18F-FDG Positron Emission Tomography Imaging of Cortical Reorganization in Spinal Trauma

Abstract

Objective: Spinal cord injury (SCI) extensively impacts the sensorimotor reorganization in the brain. The effects can be both anatomical and functional. To date, not many studies using 18F-Fluoro-2-Deoxyglucose positron emission tomography (18F-FDG PET) to evaluate metabolic changes in the brain are done. Understanding such changes is crucial for developing clinical management and evidence-based rehabilitation strategies for these patients. **Subjects and Methods:** In this study, we compared 18F-FDG PET imaging of 6 SCI patients with complete paraplegia and 19 controls. Statistical parametric mapping software was utilized to compare the images on a voxel to voxel basis (significance level $P < 0.05$ and clusters having >50 voxels). **Results:** The study showed raised metabolism in supplementary motor areas, comprehension centers, some areas in the parietal and temporal lobe, putamen and cerebellum while reduced metabolic uptake in areas like anterior cingulate gyrus, hippocampus and sensory cortical areas when SCI patients were compared against healthy controls. The frontal lobe showed varied results where certain regions showed higher metabolism while the others showed lower in patients compared with controls. **Conclusion:** Cerebral deafferentation or disuse atrophy can be linked with reduced metabolism while raised uptake can be associated with initiation and planning of movement and cognitive changes in the brain posttrauma.

Keywords: *Brain, Fluoro-2-Deoxyglucose, positron emission tomography, spinal cord injury, statistical parametric mapping*

Jigyasa Chopra,
Maria M D'souza,
Abhinav Jaimini,
Rajnish Sharma,
Sanjiv Saw,
Santosh Pandey,
Yachna Solanki

Department of Nuclear Medicine and PET-CT Imaging, Institute of Nuclear Medicine and Allied Sciences, New Delhi, India

Introduction

In the mammalian brain, the primary somatosensory and motor cortices are spatially organized such that neural activity relating to specific body parts can be somatopically mapped onto an anatomical "homunculus." This organization creates an internal body representation that is fundamental for precise motor control, spatial awareness, and social interaction.[1] In this sort of arrangement, there is a competitive battle among different parts of the body to gain space in the cortical field: the more a part of the body is used, the more cortical space it gains to the detriment of adjacent body parts.[2] This continuous reorganization is also a part of normal life and sensorimotor learning.[3,4] However, the reorganization is extreme in certain scenarios like spinal trauma.[5] Traumatic spinal cord injury (SCI) is a major source of morbidity and mortality throughout the world. A recent study in 2018 showed the overall global incidence of traumatic SCI was 10.5 cases/100,000 persons.[6] What is of concern is that the mean age of patients afflicted with SCI is merely around 33 years.[7] The injury is very disabling with the limited recovery of function expected. The quality of life (QoL) of adults with chronic Traumatic-SCI falls significantly below that of the general population in most domains.[8] It is critical to understand changes after cortical reorganization to help in better rehabilitation with minimal cognitive impairment. Neuroplasticity after SCI involves metabolic and structural changes. Magnetic resonance imaging (MRI) or computerized tomography (CT) are modalities that have been widely used to evaluate anatomical changes in such cases. Glucose metabolism provides both energy and precursors for the biosynthesis of neurotransmitters.[9] Since glucose is required at the synaptic level for neurotransmitters, we can conclude deafferentation will lead to altered glucose uptake in SCI patients. Positron emission tomography (PET) is one such functional modality that uses glucose

Address for correspondence:
Dr. Abhinav Jaimini,
Department of Nuclear Medicine and PET-CT Imaging, Institute of Nuclear Medicine and Allied Sciences, Brig SK Mazumdar Marg, Timarpur, New Delhi - 110 054, Delhi, India.
E-mail: abhinav.jaimini@gmail.com

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.ijnm_133_21

Quick Response Code:

analog 18F-Fluoro-2-Deoxyglucose (FDG) to generate 3-dimensional (3D) images of the brain. Till date, not much research has been done on the functional changes in various areas of the brain using PET as an imaging modality. Understanding both these key structural and functional sequences in such patients and defining their effects on clinical outcomes is the key to the development of evidence-based rehabilitative therapy. We undertook this study to document the changes in glucose metabolism post-SCI at around 6 months.

Subjects and Methods

Subjects

This was a prospective study, from March 2017 to January 2018, eleven patients with paraplegia post-SCI were enrolled for the FDG-PET scan. Patients also had a routine MRI examination to rule out any morphological brain lesion. The patients with any history of head injury in the past were excluded. Due to this exclusion criterion six patients who had paraplegia due to SCI in the past 4–7 months were scanned and included in the study.

A control group of 19 healthy subjects, with no history of any neurological or psychiatric illness, were included for a normal database for comparison.

All patients underwent 18F-FDG-PET/CT examination.

Fluoro-2-Deoxyglucose-positron emission tomography procedure

All subjects were required to come with 4–6 h fasting but with unrestricted water intake on the day of the PET study. Blood glucose level was measured in each case and an upper limit of 150 mg/dl was set as the cut-off for 18F-FDG injection.

Each patient was injected 245–296 MBq (5–8 mCi) of F-18 FDG intravenously followed by a rest period of 60 min with open eyes in a silent, dimly lit room. This was followed by scan acquisition on a Discovery STE16 camera (General Electric Medical Systems, Milwaukee, WI, USA). This scanner has a transaxial resolution full width half maximum (FWHM) of 5.12 mm for 3D mode at 1 cm offset from the center of the field of view.

The patient was imaged supine with the head positioned in a headrest. An initial scout of the head was followed by low dose computerized tomography (CT) (120 kVp, 110 mA) of the head for attenuation correction and anatomical localization. The patient was moved into the PET gantry and a 3D emission scan was obtained for 10 min single-bed position. Images were reconstructed using a 3D VUE algorithm and viewed on a Xeleris workstation general electric (GE). Maximum intensity projection, plain PET, and fused PET/CT images were generated. DICOM images of the Pet study were imported for "Statistical Parametric Mapping" (SPM) analysis.

Statistical parametric mapping analysis

SPM-5 (http://www.fil.ion.ucl.ac.uk/spm) which was implemented on a tool called MATLAB (https://www.mathworks.com/products/matlab.html) platform was used for voxel-based statistical analysis of images. DICOM images of patient and control groups were converted to analyze format using MRIcro medical image viewer software (http://www.psychology.nottingham.ac.uk). The images were spatially normalized and smoothed by an isotropic 10 mm FWHM filter. SPM analysis was done to characterize patient group scans using the general linear model. The patient group was compared statistically to the reference group of 19 healthy control subjects with a two-sample t-test, resulting in the generation of T statistics. The measurements were assumed to be independent and have unequal variance between levels. Proportional scaling to the global mean was used to minimize inter-subject variability. Proportional scaling basically scales each image according to a reference count, which is the global brain activity to a physiologically realistic value of 50 ml/dl/min. Hence, SPM analysis essentially compares regional differences in relative glucose metabolism. In the end, the SPM. mat file containing the specified design matrix was generated. Using this file contrasts were defined thus providing a map of voxels showing increased or decreased glucose metabolism in patient group as compared to the control group above the statistical threshold of $P < 0.05$ and a threshold of at least 50 voxels in a cluster was applied and t-maps [Figures 1 and 2] were obtained. After calculating the t statistics, SPM converts the t statistics to Z scores. Z scores are a way that SPM uses to display and analyze the P values from the t statistics [Figures 3 and 4]. The statistical "t" maps thus obtained were overlaid onto the T1-weighted MRI
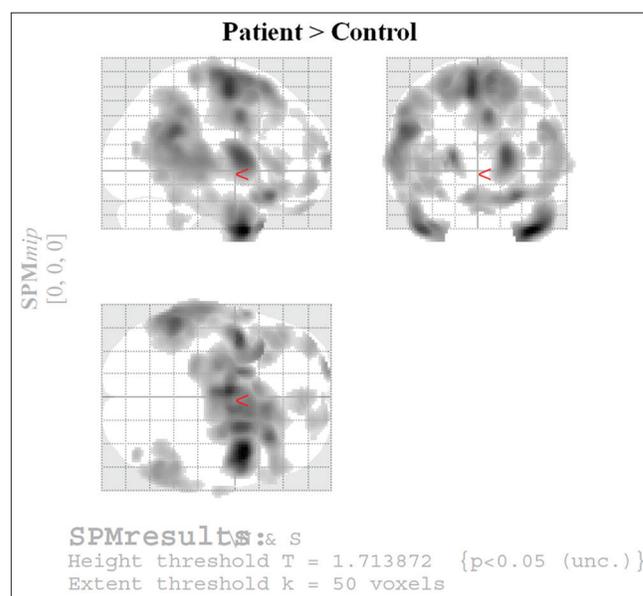

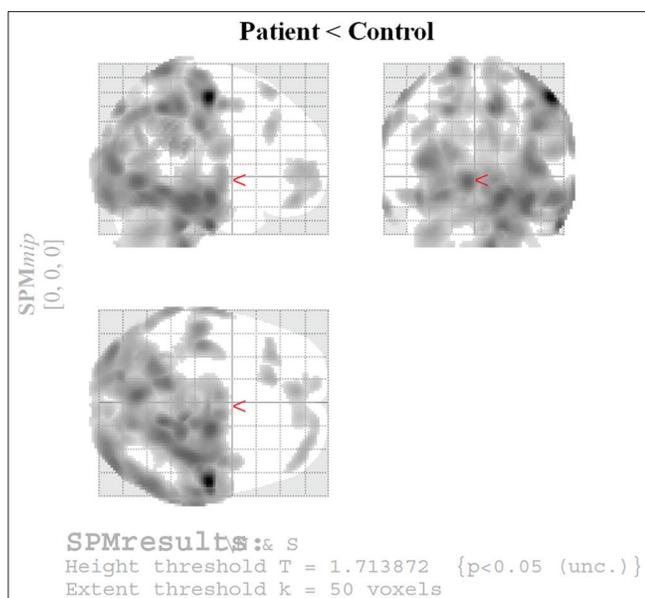**Figure 1:** Tmap image showing relatively increased 18F-FDG uptake in patients in comparison with controls

Figure 2: Tmap image showing relatively decreased 18F-FDG uptake in patients in comparison with controls

template image provided by SPM5 and saved as a portable document format for further viewing [Figure 5]. Increased glucose metabolism was represented in the "hot" colors scale and decreased glucose metabolism in "winter" colors scale. Significant clusters were further correlated using the SPM Anatomy toolbox which combines probabilistic cytoarchitectonic maps and functional imaging data.

Results

In this study, FDG PET scans of brains of 6 SCI patients (all males; mean age ± standard deviation, 39.1 ± 9.9 years; range 22–52 years) were compared with that of 19 controls. All the patients were paraplegics with a mean time interval postinjury of around 6 ± 2 months.

Analysis revealed certain cortical areas showing hypermetabolism in SCI patients in comparison to the controls [Figure 4]. These areas included bilateral supplementary motor cortex (leftsupplementary motor area [SMA] [x/y/z = –4/–4/60, Z = 4.85] and right SMA [x/y/z = 10/–2/66, Z = 4.14]), right superior temporal gyrus/Wernicke's area (x/y/z = 68/–12/4, Z = 2.32), right inferior temporal gyrus (x/y/z = 40/6/–44, Z = 5.59), left inferior temporal gyrus (x/y/z = –42/4/–42, Z = 4.65) and left medial temporal lobe (x/y/z = –34/20/–40, Z = 3.86), right angular gyrus (x/y/z = 50/–56/32, Z = 3.29), right supramarginal gyrus (x/y/z–52/–46/26, Z = 3.04) and right superior parietal lobule (x/y/z = 40/–54/56, Z = 2.52), left inferior frontal gyrus (x/y/z = –40/30/4, Z = 2.96), left middle orbital gyrus (x/y/z = –38/58/–10, Z = 2.95), right inferior frontal gyrus (x/y/z = 30/26/–18, Z = 4.22), and right superior frontal gyrus (x/y/z = 16/68/20, Z = 2.53) bilateral putamen (left putamen [x/y/z = –18/6/10, Z = 4.07) and right putamen (x/y/z = 22/4/10,

Z = 4.57]) and left cerebellum (x/y/z = –42/–42/–38, Z = 2.40).

On the contrary, hypometabolism was seen [Figure 5] in the postcentral gyrus (somatosensory cortex, x/y/z = –54/–24/58, Z = 3.31), right hippocampus (x/y/z = 20/–16/–16, Z = 4.13), right middle frontal gyrus (x/y/z = 38/52/4, Z = 2.68), left middle frontal gyrus (x/y/z = –34/30/36, Z = 2.68), left superior frontal gyrus (x/y/z = –18/28/62, Z = 2.72), and left rectal gyrus (x/y/z = –8/48/–16, Z = 2.78). The T value was generated for the left anterior cingulate cortex (ACC) (x/y/z = –6/48/6, T = 2.09), but the Z score was not generated.

Discussion

To improve the QoL of young adults with traumatic-SCI with better rehabilitation with minimal cognitive impairment, it is critical to understand changes from cortical reorganization. Neuroplasticity after SCI involves metabolic and structural changes.

The frontal cortex showed regions of hypermetabolism and hypometabolism. The frontal cortex works in association with other cortical areas and performs diverse functions such as facilitating attention to incoming stimuli from the primary sensory regions.[10] Its close functional relation to other sensorimotor areas could be an explanation of varied glucose metabolism in several areas within this lobe. It also participates with other brain regions in aspects of learning and memory, attention, and motivation.[10] Lack of motivation and depression caused by the disease burden and more dependency on others to perform daily tasks could be an explanation of the same. Many previously conducted studies have also shown decreased grey matter volume in the prefrontal cortical areas which parallels our results. In a study done by Yoon *et al*. significant structural and functional abnormalities were seen in the prefrontal cortex.[11] Furthermore, Wrigley *et al*. reported that patients with SCI had significant grey matter atrophy in the medial prefrontal cortex.[12] Chen *et al*. found bilateral grey matter volume loss in the orbitofrontal cortex (OFC), part of the frontal cortex, could have possibly shown changes because it is an important relay of the limbic system regulating feelings, generating reward activity, emotional states, and cognitive function decision making.[13,14] OFC in patients with SCI could be associated with depression and with emotional and cognitive impairment after the injury. Chen further suggested that the atrophy increased with the injury duration.[13]

Few studies have shown a decrease in the Gross merchandise value (GMV) primary motor cortex (M1)[12,13] while on the contrary, some other studies done elsewhere showed no such evidence.[15-19] In this study, there were no appreciable differences in the glucose metabolism in the primary motor areas (M1), in SCI patients compared with controls. Collaterals from the adjacent cells can lead to the continued activation of the axotomized cell and could

Statistics: p-values adjusted for search volume

set-level p	set-level c	cluster-level p corrected	cluster-level k_E	cluster-level p uncorrected	voxel-level p FWE-corr	voxel-level p FDR-corr	voxel-level T	voxel-level $(Z_=)$	voxel-level p uncorrected	mm	mm	mm
1.000	16	0.924	1585	0.050	0.001	0.001	8.29	5.59	0.000	40	6	-44
		0.004	9074	0.000	0.025	0.003	6.50	4.85	0.000	-4	-4	60
					0.301	0.011	5.11	4.14	0.000	10	-2	66
					0.305	0.011	5.10	4.13	0.000	8	4	40
		0.009	7772	0.000	0.054	0.005	6.08	4.65	0.000	-42	4	-42
					0.131	0.007	5.60	4.40	0.000	-54	-44	30
					0.583	0.017	4.64	3.86	0.000	-34	20	-40
		0.328	3284	0.008	0.072	0.005	5.92	4.57	0.000	22	4	10
					0.232	0.009	5.27	4.22	0.000	30	26	-18
					0.976	0.033	3.85	3.35	0.000	18	18	-20
		1.000	785	0.154	0.365	0.012	4.99	4.07	0.000	-18	6	10
					1.000	0.118	2.78	2.55	0.005	-32	-14	4
		1.000	87	0.649	0.987	0.037	3.77	3.29	0.001	-18	70	8
					1.000	0.104	2.88	2.63	0.004	-26	66	8
		0.810	1947	0.032	0.987	0.037	3.76	3.29	0.001	50	-56	32
					1.000	0.055	3.41	3.04	0.001	52	-46	26
					1.000	0.062	3.31	2.96	0.002	56	-54	-2
		0.997	995	0.111	1.000	0.062	3.31	2.96	0.002	-40	30	4
					1.000	0.063	3.29	2.95	0.002	-38	58	-10
					1.000	0.069	3.22	2.90	0.002	-44	36	-12
		1.000	67	0.695	1.000	0.110	2.83	2.60	0.005	42	-74	16
		1.000	344	0.339	1.000	0.123	2.75	2.53	0.006	16	68	20
					1.000	0.127	2.72	2.51	0.006	18	58	24
					1.000	0.318	1.95	1.86	0.031	4	66	18
		1.000	287	0.384	1.000	0.124	2.74	2.52	0.006	40	-54	56
		1.000	146	0.543	1.000	0.146	2.61	2.42	0.008	-40	10	36
		1.000	74	0.678	1.000	0.150	2.59	2.40	0.008	-36	58	18
					1.000	0.396	1.75	1.68	0.046	-42	56	6
		1.000	112	0.600	1.000	0.152	2.58	2.40	0.008	-42	-42	-38
		1.000	79	0.667	1.000	0.171	2.49	2.32	0.010	68	-12	4
		1.000	84	0.656	1.000	0.247	2.18	2.06	0.020	14	34	10

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 1.71, p = 0.049 (1.000) {degrees of freedom} = [1.0, 23.0]
Extent threshold: k = 50 voxels, p = 0.742 FWHM = 15.1 15.3 16.0 mm mm mm; 7.5 7.6 8.0 {voxel}
Expected voxels per cluster, <k> = 406.841 Volume: 1753000 = 219125 voxels = 434.6 resels
Expected number of clusters, <c> = 38.16   Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 459.03 ·
Expected false discovery rate, <= 0.41

Figure 3: Relatively higher glucose uptake in patients with spinal cord injury compared with controls. x,y and z coordinates in Talairach space; Z =Z score of statistical parametric mapping; P corr= Corrected p value; P uncorr=uncorrected p value; T= T value

Statistics: p-values adjusted for search volume

set-level p	set-level c	cluster-level p corrected	cluster-level k_E	cluster-level p uncorrected	voxel-level p FWE-corr	voxel-level p FDR-corr	voxel-level T	voxel-level $(Z_=)$	voxel-level p uncorrected	mm	mm	mm
1.000	8	0.000	38328	0.000	0.003	0.008	7.63	5.34	0.000	58	-18	58
					0.283	0.062	5.15	4.16	0.000	64	-16	-36
					0.308	0.062	5.10	4.13	0.000	20	-16	-16
		1.000	285	0.385	0.984	0.064	3.80	3.31	0.000	-54	-24	58
		1.000	251	0.416	0.996	0.067	3.62	3.18	0.001	-66	-48	38
					1.000	0.080	3.15	2.84	0.002	-58	-62	42
					1.000	0.240	1.83	1.76	0.039	-48	-76	42
		1.000	96	0.630	0.998	0.069	3.53	3.12	0.001	-68	-20	32
		1.000	190	0.483	1.000	0.071	3.40	3.03	0.001	-66	-10	-24
		0.959	1421	0.062	1.000	0.083	3.06	2.78	0.003	-8	48	-16
					1.000	0.089	2.94	2.68	0.004	38	52	4
					1.000	0.129	2.50	2.33	0.010	10	50	0
		1.000	112	0.600	1.000	0.087	2.99	2.72	0.003	-18	28	62
		1.000	235	0.432	1.000	0.090	2.93	2.68	0.004	-34	30	36

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 1.71, p = 0.049 (1.000) {degrees of freedom} = [1.0, 23.0]
Extent threshold: k = 50 voxels, p = 0.742 FWHM = 15.1 15.3 16.0 mm mm mm; 7.5 7.6 8.0 {voxel}
Expected voxels per cluster, <k> = 406.841 Volume: 1753000 = 219125 voxels = 434.6 resels
Expected number of clusters, <c> = 38.16   Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 459.03 ·
Expected false discovery rate, <= 0.27

Figure 4: Relatively lower glucose uptake in patients with spinal cord injury compared with controls. x,y and z coordinates in talairach space; Z =Z score of statistical parametric mapping; P corr= Corrected p value; P uncorr=uncorrected p value; T= T value

be one possible explanation for no change in metabolic activity in the M1 region.[20]

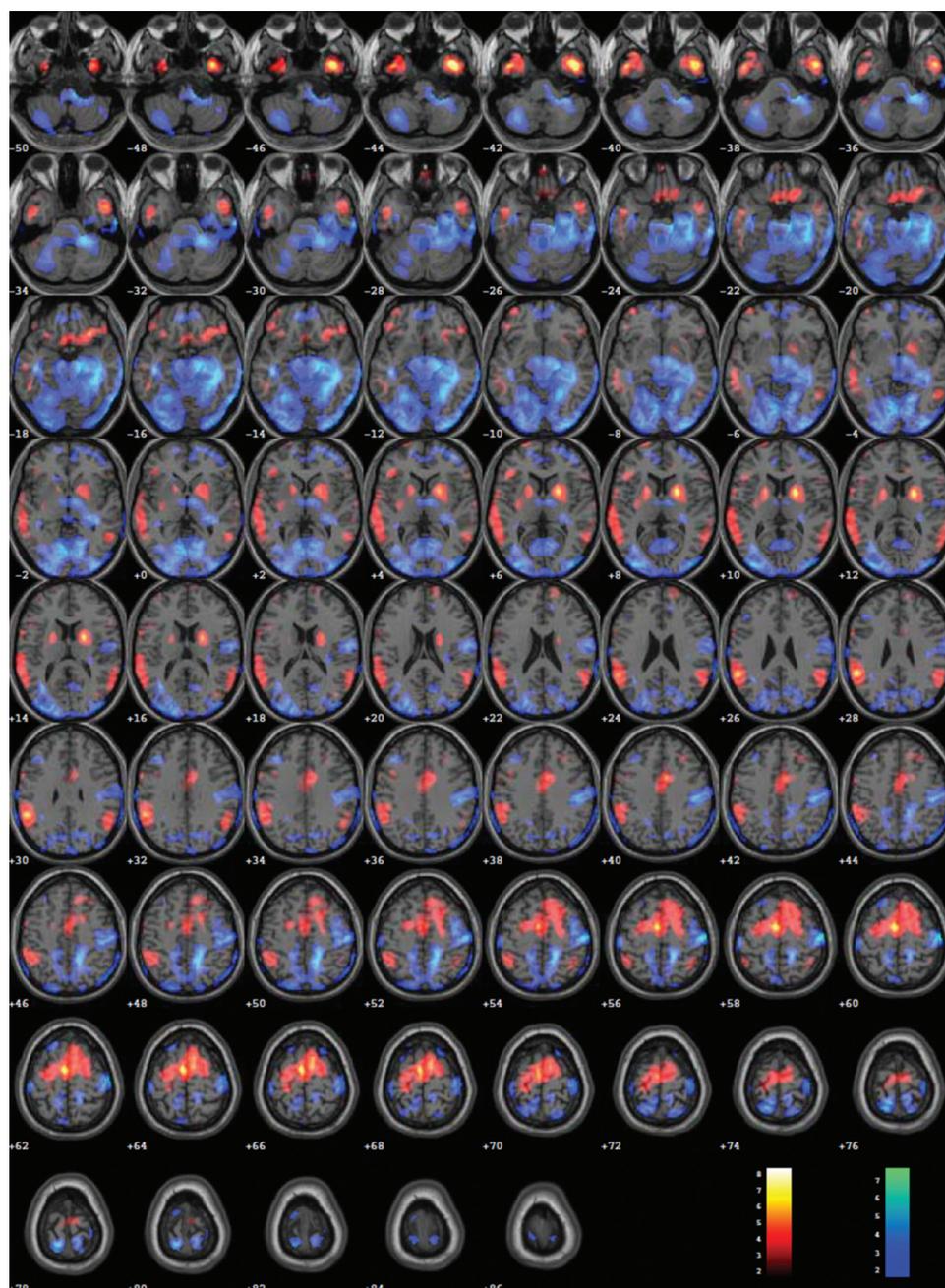Our study revealed decreased glucose metabolism in the postcentral gyrus similar to previously published

Figure 5: Slice overlay images in transaxial sections using the data represented in Hot and Winter color scales

literature.[16,18] In the somatosensory areas, a direct injury doesn't happen rather it is a result of deafferentation after SC trauma. Animal models in such cases have shown a fraction of brain shrinkage. This thus could be an explanation for altered function. Wallerian degeneration is another possible explanation.[20] Henderson *et al.* in their study via measuring the GMV showed changes in somatosensory areas and also suggested that reorganization such as the medial shift in the area of little finger representation occupying greater areas previously occupied by lower limbs lowered the further GMV changes.[21]

This study showed increased glucose metabolism in the bilateral SMA, cerebellum, and putamen. GMV in SMA was shown to be decreased in a study done by Jutzeler *et al.*[22] The mental stimulation of motor tasks and the ideation of walking can activate such areas.[23] Thus, the increased metabolism in the bilateral SMA, cerebellum, and putamen found in our study were likely due to the preparation and execution of motor tasks which the patients were unable to execute due to paraplegia. An old study done in 1997 by Roelecke showed increased glucose metabolism in SMA and putamen which matches with our results.[24]

Hou *et al.* in their study discovered that GMV was decreased in the primary motor cortex, primary somatosensory cortex, and SMA.[16] The inconsistencies between the results of different studies led Hou *et al.* to suspect that prolonged exposure to rehabilitation exercise or medication, and methodological differences between studies may contribute to the consistencies across studies.[16]

Our study also showed an increase in glucose metabolism in areas of the parietal lobes and cerebellum. Such outcomes were also seen in the study by Curt *et al.* however, showed raised uptake when the patient was asked to do hand movements in paraplegics which were compared against healthy controls.[25] The most likely explanation thus is due to higher intention to move limbs in comparison to normal controls. The dependence on upper limbs increases in these paraplegic patients to execute bodily movements.

Additionally, Wernicke's area (superior temporal gyrus) and parts of Broca's area in the left inferior frontal gyrus (pars triangularis) showed increased glucose metabolism. We believe as there is a limited motor activity in paraplegics, the brain in order to retain or increase the cognitive inputs, has to rely on other sensory systems like auditory and visual cortices. This study showed insignificantly decreased metabolism of glucose in the ACC ($T = 2.09$ and Z score not generated) and hippocampus. Some authors have reported GMV reduction in the dorsal ACC in their MRI studies.[12,13,26,22] Yoon *et al.* demonstrated both structural and functional abnormality via analyzing using both PET-CT and MRI modalities in the dACC region of the brain. Volume reduction in anatomical studies may be compared to a decrease in metabolism in functional PET studies.[11] The dorsal ACC mainly plays role in conflict monitoring between competing stimuli and provides a continuously updated prediction of expected cognitive demand to optimize future behavioral responses.[27] In SCI patients, sensory inputs have been found to be partially or fully lost. Thus the reduction in the GMV has been related to disuse atrophy in these patients.[28,29] In our study, the ACC showed lower glucose metabolism, however, no Z score was assigned by SPM, most likely due to shorter time intervals between jury and scanning.

Limitations in this study were that the number of subjects with SCI included in this study is low and the study was not done at different time intervals to establish the chronology of neuroplastic changes.

Conclusion

The changes in glucose metabolism post-SCI suggest remodelling of brain functional areas. Relatively hypermetabolism was noted in brain regions involved in attention and initiation of movement and may be related to secondary disinhibition of these regions. Hypometabolism can be attributed to disuse atrophy and neuroplastic changes in the brain.

Conflicts of interest

There are no conflicts of interest.

References

1. Dall'Orso S, Steinweg J, Allievi AG, Edwards AD, Burdet E, Arichi T. Somatotopic mapping of the developing sensorimotor cortex in the preterm human brain. Cereb Cortex 2018;28:2507-15.
2. Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. Science 1995;270:305-7.
3. Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. Nat Rev Neurosci 2009;10:647-58.
4. Barnes SJ, Finnerty GT. Sensory experience and cortical rewiring. Neuroscientist 2010;16:186-98.
5. Wall PD, Egger MD. Formation of new connexions in adult rat brains after partial deafferentation. Nature 1971;232:542-5.
6. Kumar R, Lim J, Mekary RA, Rattani A, Dewan MC, Sharif SY, *et al.* Traumatic spinal injury: Global epidemiology and worldwide volume. World Neurosurg 2018;113:e345-63.
7. Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: What learns a worldwide literature survey? Spinal Cord 2006;44:523-9.
8. Migliorini CE, New PW, Tonge BJ. Quality of life in adults with spinal cord injury living in the community. Spinal Cord 2011;49:365-70.
9. Mergenthaler P, Lindauer U, Dienel GA, Meisel A. Sugar for the brain: The role of glucose in physiological and pathological brain function. Trends Neurosci 2013;36:587-97.
10. Tamminga CA, Buchsbaum MS. Frontal cortex function. Am J Psychiatry 2004;161:2178.
11. Yoon EJ, Kim YK, Shin HI, Lee Y, Kim SE. Cortical and white matter alterations in patients with neuropathic pain after spinal cord injury. Brain Res 2013;1540:64-73.
12. Wrigley PJ, Press SR, Gustin SM, Macefield VG, Gandevia SC, Cousins MJ, *et al.* Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. Pain 2009;141:52-9.
13. Chen Q, Zheng W, Chen X, Wan L, Qin W, Qi Z, *et al.* Brain gray matter atrophy after spinal cord injury: A voxel-based morphometry study. Front Hum Neurosci 2017;11:211.
14. Rolls ET, Cheng W, Feng J. The orbitofrontal cortex: Reward, emotion and depression. Brain Commun 2020;2:fcaa196.
15. Mikulis DJ, Jurkiewicz MT, McIlroy WE, Staines WR, Rickards L, Kalsi-Ryan S, *et al.* Adaptation in the motor cortex following cervical spinal cord injury. Neurology 2002;58:794-801.
16. Hou JM, Yan RB, Xiang ZM, Zhang H, Liu J, Wu YT, *et al.* Brain sensorimotor system atrophy during the early stage of spinal cord injury in humans. Neuroscience 2014;266:208-15.
17. Crawley AP, Jurkiewicz MT, Yim A, Heyn S, Verrier MC, Fehlings MG, *et al.* Absence of localized grey matter volume

changes in the motor cortex following spinal cord injury. Brain Res 2004;1028:19-25.

18. Jurkiewicz MT, Crawley AP, Verrier MC, Fehlings MG, Mikulis DJ. Somatosensory cortical atrophy after spinal cord injury: A voxel-based morphometry study. Neurology 2006;66:762-4.

19. Mole TB, MacIver K, Sluming V, Ridgway GR, Nurmikko TJ. Specific brain morphometric changes in spinal cord injury with and without neuropathic pain. Neuroimage Clin 2014;5:28-35.

20. Freund P, Weiskopf N, Ashburner J, Wolf K, Sutter R, Altmann DR, *et al.* MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: A prospective longitudinal study. Lancet Neurol 2013;12:873-81.

21. Henderson LA, Gustin SM, Macey PM, Wrigley PJ, Siddall PJ. Functional reorganization of the brain in humans following spinal cord injury: Evidence for underlying changes in cortical anatomy. J Neurosci 2011;31:2630-7.

22. Jutzeler CR, Huber E, Callaghan MF, Luechinger R, Curt A, Kramer JL, *et al.* Association of pain and CNS structural changes after spinal cord injury. Sci Rep 2016;6:18534.

23. Porro CA, Francescato MP, Cettolo V, Diamond ME, Baraldi P, Zuiani C, *et al.* Primary motor and sensory cortex activation during motor performance and motor imagery: A functional magnetic resonance imaging study. J Neurosci 1996;16:7688-98.

24. Roelcke U, Curt A, Otte A, Missimer J, Maguire RP, Dietz V, *et al.* Influence of spinal cord injury on cerebral sensorimotor systems: A PET study. J Neurol Neurosurg Psychiatry 1997;62:61-5.

25. Curt A, Bruehlmeier M, Leenders KL, Roelcke U, Dietz V. Differential effect of spinal cord injury and functional impairment on human brain activation. J Neurotrauma 2002;19:43-51.

26. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349-56.

27. Sheth SA, Mian MK, Patel SR, Asaad WF, Williams ZM, Dougherty DD, *et al.* Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. Nature 2012;488:218-21.

28. Eidelberg E, Nguyen LH, Polich R, Walden JG. Transsynaptic degeneration of motoneurones caudal to spinal cord lesions. Brain Res Bull 1989;22:39-45.

29. Bose P, Parmer R, Reier PJ, Thompson FJ. Morphological changes of the soleus motoneuron pool in chronic midthoracic contused rats. Exp Neurol 2005;191:13-23.