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Quantitative cerebral blood flow mapping and functional connectivity of postherpetic neuralgia pain: A perfusion fMRI study

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ABSTRACT

This article investigates the effects of postherpetic neuralgia (PHN) on resting-state brain activity utilizing arterial spin labeling (ASL) techniques. Features of static and dynamic cerebral blood flow (CBF) were analyzed to reflect the specific brain response to PHN pain. Eleven consecutive patients suffering from PHN and 11 age- and gender-matched control subjects underwent perfusion functional magnetic resonance imaging brain scanning during the resting state. Group comparison was conducted to detect the regions with significant changes of CBF in PHN patients. Then we chose those regions that were highly correlated with the self-reported pain intensity as "seeds" to calculate the functional connectivity of both groups. Absolute CBF values of these regions were also compared across PHN patients and control subjects. Significant increases in CBF of the patient group were observed in left striatum, right thalamus, left primary somatosensory cortex (S1), left insula, left amygdala, left primary somatomotor cortex, and left inferior parietal lobule. Significant decreases in CBF were mainly located in the frontal cortex. Regional CBF in the left caudate, left insula, left S1, and right thalamus was highly correlated with the pain intensity, and further comparison showed that the regional CBF in these regions is significantly higher in PHN groups. Functional connectivity results demonstrated that the reward circuitry involved in striatum, prefrontal cortex, amygdala, and parahippocampal gyrus and the circuitry among striatum, thalamus, and insula were highly correlated with each element in PHN patients. In addition, noninvasive brain perfusion imaging at rest may provide novel insights into the central mechanisms underlying PHN pain.

1. Introduction

Living with chronic pain negatively impacts one's quality of life [1,4]. Peripheral neuropathic pain most frequently originates from injury or dysfunction of peripheral nerves. Recently, it has also been linked to changes in the connections among central neurons [6,41]. Postherpetic neuralgia (PHN) is a common type of neuropathic pain caused by reactivation of the varicella zoster virus. Similar to other chronic neuropathic conditions, patients with PHN show multiple signs of both peripheral and central neuropathy [28]. Yet, because few studies have explored the effects of PHN pain on brain activity [14,19], the effects of PHN pain on brain network arrangement and function are poorly understood.

Cerebral blood flow (CBF) is believed to be strongly associated with cerebral metabolism. Thus, examining changes in regional CBF (rCBF) over time has been used extensively in pain studies to map neural pathways [3,31,32]. rCBF can be quantified directly using arterial spin labeling (ASL) magnetic resonance imaging (MRI) [47,48]. Recent advances in MRI technology, including greater magnetic field strengths and improved phased array receiver coils [40,43], have increased the sensitivity of ASL, making it a realistic option for functional studies of pain [30,31].

ASL MRI can be applied to investigate both static and dynamic CBF characteristics in a single session within the same subject [48]. Static CBF is quantified by voxel-wise averaging of CBF values over the time domain and can be used to examine rCBF changes.

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Dynamic CBF analysis uses the cross-correlation between regions—in this case, the regions involved in pain—to examine the brain circuitry for processing specific pain information.

Several studies [3,29] have indicated that pain is processed in a distributed cortical network. However, the regions involved may be dependent on the specific type of pain [3,29]. Furthermore, information processing between 2 cortical areas may induce functional connectivity [35], suggesting that the cortical areas involved in the processing of pain may be functionally connected. Thus, we aimed to identify the cortical network involved in the processing of PHN pain, as well as the effects of this chronic neuropathic condition on functional connectivity as measured by resting-state brain activity. We hypothesized that compared with control subjects, PHN patients would demonstrate a unique pattern of rCBF that was highly correlated with self-reported pain intensity and internally connected by a single functional network.

2. Materials and methods

2.1. Ethics statement

This study was approved by the local ethics committee, and all subjects provided informed written consent, in line with the Declaration of Helsinki.

2.2. Subjects

Seventeen right-handed PHN patients admitted to the Peking University First Hospital Pain Clinic were recruited, of which 11 were eligible: all male patients age 59 to 73 years (mean 66 years). All participants reported a history of shingles, associated severe pain, and varicella zoster virus infection. PHN pain was localized in the left side of the body in 9 cases and the right side for 2 cases. All participants reported a history of persistent pain for at least 2 months after resolution of the acute shingles episode, with a pain intensity of at least 7 of 10 on a mechanical visual analog scale (VAS) (a measurement of pain intensity ranging from 0 to 10, with 0 meaning no pain and 10 meaning highest tolerable pain) [20]. Pain level was also assessed immediately before the functional MRI (fMRI) to ensure that participants were experiencing moderate to severe pain (ie, VAS $\geqslant 6$) during the experiment. Participants also completed standard neurological and psychological examinations, as well as standard anatomical brain MRI. Neurological examination consisted of assessments for consciousness, thinking, speaking, cranial nerve function, motor control (ie, muscle strength, muscle tone, and coordination), reflexes (ie, tendon reflex, pathological reflex), and sensation (ie, decrease or absent). The psychological examination consisted of the Mini-Mental State Examination [13].

Seven participants had prescriptions for analgesic medication such as oxycodone and/or propionic acid. Participants suffering from significant psychiatric disorders and/or brain structural abnormalities were excluded in our study. Four participants suffered from slight insomnia, and 3 of these participants were prescribed diazepam. Medications were withheld the day before and on the day of examination.

Eleven age-matched right-handed healthy male subjects were recruited as control subjects (age 56 to 73 years, mean 64 years). None suffered from any type of chronic pain, psychiatric disorders, or brain structural abnormalities, and none were taking medications that may have altered brain activity.

2.3. Data acquisition

During all brain scans, subjects were instructed to stay awake with their eyes closed and minds clear. Maximum care was taken to avoid situations that may trigger abnormal pain. fMRI was performed on a 3T Signa Excite HD scanner (GE Medical Systems, Milwaukee, WI) with an 8-element, receive-only head coil. Subjects laid in a supine position on the scanner table with head immobilized by foam padding. High-resolution anatomical images were first acquired using a 3-dimensional gradient-echo T1-weighted sequence (180 transverse slices, repetition time (TR)/echo time (TE): 25/4 ms; field of view (FOV): 230 mm^2; slice thickness: 2 mm with no gap). Anatomical images were utilized for registration of the functional images, as well as for anatomical atlas transformation.fMRI data were acquired for 8 consecutive minutes using a dual-echo spiral-out pulsed ASL sequence that interleaves pulsed ASL acquisitions with slab-selective and nonselective inversion using PICORE (proximal inversion with a control for off-resonance effects) tagging [44] and QUIPSS II (quantitative imaging of perfusion using a single subtraction). PICORE/QUIPSS II applies saturation pulses to the tagging region to control the time duration of the tagged bolus. QUIPSS II renders the pulsed ASL technique relatively insensitive to transit delays and thus ensures accurate quantification of perfusion [24,45]. The readouts utilized a slice thickness/gap of 8.0/2.0 mm with 2.9×2.9 mm^2 in-plane resolution, using a 230 mm^2 FOV with 64×64 acquisition matrix, a TR of 3000 ms, a TE1 of 3.1 ms, an inversion time (TI) of 1.5 seconds, and a 90° flip angle. After inversion, the time of the saturation pulse was 700 ms, with an 800 ms delay between saturation and excitation. Twelve axial slices were placed to cover the entire cerebrum and most of the cerebellum. The set consisted of 160 functional contiguous axial images.

2.4. Data preprocessing

fMRI preprocessing was performed with Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, University College, London, UK) and ASLtbx (http://www.cfn.upenn.edu/~zewang/ASLtbx.php) based on SPM5.

For each subject, data were motion corrected using the realignment function in SPM5. Sinc interpolation of the ASL time course was then used to create time-matched control and label images, followed by subtraction to suppress BOLD contamination [2,25]. Absolute CBF image series were generated based on a single-compartment continuous ASL perfusion model utilizing ASLtbx [42]. Functional images were reoriented with the origin at the anterior commissure before being coregistered with the corresponding anatomical image. This technique facilitates transformation to the Montreal Neurological Institute T1 template and resampling of functional images to isotropic $2 \times 2 \times 2$ mm^3 voxels. Functional data were smoothed using a Gaussian kernel of full-width half-maximum 8 mm. Finally, the functional data were detrended linearly and filtered using a bandpass filter (approximately 0.01 to 0.04 Hz).

2.5. Experimental procedure

The statistical analysis consisted of 2 primary steps. First, we determined the effects of PHN on rCBF. Second, we examined the functional connectivity between pain-related regions, as identified in step 1, to determine their interconnectivity and elucidate the underlying circuitry involved in PHN pain (experiment flowchart in Fig. 1).

2.6. Statistical analysis

The mean CBF images for each subject were averaged using Matlab 7.0. To first prove the feasibility of the ASL technique for quantifying static CBF, we computed CBF in the control group within those anatomical regions of interest (ROIs) (based on the