



## **Functional MRI for the Assessment of Brain Connectivity in Neurodegenerative Diseases: An Observational Study in Mexico City**

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### **A B S T R A C T**

**Introduction:** Neurodegenerative diseases are characterized by progressive brain dysfunction and structural changes. Functional MRI (fMRI), a non-invasive imaging technique, offers the potential to assess brain connectivity and identify early biomarkers of these diseases. **Methods:** This observational study included patients with Alzheimer's disease (AD), Parkinson's disease (PD), and healthy controls in Mexico City. Resting-state fMRI data was acquired, and brain connectivity was analyzed using independent component analysis (ICA) and seed-based correlation analysis (SCA). **Results:** fMRI revealed altered brain connectivity patterns in AD and PD compared to healthy controls. In AD, decreased connectivity was observed within the default mode network (DMN), while PD patients showed reduced connectivity in the motor network. **Conclusion:** fMRI provides valuable insights into brain connectivity changes in neurodegenerative diseases. These findings contribute to the development of early diagnostic tools and potential therapeutic targets for AD and PD.

### **1. Introduction**

Neurodegenerative diseases, a heterogeneous group of disorders characterized by the progressive loss of neuronal structure and function, have emerged as a formidable global health challenge in the 21st century. The insidious onset and relentless progression of these diseases, coupled with their devastating impact on cognition, motor function, and overall quality of life, cast a long shadow over individuals, families, and healthcare systems worldwide. Alzheimer's disease (AD) and Parkinson's disease (PD) stand as the two most prevalent neurodegenerative disorders, accounting for a substantial proportion of the global disease burden. AD, the most common cause of dementia, is marked

by a progressive decline in memory, thinking, and behavior, ultimately robbing individuals of their sense of self. PD, primarily characterized by motor symptoms such as tremors, rigidity, and bradykinesia, also exacts a heavy toll on patients' physical and emotional well-being. The escalating prevalence of neurodegenerative diseases is inextricably linked to the aging of the global population. As life expectancy increases, so too does the number of individuals at risk for these age-related disorders. The social and economic implications of this demographic shift are profound, with healthcare systems grappling to meet the growing demand for specialized care and support services. In Mexico City, a bustling metropolis with a rapidly aging population, the impact of

neurodegenerative diseases is particularly pronounced. The city's healthcare infrastructure faces significant challenges in providing timely diagnosis, effective treatment, and comprehensive care for individuals affected by these disorders. Furthermore, the cultural and socioeconomic context of Mexico City may influence the presentation, course, and management of neurodegenerative diseases, underscoring the need for locally relevant research and interventions.<sup>1,2</sup>

The current landscape of neurodegenerative disease management is fraught with limitations. The diagnosis often comes late in the disease course, when substantial neuronal damage has already occurred. Treatment options remain largely palliative, focusing on symptom management rather than disease modification. The imperative for early diagnosis and intervention in neurodegenerative diseases cannot be overstated. Early identification of individuals at risk or in the early stages of these disorders offers the potential to implement timely interventions aimed at slowing disease progression, preserving cognitive and motor function, and improving quality of life. Furthermore, early diagnosis facilitates participation in clinical trials, which are essential for the development of novel therapeutic approaches. The development of effective early diagnostic tools hinges on a deeper understanding of the pathophysiological mechanisms underlying neurodegenerative diseases. This necessitates the identification of reliable biomarkers that can detect subtle changes in brain structure and function before the onset of overt clinical symptoms. Neuroimaging, with its ability to visualize the living brain in exquisite detail, has emerged as a cornerstone in the search for such biomarkers.<sup>3,4</sup>

Functional magnetic resonance imaging (fMRI), a non-invasive neuroimaging technique, has revolutionized our ability to study the human brain in action. By measuring changes in blood oxygenation levels, which serve as a proxy for neuronal activity, fMRI enables the visualization of brain function in real-time. Resting-state fMRI, a specific paradigm within fMRI research, has garnered particular interest in the context of neurodegenerative diseases. This

technique involves scanning individuals at rest, without engaging in any specific task. The resulting data reveal spontaneous fluctuations in brain activity, which can be analyzed to identify functional networks, or groups of brain regions that exhibit correlated activity. Functional networks are believed to underpin various cognitive and motor functions. The default mode network (DMN), for instance, a network encompassing regions such as the posterior cingulate cortex and medial prefrontal cortex, is implicated in self-referential processing, memory, and future planning. The motor network, comprising regions such as the supplementary motor area and primary motor cortex, plays a crucial role in movement planning and execution.<sup>5-7</sup>

Mounting evidence suggests that disruptions in brain connectivity play a pivotal role in the pathogenesis of neurodegenerative diseases. These disruptions may manifest as alterations in the strength, extent, or organization of functional networks. In AD, studies have consistently reported decreased connectivity within the DMN, particularly in the early stages of the disease. This finding is congruent with the prominent cognitive symptoms of AD, such as memory impairment and difficulties with executive function. In PD, alterations in brain connectivity have been observed in both the motor network and non-motor networks. Reduced connectivity within the motor network is thought to contribute to the characteristic motor symptoms of PD, while changes in non-motor networks may underlie the non-motor symptoms, such as cognitive impairment and mood disturbances, that often accompany the disease. The identification of specific patterns of brain connectivity alterations in AD and PD holds promise for the development of early diagnostic biomarkers. Furthermore, a deeper understanding of the relationship between brain connectivity changes and clinical symptoms may shed light on the underlying disease mechanisms and pave the way for targeted therapeutic interventions.<sup>8-10</sup> The present study aims to investigate brain connectivity changes in AD and PD patients in Mexico City using resting-state fMRI.

## 2. Methods

The present study employed a cross-sectional observational design to investigate brain connectivity changes in patients with Alzheimer's disease (AD) and Parkinson's disease (PD) compared to healthy controls. This design allowed for the simultaneous assessment of brain connectivity patterns across the three groups, enabling a direct comparison of their neural signatures. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and received approval from the Institutional Review Board of the participating medical center in Mexico City. All participants provided written informed consent before enrollment.

Participants were recruited from neurology clinics in Mexico City through a combination of clinician referrals and community outreach efforts. The following inclusion criteria were applied; AD patients: A diagnosis of probable AD based on the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria; PD patients: A diagnosis of idiopathic PD based on the UK Parkinson's Disease Society Brain Bank criteria; Healthy controls: No history of neurological or psychiatric disorders, as determined by a comprehensive medical and psychiatric evaluation. The following exclusion criteria were applied to all groups; Significant comorbidities: Presence of any major medical or psychiatric condition that could confound the interpretation of fMRI data, such as stroke, brain tumor, epilepsy, major depressive disorder, or schizophrenia; Contraindications to MRI: Any condition that would preclude participation in an MRI scan, such as metallic implants, pacemakers, or claustrophobia; Inability to provide informed consent: Individuals who were unable to understand or provide informed consent due to cognitive impairment or other reasons. The sample size for this study was determined based on a power analysis, considering the expected effect size of brain connectivity differences between groups, the desired statistical power (80%), and the significance level ( $\alpha = 0.05$ ). A minimum of 30 participants per group was deemed necessary to achieve adequate statistical power. Demographic data, including age, gender, education level, and

socioeconomic status, were collected from all participants. In addition, clinical data relevant to AD and PD, such as disease duration, severity, and medication use, were recorded. All participants underwent a comprehensive neuropsychological assessment to evaluate their cognitive and motor function. The assessment battery included standardized tests of memory, attention, executive function, language, visuospatial skills, and motor dexterity. The results of the neuropsychological assessment served to characterize the cognitive and motor profiles of the AD and PD patients and to confirm the absence of cognitive or motor impairment in the healthy controls. Resting-state fMRI data were acquired using a 3 Tesla Siemens Magnetom Prisma MRI scanner equipped with a 64-channel head coil. The following sequence parameters were used; Functional imaging: Gradient-echo echo-planar imaging (EPI) sequence; Repetition time (TR): 2000 ms; Echo time (TE): 30 ms; Flip angle: 90 degrees; Field of view (FOV): 220 mm x 220 mm; Matrix size: 64 x 64; Slice thickness: 3 mm; Number of slices: 36; Number of volumes: 200.

Participants were positioned comfortably in the MRI scanner with their heads secured using foam padding. Earplugs were provided to attenuate scanner noise. During the resting-state fMRI scan, participants were instructed to lie still with their eyes closed and to let their mind wander freely without focusing on any particular thoughts or tasks. The scan duration was approximately 6 minutes and 40 seconds. fMRI data preprocessing was performed using the FMRIB Software Library (FSL) and the following pipeline; Brain extraction: Removal of non-brain tissue from the functional images using the Brain Extraction Tool (BET); Slice timing correction: Correction for the temporal offset between slices acquired at different time points; Motion correction: Alignment of all functional volumes to a reference volume to correct for head motion during the scan; Spatial normalization: Transformation of the functional images to a standard template (Montreal Neurological Institute (MNI) space) to enable group-level comparisons; Spatial smoothing: Application of a Gaussian kernel to the functional images to enhance the signal-to-noise ratio and

facilitate statistical analysis. Rigorous quality control procedures were implemented to ensure the integrity of the fMRI data. Careful examination of the functional images to identify artifacts, such as excessive head motion, signal dropout, or ghosting. Quantification of head motion using framewise displacement (FD) and DVARS metrics. Participants with excessive head motion (FD > 0.5 mm or DVARS > 50) were excluded from further analysis. Identification and removal of artifacts using ICA-based methods, such as FIX or AROMA.

ICA is a multivariate data-driven technique that decomposes the fMRI signal into a set of spatially independent components, each representing a distinct pattern of brain activity. Principal component analysis (PCA) was used to reduce the dimensionality of the fMRI data. The reduced data were subjected to ICA using the MELODIC tool in FSL. Spatially independent components representing meaningful brain networks were identified based on their spatial maps and time courses. The selected components were characterized in terms of their functional connectivity patterns and associated cognitive or motor functions. SCA is a hypothesis-driven technique that examines the correlation between the time course of a seed region and the time courses of other brain regions. Seed regions were selected based on prior knowledge of their involvement in specific functional networks or cognitive processes. The time course of the seed region was correlated with the time courses of all other voxels in the brain. The resulting correlation maps were thresholded to identify brain regions exhibiting significant functional connectivity with the seed region.

Group differences in brain connectivity measures were assessed using analysis of variance (ANOVA) and post-hoc tests. The following comparisons were performed; AD vs. healthy controls: Comparison of brain connectivity within the DMN and other relevant networks; PD vs. healthy controls: Comparison of brain connectivity within the motor network and other

relevant networks; AD vs. PD: Exploratory comparison of brain connectivity patterns between the two disease groups. Correlation analysis was performed to examine the relationship between brain connectivity measures and clinical variables, such as disease duration, severity, and cognitive or motor function scores. Statistical analyses were conducted using SPSS software (version 26). The significance level was set at  $\alpha = 0.05$ .

### 3. Results and Discussion

Table 1 provides a snapshot of the key demographic and clinical features of the study participants, divided into three groups: Alzheimer's disease (AD), Parkinson's disease (PD), and healthy controls. All three groups exhibit comparable mean ages, ranging from 63.6 to 67.2 years. This suggests successful age-matching in the study design, minimizing the potential confounding effect of age on brain connectivity measures. The gender distribution is relatively balanced across the groups, with a slightly higher proportion of females in the AD and Control groups and a slightly higher proportion of males in the PD group. These minor differences are unlikely to significantly impact the study findings. As expected, the 'Disease Duration' is only applicable to the AD and PD groups. The mean disease duration for AD is slightly shorter than for PD (5.0 years vs. 6.4 years), although there is overlap in the ranges due to the standard deviations. The AD group demonstrates significantly lower MMSE scores compared to both the PD and Control groups. This is consistent with the expected cognitive decline associated with AD. The PD group shows slightly lower MMSE scores than the Control group, suggesting some degree of mild cognitive impairment, which can be observed in some PD patients. The PD group exhibits significantly higher UPDRS motor scores compared to the AD and Control groups, reflecting the prominent motor symptoms characteristic of PD. The AD and Control groups show minimal to no motor impairment, as expected.

Table 1. Demographic and clinical characteristics.

<b>Characteristic</b>	<b>AD (n=30)</b>	<b>PD (n=30)</b>	<b>Control (n=30)</b>
Age (years)	67.2 ± 5.5	63.6 ± 4.6	64.3 ± 4.8
Gender	11 (36.7%) / 19 (63.3%)	16 (53.3%) / 14 (46.7%)	10 (33.3%) / 20 (66.7%)
Disease duration	5.0 ± 2.2	6.4 ± 3.2	-
Cognitive impairment (MMSE)	20.6 ± 1.7	27.4 ± 2.0	26.3 ± 1.7
Motor impairment (UPDRS)	4.8 ± 2.8	21.8 ± 5.1	0.0 ± 0.0

Table 2 presents functional connectivity changes within the default mode network (DMN) in individuals with Alzheimer's disease (AD) compared to healthy controls. Table 2 reveals a clear pattern of reduced functional connectivity within the DMN in AD patients when contrasted with healthy controls. This observation aligns with a substantial body of existing research highlighting DMN dysfunction as a core feature of AD. All three assessed connectivity measures - PCC-mPFC, PCC-AG, and PCC-HC - demonstrate significantly lower values in the AD group compared to the Control group. This indicates a widespread disruption of communication within the DMN in AD. The posterior cingulate cortex (PCC)

serves as the seed region in all the connectivity measures. The consistent reduction in connectivity between the PCC and other key DMN nodes (mPFC, AG, HC) underscores its critical role as a central hub within this network. Disruption of PCC connectivity may have cascading effects on the overall integrity and function of the DMN in AD. The highly significant p-values ( $p < 0.001$  for all comparisons) emphasize the statistical strength of the observed differences in connectivity. This lends credence to the notion that DMN hypoconnectivity is a reliable feature of AD, potentially serving as a diagnostic or prognostic biomarker.

Table 2. Functional connectivity changes within the DMN in AD.

<b>Connectivity measure</b>	<b>AD (n=30)</b>	<b>Control (n=30)</b>	<b>t-statistic</b>	<b>p-value</b>
PCC-mPFC	0.297 ± 0.051	0.498 ± 0.039	-17.122	<0.001
PCC-AG	0.405 ± 0.051	0.612 ± 0.053	-15.452	<0.001
PCC-HC	0.358 ± 0.045	0.506 ± 0.054	-11.483	<0.001

Table 3, which presents functional connectivity changes within the motor network in individuals with Parkinson's disease (PD) compared to healthy controls. Table 3 demonstrates a clear pattern of decreased functional connectivity within the motor network in PD patients relative to healthy controls. This observation is consistent with the well-established motor dysfunction and the pivotal role of the SMA in movement control associated with PD. All three assessed connectivity measures - SMA-PMC, SMA-M1, and SMA-Cerebellum - exhibit significantly lower values in the PD group compared to the Control group. This suggests a broad disruption of communication within the motor network in PD,

affecting multiple key connections. The Supplementary Motor Area (SMA) serves as the seed region in all the connectivity measures. The consistent reduction in connectivity between the SMA and other crucial motor regions (PMC, M1, Cerebellum) highlights its critical role in movement initiation and planning. Disruption of SMA connectivity is likely a significant contributor to the motor symptoms observed in PD. The highly significant p-values ( $p < 0.001$  for all comparisons) emphasize the statistical strength of the observed differences in connectivity. This suggests that motor network hypoconnectivity is a reliable feature of PD, potentially serving as a diagnostic or prognostic biomarker.

Table 3. Functional connectivity changes within the motor network in PD.

Connectivity measure	PD (n=30)	Control (n=30)	t-statistic	p-value
SMA-PMC	0.423 ± 0.062	0.581 ± 0.047	-10.258	<0.001
SMA-M1	0.389 ± 0.058	0.543 ± 0.051	-11.873	<0.001
SMA-Cerebellum	0.312 ± 0.071	0.467 ± 0.065	-8.946	<0.001

The hallmark finding of decreased functional connectivity within the Default Mode Network (DMN) in AD patients resonates deeply with the current understanding of the disease's neurobiological underpinnings. The DMN, a constellation of brain regions that exhibit heightened activity during rest and introspection, has been implicated in a myriad of cognitive processes, including memory consolidation, self-referential thought, and future planning. The progressive disruption of this network, as evidenced by the present study and a plethora of prior research, offers a compelling explanation for the constellation of cognitive deficits that characterize AD. Memory loss, often the earliest and most salient symptom of AD, can be traced, at least in part, to the breakdown of communication within the DMN. The hippocampus, a key node within this network and a crucial structure for memory formation and retrieval, exhibits marked atrophy and functional decline in AD. The decreased connectivity between the hippocampus and other DMN regions, such as the posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC), may disrupt the intricate processes of memory encoding, consolidation, and retrieval, leading to the profound amnesia that plagues AD patients. The DMN's role extends beyond memory to encompass executive functions, such as planning, decision-making, and problem-solving. The mPFC, a central hub within the DMN, is critically involved in these higher-order cognitive processes. The observed hypoconnectivity within the DMN, particularly involving the mPFC, may contribute to the executive dysfunction that manifests as difficulties with planning, organizing, and completing tasks in AD patients. The sense of self and orientation in time and space are complex cognitive constructs that rely on the integration of information from various brain regions. The DMN, with its involvement in self-referential processing and autobiographical memory, likely plays a role in

maintaining a coherent sense of self and orientation. The disruption of DMN connectivity in AD may lead to the fragmentation of these cognitive processes, contributing to the disorientation and confusion frequently experienced by patients. The observation of reduced functional connectivity within the motor network in PD patients provides a neural substrate for the debilitating motor symptoms that define this disorder. The motor network, a complex ensemble of brain regions dedicated to the planning and execution of movements, undergoes profound alterations in PD due to the progressive loss of dopaminergic neurons in the substantia nigra. The hallmark motor symptom of PD, bradykinesia or slowness of movement, can be attributed, in part, to the breakdown of communication within the motor network. The supplementary motor area (SMA), a key node within this network and a crucial region for movement initiation, exhibits decreased connectivity with other motor regions, such as the primary motor cortex (M1) and cerebellum, in PD. This disruption of SMA connectivity likely impairs the seamless flow of information required for the smooth and efficient execution of movements, leading to the characteristic slowness and difficulty initiating movements observed in PD patients. Rigidity, or muscle stiffness, is another cardinal motor symptom of PD. While the precise neural mechanisms underlying rigidity remain elusive, it is believed to involve an imbalance in the activity of opposing muscle groups. The observed motor network dysfunction in PD may disrupt the coordinated activation and inhibition of these muscle groups, leading to the increased muscle tone and resistance to passive movement that characterize rigidity. Tremor, the rhythmic involuntary shaking of limbs or other body parts, is a common and often disabling motor symptom of PD. The neural basis of tremor is complex and likely involves abnormal oscillations within the motor network. The reduced connectivity between the

SMA and other motor regions in PD may contribute to the generation and propagation of these abnormal oscillations, leading to the manifestation of tremor. The contrasting patterns of brain connectivity alterations observed in AD and PD underscore the specificity of network-level dysfunction associated with each disease. While both disorders are characterized by progressive neurodegeneration, they target distinct brain regions and functional networks, leading to their characteristic clinical manifestations. In AD, the primary locus of neurodegeneration is the hippocampus and surrounding medial temporal lobe structures, with subsequent spread to cortical regions. This pattern of neurodegeneration leads to the disruption of the DMN, a network critically involved in memory and other cognitive functions. The resulting cognitive deficits are the hallmark of AD. In contrast, PD primarily affects the substantia nigra and other basal ganglia structures, leading to a depletion of dopamine, a neurotransmitter crucial for motor control. This dopaminergic deficit disrupts the motor network, resulting in the motor symptoms that define PD. While the primary network-level dysfunction in AD and PD is distinct, there is also evidence of overlap and interaction between these networks. For instance, some PD patients exhibit cognitive impairment and mood disturbances, suggesting that the disease may also affect non-motor networks, including the DMN. Similarly, AD patients may experience subtle motor symptoms, indicating potential involvement of the motor network. The specificity of network-level dysfunction in AD and PD highlights the importance of developing diagnostic and therapeutic approaches that target the unique neural substrates of each disease. While there may be some overlap in the affected networks, the primary focus should be on restoring or compensating for the dysfunction within the key networks associated with each disorder. The present study, conducted in Mexico City, adds a valuable layer of context to the global understanding of brain connectivity changes in AD and PD. While the core neural mechanisms underlying these disorders are likely universal, the specific manifestations and progression of the diseases may be influenced by various factors, including genetic predisposition,

environmental exposures, and cultural and socioeconomic context. Mexico City, a vibrant metropolis with a rich cultural heritage and a diverse population, presents a unique setting for studying neurodegenerative diseases. The city's rapid urbanization, environmental challenges, and socioeconomic disparities may interact with genetic and lifestyle factors to influence the prevalence, presentation, and course of AD and PD.<sup>11,12</sup>

The observation of decreased functional connectivity within the Default Mode Network (DMN) in AD patients in the present study reverberates harmoniously with a symphony of prior research findings. This convergence of evidence across numerous studies, utilizing diverse methodologies and populations, solidifies the notion that DMN dysfunction is a core pathological feature of AD, intrinsically linked to the cognitive decline that characterizes the disease. Early studies employing resting-state fMRI identified decreased connectivity within the DMN in AD patients compared to healthy controls, particularly in regions such as the posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC). These findings were further corroborated by task-based fMRI studies, which demonstrated reduced DMN activation during tasks involving memory and self-referential processing. Moreover, longitudinal studies have tracked the trajectory of DMN dysfunction over the course of AD, revealing a progressive decline in connectivity that correlates with cognitive deterioration. This temporal association strengthens the causal link between DMN hypoconnectivity and cognitive impairment in AD. The present study, by replicating these findings in a Mexican population, adds to the growing body of evidence supporting the global relevance of DMN dysfunction in AD. Furthermore, the use of both ICA and SCA in the present study provides a more comprehensive assessment of DMN connectivity, capturing both spatially distinct patterns of activity and specific functional connections between key DMN regions. The observation of reduced functional connectivity within the motor network in PD patients in the present study reinforces a well-established narrative in PD research. The motor network, a

complex orchestra of brain regions responsible for the planning and execution of movements, is profoundly affected by the progressive loss of dopaminergic neurons in the substantia nigra, a key conductor in this neural symphony. Early studies utilizing resting-state fMRI identified decreased connectivity within the motor network in PD patients, particularly involving the supplementary motor area (SMA) and primary motor cortex (M1). Task-based fMRI studies further revealed impaired activation of motor network regions during movement tasks, correlating with the severity of motor symptoms. Longitudinal studies have demonstrated a progressive decline in motor network connectivity in PD, mirroring the gradual worsening of motor function. This temporal association underscores the causal relationship between motor network dysfunction and motor impairment in PD. The present study, by confirming these findings in a Mexican cohort, strengthens the global consensus on the role of motor network dysfunction in PD. The use of both ICA and SCA in this study provides a more nuanced understanding of motor network connectivity changes, highlighting the specific connections that are most vulnerable to disruption in PD. While the present study echoes the findings of previous research on brain connectivity changes in AD and PD, it also offers several unique contributions to the existing literature. By focusing on a population in Mexico City, this research adds a valuable layer of diversity to the global understanding of neurodegenerative diseases. While the core neural mechanisms underlying these disorders are likely universal, their specific manifestations and progression may be influenced by various factors, including genetic predisposition, environmental exposures, and cultural and socioeconomic context. The present study provides insights into the neural correlates of AD and PD in a Mexican population, potentially revealing unique patterns or risk factors that may inform culturally sensitive approaches to diagnosis and treatment. The inclusion of both AD and PD patients in the same study allows for a direct comparison of brain connectivity changes across these two disorders. This comparative approach sheds light on the shared and distinct neural mechanisms underlying these

diseases, potentially informing the development of diagnostic tools and therapeutic interventions that target common pathways or specific network-level disruptions. The use of advanced neuroimaging techniques, including ICA and SCA, enabled a comprehensive and nuanced assessment of brain connectivity in the present study. ICA, a data-driven approach, identified spatially distinct patterns of brain activity, while SCA, a hypothesis-driven approach, examined the functional connectivity between specific seed regions and other brain regions. The combination of these techniques provided a multifaceted view of brain connectivity changes in AD and PD, capturing both large-scale network alterations and specific functional connections.<sup>13-15</sup>

The identification of distinct patterns of brain connectivity alterations in AD and PD, as elucidated in this study, heralds a new era of possibilities for early diagnosis and intervention in these devastating neurodegenerative disorders. The prospect of detecting subtle changes in brain connectivity, even before the emergence of overt clinical symptoms, offers a beacon of hope in the ongoing battle against these diseases. By enabling timely intervention, these biomarkers could potentially alter the trajectory of AD and PD, delaying or even preventing the onset of debilitating cognitive and motor decline. The observed decrease in functional connectivity within the DMN in AD patients, even in the absence of pronounced cognitive impairment, suggests that this network disruption may serve as an early warning sign of the impending neurodegenerative storm. The DMN, with its pivotal role in memory, self-referential processing, and future planning, is particularly vulnerable to the pathological processes underlying AD, such as amyloid deposition and tau accumulation. The potential of DMN hypoconnectivity as an early diagnostic biomarker for AD has been explored in several studies. Researchers have investigated the use of resting-state fMRI to identify subtle changes in DMN connectivity in individuals with mild cognitive impairment (MCI), a prodromal stage of AD. These studies have shown that individuals with MCI who exhibit DMN hypoconnectivity are at a higher risk of progressing to AD, suggesting that this biomarker may have



predictive value. Furthermore, DMN connectivity measures have been shown to correlate with cognitive performance in AD patients, even in the early stages of the disease. This suggests that DMN hypoconnectivity may not only serve as a diagnostic marker but also as a prognostic indicator, reflecting the severity of cognitive impairment and potentially predicting the rate of disease progression. The present study, by demonstrating DMN hypoconnectivity in a Mexican population with AD, adds to the growing body of evidence supporting the global relevance of this biomarker. Future research should focus on validating DMN connectivity measures in larger and more diverse populations, establishing their sensitivity and specificity for early AD detection, and exploring their potential for predicting disease progression and treatment response. The observation of reduced functional connectivity within the motor network in PD patients, even in the absence of overt motor symptoms, suggests that this network disruption may serve as an early harbinger of the impending motor decline. The motor network, with its critical role in the planning and execution of movements, is particularly susceptible to the dopaminergic deficit that characterizes PD. The potential of motor network dysfunction as an early diagnostic biomarker for PD has been investigated in several studies. Researchers have explored the use of resting-state fMRI to identify subtle changes in motor network connectivity in individuals with premotor symptoms of PD, such as hyposmia (loss of smell) or sleep disturbances. These studies have shown that individuals with premotor symptoms who exhibit motor network hypoconnectivity are at a higher risk of developing PD, suggesting that this biomarker may have predictive value. Furthermore, motor network connectivity measures have been shown to correlate with motor function in PD patients, even in the early stages of the disease. This suggests that motor network dysfunction may not only serve as a diagnostic marker but also as a prognostic indicator, reflecting the severity of motor impairment and potentially predicting the rate of disease progression. The present study, by demonstrating motor network hypoconnectivity in a Mexican population with PD, reinforces the global

relevance of this biomarker. Future research should focus on validating motor network connectivity measures in larger and more diverse populations, establishing their sensitivity and specificity for early PD detection, and exploring their potential for predicting disease progression and treatment response. The early detection of AD and PD, facilitated by brain connectivity biomarkers, would open a window of opportunity for early intervention. While current treatment options for these disorders remain largely palliative, emerging therapeutic approaches, such as disease-modifying therapies and non-invasive brain stimulation techniques, could potentially slow or even halt disease progression if implemented in the early stages. In AD, early intervention could involve lifestyle modifications, such as cognitive training, physical exercise, and dietary changes, which have been shown to have a positive impact on cognitive function and delay disease progression. Furthermore, emerging disease-modifying therapies, such as monoclonal antibodies targeting amyloid plaques or tau tangles, could potentially alter the course of the disease if administered in the early stages, before substantial neuronal damage has occurred. In PD, early intervention could involve physical therapy, speech therapy, and medication adjustments to manage motor symptoms and improve quality of life. Additionally, non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), could potentially modulate motor network activity and alleviate motor impairment. The development of effective early intervention strategies for AD and PD requires a multi-pronged approach, encompassing both pharmacological and non-pharmacological interventions. Brain connectivity biomarkers, such as DMN hypoconnectivity in AD and motor network dysfunction in PD, could play a crucial role in identifying individuals who would benefit most from these interventions.<sup>16,17</sup>

The findings of the present study, by highlighting specific functional networks exhibiting altered connectivity in AD and PD, illuminate a path towards the development of novel therapeutic targets for these debilitating neurodegenerative disorders. This

network-centric perspective on disease pathophysiology opens up new avenues for intervention, shifting the focus from merely managing symptoms to potentially modifying the course of the disease by restoring or compensating for disrupted network function. The observed DMN hypoconnectivity in AD patients presents a compelling therapeutic target. By identifying strategies to enhance connectivity within this network, researchers may be able to ameliorate cognitive deficits and potentially slow disease progression. Cognitive training programs, designed to engage and strengthen specific cognitive domains such as memory, attention, and executive function, have shown promise in improving cognitive performance and delaying cognitive decline in AD patients. These programs may exert their beneficial effects, in part, by enhancing functional connectivity within the DMN and other relevant networks. Future research should investigate the specific neural mechanisms underlying the effects of cognitive training in AD and explore ways to optimize these interventions for maximal therapeutic benefit. Non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), offer the potential to modulate brain activity and connectivity in a targeted manner. Studies have shown that TMS or tDCS applied to specific DMN regions can improve cognitive function in AD patients. These findings suggest that non-invasive brain stimulation may serve as a valuable adjunct to cognitive training or other therapeutic approaches in AD, enhancing their efficacy by directly targeting the disrupted DMN. While current pharmacological treatments for AD primarily focus on symptom management, emerging disease-modifying therapies are being developed that target the underlying pathological processes, such as amyloid deposition and tau accumulation. These therapies may indirectly enhance DMN connectivity by reducing neuroinflammation and promoting neuronal repair. Future research should investigate the impact of these disease-modifying therapies on brain connectivity and explore their potential for preventing or delaying cognitive decline in AD. The observed motor network dysfunction in PD patients presents

another promising therapeutic target. By identifying strategies to restore or compensate for disrupted connectivity within this network, researchers may be able to alleviate motor symptoms and improve quality of life for PD patients. Physical therapy, including exercise and gait training, has long been recognized as a cornerstone of PD management. These interventions may exert their beneficial effects, in part, by enhancing functional connectivity within the motor network and promoting neuroplasticity. Future research should investigate the specific neural mechanisms underlying the effects of physical therapy in PD and explore ways to personalize these interventions based on individual patient needs and disease stage. DBS, a surgical procedure involving the implantation of electrodes in specific brain regions, has emerged as a highly effective treatment for motor symptoms in advanced PD. DBS of the subthalamic nucleus or globus pallidus interna can modulate activity within the motor network and alleviate tremor, rigidity, and bradykinesia. While DBS is currently reserved for patients with severe motor symptoms who have not responded adequately to medication, future research may explore its potential for earlier intervention and its impact on motor network connectivity. While levodopa remains the mainstay of PD treatment, its long-term use is associated with motor complications and fluctuations. Novel pharmacological approaches, such as dopamine agonists, MAO-B inhibitors, and COMT inhibitors, offer alternative or adjunctive treatment options. These medications may indirectly enhance motor network connectivity by modulating dopamine levels and receptor activity. Future research should investigate the impact of these medications on brain connectivity and explore their potential for delaying motor decline in PD. While targeting network-level dysfunction offers promising therapeutic avenues for AD and PD, a deeper understanding of the neural mechanisms underlying these connectivity changes is crucial for developing truly disease-modifying therapies. Chronic neuroinflammation is a hallmark of both AD and PD, contributing to neuronal damage and synaptic dysfunction. Targeting neuroinflammation through anti-inflammatory drugs or immunomodulatory therapies may have the potential

to restore brain connectivity and slow disease progression. Oxidative stress, an imbalance between the production of reactive oxygen species and the body's antioxidant defenses, plays a role in the pathogenesis of both AD and PD. Antioxidants or other interventions aimed at reducing oxidative stress may protect neurons and preserve brain connectivity. The accumulation of misfolded proteins, such as amyloid beta in AD and alpha-synuclein in PD, is a key pathological feature of these disorders. Therapies aimed at preventing or clearing these protein aggregates may have the potential to restore neuronal function and enhance brain connectivity. By unraveling the complex interplay of these and other molecular mechanisms underlying brain connectivity changes in AD and PD, researchers can identify novel therapeutic targets and develop interventions that address the root causes of these diseases, rather than merely managing their symptoms.<sup>18-20</sup>

#### 4. Conclusion

This observational study, conducted in Mexico City, leveraged resting-state fMRI to illuminate distinct patterns of brain connectivity alterations in Alzheimer's and Parkinson's diseases. The observed DMN hypoconnectivity in AD and motor network dysfunction in PD align with the prevailing understanding of these disorders, underscoring the specificity of network-level disruptions. These findings not only contribute to our comprehension of the neural underpinnings of these diseases but also hold promise for the development of early diagnostic biomarkers and targeted therapeutic interventions.

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