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, subcortical, 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

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...
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 neurodiagnostic 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 BTCTQ and NRS under the instruction of an occupational therapist. The C-BTCTQ, 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-point 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-BTCTQ 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 mm², spatial resolution = 1 × 1 × 1 mm³) on a Philips Achieva 3.0T MRI scanner (Philips, Best, the Netherlands) 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 mm², post-label delay = 2000 ms, label duration = 1650 ms, background suppression inversion pulses 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 round subtraction 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 mm³, 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/xjview).

**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 enrolled hands was graded as mild (48.14%), severe (25.9%) 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 (χ² = 254.19, P < 0.0001) indicated that the data set was suitable for performing factor analysis,

| 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_CM (m/s) | 26.22±12.33 |
| S_MN_Ltc (ms) | 3.4±0.84 |
| S_MN_Aptd (μV) | 9.34±6.01 |
| S_MN_CM (m/s) | 36.6±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_Ltc: distal motor latency of median motor nerve at the wrist; M_MN_W_CM: 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_Pain_Ave: average score of pain in Numerical Rating Scale; S_MN_Ltc: conduction velocity of median sensory nerve at the wrist; S_MN_CM: conduction velocity of median sensory nerve; S_MN_Ltc: distal sensory latency of median sensory nerve at the wrist.

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

| Component          | Numbness (BQNRS_Pain) | Pain (BQNRS_Pain) | Function (BQNRS_Fx) |
|--------------------|-----------------------|-------------------|---------------------|
| Boston Carpal Tunnel Questionnaire |                       |                   |                     |
| 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 | 0.474              | 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 | 0.423              |                   |                     |
| Present pain | 0.609              |                   |                     |

The rotated component matrix shows the performance of each component of the C-BCTQ in the three selected factors. 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

| 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_W_Ltc: Distal motor latency of median motor nerve at the palm; M_MN_W_CV: Conduction velocity of median motor nerve at the wrist; M_MN_W_Aptd: Compound action potential of median motor nerve at the wrist; M_MN_P_Ltc: Distal motor latency of median motor nerve at the wrist; M_MN_P_Aptd: Compound action potential 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.

As for the factors derived from NCS (Table 5), moderate correlation was found in Factor “median nerve status” with M_MN_P_Aptd (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
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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 cerebral blood flow 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 circuitry to emotional and cognitive circuitries, indicating an altered neuronal state in.
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 gyrius 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 increased 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). The altered neuronal activity in the hippocampus as observed in our studies suggests that the hippocampus can contribute to the development of pain and depression in the chronicity process following the deterioration of CTS as well.
A significant increase in rCBF was observed in contralateral areas of the somatosensory, prefrontal, and insular cortices among subjects with chronic back pain (Wasan et al., 2011). Besides, several neuroimaging studies conducted in other chronic pain models showed increased neuronal activities in the amygdala and parahippocampal gyrus (Keszthelyi et al., 2018). The intensity of pain was positively correlated with a significant increase of rCBF in the contralateral temporal lobe cluster, as well as the 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.

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 carpal tunnel syndrome (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 pain 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- Coronado 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. 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.

Conclusions

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.

Acknowledgments:
We would like to extend our gratitude to Dr. Wutao Lou, from the Department of Medicine and Therapeutics of The Chinese University of Hong Kong, China for offering guidance on MRI imaging preprocessing and analysis. Joseph Suen, from the Department of Diagnostic Radiology of The University of Hong Kong, China for his assistance in arranging MRI assessment.

Author contributions:
XD was in charge of study design, manuscript drafting and project coordination. PHLC and SYC were responsible for data collection and nerve conduction study conduction. KPL took charge of electromyopathological 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.

Conflicts of interest:
All authors declare that they have no conflict of interests.

Financial support:
None.

Institutional review board statement:
Approval for the study was obtained from the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West, China (HKU/HKWB IRB, approval no. UW17-129) on April 11, 2017.

Declaration of patient consent:
The authors certify that they have obtained the appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients have understood that their names and initials will not be published and due efforts will be made to conceal their identity.

Reporting statement:
This study followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guideline.

Biostatistics statement:
The statistical methods of this study were reviewed by the biostatisticians of The University of Hong Kong, China.

Copyright license agreement:
The Copyright License Agreement has been signed by all authors before publication.

Data sharing statement:
Individual participant data can be available by request. Individual participant data that underlies the reported results can be shared. Study Protocol and Informed Consent Form will also be available. Data will be available immediately following publication, with ending date of April 10, 2022 for investigations whose proposed use of the data has been approved by an independent review committee identified for this purpose, and for any purpose types of analysis. Proposals should be directed to wyip@hkumc.hk. To gain access, data requestors will need to sign a data access agreement.

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