Published in final edited form as:

Prog Neurobiol. 2018 February ; 161: 1–22. doi:10.1016/j.pneurobio.2017.11.004.

Brodmann Area 10: Collating, Integrating and High Level Processing of Nociception and Pain

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Abstract

Multiple frontal cortical brain regions have emerged as being important in pain processing, whether it be integrative, sensory, cognitive, or emotional. One such region, Brodmann Area 10 (BA 10), is the largest frontal brain region that has been shown to be involved in a wide variety of functions including risk and decision making, odor evaluation, reward and conflict, pain, and working memory. BA 10, also known as the anterior prefrontal cortex, frontopolar prefrontal cortex or rostral prefrontal cortex, is comprised of at least two cytoarchitectonic sub-regions, medial and lateral. To date, the explicit role of BA 10 in the processing of pain hasn't been fully elucidated. In this paper, we first review the anatomical pathways and functional connectivity of BA 10. Numerous functional imaging studies of experimental or clinical pain have also reported brain activations and/or deactivations in BA 10 in response to painful events. The evidence suggests that BA 10 may play a critical role in the collation, integration and high-level processing of nociception and pain, but also reveals possible functional distinctions between the subregions of BA 10 in this process.

Keywords

Brodmann area 10; frontal pole; pain; nociception; anatomical connection; functional imaging

1. Background

Multiple frontal cortical brain regions have emerged as being important during pain experience (Apkarian et al., 2005; Kucyi and Davis, 2015; Neugebauer et al., 2009; Tracey

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and Mantyh, 2007). Pain is a complex phenomenon that includes sensory, emotion, cognition and integration across those dimensions. The involvement of high-order cortical areas, including the frontal regions, is therefore not surprising. Previous studies regarding cortical processing of pain have primarily focused on the “traditional” nociceptive pathways such as the insula and the anterior cingulate cortex (ACC), revealing multidimensional roles of these areas from sensory encoding to affective processing (Brooks and Tracey, 2007; Coghill et al., 1999; Davis et al., 2005; Derbyshire et al., 1997; Fuchs et al., 2014; Gu et al., 2013; Price, 2000; Shackman et al., 2011; Starr et al., 2009). The contribution of specific frontal regions to pain experience, on the other hand, is still ill defined at the current stage. One such region is the frontal pole (FP)—specifically within Brodmann areas 10 (BA 10) located in the anterior medial frontal cortex. This region is located inferior to Brodmann area 9 (BA 9, superior frontal cortex) and superior to Brodmann area 11 (BA 11, the anterior extension of orbitofrontal cortex). BA 10 (Figure 1), also known as the anterior prefrontal cortex, frontopolar prefrontal cortex or rostral prefrontal cortex, is a supramodal cortex that is involved in a wide variety of functions including risk and decision making, odor evaluation, reward and conflict, pain, and working memory (Burgess et al., 2007a; Gilbert et al., 2006b; Ramnani and Owen, 2004). While there may be differences between the right and left regions, some functions are bilateral, such as pain and emotional recognition (Burgess et al., 2007b). Although not specifically focusing on BA 10, previous literature has highlighted a complex role of the prefrontal cortex (PFC) in many aspects of the subjective appraisal of pain, including in allodynia (Casey et al., 2003), cognitive control (Apkarian et al., 2005), pain modulation (Lorenz et al., 2003), empathy for pain (Godinho et al., 2012), and pain anticipation (Palermo et al., 2015; Porro et al., 2003). Taken together, the fact that this region responds in a similar manner to noxious stimuli under different conditions of consciousness (see below), suggests an integrative role of BA 10 in pain/nociception. Additionally, the connections of BA 10 to sensory systems (Barbas et al., 2011) have been described. These connections are thought to provide the highest level of integration of such information, which may contribute to cognitive processing of outcomes (Petrides and Pandya, 2007). In this review, we focus on BA 10 in the processing of pain and discuss the following topics: (1) Anatomical connections of BA 10; (2) BA 10 and associated resting state brain networks; (3) Connectivity-based parcellation within BA 10; (4) BA 10 activity in different pain models and co-activated/co-deactivated brain regions and networks; and (5) Putative roles of BA 10 in pain processing. Based on the evidence, we propose a model for the involvement of BA 10 in pain/nociception.

2. BA 10 anatomical connections: Afferent and Efferent Pathways

Previous tracer studies in macaque monkeys have revealed multiple afferent and efferent pathways of BA 10 (Petrides et al., 2012; Semendeferi et al., 2001). In those studies, BA 10 has been shown to share reciprocal connections with adjacent supramodal cortices within the PFC, as well as with the cingulate cortex, anterior temporal cortex, the insular cortex, part of the parietal regions, the thalamus (predominately the mediodorsal, ventral anterior and intralaminar nuclei), and multiple limbic structures (Burman et al., 2011b; Fuster, 2015; Ongür and Price, 2000; Petrides and Pandya, 2007; Yeterian et al., 2012) (Fig. 2). Recent imaging studies of the human brain have largely confirmed these anatomical findings from

macaque monkeys by reporting consistent structural or functional connectivity between homologous areas (Anderer et al., 2001; Di Martino et al., 2008; Euston et al., 2012; Klein et al., 2010; Liu et al., 2013; Moayed et al., 2015; Ongür and Price, 2000; Orr et al., 2015). Below, we provide a brief overview.

2.1 Intrinsic cortico-cortical connections

In non-human primates, intrinsic connections are observed between the medial portion of BA 10 and many adjacent cortical regions within the PFC, including BA 32, 24 in the “medial” network (Carmichael and Price, 1996; Cavada et al., 2000), and areas 11 and 47/12 on the “orbital” frontal surface (Petrides and Pandya, 2007; Yeterian et al., 2012). The lateral portion of BA 10 is closely associated with the lateral prefrontal cortex, particularly the BA 8Ad, 9, the rostral part of BA 46 on the dorsal surface, and the BA 45, 47 on the ventral surface (Burman et al., 2011b; Carmichael and Price, 1996).

2.2 Extrinsic cortico-cortical pathways

Three distinct long association fiber pathways that relate BA 10 to multiple remote cortical regions were previously delineated in the white matter: namely, the extreme capsule fasciculus, the uncinate fasciculus and the cingulate fasciculus (Petrides and Pandya, 2007; Schmahmann et al., 2007; Yeterian et al., 2012). Through the extreme capsule fasciculus, BA 10 is connected to the midsection of the superior temporal gyrus (areas Ts2, Ts3, and paAlt, connected with the auditory association cortex), the multisensory processing area of the superior temporal sulcus (areas IPa, TAa and TPO), and the anterior agranular insular cortex (ventral part, BA 13, 14) (Petrides and Pandya, 2007; Yeterian et al., 2012). The uncinate fasciculus connects BA 10 with the rostral superior temporal region (or the temporal pole, including area Ts1 and the temporal pro-isocortex) (Petrides and Pandya, 2007; Schmahmann et al., 2007; Von Der Heide et al., 2013), the basal nuclei of the amygdala (Barbas et al., 2011; Carmichael and Price, 1995; Fuster, 2015; Petrides and Pandya, 2007; Von Der Heide et al., 2013), and the rostral parahippocampal gyrus (Burman et al., 2011b; Carmichael and Price, 1995; Fuster, 2015; Olson et al., 2015). The cingulate fasciculus provides a dorsal route between BA 10 and the cingulate cortex, which targets both the anterior cingulate gyrus (BA 24, 32) and the posterior cingulate regions (BA 23, 30, 31) (Petrides and Pandya, 2007; Schmahmann et al., 2007). Besides these connections, recent human studies have delineated a pathway between BA 10 and the visual association cortices in the parieto-occipital areas via the fronto-occipital fasciculus (Catani et al., 2012; Orr et al., 2015; Wu et al., 2016), a pathway that has not previously been seen in monkeys.

2.3 Frontal-subcortical connections

The medial prefrontal network, including BA 10, has prominent interconnections with the thalamus, specifically the mediodorsal (MD), ventral anterior (VA) and intralaminar (IL) nuclei (Fuster, 2015; Giguere and Goldman-Rakic, 1988; Ray and Price, 1993). BA 10 also sends efferents to the basal ganglia through subcortical bundles, in particular to the dorso- and ventromedial caudate nucleus of the striatum (Ferry et al., 2000; Ongür and Price, 2000). These efferents are further projected to the MD via the ventral pallidum and the globus pallidus (Ongür and Price, 2000), constituting several basal ganglia-thalamocortical circuits (Bonelli and Cummings, 2007). Finally, many regions within and adjacent to BA 10

have been seen to communicate, either directly or indirectly (via the thalamus), with the hypothalamus (Carmichael and Price, 1996; Fuster, 2015; Ongür et al., 1998; Ongür and Price, 2000; Petrides and Pandya, 2007; Rempel-Clower and Barbas, 1998) and the midbrain periaqueductal gray (PAG) (An et al., 1998; Fuster, 2015; Linnman et al., 2012; Ongür and Price, 2000).

Taken together, the underlying anatomical structure of the region provides a basis for BA 10 to interact with the brain regions that are known to be involved in pain processing (the “pain matrix”) such as the DLPFC, ACC, thalamus, insula and amygdala. However, it may be of note that the specificity of the afferent/efferent pathways between these regions and BA 10 is not known (and is also unlikely). Moreover, while most connections reviewed above are reciprocal, some of them may not be. For instance, several tracer studies in monkeys support a unilateral pathway between BA 10 and ventral striatum by showing projections from BA 10 to striatum but not from striatum to BA 10 (Burman et al., 2011a; Ferry et al., 2000).

3. BA 10 resting state functional connectivity: large-scale brain networks

Previous functional connectivity-based studies have described several large-scale networks in the human brain that show coherent patterns of spontaneous fluctuations during resting state (see Raichle (2011) and Heine et al. (2012) for reviews). Notably, the default mode network (DMN), the executive control network (ECN) and the salience network (SN, also known as the attentional network, see below), have been described as being associated with “high-level” cognitive, executive functions (Bressler and Menon, 2010), perception (Sadaghiani et al., 2015), saliency/attention (Menon and Uddin, 2010) as well as allostasis (Kleckner et al., 2017). Other networks such as the sensorimotor network (SMN), the auditory network and the visual network, are considered to support low-order” sensorimotor and sensory functions (Bressler and Menon, 2010; Heine et al., 2012; Raichle, 2015). Recent evidence has highlighted the involvement of BA 10 in multiple cognitive networks (i.e. the DMN, ECN and SN) (Greicius et al., 2003; Menon and Uddin, 2010; Seeley et al., 2007; Sridharan et al., 2008), which we review briefly in subsequent subsections. The DMN has been linked to task-independent “internal” processes such as interoception (Kleckner et al., 2017), self-referential evaluation (Davey et al., 2016), meditation (mind-wandering) (Brewer et al., 2011), and social cognition (Schilbach et al., 2008). The ECN is thought to execute multiple control functions in response to an internal or external stimulus, e.g. attention sustention (Seeley et al., 2007), working memory manipulation (Christophel et al., 2017; Lara and Wallis, 2015), decision-making and goal-oriented planning (Chatham et al., 2011; Domenech and Koechlin, 2015). The SN is activated by behaviorally salient events (Ham et al., 2013b), and is considered to be involved in cognitive control initiation (Menon and Uddin, 2010), high-level information integration (Menon, 2011), and behavioral response regulations (Medford and Critchley, 2010; Seeley et al., 2007). The disruption of these “high-order” brain networks has been seen to be associated with dysfunctions in cognition and emotional processing across various brain disorders (Heine et al., 2012; Menon, 2011).

3.1 BA 10 and the interaction of the “cognitive” networks

While intrinsically anticorrelated in the resting state (Fox et al., 2005), the DMN and the ECN/SN are reported to exhibit distinct patterns of activities during cognitive tasks, i.e. the DMN activity is generally inhibited whereas the activity in the ECN and SN is enhanced (however, see Brewer et al. (2011); Demertzi et al. (2014) where the authors observed enhanced activity in some components of the DMN during self-referential cognitive tasks, suggesting that there may be differences related to the specific nature of the task or condition *vs.* true resting state evaluation of the networks). Such opposition of the DMN, ECN and SN activity is critically related to the adjustment, maintenance, and shift of attention as well as cognitive performance (Eichele et al., 2008; Lin et al., 2015; Prado and Weissman, 2011). Using Granger causality analysis, Uddin et al. (2009) showed that the medial PFC (mPFC, mainly BA 10) and posterior cingulate cortex (PCC) of the DMN exerted control over a “DMN-anticorrelated” network that highly overlapped the ECN and SN. However, most other studies highlighted the frontoinsula structure of the SN as the key region to initiate the switch from the DMN to the ECN when a task is engaged (Chen et al., 2013; Goulden et al., 2014; Menon and Uddin, 2010; Sridharan et al., 2008). Notably, Chen et al. (2013) induced transcranial magnetic brain stimulations to the prefrontal nodes of each network, and reported that the DMN was under inhibitive control of the ECN/SN specifically from the interactions between the lateral anterior prefrontal nodes of the ECN/SN and the medial anterior PFC of the DMN. This model is supported by recent data using chronometric or causal analysis (Gao and Lin, 2012; Goulden et al., 2014; Wen et al., 2013). For example, Wen et al. (2013) reported a significant positive correlation between the causal influence from the ECN/SN to the DMN, but not from the DMN to the ECN/SN, and subjects’ behavior performance. Nevertheless, these results suggest the anterior PFC (BA 10, medial or lateral) may play an important role in the transition between the brain resting state and the task-processing state.

3.2 BA 10 and “sensory” interactions via the salience network

Many interactions but not all, of the lateral portion of BA 10 related to somatosensory function, are modulated by the SN. The SN describes a network of brain regions that are activated by the salience of either an external stimulus, which is referred to as “the physical distinctiveness or conspicuity of a stimulus, a relative property that depends on its relationship to the other surrounding stimuli” (Legrain et al., 2011) or internal physiological conscious or unconscious feelings (Critchley et al., 2004; Ham et al., 2013a). The SN, along with the ECN, was initially considered to be within a general “task-positive network” (while the DMN being the “task-negative network”) as these two networks show co-activations across a wide range of cognitive tasks (Dosenbach et al., 2006; Fox et al., 2005). Using independent component analysis, Seeley et al. (2007) delineated a specific SN that is anchored by frontoinsula cortices (anterior insula and ventrolateral prefrontal cortex, AI and VLPFC, BA 47, 12) and dorsal anterior cingulate cortex (dorsal ACC, BA 24, 32) while sharing extensive connections with the dorsolateral prefrontal cortex (DLPFC, BA 44, 45, 46), frontal pole (lateral BA 10), temporal pole (BA 38), superior temporal gyrus (BA 22), supplementary motor area (SMA, BA 6), parietal operculum (BA 40, 48), and subcortical regions such as amygdala, ventral striatum, dorsomedial thalamus, periaqueductal gray matter (PAG), and the substantia nigra/ventral tegmental area (SSN/VTA). The SN may be

involved in monitoring or paying attention to extrinsic (sensory) and intrinsic (cognitive, emotional, physiological) processes (Borsook et al., 2013a; Craig, 2003; Menon, 2011, 2015; Uddin, 2015). From its definition and components, the SN highly overlaps the previously well-defined “attentional network” (AN) (Corbetta et al., 1993; Davis et al., 1997; Miron et al., 1989; Pardo et al., 1990; Paus et al., 1997; Petersen and Posner, 2012; Peyron et al., 1999; Posner, 2012). Using the concept of AN, previous studies have described the detection of pain with two levels, a first non-specific “arousal” level and a following more specific “oriented attention” level. However, the SN may differ from the AN in that the SN may also incorporate subconscious processing. In this paper, we use these two terms (i.e. SN and AN) interchangeably. The SN (particularly the frontoinsula cortices and dorsal ACC) is believed to act as a central hub that “integrates highly processed sensory data with visceral, autonomic and hedonic markers so that the organism can decide what to do or not to do next” (Seeley et al., 2007). Therefore, the SN potentially provides a functional pathway for the lateral portion of BA 10 to interact with the “somatosensory networks”, allowing it to take part in the sensory and emotion detection, high-level integration and regulation processes.

4. Parcellation of BA 10

Brain regions have been subdivided based on differences in anatomical structure and function. BA 10 is the largest architectonic region of the frontal lobe and is considered to contain at least 2 distinct cytoarchitectonic areas (medial-to-lateral) (Mackey and Petrides, 2010). Functional differences have been described between the lateral and medial components of BA 10 in terms of (a) contrast between basal and experimental conditions and response times (Gilbert et al., 2006a); (b) distinctions in function, e.g. working and episodic memory (lateral activations) or mentalizing (medial activations) (Gilbert et al., 2006b); and (c) differences in functional connectivity, where lateral activation showed connectivity with regions such as the ACC, the DLPFC, the AI and lateral parietal cortex, and medial BA 10 mostly showed co-activations with the PCC and temporal pole regions (Gilbert et al., 2010) (see section 3 above). These connections have an anatomical foundation in primate studies (Neubert et al., 2014); and (d) patients with BA 10 damage showed correlation between multitasking performance with volume of damage only in lateral BA 10 (Roca et al., 2011). Refinement of these features has been reported according to connectivity-based analysis showing 2 sub-regions (i.e. medial and lateral) based on diffusion tensor imaging (Moayed et al., 2015) or cytoarchitectural differences in the region (Bludau et al., 2014). Other studies have suggested 3 sub-regions that have been designated orbital (FPo), lateral (FPI), and medial (FPM) sub-regions (Liu et al., 2013; Ongür et al., 2003; Ray et al., 2015). Each area was reportedly associated with different functions based on diffusion tensor imaging (DTI) connectivity, e.g. as denoted in Liu et al. (2013): FPo—social emotion; FPI—cognitive processing; and FPM—with the DMN. However, a previous meta-analysis of 162 studies reported that the distinction in functional connectivity was not clear along a rostral-caudal or dorsal-ventral gradient (Gilbert et al., 2010). In this review, we follow the two sub-region parcellation and only discuss the differences in the connectivity and functions between the medial and the lateral portions of BA 10.

5. BA 10 and Nociception/Pain: the evidence

Although some have suggested that the putative role of BA 10 in pain may be due to the region's functional role related to "attention to sensory input" and "watchfulness" (Burgess et al., 2007b, 2007a), its explicit role in pain and nociception is not well defined in the literature. In order to evaluate the potential role of the region, we performed a literature search on imaging studies showing activation in BA 10. We have focused on 5 measures; four functional, each utilizing different methodologies, namely, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), near infrared spectroscopy (NIRS) and electroencephalography (EEG), and one structural (voxel-based morphometry on gray matter changes). The differences in the first four relate to quantitative measures (e.g., fMRI vs. PET) and temporal resolution (NIRS and EEG vs. fMRI and PET).

5.1 Search Terms

An English language literature search of BA 10 related to sensory input, brain measures was undertaken using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>). The following keywords were included to search paper titles/abstracts: "pain", "prefrontal" plus "functional MRI" (or "fMRI"), "positron emission tomography" (or "PET"), "near infrared spectroscopy" (or "NIRS"), "Electroencephalography" (or "EEG") and "voxel-based morphometry" (or "VBM"). Additional strategies included manual searches for relevant articles from the selected papers' reference lists, as well as utilization of PubMed's related articles function. Data was collated into the following brain measures of pain or nociception and tabulated as follows: (1) BOLD-fMRI (25 studies, Table 1); (2) PET (26 studies, Table 2); (3) NIRS (10 studies, Table 3); (4) EEG (4 studies, Table 4); and (4) Gray matter changes (16 studies, Table 5). Only references that presented changes in BA 10 are included. Coordinates reported in the Talairach atlas were converted into the Montreal Neurological Institute (MNI) coordinate system using the BioImage Suite coordinate converter (Lacadie et al., 2008) provided at <http://bioimagesuite.yale.edu/>.

5.2 fMRI and BA 10 (Table 1)

Table 1 lists fMRI related studies that demonstrate signal changes in BA 10. Most are experimental pain stimuli (thermal, electrical, mechanical or chemical). In the 29 different pain scenarios, activations were reported in 25 cases (86%), of which 22 were observed in the lateral portion of BA 10 (88% of the 25 cases, including 2 which involved both the medial and the lateral portions of BA 10). Within the 20 cases where clear hemispheric lateralization of lateral BA 10 activation was observed, 30% showed contralateral, 45% showed ipsilateral and 25% showed bilateral activation. While early work focused more on activations, six recent fMRI studies also reported BA 10 deactivations following pain, all of which were observed in the medial portion of BA 10 (4 bilateral, 1 contralateral and 1 ipsilateral). Of the series reported here, in the 4 studies with chronic pain subjects, the detected changes showed no particular trend with lateral or medial BA 10 or lateralization (i.e., ipsilateral or contralateral). The fMRI literature indicates that the BA 10 response to noxious stimuli in healthy subjects or chronic pain patients is present across a number of studies. However, there are missing elements in Table 1, including (1) sensitivity of activation that may vary across subjects; (2) level of pain that is required to activate BA 10;

and (3) the number of responders vs. non-responders to the stimuli. As noted above in the functional evaluation of BA 10, the region is involved in a number of processes including cognition, memory and awareness. Many of these processes are part of the experimental paradigms noted in the table.

5.3 PET and BA 10 (Table 2)

Positron Emission Tomography can be used to directly measure blood flow ($H_2^{15}O$ -PET) or cerebral metabolism (fluorodeoxyglucose-PET). In the PET studies, both lateral and medial changes were observed. Unlike the fMRI studies, it seems the medial portion is more consistently involved in the clinical pain group (4 out of the 6 clinical studies). Consistent with the fMRI data, the majority of experimental pain PET studies showed lateral activation, especially in healthy subjects. The same caveats exist as those noted for the fMRI data presented.

5.4 NIRS and BA 10 (Table 3)

As shown in Table 3, a number of NIRS studies report hemodynamic changes in BA 10. Most have been conducted in healthy subjects. The distribution of medial and lateral changes is nearly even in the data reported. Lateral BA 10 is more often associated with activations (4/5 studies), while medial BA 10 was reported to show deactivations following pain (5/5 studies).

5.5 EEG and BA 10 (Table 4)

In Table 4, we list the four EEG studies that reported changes in BA 10 neuronal activity following pain in healthy subjects (3 studies) and chronic pain patients (1 study). The involvement of medial or lateral BA 10 was determined based on source localization analysis result or the approximate location of frontopolar electrodes. Like NIRS, EEG does not have high spatial resolution and is not able to detect deep layer brain activities. Moreover, EEG studies usually describe enhanced/reduced electrical activities in difference bands (alpha, beta, theta, etc.) in pain. Although not specifically focused on BA 10, a recent review of EEG studies revealed that patients with chronic pain exhibit increase of theta and alpha band power at rest, and a decrease in the amplitude of evoked potentials after sensory stimulation and cognitive tasks (Pinheiro et al., 2016). However, this pattern is not consistently observed in the 4 reviewed studies.

5.6 Gray Matter Changes in BA 10 (Table 5)

Gray matter (GM) changes seem to reflect alterations in dendritic density and complexity (Borsook et al., 2013b). Our review of the literature consisted of chronic pain conditions. Overall, BA 10 GM volume or density was decreased in most of the studies (14 of 16 studies). It may be important to note that in the majority of these studies, GM decreases were observed in the medial portion (12 of 14 studies). Patients with chronic pain conditions often showed reduced gray matter volume in BA 10 (e.g. chronic low back pain (Apkarian et al., 2004), migraine (Valfrè et al., 2008), fibromyalgia (Kuchinad et al., 2007), see Table 5), or reduced response to experimental pain (rheumatoid arthritis (Jones and Derbyshire, 1997), chronic pain disorder (Gündel et al., 2008)). Recently, studies reported that the gray

matter volume is negatively correlated with the chronic pain intensity (Fritz et al., 2016; Krause et al., 2016; Moayedi et al., 2011; Obermann et al., 2013). The explicit function of BA 10 in pain chronification is unknown (see section 6.8), but may be more involved in disruptive emotional and cognitive processes associated with chronic pain.

5.7 Co-responding areas with BA 10 in pain revealed by fMRI and PET (Tables 6–8)

Brain regions that were reported to be co-activated/co-deactivated with the BA 10 pain response in previous fMRI and PET studies are presented in Table 6 (healthy subjects) and Table 7 (chronic pain patients). We excluded NIRS and EEG studies from this analysis due to the limited spatial coverage and imaging depth. In healthy subjects, co-activations with lateral BA 10 were commonly seen in the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), the ACC, the insular cortex, DLPFC, VLPFC, premotor area (PMA), inferior parietal lobule (IPL), subcortical structures such as the thalamus and striatum, and the cerebellar (Fig. 3a, 3b). These co-activated brain regions mainly overlapped the “task-positive” SN and ECN (see section 3). On the other hand, deactivations in the medial BA 10 following acute experimental pain were associated with deactivations mostly in the DMN such as the PCC, ACC, lateral parietal cortex (the angular gyrus), superior/middle temporal gyrus, amygdala, and parahippocampal gyrus (Fig. 3c). It may be of note that the PCC, lateral parietal cortex and/or the parahippocampal gyrus (which are sometimes referred to as the “hippocampal-cortical memory network” (Deshpande et al., 2011)) were seen to exhibit enhanced activities following pain in some of the studies (Fig. 3d). The co-activated brain regions also include, entirely or partially, the SMN (Fig. 3e), the cortical-amygdala-PAG-striatal circuit involved in emotion detection and regulation (Etkin et al., 2015) (Fig. 3f), as well as the antinociceptive network that is known to induce top-down endogenous modulation of pain (Bingel et al., 2011; Ossipov et al., 2014; Tracey and Mantyh, 2007) (Fig. 3g). These findings of functional connectivity in pain are also consistent with the anatomical studies (see Fig. 2). In chronic pain studies, while the distinct pattern of connections for lateral and medial BA 10 was largely similar, we observed a much more frequent involvement of medial BA 10 in chronic pain patients (7/9 cases with experimental pain and 5/7 cases with spontaneous pain, as opposed to 10/43 cases in healthy subjects). This trend is also observed from the results of the GM volumetric changes in chronic pain patients compared with healthy controls, where a majority of studies showed decreased GM volume or density in the medial BA 10 (Table 8). The observed volumetric abnormality may be a consequence of functional changes in chronic pain (Rodriguez-Raecke et al., 2009) such as (a) potential excitatory processes that diminish dendritic complexity as seen in other brain regions (e.g. the hippocampus, see Putcha et al. (2011)) or (b) more likely, reduced cortical activity suggesting potential inhibitory systems acting on dendritic complexity in pain and other pathological conditions (Christoffel et al., 2011; Klenowski et al., 2015; Luo et al., 2014). Other brain regions that more frequently have GM changes along with medial BA 10 include the ACC, insula, multiple prefrontal areas (including DLPFC, VLPFC and orbitofrontal cortex), superior temporal gyrus/middle temporal gyrus, striatum, hippocampus/parahippocampus and cerebellar.

6. BA 10 and Putative Roles in Pain

The data collected and presented in Figures 2–3 and Tables 1–8 provide support for the putative involvement of BA 10 in pain. Based on the data available, there are a number of trends: (1) BA 10 shares extensive anatomical and functional connections with various cortical and subcortical regions, including many that are traditionally considered to be within the so-called “pain matrix” (Iannetti and Mouraux, 2010). (2) Changes in BA 10 in response to experimental/acute or chronic pain are present. (3) Such changes are observed in a number of studies across multiple imaging modalities. (4) Acute pain seems to drive changes in the lateral BA 10, while chronic pain alters the medial BA 10. (5) Lateral BA 10 is more associated with brain activations, whereas medial BA 10 is more often deactivated with pain. (6) Chronic pain produces volume cortical decreases in medial BA 10 more often than in lateral BA 10. (7) Pain activates both cortical and subcortical pathways of BA 10, potentially enabling multiple sensory, emotional, attentional or executive control processes. Especially, medial BA 10 seems to be involved in cognitive/emotional processing in pain whereas lateral BA 10 is more involved in sensory including pain modulatory functions. The evidence provides a basis for a potential mechanism of alterations of specific dysfunctions in pain patients that relates to our current understanding of putative functions of the brain regions.

6.1 BA 10, DMN, SN and attention towards pain

As noted above, the medial portion of BA 10 has been shown to be both anatomically connected and functionally correlated with many brain regions within the DMN in pain, while the lateral BA 10 has been linked to the SN. A task or a salient event generally activates the SN (or AN) in two steps, at an arousal level first and then at an oriented attentional level if necessary. As noted in section 3.2, the arousal and attention reorientation are likely to initialize the switch from the DMN to the ECN, leading to deactivation of the DMN. Therefore, the activation of the lateral BA 10 with the SN as well as the deactivation of the medial BA 10 with the DMN observed in the above-reviewed pain studies may be a reflection of an individual’s attention towards pain, i.e. a switch of the brain focus from the “internal world” to the external pain event driven by the intrinsic salience of pain. Indeed, studies in healthy subjects have shown significantly enhanced activation or attenuated deactivation in medial BA 10 (with the affective division of the ACC) during cognitive distraction as opposed to no distraction (Bantick et al., 2002; Kucyi et al., 2013; Valet et al., 2004). In contrast, many areas of the pain matrix (e.g., thalamus, insula, cognitive division of the ACC, which has been recently re-reviewed as a system of salience detection system for pain (Legrain et al., 2011)) displayed reduced activation during distraction, supporting the behavioral results of reduced pain perception (Bantick et al., 2002). In another study, medial BA 10 and other DMN regions were seen to be deactivated during the anticipation of pain, but were re-activated during the actual pain perception (Ter Minassian et al., 2013). Additionally, Lui et al. (2008) reported stronger deactivation in medial BA 10 and perigenual ACC during painful stimuli than tactile touch, which they attributed to stronger DMN inhibition (as pain is intrinsically more salient and probably demands more attention). On the other hand, several chronic pain studies showed that the functional connectivity within the DMN and between the DMN and the medial PFC (including medial BA 10) may

be disrupted in chronic pain patients (Kucyi et al., 2014; Loggia et al., 2013; Tagliazucchi et al., 2010), and that this disruption was related to pain rumination (e.g. “*I cannot stop thinking about my pain*”) (Kucyi et al., 2014). These results were consistent with an early study showing that patients given prefrontal leucotomy exhibited reduced psychogalvanic responses related to the anticipation of pain with no change in pain tolerance (Elithorn et al., 1955).

6.2. BA 10, ECN and Pain Awareness

Frontal brain regions, including BA 10, have been implicated in executive control functions in awareness, cognition, maintenance of goals, decision-making and monitoring of bodily threat (Boschin and Buckley, 2015; Roca et al., 2011). Lesions of BA 10 in humans have resulted in diminished executive task performance, specifically the performance of goal-related behavior (Dreher et al., 2008). In a single subject clinical report of BA 10 lesions (Hoffmann and Bar-On, 2012), the authors suggested that the ‘*medial frontopolar cortex is necessary for emotional integration of internal states*’. In the context of pain, an aversive process, diminished function of BA 10, may result in behavioral consequences similar to those observed in patients with ACC lesions (Wilkinson et al., 1999). Patients who have undergone cingulotomies or ACC lesions may have pain relief (Sharim and Pouratian, 2016) or decreased pain levels (Qu et al., 2011) and may have indifference to pain (i.e., “do not care”) in which case there may be a disconnection between sensory and emotional processing. Such behaviors may be achieved by decreasing the negative affect associated with pain (Fuchs et al., 2014; LaGraize et al., 2004), and may extend to altered intention and self-initiated actions and attention (Cohen et al., 1999; Keogh et al., 2013; Oosterman et al., 2012). However, this is a complex issue since sub-regions of the ACC may contribute differently to pain and emotion (Vogt, 2005). For example, decreased pain thresholds and pain tolerance to experimental pain in these subjects have also been reported in patients after cingulotomy (Greenspan et al., 2008). A similar “I do not care” symptom is seen with pain asymbolia, which describes the inability of an individual to recognize pain as unpleasant and not causing suffering (Berthier et al., 1988). This dysfunction was observed after insular lesions and has been related to sensori-limbic dissociation. Currently, we are unaware of such specific deficit with lesions in BA 10.

Other important functional considerations for BA 10 in pain include complex processes such as error awareness. The processing of errors goes from the detection of errors to the recovery (Blavier et al., 2005; Borsook et al., 2014). Such system has been seen to take effect in the processing and learning of pain-related aversive information (Kobayashi, 2012). In many studies, the ACC stands out as a key region to evaluate error conditions and also to monitor response performance (Bush et al., 2000; Carter et al., 1998). This process is likely to interact with basal ganglia structures such as the striatum, the PAG and the dopamine system (SSN/MTA) to enhance learning and adaptation (Holroyd and Coles, 2002; Kobayashi, 2012). The medial prefrontal cortex (including BA 10) has been reported to contribute to the prediction of errors (Malekshahi et al., 2016). Other studies have shown that medial prefrontal lesions (largely within BA 10, 11 but also include part of the rostral ACC) could lead to impairments in performance monitoring and error correction (although also see Ullsperger et al. (2002)) (Stemmer et al., 2004; Turken and Swick, 2008).

The interconnectivity between frontal regions is complex in providing top-down cognitive control of emotional responses (Ray and Zald, 2012). Feed-forward and feed-back connections within BA 10 (medial and lateral divisions) and between BA 10 and other frontal regions (e.g., DLPFC, ACC) may contribute to integrated networks (viz., social emotional network, DMN, cognitive processing network) in these cognitive and emotional functions (Liu et al., 2013). Such interconnectivities have been reported to contribute to overall functions, for instance, by enhancing or suppressing processes such as attention (e.g. “clear of thoughts” before attention re-orientation) (Posner, 1994; Posner and Dehaene, 1994), or through subcortical connections (e.g., ACC-habenula) to provide “a teaching signal for value-based choice behavior” and thus avoid harmful outcomes (Vadovi ová, 2014).

Two potential pathways may exist for BA 10 to interact with motor-sensory processing regions during pain. First, the frontal nodes of the SN, e.g. the lateral prefrontal areas including part of the BA 10, have been reported to play a vital role in decision-making and goal-oriented action planning (Coutlee and Huettel, 2012). The control orders of the actions are likely to be conveyed via interactions between the SN and the ECN (Petersen and Posner, (2012), also see above), specifically from their nodes within the prefrontal cortex to the premotor cortex, guided by performance-monitoring signals from the midline structures such as the dorsal ACC (Apkarian et al., 2005; Botvinick et al., 2004). It has been suggested that the dorsal ACC may also provide a route for the medial portion of the frontal lobe and the rostral ACC to the motor areas (Holroyd and Coles, 2002), potentially allowing for the regulation of motor activities from the emotional and motivational aspects of pain. Another pathway for the prefrontal-motor crosstalk is probably through the basal ganglia and thalamus (Leisman et al., 2016). While multiple connections between the ventrolateral prefrontal cortex and basal ganglia exist (Borra et al., 2015), the prefrontal regions may exert control over the motor functions by mediating the basal ganglia inhibitive signals on the excitatory afferents from the thalamus to the motor-related regions (Chudler and Dong, 1995). This has been seen in e.g. Parkinson’s disease or Attention Deficit Hyperactivity Disorder (Cameron et al., 2010; Leisman et al., 2014).

6.3. BA 10 and Sensory-discriminative aspect of Pain

BA 10, especially its lateral portion, shares anatomical pathways and functional co-activations with multiple sensory processing areas (e.g. the SMN, thalamus and insula, see Fig. 2, Fig. 3). Specific imaging data suggested that BA 10 might play a role in the high-level evaluation and integration of the sensory-discriminative information of pain, e.g. relating to the encoding of different pain intensities. Several previous studies observed a significant negative correlation between the subject’s perceived pain intensity and the response in either the medial (Porro et al., 1998; Seminowicz and Davis, 2006) or the lateral BA 10 (Jantsch et al., 2005; Wiech et al., 2006), while other studies reported a positive correlation (Barati et al., 2013; Derbyshire et al., 1997). However, such correlation of BA 10 activity with pain intensity was not always present (Coghill et al., 1999). In fact, a recent study has shown that the main brain region to exhibit activity changes in parallel to pain perception is the posterior insula (Segerdahl et al., 2015). In an attempt to distinguish the brain regions involved in sensory encoding from those associated with cognitive evaluation,

Kong et al. (2006) showed that the lateral BA 10, along with other lateral prefrontal areas, was only activated during an individual's emotional and cognitive constructs of pain.

6.4 BA 10 and Affective-Motivational aspect of Pain

Affective-motivational functioning within BA 10 in pain can be inferred through its connectivity, placebo and opioid processing. Numerous anatomical interconnections of BA 10 with other prefrontal cortical areas and ACC have been described (see above sections of BA 10 connection). The involvement of the prefrontal structures and the ACC in the affective-motivational processing of pain has been reported by multiple studies (Bushnell et al., 2013; Coghill et al., 2003; Derbyshire et al., 1994; Rainville et al., 1997). Placebo may modulate the affective aspects of pain ("*I believe I am going to be less bothered by pain now*") (Lieberman et al., 2004; Nemoto et al., 2007) through shared emotion appraisal circuitry (Ellingsen et al., 2013). The lateral BA 10 has been related to placebo analgesia (Amanzio et al., 2013; Petrovic et al., 2010; Watson et al., 2009), hypnotic analgesia (especially, to the mediation of hypnotic suggestions) (Nusbaum et al., 2011; Rainville et al., 1997, 1999) and has been shown to exhibit greater activation with placebo than with opioid (remifentanyl) during pain (Bingel et al., 2011). Such emotional modulation of pain may be achieved by the co-activations of the lateral BA 10 with the cortical-amygdala-PAG-striatal network that is known to be critical in the regulation of negative emotions (Buhle et al., 2013; Cho et al., 2013).

6.5 BA 10 and Pain Modulation

A number of processes affecting cortical regions may contribute to pain modulation including analgesics, and CNS stimulation. Previous work, using PET, reported activation in the medial BA 10 following fentanyl administration (Firestone et al., 1996). Others have reported that the lateral BA 10 was activated during an opioid (remifentanyl) administration and suggested that these brain areas might participate in pain modulation or alertness (Wagner et al., 2001). However, these studies did not induce any painful stimuli with or without the administration of opioids. Therefore, they are not able to elucidate the specific effects of the analgesic-specific effect on BA 10. Activation in the lateral BA 10 was also observed in stimulation-induced analgesia (Kishima et al., 2010; Peyron et al., 2007). Connectivity analysis revealed that the activation of lateral BA 10 was significantly correlated with activities in the antinociceptive network (e.g. DLPFC, pregenual ACC, thalamus, PAG, and pons, as also seen in Fig. 3), supporting a top-down pain modulation pathway (Peyron et al., 2007). Besides, effective control of chronic pain with stimulation (Ohn et al., 2012; Yoon et al., 2014) or placebo-induced (Hashmi et al., 2012) analgesia was reported to result in reduced activity in lateral BA 10. In further support of BA 10 involvement in pain modulation, one study observed that patients with complex regional pain syndrome showed higher opioid receptor binding potential (i.e. loss of receptors) in lateral BA 10 (along with DLPFC) but lower potential in amygdala and parahippocampal cortex than observed in healthy controls (Klega et al., 2010).

6.6 BA 10 and Memory

The frontal areas are involved in episodic memory and such a process may allow for future (prospective memory) retrievals (Underwood et al., 2015). Aversive stimuli have an effect on

prospective memory as observed by activation in (right) BA 10, and the authors suggest that the region is involved in specific goal-directed behavior (Rea et al., 2011). In the context of pain, such a process of evaluating the past for future conduct would seem like a relevant behavior related to analgesic drive/choice (Borsook et al., 2013a), pain protection/fear of pain (Nelson and Churilla, 2015), or pain avoidance (Claes et al., 2015). Our findings of brain connectivity in pain shows the medial BA 10 may interact with other areas implicated in episodic memory (i.e. the cortical-hippocampal memory network, see Fig. 3). Indeed, the interplay between the medial prefrontal cortex and the hippocampal structures and its role in the encoding, consolidation and retrieval of memory have been highlighted many times in the literature (see Preston and Eichenbaum (2013) for a recent review). For example, Bingel et al. (2007) observed increased activity in the subgenual ACC and parahippocampal gyrus to repetitive painful stimulus over time, which may be related to pain memorization. Moreover, connectivity studies in chronic pain have reported increased functional connectivity with the medial BA 10/frontal regions and the hippocampus (Khan et al., 2014).

6.7 BA 10 and the Stress, Anxiety and Fear Response of Pain

Several studies indicated that the interconnectivity and functions of various brain systems/regions (e.g. prefrontal areas including medial BA 10, amygdala and PAG) were modulated when subjects were exposed to an unpredictable threat (Gold et al., 2015; Mobbs et al., 2007). This is likely to be reflected by the co-activation of the cortical-amygdala-PAG-striatal network following pain stimulus (Fig. 3). The hyperactivity of the amygdala could induce inhibitions to medial prefrontal neural activity, which might be independent to the affective attributes of stimulus processing (Garcia et al., 1999; Pérez-Jaranay and Vives, 1991). An animal model of arthritis pain revealed medial prefrontal activity is receptor-dependent (Ji and Neugebauer, 2011). The authors suggested that such inhibitory effect on the medial PFC from amygdala hyperactivity might be responsible for the cognitive deficits seen in chronic pain (Ji et al., 2010; Neugebauer, 2015). In stress disorders, the altered coupling of medial PFC, amygdala and hippocampus was also shown to be crucial (Shin et al., 2006). The associated anxiety and fear may have divergent effects on an individual's measures of pain, leading to potential hyperalgesia or hypoalgesia (Rhudy and Meagher, 2000). For example, a study comparing uncontrollable pain with self-controllable pain suggested that the increased connectivity between medial BA 10 and pain processing areas might be the key to produce the uncontrollability-induced pain facilitation (Bräscher et al., 2016). Hence, it was suggested that the BA 10 may act as an integrator of information that produces a threat detection system (Laeger et al., 2014). Indeed, animal models showed that lesions in the medial PFC could lead to confusions in managing threat (Morgan and LeDoux, 1995). In addition, the complex interactions of BA 10 in memory may contribute to autonomic changes involving brain regions such as the anterior insula. King et al. (2009) reported deactivation in BA 10 was associated with trauma recall and ACTH response.

6.8 BA 10 and Pain Chronification: Acute to Chronic Translocation of BA 10 Function

Chronic pain frequently results in cognitive impairment (see Moriarty et al. (2011) for a review), where BA 10, a region that is known to play a vital role in the integration of information and coordination of multiple cognitive processes (Burgess et al., 2007b, 2007a; Ramnani and Owen, 2004), may be involved. Burgess and colleagues have suggested that

the “rostral prefrontal cortex (PFC; approximating area 10) supports a cognitive system that facilitates either stimulus-oriented or stimulus-independent attending” (Burgess et al., 2007b). The gray matter decrease associated with chronic pain within the BA 10/ orbitofrontal area has been shown to correlate with disease duration (Krause et al., 2016). These changes can be reversed upon adequate treatment of chronic pain (May, 2008). We suggest that these differences may result from the alterations in brain networks in the transition from acute to chronic pain. However, the possibility that such differences are a consequence of other surrogate changes (e.g. in behavior, physical activities, cognitive performance, or mood) in this process cannot yet be ruled out.

7. Model: BA 10 in Nociception and Pain

Most of the previous work on BA 10 has focused on its functions relating to cognitive processing (Koechlin et al., 1999; Roca et al., 2011; Volle et al., 2011). The components that we address are in support of a proposed model for the region’s involvement in various aspects of nociception and in pain chronification, which we present below. However, it should be noted that the specific nature of such BA 10 involvement is unclear. Many other cortical and subcortical brain regions may also participate in the response to nociception or contribute to the chronic pain state (Bushnell et al., 2013; Kucyi and Davis, 2016).

1. *BA 10 anatomical connections with Pain Processing Regions:* Numerous imaging studies provide support for a role of BA 10 in nociceptive and pain processing. The afferent and efferent connections between BA 10 and the rest of the brain are summarized above. Of note, BA 10 sees direct connections with multiple sensory processing areas (especially in the superior/middle temporal gyrus and in the parieto-occipital region), and with subcortical regions such as the thalamus, hypothalamus, basal ganglia (striatum), amygdala, and brainstem structures including the PAG.
2. *BA 10 and co-activated/co-deactivated brain regions in pain.* The activation of lateral BA 10 following pain is seen to be with co-activations mainly in brain regions involved in the ECN and the SN (such as DLPFC, ACC, insula, IPL, SMA, PMA, thalamus), in the sensorimotor network (SI, SII), in the emotional regulation network, as well as in the antinociceptive pathway. On the other hand, co-deactivations with the medial BA 10 are commonly seen in the other DMN regions including PCC, lateral parietal cortex, MPFC, lateral temporal cortex, ACC and parahippocampal gyrus, as well as in amygdala and occipital lobe. Medial BA 10 activity was also seen to be associated with changes in the regions involved in episodic memory retrieval.
3. *BA 10 and distinct lateral-medial functions in pain.* Based on the anatomical and functional connectivity and the putative roles of BA 10 reviewed above, we propose that the medial BA 10 and lateral BA 10 may be associated with distinct functions in pain processing. These functions are likely to be carried out by BA 10 interactions with different brain networks (Fig. 4). The lateral portion may play a role in the high-level integration of nociceptive information received from sensory and emotional pathways. Outputs from the integration may relate to

differences between predominantly acute (nociceptive) and chronic (emotional/cognitive) pain processing. Lateral BA 10 may also exert its control over the perception of pain through its connection with the DLPFC, ACC, hypothalamus and PAG, a pathway that is known to induce top-down pain modulation. On the other hand, the deactivation of medial BA 10 with other DMN regions may reflect a subject's attention towards pain. Its interactions with the medial pain system, such as the ACC, may be responsible for the motivational and emotional aspects of pain (e.g. pain unpleasantness and other negative feelings). In addition, it is a region that may be involved in aversive processing through memory of the preceding process, memory of the ongoing process including pain vs. analgesia, and integrated in an overall stress response.

4. *BA 10 and pain chronification.* Preliminary evidence suggests that the medial and lateral components of BA 10 may contribute differently in acute and chronic pain (with lateral BA 10 being more active following acute pain in healthy subjects and medial BA 10 more involved in chronic pain patients). These differences presumably reflect alterations in brain networks in the transition from acute to chronic pain.

8. Caveats

We would like to point out a few caveats of BA 10's involvement in pain/nociception:

First of all, the involvement of BA 10 and large-scale brain networks in acute and chronic pain conditions described in this work (section 6 and Fig. 4) is based on inferences from the observed co-activated/co-deactivated brain regions as well as their putative functions revealed in previous studies. It should be noted that while resting state brain networks have become a focus of investigation in the literature, there is little information on their specific functional significance (viz., how differently brain regions coalesce with respect to functions and the nature of the functions). For the most part, studies attributing "functions" to these supposed brain networks are correlational, and the functional significance of these networks is largely unknown. Therefore, our understandings on the roles of these brain networks in pain remain to be hypothetical.

Second, in this study we only review the reports of pain studies noting BA 10 response. Indeed, a search term for "BA 10" and "pain" in PubMed yields few papers, as this region has not been the main focus of previous pain studies. It should be noted that this review does not provide information on the proportion of pain studies where other brain regions were activated in the absence of any BA 10 contribution, therefore not allowing for complete assessment of the "necessity" of BA 10 involvement in the different aspects of pain experience. Instead, we provide multiple tables across various imaging modalities and pain models to support a role of BA 10 in many functions associated with pain. In doing so, we wish to bring an overview of what BA 10 activity following pain could mean (e.g. activations or deactivations, in medial or lateral portion) and, at the same time, highlight the importance of this region that perhaps needs to receive more attention in future pain studies.

Finally, we would like to emphasize that few brain regions have response specificity, and BA 10 is certainly not one of them. While we provide support for a role of BA 10 in pain processing, it should be noted that other frontal regions (many connected with BA 10 including but not limited to the ACC, DLPFC and OFC), have been established for pain and other processes. The dorsal prefrontal cortex and cingulate cortex are good examples of multifunctional brain regions (Blumenfeld et al., 2011; Vogt et al., 1992). While many pain studies report changes in function and structure in pain, these regions are nevertheless involved in multiple functions. The literature search terms used in this study (which does not specify explicitly “BA 10” but used “prefrontal” to overcome the limited number of studies specifically focusing on BA 10) cannot distinguish the concomitant activity changes in BA 10 with other prefrontal regions (which is natural for BA 10 as a high-order multimodal area). However, the destruction of many forebrain structures including BA 10 does seem to profoundly alter a subject’s behavioral reactions and attitudes, including to pain. For example, LaGraize et al. (2004) observed that ACC lesions did not change mechanical hypersensitivity but the behavioral responses in neuropathic pain (although also see Daum et al. (1995) where frontal lesions were reported to increase pain threshold to external stimuli). The information provided in this review attempts to contribute a summary of a putative role of BA 10 in the integrative function of cortical response to pain and nociception, and we suggest that the region may play a significant role in pain—particularly the emotional and cognitive integration. As pain is a major threat to survival salience, it may be construed that many of these functions contribute to the integrative processing of the brain management in the painful/nociceptive state.

9. Conclusions

In the context of pain, we propose that BA 10, a region that may attract less attention in the previous work, is an important region that participates to the evaluation of acute or ongoing pain in the context of “higher cortical function” of cognitive processing—the past, the future and its implications on the individual’s behavior. Specifically, we show that the subregions of BA 10, medial or lateral, have different anatomical and functional connections, and may serve distinct functions related to various aspects of pain processing. While we highlight the involvement of BA 10 across multiple pain conditions, it should also be noted that this region is known to be involved in the evaluation of (almost all) salient stimuli related to potential behavioral significance (Burgess et al., 2007b; Herigstad et al., 2015; Roca et al., 2011). In the same manner that the nucleus accumbens is involved in multiple reward and aversive stimuli, we suggest that BA 10 is modulated in acute and chronic pain that may provide (1) new insights into pain neurobiology including pain chronification and (2) a potential marker for pain/nociception utilizing accessible technologies such as NIRS and EEG (e.g. see Aasted et al. (2016); Peng et al. (2018)). It may thus subserve as an integrator of pain or painful information and utilize executive functional processing to derive the best outcome (Snow, 2016; Underwood et al., 2015).

Acknowledgments

Funding sources: This work was supported by the National Institute of Health (NIH) and National Institute of General Medical Sciences (NIGMS) grant NIH-NIGMS 1-R01-GM104986 and the Mayday Fund, New York.

We acknowledge Dr. Andrew M. Youssef for providing one of the figures, and the three anonymous reviewers for their comments that helped improve this manuscript.

List of symbols and abbreviations

ACC	Anterior cingulate cortex
AI	Anterior insula
AN	Attentional Network
BA	Brodmann area
BOLD	Blood oxygenation level dependent
CNS	Central nervous system
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DTI	Diffusion tensor imaging
ECN	Executive control network
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
FP	Frontal pole
FPm	Medial frontal pole
FPI	Lateral frontal pole
FPo	Orbital frontal pole
GM	Gray matter
ICN	Intrinsic connectivity network
IL	Intralaminar (thalamic nucleus)
IPa	Deep cortical structure in the rostral segment of the superior temporal sulcus
IPL	Inferior parietal lobule
MD	Mediodorsal (thalamic nucleus)
MNI	Montreal neurological institute
mPFC	Medial prefrontal cortex
NIRS	Near infrared spectroscopy
OFC	Orbitofrontal cortex

paAlt	Lateral parakoniocortex
PAG	Periaqueductal gray
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
PMA	Premotor area
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SMA	Supplementary motor area
SMN	Sensorimotor network
SN	Salience network
SSN	Substantia nigra
TAa	Architectonic subdivision of the superior temporal sulcus
TPO	Polysensory region of the superior temporal sulcus
Ts1	Superior temporal area 1
Ts2	Superior temporal area 2
Ts3	Superior temporal area 3
VA	Ventral anterior (thalamic nucleus)
VBM	Voxel-based morphometry
VTa	Ventral tegmental area

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Highlights

- We review the anatomical connections and functional connectivity of Brodmann Area 10.
- We present evidence from literature of the involvement of BA 10 in response to pain.
- A model describing the role of BA 10 in pain processing is proposed.

Figure 1.
Depiction of Brodmann Area 10.

Figure 2.

Major anatomical connections between Brodmann area 10 and cortical/subcortical brain regions.

Abbreviations: ACC – anterior cingulate cortex; PCC – posterior cingulate cortex; MPFC – medial prefrontal cortex; OFC – orbitofrontal cortex; LPFC – lateral prefrontal cortex; IPL – inferior parietal lobule; PFG – part of rostral inferior parietal convexity; PG – part of caudal inferior convexity; SII – secondary somatosensory cortex; STG – superior temporal gyrus; STS – superior temporal sulcus; TAa – architectonic subdivision of the superior temporal sulcus; TPO – polysensory region of the superior temporal sulcus; Ts1 – superior temporal area 1; TPC – temporopolar cortex; BL – basolateral; BM – basomedial; MD – mediodorsal; IL – intralaminar; PV – paraventricular; PAG – periaqueductal gray.

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- (2) ACC and PCC: Kobayashi and Amaral (2003), Kobayashi and Amaral (2007) (Monkey), Petrides and Pandya (2007) (Monkey), Orr et al. (2015) (Human).
- (3) Rostral STG: Petrides and Pandya (2007) (Monkey), Saleem et al. (2008) (Monkey).
Amygdala: Carmichael and Price (1995) (Monkey), Burman et al. (2011a) (Monkey).
Parahippocampus: Kondo et al. (2005) (Monkey), Saleem et al. (2008) (Monkey), Burman et al. (2011b) (Monkey).
- (4) Visual association cortex: Catani et al. (2012) (Human), Orr et al. (2015) (Human), Wu et al. (2016) (Human).
- (5) Insula cortex: Makris and Pandya (2009) (Human), Saleem et al. (2008) (Monkey), STG, STS, auditory association cortex: Ban et al. (1991) (Monkey), Hackett et al. (1998) (Monkey), Romanski et al. (1999) (Monkey), Petrides and Pandya (2007) (Monkey), Makris

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(6)IPL, parietal operculum: Makris et al. (2005) (Human), Petrides and Pandya (2006) (Monkey), Schmammann et al. (2007) (Monkey).

(7)Thalamus: Ray and Price (1993) (Monkey), Bachevalier et al. (1997) (Monkey), Burman et al. (2011a) (Monkey). Midbrain PAG: An et al. (1998) (Monkey), Sillery et al. (2005) (Human), Hadjipavlou et al. (2006) (Human), Burman et al. (2011a) (Monkey). Midbrain pons: Arnsten and Goldman-Rakic (1984) (Monkey), Petrides and Pandya (2007) (Monkey). Hypothalamus: Ongür et al. (1998) (Monkey), Rempel-Clower and Barbas (1998) (Monkey), Burman et al. (2011a) (Monkey). Striatum: Selemon and Goldman-Rakic (1985) (Monkey), Ferry et al. (2000) (Monkey), Leh et al. (2007) (Human).

Figure 3.

Topography of Medial and Lateral BA 10 Interactions with Structures Involved with Resting State Networks in pain (summarized from Table 5 and 6).

The co-activated/co-deactivated regions entirely or partially overlap the following brain networks: (a) Salience Network (Arousal and Oriented Attention Network): VLPFC, insular cortex, dorsal ACC, Inferior parietal lobule, SMA, thalamus, PAG, striatum, amygdala. (b) Executive Control Network: DLPFC, pregenual ACC, premotor area, SMA, inferior parietal lobule, insular cortex. (c) Default Mode Network: Medial anterior prefrontal cortex, ACC, MPFC, lateral temporal cortex, PCC, lateral parietal cortex, hippocampal/parahippocampal formation, and amygdala. (d) Hippocampal-Cortical Memory network: PCC, lateral parietal cortex, hippocampal/parahippocampal formation. (e) Sensorimotor Network: premotor area, SMA, SI, SII, cerebellar. (f) Cortical-amygdala-PAG-striatal circuit: dorsal ACC, insular cortex, PAG, striatum, amygdala. (g) Antinociceptive network: DLPFC, pregenual ACC, thalamus, PAG.

Figure 4.

Model of BA 10 roles and functions in nociception and pain. Red arrows indicate activating processes whereas blue arrows indicate deactivating processes.

Medial BA 10: (1) Default Mode Network → Medial BA 10: attention towards pain; (2) Hippocampal-Cortical Memory Network → Medial BA 10: Episodic memory retrieval on previous nociception/pain experience; (3) Emotion Network ↔ Medial BA 10: Affective and emotional processing (unpleasantness of pain), coding of fear, stress and anxiety. Lateral BA 10: (4): Emotional Network → Lateral BA 10: Integration of the affective aspect of pain. (5) Lateral BA 10 → Emotional Network: Emotional modulation of pain; (6) Sensorimotor Network → Lateral BA 10: Integration of the sensory aspect of pain; (7) Salience Network (Attentional network) → Lateral BA 10: detection of the salience of pain, first at a nonspecific arousal level then at a specific oriented attention level; (8) Lateral BA 10 → Executive Control Network: situation evaluation, decision making and planning towards pain-related executive functions; (9) Lateral BA 10 → Antinociceptive Network: Endogenous top-down pain modulation.

Table 1

BOLD-fMRI measures of pain response in BA 10.

References	Subject	Pain stimulus type	Stimulus location	BOLD response	Location within BA 10 (MINI Coordinate of peak voxel)
Baron et al. (1999)	Healthy	Capsaicin-induced allodynia	Low forearm	Activation	Lateral portion (-29, +60, +22), contralateral to stimulus
Becerra et al. (1999)	Healthy	Evoked thermal (heat)	Dorsum of hand	Activation	Lateral portion (+26, +47, +12), contralateral to stimulus
Tracey et al. (2000)	Healthy	Evoked thermal (cold)	Dorsum of hand	Activation	Lateral portion (+29, +57, +3), contralateral to stimulus
Apkarian et al. (2001)	Chronic pain	Evoked thermal (heat)	Chronic pain hand	Activation	Medial portion, contralateral to stimulus
Frankenstein et al. (2001)	Healthy	Evoked thermal (cold)	Dorsum of foot	Activation	Lateral portion (-34, +50, +14), contralateral to stimulus
Fulbright et al. (2001)	Healthy	Evoked thermal (cold)	Foot	Activation *	Lateral portion, slightly lateralized to the right side
Kurata et al. (2002)	Healthy	Evoked thermal (heat)	Forearm	Activation	Lateral portion (+43, +41, +21), ipsilateral to stimulus
Coghill et al. (2003)	Healthy	Evoked thermal (heat)	Lower leg	Activation	Lateral portion (+31, +67, -1) (+33, +66, -10), ipsilateral to stimulus
Strigo et al. (2003)	Healthy	Evoked thermal (heat)	Upper chest	Activation	Lateral portion (+42, +50, -2), on the right side
Cook et al. (2004)	Healthy	Evoked thermal (heat)	Thenar surface of hand	Activation	Lateral portion (-24, +57, +27), ipsilateral to stimulus
	Fibromyalgia	Evoked thermal (heat)	Thenar surface of hand	Activation	Lateral portion (-45, +46, +10), ipsilateral to stimulus
Derbyshire et al. (2004)	Healthy	Evoked thermal (heat)	Palmar surface of hand	Activation	Lateral portion (-48, +42, +18) (-40, +54, -2), contralateral to stimulus
Valet et al. (2004)	Healthy	Evoked thermal (heat)	Volar forearm	Activation *	Lateral portion, bilateral, L (-36, +50, +12), R (+36, +52, +14)
Jantsch et al. (2005)	Healthy	Evoked mechanical	Finger	Activation	Lateral portion, bilateral, L (-20, +59, +11), R (+20, +61, +15)
					Medial portion (+10, +68, +16), contralateral to stimulus
Mohr et al. (2005)	Healthy	Evoked electrical	Tooth (incisor)	Activation	Lateral portion, bilateral, L (-20, +59, +11) (-35, +50, +19), R (+20, +61, +15) (+38, +44, +21)
		Evoked thermal (heat)	Thenar surface of hand	Activation	Lateral portion (+26, +54, -4), ipsilateral to stimulus

References	Subject	Pain stimulus type	Stimulus location	BOLD response	Location within BA 10 (MNI Coordinate of peak voxel)
Moulton et al. (2005)	Healthy	Evoked thermal (heat)	Dorsum of foot	Activation	Lateral portion (+39, +50, 0), contralateral to stimulus
Zambreanu et al. (2005)	Healthy	Heat/capsaicin-induced second hyperalgesia	Lower leg	Activation *	Lateral portion (+22, +62, 10), ipsilateral to stimulus
Albuquerque et al. (2006)	Healthy	Evoked thermal (heat)	Masseter	Deactivation Activation	Medial portion, contralateral to stimulus Medial portion (+6, +58, +1), ipsilateral to stimulus
Baliki et al. (2006)	Chronic back pain	Spontaneous back pain		Activation	Medial portion, bilateral, (+18, +60, +12)
Gündel et al. (2008)	Healthy	Evoked thermal (heat)	Inner forearm	Activation	Lateral portion (-45, +45, -9), ipsilateral to stimulus
	Somatoform pain disorder	Evoked thermal (heat)	Inner forearm	Deactivation **	Medial portion (+6, +54, -16), mainly contralateral to stimulus
Lui et al. (2008)	Healthy	Evoked mechanical	Dorsum of hand	Deactivation	More medial portion, bilateral, (-15, +57, 0)
Schoedel et al. (2008)	Healthy	Evoked mechanical	Finger	Activation	Lateral portion, bilateral, L (-17, +59, +9), R (+44, +50, +10)
Kong et al. (2010)	Healthy	Evoked thermal (heat)	Medial forearm	Activation	Lateral portion (+42, +46, +4), ipsilateral to stimulus
		Evoked thermal (heat)	Medial forearm	Deactivation	Medial portion, bilateral, (-4, +64, +28)
Rottmann et al. (2010)	Healthy	Evoked electrical	Dorsum of hand	Activation	Lateral portion (+37, +60, +16), ipsilateral to stimulus
Tseng et al. (2010)	Healthy	Evoked thermal (heat)	Dorsum of foot	Activation	Lateral portion, bilateral, L (-30, +34, +10), R (+40, +54, +14)
Loggia et al. (2012)	Healthy	Evoked mechanical (pressure)	Calf (leg)	Activation	Lateral portion (+42, +52, +22), contralateral to stimulus
				Deactivation	Medial portion (-4, +68, +18), bilateral
Quion et al. (2014)	Healthy	Evoked thermal (heat)	Dorsal forearm	Deactivation	Medial portion, bilateral, L (-5, +53, +12), R (+10, +63, +11)

* Compared with innocuous stimulus.

** Compared with healthy controls

Table 2

PET measures of pain response in BA 10.

References	Subjects	Pain stimulus type	Location	Response	Location within BA 10 (MINI Coordinate of peak voxel)
Derbyshire et al. (1994)	Healthy	Evoked thermal (heat)	Back of hand	rCBF activation *	Lateral portion (+27, +45, +8), ipsilateral to stimulus
	Atypical facial pain	Evoked thermal (heat)	Back of hand	rCBF deactivation *	Medial portion (+7, +52, -7), ipsilateral to stimulus
Rosen et al. (1994)	Coronary artery disease	Evoked angina (chest pain)		rCBF activation	Medial portion, bilateral, L (-14, +60, -7), R (+15, +58, -7)
Hsieh et al. (1996b)	Healthy	Evoked chemical (ethanol)	Lateral aspect of upper arm	rCBF activation *	Lateral portion (+21, +48, +29), ipsilateral to stimulus
Hsieh et al. (1995)	Painful neuropathy (trauma/injury)	Spontaneous neuropathic pain		rCBF activation	Lateral portion, bilateral, L (-47, +51, -11), R (+43, +59, -12)
Casey et al. (1996)	Healthy	Evoked thermal (cold)	Hand	rCBF activation *	Lateral portion (+27, +45, +19), ipsilateral to stimulus
Hsieh et al. (1996a)	Episodic cluster headache	Nitroglycerin-induced cluster headache		rCBF deactivation	Medial portion (+14, +67, -1)
Vogt et al. (1996)	Healthy	Evoked thermal (heat)	Dorsum of hand	rCBF deactivation	Lateral portion (-25, +56, -11)
Derbyshire et al. (1997)	Healthy	Evoked thermal (heat)	Back of hand	rCBF deactivation *	Medial portion (-10, +45, -8), contralateral to stimulus
				rCBF activation *	Lateral portion, bilateral, L (-33, +47, +4), R (+31, +51, +3)
Derbyshire and Jones (1998)	Healthy	Evoked thermal (heat)	Hand	rCBF activation *	Lateral portion (+31, +45, +21), ipsilateral to stimulus
Iadarola et al. (1998)	Healthy	Capsaicin-induced allodynia	Volar forearm	rCBF activation	Lateral portion, bilateral, L (-35, +46, -11), (-37, +42, -3), R (+37, +46, +2), (+21, +53, -9)
				rCBF activation *	Lateral portion, bilateral, L (-31, +53, -10), R (+29, +49, -10), (+37, +44, +2), (+19, +50, 0), (+17, +53, -8)
Peyron et al. (1998)	Lateral medullary infarct	Post-stroke allodynia	Thigh/Forearm (affected side)	rCBF deactivation	Medial portion (+13, +53, +10), contralateral to stimulus
		Evoked electrical	Thigh/Forearm (unaffected side)	rCBF deactivation	Medial portion (+9, +60, +15), ipsilateral to stimulus
Hsieh et al. (1999)	Painful trigeminal neuropathy	Spontaneous neuropathic pain		rCBF deactivation	Medial portion (-8, +65, -1) Lateral portion (+36, +56, -3)

References	Subjects	Pain stimulus type	Location	Response	Location within BA 10 (MNI Coordinate of peak voxel)
Kupers et al. (2000)	Chronic facial pain	Spontaneous neuropathic pain		rCBF activation	Medial portion (-17, +66, -5) Lateral portion (-21, +52, +30)
Casey et al. (2001)	Healthy	Evoked thermal (heat)	Volar forearm	rCBF activation	Lateral portion (+47, +50, +2), contralateral to stimulus
Witting et al. (2001)	Healthy	Evoked chemical (capsaicin)	Volar forearm	rCBF activation *	Lateral portion, bilateral, L (-41, +32, +10), R (+39, +53, -15)
		Capsaicin-induced allodynia	Volar forearm	rCBF activation *	Lateral portion, bilateral, L (-33, +49, +21), (-34, +56, -15), (-39, +46, -4), R (+39, +57, -16)
Lorenz et al. (2002)	Healthy	Evoked chemical (capsaicin)	Volar forearm	rCBF activation	Lateral portion (-26, +54, 0), ipsilateral to stimulus
		Evoked thermal (heat)	Volar forearm	rCBF activation	Lateral portion (+40, +51, -3), contralateral to stimulus
		Capsaicin-induced allodynia	Volar forearm	rCBF activation	Lateral portion, bilateral, L (-24, +54, +5), R (+38, +51, +1)
		Capsaicin-induced hyperalgesia	Volar forearm	rCBF activation	Lateral portion, bilateral, L (-24, +58, -4), R (+38, +51, -2)
Kupers et al. (2004)	Healthy	Evoked chemical (hypertonic saline)	Masseter muscle	rCBF activation	Lateral portion (+32, +48, +12), ipsilateral to stimulus
		Hypertonic saline-induced allodynia	Area around masseter muscle	rCBF activation	Lateral portion, bilateral, L (-48, +52, +21), R (+32, +40, +17), (+43, +44, 0)
Brefel-Courbon et al. (2005)	Healthy (after an oral levodopa challenge)	Evoked thermal (cold)	Hand	rCBF activation	Lateral portion (-31, +51, -18), contralateral to stimulus
Thunberg et al. (2005)	Healthy	Evoked chemical (hypertonic saline)	Erector spinae muscle	rCBF activation [‡]	Medial portion (-14, +60, +34), contralateral to stimulus
				rCBF deactivation [‡]	Lateral portion (+34, +44, +30), ipsilateral to stimulus
					Lateral portion (+31, +52, +9), (+33, +51, -9), contralateral
Sprenger et al. (2007)	Cluster headache	Spontaneous headache		Hypermetabolism	Medial portion (+12, +66, +7) (+17, +66, -6) (+3, +64, +5), contralateral to headache
Chen et al. (2008)	Brachial plexus avulsion	Headache or resting state (no pain)		Hypometabolism **	Lateral portion (-42, +42, +21), ipsilateral to stimulus
		Spontaneous neuropathic pain		Hypermetabolism	Lateral portion (-22, +56, +6), ipsilateral to stimulus
van Oudenhoove et al. (2009)	Healthy	Evoked mechanical (balloon distension)	Proximal stomach	rCBF deactivation	Medial portion (+6, +66, 0), (0, +56, +12)

References	Subjects	Pain stimulus type	Location	Response	Location within BA 10 (MNI Coordinate of peak voxel)
Kupers et al. (2011)	Chronic Posttheriotomy pain	Evoked mechanical (wind-up pain)	Operated groin area	rCBF activation	Lateral portion (+46, +48, -4), ipsilateral to stimulus
				rCBF deactivation	Medial portion, bilateral
Peyron et al. (2013)	Neuropathic pain (various causes)	Evoked thermal (heat)	Skin (non-painful side)	rCBF activation	Lateral portion (+32, +54, +14), (+38, +50, +6), ipsilateral to stimulus
Yoon et al. (2013)	Spinal cord injury	Chronic neuropathic pain		Hypometabolism**	Medial portion (-2, +54, +8)
					Lateral portion (-34, +54, +22)
Maniyar et al. (2014)	Migraine without aura	Nitroglycerin-induced migraine		rCBF activation	Lateral portion (+39, +42, +15)

* Noxious stimuli compared with innocuous stimuli.

** Patients compared with healthy controls.

Headache patients during the cluster period but out of acute pain compared with identical patients scanned again during the remission period,

*Response to late pain. PET scan performed after 21 minutes after start of infusion.

NIRS-measures of pain response in BA 10. The coordinate of the detected response was not reported in most of the studies due to the limited spatial resolution of the NIRS technique.

Table 3

References	Subject	Pain stimulus type	Stimulus location	Response	Response location within BA 10
Gélinas et al. (2010)	Cardiac surgery (in awake and in anesthetized conditions)	Evoked mechanical (e.g. injection, incision, and thorax opening)	Multiple sites (e.g. forearm and thorax)	Activation	Lateral portion, on both sides
Barati et al. (2013)	Healthy	Evoked thermal (cold)	Hand	Activation	Lateral portion, bilateral to stimulus
Lee et al. (2013)	Healthy	Evoked mechanical (pressure)	Finger	Activation	Lateral portion, contralateral to stimulus
Holper et al. (2014)	Healthy	Evoked mechanical (pressure)	Low back	Deactivation	More lateral portion, bilateral to stimulus
Sakuma et al. (2014)	Healthy	Evoked mechanical (pressure)	Gingiva	Deactivation	Medial portion, contralateral to stimulus
Yücel et al. (2015)	Healthy	Evoked electrical	Finger	Deactivation	Medial portion, bilateral to stimulus
Aasted et al. (2016)	Healthy	Evoked electrical	Finger	Deactivation	More medial portion, bilateral to stimulus
Becerra et al. (2016)	Healthy	Evoked mechanical (Colonoscopy insufflation)	Colon	Deactivation	Medial portion, on the left side
Kussman et al. (2016)	Arrhythmias (under general anesthesia)	Evoked thermal (Catheter ablation of arrhythmias)	Heart	Deactivation	More medial portion, on both sides
Yennu et al. (2016)	Healthy	Evoked thermal (heat)	Forearm and TMJ	Activation	Lateral portion, bilateral to stimulus

TMJ: Temporomandibular joint.

Table 4

EEG-measures of pain response in BA 10.

References	Subject	Pain stimulus type	Stimulus location	Response	Response location within BA 10
Bromm and Chen (1995)	Healthy	Evoked thermal (heat)	Hand	Evoked cortical potential increase	More medial portion, midline
Chang et al. (2004)	Healthy	Evoked chemical (capsaicin)	Forearm	Delta band power increase	Lateral portion, contralateral to stimulus
Stern et al. (2006)	Chronic pain	Spontaneous neurogenic pain		Low beta band power increase	Medial portion, bilateral
					Lateral portion, on the left side
Shao et al. (2012)	Healthy	Evoked thermal (cold)	Hand	Alpha band power decrease	More medial portion, bilateral
				Beta band power increase	More medial portion, bilateral

Table 5

Gray matter changes in chronic pain in BA 10

References	Subject	Gray matter changes	Location within BA 10 (MNI coordinates of peak voxel)
Rocca et al. (2006)	Frequent migraine	GM density decrease	Medial portion (-8, +58, -6), involve both hemispheres Lateral portion (-31, +64, +11)
Kuchinad et al. (2007)	Fibromyalgia	GM density decrease	Medial portion (+2, +55, +25)
Kim et al. (2008)	Episodic migraine	GM volume decrease	Medial portion (0, +64, +24)
Valfrè et al. (2008)	Chronic migraine	GM volume decrease*	Lateral portion (-44, +50, +8)
Rodriguez-Raecke et al. (2009)	Hip osteoarthritis	GM density decrease	Medial portion (+6, +62, -12), (+9, +66, 13)
Valet et al. (2009)	Chronic pain disorder (various causes)	GM density decrease	Medial portion (-10, +66, -5), (-7, +53, +22) Lateral portion (-42, +54, -7)
Wrigley et al. (2009)	Spinal cord injury	GM volume decrease	Medial portion, bilateral
Moayed et al. (2011)	Temporomandibular disorder	GM volume increase	Lateral portion (-31, +48, +6)
Obermann et al. (2013)	Trigeminal neuralgia	GM volume decrease	Both medial and lateral portions (+20, +66, -9)
Rodriguez-Raecke et al. (2013)	Hip osteoarthritis	GM density decrease	Medial portion (+10, +67, +13), (-14, +68, +2) Lateral portion (+48, +47, -9)
Yoon et al. (2013)	Spinal cord injury (neuropathic pain)	GM volume decrease	Lateral portion (-38, +51, +8)
Khan et al. (2014)	Burning mouth syndrome	GM volume decrease	Medial portion (-8, +56, +4)
Luchtmann et al. (2014)	Lumbar disc herniation (chronic back pain)	GM volume decrease	Medial portion (-4, +57, -5) Lateral portion (+51, +52, -6)
Pleger et al. (2014)	Complex regional pain syndrome	GM density increase	Medial portion (+1.5, +52.5, +16.5),
Fritz et al. (2016)	Chronic back pain	GM volume decrease	Medial portion, bilateral, L (-6, +62, +9), R (+15, +50, -12)
Krause et al. (2016)	Poststroke pain	GM volume decrease	Lateral portion, contralateral to lesion
Yang et al. (2017)	Chronic headache	GM volume decrease	Lateral portion (+23, +56, +16)

* Compared with episodic migraine patients

Table 6

Brain regions showing co-activations/co-deactivations with BA 10 following evoked pain on healthy subjects

Cortical regions														Subcortical regions										CB		
BA 10 L	M	ACC, MCC 24,32	PCC 23,31	INS 13	DLPFC 8,9,46	VLDFC 44, 45, 47	OFC 11	MPFC 6,8,9	PMA 4,6	SMA 6	SI 1,2,3	SH 2,40,43	SPL 7	IPL 40,39	OL 17,18,19	STG/MTG 22,38	AMY	STR	Ca	Pu	TH MD	Hypo-TH	Hc/Pa raHc	BS PAG, NC		
Response to noxious stimuli v.s. resting state																										
Baron et al. (1999)	↑C				↑B						↑C	↑C														
Becerra et al. (1999)	↑C	↑B	↑I	↑B	↑I					↑I	↑C	↑B				↑B	↓					↓			↑	
Tracey et al. (2000)	↑C																									
Frankenstein et al. (2001)	↑C	↑B		↑I								↑I		↑I												
Kurata et al. (2002)	↑I	↑B		↑B					↑B			↑B				↑B		↑								
Coghill et al. (2003)	↑I	↑C		↑I							↑C										↑				↑	
Sirigo et al. (2003)	↑R	↑L	↑L	↑B							↑B	↑B	↑B	↑B				↑							↑	
Cook et al. (2004)	↑I		↑I	↑B	↑C					↑C				↑C											↑	
Derbyshire et al. (2004)	↑C	↑B		↑B	↑C							↑C		↑B							↑				↑	
Jantsch et al. (2005) FING	↑B	↑B		↑B	↑B	↑B			↑B		↑B	↑B					↑									
Jantsch et al. (2005) TOOT	↑B	↑B		↑B	↑B	↑B			↑B		↑I	↑B														
Mohr et al. (2005)	↑I	↑B		↑B							↑C	↑B					↑									
Moulton et al. (2005)	↑C			↑C		↑B				↑C	↑B	↑B														
Gündel et al. (2008)	↑I		↑B	↑B	↑C			↑C				↑C		↑B							↑					
Lui et al. (2008)		↑B	↓B	↑C	↑B	↑B		↑B			↑B			↑B												
Schoedel et al. (2008)	↑B	↑C			↑B	↑B		↑B	↑B	↑B	↑B	↑C		↑B		↑C										

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Cortical regions														Subcortical regions										CB
BA 10 L	M	ACC, MCC 24,32	PCC 23,31	INS 13	DLPFC 8,9,46	VLDFC 44,45,47	OFC 11	MPFC 6,8,9	PMA 4,6	SMA 6	SI 1,2,3	SH 2,40,43	SPL 7	IPL 40,39	OL 17,18,19	STG/MTG 22,38	AMY	STR Ca Pu	TH MD	Hypo-TH	Hc/Pa raHc	BS PAG, NC	CB	
Kong et al. (2010) Low pain	↑B	↑B	↑B	↑B	↑B	↑I	↑B	↑B	↑B	↑B	↑C	↑C	↑C	↑I	↑B	↑B		↑	↑	↑	↑		↑↑	
Kong et al. (2010) High pain	↑B	↑↑B	↑B	↑B	↑B	↑B		↓C			↑B	↑B		↓I	↑B	↑B		↑	↑			↑	↑	
Rotman et al. (2010)	↑I	↑B		↑B		↑B					↑B	↑B		↑I		↑B			↑					
Tseng et al. (2010)	↑B	↑B		↑B	↑B	↑B		↑B	↑I	↑C	↑C	↑B					↑							
Loggia et al. (2012)	↑C		↓B	↑C	↑C	↑C	↓I	↑B	↓B	↓B	↓I	↑C	↑C	↑C	↓I	↓B	↓	↑C	↓I	↓	↓		↓	
Quiron et al. (2014)	↑B	↑B	↑B	↑B	↑B	↑B		↑B	↓B	↓B	↓B	↑B	↑B	↓B	↑B		↓	↑	↑	↑	↓		↑	
Vogt et al. (1996)	↓B	↑C	↓B	↑B	↑↑C	↓B		↓B					↓B	↓B	↑↑I	↑↑I			↑					
Iadarola et al. (1998)	↑B	↑B		↑B	↑C	↑C		↑I	↑B		↑C	↑B		↑B				↑						
Casey et al. (2001)	↑C	↑C		↑C	↑B	↑B			↑B															
Lorenz et al. (2002) CHEM	↑I	↑C		↑I	↑B													↑	↑					
Lorenz et al. (2002) HEAT	↑C	↑C		↑B								↑C		↑C					↑	↑				
Lorenz et al. (2002) ALLO	↑B	↑C		↑B	↑B							↑C		↑C				↑	↑	↑				
Lorenz et al. (2002) HPAG	↑B	↑C		↑B	↑B							↑C						↑	↑					
Kupers et al. (2011) CHEM	↑I	↑C	↓I	↑B				↑I					↑C	↑I			↓	↑				↑	↑	
Kupers et al. (2001) ALLO	↑B	↑C		↑B	↑B		↑I		↑B		↑C			↑I			↓	↑	↑	↑	↓		↑	
van Oudenhove et al. (2009)	↑R	↑B	↓B		↑R	↑R		↑B			↓B			↑R	↓B	↑B	↓	↓			↓			
Response to noxious stimuli v.s. innocuous stimuli																								

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Cortical regions															Subcortical regions										CB		
BA 10	M	ACC, MCC	PCC	INS	DLPFC	VL/PFC	OFC	MPFC	PMA	SMA	SI	SII	SPL	IPL	OL	STG/MTG	AMY	STR	Ca	Pu	TH	MD	Hypo-TH	Hc/Pa	raHc	BS	PAG, NC
Fulbright et al. (2001)	↑R	↑B			↑R		↑L								↑R												
Valet et al. (2004)	↑B	↑C	↑C	↑B						↑C	↑C	↑B		↑B				↑			↑						↑
Zambreanu et al. (2005)	↑I	↑B	↑B	↑B						↑B	↑C	↑C	↑I	↑I							↑				↑		↑
Albuquerque et al. (2006)	↑I ↓C	↑I	↓I	↑I	↑I	↑I	↑B							↑I	↓C			↑			↑						↑
Derbyshire et al. (1994)	↑I	↑B						↓C						↑I	↓C			↑									↑
Hsieh et al. (1995a)	↑I	↑B	↑B	↑B	↓B		↑B	↑B	↑B	↑B	↑B			↑↑B	↓I	↓B		↑				↑					↑
Casey et al. (1996)	↑I	↑B		↑B				↑B			↑C							↑									↑
Derbyshire et al. (1997)	↑B	↑B ↓C	↑C	↑C	↑B	↑B		↑B	↑B	↓B	↑I ↓B			↑B	↓B		↓	↑			↑		↑				↓
Derbyshire and Jones (1998)	↑I	↑B		↑C	↑I	↓C	↓I					↑C						↑			↑					↑I ↓B	
Iadorola et al. (1998)	↑B									↑C	↑C	↑I		↑I				↑									↑
Witting et al. (2001) CHEM	↑B	↑C	↑I	↑I	↑I	↑I	↑C			↑C	↑C	↑C			↑C						↑						↑
Witting et al. (2001) ALLO	↑B	↑C		↑B	↑B					↑C	↑C	↑C			↑C												↑

* Abbreviations: ACC-Anterior cingulate cortex; MCC-middle cingulate cortex; PCC-posterior cingulate cortex; INS-insula; DLPFC-dorsolateral prefrontal cortex; VLPFC-ventrolateral prefrontal cortex; MPFC-medial prefrontal cortex; PMA-premotor area, SMA-supplementary motor area; SI-primary somatosensory cortex; SII-secondary somatosensory cortex; SPL-superior parietal lobule; IPL-inferior parietal lobule; OL-occipital lobe; STG-superior temporal gyrus; MTG-middle temporal gyrus; AMY-amygdala; STR-striatum; Ca-Caudate nucleus; Pu-putamen; TH-thalamus; MD-mediodorsal nuclei; HypoTH-hypothalamus; HC-hippocampus; ParaHC-parahippocampus; BS-brainstem; PAG-periaqueductal gray; NC-nucleus cuneiformis; CB-cerebellum; I-ipsilateral; C-contralateral; B-bilateral; R-right; L-left; FING-finger; TOOT-tooth; CHEM-chemical; ELEC-electrical; ALLO-allodynia; HPAG-hyperalgesia.

Table 7
Brain regions showing co-activations/co-deactivations with BA 10 in patients with chronic pain following external painful stimuli or spontaneous pain

Cortical regions														
Subcortical regions														
BA 10 L	M	ACC, MCC 24,32	PCC 23,31	INS 13	DLPFC 8,9,46	VLPFC 44,45,47	OFC 11	MPFC 6,8,9	PMA 4,6	SMA 6	SI 1,2,3	SII 2,40,43	SPL 7	IPL 40,39
STG/MTG 22,38														
OL 17,18,19														
AMY														
STR														
Ca Pu														
TH MD														
Hypo TH														
Hc/Pa raHe														
BS PAG, NC														
CB														
Response to externally applied painful stimuli during chronic pain v.s. pain-blocked state														
Apkarian et al. (2001)														
		↑C	↑C											
Response to externally applied painful stimuli v.s. baseline (no pain period)														
Cook et al. (2004)														
	↑I			↑B									↑B	
Peyron et al. (1998) ALLO														
	↓C	↓I	↓I	↑C	↑C					↑C	↑C		↑B	↓B
Peyron et al. (1998) ELEC														
	↓I			↑C	↑C	↑I			↑C				↑B	↓B
Kuper et al. (2000)														
	↑L	↑L	↑L	↑L	↑L	↑L	↑R			↓L			↓L	↑
Kuper et al. (2011)														
	↑I	↓B	↑I	↑B	↑I	↑B	↑I	↑C	↑C		↑I	↑C	↓B	↑
Peyron et al. (2013)														
	↑I			↑B	↑I	↑I					↑B			
Response to externally applied painful stimuli v.s. the response in healthy controls														
Gündel et al. (2008)														
		↓C		↑C						↑C	↑I		↑I	↑
Response to externally applied painful stimuli v.s. externally applied non-painful stimuli														
Derbyshire et al. (1994)														
	↓I	↑B	↓I	↓C	↑C	↓C		↓C				↓I	↓C	↓B
Response to spontaneous pain compared v.s. baseline														
														↑

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Cortical regions													
Subcortical regions													
BA 10	M	ACC, MCC	PCC	INS	DLPFC	VLPFC	OFC	MPFC	PMA	SMA	SI	SII	SPL
L		24,32	23,31	13	8,9,46	44,45,47	11	6,8,9	4,6	6	1,2,3	2,40,43	7
Baliki et al. (2006)	↑B	↑B											
Rosen et al. (1994)	↑B	↑B	↓R		↑B	↑B							↓L
Hsieh et al. (1995b)	↑B	↑R	↓L	↑B	↑B	↑B						↑B	↑B
Hsieh et al. (1996)	↓L	↑R	↑R	↑B	↑B	↑B			↑B	↑R			↓B
Hsieh et al. (1999)	↑R	↑L			↓B			↓R					
Maniyar et al. (2014)	↑R			↑R					↑R	↑L			↑R
Response to spontaneous pain v.s resting state of healthy controls													
Yoon et al. (2013)	↓L	↑R			↓L								

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Table 8

Brain regions showing gray matter changes along with BA 10 in patients with chronic pain compared with healthy controls

Cortical regions														Subcortical regions														
BA 10	ACC, MCC	PCC	INS	DLPFC	VL PFC	OFC	MPFC	PMA	SMA	SI	SII	SPL	IPL	OL	STG/MTG	AMY	STR	Ca	Pu	TH	MD	Hypo	TH	He/Pa	raHe	BS	PAG, NC	CB
↕B	↕B	↕B		↕B	↕B		↕L								↕B								↕			↕		
Rocca et al. (2006)																												
Kuchinad et al. (2007)	↕B	↕B	↕L																				↕					
Kim et al. (2008)	↕L	↕L	↕R	↕B	↕B	↕R	↕B	↕B				↕R	↕R	↕R														
Rodriguez-Raecke et al. (2009)	↕B	↕B		↕B		↕B	↕R			↕R	↕L				↕B	↕									↕			↕
Valet et al. (2009)	↕L	↕B	↕L	↕B	↕B	↕B														↕			↕					↕
Wrigley et al. (2009)	↕B	↕B	↕B			↕B		↕L							↕B		↕				↕							
Moayedi et al. (2011)	↕L				↕L				↕R											↕								
Obermann et al. (2013)	↕R	↕B	↕B	↕R					↕L	↕L		↕L								↕								↕
Rodriguez-Raecke et al. (2013)	↕R	↕B	↕L	↕R	↕R										↕B													↕
Yoon et al. (2013)	↕L		↕R	↕B																								
Khan et al. (2014)	↕L																						↕					
Luchtmann et al. (2014)	↕R	↕L	↕R	↕R	↕B			↕L				↕L			↕R		↕								↕			↕
Pleger et al. (2014)		↕B						↕C																				
Fritz et al. (2016)	↕B		↕L	↕R	↕L																							
Krause et al. (2016)	↕C		↕B		↕I	↕C					↕B				↕C		↕											