

## Elucidating the role of endogenous opioids in the regulation of social pain

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The perception of pain is but one component of an emotional system which can regulate simple behaviors, such as a recoiling reflex, to convoluted neurotic behaviors characterizing severe mental health disorders. Although the perception of physical pain is crucial for navigating our physical world, the perception of *social pain* is equally as important, at the very least, for human survival.

Anyone who has lived long enough in this world can tell you just how painful a broken heart is or how painful it is to experience loss. These forms of social pain are thought to result from the same emotional system that regulates the affective component of pain perception, that is, the emotional feeling of unpleasantness usually associated with physical pain [1]. Historical descriptions of patients who had undergone cingulotomy for the treatment of chronic pain reported how they were aware of, and able to, localize pain sensations but felt no distress or suffering [2]. In other words, they seemed to lack an emotional reactivity to painful stimuli after the surgery. In later studies, the brain regions regulating the experience of social pain were shown to also include the anterior cingulate cortex (ACC) as well as the anterior insula (AI) and dorsal medial thalamus (DMT). For example, in humans, imaging studies have shown that situations of social exclusion, which increases social distress, were correlated with increased brain activity in the ACC and AI [3].

As it is clear that the perception of social pain plays a large role in how we experience the world, I believe dysfunctions in this emotional system will result in serious consequences to human health and well-being. Specifically, I have worked in the lab of Dr. Gustavo Turecki at



Accordingly, we quantified the expression of endogenous opioid receptor and peptide mRNA in the ACC, AI, and DMT brain regions of suicide completers and compared them to subjects who died from causes other than suicide. Specifically, I quantified the expression of the orphanin FQ, or nociceptin, opioid sub-system. Using quantitative reverse transcription polymerase chain reaction, I found that suicide completers showed a significantly reduced expression of the pre-pro-nociceptin mRNA, the transcript of the endogenous opioid peptide, in the caudal ACC (Figure. 1).

With these recent findings, new avenues for further investigation have opened up. The nociceptin opioid sub-system has been implicated in the HPA axis response to stress and in natural and learned anxiety-like behavior [10]. As the nociceptin receptor is a G-protein coupled receptor, G-protein coupled receptor assays will be done to determine whether changes in the sensitivity or functional activity of the nociceptin system have occurred in association with the observed decrease of pre-pro-nociceptin mRNA in suicide completers (Figure. 2). Furthermore, whether the expression of the opioid system is regulated epigenetically as a function of life experiences will also be investigated. For example, one animal study has shown that severe traumatic life experiences can disrupt the ability of mice to distinguish between harmful and safe environments, reflecting an animal model for post-traumatic stress disorder (PTSD) [11]. In addition, this behavioral consequence was associated with altered nociceptin receptor expression in the amygdala of traumatized mice compared to non-traumatized ones. Interestingly, it has been proposed that the ACC and amygdala are components of an emotional fear processing system, whereby the amygdala is important for the identification of e450.79 Tm.0 1 477.1 257.57 Tm[(I)] of 0

regulation of social pain, which may influence the ability to learn, directed by the fear-emotional neural system.

As I believe our emotions are key tools used in directing our behaviors to avoid harmful or painful stimuli, a dysfunctional emotional system that produces inappropriate behaviors, or one that prevents the escape from these feelings of social pain, may result in suicide. With a better understanding of the neurobiological underpinnings of social pain and the systems that regulate its perception and the behaviors that arise as a result, I hope we will aid the development of effective and appropriate treatments that either reverse, or at least better manage, implicated mental illnesses.

**Figure 2**

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