Original Article

A Study of Diffusion Tensor Imaging in Central Post-Stroke Pain: Traveling Beyond the Pain Pathways

Camelia Porey, Suprava Naik[1], Sanjeev Kumar Bhoi, Menka Jha, Priyanka Samal

Departments of Neurology and [1]Radiodiagnosis, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

Abstract

Introduction: Central post-stroke pain (CPSP), seen in the aftermath of a stroke, is an underdiagnosed entity but quite a disabling complication. All the postulated theories regarding the pathogenesis of CPSP point to its origin in the central pain pathways. However, this study attempts to demonstrate the role of other contributing areas in the generation of CPSP. **Materials and Methods:** In this single-center tertiary care hospital-based study, 24 patients with both ischemic and hemorrhagic strokes of variable durations were recruited, and Magnetic Resonance Imaging (MRI) imaging with diffusion tensor imaging (DTI) acquisition was done. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of the spinothalamic tract (STT), corticospinal tract (CST), superior thalamic radiation (STR), basal ganglia (BG), and primary somatosensory cortex (SSC) were compared between normal and abnormal sides and also in extrathalamic lesions separately. **Results:** Significant differences with lower FA were noted in STT, CST, STR, and SSC and higher ADC values in BG, STR, CST, and SSC on comparison between the normal and lesion sides. On individual sub-analysis, ischemic stroke had significant changes in the FA value of CST and the ADC value of STR and CST, while hemorrhagic stroke had significant changes in the FA and ADC values of STR and SSC, as well as the FA value of STT. In the analysis of the extrathalamic strokes, significance persisted in all the studied parameters except the BG. The CST abnormalities were evident even in patients with clinical motor improvement. On multivariate analysis, visual analogue scale score severity was correlated with thalamic lesions. **Conclusion:** Contrary to the belief that STT is solely responsible for CPSP, the role of CST, STR, BG, and SSC as contributing areas is evident from this study and may be more well established if studied in a larger population.

Keywords: Apparent diffusion coefficient, corticospinal tract, extrathalamic stroke, fractional anisotropy, somatosensory cortex, superior thalamic radiation

Introduction

Central post-stroke pain (CPSP) is defined by the International Association for the Study of Pain (IASP) as the pain that occurs as a direct consequence of a stroke when the lesion occurs due to damage to the somatosensory system.[1] CPSP is considered to be a persistent neuropathic pain of central origin occurring post-stroke that cannot be attributed to peripheral (nociceptive or neurogenic) origins.[2] Descriptions of CPSP can range in various forms, from aching, dull, and throbbing to sharp, stabbing, shooting, freezing, or burning pain with variable onset from a few days to a few months after stroke onset. The pooled prevalence of CPSP in patients with stroke at any location has been shown to be around 11%, which can increase to more than 50% in the subgroups with medullary or thalamic strokes.[3]

Originally, "Thalamic syndrome" was described by Déjerine and Egger in 1903 and formally defined in 1938 by George Riddoch with the description: "spontaneous pain and painful overreaction to objective stimulation resulting from lesions confined to the substance of the central nervous system, including dysesthesia of a disagreeable kind."[4] Several theories regarding the generation of CPSP have been suggested over time, involving the lateral pain system, which is a sensory component and pain discrimination carried by the lateral spinothalamic tract (STT), and the medial pain system, which is a component of affective and motivational pain carried by the medial STT.[5]

The central sensitization theory states that CNS lesions cause loss of facilitation and increased neuronal excitability. The disinhibition theory describes the imbalances between the interactions of brainstem nuclei, spinal cord, and thalamocortical circuits. Change in the plasticity of the STT as demonstrated by functional MRI, thalamic hyperactivity produced by an increased burst of firing neurons in the ventral caudal nucleus, and the dynamic reverberation theory suggesting derangement of the oscillatory pattern in the thalamocortical circuit are a few other theories of CPSP.[5]

Address for correspondence: Dr. Sanjeev Kumar Bhoi, Department of Neurology, All India Institute of Medical Sciences, Bhubaneswar - 751 019, Odisha, India.
E-mail: sanjeev_bhoi@rediffmail.com

Submitted: 30-Apr-2023 **Revised:** 10-Aug-2023 **Accepted:** 13-Aug-2023
Published: 25-Sep-2023

DOI: 10.4103/aian.aian_378_23

Thus, contrary to the conventional belief of involvement of thalamus and STT fibers in producing CPSP, morphological changes in the other white matter tracts connecting the thalamus and sensory and motor cortical areas may also be responsible.[6] In this study, we attempted to evaluate changes in the different areas consisting of the STT, corticospinal tract (CST), superior thalamic radiation (STR), basal ganglia (BG) (putamen and globus pallidus), and primary somatosensory cortex (SSC) in CPSP patients.

Materials and Methods

This was a hospital-based prospective case-control study conducted in a single-center tertiary care hospital in India. The study protocol was approved by the Institutional Ethics Committee (IEC/AIIMS BBSR/PG Thesis/2020-21/13). Twenty-four patients presenting with CPSP with a past history of stroke underwent imaging for assessment. Adult patients presenting with the first-ever incidence of stroke, either ischemic or hemorrhagic and moderate-to-severe CPSP, quantified by a score ≥5 on the visual analogue scale (VAS) out of 10, were included in the study. Venous and cardioembolic strokes were excluded. Each patient served as his own control as an imaging comparison was made between the involved and uninvolved sides of pain. The imaging was done on the first presentation to the hospital, irrespective of the time of onset of stroke or duration of existing CPSP.

MRI protocol

All the patients underwent MRI of the brain in a 3T-MRI scanner (Discovery 750W, GE Healthcare) using a 40-channel head coil with the following protocol: Axial T1WI: (TR/TE: 700/24.0 ms; FOV ~ 22.0 × 20 cm; NEX: 2.00); Axial T2WI: (TR/TE: 5757/85.0 ms; FOV ~ 22.0 × 20 cm NEX: 1.00); Axial FLAIR: (TR/TE: 9000/90.0 ms; FOV 22.0 × 20 cm, NEX: 2.00, TI-2600); Axial DWI:(TR/TE: 10143/77.4 ms; two b-values: 0, 1000); 3D Axial SWAN: (TR/TE: 47/25 ms; NEX: 1); and 3D Axial T1- BRAVO: (TR/TE: 7.8/3.0 ms; NEX: 1.00; Slice thickness ~ 0.5 mm). All the 2D sequences were 5 mm thick with a 0.5 mm interslice gap. Axial diffusion tensor imaging (DTI): (TR/TE: 8000/76.7 ms; diffusion direction: 27, NEX: 1.00; slice thickness: 3.0 mm with no interslice gap; FOV: 22x20 sq cm.).

DTI acquisition and image processing

Post-processing of DTI was done in the Readyview tool of the AWS system. Regions of interest (ROIs) were kept for STT in the bilateral posterolateral medulla, CST at the level of the anterior pons, STR at the ventrolateral thalami, BG (putamen and globus pallidus), and primary SSC (the post-central gyrus of the parietal lobe) in the colored fractional anisotropy (FA) map [Figure 1]. The ROI was then cloned to the FA and apparent diffusion coefficient (ADC) images of the corresponding series of images, and the average values of FA and ADC were noted. Values of ADC and FA were recorded for both the symptomatic and asymptomatic sides.

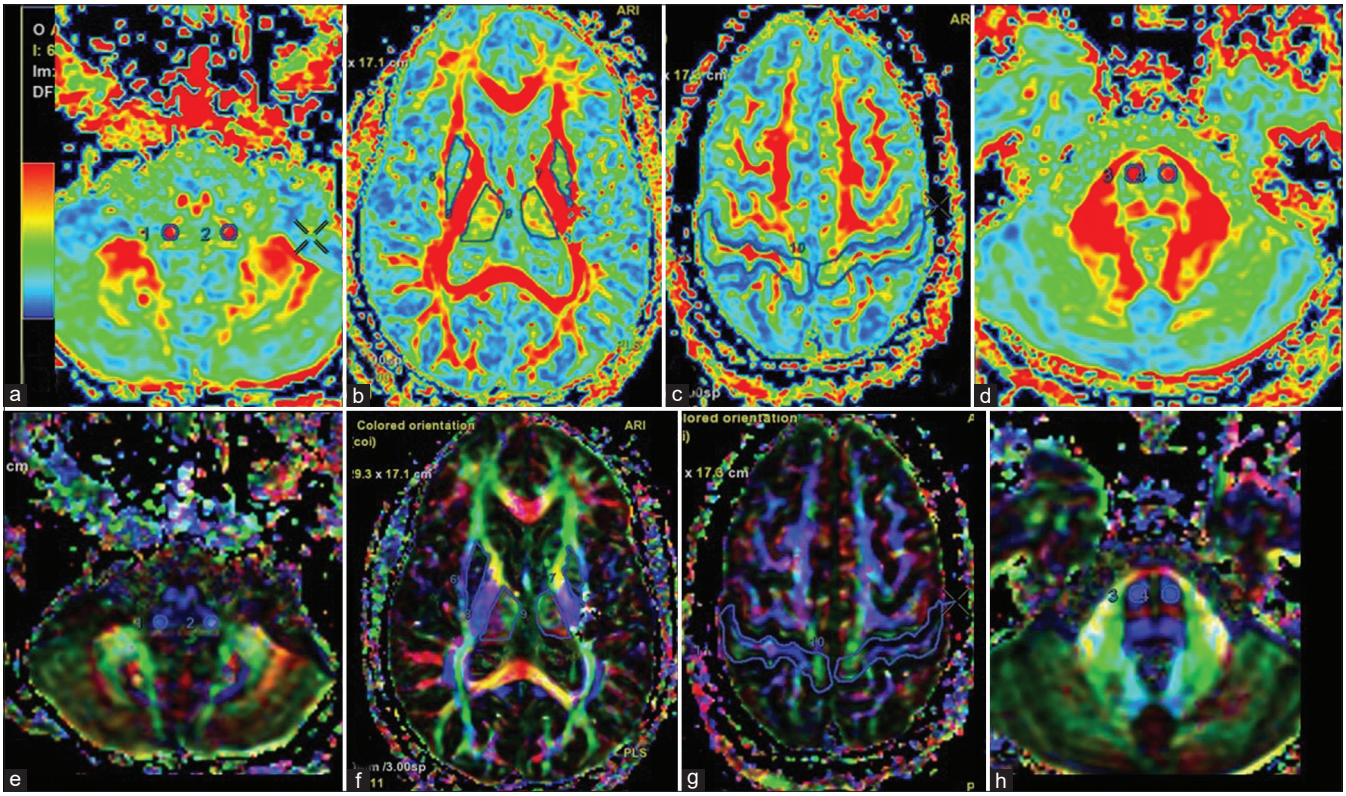

Figure 1: Colored FA maps of DTI images show the placement of ROIs in the posterolateral medulla (a), bilateral thalami and BG (b), parietal cortex (c), and corticospinal tract (d) at the level of the pons. 2nd row (e–h) red green and blue colored orientation of the corresponding areas of the 1st row

All statistical analyses were performed using SPSS software for Windows version 23. A *P*- value of <0.05 was considered significant with a 95% confidence interval.

Results

Among the 24 patients included in the study, 11 had ischemic and 13 had hemorrhagic strokes, followed by CPSP. The mean age was 62.54 ± 9.71 years, with a distribution of 13 (54.1%) males and 11 (45.8%) females. Ischemic stroke was present in 11 (45.8%) and hemorrhagic stroke in 13 (54.1%) patients, with right-sided stroke in 17 (70.8%). The mean interval from stroke to onset of CPSP was 6.87 ± 13.76 months, and the mean duration of CPSP before imaging was 6.82 ± 11.07 months. The VAS score at baseline was 7.38 ± 0.87. Nine (37.5%) patients had thalamic strokes, and the rest had extrathlamic lesions. Small vessel changes, the presence of microhemorrhages, and bilateral lesions on imaging were also noted [Table 1].

On comparing the values between the normal and abnormal sides, there were significantly lower FA values for STR (P = 0.016), CST (P = 0.002), STT (P = 0.001), and SSC (P = 0.001) on the abnormal side. Also, on comparing the ADC values, significantly higher ADC values were recorded in BG (P = 0.049), STR (P = 0.001), CST (P = 0.002), and SSC (P = 0.012) [Table 2].

On sub-analysis of each type of stroke in the ischemic group, significant differences in the abnormal side were noted in FA of CST and ADC of STR and CST. In the hemorrhagic group, FA and ADC values of STR, FA of STT, and FA and ADC values of SSC were found to be significantly changed on the lesional side.

On further attempting to analyze the areas of possible involvement in CPSP among the extrathalamic strokes, significant differences were obtained in FA values in STR (P = 0.031), CST (P = 0.001), STT (P = 0 002), and SSC (P = 0.006) and in the ADC values of STR (P = 0.012), CST (P = 0.012), STT (P = 0.057), and SSC (P = 0.006) [Table 3]. The graphical representation of all the results is given in Figure 2.

A multivariate analysis to establish the propensity for thalamic or extrathalamic location of the lesions by one-way multivariate analysis of variance (one-way MANOVA) revealed that among the parameters studied (age, type of stroke, stroke to CPSP onset duration, side of stroke, and VAS score), VAS score severity was correlated with thalamic lesions (R^2 =0.216, P = 0.022)

Discussion

DTI is an imaging modality that yields quantitative measures for tissue water mobility as a function of the direction of water motion and is probed by the application of diffusion-sensitization gradients in multiple

Table 1: Demographic profile of the study population

Variables	Population value
Age (years)	62.54±9.71
Gender	
Male	13 (54.1%)
Female	11 (45.8%)
Type of stroke	
Ischemic	11 (45.8%)
Hemorrhagic	13 (54.1%)
Thalamic	9 (37.5%)
Extrathalamic	15 (62.5%)
Maximum power on the affected side (MRC grade 0–5) at time of MRI evaluation	3.79±0.16
Onset of CPSP (months)	6.87±13.76
Duration of CPSP	6.82±11.07
CPSP	
Right side	17 (70.8%)
Left side	7 (29.1%)
Baseline VAS score	7.38±0.87
Small vessel changes	15 (62.5%)
Microhaemorrhages	9 (37.5%)
Bilateral involvement	8 (33.3%)

CPSP=Central post-stroke pain, FA=fractional anisotropy, ADC=apparent diffusion coefficient, BG=basal ganglia, CST=corticospinal tract, STR=superior thalamic radiation, STT=spinothalamic tract, SSC=primary somatosensory cortex

Table 2: Wilcoxon signed rank test comparing the overall DTI parameters of the normal and abnormal sides. (n=24, upper half) and individually significant DTI parameters in ischaemic and hemorrhagic stroke (lower half)

Variables	Normal side value	Abnormal side value	*P*
BG FA	0.207±0.051	0.207±0.046	0.954
BG ADC	8.506±1.614	9.004±1.595	0.049
STR FA	0.283±0.079	0.261±0.075	0.016
STR ADC	8.477±0.919	9.714±2.394	0.001
CST FA	0.501±0.057	0.446±0.105	0.002
CST ADC	7.532±0.657	8.385±1.917	0.002
STT FA	0.468±0.062	0.429±0.075	0.001
STT ADC	7.207±0.881	7.523±0.908	0.084
SSC FA	0.275±0.030	0.245±0.251	0.001
SSC ADC	7.926±0.735	9.178±3.296	0.012
Relevant DTI parameters			
Ischemic stroke (n=11)			
STR ADC	8.663±1.158	9.162±1.244	0.041
CST FA	0.498±0.059	0.409±0.108	0.009
CST ADC	7.700±0.479	8.486±0.882	0.013
Hemorrhagic stroke (n=13)			
STR FA	0.248±0.064	0.250±0.065	0.025
STR ADC	8.320±0.666	10.18±3.029	0.004
STT FA	0.471±0.051	0.435±0.046	0.007
SSC FA	0.281±0.034	0.255±0.030	0.005
SSC ADC	7.683±0.562	8.263±0.716	0.009

CPSP=Central post stroke pain, FA=fractional anisotropy, ADC=apparent diffusion coefficient, BG=basal ganglia, CST=corticospinal tract, STR=superior thalamic radiation, STT=spinothalamic tract, SSC=primary somatosensory cortex

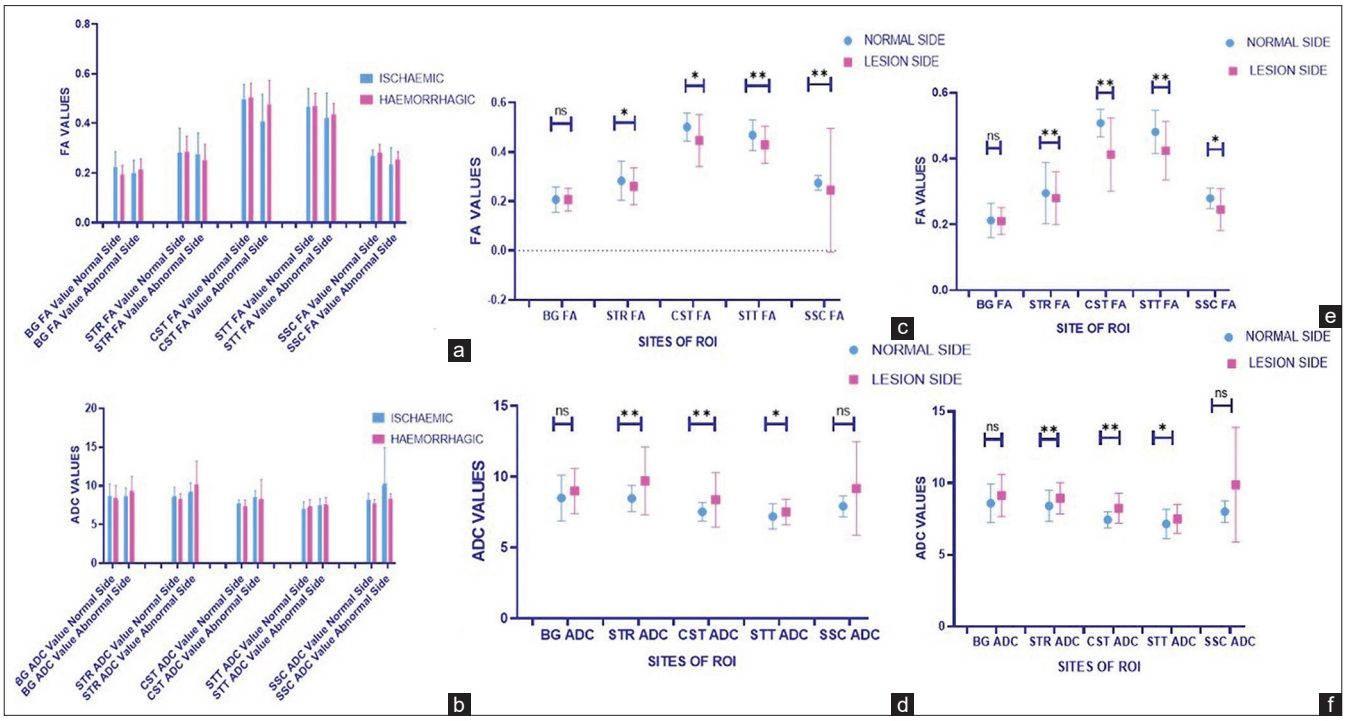

Figure 2: (a) FA values for the normal and abnormal sides in BG, STR, CST, STT, and SSC. (b) ADC values for normal and abnormal sides in BG, STR, CST, STT, and SSC. (c) Summary plot showing the overall mean and standard deviation of the FA values of individual ROIs. (d) Summary plot showing the overall mean and standard deviation of ADC values for individual ROIs. (e) Summary plot showing the mean and standard deviation of the FA values in individual ROIs in extrathalamic strokes. (f) Summary plot showing the mean and standard deviation of ADC values in individual ROIs in extrathalamic strokes. *P* -values (ns = non-significant, * = <0.05,** = <0.01, *** = <0.001), FA = fractional anisotropy, ADC = apparent diffusion coefficient, BG = basal ganglia, STR = superior thalamic radiation, CST = corticospinal tract, STT = spinothalamic tract, SSC = primary somatosensory cortex

Table 3: Wilcoxon signed rank test comparing DTI parameters of the normal and abnormal sides in extrathalamic strokes. (*n*=15)

Variable	Normal side	Lesion side	*P*
BG FA	0.212±0.052	0.210±0.041	0.932
BG ADC	8.592±1.339	9.144±1.476	0.099
STR FA	0.295±0.093	0.280±0.080	0.031
STR ADC	8.416±1.074	8.955±1.096	0.012
CST FA	0.508±0.042	0.412±0.111	0.001
CST ADC	7.448±0.569	8.250±1.050	0.012
STT FA	0.481±0.066	0.424±0.089	0.002
STT ADC	7.162±1.013	7.506±1.013	0.057
SSC FA	0.279±0.031	0.245±0.064	0.006
SSC ADC	8.019±0.754	9.881±4.007	0.006

CPSP=Central post stroke pain, FA=fractional anisotropy, ADC=apparent diffusion coefficient, BG=basal ganglia, CST=corticospinal tract, STR=superior thalamic radiation, STT=spinothalamic tract, SSC=primary somatosensory cortex

directions.[7] DTI measures such as FA explain the strength of the orientational organization of microstructures; radial diffusivity (RD) and ADC signify sensitivity to myelin/axon non-specific physiopathology states. In neurological conditions, reduced FA and increased ADC or RD are attributed to demyelination, loss of axons, or an interrupted connection.[8]

DTI for demonstrating white matter tracts in various forms of pain exists in previous literature. In a narrative, Yang *et al*.[9] suggested that DTT may be beneficial in identifying the pathophysiological mechanisms of neuropathic pain of various origins, including central pain caused by brain injuries, trigeminal neuralgia, sciatica, temporomandibular disorders, episodic cluster headache, traumatic brain injury-induced chronic headache, ankle muscle proprioception in low back pain, chronic irritable bowel syndrome, chronic pelvic pain, cervical spondylosis-induced pain, chronic musculoskeletal pain, and analgesia in response to pain stimuli disorders. Sundgren *et al*.,[7] in their study of fibromyalgia patients, termed the structures of the primary and secondary somatosensory cortices, the insula, the anterior cingulate, the thalamus, the dorsal lateral prefrontal cortex, and the BG collectively as the "pain matrix." Among utility in neurointervention, DTI of thalamic fibers has been used to monitor changes before and after deep brain stimulation of ventroposterolateral nucleus of the thalamus in chronic pain.[10]

Among different studies for motor deficit in stroke, in a review by Moura *et al*. FA measured at an early phase after stroke was stated as a potential predictor of motor recovery in the majority of the studies.[11,12] Werring *et al*.,[13] in their study, demonstrated reduced FA associated with cerebral infarction in CST remote from the lesion in ischemic stroke. Puig *et al*.[14] stated that recovery of motor function involves remodeling of

the CST proper and/or a greater reliance on alternative motor tracts through plasticity. DTI-metrics represent promising clinical biomarkers to predict motor recovery and to monitor and predict the response to neurorehabilitative interventions.

There are limited studies concerning the correlation of the CPSP with the DTI parameters. Seghier *et al*. reconstructed DTI maps in a hemorrhagic stroke patient with CPSP that showed a marked loss of anisotropy in the posterior third of the posterior arm of the right internal capsule as a result of the residual hemorrhagic cavity. There was a reduction in the fiber density of the lateral thalamocortical tract within the spinothalamocortical nociceptive system, whereas the spinothalamic and the medial thalamocortical fibers were spared.[15] In a study by Hong *et al.*, in a cohort of 34 patients with preserved STT and 18 patients with disrupted STT in hemorrhagic stroke, the prevalence of CPSP was higher in the former group. A decrease in FA value and an increase in MD value of STT were noted in both the CPSP and non-CPSP subgroups compared with the control. The same authors in another cohort of 30 hemorrhagic stroke patients demonstrated the laterality index, that is, the difference in tract volume (TV) between the affected and the normal hemisphere, to be lower in the CPSP group compared to the non-CPSP group.[16,17] In a mini-review by Jang *et al*., values of the FA and TV of STT were decreased by more than two standard deviations in patients with ischemic stroke compared to normal controls and the authors concluded that STT injury is a pathophysiological mechanism of CPSP in patients with cerebral infarcts.[18,19] In another comparative study by Park *et al*., FA for the STT and STR of the CPSP group were lower than those for the stroke control (without CPSP) and normal control groups. The FA of CST and anterior thalamic radiation (ATR) did not differ between the CPSP and stroke groups. The fiber numbers of CST, STT, ATR, and STR for the CPSP and stroke control groups did not differ from each other.[6]

In our study, we found significantly lower FA values of STR, CST, STT, and SSC and higher ADC values in BG, STR, CST, and SSC between the normal and affected sides, which is in accordance with prior literature, indicating the participation of all the involved pathways in the generation of CPSP. This pattern was maintained when analyzed for the extrathalamic strokes as well, signifying the pivotal role of these areas. Individually, CST involvement was more observed in the ischemic group, whereas a prominent involvement of the STR, STT, and SSC was noted in the hemorrhagic group. The cause of this differential involvement in the subgroups may depend upon the location of the lesion, prior small vessel changes, or the variable duration of the stroke to CPSP or CPSP to imaging duration, all of which can modify the DTI parameters. But whether the involved areas are characteristically predisposed to the generation of CPSP as a signature of the type of stroke remains to be seen if studies are conducted in a larger cohort. The concurrence of CST abnormalities in our patients, despite motor improvement in most of them, clinically signifies neuronal plasticity and alternate motor pathway regeneration.

Our study is, to the best of our knowledge, the first to demonstrate the extensive white matter tract involvement in patients with CPSP irrespective of their duration of stroke and also the first to demonstrate thalamic and other pain fiber involvement in extrathalamic strokes.

A limitation to our study interpretation is that some of our patients had radiologically bilateral lesions and thus may have affected the so-called normal side values, whereas few studies have resorted to DTI parameter measurement in healthy controls for comparison. A second issue is our limited sample size and the cross-sectional observation of the imaging parameters. Further follow-up to document the changes in the studied area would have established a better association.

Conclusion

This study highlights the importance of white matter tracts other than the conventional pain pathways in CPSP and may in the future serve as a predictive biomarker prior to CPSP onset or a prognostic biomarker following any drug or neuromodulation therapy. A larger population-based study may be recruited in this regard for further study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Widyadharma IPE, Tertia C, Wijayanti IAS, Barus JFA. Central post stroke pain: What are the new insights? Rom J Neurol 2021;20. doi: 10.37897/rjn. 2021.1.4.
2. Henry JL, Lalloo C, Yashpal K. Central poststroke pain: An abstruse outcome. Pain Res Manag 2008;13:41-9.
3. Liampas A, Velidakis N, Georgiou T. Prevalence and management challenges in central post-stroke neuropathic pain : A systematic review and meta-analysis. Adv Ther 2020;37:3278-91.
4. Treister AK, Hatch MN, Cramer SC, Chang EY, Diego S, Beach L, *et al*. Demystifying post-stroke pain : From etiology to treatment PM R 2018;9:63-75.
5. Klit H, Finnerup NB, Jensen TS. Central post-stroke pain : Clinical characteristics, pathophysiology, and management. Lancet Neurol 2009;8:857-68.
6. Park JG, Hong BY, Park H-Y, Yoo YJ, Lim SH. Alteration of white matter in patients with central. J Pers Med 2021;417:9-11.
7. Sundgren PC, Petrou M, Harris RE, Fan X, Foerster B. Diffusion-weighted and diffusion tensor imaging in fibromyalgia patients: A prospective study of whole brain diffusivity, apparent diffusion coefficient, and fraction anisotropy in different regions of the brain and correlation with symptom severity. Acad Radiol 2007;14:839-46.
8. Zhang Y, Furst AJ. Brainstem diffusion tensor tractography and clinical applications in pain. Front Pain Res (Lausanne) 2022;3:840328. doi: 10.3389/fpain. 2022.840328.
9. Yang S, Kwon S, Chang MC. The usefulness of diffusion tensor tractography in diagnosing neuropathic pain : A narrative review. Front Neurosci 2021;15:591018. doi: 10.3389/fnins. 2021.591018.
10. Kovanlikaya I, Kaplitt M. Treatment of chronic pain: Diffusion tensor imaging identification of the ventroposterolateral nucleus confirmed with successful deep brain. Stereotact Funct Neurosurg 2014;92:365-71.
11. Moura LM, Luccas R, De Paiva JPQ, Amaro E, Leemans A, Leite C, *et al*. Diffusion tensor imaging biomarkers to predict motor outcomes in stroke : A narrative review. Front Neurol 2019;10:445.

12. Mahmoud BE, Mohammad ME, Serour DK. What can DTI add in acute ischemic stroke patients? Egypt J Radiol Nucl Med 2019;50:67.
13. Werring DJ, Toosy AT, Clark CA, Parker GJ, Barker GJ, Miller DH, *et al*. Difusion tensor imaging can detect and quantify corticospinal tract degeneration after stroke. J Neurol Neurosurg Psychiatry 2000;69:269-72.
14. Puig J, Blasco G, Schlaug G, Stinear CM, Daunis-i-estadella P, Biarnes C, *et al*. Diffusion tensor imaging as a prognostic biomarker for motor recovery and rehabilitation after stroke. Neuroradiology 2017;59:343-51.
15. Seghier ML, Lazeyras F, Vuilleumier P, Schnider A, Carota A. Functional magnetic resonance imaging and diffusion tensor imaging in a case of central poststroke pain. J Pain 2005;6:208-12.
16. Hong JH, Bai DS, Jeong JY, Choi BY. Injury of the spino-thalamo-cortical pathway is necessary for central post- stroke pain. Eur J Neurol 2010;64:163-8.
17. Hong JH, Choi B, Chang CH, Kim SH. The prevalence of central poststroke pain according to the integrity of the Spino-Thalamo-Cortical pathway. Eur J Neurol 2012;67:12-7.
18. Jang SH, Seo JP, Lee SJ. Diffusion tensor tractography studies of central post-stroke pain due to the spinothalamic tract injury: A mini-review. Front Neurol 2019;10:10-5.
19. Jang SH, Lee J, Yeo SS. Central post-stroke pain due to injury of the spinothalamic tract in patients with cerebral infarction: A diffusion tensor tractography imaging study. Neural Regen Res 2017;12:2021-4.