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Review Article

Is there hemispheric specialization in the chronic pain brain?

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ABSTRACT

Organismal bilateral symmetry is associated with near-identical halves of the central nervous system, with certain functions displaying specialization through one brain hemisphere. The processing of pain in the brain as well as brain plasticity in the context of painful injuries have garnered much attention in recent decades. Noninvasive brain imaging studies in pain-free human subjects have identified multiple brain regions that are linked to the sensory and affective components of pain. Longlasting adaptations in brains of chronic pain sufferers have likewise been described, suggesting a mechanism for pain chronification. Invasive molecular and biochemical studies in animal models have expanded on these findings, with added emphasis on the role of specific genes and molecules involved. To date, the extent of hemispheric asymmetry in the context of pain is not well-understood. This topical review evaluates the evidence of hemispheric specialization observed in humans and rodent models of pain and compares it to findings where such asymmetry is absent. Our review shows conflicting information regarding the existence of pain-related asymmetry, and if so, the side to which it can be localized. This could be due to the heterogeneity of pain processing pathways, heterogeneity in study parameters, as well as differences in data reporting. With the advent of progressively sophisticated non-invasive tools that can be used in human subjects, in addition to more precise methods to visualize and control specific brain regions or neuronal ensembles in animal models, we predict that the next few decades will witness a better understanding of the supraspinal control and processing of chronic pain, including the role of each of its hemispheres.

List of abbreviations

ACC	Anterior cingulate cortex
CNS	Central nervous system
CeA	Central nucleus of the amygdala
CC	Corpus callosum
DLPFC	Dorsolateral prefrontal cortex
ERK	Extracellular Signal-regulated Kinase
fMRI	Functional magnetic resonance imaging
HS	Hemispheric specialization
LH	Left hemisphere
PET	Positron emission tomography
PFC	Prefrontal cortex
S1	Primary somatosensory cortex
RH	Right hemisphere
S2	Secondary somatosensory cortex
MOR	μ-opioid receptor

1. Introduction

Hemispheric specialization (HS) - the differential connectivity and function of the right hemisphere (RH) and left hemisphere (LH) - is not well described in other mammals, except for some of our closest relatives in the *Homo sapiens* evolutionary line (Gazzaniga, 2000; Wey et al., 2014). Such observations have allowed for hypothesizing that connectivity between the hemispheres must have evolved to foster an increase in cortical capabilities by allowing for lateralization of functions to a specific hemisphere, eliminating the need for the entire brain to be involved in the same task. During development, connectivity via the corpus callosum (CC) is shown to decrease, thus reducing the presence of inter-hemispheric communication, and fostering intra-hemispheric connectivity (Gazzaniga, 2000).

It has become increasingly evident that brain alterations are closely linked to pain chronification and pain-related co-morbidities both in pain patients and preclinical models. Despite the multiple manuscripts reviewing the specific supra-spinal areas that are altered in chronic pain

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(for example, see (Barroso et al., 2021)), to date, there are no review articles discussing the extent of HS of brain plasticity in the context of experimental and pathological pain.

2. Brain activity in the context of experimental pain in pain-free subjects

Prior to investigating the extent of pain-related brain activity and plasticity, it would be useful to discuss the brain areas that are active in the context of acute painful stimuli. Since the advent of non-invasive brain imaging techniques a few decades ago (positron emission tomography [PET], functional magnetic resonance imaging [fMRI], etc.), there has been a wealth of studies aimed at defining a pain network, with areas such as the primary and secondary somatosensory cortices, anterior cingulate cortex (ACC) and insular cortex, as well as the thalamus and brainstem showing activity in response to various experimental pain paradigms (contact heat, cold, ischemia, electric shock, etc.) (Apkarian et al., 2005). The subsequent paragraphs will summarize findings of brain asymmetry in the context of experimental pain (thermal, electrical, visceral, and inflammatory) both in humans and other animals.

In pain-free human subjects participating in experimental paradigms, innocuous and painful thermal stimulation of the right and left ventral forearms were shown to be associated with the activation of a portion of the right thalamus, inferior parietal cortex, dorsolateral prefrontal cortex (DLPFC), and dorsal frontal cortex, regardless of the original site of stimulus presentation (Coghill et al., 2001). In the same study, other areas such as the primary (S1) and secondary (S2) somatosensory cortices, insular cortex, bilateral regions of the cerebellum, putamen, thalamus, ACC, and frontal operculum, all showed contralateral activation. There was no evidence of a HS involvement in the processing of pain intensity (Coghill et al., 2001). Asymmetries for pain intensity perception in the RH were observed without correlations to motor hemispheric lateralization in an experimental model of heat pain following the immersion of the right hand and then left hand in a hot water bath (Lugo et al., 2002), further complementing possible pain-related lateralization. FMRI analysis in a model of experimental electric shock pain in healthy subjects highlighted five brain areas (medial/superior frontal gyri, inferior parietal lobule, middle frontal gyrus, inferior frontal gyrus, anterior cingulate) that were highly active in the RH following the stimulation of small diameter pain fibers in the right and left index fingers (Symonds et al., 2006).

RH asymmetry is less clear in the context of visceral pain. In addition to bilateral activation of the insula and the ACC and posterior cingulate cortices, predominant activation of the right amygdala and right hippocampus has been observed in fMRI studies following visceral pain stimulation (gastric distention) in healthy subjects (Lu et al., 2004). In contrast, visceral pain stimulation using rectal distention induced activation in the left prefrontal cortex (PFC), left cerebellum, right supplementary motor area, right posterior insula, in addition to bilateral activation of S1, S2, anterior insula, thalamus, caudate, putamen, etc. (Moisset et al., 2010). Finally, the right anterior insula has demonstrated involvement in the anticipation of pain (Woo et al., 2015) and is highly interconnected with somatosensory regions (Chang et al., 2013).

The development of preclinical animal models has afforded the use of invasive techniques and multiple approaches have been taken to study hemispheric lateralization in rodent pain models. For example, the central amygdala has been studied using optogenetic tools to analyze its response to noxious urinary bladder distension, with the results suggesting a much more relevant pronociceptive role for the right and an anti-nociceptive role to the left central nucleus of the amygdala (CeA) (Sadler et al., 2017). The role for the right amygdala was also noted in the context of peripheral inflammation where extracellular signal-regulated kinase (ERK) activation was observed in the right amygdala 3 h after formalin administration in the right hindpaw (Carrasquillo and Gereau, 2007), and the blockade of ERK activation in the right, but not left, CeA decreases inflammation-induced peripheral hypersensitivity regardless of the side of hindpaw formalin injection (Carrasquillo and Gereau, 2008). Similarly, formalin injection in the rat upper lip resulted in increased CeA activity, regardless of the side of inflammation (Miyazawa et al., 2018). Conversely, chemogenic activation of the gamma-aminobutyric acid-ergic neurons in the right CeA was shown to result in sensitization in bilateral hindpaws, even in the absence of inflammation (Sugimoto et al., 2021). It is noteworthy that many studies focus on the right amygdala [for example, see (Adedoyin et al., 2010; Yamamoto et al., 2021), and thus, "publication bias" may be present. With the advent of smaller devices, bilateral imaging may be more commonplace (Rebusi Jr. et al., 2021). Finally, in mice where acute inflammatory pain was induced in the left hindpaw, increased activity in the right insular cortex, right nucleus accumbens, right globus pallidus, bilateral caudate putamen, right primary/secondary somatosensory cortex, bilateral thalamus, right amygdala, bilateral substantial nigra, and left ventral tegmental area was observed using enhanced MRI (Arimura et al., 2019).

Despite the limited availability of subjects, studies in split-brain patients could provide unique insight into HS of the pain experience. Since the CC connects the 2 hemispheres, somatosensory processes are largely lateralized in split-brain patients where the CC has been severed, with stereognostic information interpreted by one hand being unavailable to the ipsilateral hemisphere (Gazzaniga, 2000). In a case study of an individual with total callosal transection, low intensity noxious thermal stimuli ipsilateral to the responding cerebral hemisphere were poorly perceived and rated low on the visual analog scale. In contrast, high intensity noxious heat stimuli were rated as very intense and unpleasant, suggesting that the mechanisms behind pain experience/perception are present, despite a potential change in their activation threshold (Stein et al., 1989). More recently, a study of a group of 3 split-brain patients showed that, compared to control subjects, unilateral painful mechanical stimulation of the right and then left hand activates the ipsilateral cortex, at least partially, in a CC-independent manner (Fabri et al., 2002).

It is important to note that, given the same noxious stimulus, the side of stimulation can result in different perceptions regarding pain intensity as evidenced by a study demonstrating higher pain scores for the left hand when subjected to painful heat (Lugo et al., 2002). In a study using noxious cold stimulation, no differences in pain threshold or intensity between the two hands were observed, both in right- and left-handed individuals (Pud et al., 2009). However, cold pain tolerance was reduced in the left hand in right-handed subjects (Pud et al., 2009). In contrast, a study of deep pain thresholds failed so show left-right differences in distal limbs in healthy subjects (Rolke et al., 2005).

3. Chronic pain representation in the brain

While section 2 focused on the brain regions that are active after acute pain, some of the structures in the "pain matrix" are also responsible for its persistence. Substantial evidence supports the idea that chronic pain is a form of nociceptive memory, with the involvement of areas such as the PFC and ACC, the amygdala and the hippocampus (Eto et al., 2011; Li et al., 2010; Tajerian et al., 2013). Brain activation in response to experimental pain includes both nociceptive processing as well as the perception of acute pain. This is in contrast to how pain is represented in the brain as a result of chronic exposure to painful conditions, which could be linked more closely to how pain is "stored" in the brain. It is, therefore, important to note that it is not possible to directly compare data attained from experimental pain models to that collected from pain patients due to the long-lasting brain alterations in pain conditions (Hashmi et al., 2013).

One strategy to determine the presence of HS in the context of pain is to compare between conditions where the pain is lateralized to one side of the body versus cases of generalized pain (Fig. 1, "Type of pain").

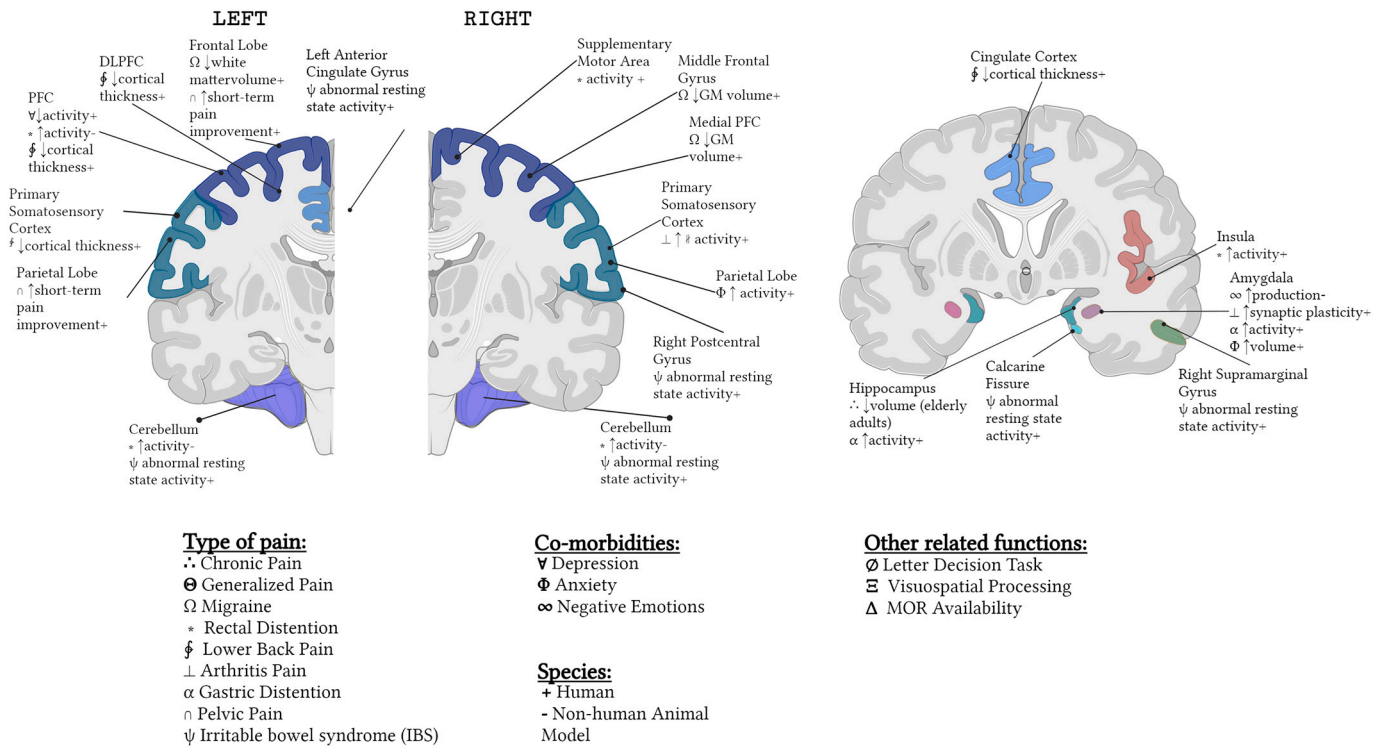

Fig. 1. Summary of brain hemispheric localization of acute and chronic pain from animal models and pain patients. Image illustrated using Biorender© software.

3.1. Lateralized painful conditions (arthritis, complex regional pain syndrome, neuropathy)

Electrophysiological studies conducted by Ji and Neugebauer were seminal in demonstrating hemispheric asymmetry in the responsiveness of neurons to noxious stimuli in pain models (Ji and Neugebauer, 2009). The study found that the average receptive field size of right CeA neurons were significantly larger than left CeA neurons following induction of knee joint arthritis, with the left neurons presenting no change. Increases in right neuronal activity was also noted in the osteoarthritis pain model, while lacking for left CeA neurons. RH lateralization is thus evident by this model, regardless of the side of injury. In osteoarthritic patients however, this pattern is not observed and the contralateral ACC and motor cortex displayed decreased gray matter volume compared to control subjects (Barroso et al., 2020). Similarly, complex regional pain syndrome patients were shown to have an enlarged S1 area on the unaffected side (Di Pietro et al., 2015).

In a rat model of neuropathy, it was shown that neuronal activity was higher in the left CeA at 2 and 6 days after nerve injury, whereas activity in the right CeA became dominant 2 weeks after surgery, regardless of the side of injury (Goncalves and Dickenson, 2012). Similarly, following chronic nerve constriction, increased usage of serotonin as well as increased levels of 5-Hydroxyindoleacetic acid, the main metabolite of serotonin, has been observed in the right dorsomedial striatum (Gemikonakli et al., 2019). Interestingly, this study also found that CeA activation can be higher in the LH during the first week following injury, and that this high activation transitions towards the RH after two weeks. Finally, the restraint-induced acute stress caused more monoamine alterations in the right dorsomedial and dorsolateral striata compared to the chronic constriction model, suggesting that the modulation of chronic stress can also be traced primarily to the right hemisphere (Gemikonakli et al., 2019).

3.2. Non-lateralized pain (migraine, back pain, pelvic and visceral pain)

Decreased white matter volume was observed in the left frontal lobe of migraine patients (Palm-Meinders et al., 2017). More recently, in a study of patients with episodic migraines, it was shown that patients without clinical care had decreased gray matter volume in the right dorsomedial PFC compared to those who received clinical care (Burrowes et al., 2021). Decrease in cortical thickness is also a common finding in pain patients. A study analyzing individuals suffering from chronic lower back pain presented decreased cortical thickness in the left DLPFC, left S1, right ACC, and others (Seminowicz et al., 2013). Post-treatment, patients saw increased cortical thickness in the left DLPFC, implying reversible structural changes. Similarly, studies in patients suffering from subacute back pain have shown diminished gray matter volume in the nucleus accumbens, as well in both the right and left insula, with more significant changes observed in the right insula (Baliki et al., 2012).

In patients with urologic chronic pelvic pain, networks in left frontal and parietal cortices were shown to contribute most to predicting short-term pain improvement (Kutch et al., 2017). In a meta-analysis of resting state brain activity in patients with irritable bowel syndrome, abnormalities in the left calcarine fissure, right postcentral gyrus, left cerebellum, left anterior cingulate and the paracingulate gyrus,right supramarginal gyrus, and right middle frontal gyrus were shown to be most consistent (Su et al., 2022). No evidence of HS was observed in a macaque model of painful naturally-occurring endometriosis, with significant activation of bilateral insula and thalamus in response to non-noxious force application to the abdominopelvic region (Yano et al., 2019).

3.3. Insights from pharmacotherapy and endogenous pain modulation

The impact of analgesic agents on pain perception may reflect HS in central pain processes. In rodents undergoing general anesthesia, calcium imaging showed that a common ensemble of inhibitory CeA neurons are involved in pain suppression, with only partial lateralization of function (Hua et al., 2020). Commonly used analgesics, such as opioids and serotonin-norepinephrine reuptake inhibitors, have shown to exert changes in resting functional connectivity in a hemisphere specific

manner in healthy human subjects (Gear et al., 2013; Hansen et al., 2018), with particular changes in brain areas known to be part of the brain "pain matrix", including the ACC (Gorka et al., 2014). Such evidence of HS is also apparent in pain subjects where alterations in the brain's μ-opioid receptor (MOR) system in the context of chronic pain are associated with hemispheric discrepancies in MOR availability, with a greater presence of the receptor system in the RH (Kantonen et al., 2020). Similarly, data from randomized controlled trials have shown that exposure to oral morphine for 1 month is associated with decreased gray matter volume in the right amygdala of back pain patients (Lin et al., 2016; Younger et al., 2011). Both the pain brain and the MOR system's preponderance within a specialized brain hemisphere are suggested to induce psychiatric comorbidities such as major depression (Kennedy et al., 2006) and anxiety disorders (Desai et al., 2020).

Additional indirect evidence of HS comes from a study of experimental pain in patients with Parkinson's disease, where dopaminergic treatment resulted in increased pain perception only in patients where the disease was left-side predominant, regardless of the side that the experimental pain stimulus was applied (Granovsky et al., 2013).

4. Pain-related co-morbidities

Comorbidities that are often associated with pain demonstrate HS (Fig. 1, "Co-morbidities") with recent electrophysiology and neuroimaging studies having revealed asymmetry in depressive and anxiety disorders (Bruder et al., 2017). For example, depression seems to be associated with right hemispheric hyperactivity (Hecht, 2010) and alpha asymmetry in patients with comorbid anxiety demonstrates greater activity in the right parietal lobe than the left (Li et al., 2018). fMRI scans found reduced left PFC activity in depressed patients, denoted by EEG alpha asymmetry. This may downregulate the amygdala's response to negative emotional processing. In fact, structural differences in the amygdala are typical implications of individuals with anxiety disorders. Upon completing MRI scans that tested amygdalar volume differences among adults with/without generalized and social anxiety disorders, the social anxiety disorder group exhibited greater right amygdala size than the generalized anxiety disorder group, suggesting that greater social anxiety is associated with an enlarged amygdala volume (Suor et al., 2020). Other studies have indicated that greater activity in the left anterior brain regions is associated with increased pain catastrophizing (Jensen et al., 2015).

Pain is known to have significant emotional-affective influences. Particularly, the amygdala is of critical importance in the emotional response to pain, due to its role in the reward system, decision-making, memory modulation, and emotional responses (Corder et al., 2019; Yang and Chang, 2019). Animal models have shown that activation of the right amygdala, rather than the left amygdala, is predominantly involved in producing negative emotions that can be present in some chronic pain patients (Baker and Kim, 2004). In preclinical models of lateralized injury, and, in the absence of evidence regarding the baseline mechanical sensitivity thresholds between the right and left hindlimbs, there is indication for differential severity of pain-associated anxiety depending on the side of the injury. For instance, compared to neuropathy in the right leg, neuropathy in the left leg of the rat is associated with decreased exploration time in the open arms of the elevated plus maze, indicative of increased anxiety (Leite-Almeida et al., 2012). Interestingly, this observed asymmetry is paralleled by bilateral medial and orbital PFC activation, regardless of the side injured (Leite-Almeida et al., 2014).

5. Mechanistic implications

While this review specifically highlights evidence of HS in the context of experimental and pathological pain, the data from the primary literature remains somewhat unclear with the same brain areas showing right or left activation in comparable pain contexts. Furthermore, there are multiple reports where both hemispheres were studied and were found to be similarly altered [for example, see (Cheng et al., 2011)]. For example, compared to healthy control subjects, decreased cerebellar white matter volumes were observed bilaterally in migraine patients (Bilgic et al., 2016). Similarly, in a study of fibromyalgia patients, bilateral changes were observed in resting state insula–default mode network connectivity at the theta band (Hsiao et al., 2017). For the asymmetrical activation reports summed in sections 2–4, it is apparent that many other areas are activated bilaterally, strongly suggesting that asymmetry in pain representation may not necessarily reflect how the general experience of pain is encoded in the brain, and that many basic pain pathways are bilateral. The perception and the experience of pain are complex and multi-dimensional and it is plausible that certain aspects of the pain experience, including the affective components of pain and pain-related comorbidities, show HS that may be difficult to discern, particularly in the earlier timepoints during pain progression.

Pain is a network system regulated by pathways at the cortical, subcortical, spinal, and peripheral levels (Yi and Zhang, 2011). What are the advantages for an asymmetrical vs. symmetrical pain representation? It can be argued that lack of laterality in higher CNS regions is advantageous because it increases the salience of its memory, where a unilateral brain lesion in a pain area would not curtail the pain experience. However, to date, it is unclear whether non-lateralized pain is a more salient experience than pain with clear brain asymmetry. On the other hand, asymmetrical representation implies converging output where it is hypothesized that transferring sensory information is maximally efficient when sensory information is asymmetrically augmented from the non-dominant to the dominant hemisphere (Endrass et al., 2002; Nowicka et al., 1996; Stephan et al., 2007). In addition to increased efficiency, another reason lateralized representation could be advantageous if the network makes use of areas that are not directly involved in pain, that display functional specialization unilaterally. For example, studies in commissurotomy patients have shown right HS in matching ambiguous information to appearances while the LH seemed to be specialized in matching the ambiguous information to conceptual categories (Levy and Trevarthen, 1976). Similarly, the block design test from the Weschler Adult Intelligence scale indicates that HS is evident for sensorimotor tasks, as the RH performed significantly better than the left (Gazzaniga, 1995). The administration of the nonsense wire figure test revealed the same results, as the ability underlying this test was specialized in the RH (Milner and Taylor, 1972). These findings suggest a dissociation of hemispheric processing, and a convergence of information to one specialized hemisphere in the context of cognitive control, which could be relevant to the pain brain.

6. Conclusions

The study of HS revolves around the identification of asymmetries within each hemisphere, and the structural and functional properties that characterize these differences. Our review shows conflicting information regarding the existence of pain-related asymmetry, and if so, the side to which it can be localized (Fig. 1). Most of our data comes from human subjects where, due to ethical limitations, the data is restricted to case studies and correlations. Since there is a significant learning component to pain chronification, brain lateralization could potentially be influenced by previous lateralized injuries or other life experiences. The heterogeneity of patient populations therefore makes the identification of individual confounding variables quite challenging. Similarly, the absence of mechanistic studies makes it difficult to distinguish between brain alterations causing pain and those consequent to it. Furthermore, the use of non-invasive tools such as PET and MRI limits the parameters that can be measured. There are many aspects of brain plasticity (neuronal dendritic morphology (Metz et al., 2009; Tajerian et al., 2014), glial abundance and morphology (Barcelon et al., 2019), extracellular changes (Tajerian et al., 2018), etc.) that have been

observed in animal models that would not be detectable by such imaging tools. Additionally, pain is mediated by both noxious input as well as cognitive self-control, each with unique functional and anatomical correlates (Woo et al., 2015), making it difficult to reliably identify the signature of chronic pain in the brain.

There could be sex and gender differences involved in asymmetrical plasticity in the context of pain. For example, in older adults with chronic pain, patients demonstrated smaller right and total hippocampal volumes. Furthermore, in women only, volume was significantly reduced in in the chronic pain group in the right CA2–3 and right CA4-dentate gyrus regions of the hippocampus, left presubiculum, and left fimbria (Ezzati et al., 2014). Such sex and gender differences must be viewed within the larger differences in the brain's functional organization. For example, women present a larger anterior commissure and CC and have also shown superior interhemispheric communication compared to men (Allen and Gorski, 1991; Ingalhalikar et al., 2014; Shiino et al., 2017).

With an increase in public awareness of chronic pain paralleled by greater numbers of scientific research publications in the pain field, it is likely that we should soon overcome limitations stemming from data availability regarding brain mechanisms of pain processing and adaptation. This is particularly true for clinical populations that are either underrepresented or make up only a small subset of the larger population. For instance, most studies were conducted in right-handed individuals, making it impossible to ascertain whether the observations were due to motor or behavioral dominance of the right body or an independent indication of HS. It is noteworthy that a recent publication found that cerebral integration of bilateral nociceptive inputs is similar between right- and left-handed individuals (Northon et al., 2021). Ongoing refinement in methodological reporting will inevitably improve data availability as well. Currently, many animal studies either exclusively study the contralateral brain areas or do not specify in the methodology whether the right or left brain areas were studied, leaving us with the assumption that both sides were pooled together.

Our understanding of central mechanisms of pain and its chronification is rapidly evolving, yet, the identification of exact pain centers remains incomplete. With the advent of progressively sophisticated non-invasive tools that can be used in human subjects, in addition to more precise methods to visualize and control specific brain regions or neuronal ensembles in animal models, we predict that the next few decades will witness a better understanding of the supraspinal control and processing of chronic pain, including the role of each of its hemispheres.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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