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Prog Neurobiol. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Prog Neurobiol. 2021 January ; 196: 101891. doi:10.1016/j.pneurobio.2020.101891.

Left and Right Hemispheric Lateralization of the Amygdala in Pain

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Abstract

Hemispheric asymmetries within the brain have been identified across taxa and have been extensively studied since the early 19th century. Here, we discuss lateralization of a brain structure, the amygdala, and how this lateralization is reshaping how we understand the role of the amygdala in pain processing. The amygdala is an almond-shaped, bilateral brain structure located within the limbic system. Historically, the amygdala was known to have a role in the processing of emotions and attaching emotional valence to memories and other experiences. The amygdala has been extensively studied in fear conditioning and affect but recently has been shown to have an important role in processing noxious information and impacting pain. The amygdala is composed of multiple nuclei; of special interest is the central nucleus of the amygdala (CeA). The CeA receives direct nociceptive inputs from the parabrachial nucleus (PBN) through the spino-parabrachio-amygdaloid pathway as well as more highly processed cortical and thalamic input via the lateral and basolateral amygdala. Although the amygdala is a bilateral brain region, most data investigating the amygdala's role in pain have been generated from the right CeA, which has an overwhelmingly pro-nociceptive function across pain models. The left CeA has often been characterized to have no effect on pain modulation, a dampened pro-nociceptive function, or most recently an anti-nociceptive function. This review explores the current literature on CeA lateralization and the hemispheres' respective roles in the processing and modulation of different forms of pain.

Keywords

pain; amygdala; brain lateralization; left vs right brain; central amygdala; functional lateralization

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Introduction

"Nous parlons avec l'hémisphère gauche." These immortal words concluded Paul Broca's mid-19th century treatise on the lateralization of language function in humans. Broca found that patients who suffered from left brain injuries demonstrated interruptions in their speech production (i.e. motor output) (Ocklenburg and Gunturkun, 2017). However, other patients who suffered from the same injuries on the right side of the brain did not show the same speech deficits (Ocklenburg and Gunturkun, 2017). In another series of famous studies, German neurologist Carl Wernicke identified a distinct left temporal area responsible for speech fluency and syntax (Rogers *et al.*, 2013). These experiments provided a foundation for neuroscientists and psychologists to begin to explore anatomical specialization within the brain and how lateralization can influence diverse behaviors and functions. There is a direct line from these early observations in humans to the explosion of lateralization data in the mid 20th century (Ocklenburg and Gunturkun, 2017) in a variety of organisms and to this review. We focus on exciting new data that has emerged in the last 20+ years showing that left-right hemispheric lateralization of the amygdala in the mammalian brain may have a critical impact on both acute and chronic pain.

Evolution through natural selection appears to be a major driver of asymmetrical left-right lateralization within nervous systems. Lateralization is present across diverse taxa, from invertebrates to humans (Ocklenburg and Gunturkun, 2017; Rogers *et al.*, 2013). It is likely that nearly all organisms with bilateral body plans (phylum *Bilateria*) carry the potential for asymmetry in the nervous system. Evidence for left/right side lateralization has been found in primates, zebrafish (Rogers and Vallortigara, 2017), nematodes (Rogers and Vallortigara, 2017), insects (Rogers and Vallortigara, 2017) and songbirds (Rogers *et al.*, 2013). This lateralization comes in the form of anatomical lateralization (Ocklenburg and Gunturkun, 2017), gene expression lateralization (Varlet and Robertson, 1997), and finally functional lateralization. Often these different "types" of lateralization are intertwined. That is, changes in gene expression on one side of the nervous system can lead to changes in local growth (anatomy), and ultimately functional output. Upon this foundation, well-known asymmetric specialization, such as the functional lateralization of language and visual processing in humans, likely evolved over top of existing anatomical asymmetry (Levy, 1977).

Although brain lateralization has been known to neuroscience and psychology since 1861, the advent of modern neuroscience techniques, including electrophysiology and functional imaging, has greatly expanded our understanding of lateralization and its impact to the normal and diseased nervous system. Findings from human imaging studies suggest that lateralization within the brain may actually be the norm rather than an exception (Sergerie *et al.*, 2008; van Elst *et al.*, 2000). That is, a multitude of imaging studies find some evidence of lateralized differences in activation, structure, and/or functional connectivity. These data, in turn, are providing new hypotheses for the pathophysiology of neurological disease. By comparing imaging data from individuals with acute disease to those in the chronic state, neuroscientists are learning about the plasticity that drives chronicity (Simons *et al.*, 2014). An area where evidence of lateralization is expected to make a large impact is the field of pain.

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The peripheral nervous system, where noxious stimuli are detected, shows evidence of anatomical lateralization. Pain and temperature sensory information is transmitted directly to the brain via the lateral spinothalamic tract, though various other indirect (spinomedullary and spinobulbar projections) pathways exist (Wall *et al.*, 1999). The majority of nociceptive information is transmitted from sensory fibers to superficial laminae I and II of the dorsal horn of the spinal cord, but a small percentage synapse into deeper laminae (IV, V, VII, and VIII) as well (Wall *et al.*, 1999). After local processing of the afferent signal in internal dorsal horn circuits, secondary projection neurons decussate (approximately 90%) and carry the nociceptive signal out of the contralateral side of the spinal cord and terminate in the lateral parabrachial nucleus (PBN), periaqueductal grey (PAG), nucleus of the solitary tract, and various nuclei of the thalamus (Wall *et al.*, 1999). Thus, nociceptive information sensed on the left side of the body is largely processed in the right hemisphere of the brain and vice versa (Hudspeth *et al.*, 2013). This anatomical lateralization of pain inputs then provides the theoretical foundation for functional lateralization in the brainstem and brain. Although numerous areas within the brain show preliminary evidence for functional lateralization in the context of pain, no area has shown greater capacity for left and right differences in input and output than the amygdala.

The amygdala was first described in the 19th century, named because of the almond shape of one of its many nuclei (LeDoux, 2007). The amygdala is known for playing a role in emotional processing (Phelps and LeDoux, 2005; Sergerie *et al.*, 2008), fear (LeDoux, 2007), stress (Adamec *et al.*, 2005; Li *et al.*, 2017; Nation *et al.*, 2018; Rauch *et al.*, 2000), and other affective disorders, such as anxiety and depression (Myers and Greenwood-Van Meerveld, 2010; Narita *et al.*, 2006; Tran and Greenwood-Van Meerveld, 2012). The amygdala consists of the lateral, basolateral, central, and medial nuclei (Janak and Tye, 2015). In the context of lateralization, the central nucleus of the amygdala (CeA) is of great interest. The CeA has been implicated in modulating emotional processes and it is known to have a role in fear and threat-conditioning (Baker and Kim, 2004; Haubensak *et al.*, 2010; Li *et al.*, 2013). The CeA itself is largely GABAergic and has different functional subnuclei, including the central medial amygdala (CeM), the lateral central amygdala (CeL) and the capsular central amygdala (CeC) (Figure 1) (Cassell *et al.*, 1999; Paxinos and Franklin, 2019; Veinante *et al.*, 2013). Because scientific nomenclature evolves and changes over time, some of the literature discussed throughout this review uses different names or abbreviations to refer to the part of the CeA investigated. For example, the CeC is a relatively new, independent subdivision of the CeA; previously, the CeC was included as a part of the CeL or referred to as the CeLC. For the purpose of this review, we will utilize the most recent abbreviations for the CeA (CeM, CeL, and CeC) as defined by the fifth edition of Paxinos and Franklin's mouse brain atlas. Because the CeC receives direct input from the PBN via the spino-parabrachio-amygdaloid pathway, it has been referred to as the "nociceptive amygdala" and has been thought to be responsible for attaching emotional valence to incoming nociceptive information (Neugebauer *et al.*, 2004). Most studies investigating the amygdala in the context of pain are therefore looking at neurons located in the CeC, even though the nomenclature used in the literature likely varies depending on year of publication. The CeC includes both nociceptive specific (Ji and Neugebauer, 2009) as well as wide-dynamic range neurons (Ji and Neugebauer, 2009) and has both local connections as

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well as external projections. Local connections include the lateral central amygdala (CeL), the medial central amygdala (CeM) and the basolateral amygdala (BLA) (Veinante *et al.*, 2013). External projections include the thalamus, the PBN, hypothalamus, the hippocampus and the PAG (Veinante *et al.*, 2013) (Figure 1). These amygdala circuits have recently been extensively reviewed (Thompson and Neugebauer, 2018; Veinante *et al.*, 2013).

Many studies of the amygdala, especially in rodent models, have assumed equal input to and output from the left and right CeA. Typically, researchers have manipulated and recorded from both hemispheres or focused on one side (typically the right) assuming an equivalent effect on the opposite side (Carrasquillo and Gereau IV, 2008; Ji and Neugebauer, 2009). Data collected over the last 20 years has suggested that the left and right amygdala may show functional lateralization in the context of pain and nociception. When the left and right amygdala have been distinctly evaluated, the general trend is that the right CeA is pronociceptive while the left has a minimal role in pain (Carrasquillo and Gereau IV, 2008; Carrasquillo and Gereau, 2007; Han and Neugebauer, 2004; Ji and Neugebauer, 2009; Neugebauer and Li, 2003). However, recently the left CeA has been found to have an anti-nociceptive effect in the context of bladder pain (Sadler *et al.*, 2017b), making the idea of amygdala lateralization even more compelling. In this review, we will present all of the current evidence for amygdala lateralization. This review represents the first time that these data on amygdala lateralization have been systemically cataloged and reviewed. We will begin by focusing on early evidence from the literature of amygdala lateralization in the fear/threat conditioning field to provide context for more recent data from the pain field. Next, we will present data from unilateral studies (i.e. right or left amygdala only studies) in different pain models as well as the cadre of newer studies that have separately manipulated or measured the left and right amygdala in single studies of pain. Overall, our goal is to present the data to show both evidence for lateralization of the amygdala in pain and to highlight the existing controversies, mysteries, and questions that remain in the field.

Amygdala Lateralization in Emotion, Fear, and Stress

Early investigation of emotional processing via clinical EEG in humans revealed hemispheric differences in how various emotions are processed (Ahern and Schwartz, 1985). The left hemisphere seemed to be more involved in processing stimuli linked to positive emotions whereas the right hemisphere was more active in response to negative stimuli associated with aversive emotions (Ahern and Schwartz, 1985). Such observations led researchers to develop “the valence hypothesis,” which states that the left hemisphere is specialized to process positive emotions while the right hemisphere is specialized to process negative emotions (Ahern and Schwartz, 1985). This general finding of valence differences in the left and right hemispheres extends to the amygdala (Lee *et al.*, 2004).

Recent fMRI data has generally continued to support the valence hypothesis in healthy humans (Baas *et al.*, 2004). This normal amygdala lateralization is often altered in patients with mental health disorders, including anxiety (Hahn *et al.*, 2011; Phan *et al.*, 2009), depression (Drevets *et al.*, 1992; Farahbod *et al.*, 2010), post-traumatic stress disorder (Rauch *et al.*, 2000), schizophrenia (Kosaka *et al.*, 2002; Taylor *et al.*, 2002), and bipolar disorder (Chepenik *et al.*, 2010), where the pathology of these diseases is linked to abnormal

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amygdala activity. These findings suggest that lateralization of the amygdala is both a normal phenomenon and provides a footing for understanding acute pathology and the transition to the chronic disease state.

Although there is asymmetry to the way the amygdala processes certain emotions that corresponds to the valence hypothesis (Baas *et al.*, 2004; Hamann and Mao, 2002), amygdalar processing of more dynamic stimuli, such as fear, complicates the valence hypothesis. Fear is a multifaceted process that requires communication across brain regions, the involvement of complex circuits, and the generation of evolutionarily derived escape behaviors and coping mechanisms; a stimulus that involves such extensive processing cannot be confined to a single hemisphere or a single anatomical substrate. Conditioned fear or threat behavior has a strong basis in the right amygdala based on rodent research (Baker and Kim, 2004; Han *et al.*, 2015; Haubensak *et al.*, 2010; Ji *et al.*, 2018; Watabe *et al.*, 2013), as the valence hypothesis would suggest, and is primarily involved in the consolidation and storage of memories associated with aversive consequences (Coleman-Mesches *et al.*, 1996). However, human imaging data reveals that the left amygdala is predominantly activated and more strongly correlated with fear responses associated with visual threat cues (Hardee *et al.*, 2008; Markowitsch, 1999; Phelps *et al.*, 2001). Part of this discrepancy in fear processing by the right or left amygdala might be due to the fact that fearful stimuli are processed differently depending on if they are visual or verbal (Phelps *et al.*, 2001), or consciously or unconsciously learned (Morris *et al.*, 1998). Additionally, fear is a complicated experience, and the context, how the stimulus is presented and learned, and the emotional state of the individual all play an important role in how the amygdala reacts to fearful stimuli. A meta-analysis of human neuroimaging studies investigating amygdala activation in response to a variety of emotional stimuli suggested that much of the reported amygdala laterality is due not to differences in overall activation between hemispheres but to differences in the temporal dynamics of the activation; a stimulus will often elicit a short term response in the right amygdala but a more sustained response in the left amygdala (Sergerie *et al.*, 2008). Such temporal lateralization showcases the functional left/right amygdala activation differences that contribute to emotional processing and responding to stressors.

Investigation of fear and stress in animal models reveals similar inconsistencies in amygdalar processing that parallel the temporal lateralization seen in human neuroimaging studies. Lesion studies in rodents reveal that both left and right amygdala are necessary for fear conditioning, but only the right amygdala is ultimately required for retention of contextual fear (Baker and Kim, 2004). Subjecting rats to predator stress results in potentiation in the right amygdala and depression in the left amygdala directly following stress; however, while the right amygdala continues to exhibit potentiation for up to 11 days post stress, the short term depression in the left amygdala fades by 9 days post stress and is replaced by afferent potentiation as well (Adamec *et al.*, 2005). This potentiation is NMDA receptor dependent in the right amygdala but non-NMDA receptor dependent in the left amygdala, suggesting that there are different mechanisms for potentiation in the context of stress depending on the hemisphere (Adamec *et al.*, 2005). The differences in how the right and left amygdala respond to stimuli are likely due to divergent mechanisms that result in different time courses of activation due to combination of differential inputs and post-

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synaptic processes. Ultimately, the left and right amygdala seem to have distinctive but complementary roles in the processing of emotions that makes it possible to produce rapid and appropriate emotional and behavioral responses to complex stimuli.

It is worth noting that sex differences have been found in many brain areas and greatly influence a wide variety of behaviors, including but not limited to emotion, memory, pain perception, and disease states. Hemispheric lateralization of the amygdala specifically has been shown to be highly dependent on sex in both human and some rodent studies (Cahill, 2006). For example, fMRI studies in healthy humans show that emotional memory predominantly activates the left amygdala in women but the right amygdala in men (Cahill *et al.*, 2004). Hemispheric lateralization of the amygdala even varies at baseline between the sexes: PET imaging of cerebral blood flow demonstrates that the right amygdala has higher activation and connectivity with other brain regions in men at rest while the left amygdala shows the same pattern in women (Kilpatrick *et al.*, 2006). Compared to the wealth of sex differences observed in human neuroimaging data, far fewer amygdala-specific sex differences have been studied in rodents. Male mice and rats were found to have larger amygdala volume and larger amygdala neuron somata size than females (Johnson *et al.*, 2008; Pfau *et al.*, 2016). The right amygdala, but not left, was also found to modulate memory storage in male rats (LaLumiere and McGaugh, 2005). This study did not include female rats, however, so whether this amygdala lateralization is sex specific remains unknown. Additionally, these amygdala studies in rodents focus on amygdala nuclei other than the CeA. How sex as a biological variable influences amygdala lateralization in rodents in the context of pain has not yet been systematically investigated. It is important to recognize that until sex is considered as a critical variable, our interpretation of the current literature is limited and the conclusions we are able to draw from the data presented will be incomplete.

Amygdala Lateralization and Pain

Pain is an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage, as defined by the International Association for the Study of Pain (Loeser and Treede, 2008). The amygdala, due to its well-defined role in emotional processing and more recently described involvement in nociceptive processing, is uniquely positioned to influence the experience of pain (Andreoli *et al.*, 2017; Carrasquillo and Gereau IV, 2008; Ji and Neugebauer, 2009; Neugebauer and Li, 2003; Veinante *et al.*, 2013). In the context of human neuroimaging, many studies have identified the amygdala as an important brain region activated in the context of a variety of pain modalities and demonstrated that the amygdala undergoes changes as a result of both experimentally induced and chronic pain (As-Sanie *et al.*, 2012; Simons *et al.*, 2014). As described above, the central nucleus of the amygdala (CeA) is the main output nucleus of the amygdala; the CeA receives and integrates both nociceptive input and polymodal emotional input from a variety of brain regions, modulating both pain and affect (Figure 1). Although other amygdala nuclei (lateral and basolateral amygdala, as well as the bed nucleus of the stria terminalis, referred to as the “extended amygdala”) are also involved in pain, this review focuses on the role of the CeA in pain modulation. It is important to note that while it is fairly easy to discuss animal studies that specifically investigate the CeA, human

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neuroimaging studies are more complicated. The resolution of neuroimaging techniques is not fine enough to pinpoint different amygdala subnuclei. Therefore, we can only narrow down human imaging data presented to the level of “amygdala”, which may include basolateral, lateral, and central amygdala. As the studies described investigate pain, it is reasonable to assume results discussed apply to the CeA, even if the spatial resolution is not CeA specific.

As a general rule, the right amygdala seems to play a more pro-nociceptive function with the left amygdala having no role, a reduced pro-nociceptive function, or in some studies a novel anti-nociceptive role in the context of acute and chronic injury. As we describe and analyze the existing literature below, we will pay special attention to studies that do not fit well into this lateralization model. As we will see, some of the inconsistencies that have been observed appear to be associated with different types of pain, such as somatic versus visceral pain, or the targeting of different cell types within the amygdala.

Bilateral brain regions are often assumed to have the same function. As a result, experiments often utilize either bilateral or side-randomized manipulation to explore the role of these areas. Both of these approaches prevent accounting for the possibility that the two brain regions may actually serve different purposes or not contribute to the experimental outcome equally. For example, rats with neuropathic pain have increased amygdala cell volume and cell number two months after injury, and animals exhibit increased depression-like behavior, analogous to the increased depression humans with prolonged pain develop (Dworkin and Gitlin, 1991; Gonçalves *et al.*, 2008). However, in that study, the authors neglected to separate data by side, so it is impossible to determine if the increased amygdalar volume is unique to the amygdala hemisphere that is contralateral to the neuropathic injury or if it also seen in the ipsilateral amygdala hemisphere with respect to the injury. If and how the left and right amygdala contribute equally to pain remains relatively understudied and poorly understood. Here, we review existing literature that investigates the role of the left and/or right CeA in the context of pain in order to gain insight into how these hemispheric brain regions interact in order to modulate pain. We have organized this information based on the pain model used.

Inflammatory Pain

As described above, the most direct path for nociceptive information from sensory neurons to reach the amygdala is through the spino-parabrachio-amygdaloid pathway. Parabrachial nucleus (PBN) projection neurons to the CeA are of great interest when investigating pain modulation by the CeA, as this input contains relatively pure nociceptive information that has not been highly processed by other cortical and thalamic brain regions (Figure 1). This PBN circuit is critical to fear conditioning studies in rodents using nociceptive unconditioned stimuli (Sato *et al.*, 2015). Tracing studies in rats suggest that the left and right CeA receive equal, primarily ipsilateral input from the PBN (Bernard *et al.*, 1993). During stimulation of both the left and right periphery, nociceptive signals reach both the left and right PBN and left and right CeA. Newer evidence suggests that even unilateral stimulation of the periphery activates both the left and right PBN in rat (Miyazawa *et al.*, 2018). The potential for each PBN to send nociceptive information to the ipsilateral CeA

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makes differences observed in left and right CeA activity increasingly more interesting. Unilateral injection of formalin in the face of rats increases neuronal activation (*c-Fos*) bilaterally in the PBN, but the right CeA has consistently higher neuronal activation than the left CeA, regardless of the side of inflammation (Miyazawa *et al.*, 2018). Neuroimaging in mice has also revealed that right amygdala activation is increased following formalin in the left paw, and chemogenetic inhibition of the right amygdala decreases formalin-induced activation of multiple bilateral brain regions, suggesting that right amygdala activation in necessary for bilateral inflammatory pain-induced changes in activation (Arimura *et al.*, 2019). The right CeA shows disproportionately higher activation of extracellular signal-regulated kinase 1/2 (ERK1/2) after formalin as well, regardless of the side of formalin-induced paw injury in mice (Carrasquillo and Gereau, 2007). Pharmacologic inhibition of ERK 1/2 phosphorylation in the right CeA, but not the left CeA, of mice is able to reverse inflammation-induced mechanical hypersensitivity in both paws (Carrasquillo and Gereau IV, 2008).

Interestingly, inflammation-induced pain causes molecular changes in the central amygdala as well as behavioral effects that vary depending on age; middle-aged and old mice not only exhibit more nociceptive spontaneous behaviors in response to formalin injected in the right rear paw and develop persistent pain, but they also exhibit increased levels of activated ERK 1 and metabotropic glutamate receptor 5 (mGluR5) in the right but not left CeA compared to young mice (Sadler *et al.*, 2017a). Inherent differences in expression of various proteins and receptors likely contribute to the right CeA's dominant role in the modulation of inflammatory pain, but little has been done to compare gene expression differences across the right and left CeA. mGluR5 represents a notable example of the potential for baseline expression differences to drive lateralized responses. mGluR5 is intrinsically more highly expressed in the right CeA, and mGluR5 activation in the right CeA of mice is sufficient to induce ERK activation (Kolber *et al.*, 2010). Further, mGluR5 inhibition in the right CeA prevents both ERK activation and formalin-induced pain-like hypersensitivity (Kolber *et al.*, 2010), indicating that activation of mGluR5 is necessary for ERK activation and therefore paw inflammation-induced hypersensitivity in both the left and right hind paw. Inflammation-induced hypersensitivity of the right hind paw is also associated with an increase in kappa opioid receptor (KOR) binding in the ipsilateral CeA in mice, in contrast to other opioid receptors, which are downregulated in the context of injury (Narita *et al.*, 2006).

Although the left and right CeA receive equal input from the PBN, rodent studies suggest that transmission at the PBN-CeA synapse is potentiated only in the right CeA in the context of inflammatory pain, regardless of the side of injury (Miyazawa *et al.*, 2018; Sugimura *et al.*, 2016). Inflammation-induced potentiation is dependent on the presence and activity of calcitonin gene-related peptide (CGRP) (Shinohara *et al.*, 2017). CGRP is a neuropeptide involved in pain processing throughout the central and peripheral nervous systems and is highly expressed in neurons along the spino-parabrachio-amygdaloid pathway, including those that project from the PBN to the CeA (Dobolyi *et al.*, 2005; Lu *et al.*, 2015). In mice, CGRP-positive input from the PBN to CeA is involved in nociceptive transmission in the right CeA (Lu *et al.*, 2015), and infusion of CGRP into the right CeA is able to increase pain-like behaviors in naïve rats (Han *et al.*, 2010). Electrophysiology experiments in

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rodents suggest that CGRP drives potentiation in the right CeA by increasing the amplitude of NMDA-mediated EPSCs (Han *et al.*, 2010; Okutsu *et al.*, 2017), most likely through CGRP receptor-driven activation of protein kinase A (PKA) (Han *et al.*, 2005). In another study, pharmacological infusion of CGRP into the left CeA of naïve rats increases mechanical hindlimb threshold (side not specified), suggesting an anti-nociceptive effect (Xu *et al.*, 2003). It is possible that CGRP has different roles in the left and right CeA, or its role could depend on pain modality or chronicity. The modulation of inflammatory pain may be lateralized to the right CeA due to intrinsic differences in expression of CGRP, CGRP receptors, or some downstream signaling molecule, but these potential differences remain unexplored.

Despite overwhelming evidence for the involvement of the right CeA in driving inflammatory pain, an analgesic neural ensemble activated by general anesthesia (GA) has recently been discovered in the bilateral CeA (CeA_{GA}) of mice (Hua *et al.*, 2020). In the context of inflammatory pain, activation of right CeA_{GA} neurons decreases formalin-induced pain-like behaviors while inhibition of right CeA_{GA} neurons restores formalin-induced pain-like behavior, regardless of the side of injury (Hua *et al.*, 2020). Whether or not activation of left CeA_{GA} has similar effect in inflammatory pain has not been explored. However, activation of left or right CeA_{GA} neurons were shown to have analgesic effects at baseline, decreasing mechanical, heat, and cold sensitivity bilaterally in the hind paws (Hua *et al.*, 2020). Interestingly, activation of right but not left CeA_{GA} neurons decreases baseline facial mechanical sensitivity, suggesting that there is some aspect of hemispheric lateralization to the effects of these CeA_{GA} neurons (Hua *et al.*, 2020).

Arthritis Pain

Both human and animal studies demonstrate changes in the right amygdala as a result of arthritic pain. Structural MRI data from patients with rheumatoid arthritis shows decreased right amygdalar volume compared to healthy patients (Wartolowska *et al.*, 2012). While rheumatoid arthritis is typically experienced bilaterally, this study neglects to mention if patients are experiencing rheumatoid arthritis bilaterally or only on the left of right side of the body. Functional neuroimaging in men and women with left or right knee osteoarthritis exhibit greater right amygdala activation in response to experimentally evoked pain via thermode application to the arthritic knee (Kulkarni *et al.*, 2007). In preclinical animal models, neurons in the right CeA of male rats have a much larger receptive field than neurons in the left CeA. These right CeA receptive fields appear to be bilateral compared to contralateral receptive fields of the left CeA neurons. Additionally, arthritis-like injury increases the receptive field of neurons only in the right CeA and does not change the receptive field of left CeA neurons regardless of the side of injury (Ji and Neugebauer, 2009), indicating a right CeA dominance in arthritic pain models. The right CeA also exhibits increases in neuronal activity and enhanced transmission of nociceptive input from the PBN in arthritic rats, no matter which side of the body arthritis is induced on (Han *et al.*, 2005; Ji and Neugebauer, 2009; Neugebauer and Li, 2003; Neugebauer *et al.*, 2003).

Similar to inflammatory pain, pain-induced plasticity observed in the right CeA following arthritis in rodents is dependent on both NMDA and CGRP receptor function (Fu *et al.*,

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2008; Han *et al.*, 2005). CGRP receptor activation in the right CeA increases NMDA-mediated excitatory currents at the PBN-CeA synapse in mice, but the mechanism driving this facilitation is still unclear (Okutsu *et al.*, 2017). PKA activation is necessary for arthritis-induced increases in right CeA neuronal activity in rats (Ji and Neugebauer, 2009), so it is likely that CGRP receptor activation facilitates activation of PKA in the right CeA, which has downstream effects on NMDA receptor function to enhance synaptic transmission (Okutsu *et al.*, 2017). Non-NMDA receptors are likely also important in arthritis-driven increases in right CeA pain plasticity in rats, as they contribute to both nociceptive and non-nociceptive transmission under normal conditions and are enhanced in the arthritic condition (Li and Neugebauer, 2004a). Therefore, non-NMDA receptors may be important for mediating enhanced glutamatergic transmission to the right CeA that potentiates both nociceptive and non-nociceptive sensory signals in the arthritic state (Li and Neugebauer, 2004b); mGluRs 1 and 5 have increased expression in the right CeA in the arthritic pain state (right knee). mGluR5 in the right CeA contributes to the facilitation of synaptic transmission under control conditions and mGluR1 is involved in right knee arthritis-induced pain-like behaviors (Han and Neugebauer, 2005; Neugebauer *et al.*, 2003). It is likely that mGluR1 is recruited in the arthritic state, contributing to pain-induced facilitation (Neugebauer *et al.*, 2003).

Although the right CeA seems to be dominant in the modulation of arthritis pain, a role for the left CeA in arthritic pain has been found in both humans and rodents. Male and female patients with knee arthritis exhibit increases in left amygdala activity measured via PET imaging during spontaneous arthritis pain compared to the pain free state, regardless of the side of arthritis injury (Kulkarni *et al.*, 2007). This is in contrast to the increase in right amygdala activity seen in arthritis patients during experimental pain evoked via a thermode. Overall, these data suggest that the hemispheres may respond differently to distinct stimuli (Kulkarni *et al.*, 2007). In rats, PKA inhibition reverses left knee arthritis-driven increases in neuronal activity in the right CeA but has no effect in the left CeA (Ji and Neugebauer, 2009). Elevations in cAMP increases neuronal activity in both the left and right CeA, though, suggesting that the left CeA may have the ability to contribute to arthritis-induced pain modulation via cAMP signaling but has developed mechanisms to prevent arthritis-induced PKA activation (Ji and Neugebauer, 2009). The role of the left CeA and the extent to which it is involved in arthritic pain is still unclear, and much more left CeA specific investigation must be conducted in order to elucidate its contribution to the modulation of arthritis pain.

Visceral Pain

The right CeA has been noted for changes in activation and functional connectivity in humans and animals as a result of visceral pain. fMRI studies in healthy male and female patients reveal increases in right amygdala activation during noxious gastric distention (Lu *et al.*, 2004). Interestingly, women with chronic irritable bowel syndrome (IBS) exhibit deactivation of the right amygdala during anticipation of rectal distention but stable activation during actual distention (Naliboff *et al.*, 2006). Researchers have posited that amygdalar deactivation is a coping strategy for aversive but unavoidable stimuli, even if the activation during pain remains constant. Alternatively, differences in amygdalar activation

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and deactivation may be due to the subjects being in an acute versus chronic pain state. An fMRI study of female twins with and without bladder pain found that the women with bladder pain exhibit elevated connection between the right amygdala and the periaqueductal grey (PAG) as well as other brain regions during distention compared to the healthy twin (Kleinhans *et al.*, 2016).

Preclinical animal studies also find right amygdala involvement in visceral pain modulation. Rats undergoing colorectal stimulation exhibit increased neuronal activity in the right CeA measured via quantity of immediate early gene *c-fos* (Lazovic *et al.*, 2005). fMRI studies also demonstrate increased right amygdala activation in response to noxious colorectal stimulation in female rats with estrogen dependent stress-induced visceral pain (Hubbard *et al.*, 2016). Additionally, there is increased neuronal excitability and transmission at the PBN-CeA synapse in the right CeA of rats with zymosan-induced colitis (Han and Neugebauer, 2004). Interestingly, the changes in intrinsic membrane properties that lead to this potentiation in the right CeA as a result of colitis in rats are different than those of arthritis pain (Han and Neugebauer, 2004), indicating that pain-induced potentiation observed in the right CeA is a result of different mechanisms depending on the source of nociceptive information. Manipulation of neuronal activity in the right CeA is also able to influence visceral pain behaviorally and physiologically in rodents; mGluR5, already established as an important driver in the potentiation of pain transmission in the right CeA, is also vital to modulating visceral pain, as pharmacological blockade of right CeA mGluR5 is able to reduce bladder pain-like responses in mice (Crock *et al.*, 2012).

Pain-related changes in the left amygdala are also seen in visceral pain conditions; the fMRI study of twin women with bladder pain referenced above found that women with chronic bladder pain have increased connectivity between the left amygdala and PAG at baseline compared to the healthy twin, and that this connectivity then decreases after bladder distention (Kleinhans *et al.*, 2016). Similarly, female patients with IBS exhibit increased activity in the left amygdala during rectal distention compared to healthy controls (Berman *et al.*, 2008), and women with urologic chronic pelvic pain and endometriosis have increased gray matter volume in the left amygdala compared to healthy patients (As-Sanie *et al.*, 2012). This increase is correlated with shorter symptom duration in the long term (Bagarinao *et al.*, 2014), suggesting that these left amygdala gray matter changes are somehow involved in the symptomology of chronic pelvic pain. Further, the left amygdala of female patients with urologic chronic pelvic pain has increased functional connectivity with the posterior cingulate cortex (Martucci *et al.*, 2015), a connection that is positively associated with urologic symptom as well as pain severity (Martucci *et al.*, 2015). It is likely that the left amygdala contributes significantly to the affective components of visceral pain.

Preclinically, acid-induced visceral pain has been found to increase *c-fos* activation in the left amygdala of rats compared to control animals (Nakagawa *et al.*, 2003). Unfortunately, activation of *c-fos* in the right CeA was not measured in this study, so it is impossible to determine if this is a unilateral or bilateral effect and how this increase compares to the right CeA. Increases in left amygdala activation have also been found in response to noxious colorectal distention in female rats via fMRI (Hubbard *et al.*, 2016). There is a scarcity of left CeA specific studies in visceral pain, likely due to the right CeA's well documented role

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in other pain models, leading to an *a priori* bias to focus just on the right side. Human studies clearly indicate involvement of the left amygdala in visceral pain, though it's role may be involved more in modulating the affective components and symptom severity. It is difficult to tease apart visceral hypersensitivity and affective symptomology in animal studies, so it remains challenging to determine the possible affective influence of the left CeA on visceral pain.

Both the left and right amygdala contribute to visceral pain modulation, but a definitive role for each and how they work together remains largely unknown and unexplored. While increases in neuronal activity in the left and right CeA are likely indicative of pain induced changes contributing to modulating and maintaining pain, it is still unclear how these changes are influencing the pain experience. fMRI imaging reveals that the right amygdala of women with bladder pain sees an increase in functional connectivity with the PAG during distention, but the left amygdala exhibits a decrease in this same connectivity following distention (Kleinhans *et al.*, 2016). A collection of neuroimaging studies beyond visceral pain supports the idea that the left and right amygdala have distinct roles in pain processing. A meta-analysis of 40 neuroimaging studies found that the right amygdala was consistently more active in experimental pain studies but the left amygdala was more active in clinical pain patients (Simons *et al.*, 2014). It is possible that the left and right amygdala's opposing patterns of dominance to experimental and clinical pain are the result of distinct contributions to either acute or chronic pain; it may be that the right amygdala is more involved in acute pain (i.e. experimental pain) while the left amygdala is dominant in chronic pain (i.e. clinical pain).

Unilateral side specific manipulations of neuronal activity in the left or right CeA of animals results in unique and opposing differences in pain-like behavior and physiology. For example, nonspecific optogenetic activation of neurons in the left or right CeA reveals divergent functions of the two nuclei in the context of peripheral bladder stimulation. Activation of the right CeA increases physiological responses to urinary bladder distention and increases mechanical abdominal sensitivity in mice (Sadler *et al.*, 2017b) (Crock *et al.*, 2012). This right CeA effect could be replicated with pharmacological application of pituitary adenylate cyclase-activating peptide (PACAP) prior to bladder stimulation. The PACAP effect was independent of the side of the body for which physiological measurements were made. PACAP had no effect on bladder pain-like changes when injected in the left CeA. However, physiological responses to urinary bladder distention also increased during optogenetic inhibition of the left CeA, suggesting an ongoing, analgesic output of the left CeA in naïve mice independent of PACAP (Sadler *et al.*, 2017b). Following bladder sensitization, optogenetic activation of the left CeA reduces abdominal mechanical hypersensitivity, a measure of referred bladder pain (Sadler *et al.*, 2017b). These data suggest that the analgesic capability of the left CeA could be harnessed to reduce pain (Sadler *et al.*, 2017b). Whether this is also the case in chronic pain is interesting to consider, as the shift from acute injury to chronic pain may also shift amygdala output and affect neuronal activity of the left and right CeA differently. Other studies have failed to find differences in pain modulation with left versus right modulation, though; bilateral activation of the CeA with cortisol pellets in rats is sufficient to increase reflexive responses to

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colorectal distention, but neither right nor left amygdala unilateral stimulation is sufficient to cause visceral hypersensitivity (Tran and Greenwood-Van Meerveld, 2012).

Neuropathic Pain

Similar to other pain models, neuropathic pain increases neuronal activity in the right CeA by facilitating transmission at the PBN-CeA synapse and potentiates pain-like behaviors (Ikeda *et al.*, 2007). Mice with left leg neuropathic pain show increases in expression of corticotrophin-releasing factor (CRF) in the CeA (side not a variable) (Andreoli *et al.*, 2017). CRF-expressing neurons are a main output population of the CeA (Pomrenze *et al.*, 2015), and overactivation of CRF-expressing cells in the CeA is thought to be an important contributing factor in pain chronification (Andreoli *et al.*, 2017). CRF neurons in the CeA are largely under inhibitory control of enkephalinergic (Enk) interneurons, which modulate amygdala projections and help modulate the descending regulation of pain via the PAG (Paretkar and Dimitrov, 2019). However, the laterality of these effects and side-specific influence of the amygdala remains unexplored. Interestingly, the right CeA regulates neuropathic pain via differential activation of two non-overlapping cell populations. PKCd-expressing cells in the right CeA are sensitized after left-sided neuropathic injury, but somatostatin-expressing cells are inhibited by injury (Wilson *et al.*, 2019). Chemogenetic activation of right CeA PKCd cells increases mechanical sensitivity, and silencing these cells in animals with neuropathic injury reduces pain, suggesting a pro-nociceptive function for these neurons and a role in sustaining chronic pain (Wilson *et al.*, 2019). Furthermore, chemogenetic activation of somatostatin cells in the right CeA decreases left paw mechanical sensitivity while inhibition of right CeA somatostatin in naïve animals increases pain (Wilson *et al.*, 2019). Whether this cell-type specific bidirectional modulation of pain extends to left amygdala remains unknown. Interestingly, the analgesic neural ensemble of CeA_{GA} neurons recently discovered in mice is a heterogenous population that includes PKCd-expressing neurons (Hua *et al.*, 2020). The extent of overlap between right CeA PKCd pain driving neurons in Wilson *et al* 2019 and the PKCd CeA_{GA} neurons remains to be determined. Activation of right CeA_{GA} neurons decreases bilateral mechanical sensitivity and spontaneous pain-like behaviors in mice with right side neuropathic injury (Hua *et al.*, 2020). Whether or not left CeA_{GA} neurons have a similar effect in neuropathic pain was not tested.

The right CeA's role in modulating classical behavioral symptoms of neuropathic pain is also highly dependent on the side of injury and sensory modality (Cooper *et al.*, 2018). While the right CeA is vital for the development of mechanical allodynia, hyperalgesia, and cold hypersensitivity when the injury is in the contralateral (Ieft) leg, the right CeA is only necessary for modulation of hyperalgesia when the injury is in the ipsilateral leg; inactivation of the right CeA with lidocaine increases mechanical thresholds to von Frey as well as reduces withdrawal duration to pinprick and acetone only when the injury is in the left leg (Cooper *et al.*, 2018). When the injury is in the right leg, though, inactivation of the right CeA only reduces pinprick withdrawal duration and does not affect von Frey or acetone responses (Cooper *et al.*, 2018).

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Unlike in other pain models, group I mGluRs, including mGluR1 and mGluR5, in the right CeA of rats have little to no effect on left leg neuropathic pain-induced pain-like behavior. mGluRs 1 and 5 do, however, mediate emotional pain-like behaviors associated with nerve injury, including aversive place conditioning (Ansah *et al.*, 2010). Similarly, kappa opioid receptors (KOR) in the right CeA are important for mediating the aversive components of left side neuropathic pain, determined via conditioned place preference, but have no effect on mechanical hypersensitivity (von Frey) in rats (Navratilova *et al.*, 2019). Pain-like behaviors associated with left side nerve injury are accompanied by increases in right CeA neuronal activity at the PBN-CeA synapse in rats (Gonçalves and Dickenson, 2012; Ikeda *et al.*, 2007); however, the mechanisms driving PBN-CeA potentiation may be different than other types of pain. In contrast to inflammatory, visceral, and arthritic pain, this potentiation does not seem to be NMDA receptor dependent, suggesting that the molecular mechanism responsible for increasing potentiation in the right CeA in the context of neuropathic pain is distinct from other types of pain (Ikeda *et al.*, 2007). It is possible that NMDA receptors play a role in the maintenance of neuropathic pain through non PBN-CeA pathways, including input from the BLA projections or CeA interneurons (Ansah *et al.*, 2010). Further investigation is needed in order to elucidate the specific mechanisms modulating different neuropathic pain symptoms in the right CeA, as they seem to be distinct from other types of pain.

Though the left CeA is less often the main focus, it is also fundamental to the modulation of neuropathic pain. Inactivation of the left amygdala is required for reduction in mechanical allodynia induced by contralateral (right) leg neuropathic pain in rats (Cooper *et al.*, 2018), and mGluR5 activation in the left amygdala is sufficient to induce right side only mechanical sensitivity in uninjured mice (Kolber *et al.*, 2010). Ablation of left but not right CeA CRF projection neurons to the locus coeruleus decreases mechanical sensitivity following left leg neuropathic injury (Andreoli *et al.*, 2017). Furthermore, the left amygdala exhibits an increase in spontaneous and evoked neuronal activity compared to the right amygdala following left side neuropathic injury, although this increase is not long lasting (2–6 days) (Gonçalves and Dickenson, 2012). Interestingly, in that same study neuronal activity in the right amygdala is increased compared to the left amygdala 14 days after nerve injury (Gonçalves and Dickenson, 2012), suggesting that time-dependent differences in activation are important in the development of the chronic state after neuropathic injury. The time staggered activation of the left and right amygdala may be indicative of different functions as pain shifts from acute to persistent to chronic.

Conclusions

Pain, aversion, anxiety, and fear are processed in the amygdala and there is considerable overlap in the cell types involved in each. At the same time, the mechanisms involved in modulating different types of pain are not always consistent. The amygdala's influence on pain modulation is by no means limited to the cell types or mechanisms discussed here, and substantial gaps in the circuitry, connections, and mechanisms involved in pain processing in the amygdala remain. Further, hemispheric lateralization of the amygdala in the context of pain is a new but quickly emerging area of study, and there is significant progress still to be made. Currently, amygdala lateralization is most clearly observed in conditions where the

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pain is not limited to one side of the body, such as in visceral pain conditions like bladder or colorectal pain. Human and animal studies of visceral pain indicate differential activation patterns (Kleinhans *et al.*, 2016; Lazovic *et al.*, 2005; Lu *et al.*, 2004; Naliboff *et al.*, 2006) and suggest imbalanced or even opposing functions of the left and right amygdala (As-Sanie *et al.*, 2012; Berman *et al.*, 2008; Sadler *et al.*, 2017b). Such clear hemispheric lateralization is not so easily observed in other pain models, though. Decussation of sensory afferents complicates the interpretation of lateralization when the pain is confined to a single side of the body, such as inflammatory, neuropathic, or arthritic pain models that are concentrated in one limb. Seemingly contradictory or asymmetrical roles of the CeA in relation to pain modulation may stem from simple differences in cell type or receptor abundance or perhaps variations in downstream pathways that lead to functional differences between hemispheres. It is also likely that the amygdala is not the only pain/affective brain area to show functional lateralization, and such phenomena may be observed upstream or downstream in the pain processing pathway. With all of the evidence for side-specific amygdalar differences in neuronal activity and plasticity, lateralized studies are especially necessary to fully elucidate the changes that happen in the amygdala during pain and how specific cell types in each hemisphere change and influence each other.

When evaluating any example of functional lateralization, it is valuable to consider the purpose of such lateralization. Lateralization has been hypothesized to (1) deal with functional incompatibility when interacting with the environment (i.e. attending to both the changing and non-changing parts of the environment) (2) provide opportunities for multi-tasking (3) improve success or performance on tasks and (4) help influence whether approach or avoidance behaviors are initiated. Here, we present some speculative ideas about lateralization of the amygdala in the context of pain.

First and foremost, we consider lateralization in the context of acute pain and injury (Figure 2). During acute injury, neuronal activity and excitability in the right CeA increases, driving pain and therefore motivating evolutionarily beneficial escape or harm reduction behaviors. As the pain persists, overactivation of neurons in the right CeA fades and returns to baseline spontaneous activity, and neuronal excitability in the left CeA increases to drive pain relief. Such an effect may be driven by differences in temporal activation of specific “pro-“ and “anti-nociceptive” cell types, such as PKCd and somatostatin (Wilson *et al.*, 2019), or it may be the result of similar cell types but different mechanisms, including activation of different downstream signaling cascades. This balancing act between activation of the left and right CeA is therefore able to modulate acute pain, which is important for detecting possible damage; nociceptive signals warn of potential harm and protect damaged tissue during healing, but they eventually cease when the stimulus is removed or healing is complete. In some circumstances, such a lateralized system might be engaged to actually drive left amygdala analgesia. This might occur during a stressful or life-threatening situation in which suppression of the pro-nociceptive right CeA would provide the opportunity to attend to survival over pain. Here, the overarching hypothesis is that lateralization in the amygdala provides for fine-tuning the immediate response to injury and how that response changes over time. This hypothesis harkens back to explanations for functional lateralization in language areas in the brain providing for specialization over redundancy.

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In chronic pain conditions, the balance of this system is likely disturbed, resulting in persistent pain. This imbalance may be due to 1) maintenance of neuronal hyperexcitability in the right CeA that is able to surpass the pain blocking effect of the left CeA, or 2) lack of activation of left CeA neurons to counteract the right CeA's pain-driving effect. Amygdala lateralization in the context of pain is only beginning to be acknowledged and explicitly explored, and there are a multitude of different elements to consider that will vary greatly based on pain modality. We acknowledge that this hypothesis remains relatively broad, but the specific intricacies necessary to fully understand how amygdala lateralization functions across pain models will only be clarified with further studies that specifically address side as a variable.

Acknowledgements

We thank Dr. Michael Gold for his critical reading and helpful edits on this manuscript. This work was supported by funding from the National Institute of Diabetes and Digestive and Kidney Diseases grants F31 DK12148401 and R01 DK115478-01.

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Highlights

- The amygdala has a long-standing history of hemispheric lateralization in emotion
- The CeA's unique role in pain processing is thought to be right hemisphere dominant
- Recent findings suggest the left CeA also plays an important role in pain processing
- Growing evidence reveals CeA lateralization across a variety of pain models
- CeA lateralization should be examined in future pain studies

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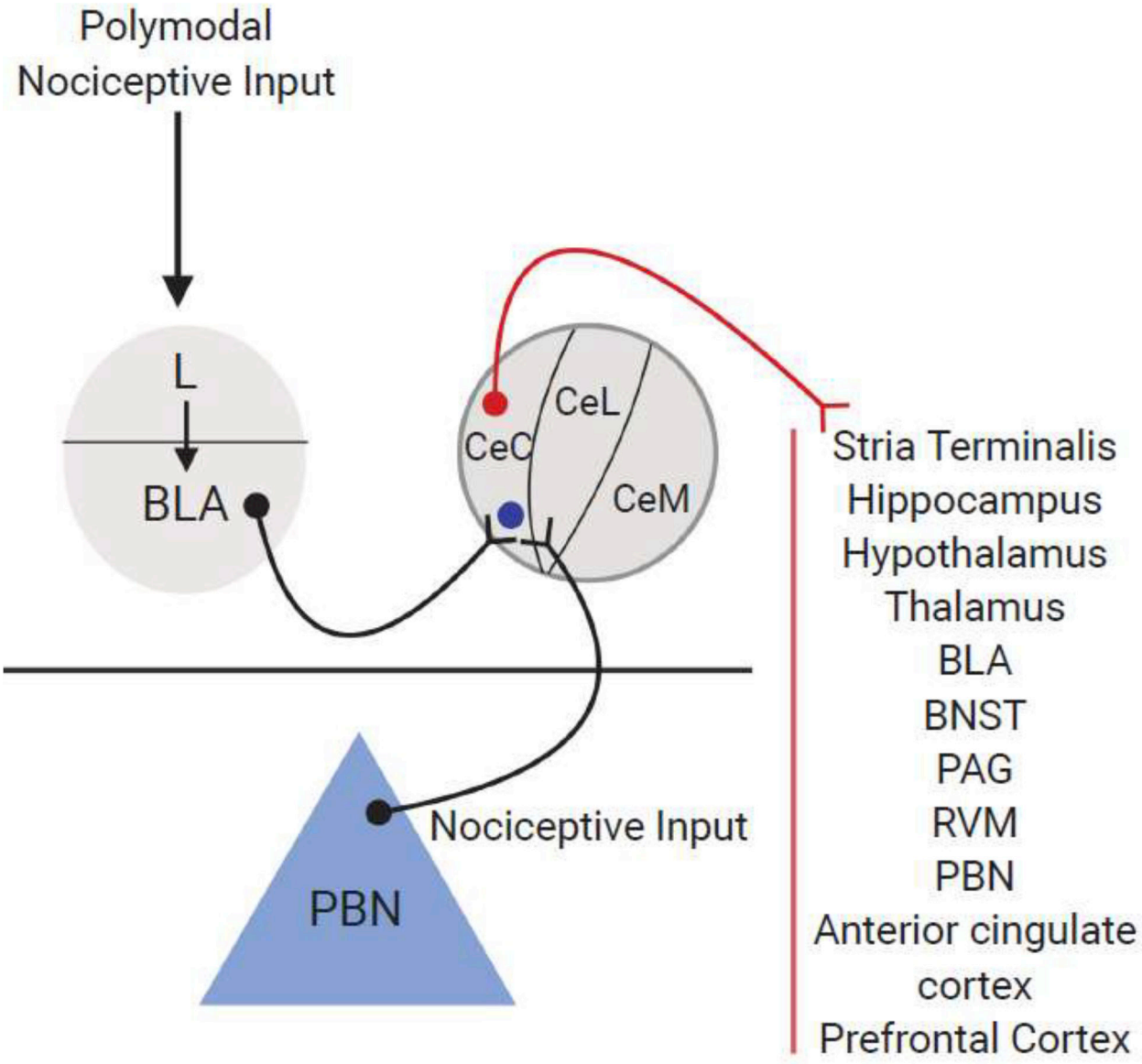

Figure 1:

Overview of inputs and outputs of the central amygdala (CeA). Nociceptive input to the CeC is received from the PBN, whereas polymodal input is received from the thalamus and other amygdala nuclei. Outputs are highlighted by the red output neuron to various other brain regions. *PBN: parabrachial nucleus; L: lateral amygdala; BLA: basolateral amygdala; CeC: capsular central amygdala; CeL: lateral central amygdala; CeM: medial central amygdala; BNST: bed nucleus of the stria terminalis; PAG: periaqueductal gray; RVM: rostral ventral medulla*.

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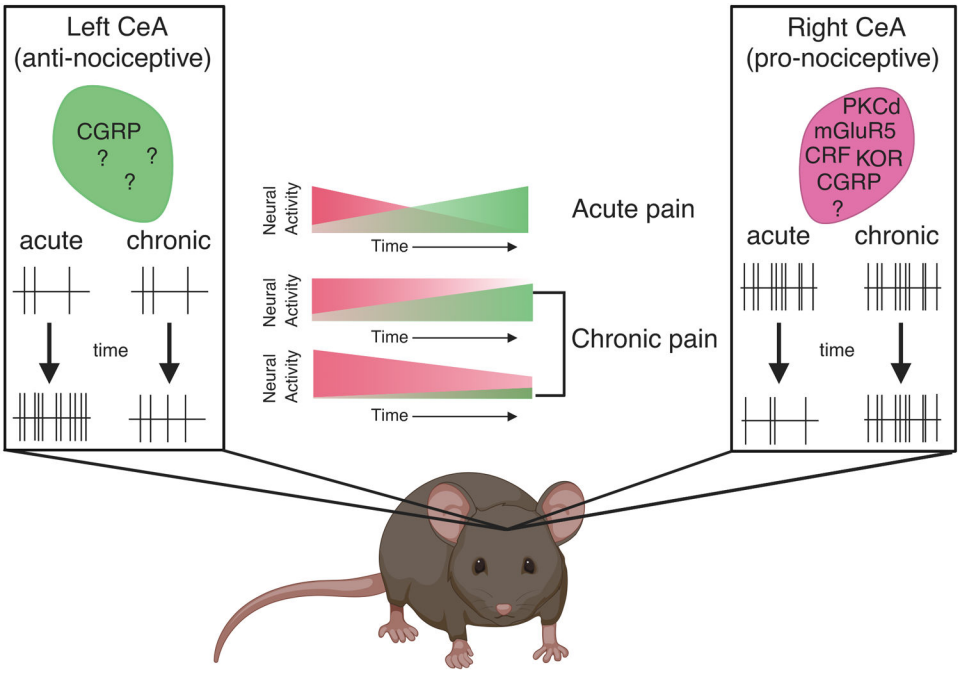

Figure 2:
Hypothesized model for how amygdala lateralization works in acute and chronic pain.

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Table 1:

Summary of key findings referred to in text. R: right; L: left; CeLC: laterocapsular central amygdala; CFA: Complete Freund's Adjuvant; SNL: spinal nerve ligation; GFD: gastric fundus distention; IBS: irritable bowel syndrome; UCPP: urologic chronic pelvic pain; CRD: colorectal distention; UBD: urinary bladder distention; CPP: chronic pelvic pain; SNC: sciatic nerve cuff; SNI: spinal nerve injury; CCI: chronic constriction injury.

	reference	pain model	species	sex	CeA nucleus (nucleus stated in original paper if different)	CeA side investigated/ manipulated	side of injury	time after injury	key findings
Naïve	Han et al 2010	naïve	rat	m	CeC (CeLC)	right	none	n/a	CGRP increases EPSCs at R PBN-CeA synapse; CGRP in R CeA increases vocalizations and decreases hindlimb withdrawal thresholds
	Okutsu et al 2017	naïve	mouse	m	CeC	right	none	n/a	CGRP increases NMDAR-mediated EPSCs at R PBN-CeA synapse
	Xu et al 2003	naïve	rat	m	CeA	left	none	n/a	CGRP in the L CeA decreases mechanical and thermal hindlimb thresholds
	Hua et al 2020	naïve	mouse	m & f	CeA	both	none	n/a	activation of L CeA neurons captured by anesthesia has no effect on L or R facial mechanical sensitivity, but decreases mechanical, heat, and cold sensitivity in the L and R hind paws of naive animals. Activation of R CeA neurons captured by anesthesia decreases L and R facial and paw mechanical sensitivity as well as L and R hind paw heat and cold sensitivity.
Inflammatory Pain	Miyazawa 2018	formalin	rat	m	CeC (CeLC)	both	both	0–60 min post injection	L or R formalin cheek injection increases R CeA cFos,

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	reference	pain model	species	sex	CeA nucleus (nucleus stated in original paper if different)	CeA side investigated/ manipulated	side of injury	time after injury	key findings
									potentiates transmission at R but not L PBN-CeA synapse
	Arimura et al 2019	formalin	mouse	m	amygdala	both, right	left	2 and 6 hr post injection	R amygdala activation is increased after left paw formalin; inhibition of R amygdala decreased formalin-induced activation of a variety of brain regions
	Carrasquillo and Gereau 2007	formalin	mouse	m	CeC	both	right	0–2 hr post injection	blockade of ERK in R CeA reverses formalin-induced paw hypersensitivity
	Carrasquillo and Gereau 2008	formalin	mouse	m	CeA	both	both	3 hr post injection	Increased ERK in R CeA following L or R hind paw formalin; Blockade of ERK in R but not L CeA reduced formalin-induced hind paw hypersensitivity
	Sadler et al 2017a	formalin	mouse	m	CeA	both	right	0–60 min post injection	formalin in R hind paw increased ERK and mGluR5 in R but not L CeA
	Kolber et al 2010	formalin, naïve	mouse	m	CeC (CeLC)	both	right	3 hr post injection	R CeA mGluR5 activation induces bilateral hind paw hypersensitivity, L CeA mGluR5 activation induces R hind paw hypersensitivity; R CeA mGluR5 inhibition reverses bilateral hind paw formalin-induced hypersensitivity
	Narita et al 2006	CFA, SNL	rat	m	amygdala-BLA and CeA	right	right	4 weeks post	binding of KOR increased following

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	reference	pain model	species	sex	CeA nucleus (nucleus stated in original paper if different)	CeA side investigated/ manipulated	side of injury	time after injury	key findings
								injection/ surgery	inflammatory but not neuropathic pain
	Sugimura et al 2016	formalin	mouse	m	CeC	both, data pooled	left	24 hr post injection	formalin in the left hind paw increases EPSCs in R and L CeA
	Shinohara et al 2017	formalin	mouse	m & f	CeC	right	left	0–6 hr post injection	CGRP KO mice had attenuated potentiation at R PBN-CeA synapse and decreased bilateral hind paw hypersensitivity following L hind paw formalin injection
	Lu et al 2015	formalin	mouse	m	CeC	both	both	1.5 hr post injection	GABAergic CeA neurons receive CGRP input from the PBN; these neurons and are activated in R CeA by formalin to either R or L hind paw
	Hua et al 2020	formalin	mouse	m & f	CeA	right	both	0–18 minutes post injection	Activation of R CeA neurons captured by anesthesia inhibited formalin-induced pain-like behaviors regardless of side of injury, and inhibition of these neurons reinstates pain-like behaviors after spontaneous formalin-induced behaviors subside.
Arthritis Pain	Han, Li, and Neugebauer 2005	kaolin arthritis	rat	m	CeC (CeLC)	right	left	6 hr post injection	CGRP receptor antagonists in R CeA reverse synaptic plasticity in L knee arthritic rats via PKA modulations of NMDARs

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	reference	pain model	species	sex	CeA nucleus (nucleus stated in original paper if different)	CeA side investigated/ manipulated	side of injury	time after injury	key findings
	Wartolowska et al 2012	rheumatoid arthritis	human		amygdala	both	both/not specified	n/a	patients with rheumatoid arthritis have decreased R amygdala volume
	Kulkarni et al 2007	osteoarthritis	human	m & f	amygdala	both	both	n/a	increase in L amygdala activity in arthritis pain versus pain free state, but increase in R amygdala activity during experimentally induced pain compared to pain free state
	Ji and Neugebauer 2009	kaolin arthritis, naïve	rat	m	CeC (CeLC)	both	both	up to 5 hr post injection	R CeA neurons have larger receptive fields than L CeA neurons in naïve and arthritic rats; R but not L CeA neurons increase firing after arthritis regardless of side of injury; PKA inhibition decreases arthritis-induced increases in R CeA neuronal activity
	Neugebauer and Li 2003	kaolin arthritis	rat	m	CeC	right	left	6–18 hr post injection	multireceptive R CeA neurons have expanded receptive field size and enhanced responses to noxious mechanical but not thermal stimuli following arthritis; nociceptive-specific neurons do not change after arthritis
	Neugebauer et al 2003	kaolin arthritis	rat	m	CeC	right	left	6–8 hr post injection	arthritic rats have enhanced nociceptive PBN transmission to R CeA; Blocking mGluR1 has no effect in normal rats but reduces

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	reference	pain model	species	sex	CeA nucleus (nucleus stated in original paper if different)	CeA side investigated/ manipulated	side of injury	time after injury	key findings
									synaptic potentiation in arthritic rats; blocking mGluR5 has no effect decreases synaptic transmission in normal rats but has no effect in arthritic rats
	Fu et al 2008	kaolin arthritis	rat	m	CeC (CeLC)	right	left	6 hr post injection	PKA and ERK inhibitors prevent synaptic plasticity in R CeA of arthritic rats but not control rats; inhibition of R CeA NMDAR prevents increases in spinal reflex and vocalization seen in arthritic rats
	Li and Neugebauer 2004	kaolin arthritis	rat	m	CeC	right	left	6–12 hours post injection	blocking mGluR1 in R CeA inhibits sensitized neurons after left knee arthritis but has no effect at baseline; blocking R CeA mGluR5 inhibits brief and prolonged nociceptive responses at baseline and after left knee arthritis.
	Han and Neugebauer 2005	kaolin and carageenan arthritis	rat	m	CeA	right	left	6 hr post injection	mGluR1 and 5 in the R CeA contribute to vocalizations induced arthritis pain
Visceral Pain	Lu et al 2004	healthy adults (GFD)	human	m & f	amygdala	both	n/a	n/a	increases in R amygdala activation in response to gastric distention
	Naliboff et al 2006	IBS	human	f	amygdala	both	n/a	n/a	R amygdala deactivation during anticipation of rectal distention
	Kleinhans et al 2016	UCPP	human	f	amygdala	both	n/a	n/a	UCPP patients have elevated L

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	reference	pain model	species	sex	CeA nucleus (nucleus stated in original paper if different)	CeA side investigated/ manipulated	side of injury	time after injury	key findings
									amygdala-PAG connectivity at baseline that decreases post distention but elevated R amygdala-PAG connectivity post distention
	Lazovic et al 2005	naïve (CRD)	rat	m	amygdala	both	n/a	2 hr post CRD	increased cFos in R CeA in response to colorectal distention
	Hubbard et al 2016	stress-induced visceral pain	rat	f	amygdala	both	n/a	pre stress, 2 days & 18 days post stress	noxious visceral stimulation increases L amygdala activation across groups; increase in R amygdala activation of rats with stress-induced visceral pain
	Han and Neugebauer 2004	zymosan colitis	rat	m	CeA	right	n/a	6–7 hr post zymosan	enhanced transmission at R PBN-CeA synapse but not R BLA-CeA synapse; R CeA neurons in colitis rats did not show changes in intrinsic membrane properties seen in R CeA neurons of rats with arthritis
	Sadler et al 2017b	naïve & CYP-cystitis (UBD)	mouse	f	CeA	both	n/a	1 day post CYP	R CeA activation increases bladder pain in normal and CYP mice; PACAP in R CeA increases bladder pain; L CeA inhibition increases bladder pain
	Crock et al 2012	naïve (UBD)	mouse	f	CeA	right	n/a	n/a	mGluR5 activation in R CeA increases bladder pain; blocking mGluR5 in R CeA reduces bladder pain

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	reference	pain model	species	sex	CeA nucleus (nucleus stated in original paper if different)	CeA side investigated/ manipulated	side of injury	time after injury	key findings
	Berman et al 2008	IBS	human	f	amygdala	both	n/a	n/a	increased L amygdala activation during rectal distention
	As-Sanie et al 2012	endometriosis, UCPP	human	f	amygdala	both	n/a	n/a	increased gray matter volume in L amygdala in patients with endometriosis and UCPP
	Bagarinao et al 2014	CPP	human	f	amygdala	both	n/a	n/a	increased gray matter in L amygdala in patients with CPP; L amygdala activation is correlated with shorter symptom duration
	Martucci et al 2015	CPP	human	f	amygdala	both	n/a	n/a	increased L amygdala-posterior cingulate cortex functional connectivity
	Nakagawa et al 2003	acetic acid	rat	m	CeA	left	n/a	1 hr	increase in L CeA cFos expression after acetic acid injection
	Tran et al 2012	naïve (CRD)	rat	m	CeA	both	n/a	n/a	bilateral CeA corticosterone increases colorectal pain, but unilateral R or L corticosterone injections increases colorectal pain
Neuropathic Pain	Ikeda et al 2007	SNL	rat	m & f	CeA	both	left	6–7 days post surgery	increased transmission at R PBN-CeA synapse after SNL
	Andreoli et al 2017	SNC	mouse	m	CeL, CeC	both	left	0–15 days post surgery	SNC increases CRF expression in the CeA (averaged L & R); ablation of L but not R CeA CRF projections to LC decreases SNC-induced mechanical sensitivity

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	reference	pain model	species	sex	CeA nucleus (nucleus stated in original paper if different)	CeA side investigated/ manipulated	side of injury	time after injury	key findings
	Paretkar and Dimitrov 2019	SNC	mouse	m	CeC (CeL)	bilateral	left	5–45 days post surgery	bilateral activation of CeA enkephalin neurons decreases R hind paw SNC-induced hypersensitivity
	Wilson et al 2019	SNC, naïve	mouse	m	CeA	right	both	7 days post surgery	R CeA PKCd cells are sensitized by SNC; activating R CeA PKCd cells increases mechanical sensitivity in naïve animals and inhibiting them in SNC animals decreased mechanical and thermal hypersensitivity; R CeA SST cells are inhibited by SNC; activating R CeA SST cells in SNC animals reverses mechanical hypersensitivity and inhibiting them in naive animals causes mechanical sensitivity
	Cooper et al 2018	SNI	rat	m	CeA	both	both	14 days post surgery	inactivation of R CeA prevents mechanical and cold hypersensitivity post left leg SNI; L CeA inactivation prevents mechanical hypersensitivity post right leg SNI
	Ansah et al 2010	SNI	rat	m	CeA	bilateral; R or L unilateral	left	1 or 8 weeks post surgery	mGluR1 and 5 have little to no effect on mechanical hypersensitivity post SNI; mGluR1 increases emotional pain-like behavior
	Navratilova et al 2019	SNL	rat	m	CeC (CeLC)	right	left	4 weeks post surgery	blockade of KOR in the R CeA eliminates

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	reference	pain model	species	sex	CeA nucleus (nucleus stated in original paper if different)	CeA side investigated/ manipulated	side of injury	time after injury	key findings
									the aversiveness of left leg SNL pain but does not affect mechanical hypersensitivity; R CeA KOR blockade decreased firing of CeA neurons in SNL but not control rats
	Gonçalves et al 2012	SNL	rat	m	CeA	both	both	2–14 days post surgery	spontaneous and stimulus evoked neuronal activity is increased in L CeA 2 and 6 days post SNL, but R CeA neuronal activity is increased 14 days post SNL regardless of side of injury
	Hua et al 2020	CCI	mouse	m & f	CeA	right	both	7 days post surgery	Activation of R CeA neurons captured by anesthesia decreases L and R cheek mechanical sensitivity, decreases spontaneous face wiping, and exhibits place preference