Research Article

Neural plasticity secondary to carpal tunnel syndrome: a pseudo-continuous arterial spin labeling study

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Abstract

Conventional neuroimaging techniques cannot truly reflect the change of regional cerebral blood flow in patients with carpal tunnel syndrome. Pseudo-continuous arterial spinning labeling (pCASL) as an efficient non-invasive neuroimaging technique can be applied to directly quantify the neuronal activities of individual brain regions that show the persistent symptoms owing to its better spatial resolution and increased signal-to-noise ratio. Therefore, this prospective observational study was conducted in 27 eligible female carpal tunnel syndrome, aged 57.7 ± 6.51 years. Psychometric tests, nerve conduction studies and pCASL neuroimaging assessment were performed. The results showed that the relevant activated brain regions in the cortical, subcrotical, and cerebral regions were correlated with numbness, pain, functionality, median nerve status and motor amplitude of median nerve (K = 21–2849, r = –0.77–0.76, P < 0.05). There was a tendency of pain processing which shifted from the nociceptive circuitry to the emotional and cognitive one during the process of chronic pain caused by carpal tunnel syndrome. It suggests the necessity of addressing the ignored cognitive or emotional state when managing patients with carpal tunnel syndrome. Approval for this study was obtained from the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West, China (HKU/HA HKW IRB, approval No. UW17-129) on April 11, 2017. This study was registered in Clinical Trial Registry of The University of Hong Kong, China (registration number: HKUCTR-2220) on April 24, 2017.

Key Words: Boston carpal tunnel questionnaire; carpal tunnel syndrome; cognitive; nerve conduction studies; pain; principal component analysis; pseudo-continuous arterial spin labeling

Chinese Library Classification No. R445; R741; R745

Introduction

As a commonly seen peripheral never entrapment, carpal tunnel syndrome (CTS) is reported to have an overall prevalence of 2–3%, accumulative incidence rate of 8% and around 10% of lifetime risk in general population (Atroshi et al., 1999; Rempel et al., 1999; Werner and Andary, 2002). Alternatively, CTS can be classed as chronic pain disorder, with primary symptoms such as sustained paresthesia, tingling and sometimes it may even generate pain itself (You et al., 1999; Maeda et al., 2016). Nerve conduction studies (NCS) have been commonly used in the diagnosis and severity classification of the disease (Bland, 2000). Meanwhile, the Boston Carpal Tunnel Questionnaire (BCTQ) and Numerical Rating Scale (NRS) are frequently used to describe the comprehensive symptoms and impaired functionality when the disorder occurs (de Carvalho Leite et al., 2006).

In recent years, it has been increasingly recognized that the factors beyond nociceptive input can play an important role in pain perception (Bushnell et al., 2013). Besides, there is clinical evidence suggesting that pain perception can be sustained even after the decline or in the absence of nociceptive stimuli (Baliki and Apkarian, 2015). This is consistent with the Hebbian plasticity mechanisms (Hebb, 1949). It suggests that altered central processing and cortical plasticity could have occurred following chronic pain symptoms (Tinazzi et al., 1998; Baliki and Apkarian, 2015). In addition, successive neuroimaging studies have also revealed the altered properties for CTS in primary somatosensory cortices of the brain (Dhond et al., 2012; Maeda et al., 2013, 2014, 2016). However, blood oxygenation level-dependent (BOLD) functional MRI (fMRI) has been reported to be used as a neuroimaging technique to study the disorder (Dhond et al., 2012; Maeda et al., 2013, 2014, 2016; Dai et al., 2016). Considering the nature of spontaneous pain in chronic state, such task-based neuroimaging technique may be incapable to fully disclose the genuine symptomatic state since the symptoms of CTS may persist even without any stimuli. In addition, the BOLD signal can be complicated as i) it shows limited spatial specificity, ii) it cannot directly quantify neuronal activities, iii) it has unnecessary background noise generated due to the change in blood flow (Maleki et al., 2013; Chen et al., 2015).

To compensate for the technical pitfalls of the conventional neuroimaging technique in chronic pain studies, application of arterial spin labelling (ASL) fMRI technique is increasingly

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common in neuroscience studies (Owen et al., 2008, 2010). By taking the endogenous water as its tracer, this method can be applied to acquire image paired with a labeled one. In this process, the inflowing blood can be magnetically labeled, and a control image can be generated. This process can facilitate detection of the resting brain networks (RBNs) by means of seed-based analysis and brain mapping (De Luca et al., 2006; Viviani et al., 2011; Liang et al., 2012). In addition, it can make RBNs at the tissue-air interfaces observed more clearly. Featuring its relatively higher spatial resolution and less background noise compared to BOLD technique, pseudo-continuous ASL or pulsed-continuous ASL (pCASL) has been used to directly quantify the regional cerebral blood flow (rCBF) at resting state in a variety of chronic pain studies such as osteoarthritis of the carpometacarpal joint, osteoarthritis and shoulder pain (Keszthelyi et al., 2018). Therefore, it is speculated that pCASL is more appropriate to quantify RBNs following CTS. Nevertheless, there has yet to be any studies where pCASL is used as neuroimaging technique to describe the neuronal activities at resting state in CTS subjects presenting with sustained symptoms and worsening median nerve condition. In addition, previous CTS studies focused on alternation at cortical level whereas much remains unknown at subcortical level. Therefore, the primary objective of this study was to investigate how neuronal activities at both cortical and subcortical regions were modulated by carpal tunnel syndrome through analyzing its association with rCBF in individual brain region measured by pCASL.

Subjects and Methods

Subjects

Approval for this prospective study was obtained from the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West, China (HKU/HA HKW IRB, approval No. UW17-129) on April 11, 2017. This study was registered in Clinical Trial Registry of The University of Hong Kong, China (registration number: HKUCTR-2220) on April 24, 2017 and was performed in strict accordance with the *Declaration of Helsinki*.

The subjects were initially screened by an experienced hand surgeon at the outpatient hand clinic of a general hospital affiliated to The University of Hong Kong, China. Those with positive signs confirmed by Phalen's test and Tinel's Sign (Kuschner et al., 1992) were referred to the clinical neuro-diagnostic unit for diagnostic confirmation. A physician with 20 years of experience in clinical neurophysiological diagnostics took charge of diagnosis and severity classification of CTS. Soon after NCS, the individuals were recruited by convenience sampling and were required to complete the Chinese version of BCTQ (C-BCTQ) (Lue et al., 2014) and NRS (Jensen et al., 2006) under the guidance of an occupational therapist. Then, the pCASL assessment was conducted for each subject at a scheduled time in the Department of Diagnostic Radiology of The University of Hong Kong, China no longer than 2 weeks after completing the NCS and questionnaires.

The inclusion criteria of subjects are as follows: (1) Asian female subjects aged between 50–65 years; (2) right handedness; (3) diagnosis of CTS confirmed by nerve conduction studies and clinical provocative tests (Phalen's test and Tinel Sign) as described here: i) NCS: distal motor latency (DML) > 4.5 ms, sensory conduction velocity (SCV) and/or motor conduction velocity (MCV) < 50 m/s and ii) clinical symptoms persistent for at least over 3 months, with positive results of Tinel Sign and Phalen's test (Bland, 2000). Meanwhile, the exclusion criteria are as follows: (1) comorbidities including rheumatoid arthritis, gout, diabetes mellitus, cardiopulmonary disease, cancer, wrist fracture, cervical radiculopathy, myelopathy, neurological disorders and other peripheral neuropathies; (2) surgical history at the wrist; and (3) any of contraindications for MRI assessment such as metal materials e.g. artificial cardiac pacemaker, inside body.

NCS

NCS were performed using the Nicolet EDX system (Nicolet, Middleton, WI, USA). Sensory nerve function was assessed by placing recording rings at the 2nd finger, followed by orthodromic stimulation. In the meantime, the median motor nerve was measured by stimulation at the palm, wrist and elbow in the anatomical locations as specified in our previous studies (Deng et al., 2019). A collection was conducted of the corresponding NCS variables such as distal latencies at the palm and wrist (M_MN_P_Ltc: distal motor latency of median motor nerve at the palm; M_MN_W_Ltc: distal motor latency of median motor nerve at the wrist; S_MN_Ltc: distal sensory latency of median sensory nerve at the wrist), amplitude (M_MN_P_Aptd: compound action potential of median motor nerve at the palm; M_MN_W_Aptd: compound action potential of median motor nerve at the wrist; S_MN_Aptd: amplitude of median sensory nerve) and velocities (M_MN_W_CV: conduction velocity of median motor nerve at the wrist; S_MN_CV: conduction velocity of median sensory nerve) in both sensory and motor median nerves.

Psychometric assessment

Soon after NCS assessment, the subjects were required to complete the C-BCTQ and NRS under the instruction of an occupational therapist. The C-BCTQ, which was translated by going through a rigorous process to adapt the Chinese culture, has been validated as a disease-responsive measure to be commonly applied among Chinese CTS subjects (Lue et al., 2014). It consists of two subscales. The 11-item symptom severity scale is used to indicate the severity of the symptom, where the items 1–5 are pain-related questions while 6–10 evaluate paresthesia-relevant symptoms. Meanwhile, the 8-item functional status scale is purposed to describe the impact of the symptoms on functionality. The subjects were required to score the severity of their symptoms based on a 5-piont likert scale, ranging from 1 (no relevant symptoms) to 5 (the worst relevant symptoms) for symptom severity scale as well as their difficulty in performing functional tasks, ranging from 1 (no difficulty) to 5 (cannot perform the activity at all) for functional status scale. The two subscale scores were calculated by averaging the sub-total score of relevant items. On the other hand, NRS was used in combination with C-BCTQ to record the least, most, present and average pain as well as the numbness score over the past 24 hours based on an 11-point likert scale ranging from 0 (no relevant symptoms) to 10 (unbearable symptoms) so as to inform a stable clinical symptomatic trait.

Image acquisition

Structural brain MRI data was obtained with a multi-echo MPRAGE T1-weighted pulse sequence (repetition time = 6.9 ms, echo time = 3.2 ms, flip angle = 8°, slices = 160, sagittal acquisition, field of view = 240 × 240 mm^2, spatial resolution = 1 × 1 × 1 mm^3) on a Philips Achieva 3.0T MRI scanner (Philips, Best, the Netherland) with a 32-channel head coil. The assessment of rCBF throughout the entire brain was conducted via 20 pairs of labeled pCASL images. The protocol is detailed as follows: repetition time = 4500 ms, echo time = 16 ms, flip angle = 90°, slice thickness = 7 mm, 17 slices, image reconstruction matrix = 80 × 80, field of view = 240 × 240 mm^2, post-label delay = 2000 ms, label duration = 1650 ms, background suppression inversion pules at 1680 ms and 2760 ms respectively after the saturation pulse. An equilibrium magnetization image (M0) (repetition time = 8000 ms, echo time = 14 ms) was collected as well prior to the pCASL image collection.

Image preprocessing

pCASL images were preprocessed using Statistical Parametric Mapping software (SPM12, https://www.fil.ion.ucl.ac.uk/spm/) on the Matlab platform (MathWorks, Natick, MA, USA). The

pCASL images were first realigned to the mean of the images to modulate the rigid-body head motion. The participants with head motion larger than 3 mm or 3° were excluded. A total of 35 female subjects were initially recruited for MRI scanning. The MRI images obtained from 8 subjects were excluded due to poor image quality such as large head motion and image artefacts. Therefore, 27 subjects were included in group analysis. The averaged surround subtractions of labeled and control images, M0 and T1 images were then co-registered to the mean of motion-corrected control image. The rCBF was quantified using the single compartment kinetic model (Alsop et al., 2015). The estimated rCBF image was non-linearly normalized to the standard MNI space using the DARTEL toolbox, resampled to 3 × 3 × 3 mm^3, and spatially smoothed with an 8-mm full-width at half maximum (FWHM) Gaussian kernel. Three cases whose left hands were more affected, so the images of these three cases were flipped for consistent comparison.

Statistical analysis

SPSS 24.0 software (IBM, Armonk, NY, USA) was applied to conduct data analysis. The demographics, clinical tests, and NCS of the recruited subjects were obtained descriptively. To identify the unobserved dimensions of the clinical psychometric tests and NCS, factor analysis was conducted by reducing and categorizing the similar variables into fewer unobserved variables. The principal component analysis (PCA) was carried out for the extraction of variables while varimax rotation was performed to interpret the factors.

After taking those obtained factors into account as a unit, normality and equal variance were examined using Shapiro-Wilk test and Levene's test respectively. Results showed that variables in both C-BCTQ and NRS were not normally distributed. Therefore, the Spearman's rank correlation test was conducted to investigate the correlation between the factors derived from clinical psychometric tests.

The relationship between the factors derived from clinical psychometric tests, NCS and cerebral neuronal activities was explored using the Statistical Analysis Module in the toolbox of Data Processing and Analysis for Brain Imaging (DPABI) (Yan et al., 2016), with age and global CBF taken as covariates. Multiple comparisons correction was performed by the AlphaSim test (voxel-level $P < 0.05$, 1000 iterations of Monte Carlo simulations) using xjView toolbox (http://www.alivelearn.net/xijview).

Results

Demographic, clinical and neurophysiological characteristics

The descriptive statistics of demographics, clinical and neurophysiological findings are shown in **Table 1**. The recruited 27 subjects had CTS for 2.5–9.0 years. The injury of the most enrolled hands was graded as mild (48.14%), severe (25.9%) or moderate-to-severe level (11.1%). On the other hand, the symptomatology and functional score reflected in multiple questionnaires revealed the recruited subjects suffered from a mixed symptom of numbness and pain, with their functionality impaired as a result of the sustained symptoms.

Table 1 | **Demographics, nerve conduction studies and clinical symptomatology**

Demographics	
N	27
Age (yr)	57.7±6.51
Gender (male/female, *n*)	0/27
Hand dominance [right/left, *n*(%)]	19(70.4)/8(29.6)
Symptom duration (mon)	69.26±39.29
Parameters of nerve conduction studies	
M_MN_P_Ltc (ms)	2.04±0.33
M_MN_P_Aptd (mV)	13.37±20.76
M_MN_W_Ltc (ms)	5.34±1.6
M_MN_W_Aptd (mV)	7.77±2.24
M_MN_W_CV (m/s)	26.22±12.33
S_MN_Ltc (ms)	3.4±0.84
S_MN_Aptd (μV)	9.34±6.01
S_MN_CV (m/s)	36.61±10.4
Severity evaluation according to Bland's classification frequency [*n*(%)]	
Mild	13(48.14)
Mild to moderate	1(3.7)
Moderate	3(11.1)
Moderate to severe	3(11.1)
Severe	7(25.9)
C-BCTQ score	
BQ_PainQ	1.90±0.902
BQ_NumbQ	2.28±0.931
BQ_I_Ave	2.02±0.788
BQ_II_Ave	2.06 ±0.697
NRS score	
NRS_Pain_Ave	0.99±1.06
Least pain	1.3±2.42
Most pain	4.39±3.07
Present pain	2.04±2.64
NRS_Numb_Ave	2.58±2.38
Least numbness	1.3±2.42
Most numbness	4.39±3.07
Present numbness	2.04±2.64

BQ_I_Ave: Average score of symptom severity scores; BQ_II_Ave: average score of functional status scores; BQ_NumbQ: average score of numb-related items; BQ_PainQ: average score of pain-related items; C-BCTQ: Chinese version of Boston carpal tunnel questionnaire; M_MN_P_Aptd: compound action potential of median motor nerve at the palm; M_MN_P_Ltc: distal motor latency of median motor nerve at the palm; M_MN_W_Aptd: compound action potential of median motor nerve at the wrist; M_MN_W_CV: conduction velocity of median motor nerve at the wrist; M_MN_W_Ltc: distal motor latency of median motor nerve at the wrist; NRS: Numerical Rating Scale; NRS_Numb_Ave: average score of numb in Numerical Rating Scale; NRS_Pain_Ave: average score of pain in Numerical Rating Scale; S_MN_W_Aptd: amplitude of median sensory nerve; S_MN_CV: conduction velocity of median sensory nerve; S_MN_Ltc: distal sensory latency of median sensory nerve at the wrist.

Factor analysis of clinical psychometric tests and NCS

In clinical psychometric tests, both the Kaiser-Meyer-Olkin (KMO = 0.516) measure and Bartlett's test of Sphericity (χ^2 = 448.93, $P < 0.0001$) indicated that the data set can be applied to factor analysis. Three hidden factors were identified via principal component analysis (PCA), as indicated in **Table 2**, including "numbness" (BQNRS_Numb), "pain" (BQNRS_Pain) and "function" (BQNRS_Fx), accounting for 60% of the total variance as explained.

As for NCS, both the Kaiser-Meyer-Olkin (KMO = 0.568) and Bartlett's test of Sphericity (χ^2 = 254.19, $P < 0.0001$) indicated that the data set was suitable for performing factor analysis, with 76.79% of the total variance explained. As shown in **Table 3**, loading variables such as latency, amplitude, and velocity were classified as Factor One to reflect both the sensory and motor median nerve conditions, whereas the amplitudes of median motor nerves were classified as Factor Two. Factor One was defined as "median nerve status" (NCS_SM_MN) and Factor Two as "amplitude of median motor nerve" (NCS_MMN_Aptd).

Correlation of clinical psychometric tests with NCS

The correlation between factors derived from clinical psychometric tests is shown in **Table 4**. As for the factors derived from PCA, Factor "numbness" was found to be closely associated with BQ_NumbQ (r = 0.899), BQ_I_Ave (r = 0.745) and NRS_Numb_Ave (r = 0.835) respectively. Similarly, the close correlation was also found in Factor "pain" with BQ_PainQ (r = 0.821) and NRS_Pain_Ave (r = 0.882), respectively. As for

Table 2 | **Factor analysis of clinical psychometric tests**

Boston Carpal Tunnel Questionnaire	Component		
	Numbness (BQNRS_ Numb)	Pain (BQNRS_ Pain)	Function (BQNRS_ Fx)
I. Symptom severity			
1. Severity of pain at night		0.762	
2. Pain awakening		0.788	
3. Presence of pain during daytime		0.708	
4. Frequency of pain during daytime		0.667	
5. Duration of episode of pain		0.600	
6. Presence of numbness	0.690	0.377	
7. Presence of weakness	0.696	0.485	
8. Presence of tingling	0.611		0.418
9. Severity of numbness/tingling at night	0.559	0.515	
10. Numbness/tingling awakening	0.356	0.826	
11. Difficulty with grasping	0.789	0.368	
II. Functional status			
1. Writing			0.573
2. Buttoning of clothes	0.474		0.386
3. Holding a book while reading			0.863
4. Gripping of a telephone handle			0.736
5. Opening of jars			0.623
6. Household chores			0.678
7. Carrying of grocery bags	0.359		0.668
8. Bathing and dressing	0.474		
Numerical Rating Scale			
Least numbness	0.917		
Present numbness	0.885		
Most numbness	0.620		
Least pain			
Present pain	0.423		
Most pain		0.409	

The rotated component matrix shows the performance of each component of the C-BCTQ in the three selected factors. The items with absolute values > 0.3 were listed in the table. The presence of numbness, presence of weakness, severity of numbness/tingling at night, numbness/tingling awakening and difficulty with grasping are factorially complex since they load Factors one and two simultaneously (The value was not shown in Factor two as it was below 0.3). The presence of tingling, buttoning of clothes and carrying of grocery bags are factorially complex as they load Factors one and three simultaneously. These variables are removed as they reduce the internal consistency of the test while the remaining loading variables are taken into account as a unit since each of the rest loads just one factor. BQNRS: Boston carpal tunnel questionnaire and numerical rating scale.

Table 3 | **Factor analysis of nerve conduction studies**

Nerve conduction studies	Component	
	Median nerve status (NCS_SM_MN)	Amplitude of median motor nerve (NCS_MMN_Aptd)
S_MN_CV	0.979	
S_MN_Ltc	–0.960	
M_MN_W_Ltc	–0.942	
M_MN_W_CV	0.932	
S_MN_Aptd	0.776	
M_MN_P_Ltc	–0.704	
M_MN_P_Aptd		0.810
M_MN_W_Aptd		0.762

The rotated component matrix shows the performance of each component of NCS in the three selected factors. Items with absolute values > 0.3 were listed in the table. M_MN_P_Aptd: Compound action potential of median motor nerve at the palm; M_MN_P_Ltc: distal motor latency of median motor nerve at the palm; M_MN_W_Aptd: compound action potential of median motor nerve at the wrist; M_MN_W_CV: conduction velocity of median motor nerve at the wrist; M_MN_W_Ltc: distal motor latency of median motor nerve at the wrist; NCS_MMN_Aptd: amplitude of median motor nerve (Factor two); NCS_SM_MN: factor "median nerve status (Factor one); S_MN_CV: conduction velocity of the sensory median nerve; S_MN_Ltc: distal sensory latency of median nerve.

functional status, Factor "function" was closely correlated with BQ_II_Ave (r = 0.756).

As for the factors derived from NCS (**Table 5**), moderate correlation was found in Factor "median nerve status" with M_MN_P_Ltc (r = –0.66) and S_MN_Aptd (r = 0.694) while strong correlation was found with M_MN_W_Ltc (r = –0.939) and M_MN_W_CV (r = 0.948), respectively. On the other hand, close correlation was found in Factor "amplitude of median motor nerve" with M_MN_P_Aptd (r = 0.947) and M_MN_W_Aptd (r = 0.952) respectively.

Correlation analysis between symptomatology, functionality, NCS and activated brain regions

As shown in **Table 6**, Factor "numbness" was positively correlated with the cerebellum (K = 94, r = 0.74, P < 0.01), fusiform (K = 165, r = 0.69, P < 0.01), angular gyrus (K = 87, r = –0.68, P < 0.01), temporal superior (K = 79, r = 0.74, P < 0.01) and inferior lobes (K = 61, r = 0.74, P < 0.01) at contralateral hemisphere as well as ipsilateral temporal inferior lobe (K = 103, r = 0.7, P < 0.01), with its correspondent neuroimaging shown in **Figure 1**. In comparison, Factor "pain" was positively correlated with contralateral temporal pole lobe and

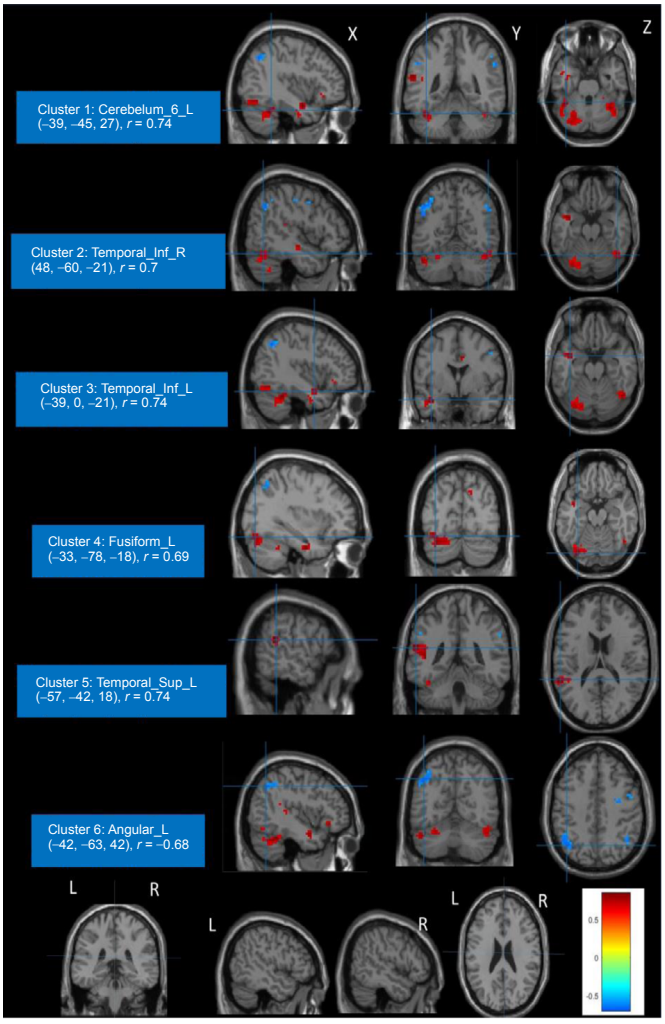

Figure 1 | **Correlation of Factor "numbness" with brain regions in patients with carpal tunnel syndrome.**
Blue color indicates decreased neuronal activities whereas red color indicates increased neuronal activities. Factor "numbness" was positively correlated with the cerebellum (K = 94, r = 0.74), fusiform (K = 165, r = 0.69), temporal superior (K = 79, r = 0.74) and inferior lobes (K = 61, r = 0.74), while it was negatively correlated with angular gyrus (K = 87, r = –0.68) at contralateral hemisphere as well as ipsilateral temporal inferior lobe (K = 103, r = 0.7). All P < 0.01. Cerebelum_6: Lobule VI of cerebellar hemisphere; Inf: inferior; L: left; R: right; Sup: superior.

postcentral lobe (K = 53–62, r = 0.72–0.77, P < 0.01) but it was negatively correlated with contralateral putamen (K = 67, r = –0.77, P < 0.01) and ipsilateral temporal middle gyrus (K = 68, r = –0.75, P < 0.01), with its correspondent neuroimaging displayed in **Figure 2**. Lastly, Factor "function" was positively correlated with CBF in contralateral occipital middle (K = 103, r = 0.72, P < 0.01), parietal inferior lobe (K = 97, r = 0.76, P < 0.01), ipsilateral temporal middle (K = 29, r = 0.73, P < 0.01) and Rolandic operculum (K = 25, r = 0.71, P < 0.01), but it was negatively correlated with ipsilateral postcentral (K = 41, r = –0.68, P < 0.01) and frontal middle orbital gyrus (K = 21, r = –0.67, P < 0.01), with its neuroimaging displayed in **Figure 3**.

Meanwhile, Factor "median nerve status" was correlated with contralateral cerebellum (K = 1723, r = –0.62, P < 0.05), temporal middle lobe (K = 178, r = –0.62, P < 0.05) and occipital middle lobe (K = 213, r = 0.6, P < 0.05), with its correspondent neuroimaging shown in **Figure 4**. Factor "motor amplitude of median nerve" was negatively correlated with contralateral hippocampus (K = 227, r = –0.7, P < 0.05), temporal middle gyrus (K = 117, r = –0.55, P < 0.05) and precuneus (K = 336, r = –0.57, P < 0.05), ipsilateral cerebellum crus II of cerebellar hemisphere (K = 250, r = –0.61, P < 0.05) and middle temporal lobe (K = 126, r = –0.58, P < 0.05) but it was positively correlated with contralateral precentral gyrus (K = 2849, r = 0.84, P < 0.05), with its corresponding neuroimaging displayed in **Figure 5**.

Following Alphasim correction, the results showed no clusters remaining significant among factors derived from clinical psychometric tests (factor numbness: K = 1025, P = 0.049; pain: K = 629, P = 0.049; function: K = 563, P = 0.049). In comparison, the clusters of contralateral cerebellum (K = 1723) and precentral gyrus (K = 2849) derived from factors in NCS remained significant according to Alphasim multiple comparisons (Factor "median nerve status": K = 941, P = 0.048; Factor "amplitude of motor median nerve": K = 753, P = 0.049). Therefore, with the overall result taken into account, it indicates increased neuronal activities in brain regions that perform emotional and cognitive functions following the worsening of median nerve status and clinical symptoms. It implies a transitional shift from nociceptive circuitry to emotional and cognitive circuitries in the process of pain chronicity in CTS.

Discussion

To the best of our knowledge, this is the first study to investigate the resting-state neuronal activity changes in the brain regions following sustained symptoms of CTS by applying pCASL technique. Our findings revealed a tendency of pain processing that shifted from nociceptive circuity to emotional and cognitive circuities, indicating an altered neuronal state in

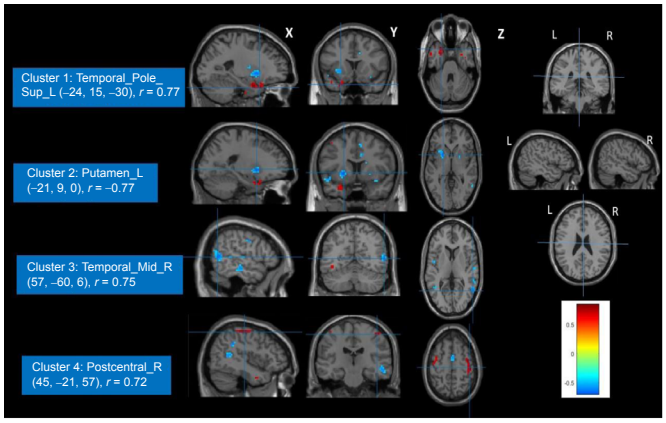

Figure 2 | **Correlation of Factor "pain" with brain regions in patients with carpal tunnel syndrome.**
Blue color indicates decreased neuronal activities whereas red color indicates increased neuronal activities. Factor "pain" was positively correlated with contralateral temporal pole lobe and postcentral lobe while negatively correlated with contralateral putamen and ipsilateral temporal middle gyrus. L: Left; Mid: middle; R: right; Sup: superior.

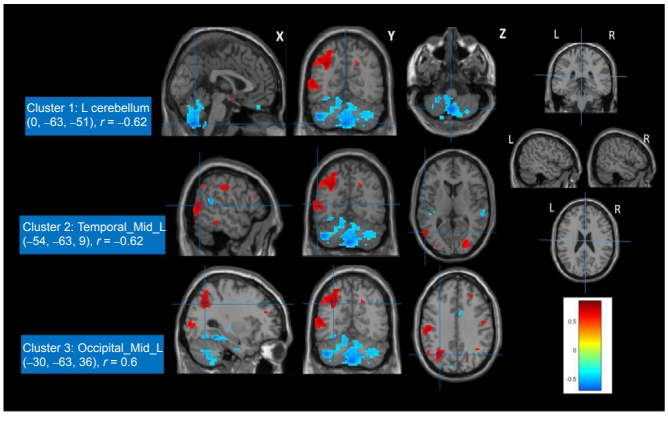

Figure 4 | **Correlation of Factor "median nerve status" with brain regions in patients with carpal tunnel syndrome.**
Blue color indicates decreased neuronal activities whereas red color indicates increased neuronal activities. Factor "median nerve status" was correlated with contralateral cerebellum, temporal middle lobe, and occipital middle lobe. L: Left; Mid: middle; R: right.

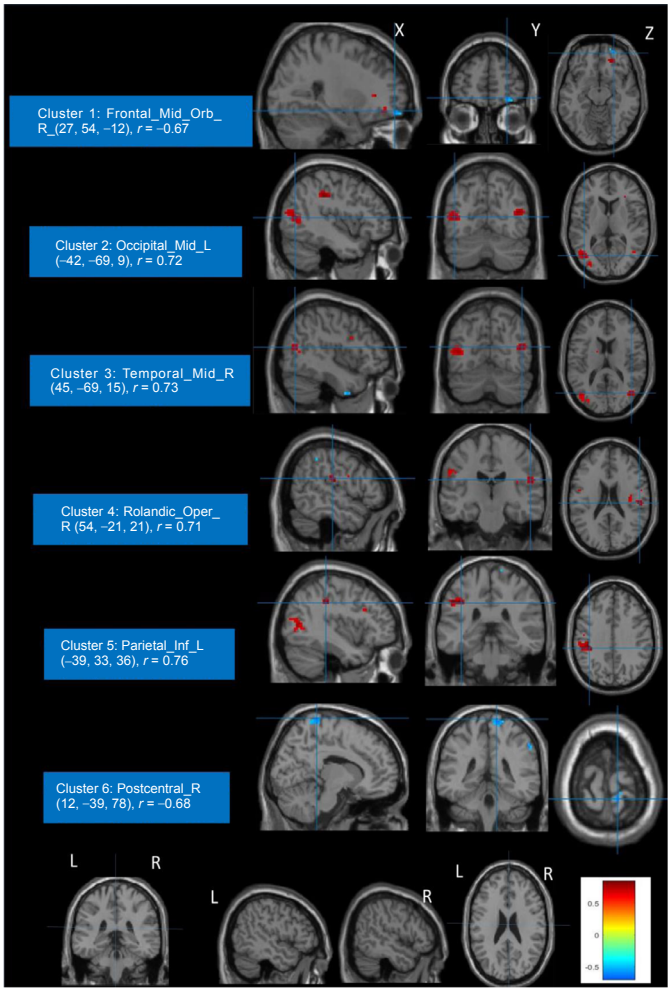

Figure 3 | **Correlation of Factor "function" with brain regions in patients with carpal tunnel syndrome.**
Blue color indicates decreased neuronal activities whereas red color indicates increased neuronal activities. Factor "function" was positively correlated with cerebral blood flow in contralateral occipital middle and parietal inferior lobe, as well as in ipsilateral temporal middle and Rolandic operculum while it was negatively correlated with ipsilateral postcentral and frontal middle orbital gyrus. Inf: Inferior; L: left; Mid: middle; Oper: operculum; Orb: orbital; R: right.

Table 4 | **Correlation of matrix for clinical psychometric tests**

	BQ_PainQ	BQ_NumbQ	BQ_I_Ave	BQ_II_Ave	NRS_Numb_Ave	NRS_Pain_Ave	BQNRS_Numb	BQNRS_Pain	BQNRS_Fx
BQ_PainQ	–								
BQ_NumbQ	0.666**								
BQ_I_Ave	0.872**	0.929**							
BQ_II_Ave	0.429**	0.552**	0.553**						
NRS_Numb_Ave	0.374	0.729**	0.614**	0.526**					
NRS_Pain_Ave	0.612**	0.258	0.445**	0.242	0.294				
BQNRS_Numb	0.373	0.899**	0.745**	0.353	0.835**	0.224			
BQNRS_Pain	0.821**	0.240	0.522*	0.182	0.084	0.882**	0.068		
BQNRS_Fx	0.260	0.175	0.246	0.756**	0.267	–0.033	–0.042	–0.042	–

Spearman's correlation coefficients are shown. *P < 0.05, **P < 0.01. BQ_I_Ave: average score of symptom severity scores; BQ_II_Ave: average score of functional status scores; BQ_NumbQ: Average score of numb-related items; BQ_PainQ: Average score of pain-related items; BQNRS_Numb: Factor "numbness" integrated in Boston Carpal Tunnel Questionnaire and Numerical Rating Scale; BQNRS_Pain: Factor "pain" integrated in Boston Carpal Tunnel Questionnaire and Numerical Rating Scale; BQNRS_Fx: Factor "functional status" integrated in Boston Carpal Tunnel Questionnaire and Numerical Rating Scale; NRS_Numb_Ave: average score of numb in Numerical Rating Scale; NRS_Pain_Ave: average score of pain in Numerical Rating Scale.

Table 5 | **Correlation of matrix for nerve conduction studies**

	M_MN_P_Ltc	M_MN_P_Aptd	M_MN_W_Ltc	M_MN_W_Aptd	M_MN_W_CV	S_MN_Ltc	S_MN_Aptd	S_MN_CV	NCS_SM_MN	NCS_MMN_Aptd
M_MN_P_Ltc	–									
M_MN_P_Aptd	–0.08									
M_MN_W_Ltc	0.629**	–0.040								
M_MN_W_Aptd	–0.314	0.873**								
M_MN_W_CV	–0.607**	0.079	–0.961**							
S_MN_Ltc	0.654**	–0.003	0.965**	–0.249						
S_MN_Aptd	–0.377	0.131	–0.611**	0.186	0.678**					
S_MN_CV	–0.670**	0.013	–0.957**	0.267	0.951**	–0.989**				
NCS_SM_MN	–0.660**	–0.062	–0.939**	0.192	0.948**	–0.974**	0.694**	0.973**		
NCS_MMN_Aptd	–0.154	0.947**	–0.090	0.952**	0.122	–0.042	–0.098	0.056	–0.018	–

*P < 0.05, **P < 0.01. M_MN_P_Ltc: Distal motor latency of median motor nerve at the palm; M_MN_P_Aptd: compound action potential of median motor nerve at the palm; M_MN_W_Ltc: distal motor latency of median motor nerve at the wrist; M_MN_W_Aptd: compound action potential of median motor nerve at the wrist; M_MN_W_CV: conduction velocity of median motor nerve at the wrist; S_MN_Ltc: distal sensory latency of median sensory nerve at the wrist; S_MN_W_Aptd: amplitude of median sensory nerve; S_MN_CV: conduction velocity of median sensory nerve; NCS_SM_MN: factor "median nerve status (Factor one); NCS_M_Aptd: amplitude of median motor nerve (Factor two).

the process of pain chronicity among the CTS subjects. It may indicate the possible ignorance in diagnostic and therapeutic areas for the current clinical management of CTS, which requires innovative clinical regime when managing CTS.

In chronic pain, it is widely recognized that emotional and cognitive factors should be taken into consideration regardless of nociceptive input in pain perception (Baliki and Apkarian, 2015). A similar resting-state fMRI study demonstrated that synaptic activity, reflected by the amplitude of low-frequency fluctuation (ALFF), can be reduced in bilateral primary/secondary somatosensory cortex (Lu et al., 2017). Since ALFF is considered to be coupled with rCBF and subjected to the neuronal activities of the brain, this finding is consistent with our findings, which consistently revealed decreased rCBF in precentral and postcentral gyrus associated with the deterioration of hand function (Cluster 6 in **Figure 3**, r = –0.68) and median nerve status (Cluster 6 in **Figure 5**, r = 0.84). In the meantime, the increased rCBF in brain regions irrelevant to nociceptive input, such as the cerebellum, temporal lobe and hippocampus, were involved as well.

The cerebellum has long been considered as associated with non-motor functions (Moulton et al., 2010). Anatomically, the cerebellum receives diminishing afferents from the cortical areas, which involves primary motor cortex, supplementary motor cortex, primary somatosensory cortex, and the superior parietal lobe (Schmahmann, 1996). Meanwhile, zona incerta as a site for the expression of chronic pain also projected its fibers to the inferior olive of the cerebellum (Masri et al., 2009). It is agreed that chronic pain is comorbid and is possible to be accompanied by psychiatric disorders, with the cerebellum bearing association with depression and pain (Gureje et al., 2001; Wilson et al., 2002). Besides, the elevated neuronal activities at the resting state in the anterior area of the cerebellum and the abnormal feedback to the input resulting in diverse affect were also reported in previous studies focusing on the patients suffering from depression (Fitzgerald et al., 2008). The change of neuronal activity in the cerebellum as observed in our studies suggests that the cerebellum can contribute to the development of pain and depression in the chronicity process following the deterioration of CTS as well.

On the other hand, the hippocampus is considered as one of the primary brain structure in the limbic system, and is responsible for learning, memory, response to stress and mood modulation (Grilli, 2017). It is universally agreed that the altered neuronal activities in the hippocampus following chronic pain disorder can interact with the medial and lateral prefrontal cortical circuitry by learning. In this process, the pain perception may have altered from mere nociceptive input to emotional suffering, thus resulting in cortical reorganization (Mansour et al., 2014). In our studies, it was identified that the increased neuronal activities in contralateral hippocampus (cluster 2 in **Figure 5**, r = –0.7) and decreased activities in precentral gyrus (cluster 6 in **Figure 5**, r = 0.84) were associated with the declining amplitude of the median motor nerve, which indicates the possible cortical reorganization as the disease progressed. It may be in line with the findings of the decreased cortical thickness in precentral gyrus in a study involving 38 CTS subjects as alternation in neuronal activities can result in the change of brain structure (Maeda et al., 2016).

In this regard, the pain perception may be reflected from its pure sensory properties to more complex emotional states,

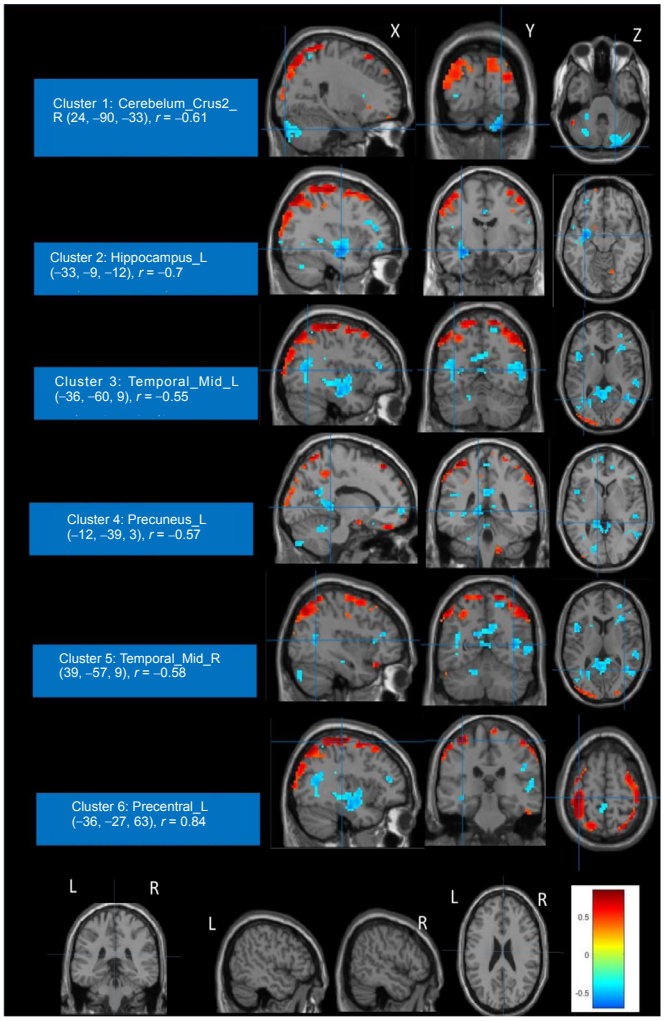

Figure 5 | **Correlation of Factor "motor amplitude of median nerve" with brain regions in patients with carpal tunnel syndrome.**
Blue color indicates decreased neuronal activities whereas red color indicates increased neuronal activities. Factor "motor amplitude of median nerve" was negatively correlated with contralateral hippocampus, temporal middle gyrus and precuneus, ipsilateral cerebellum crus II of cerebellar hemisphere and middle temporal lobe while positively correlated with contralateral precentral gyrus. Crus2: Crus II of cerebellar hemisphere; L: left; Mid: middle; Oper: operculum; Orb: orbital; R: right.

Table 6 | **Summary of correlation between symptomatology, functionality and nerve conditions and brain ROI activations at resting state among CTS subjects**

Derived factors	Anatomical locations	Cluster size (*K*-value)	*r*-value	Peak coordinate		
				X	*Y*	*Z*
Numbness (BQNRS_ Numb)	Cerebellum_6_L	94	0.74	–39	–45	27
	Temporal_Inf_R	103	0.70	48	–60	–21
	Temporal_Inf_L	61	0.74	–39	0	–21
	Fusiform_L	165	0.69	–33	–78	–18
	Temporal_Sup_L	79	0.74	–57	–42	18
	Angular_L	87	–0.68	–42	-63	42
Pain (BQNRS_Pain)	Temporal_Pole_ Sup_L	62	0.77	–24	15	–30
	Putamen_L	67	–0.77	–21	9	0
	Temporal_Mid_R	68	–0.75	57	–60	6
	Postcentral_R	53	0.72	45	–21	57
Function (BQNRS_Fx)	Frontal_Mid_ Orb_R	21	–0.67	27	54	–12
	Occipital_Mid_L	103	0.72	–42	–69	9
	Temporal_Mid_R	29	0.73	45	–69	15
	Rolandic_Oper_R	25	0.71	54	–21	21
	Parietal_Inf_L	97	0.76	–39	–33	36
	Postcentral_R	41	–0.68	12	–39	78
Median Nerve Conditions (NCS_SM_ MN)	Cerebellum_L	1723	–0.62	0	63	–51
	Temporal_Mid_L	178	–0.62	–54	–63	9
	Occipital_Mid_L	213	0.60	–30	–63	36
Amplitude of median motor nerve (NCS_MMN_ Aptd)	Cerebelum_ Crus2_R	250	–0.61	24	–90	–33
	Hippocampus_L	227	–0.70	–33	–9	–12
	Temporal_Mid_L	117	–0.55	–36	–60	9
	Precuneus_L	336	–0.57	–12	–39	3
	Temporal_Mid_R	126	–0.58	39	–57	9
	Precentral_L	2849	0.84	–36	–27	63

BQNRS: Boston carpal tunnel questionnaire and numerical rating scale; BQNRS_Fx: Factor "functional status" integrated in Boston Carpal Tunnel Questionnaire and Numerical Rating Scale; Cerebelum_6: lobule VI of cerebellar hemisphere; Crus2: crus II of cerebellar hemisphere; Inf: inferior; L: left; Mid: middle; NCS_MMN_Aptd: amplitude of median motor nerve (Factor two); NCS_SM_MN: factor "median nerve status (Factor One); Oper: operculum; Orb: orbital; R: right; ROI: region of interest; Sup: superior.

and associated with pain memory formatted and learnt, thus resulting in pain persistence even in the absence of physical stimuli. Our findings strengthened the notion of dysfunction in limbic system as a mechanism contributory to the persistence of pain (Kulkarni et al., 2007; Howard et al., 2012; Hashmi et al., 2013). It confirms the possible ignorance of emotional sufferings when managing CTS, thus making it necessary for adjusting the current clinical regime.

In addition, there are a variety of previous task-related neuroimaging studies conducted in other chronic musculoskeletal or neuropathic pain disorders. The increased rCBF in the contralateral temporal lobe cluster, as well as the amygdala and parahippocampal gyrus was reported in a group of 38 patients with carpometarcarpal osteoarthritis (Keszthelyi et al., 2018). Besides, the intensity of pain was positively correlated with the amygdala, hippocampus, putamen, brain stem, thalamus in 43 patients with knee osteoarthritis (Cottam et al., 2016). As revealed by another study conducted on chronic lower back pain, the worsening of ongoing chronic pain was associated with a significant increase of rCBF in somatosensory, prefrontal, and insular cortices among subjects with chronic lower back pain (Wasan et al., 2011). Besides, a significant increase in rCBF was observed in contralateral primary somatosensory/motor cortex and amygdala among patients with postherpetic neuralgia pain (Liu et al., 2013). Apparently, neuronal alternation in the brain areas irrelevant to sensory and motor functions was involved in the task-designed chronic pain studies. In our study, it was invariably found that the involvement of subcortical brain regions in CTS was indicative of a transitional shift of the perception of the brain towards pain from the circuitry in charge of nociceptive input to the emotion-based one. It is thus speculated that pain perception may be changed from nociceptive response to pain memorization in the chronicity process.

The factor analysis was conducted to combine multiple items which share the similar concept in clinical outcome measurement tools and NCS respectively to better delineate the dimensions of CTS from clinical and neurophysiological perspectives. The hidden factors identified in both clinical questionnaires and NCS were similar to previous studies on clinical correlation where the same method was applied (Robinson et al., 1992; Ortiz-Corredor et al., 2011; Lue et al., 2015). It is agreed that the factor analysis focuses on relationship among variables (Xs) whereas the regression model lays emphasis on the relationship between predictors and (Xs) and Y. Obviously, the factor analysis is more appropriate for our study.

Nevertheless, our findings may be overstated due to some

drawbacks. Firstly, our study is constrained by its cross-sectional design. The sample size was small without the involvement of healthy control group. There is a possibility for the result to be overstated without the involvement of brain performance at resting state in the matched healthy control group. In addition, only female patients were investigated to prevent gender bias. A more convincing result can be obtained following a longitudinal study to examine the changes in rCBF after treatment, with the involvement of healthy control group.

Conclusion

Our findings indicate a tendency of brain activities at resting state shifting from the nociception-responsive base to a more complex state with emotional and cognitive factors involved. It suggests the necessity to innovate the existing clinical management from diagnostic and therapeutic perspectives to taking those ignored areas into account when managing CTS patients.

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Author contributions: *XD was in charge of study design, manuscript drafting and project coordination. PLHC and SYC were responsible for data collection and nerve conduction studies conduction. KPL took charge of electroneurophysiological diagnosis, expertise guidance, and clinical consultation. YH was responsible for expertise advice and consultation. WYI conceived the study and was also responsible for case screening, study oversight, expertise advice and consultation. All authors approved the final version of this study.*

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