في بعض مناطق CEN لدى مرضى التصلب المتعدد، مما قد يعكس فرط نشاط تعويضي استجابةً لانقطاعات الشبكة. والجدير بالذكر أن شبكة البروز أظهرت انخفاضات ثابتة في جميع المقاييس الثلاثة، مما يشير إلى ضعف وظيفي واسع النطاق في مناطق الدماغ المسؤولة عن دمج المحفزات وتحديد أولوياتها.

الخلاصة

تُسلّط هذه النتائج الضوء على فائدة التصوير بالرنين المغناطيسي الوظيفي rs-fMRI في الكشف عن التغيرات الدقيقة، وإن كانت ذات دلالة إحصائية، في وظائف الدماغ، والتي لا تظهر دائمًا من خلال التصوير الهيكلي. تُسهم هذه الدراسة في مجموعة متزايدة من الأدلة التي تدعم دور خلل الشبكة الثلاثية في التصلب المتعدد، وتُعزز إمكانات علامات التصوير الوظيفي في التشخيص المبكر، والمراقبة السريرية، وتخطيط العلاج المُخصّص لمرضى التصلب المتعدد.

الكلمات المفتاحية: التصلب المتعدد، التصوير بالرنين المغناطيسي الوظيفي في حالة الراحة، نموذج الشبكة الثلاثية، نشاط الدماغ، الإتصال الوظيفي.