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Research Article

State of Brain Networks in Long Covid: Post Mild to Moderate Acute Covid -19 Disease

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Abstract

Background: Long Covid is a well-known entity in patients who recovered from acute Covid-19 disease and this phase is dominated by neurological complaints chiefly fatigue, palpitations and sleep disorders. This study was designed to assess the functional connectivity of the major brain networks in patients who recovered from mild to moderate Covid-19 disease.

Methods: A observational study comprising of 100 consecutive symptomatic patients without any prior neurological disorder was conducted using resting state (rs) functional MRI. Post processing was done for both in-network and between-network connectivity of eight major brain networks and results statistically analyzed and correlated with clinical symptoms.

Results: 91% patients presented with fatigue and showed marked reduced activity of medial frontal cortex (MFC) of the default mode network (DMN) with reduced functional connectivity (FC) of DMN with Salience (SALIEN) network, Sensorimotor network (SMN), Dorsal attention network (DAN) with compensatory overactivity of right lateral posterior parietal node (LPP) which was a characteristic feature. PTSD was second commonest with 80% patients showing reduced FC of DMN, SALIEN, Language network (LANGN) with overactivity of Visual network (VISN) and the cerebellum. 77% patients had anosognosia and showing characteristic overactivity of basal ganglia network (BGN) with reduced FC of DMN, SALIEN, SMN.

Conclusion: Long covid patients show major altered FC of both in and between networks with DMN being most commonly affected with severely reduced FC of MFC. Fatigue patients showed a characteristic signature of overactive right LPP. PTSD patients had increased VISN and cerebellar BOLD activity while in anosgnosia a characteristic BGN over activity was seen.

Key words: Long covid; Covid-19; Functional MRI; Fatigue; Anosognosia; PTSD; Default mode network.

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Introduction

The world has just passed through pandemic of novel Covid-19 disease and with the threat of another wave in different parts of world it is important not to forget that many patients who recovered from the prior two waves of Covid-19 continued to remain symptomatic – post acute covid-19 disease (PACS)/long covid-19 Carfi et al, Davis et al [1,2] and in some patients this phase continued up till 9-12 months Logue et al [3]. Almenia et al [4] showed that 34% of recovered patients of acute covid-19 showed symptoms of fatigue, muscle weakness, insomnia, palpitations, headache and lack of interest. Studies based on clinical testing also demonstrated the presence of cognitive defects in long covid-19 on both short and long-term basis [5-8]. However only few studies have been done showing the involvement of brain networks in long covid-19 in patients. Most of these studies done have been on patients with olfactory dysfunction, PTSD or persistent fatigue following post covid-19 recovery [9-14]. The researchers did not come across any single study evaluating the entire spectrum of brain network changes in symptomatic patients of long covid-19 disease. Hence in this study was designed to use resting state (rs)-fMRI to evaluate the changes in functional connectivity (FC) of the brain both in-network and between- networks of eight major connectivity networks to assess the affect of long covid-19 and to correlate the findings with the symptoms of these patients.

Material and methods

This was an observational study comprising of 100 patients of recovered post mild to moderate acute covid-19 disease who were symptomatic for a period of at least 4-10 weeks following recovery from acute phase. Permission was obtained from local ethics and review institutional review board (AD/11/21). Informed consent along with detailed history and clinical findings along with patient demographics were recorded. Any patient with prior history any neurological or psychiatric problem or any history of drug abuse was excluded. 10 healthy patients with no history of prior covid-19 nor any neurological problem were enrolled as controls. The symptoms of all patients were recorded. Patients were assessed by Fatigue assessment score (FAS) with no fatigue as below score of 10 and maximum of 50 [15]. PCL-5 scoring [16] was done for suspected PTSD and anosognosia patients on a severity score of 0-80.

FMRI protocol

The study was done a 1.5 Tesla 0 (Amira, Siemens AG) using standard head coil with a 10-minute resting fMRI protocol. Patients were told to lie still with eyes open and relax while undergoing the scan. Echo planar imaging bold protocol was used with TR/TE of 1300/45 msec with bandwidth 1906 Hz with echospacing 0.63 msec matrix 224x224. 3 D MPRAGE sequence was done for T1 anatomical image with TR/TE 1780/2.79 msec with slice thickness of 1.0mm.

Post processing

Post processing was done using Functional Connectivity Toolbox (CONN) version 18.b MATLAB (Mathworks, Inc., Natick, MA, USA) and SPM version SPM12. functions (Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing consisted of rs-

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fMRI data realignment, coregistration to individual anatomical data, segmentation of white and grey matter and cerebrospinal fluid, normalization to a standard brain template in the Montreal Neurological Institute (MNI) coordinate space and smoothing by an 8-mm full-width half maximum. maximum Gaussian kernel. From the individual datasets first level covariates were calculated for realignment and confounding effects defined as motion regressors, QC time series and scrubbing to filter out excessive motion spikes white matter and the data was band-pass filtered (0.008–0.09 Hz). Second level covariates were calculated for all subjects and included QC valid and invalid scans, QC maximum and mean motion, QC GS change, QC white matter and CSF volumes QC BOLD data and QC GCOR rest.

ROI-ROI analysis was done for all single subjects to determine FCy values for each individual within the eight predefined ROIs defined as default mode network (DMN), Salience (SALIEN), sensorimotor (SMA), visual network (VIN), Frontoparietal (EXEN) network, Basal ganglia network (BGN), Dorsal attention network (DAN) and language network (LANGN). Second level all subject analysis was done using ROI-ROI and voxel – voxel analysis using graph theory as well connectome ring method to study both the in-network nodes and FC as well as in between FC.

Statistical analysis

Distribution analysis of the patient demographic was done using Analyse-it software (Leeds UK) while FC analysis was done using SPM 12. The Uncorrected p value was fixed at <0.05 as statistically significant and p<0.001 for p FDR (false discovery rate) with significance of threshold clustering for nodes was set at p<0.05. Significance for the signal changes in the nodes was determined by the Beta values of the in networks nodes along with two tailed t values. The results were calculated for long covid-19 groups as well controls for all the networks.

Results

The Study comprised of 100 patients post covid-19 and 10 controls with demographics of the long covid1- group shown in (Table 1). The mean age was 50 years ± 2.7 years with 83% being males and 17% females. 75% were patients who had mild acute covid-19 disease. The most common symptom was chronic fatigue in 83% followed by anosognosia 41%, palpitations in 28% and sleep disturbances in 21%. There were 19% patients with less than 10 PCL-5 score but had memory deficits. The mean age of patients in control group was 48 years ± 2.4 years. Individual first level analysis revealed altered in- network FCs in 91% patients of fatigue. The Default mode network was commonest affected and showed reduced nodal strength of the medial frontal node (MFC) with beta of 0.33 compared to 0.88 of control group (Figure 1,2) (Table 2). 90% patients also showed reduced in-between network FC of DMN, SALIEN, SMN and DAN with increased FC of right lateral posterior parietal node in patients with fatigue (Table 3) (Figure 2,3). Similarly, 80% of PTSD showed reduced FC network of the DMN, SALIEN, LANG and DAN but with increased VIN and Cerebellar FC (Figure 3).

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77% patients with anosognosia also showed reduced activity of the DMN with reduced connectivity of DAN, SALIEN and SMN but with increased BGN activity (Figure 4).

S.no.	Variable	Mean Value
1	Age	50 ± 2.7
2	Sex	
	Males	83
	Females	17
3	Acute Long Covid	14.5 wks ± 3
	Mean duration PACS	
	Mild	75
	Moderate	25
4	Fatigue	83
5	Anosognosia	41
6	Anosmia	15
7	Palpitations	28
8	Breathlessness	11
	Sleep disturbances	21
	Memory Disturbance	11
	Language Disturbance	7
	Lack of Interest	19
9	*FAS	21 ± 6
10	PCL-5	34 ± 3

Table 1: Patient Demographics. *FAS: Fatigue Assessment Score.

Network	Beta	T Value	p-UNC	p-FDR
Default Mode (DMN)	0.61	12.35	0.00001	0.00011
Executive (FPN)	0.23	4.5	0.001	0.005
Language (LANGN)	0.66	10.8	0.0002	0.0006
Salience (SAN)	0.84	21.6	0	0
Somatosensory (SMN)	0.9	9	0	0
Visual (VN)	0.87	36	0	0
Dorsal Attention (DAN)	0.32	9	0.00009	0.00017
Basal Ganglia (BGN)	0.28	16.5	0	0

Table 2: Network Beta and T values of Long Covid patients.

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S no.	Symptoms	In Networks	Between Networks			
1	Fatigue	91%	90%	DMN: SALIEN, SMA, DAN, (REDUCED)	RLPP(Hyper)	
2	Anosognosia	77%	84%	DMN: SALIEN, SMA DAN, (REDUCED)	BGN(HYPER)	BGN(HYPER)
3	PTSD	80%	99%	DMN: SALIEN, DAN, LANG (REDUCED)	VISN, CEREBELLAR(HYPER)	VISN, CEREBELL(HYPER)

Table 3: Relation of symptoms and functional connectivity.

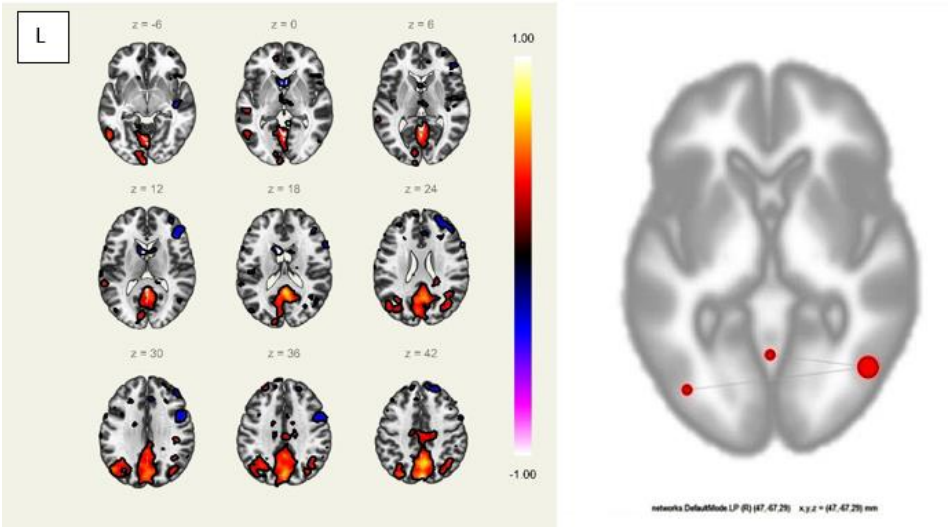

Figure 1: Axial rs-FMRI study showing absent activation of MFC in default mode network in patient with long Covid-19 disease with Graph analysis of patients of long covid showing absent MFC with reduced edges in the DMN network with hyperactive right lateral posterior parietal node.

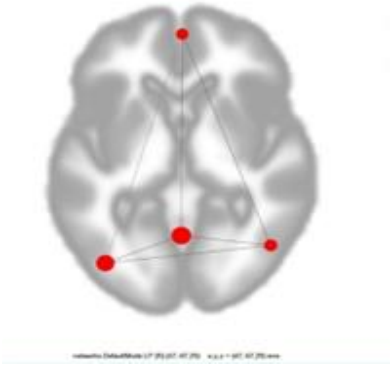

Figure 2: Graph analysis of the DMN in control group showing normal functional connectivity in DMN.

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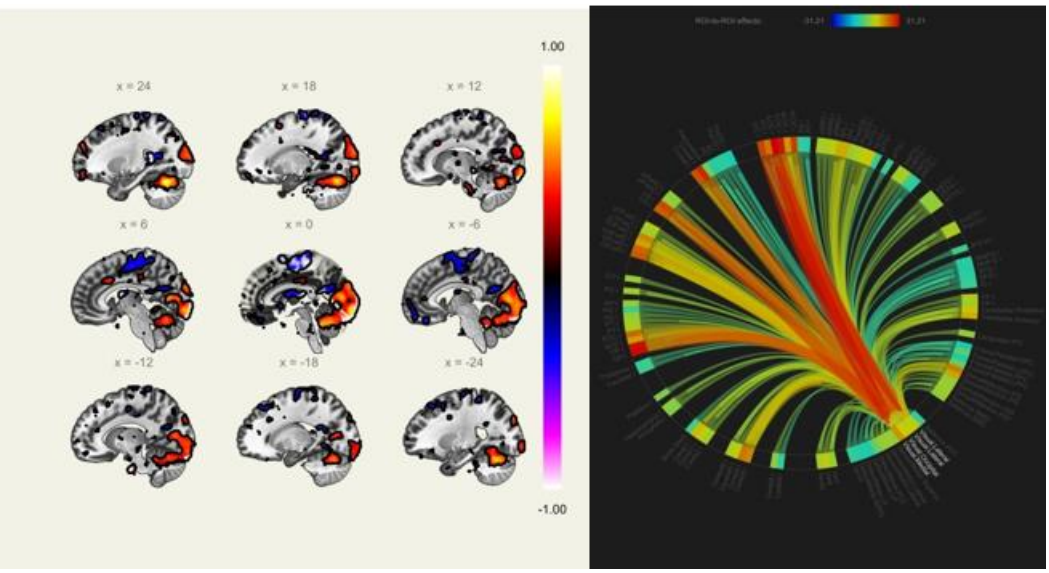

Figure 3: Saggital BOLD image showing increased activity in the occipital lobe and in the cerebellum in a patient with PTSD with the connectome showing increased FC between Visual network, SALIEN nodes, Posterior cingulate gyrus and the hippocampus.

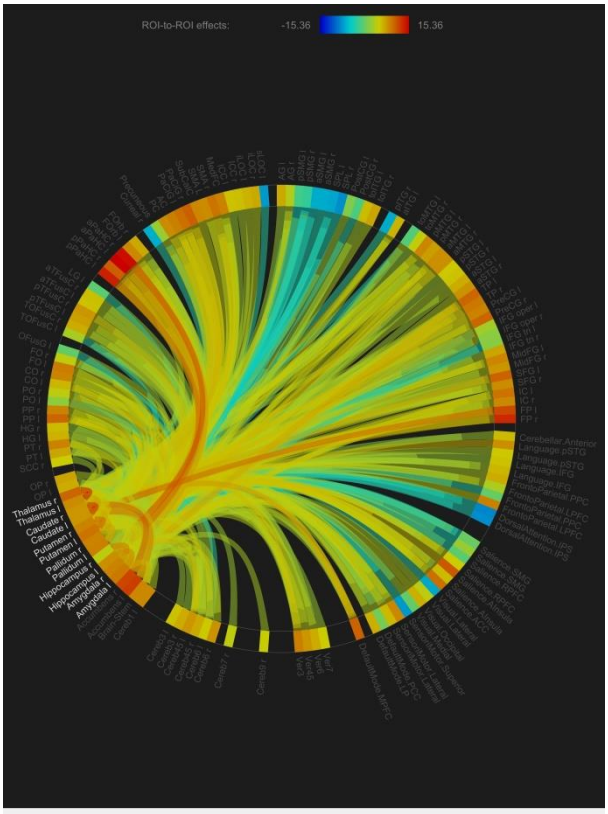

Figure 4: Connectome of patients with Anosognosia showing increased BGN activity with reduced connectivity with DMN, SALIEN and DAN.

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FC patterns in major networks

DMN

The DMN was the most common affected network in long covid-19 patients with Medial frontal cortex (MFC) showing gross reduced activity. There was also loss of edges between MFC and posterior cingulate cortex (PCC) and also with left posterior parietal node (lLPP) however DMN showed compensatory increased activity in the Right posterior parietal node (rLPP) which was the signature of patients with fatigue (Figure 2). Note was also made of reduced between-network activity of DMN with salience (SALIEN) network on connectome compared to control group (Figure 5a, b). Increased activity with basal ganglia network (BGN) was seen in patients with anosognosia and with visual networks (VIN) and Cerebellar networks on PTSD (Table 2).

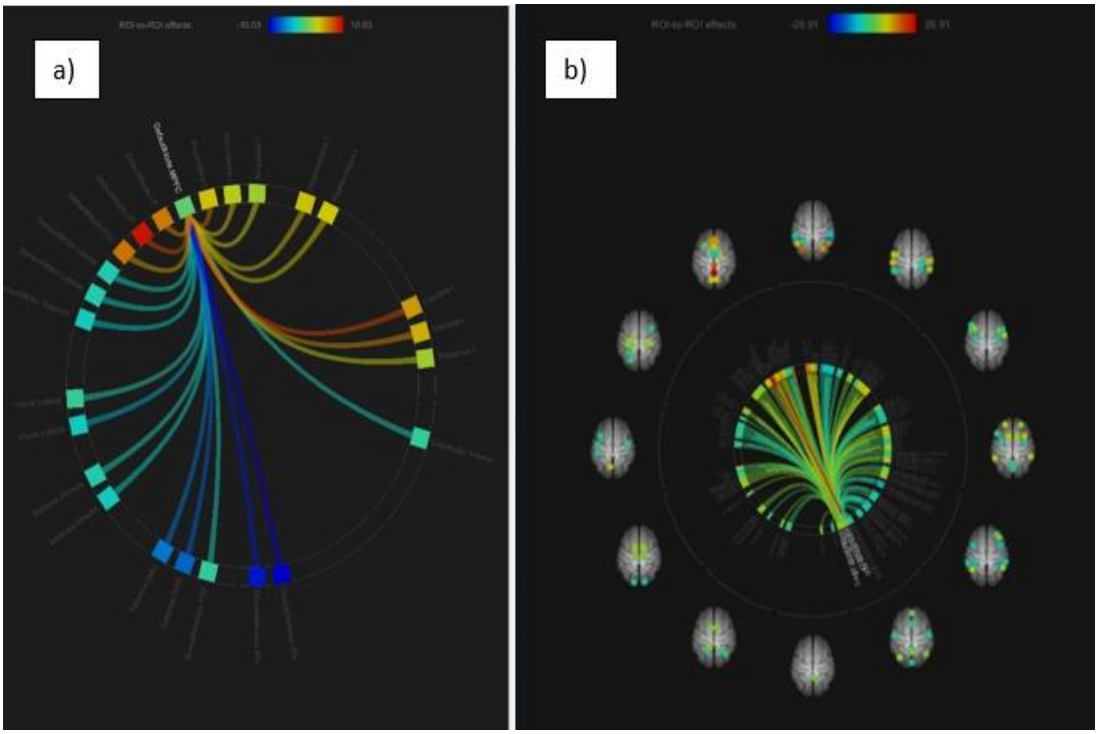

Figure 5: a) Connectome showing reduced connectivity of MFC of the DMN with reduced connectivity with DAN, SALIEN along with increased activity of right LPP of DMN.b) Connectome of the DMN in control group showing normal FC pattern of MFC.

SALIEN

Salience network also showed alteration in the in- network with reduced activity of the left anterior insula with reduced edges of FC in bilateral insula and ACC along with reduced connectivity of the supra marginal gyri with right insular dominance (Figures 6,7). Between -network connectivity showed reduced FC with DMN, EXEN and hippocampus (Figure 7). However normal activity with sensimotor (SMN) and VIN was observed.

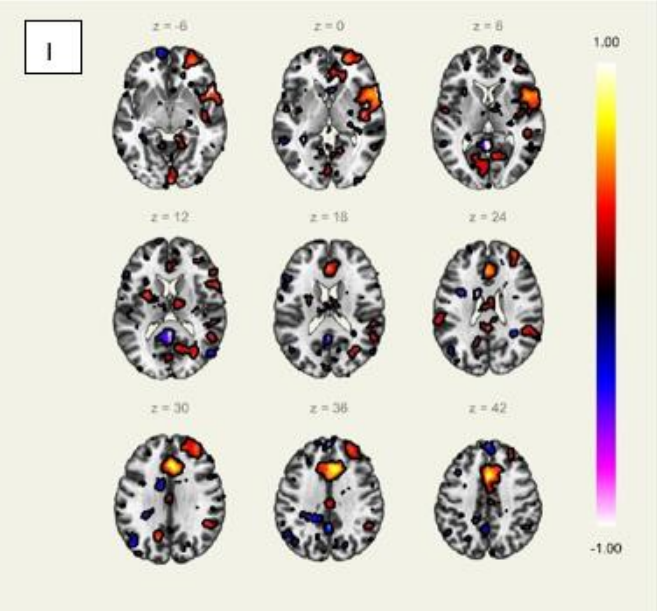

Figure 6: Axial bold image showing reduced activity in left anterior insula of SALIEN.

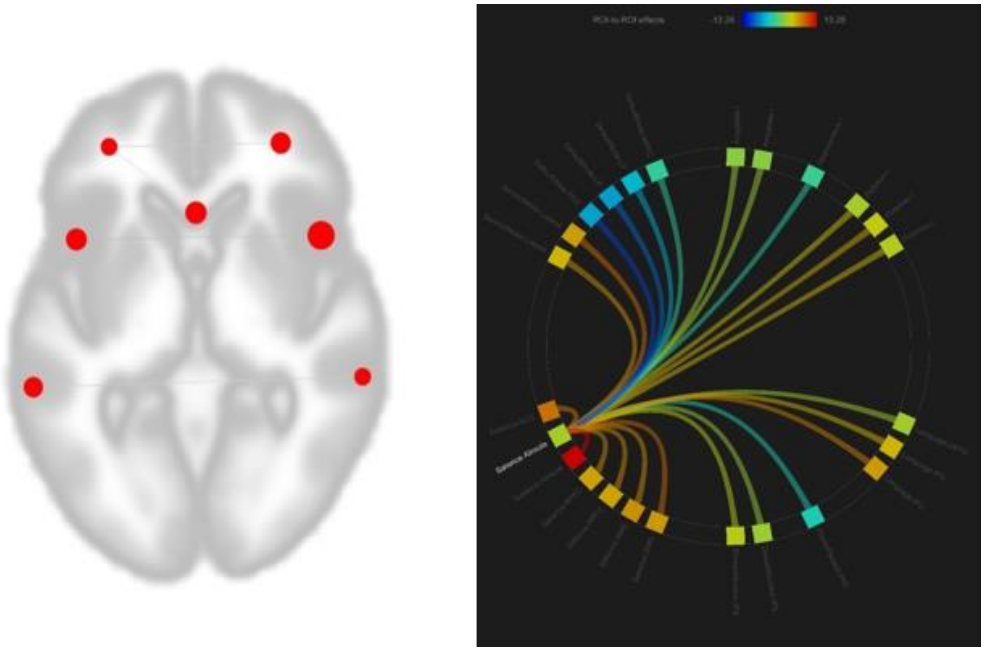

Figure 7: Graph analysis of SALIEN showing reduced edges of FC in bilateral insula and ACC along with reduced connectivity of the supra marginal gyri with right insular dominance with connectome showing reduced FC of insula with SALIEN, DMN, EXE and hippocampus.

EXEN

No significant change was seen in the executive network in long covid-19 patients (Figure 8).

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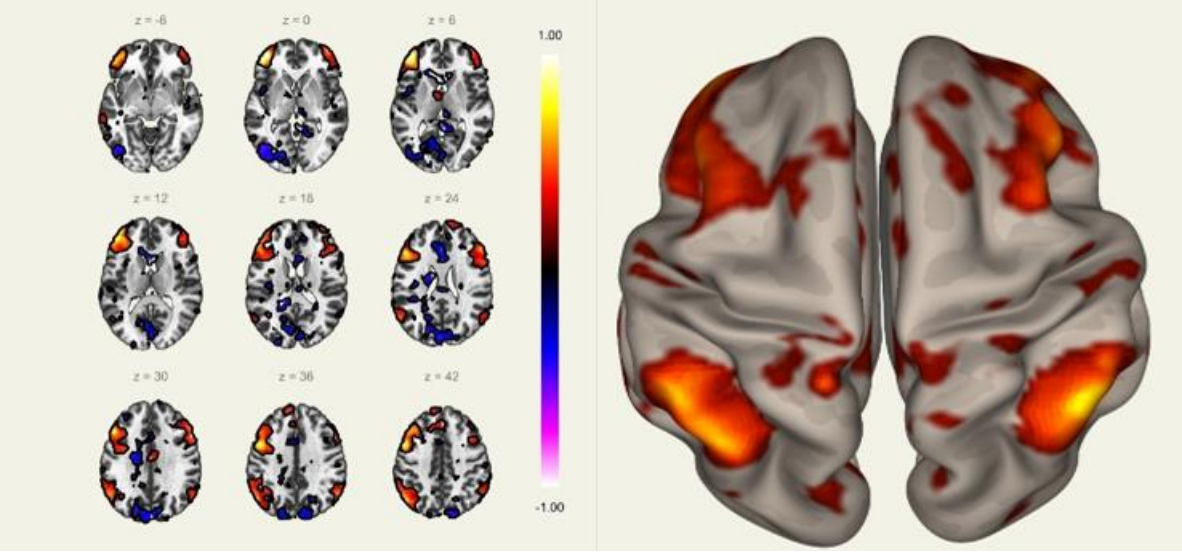

Figure 8: Axial bold image with 3 D depiction of normal activity of bilateral frontoparietal nodes.

BGN

The limbic basal ganglia network however showed marked increased activity in all the nodes with overall beta of 0.28 with maximum BOLD effect in the b/l hippocampi, left para hippocampal regions and in the thalami (Figure 9).

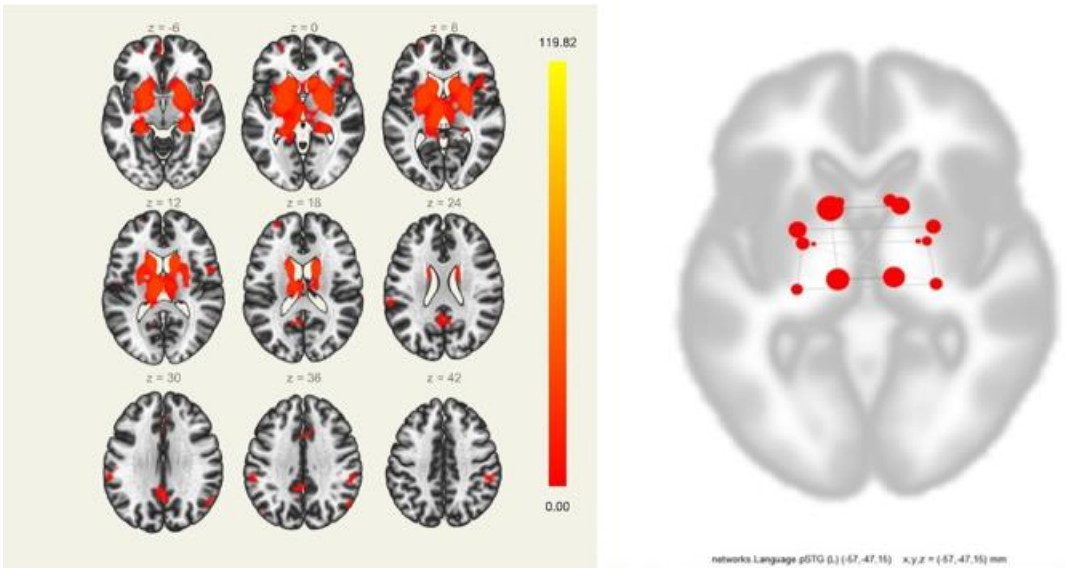

Figure 9: Axial BOLD image and graph analysis showing increased bilateral basal ganglia and thalamic activity.

VISN

Similar symmetrical increased activity was observed in both occipital lobes in the visual networks (Figure 10) with reduced FC with DMN in lLPP node in patient with PTSD.

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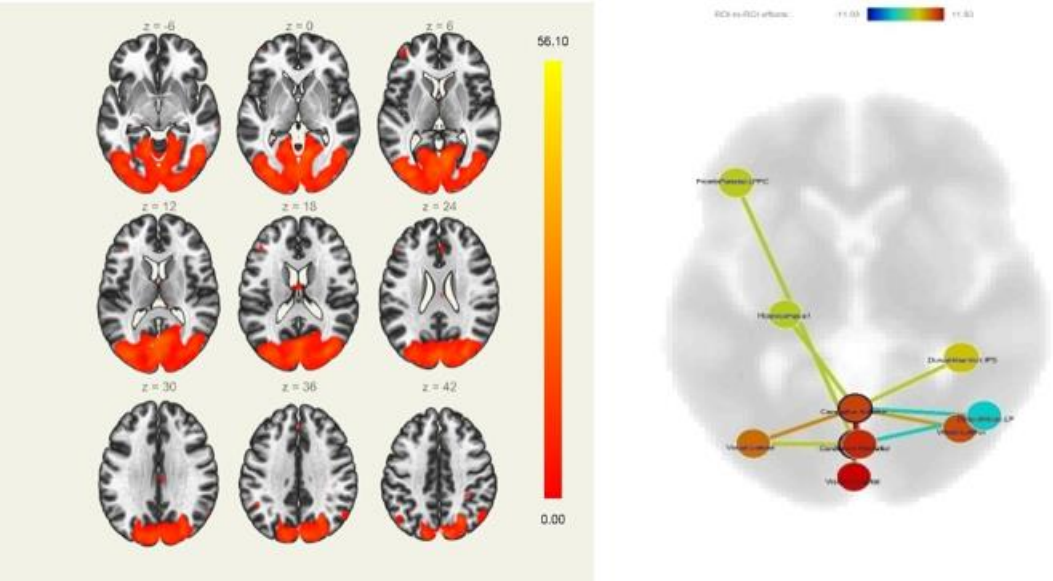

Figure 10: Axial BOLD and 3D images of showing increased VISN and Cerebellar activation with reduced DMN and SALIEN FC with dominant left FPN.

LANGN

Language network also showed asymmetrical compensatory activity in left angular cortical node with reduced nodal activity on rt side (Figure 11). In between networks showed altered FC with PCC of DMN, SMN, Hippocampus, DAN in patients with Anosognosia.

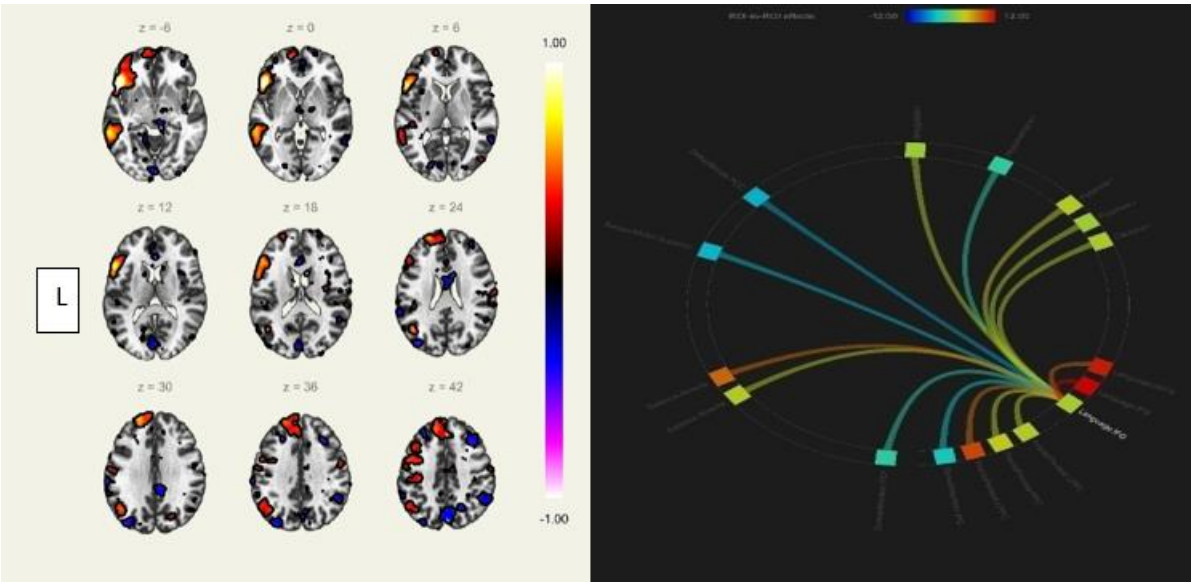

Figure 11: Axial BOLD image with connectome showing increased activation of left anterior insular cortex with absent activation of right anterior insula and temporal nodes with reduced in-between connectivity of LANGN with DMN, DAN, SMN, SALIEN and hippocampus.

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SMN

In network FC did not show any change in SMN while some hyperactivity was seen with basal ganglia caudate nuclei (Figure 12).

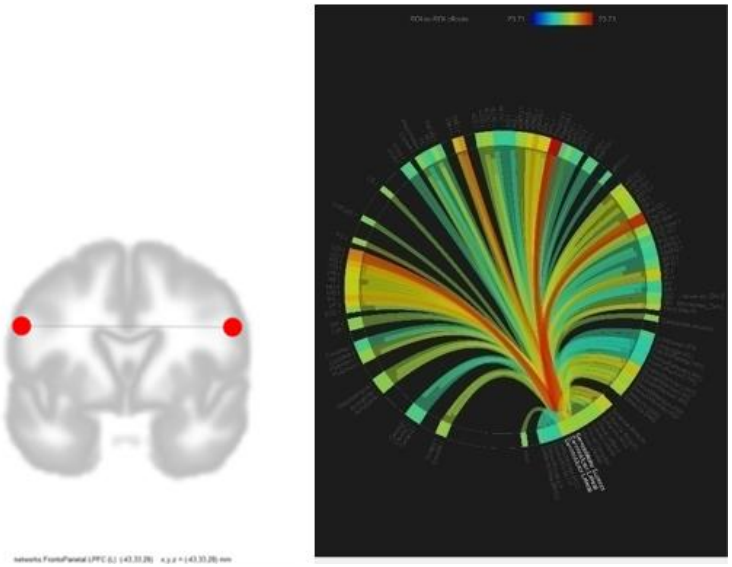

Figure 12: Graph analysis showing symmetrical activation and FC of SMN nodes with normal connectome.

DAN

DAN showed no change in FC in -network connectivity while altered FC was seen between connectivity of DAN IPS and FEF with DMN, Hippocampus and BGN with compensatory hyperactivity with Right Posterior parietal lobe in patients with Fatigue, PTSD (Figure 13).

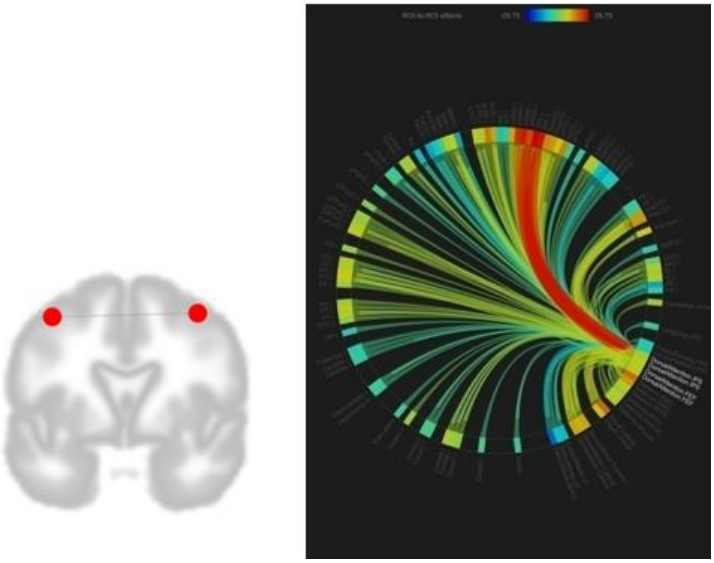

Figure 13: Graph analysis of normal DMN with connectome showing reduced FC with SMN, DAN and SALIEN with increased FC with the supramarginal node.

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Discussion

The results from this study showed a much higher prevalence of symptoms in long covid patients who recovered mild to moderate acute Covid-19 disease. Fatigue, palpitations and sleep disturbances were the commonest symptoms. Similar observations were reported by Lopez et al., [17] and Townsend et al., [18] but post severe covid-19 disease. The present study demonstrated altered FC in long covid-19 disease when compared to HCs in the form of both in- network as well as in-between network connectivity on a larger scale involving five major brain networks. Studies done by Ismail et al. [19], Fischer et al. [20], Gay et al., [21] and Hafiz et al. [14] reported altered FC in cohorts of patients with fatigue and PTSD alone. Current study showed alterations of FC in five large scale network alterations in DMN, SALIEN, BGN and VISN and LANG networks which accounted for the major long covid symptoms of fatigue PTSD, anosognosia and anxiety. The MFC node of the DMN was the severest affected both in terms of strength as well as connectivity in both in-network and in-between networks. 86% patients had long covid fatigue and showed FC loss of MFC activity in all the patients while 81% had dysfunctional connectivity of DMN with SALIEN, DAN with characteristic hyperactivity of Right LPP with concurrent loss of edges of R LPP node with remaining network which has not been reported earlier. Patients with higher activity in LPP had higher FAS scores. Prior studies done by Silva et al., [22] showed increased FC between the PCC and angular gyri and correlated with fatigue scores which was not seen in the current study, similarly Boissoneault et al., [23] only showed altered FC's of DMN in patients with chronic fatigue syndrome patients without no nodal hyperactivity. Wortinger et al., [24] in their study showed altered between network connectivity of SALIEN with posterior parietal cortex in chronic fatigue syndrome which in the study was seen in the study. Researchers feel that hyperactivity of RLPP correlates well with severity of fatigue as was shown in study by Hafiz et al., [21] who demonstrated increased grey matter volume of LPP in chronic fatigue patients which is the likely result of the hyperactivity of this node.

PTSD was defined by Shalev et al., [25] as the development of symptoms related to intrusion, avoidance, negative alterations in cognitions and mood, and arousal and reactivity following exposure to a traumatic event there as some patients (11% in the present study) who did not meet full diagnostic criteria of PTSD but had functional impairments similar to results reported by Westphal et al., [26]; Varela et al. [27]. Present study showed incidence of 42% with lack of awareness and unspecified cognitive decline with absent structural alterations similar to studies by Mahmoud et al. [28], Khoo [29], Pilotto et al. [30]. Symptoms correlated with altered FC of DMN and weaker in-between network patterns of nodes in DMN with DAN, SALIEN, LT FPN, SMA, LANG networks and with hippocampus. There was a characteristic strong connectivity with VISN and the cerebellar network which increased the level of symptoms with addition of general anxiety to PTSD clinical state. While Fischer et al., [20] explained PTSD in post covid-19 to reduced DMN alone the study showed that in patients with PTSD the reduced activity of left

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FPN and SALIEN dominated PTSD symptoms as the cause. The left anterior insula node particularly showed edge deficits between multiple nodes in SALIEN, while for in-between networks there was reduced FC with DMN, FPN was seen. In a study by Chenz et al. [12] connectome patterns of the PTSD were studied in pre covid patients and it was seen that PTSD prone patients had reduced FPN activity which was similar the patterns of the current study. Chenz et al. suggested that this caused reduced top-bottom control of the networks. The study also showed altered FC in LANG network which had reduced FC of LANGN with DMN, DAN, and SMN but with compensatory hyperactivity in left insula in 99% in PTSD and resulted in verbal and language disturbances.

Voruz et al., [31] studied anosognosia patients post Covid-19 and demonstrated lack of FC not only in- network DMN but with hippocampus and DAN. Ries et al., [32] also showed reduced connectivity of MFC, FPN and hippocampus. The researchers observed altered in- network FC of DMN alone but with altered FC of in-between networks with SMN, DAN and EXECN which were not seen in any prior study. The altered FC with SMN was important finding as it explained the lack of response to olfactory sensations and other somato sensory perceptions including memory disturbances in these patients. Altered FC SMN could also explain the finding of happy hypoxia seen in the acute phase. Hallam et al., explained the symptoms in patients with alzheimers disease based on the altered FC of DMN with SMN. The study also observed significant compensatory hyper FC with BGN in anosognosia which was not seen in patients with fatigue alone or PTSD in the study. Increased BGN was more commonly seen in patients with long covid with longer duration of symptoms. This may also explain for increased volume of grey matter of BGN reported by Hafiz et al., [21] in chronic fatigue syndrome. However, it is interesting to note that in the study patients with pure fatigue did not show altered FC of BGN.

To conclude the study describes high prevalence of symptoms of fatigue, PTSD, anosognosia in long covid patients following mild to moderate acute covid-19 disease. It also elucidates in detail the changes of altered FC in- network and in-between networks of five major brain networks with MFC of DMN being most severely affected. Characteristic patterns of involvement with hyperactivity of right LPP node was seen in long Covid-19 patients while increased connectivity of VISN and cerebellar networks was seen in PTSD. Anosognosia patients showed increased BGN activity along with hypo activation of other described networks.

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