UNDERSTANDING THE LONG-TERM IMPACT OF COVID-19 ON HUMAN BRAIN: AN MRI BASED STUDY

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by

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to the

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Dedicated to

My Parents

Certificate

This is to certify that the thesis entitled **"Understanding the Long-Term Impact of COVID-19 on Human Brain: An MRI Based Study"** being submitted by **Ms. Sapna S Mishra** to the Department of Electrical Engineering, Indian Institute of Technology Delhi, for the award of the degree of **Doctor of Philosophy** is the record of the bonafide research work carried out by her under our supervision. In our opinion, the thesis has reached the standards fulfilling the requirements of the regulations relating to the degree.

The results contained in this thesis have not been submitted either in part or in full to any other university or institute for the award of any degree or diploma.

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Abstract

The COVID-19 pandemic has had a profound impact worldwide, not only due to its acute effects but also because of its long-term health consequences, particularly neurological and cognitive impairments. Many individuals who have recovered from COVID-19 continue to experience symptoms such as cognitive dysfunction, memory deficits, attention deficits, fatigue, insomnia, and brain fog, collectively termed as post-COVID syndrome (PCS). Despite increasing recognition of these persistent symptoms, the neurobiological mechanisms underlying PCS are still poorly understood. This thesis systematically investigates the long-term impact of COVID-19 on brain structure, white matter microstructure, functional connectivity, and cerebral blood flow using an exploratory multi-sequence Magnetic Resonance Imaging (MRI) approach. A controlled cross-sectional study was conducted, involving a cohort of COVID-19 recovered patients (CRPs) and a matched group of healthy controls (HCs). Participants underwent a comprehensive MRI scan session, including T1-weighted MRI, diffusion-weighted imaging (DWI), resting-state functional MRI (rs-fMRI), and Arterial Spin Labeling (ASL) imaging. These images were analysed to investigate the morphology, microstructure, function, and perfusion in the brain, respectively.

T1-weighted imaging was employed to assess morphological changes in cortical and subcortical regions. Macro-scale analyses highlighted volumetric changes in subcortical components of the basal ganglia and the limbic system. Morphometric analyses, including voxel-based morphometry (VBM) and surface-based morphometry (SBM), revealed significant gray matter volume reduction and cortical thickness alterations in several brain regions, including the orbitofrontal cortex, medial prefrontal cortex, and the superior temporal gyrus. Further, analyses of white matter microstructure using DWI revealed significant alterations in the CRPs. Tract-Based Spatial Statistics (TBSS) and Automated Fiber Quantification (AFQ) revealed significant white matter disruptions in CRPs, particularly in the uncinate fasciculus,

cingulum bundle, inferior longitudinal fasciculus, and the inferior fronto-occipital fasciculus. Fixel-Based Analysis (FBA) was employed to study and quantify white matter microstructure at the sub-voxel level using fiber density and cross-sectional measures, highlighting changes in the tracts of the limbic system. These findings show that COVID-19 has a significant impact on the integrity of major white matter tracts that could be linked with cognitive processing, memory, and emotion in the brain.

Functional connectivity alterations were examined using resting-state fMRI, focusing on large-scale brain networks. Independent Component Analysis (ICA) and thalamocortical functional connectivity analyses revealed significant disruptions in the default mode network (DMN), salience network, and thalamocortical connectivity of mediodorsal thalamic nuclei in CRPs. Reduced functional connectivity within the DMN, particularly between the posterior cingulate cortex, medial prefrontal cortex, and the caudate nucleus, was observed, which could be associated with difficulties in sustained attention, multitasking, and lack of sleep. Additionally, altered thalamocortical interactions suggest disruptions in key circuits involved in memory recollection. Notably, it was observed that while functional dysfunction was prominent only in hospitalized CRPs, abnormalities in morphology and white matter integrity were consistent across survivors of mild and severe COVID-19 infections. Cerebral perfusion was assessed using ASL-MRI to evaluate alterations in blood flow, which could contribute to the neurological symptoms observed in PCS. Results of our study did not highlight a significant impact of COVID-19 on blood flow.

This research provides compelling evidence of morphological, microstructural, and functional changes in individuals recovering from COVID-19, supporting the hypothesis that the virus has long-term neurological effects. The integration of multi-sequence MRI techniques allows for a comprehensive understanding of brain health. Using the findings of this thesis, we proposed a series of hypotheses to facilitate future investigations on the underlying neurological mechanisms behind the characteristic symptoms of PCS, brain fog, fatigue, insomnia, and memory problems. The findings of this study have significant implications for public health, clinical management, and rehabilitation strategies aimed at mitigating the long-term neurological consequences of COVID-19. Future work should focus on longitudinal studies to determine whether these changes are progressive or reversible over time. Additionally, further investigations into the relationship between specific post-COVID symptoms and neuroimaging biomarkers will be essential to develop targeted interventions. This thesis lays the

foundation for future research exploring specific neural correlates of PCS and therapeutic strategies to support COVID-19 survivors experiencing persistent cognitive and neurological challenges.

सार

कोविड–19 महामारी ने पूरे विश्व पर गहरा प्रभाव डाला है, न केवल इसके तात्कालिक प्रभावों के कारण, बल्कि इसके दीर्घकालिक स्वास्थ्य प्रभावों के कारण भी, विशेष रूप से तंत्रिका तंत्र और संज्ञानात्मक क्षमताओं से जुड़ी हानियों के रूप में। कई ऐसे व्यक्ति जो कोविड–19 से स्वस्थ हो चुके हैं, वे अब भी संज्ञानात्मक गड़बड़ी, स्मृति की कमी, ध्यान केंद्रित करने में कठिनाई, थकान, अनिद्रा और मानसिक धुंध जैसे लक्षण अनुभव कर रहे हैं, जिन्हें सामूहिक रूप से "पोस्ट–कोविड संलक्षण" कहा जाता है। यद्यपि इन लक्षणों को लेकर जागरूकता बढ़ रही है, फिर भी इसके पीछे के जैविक और तंत्रिकीय तंत्र अभी स्पष्ट नहीं हो पाए हैं।

यह शोध प्रबंध कोविड–19 के दीर्घकालिक प्रभावों का मस्तिष्क की संरचना, श्वेत पदार्थ की सूक्ष्म संरचना, कार्यात्मक संपर्क और मस्तिष्कीय रक्त प्रवाह पर अध्ययन करता है, जिसमें बहु–माध्यमीय मैग्नेटिक रेज़ोनेंस इमेजिंग पद्धति का उपयोग किया गया है। एक नियंत्रित पार–अनुपातीय अध्ययन के अंतर्गत कोविड–19 से स्वस्थ हुए व्यक्तियों के एक समूह तथा उनके आयु और लिंग से मेल खाते स्वस्थ व्यक्तियों के एक अन्य समूह को शामिल किया गया। प्रतिभागियों के मस्तिष्क का व्यापक रूप से निरीक्षण किया गया, जिसमें टी–1 वज़नित मैग्नेटिक रेज़ोनेंस इमेजिंग, प्रसरण वज़नित छायाचित्रण, विश्राम अवस्था कार्यात्मक मैग्नेटिक रेज़ोनेंस इमेजिंग, और धमनीय स्पिन लेबलिंग इमेजिंग सम्मिलित थे। इन छवियों के माध्यम से मस्तिष्क की आकृति, सूक्ष्म संरचना, कार्य और रक्त प्रवाह की जानकारी प्राप्त की गई।

टी–1 वज़नित छायाचित्रण का उपयोग मस्तिष्क की बाह्य और आंतरिक संरचनाओं में रूपात्मक परिवर्तनों के अध्ययन हेतु किया गया। विश्लेषण से मस्तिष्क के बेसल गैन्ग्लिया और लिम्बिक प्रणाली में आकार संबंधी बदलाव पाए गए। वॉक्सेल आधारित और सतही माप विश्लेषणों ने कई मस्तिष्क क्षेत्रों जैसे ऑर्बिटोफ्रंटल प्रीफ्रंटल प्रांतस्था और उच्चतर शंखीय गाइरस में ग्रे पदार्थ की मात्रा में कमी और प्रांतस्था की मोटाई में बदलाव दर्शाया।

प्रसरण वज़नित छायाचित्रण के माध्यम से श्वेत पदार्थ की सूक्ष्म संरचना में भी उल्लेखनीय बदलाव पाए गए। तंतु–आधारित सांख्यिकीय विधियों और स्वचालित तंतु परिमाणन पद्धति द्वारा यह पता चला कि कोविड–19 से स्वस्थ हुए व्यक्तियों के मस्तिष्क में विशेषकर अनसिनेट संकुल, सिंगुलम समूह, निम्न अनुदैर्ध्य संकुल और निम्न फ्रंटो–ऑक्सिपिटल संकुल में श्वेत पदार्थ का क्षरण हुआ है। एक विशेष विश्लेषण पद्धति द्वारा इन तंतुओं में रेशों के घनत्व और आकार का भी सूक्ष्म स्तर पर आकलन किया गया, जिससे लिम्बिक तंत्र से संबंधित तंतुओं में परिवर्तन स्पष्ट हुआ। ये निष्कर्ष दर्शाते हैं कि कोविड–19 का मस्तिष्क के उन भागों पर महत्वपूर्ण प्रभाव है जो स्मृति, भावनाओं और सोचने

की प्रक्रिया में अहम भूमिका निभाते हैं।

विश्राम अवस्था कार्यात्मक छायाचित्रण के माध्यम से मस्तिष्क के प्रमुख कार्यात्मक तंत्रों में बदलाव का अध्ययन किया गया। स्वतंत्र घटक विश्लेषण और थैलेमस–प्रांतस्था कार्यात्मक संपर्क का विश्लेषण कर यह पाया गया कि कोविड–19 से स्वस्थ हुए व्यक्तियों में डिफॉल्ट मोड तंत्र, महत्त्व तंत्र, तथा थैलेमस और प्रांतस्था के बीच के संबंधों में गड़बड़ी है। डिफॉल्ट मोड तंत्र के भीतर, विशेष रूप से पश्च सिंगुलेट प्रांतस्था, मध्य प्रीफ्रंटल प्रांतस्था, और कॉडेट केंद्रक के बीच संपर्क में कमी देखी गई, जो निरंतर ध्यान बनाए रखने, बहुकार्य करने और नींद की कमी से जुड़ी समस्याओं से संबंधित हो सकती है। थैलेमस और प्रांतस्था के बीच संपर्क में बदलाव स्मृति पुनःस्मरण से जुड़ी कार्यप्रणालियों के विघटन को दर्शाते हैं। यह भी देखा गया कि कार्यात्मक गड़बड़ियाँ विशेष रूप से उन व्यक्तियों में थीं जिन्हें कोविड–19 के कारण अस्पताल में भर्ती किया गया था, जबकि संरचनात्मक और श्वेत पदार्थ की हानि सभी संक्रमण स्तरों (मामूली और गंभीर) में देखी गई। धमनीय स्पिन लेबलिंग तकनीक द्वारा मस्तिष्क में रक्त प्रवाह के आकलन से यह निष्कर्ष निकाला गया कि कोविड–19 का रक्त प्रवाह पर विशेष प्रभाव नहीं पड़ा है।

यह शोध कोविड–19 से उबरने वाले व्यक्तियों में मस्तिष्क की आकृति, संरचना और कार्य में स्थायी परिवर्तन के सशक्त प्रमाण प्रस्तुत करता है, जिससे यह धारणा बलवती होती है कि यह वायरस मस्तिष्क पर दीर्घकालिक तंत्रिकीय प्रभाव छोड़ता है। बहु–माध्यमीय मैग्नेटिक रेज़ोनेंस इमेजिंग तकनीकों के समन्वित उपयोग से मस्तिष्क स्वास्थ्य की समग्र समझ विकसित की जा सकती है। इस शोध के निष्कर्षों के आधार पर हमने यह प्रस्तावित किया है कि पोस्ट–कोविड संलक्षण में देखे जाने वाले लक्षण जैसे मानसिक धुंध, थकान, अनिद्रा और स्मृति समस्याएं संभावित रूप से मस्तिष्क में हुए जैविक और संरचनात्मक परिवर्तनों से जुड़ी हैं।

इस अध्ययन के निष्कर्ष सार्वजनिक स्वास्थ्य नीतियों, चिकित्सा प्रबंधन और पुनर्वास रणनीतियों के लिए अत्यंत महत्त्वपूर्ण हैं, जिनका उद्देश्य कोविड–19 के दीर्घकालिक तंत्रिकीय प्रभावों को कम करना है। आगे के शोधों को इन परिवर्तनों की दीर्घकालिक प्रवृत्ति और संभावित पुनर्प्राप्ति की संभावना का मूल्यांकन करने के लिए अनुवर्ती अध्ययन के रूप में किया जाना चाहिए। इसके साथ ही विशेष पोस्ट–कोविड लक्षणों और मस्तिष्क छायाचित्रण से प्राप्त संकेतकों के बीच संबंधों पर और अधिक शोध करना आवश्यक होगा ताकि लक्षित उपचार पद्धतियाँ विकसित की जा सकें। यह शोध प्रबंध उन उपचारात्मक उपायों की खोज की नींव रखता है, जो उन कोविड–19 उत्तरजीवियों की सहायता कर सकते हैं जो दीर्घकालिक संज्ञानात्मक और तंत्रिकीय समस्याओं का सामना कर रहे हैं।

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List of Abbreviations

COVID-19	Coronavirus Disease
CRP	COVID-19 Recovered Patients
HC	Healthy Controls
MRI	Magnetic Resonance Imaging
ROI	Region of Interest
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
WHO	World Health Organization
GM	Gray Matter
WM	White Matter
CSF	Cerebrospinal Fluid
FA	Fractional Anisotropy
MD	Mean Diffusivity
AD	Axial Diffusivity
RD	Radial Diffusivity
TBSS	Tract-Based Spatial Statistics
AFQ	Automated Fiber Quantification
FBA	Fixel-Based Analysis
CBF	Cerebral Blood Flow
ASL	Arterial Spin Labeling
PCASL	Pseudo-Continuous Arterial Spin Labeling
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
FWE	Family-Wise Error
FDR	False Discovery Rate