Journal of Clinical and Medical Research

ISSN: 2582-4333
Kapoor A, 2023- J Clin Med Res
Research Article

Imaging Phenotypes of Stress Based on Functional MRI

Atul Kapoor*

Department of Magnetic resonance Imaging, Dept of Radiology, Advanced Diagnostics and Institute of Imaging, Amritsar, Punjab, India

***Corresponding Author:** Atul Kapoor, Department of Magnetic resonance Imaging, Dept of Radiology, Advanced Diagnostics and Institute of Imaging, Amritsar, Punjab, India.

Received Date: 02-08-2023

Accepted Date: 02-20-2023

Published Date: 02-28-2023

Abstract

Background: Stress is an adaptive response to daily challenges faced by the body to maintain its internal homeostasis. The pathophysiology of stress has been described based on the role of the sympatho-adrenergic system and the hypothalamic-pituitary-adrenal axis. Few studies have been done describing the role of functional MRI and PET to study the patterns of brain involvement in symptomatic patients.

Methods: The author studied 50 post-acute covid-19 syndrome patients one year after the acute episodes along with 10 healthy control patients. Based on the patterns of stress on imaging the patients were phenotyped on the severity of the changes of stress into a classification system.

Results: The results of the study showed a distinct temporal pattern of changes based on the severity of chronic stress. Class II and III Group patients on imaging formed the largest number 32(64%) and also showed good correlation with PCS-10 scores which were moderate in this group. The supra optic nucleus followed by para ventricular nuclei were the commonest affected during stress. The study showed that involvement of DMN and SALIEN was seen as the severity of stress progressed to a burn out stage IV which resulted in hypoactivation of all major networks and hypothalamic nuclei. Hippocampal and amygdala volumetric changes alongwith altered asymmetry was seen in class II-IV groups.

Conclusion: The author concluded that functional MRI could detect the pattern of changes of stress and the findings not only can be helpful in the diagnosis but also in planning management of these patients.

Key words: Functional MRI; Stress; Default mode network; Salience network; Post traumatic stress disorder.

Introduction

Stress is defined as an adaptive response to challenge posed by stressor to a living being to maintain its internal milieu. It was also described by Canon as fight or flight response [1]. Selye, et al. [2] was the first to define stress from a biological point of view as "a

nonspecific response of the body to any demand made upon it". The stress response of the body in daily life is therefore an essential survival mechanism but many times becomes maladaptive thus resulting in many pathological states namely anxiety, depression, PTSD, altered immunity and other somatic and cardiovascular problems. Thereafter the concept of the physiology of stress has also been constantly evolving over the last many decades and the role of the brain especially the sympathetico- adrenal axis, hypothalamic-pituitary axis has now been established as the primary pathways involving stress response. Covid-19 pandemic has ended but there are 25-70% of recovered acute Covid-19 patients who continue to remain symptomatic mainly due to neurological manifestations of ongoing inflammation and from the persistent activation of stress mechanisms of the body. Studies have been done by Dayas, et al. [3], Kloe, et al. [4], Fenoglio, et al. [5] and Herman, et al. [6] using PET and have shown patterns of brain involvement in PACS patients along with functional studies Kapoor, et al. [7] to elicit the dysfunctional connectivity of brain networks however no study has been done so far to show the neurobiology of stress in such patients. The author studied 50 patients with functional neurological manifestations at one year of recovered post covid-19 disease (PACS) at one year using rs-fMRI. The author classified the levels of stress based on the functional connectivity and activation of the stress system of the brain and also evaluated the structural correlates related to changes in hippocampus and amygdala.

Material and methods

A retrospective study of 50 PACS patients with 10 healthy controls was done after obtaining approval from the local institutional ethics and review board. Clinical and Imaging data of 50 patients of PACS were archived from the institutional HIS-RIS PACS system. All data was anonymised. Patient demographics were obtained along with history and duration of acute Covid-19 disease and current symptoms recorded along with PCS-10 scores [8]. MRI studies were done on the 1.5 Tesla MRI (Siemens Amira) system using T1 MPRAGE sequences for anatomical assessment of the brain. Resting fMRI sequences was done using Echo planar imaging bold protocol was used with TR/TE of 1300/45 msec with bandwidth 1906 Hz with echo spacing 0.63 msec matrixes 224 x 224. 3 D MPRAGE sequence was done for T1 anatomical image with TR/TE 1780/2.79 msec with slice thickness of 1.0mm. MRI resting state images were processed using MRI resting state analysis software v.01.4 on Siemens Syngo-Via Frontier system. Both the data sets were then co-registered followed by motion correction. The data sets were preprocessed for rigid-body motion compensation of the fMRI time series, temporal band-pass filtering, spatial smoothing and Slice timing correction. ROI-ROI GLM protocol was used to assess the Functional connectivity of default mode network (DMN), salience network (SALIEN). BOLD activation of the stress system consisting of six nodes in the region of the hypothalamus were looked for and the findings recorded .The status of the other two main networks i.e. Visual (VIS) and Somatosensory (SOS) were also recorded. Based on the patterns of activation the author

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proposed an Imaging classification of Stress (Table 1) and classified these into four classes of stress and correlated these with the PCS-10 scores. Volumetric analysis was done using automated brain volumetric analysis Vol Brain online system [9] version 1.0. Automated report of the hippocampal and amygdala volumes was calculated along with an asymmetry index. All segmentation protocols were used as per algorithm by Winterburn, et al. [3].

S. No.	Stress class	Network status
1	Class 0	Normal DMN FC
		Absent activation of Hypothalamic nuclei
2	Class I	Hypo MFC with active SON
3	Class II	Hypo DMN with Active SON, PVN and MAMM.
4	Class III	Hypo DMN and multiple FC networks. Active PVN, MAMM
5	Class IV (burn out phase)	Hypoactive multiple FC and Hypothalamic nuclei

Table 1: Kapoor Classification of stress on imaging. *DMN: Default Mode Network; *FC: Functional Connectivity; * MFC: Medial Frontal Cortex; *SON: Supra Optic Nuclei; *PVN: Paraventricular Nuclei; *MAMM: Mammillary Nuclei.

Results

The mean age of the patients was 48 ± 4.5 years with 39 being males and 11 female patients. The patient demographics are listed in Table 2. Normal DMN and SALIEN network connectivity with BOLD activation was seen in all 10 healthy controls (Figure 1). Group with moderate scores on PSS-10 formed the maximum number of patients 32(64%) followed by 12(24%) patients with mild PSS-10 score while 6 patients (12%) were in the severe class. Imaging based Classification showed 8(16%) patients in class I, 15(30%) and 17(34%) in class II, III respectively while 10(20%) patients were in class IV with correlation of 0.80 ($p<0.005$). Class I patients showed normal functional connectivity of all major default networks with activation of supra optic nucleus (Figure 2).

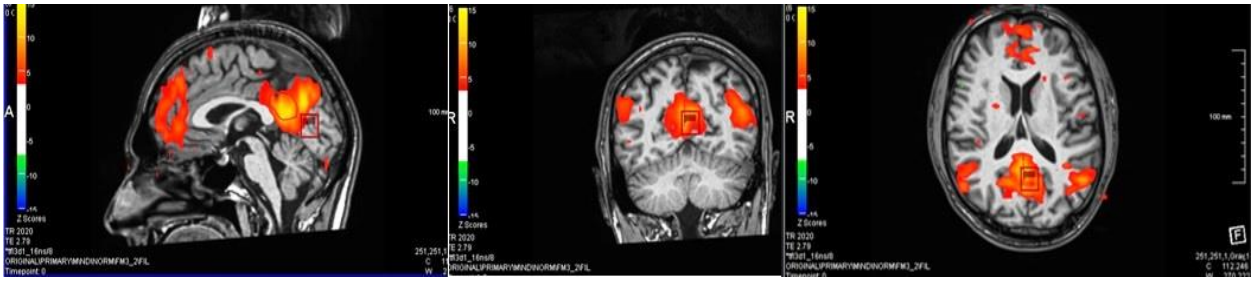

Figure 1: rs-fMRI multiplanar images showing normal default mode network connectivity in healthy control.

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Sno.	Parameter	Mean	SD
1.	Age	48 (years)	± 4.5
2.	Sex		
a)	Males	39	
b)	Females	11	
3.	PSS-10		
a)	Mild (0-13) patients	6	
b)	Moderate (14-26) patients	32	
c)	Severe (27-40) patients	12	
4.	Stress Class		
	Class 0	10	
	Class I	8	
	Class II	17	
	Class III	15	
	Class IV	10	
5.	Clinical Diagnosis		
a)	Stress alone	17	
b)	Anxiety	7	
c)	Depression	4	
d)	Anosognosia	9	
e)	PTSD	13	

Table 2: Demographics.

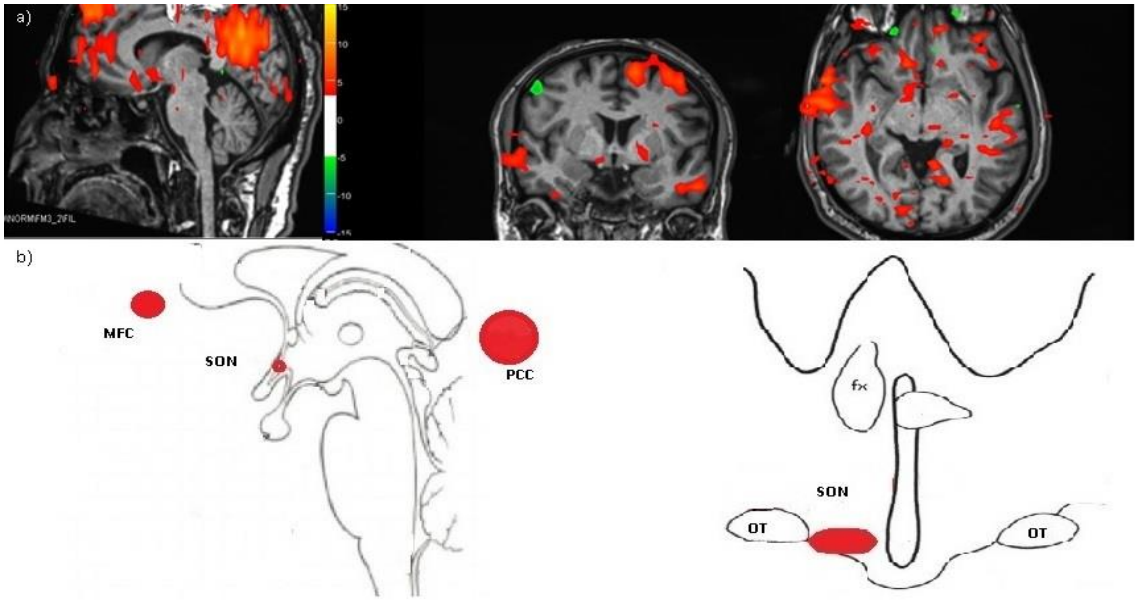

Figure 2: Stress Class I patient showing normal Default mode network with activation of the right supra optic nucleus with b) line drawing of activation nuclei. MFC: medial frontal cortex; SON: supra optic nuclei, PCC; posterior cingulate cortex; OT: optic tract; Fx: fornix.

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The volumetric analysis of hippocampi and amygdala showed normal right to left asymmetry of 7-8% with mean volumes of 3.64 cm3 and 0.81 cm3 of right side which was slightly less than those of the HC group (Figure 3) (Table 3). Class II patients showed reduced activation of the medial frontal cortex (Figure 4) with mild reduced activity of the DMN along with activation of supra optic nucleus. There was no change in the hippocampal and amygdala volumes compared to class I patients however a change of asymmetry was seen with left to right predominance (Figure 5).

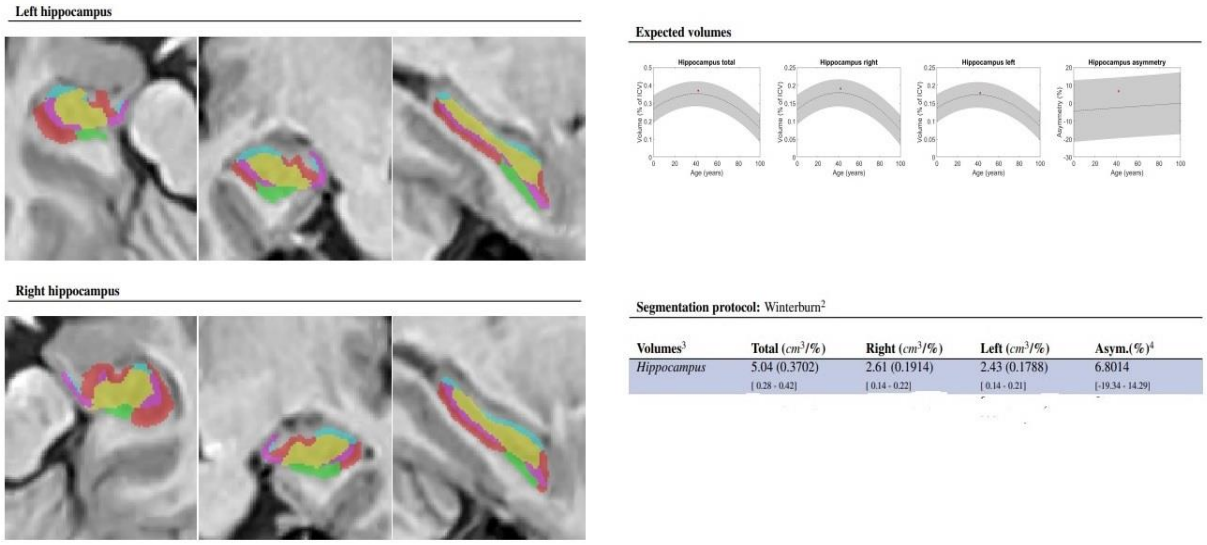

Figure 3: Hippocampal segmentation with volume analysis showing a positive right to left asymmetry of 6.8% in Stress class I patient.

Class	Right		Left		Asymmetry
	Hippocampus	Amygdala	Hippocampus	Amygdala	
HC/Class 0	4.4	0.86	3.7	0.8	R>L
Class I	3.64	0.81	3.4	0. 76	R>L
Class II	3.69	0.71	3.94	0.75	L>R
Class III	4.23	0.87	4.25	0.8	L>R
Class IV	4	0.87	3.98	0.88	NO DIFF

Table 3: Hippocampal and Amygdala Mean volumes (cm3) in Stress. HC: Healthy Controls.

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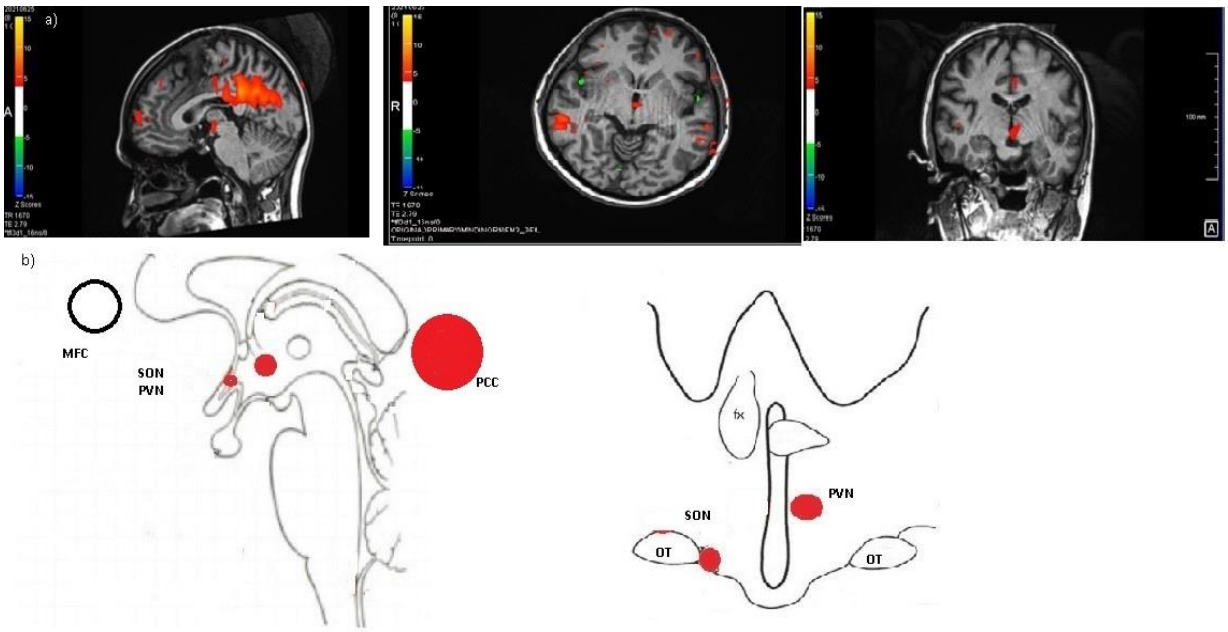

Figure 4: rs-fMRI of Stress Class II patient showing. a). reduced activation of medial frontal cortex along with activation of supra optic nucleus, b). line drawing depicting the same. MFC: Medial Frontal Cortex, PVN: Paraventricular Nucleus.

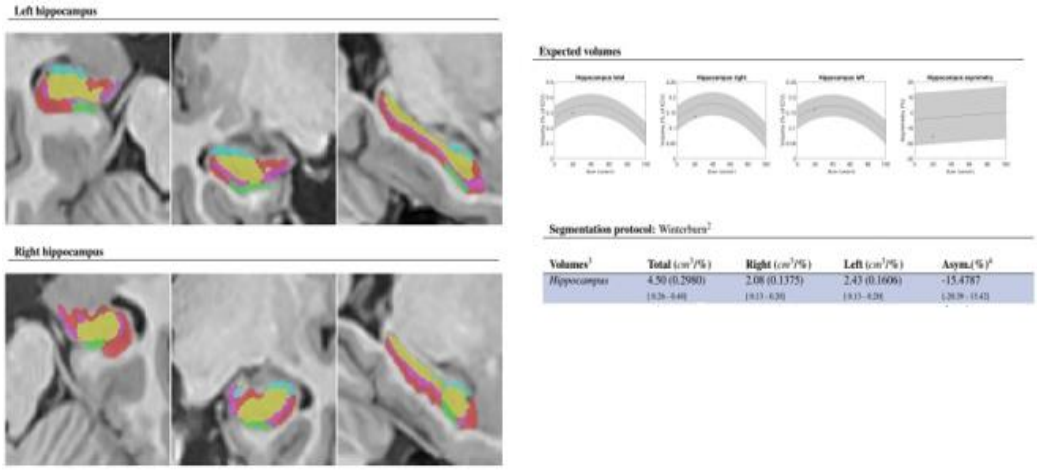

Figure 5: Stress class II patient showing altered left to right asymmetry of -15.4% of the hippocampi.

Class III patients showed marked reduced activity of the DMN with reduced BOLD activation of medial frontal cortex and posterior parietal nodes along with activation of supra optic, para ventricular and or mammillary nuclei (Figure 6). In 7(14%) patients there was dysfunctional connectivity of the SALIEN network, basal ganglia and cerebellar activation with increased activation of the amygdala (Figure 7). The hippocampal volumes and amygdala showed increased volumes especially the amygdala with persistent left to right asymmetry (Figure 7). In class IV patients there was

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overall reduced BOLD activation of multiple major networks with hypo activation of all hypothalamic nuclei with the hippocampi and amygdala also showing loss of asymmetry with no difference in the sizes (Figures 8 and 9).

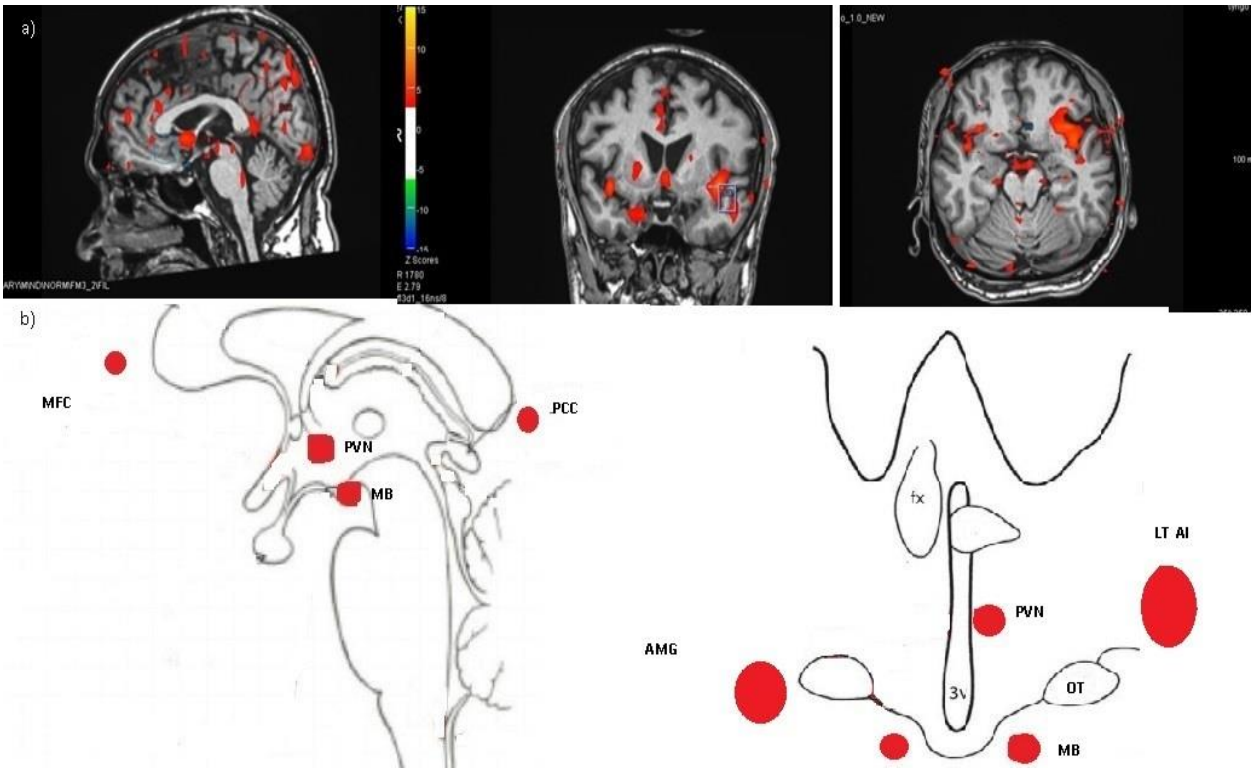

Figure 6: Stress Class III patient with a). BOLD maps showing hypoactivation of medial frontal cortex, posterior cingulate cortex with dysfunctional salience network alongwith activation of PVN, alongwith increased activity of right amygdala and both mammillary nuclei b). Line drawing showing the various activation nodes. AMG: Amygdala; LT AI; Left Anterior Insula, MB: Mammillary Bodies.

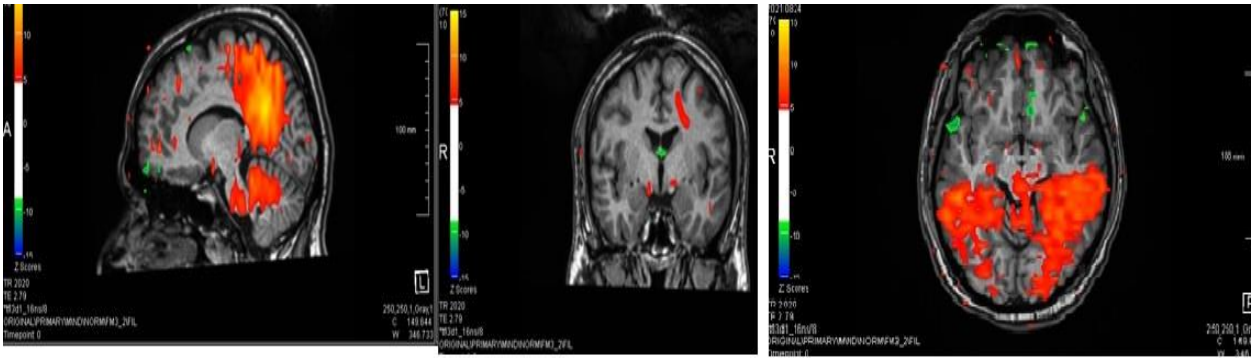

Figure 7: Stress class III patient showing dysfunctional default mode network with increased activity of posterior cingulate cortex, reduced medial frontal cortex activity with activation of bilateral supra optic and mammillary nuclei with increased bitemporo occipital and cerebellar activation.

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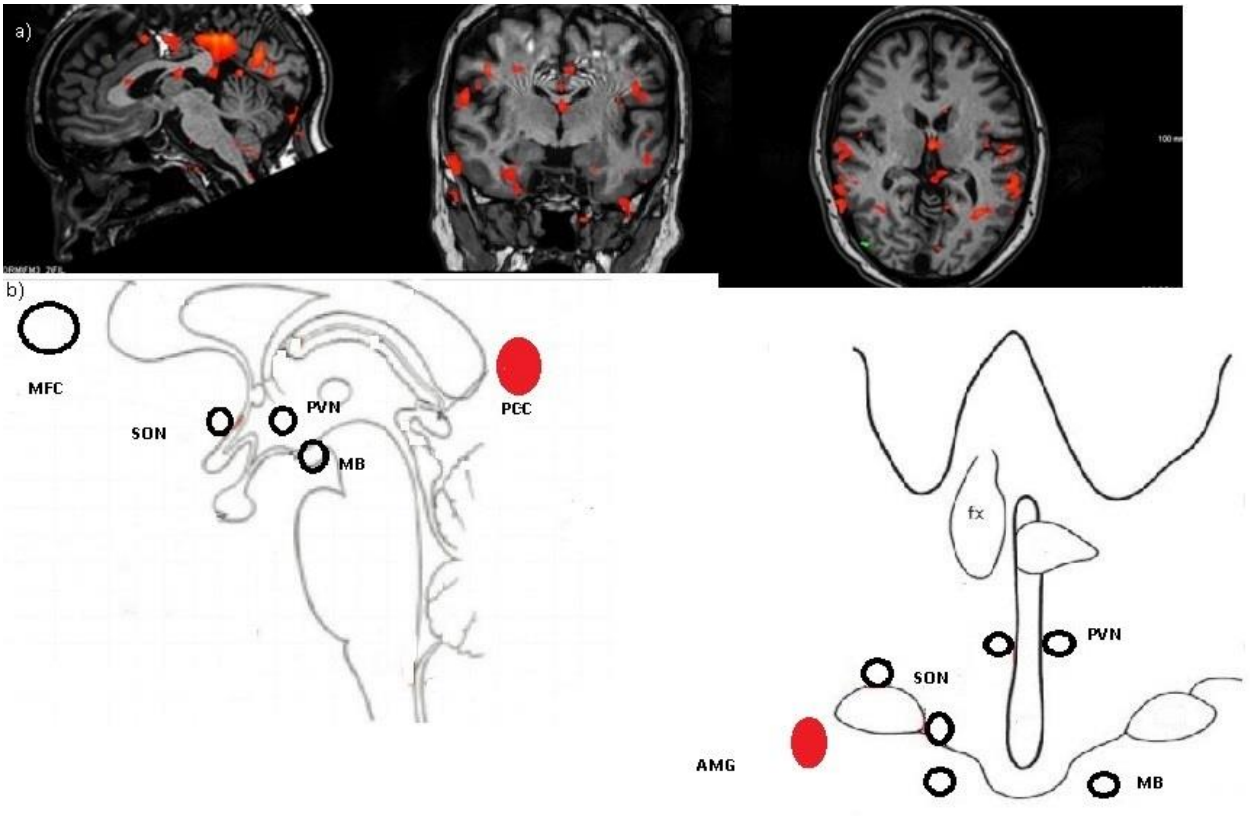

Figure 8: Stress class IV patient. a). With hypoactivation of default mode network with hypoactivation of all hypothalamic nuclei with activation of right amygdala b). Line drawing showing the same.

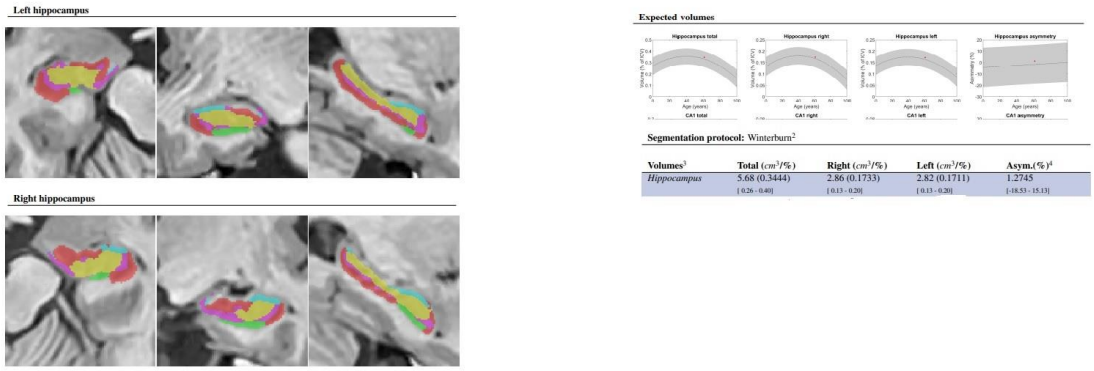

Figure 9: Hippocampal 3 D segmentation and volumetric analysis showing loss of asymmetry.

Discussion

Stress is an adaptive mechanism of the body as response to a stressor. The role of the central nervous system is well established to not only initiate but to modulate this mechanism. The brain-hypothalamic-pituitary axis is also known to play a key role in chronic or long-lasting stress and many experimental studies have been done to demonstrate the same (10-11). Recently

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Farber, et al. [12] used human endotoxemia model showed that there were six hypothalamic nuclei modulating stress mechanism and were linked to three major networks i.e. DMN, SALIEN and VIS and SOS in three clusters which regulate the response to stress by secretion of Corticotrophin release hormone(CRF), ACTH and antidiuretic hormone(ADH). They also showed that there was a reciprocal control of these by release of oxytocin and also by increased stimulation of limbic pathways to stress. Earlier studies done also showed the connectivity of these nuclei to the three major networks [13-15]. The findings of the current study conform to the observations made by Farber, et al. [12] and other studies about the role of hypothalamic nuclei in stress and its effects on the brain connectivity, current study for the first time elicits the temporal changes in the brain in response to degree of stress which correlate with clinical status and PCS-10 scores. Based on these temporal changes the present study proposes the classification of stress into imaging-based phenotypes which depicts not only the stress severity but also the structural changes. The study shows that in chronic stress Class I patients the stress response is initiated by activation of supra optic nucleus which is responsible for ADH and oxytocin secretion as the first neurological response of the brain. ADH is a known vasoconstrictor by its action on V1, V2 receptors and causes activation of noradrenergic pathways and increased noradrenaline levels. It also acts on V1a and V1b receptors in the brain and causes ACTH secretion by the anterior lobe of the pituitary. In this stage of stress, the functional connectivity of all the 1 major pathways remains unaffected as is also the Hippocampal and amygdala asymmetry. The effects of ADH result in a controlled stress response in this stage due to peripheral immuno neutralisation concurrently released oxytocin and also by negative feedback loop of ACTH- Cortisol release and the same has been suggested by Gibbs, et al. [16], Zhang, et al. [17]. In Stress class II patients, the author observed the persistent activation of supra optic nucleus but with reduced BOLD activation of medial frontal cortex and DMN with reversal of the hippocampal asymmetry with increased neurogenesis in the left hippocampus in the present study. The findings of this stage suggest the failing effects of oxytocin on ACTH neutralisation resulting in increased receptor sensitivity of cortisol in the left hippocampus which triggers positive neurogenesis as a sequel to stress response as demonstrated by Lyon, et al. [18]. Similar changes of increased neurogenesis may also be seen in MFC however the medial frontal cortex node of DMN being more sensitive to increasing stress levels shows reduced activity in this stage. Stress class III patients in the present study formed the largest group of patients and showed activation of the para ventricular nucleus of hypothalamus which is the key node for ACTH secretion. Persistent increased levels of the body cortisol result in increased hypoactivation of medial frontal cortex and likely neuronal loss. This reduces the top down control of medial frontal cortex on the limbic system and can also cause dysfunction of SALIEN, VIS and SOS networks causing cognitive and mood changes. Increased amygdala activation due to lack of medial frontal cortex control was also seen patients in this stage. The study showed the largest number (30%) of patients

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in this Class and included symptomatic patients of coexisting anxiety, PTSD and continued fatigue. Persistence of structural changes in hippocampus and amygdala were also seen in this stage but with higher negative asymmetry reconfirming the above sequence of temporal changes of stress. Bremmer, et al. [19] along with other studies [20-22] have shown a similar role of hippocampus and amygdala in increased stress both in PTSD and trauma exposed non-PTSD patients. They showed hippocampal enlargement as a mechanism to develop resilience to stress as observed in this class of patients in the current study. Stress class IV patients showed persistent severe hypoactivation of major brain networks with loss of asymmetry of the hippocampi and amygdala. Stress Class IV patients in the present study i.e. the 'burn out' stage were those with severe hypoactivation of functional connectivity of the major networks with hypoactive hypothalamic nuclei with loss of hippocampal asymmetry thus reflecting increased neuronal loss at these sites and further lack of not only top down control but also reduced limbic activity. Chenani, et al. [23] showed in experimental study that repeated exposure to stress i.e. chronic stress not only caused structural changes in hippocampus of rats but also reduced their theta power oscillations which is responsible for learning memory, synaptic control with neobrain and neuronal plasticity. Kloet, et al. [24] also postulated that chronic stress causes hypercortisolemia leading to structural changes in the hippocampus and prefrontal cortex by mineralocorticoid and glucocorticoid receptor genes thus creating stress prone phenotypes which concurs with the stress IV class of patients in the current study with altered structural and functional patterns of brain connectivity.

Conclusion

To conclude the study highlights the use of current state of art neuroimaging technique using f-MRI to classify imaging phenotypes of stress patients to understand the temporal changes of stress neurobiology. The study elicits the potential of f-MRI to change the paradigm of making diagnosis from history taking alone to that combined with imaging. This can be of help to the physicians to plan treatment management strategies and also can be of use in the post treatment follow up of these patients. The study has few potential limitations i.e., only cohort of PACS patients was studied one year after recovery, serum cortisol levels were not assessed and volumetric estimations of prefrontal areas were not done.

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