**Chapter 4**

**Pain perception and the brain**

In this chapter I discuss details on pain neurophysiology, with emphasis on brain as opposed to spinal cord and receptors. The ensuing discussion of the brain areas involved with chronic and acute pain is presented to provide information on the areas that have been associated with pain perception and control with the goal of later explaining how the DSM explains the involvement of each area.

Nociceptors convey information to the spinal cord along the Aδ (faster conducting, relatively larger, and myelinated axons) and C (slower conducting, smaller, and unmyelinated axons) fiber pathways. Most nociceptive afferents make synaptic contact in Rexed laminae I and II of the spinal cord, while low threshold Aβ afferents (mainly sensitive to touch, but also second-order nociception) synapse in laminae III to V. There are two brain areas receiving direct input from the C fibers; the parabrachial nucleus (PBN) and the thalamus. The PBN sends input to the central nucleus of the amygdala (CeA) involved in emotional reactions to pain. The laminae IV and V input goes to the thalamus and periaqueductal gray (PAG). The PAG activation can allow pain control via activation of the descending serotoninergic and adrenergic neurons which, in turn, drive laminae II interneurons which release enkephalins onto incoming nociceptor afferents and spinothalamic neurons.

Via the spinothalamic tract there is nociceptor input to the thalamus that involves two separate cerebral cortical pathways. Of great relevance to the psychological impact of chronic pain is the medial pain pathway to the cortex. There are thalamic connections from the smaller, unmyelinated peripheral C fibers associated with the punishing, motivational, and emotional aspects of pain (sometimes referred to as second pain). This involves projections including and beyond the VPC which includes the ventrocaudal mediodorsal nucleus (Mdvc), medial nucleus of the posterior group (POm), and posterior part of the ventral medial nucleus (VMpo). Mdvc provides input to the ACC while POm and VMpo provide input to the insula. Vogt (2005) notes both spinothalamic tract and parabrachial nucleus (PBN) input to the ILN which provides input to the middle cingulate cortex (MCC).

The “pain matrix” (Schweinhardt and Bushnell, 2010) refers to the network of brain regions involved with the sensory-discriminative and cognitive-affective aspects of pain. In reaction to noxious stimuli, Peirs and Seal (2016) note fMRI has shown coordinated activation of the thalamus, ACC, insular cortex, S1 and S2 somatosensory cortices, prefrontal cortex (PFC), basal ganglia, cerebellum, and amygdala. However, those authors also note that many of these same areas can be activated by non-nociceptive stimuli. The position of the DSM is that different circuits of cortical columns are contained within the same brain regions and it is necessary to understand the design to better interpret the role of the involved circuitry. This is analogous to circuit boards in a television; a board involved with sound may interconnect with the one involved with video, and both activate when the television is switched on. However, it is impossible to know how the boards function and fix problems without a knowledge of the individual circuits of each board. This example also provides an understanding that there are circuits within the boards and a circuit connecting the two boards, just as the current paper discusses interareal cortical circuits of columns and the connection of those localized columnar circuits to other cortical areas and subcortical structures. The typical level of discussion in brain scan studies involves the areas of the cortex, which is the same as discussing results at the level of the circuit boards.

Wiech (2016) discussed the influences of cognitive processes on pain perception in relation to neural structures. Factors documented to impact pain perception are attention, anticipation, catastrophizing, reappraisal, and perceived control. Reddan and Wager (2018) discuss the use of multivariate predictive modeling, called the Neurologic Pain Signature (NPS), in an attempt to better define brain features related to pain. They report that greater activity in the ACC, insula, S2, and thalamus, predicted more pain. In contrast, greater activity in the ventromedial PFC (vmPFC) and precuneus predicted less pain. Wiech (2016) notes the “pain matrix” has historically been divided into the sensory-discriminative system, which includes the lateral thalamus, S1, and S2, and the cognitive-affective system, which includes the anterior insula and ACC. Thus, the NPS includes locations of both divisions.

Woo, Roy, Buhle, and Wager (2015) found NAc to vmPFC connectivity mediates the effects of cognitive self-regulation on pain independent of noxious stimulus intensity. Wiech (2016) proffered the idea that the mesolimbic network may integrate sensory, cognitive, and affective aspects to give rise to the unified pain experience. The role of attention on pain perception was also discussed by Wiech, noting the aforementioned descending pain control system as one circuit. One of the other two systems is the “salience network” that is involved in the detection of biologically relevant stimuli. It involves dlPFC, MCC, aIns, and temporoparietal junction (TPJ). The other attention system is the default mode network (DMN) that includes the mPFC, posterior cingulate cortex (PCC), precuneus, lateral parietal lobe, and medial temporal lobe. The DMN is engaged when focused away from pain while the salience network activates when attention is spontaneously focused on pain.

A final system of importance was identified in one study (Cai et al., 2018) and includes the amygdala. The PBN receives collateral projections (i.e., the main projections are to the thalamus as previously discussed) from peripheral nociceptors. This suggests that peripheral pain signals can directly activate emotional responses without cortical processing. In contrast, activation of the excitatory pathway from basolateral amygdala (BLA) opposes the negative emotion behaviors and induces behaviors of reward. The BLA conveys processed corticolimbic signals to CeA. The authors concluded the BLA to CeA circuit may be a top-down mechanism for cognitive control of negative emotions related to pain.

In summary, the following areas have been identified in brain pain perception and control: thalamus, S1, S2, insula, middle temporal gyrus, precuneus, PHG, dlPFC, vlPFC, vmPFC, OFC, ACC, MCC, NAc, caudate, putamen, PAG, PBN, amygdala, and cerebellum. The salience network and DMN have been implicated in attention toward or away from pain. In relation to neuroimaging in non-human animal models, chronic pain brain alterations are most commonly observed in regions associated with emotion and motivation, including PFC, ACC, hippocampus, amygdala, basal ganglia, and NAc.