in Psychology

REVIEW
published: 14 November 2019
doi: 10.3389/fpsyg.2019.02527

Edited by:
Qinghua He,
Southwest University, China

Reviewed by:
Jixin Liu,
Xidian University, China
Yiheng Tu,
Harvard Medical School,
United States

INTRODUCTION

As a substantial worldwide health problem, chronic back pain (CBP) is one of the most frequent complaints and the second most common symptom reported by patients during their primary physical care visits (Mantyselka et al., 2001; Vogt et al., 2005

TABLE 1 | Evaluation of cortical alterations in

TABLE 3 | Evaluation of cortical alterations in CBP patients using the MRS technique.

Author, year	Methods	Patients	Controls	Main ndings (patients compared with controls)
Grachev et al., 2000	^{1}H-MRS	Nine CLBP	11 Healthy controls	Alterations in the human brain chemistry in patients Decreased NAA and Glu in the dlPFC No chemical concentration differences in brain regions, such as the cingulate, sensorimotor, etc. Abnormal interrelationship between chemicals within and across brain regions A speci c correlation between regional chemical concentration and perceptual scores of anxiety and pain
Grachev et al., 2001	^{1}H-MRS	Nine CBP	16 Healthy controls	Alterations in NAA levels of the dlPFC and OFC Correlations between the levels of brain regional NAA (the OFC and dlPFC) and perceptual measures of pain in CBP patients Correlation between the NAA changes of the OFC and measures of anxiety in CBP patients
Grachev et al., 2002	^{1}H-MRS	12 CLBP with symptoms of anxiety	16 Healthy controls	An exact correlation between perception and brain chemical contents The dlPFC and OFC were considered as the best related chemical-perceptual network to pain The relationship between chemical-anxiety networks was best related to the OFC chemistry in controls and to the dlPFC, OFC, cingulate, and thalamus in CLBP patients The region best related to the affective component of pain was the cingulate cortex
Grachev et al., 2003	^{1}H-MRS	10 CBP with depression	10 Healthy controls	Decreased NAA levels in the right dlPFC Strong correlation between depression levels of CBP patients and the levels of NAA levels in the right dlPFC Weak correlation between the levels of pain levels and levels of NAA in the right dlPFC of CBP patients (compared to depression-NAA correlations)
Gussew et al., 2011	^{1}H-MRS	10 CLBP	10 Healthy controls	Decreased levels of Glu in the ACC Decreased levels of Gln in the anterior INS, ACC, and thalamus Decreased levels of NAA in the anterior INS and ACC Decreased levels of mI was reduced in the ACC and thalamus No signi cant changes for Cr
Sharma et al., 2011	^{1}H-MRS	11 CLBP	11 Healthy controls	Correlations between metabolite concentrations and pain characteristics Decreased NAA and Cho in the left S1 Lower correlations between all metabolites (NAA, Cho, mI, Glu, and Gln) in the right S1 Higher and signi cant correlations between left and right mI levels and between left mI and right Cho Negative correlation between left and right NAA levels and pain duration Positive correlation between right Glu/Gln concentrations and pain severity Signi cant changes in the neuronal–glial interactions in S1
Sharma et al., 2012	^{1}H-MRS	19 CLBP	14 Healthy controls	Lower right M1 NAA No signi cant differences in the Left M1 NAA and mI No signi cant correlations between pain characteristics and M1 neurochemical contents
Siddall et al., 2006	^{1}H-MRS	32 CLBP	33 Healthy controls	Signi cant differences in the chemical levels of ACC, thalamus, and PFC of patients compared with the ones of healthy subjects with accuracies of 100%, 99%, and 97%, respectively

^{1}H-MRS, single-voxel proton magnetic resonance spectroscopy; CBP, chronic back pain; CLBP, chronic low back pain; NAA, N-acetyl aspartate; Glu, glutamate; Gln, glutamine; Cr, creatine; mI, myo-inositol; Cho, choline; PFC, prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; OFC, orbital frontal cortex; INS, insula; S1, primary somatosensory cortex; M1, primary motor cortex.

unpleasantness (Schmidt-Wilcke et al., 2006). Importantly, the structural abnormalities in the brain can be reversed by e ective CBP treatments. For example, increased cortical thickness in the left dlPFC after treatment could be observed in CBP patients compared to that before treatment, and such improvement in brain structure was positively correlated with the reduction of pain and physical disability (Seminowicz et al., 2011, 2013). All these morphological ndings indicated that CBP is accompanied by brain atrophy in regions commonly associated with pain processing and modulation, which has a great in uence on pain chronicity (Li and Hu, 2016).

As an e ective technique to map white matter (WM) tractography in the brain (Pierpaoli et al., 1996; Basser and Jones, 2002), di usion tensor imaging (DTI) has been used to study the WM architecture and integrity in CBP patients (Buckalew et al., 2010; Ceko et al., 2015). Lower WM integrity of the splenium of the corpus callosum was found in disabled CBP patients (Buckalew et al., 2010), and importantly, negative correlation between total months of CBP and WM integrity of the splenium of the corpus callosum was observed. In addition, Vania Apkarian and his colleagues tracked brain properties in subacute back pain patients longitudinally for 1 year (Mansour et al., 2013)

and 3 years (Vachon-Presseau et al., 2016), as their pain either recovered or transitioned to chronic pain. Testing the role of the corticolimbic system in the development of CBP, Vania Apkarian and his colleagues observed that the dorsal medial prefrontal cortex (mPFC)-amygdala-nucleus accumbens network contributing to risk of chronic pain, which suggested that corticolimbic neuroanatomical factors were important features to predispose subacute back pain patients to recover from or transition to chronic pain (Vachon-Presseau et al., 2016).

The resting state fMRI and task fMRI are normally applied to investigate functional alterations in CBP patients by measuring the spontaneous blood-oxygen-level dependent (BOLD) activities of brain networks at resting state (Baliki et al., 2006; Barkhof et al., 2014; Vachon-Presseau et al., 2019; Zhang et al., 2019) and the evoked BOLD responses during pre-de ned tasks/stimuli (Aine, 1995; Lindquist, 2008), respectively. Previous studies using resting state fMRI revealed that CBP patients exhibited reduced deactivation in the mPFC, amygdala, and posterior cingulate cortex, which were considered as key brain regions in the default mode network (DMN) (Baliki et al., 2008). The disruptions of the DMN were related to the cognitive and behavioral impairments associated with chronic pain (Baliki et al., 2008). Additionally, the resting state functional connectivity (FC) of the DMN network was reported to be in uenced by negative mood in CBP patients, which implied that the abnormalities of the DMN were related to the information processing of a ective-motivational aspect of pain (Letzen and Robinson, 2017). Apart from the DMN network, decreasimpairments associated with

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by the duration and intensity of their chronic pain (Tamburin et al., 2014). Consistent with this behavioral result, the ERP data showed abnormal feedback processing in CBP patients during the Iowa gambling task (Tamburin et al., 2014). Speci cally, the amplitude of feedback-related negativity (FRN) was higher in wins than in losses in healthy controls, while the opposite results were obtained in CBP patients; the amplitude of P300 was higher in wins than in losses in healthy controls, whereas no signi cant di erence was observed in CBP patients. The abnormal feedback cognitive processing resulting in the impairments in the work and family settings were often reported by CBP patients (Tamburin et al., 2014). Moreover, CBP patients showed a lower amplitude of the later P260 component in somatosensory ERPs evoked by painful electrical stimuli, which also suggested the de ciency of higher cognitive functions in CBP patients (e.g., the function related to a ective distress) (Diers et al., 2007).

Accompanied by the long-term changes of cortical function, cortical reorganization in CBP patients due to the processes of neuronal plasticity was well documented (Flor et al., 1997a; Wiech et al., 2000). Demonstrated by an MEG study, alterations in the somatotopic organization of the S1 were observed in CBP patients (Wiech et al., 2000). Speci cally, being elicited by intracutaneous electrical stimuli with di erent intensities (from non-painful to painful), the maximal response in the primary somatosensory cortex was shifted more medially in CBP patients than in healthy controls (Flor et al., 1997a). Importantly, such brain reorganization was correlated with subjective pain ratings (Wiech et al., 2000). In summary, chronic pain is accompanied by cortical reorganization, an important neural marker indicating the persistence of the pain experience and the dysfunction of cortical processing. However, the potential relationships between ndings obtained using EEG/MEG and MRI techniques in evaluating cortical alterations in CBP patients remain to be elucidated.

MRS Studies

Chemical changes in the brain of CBP patients can be detected using in vivo single-voxel proton MRS (^{1}H-MRS), which is able to provide additional evidence on abnormal brain alterations associated with chronic pain (Gussew et al., 2011; Zhao et al., 2017). Several MRS studies showed that a reduced level of N-acetyl aspartate (NAA) was observed in several brain regions of CBP patients, including the dlPFC, orbitofrontal cortex (OFC), anterior INS, ACC, and thalamus (Grachev et al., 2000, 2003; Gussew et al., 2011; Sharma et al., 2011, 2012). In addition, some studies reported that CBP patients had reduced levels of glutamate (Glu) in the ACC (Gussew et al., 2011), glucose in the dlPFC (Grachev et al., 2000), and myo-inositol (mI) in the ACC and thalamus (Gussew et al., 2011). These brain chemical imbalances were negatively correlated with pain intensity in CBP patients (Grachev et al., 2000). Importantly, certain changes in brain chemistry were shown to be highly correlated with psychological factors (Siddall et al., 2006). For example, the levels of NAA in the right dlPFC and OFC were, respectively, correlated with depression (Grachev et al., 2003) and anxiety (Grachev et al., 2001, 2002

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