



Pain and suicidality: Insights from reward and addiction neuroscience



Igor Elman^{a,*,1}, David Borsook^{b,1}, Nora D. Volkow^{c,1}

^a Providence VA Medical Center and Cambridge Health Alliance, Harvard Medical School, 26 Central Street, Somerville, MA 02143, USA

^b P.A.I.N. Group, Boston Children's Hospital, Departments of Anesthesiology and Radiology, Department of Psychiatry and Radiology, Massachusetts General Hospital and Department of Psychiatry, McLean Hospital, Harvard Medical School, Boston, MA, USA

^c National Institute on Drug Abuse, Bethesda, MD, USA

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ABSTRACT

Suicidality is exceedingly prevalent in pain patients. Although the pathophysiology of this link remains unclear, it may be potentially related to the partial congruence of physical and emotional pain systems. The latter system's role in suicide is also conspicuous during setbacks and losses sustained in the context of social attachments. Here we propose a model based on the neural pathways mediating reward and anti-reward (i.e., allostatic adjustment to recurrent activation of the reward circuitry); both are relevant etiologic factors in pain, suicide and social attachments. A comprehensive literature search on neurobiology of pain and suicidality was performed. The collected articles were critically reviewed and relevant data were extracted and summarized within four key areas: (1) physical and emotional pain, (2) emotional pain and social attachments, (3) pain- and suicide-related alterations of the reward and anti-reward circuits as compared to addiction, which is the premier probe for dysfunction of these circuits and (4) mechanistically informed treatments of co-occurring pain and suicidality. Pain-, stress- and analgesic drugs-induced opponent and proponent states of the mesolimbic dopaminergic pathways may render reward and anti-reward systems vulnerable to sensitization, cross-sensitization and aberrant learning of contents and contexts associated with suicidal acts and behaviors. These findings suggest that pain patients exhibit alterations in the brain circuits mediating reward (depressed function) and anti-reward (sensitized function) that may affect their proclivity for suicide and support pain and suicidality classification among other "reward deficiency syndromes" and a new proposal for "enhanced anti-reward syndromes". We suggest that interventions aimed at restoring the balance between the reward and anti-reward networks in patients with chronic pain may help decreasing their suicide risk.

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Abbreviations: ACC, anterior cingulate gyrus; AMY, amygdala; BLA, basolateral complex of the amygdala; BNST, bed nucleus the striaterminalis; CEA, central nucleus of the amygdala; CRF, corticotropin-releasing factor; DA, dopamine; DBS, deep brain stimulation; DMN, default-mode network; DSM-IV TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision; DRG, dorsal root ganglion; GABA, gamma-aminobutyric acid; HB, habenula; HT, hypothalamus; INS, insula; LC, locus coeruleus; NAc, nucleus accumbens; NE, norepinephrine; NR, raphe nuclei; PAG, periaqueductal gray matter; PFC, prefrontal cortex; PTSD, posttraumatic stress disorder; RF, reticular formation nuclei; S₁, primary somatosensory cortex; S₂, secondary somatosensory cortex; VT, ventral tegmentum.

* Corresponding author. Tel.: +1 617 5910919; fax: +1 617 5916054.

E-mail address: ielman@cha.harvard.edu (I. Elman).

¹ The authors equally contributed to this work.

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1. Background

1.1. Introduction

There is but one truly serious philosophical problem and that is suicide. Judging whether life is or is not worth living amounts to answering the fundamental question of philosophy.

Albert Camus. *The Myth of Sisyphus* (1942)

On October 21st 1805, the memorable day of the Battle of Trafalgar, Admiral Lord Horatio Nelson wrote his will and emerged on the flagship deck in full uniform decorated with military orders glittering in the warm sun that stood high in the clear skies of Spain. The Admiral emphatically rebuffed comrades’ pleas for a less flashy attire, so to avoid being a conspicuous target for the Napoleon’s fleet snipers. Unsurprisingly he was seriously wounded shortly before the conclusion of the Battle, but rejected receipt of the medical care immediately available on board of the flagship. Even though it may appear that Nelson was seeking to die, we will probably never find out what exactly was going through his mind. The hero’s glory was then at its zenith inevitably hinting to the only possible downward life trajectory that may be henceforth perceived as bland and unfulfilling in comparison to the fleeting triumph and exhilaration evoked by the grandiose victory. Nelson was also exasperated by the hypocritical moral values of the British monarchy insultingly denying societal recognition from his beloved lady and from their daughter. Furthermore, long-lasting and excruciating phantom-like pain caused by an amateurish amputation of the right arm performed a few years beforehand might have been yet another factor pushing Nelson to the precipice.

The link between pain and suicide has indeed been consistently documented in numerous epidemiological surveys (Fishbain, 1999; Ilgen et al., 2010; Ratcliffe et al., 2008; Tang and Crane, 2006). This link remains rather specific even after accounting for negative affective states (Blackburn-Munro and Blackburn-Munro, 2001; Edwards et al., 2006; Fishbain et al., 1997) and for the perceived severity of pain symptoms (Edwards et al., 2006; Fisher et al., 2001; Smith et al., 2004). For most people the act of suicide, defying instincts, fears and societal taboos is incomprehensible and even mysterious. Suicidality could be attributed to a constellation of developmental, environmental, social, psychological, psychiatric, medical, molecular, genetic, demographic and vocational factors (Durkheim, 1952; Ernst et al., 2009; Goldsmith, 2002; Van Orden et al., 2010). In the context of pain, low expectancy for subjective well-being (Meulders et al., 2012; Takahashi, 2011), conditioned fear (De Peuter et al., 2011) and avoidance behavior (Schrooten et al., 2012) are also considered among contributing causes. Nonetheless, the mere fact that the

incidence of people’s willingness to part with the most precious possession they have, their life, remains by and large stable and unremitting over years despite at times extraordinary interventions and tight monitoring (Goldsmith, 2002) calls for further deepening of the insights into this enigmatic problem.

The current review will define interactions between pain and suicidality by examining the role of neural pathways mediating reward and anti-reward viz., allostatic adjustment to recurrent activation of the reward circuitry (Koob and Le Moal, 2005) that may have important implications for the two conditions (Apkarian, 2010; Blum et al., 2008; Niikura et al., 2010). Owing to well-defined disruptions of reward/anti-reward function in addiction, it serves as a comparison backdrop for understanding pain and suicidality. To that end, we attempt to bring together the prevailing and complementary theories on the nature of addiction. We will argue that addiction’s dimensional and interactive measures rather than a categorical adherence to a single theoretical framework are essential for a comprehensive clinical and scientific formulation of the complex biopsychosocial phenomena of pain and suicidality.

In addition to general introduction of the main papers’ themes, as noted above, Section 1 provides epidemiological and clinical context of the discussed entities. Section 2 discusses putative neurobiology of pain as it is involved in the sensory, emotional and reward/anti-reward function. Section 3, the main portion of the paper, pertains to the role played by reward and anti-reward systems in pain and in suicidality. Social attachment is used here to illustrate normative reward/anti-reward function and to compare it to that in pain, in suicidality and in addiction. In Section 4 specific evidence for testable hypotheses on therapeutic and preventive interventions based on mechanistically-informed psychopharmacological interventions is discussed. Section 5 presents final summary and conclusions.

Death and mortality are arguably the most integral problems of human condition, faced by any individual in the course of life and are inextricably linked to the questions dealing with the meaning of life and with how death may impact such a meaning. These questions are certainly far from ever been resolved. Also, because the awareness of life’s finality in conjunction with the freedom to choose whether “to be or not to be” are exclusive attributes of human nature, the present review does not draw heavily upon preclinical research. On the other hand, since literature and poetry is purported to help us surmising universal truths from individual examples (Aristotle, 1920), we selected several citations from countless volumes of literary and philosophical work that are intended to place the discussed themes into relevant scientific and humanistic contexts. This may inevitably generate an impression of reductionism and oversimplification. We are aware that inquiry into the mind-body conundrum, into philosophical meanings of

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