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The Emotional Brain as a Predictor and Amplifier of Chronic Pain

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Abstract

Human neuroimaging studies and complementary animal experiments now identify the gross elements of the brain involved in the chronification of pain. We briefly review these advances in relation to somatic and orofacial persistent pain conditions. First, we emphasize the importance of reverse translational research for understanding chronic pain—that is, the power of deriving hypotheses directly from human brain imaging of clinical conditions that can be invasively and mechanistically studied in animal models. We then review recent findings demonstrating the importance of the emotional brain (i.e., the corticolimbic system) in the modulation of acute pain and in the prediction and amplification of chronic pain, contrasting this evidence with recent findings regarding the role of central sensitization in pain chronification, especially for orofacial pain. We next elaborate on the corticolimbic circuitry and underlying mechanisms that determine the transition to chronic pain. Given this knowledge, we advance a new mechanistic definition of chronic pain and discuss the clinical implications of this new definition as well as novel therapeutic potentials suggested by these advances.

Keywords: neuroimaging, limbic system, learning, motivation, d-cycloserine, l-dopa

Introduction

Chronic pain imparts a huge toll on society. Its burden continues to increase both inside and outside the United States, and it is a leading source of disability worldwide (Murray and Lopez 2013). Until recently, mechanisms underlying chronic pain had remained minimally understood, and therapeutic options were limited. However, in the past few years, there have been important new advances in the topic, which, we contend, have been driven primarily by studying the clinical condition via peering inside the brain of chronic pain patients, complemented by animal model experiments where equivalents for the human condition are investigated to reveal detailed cellular and molecular mechanisms. The combination of approaches has begun to provide a rich tapestry of brain circuitry and mechanisms that seem to control chronic pain. These studies are at the threshold of overturning long-standing views on the subject and providing insights for the development of new and, ideally, more efficient therapeutic options for these conditions. We briefly review this literature, emphasizing novel mechanistic concepts.

Sensory and Behavioral Definitions of Nociception and Pain

Pain as a conscious perception can be viewed from its qualia properties—that is, the transformation of mechanical, thermal, and chemical sensory inputs into a subjective awareness of being in pain. Alternatively, and maybe complementarily, pain can be viewed from the perspective of its effects on motivated behavior, inducing fight or flight or inhibition of the use of body parts to promote healing. From the classical sensory representation or qualia viewpoint, nociception is conceptualized as the machinery providing the signal for the sensation of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (http://www.iasp-pain.org/Taxonomy) and pain as the perception associated with enhanced nociceptive signaling. As most organisms, especially humans, live a life essentially free of injuries and pain in a naturally noxious environment and since lack of nociceptors dramatically diminishes life span, we recently proposed that healthy everyday behavior is contingent on subconscious nociceptive protection of tissue, forcing a new definition for nociception and acute pain (Baliki and Apkarian 2015). We thus deem nociceptive mechanisms the machinery appropriate for protecting the body from injury, while pain signals the failure or the potential for failure of protecting the body from injury. Within this set of definitions, chronic pain—pain that persists in the absence of stark inputs or past the healing process—can be deemed only pathologic, as it is no longer coupled with an appropriate behavioral repertoire.

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Necessity of Human Neuroimaging to Begin Understanding Chronic Pain

The classical animal model–based studies of chronic pain mechanisms all begin with an injury and document its peripheral, spinal, and supraspinal consequences. This approach is implicitly based on the assumption that the injury is the primary controller of pain chronification. By design, such models are intended to reproduce predictable consequences of chronic pain, rather than delineate its risk factors and predispositions. In contrast, the clinical reality is that most patients who experience a similar injury exhibit variable clinical outcomes. In the majority, pain subsides as the injury resolves within a normal healing period. However, a minority develop chronic pain that may persist for years or decades. Therefore, the clinical data reinforce that the injury alone is not sufficient to understand mechanisms of chronic pain, thereby imposing the burden to establish the extent to which given animal models exhibit appropriate correspondences with human brain (or otherwise) markers for chronic pain.

Perhaps the most important message here is that before the advent of neuroimaging studies, our knowledge of the mechanisms of chronic pain was limited to peripheral and spinal cord reorganization, whereas the rest of the brain was assumed to passively reflect these processes. Human neuroimaging studies examining brain properties in patients with chronic pain have unequivocally established that different chronic pain conditions are associated with distinct brain properties. Therefore, at least for the foreseeable future, hypotheses regarding chronic pain must rely on observations made by peering into the brain of various types of clinical pain conditions.

Distinguishing between Acute and Chronic Pain

Ample evidence now shows that the anatomy and physiology of the brain in chronic pain is distinct from that of healthy subjects experiencing acute pain (Apkarian et al. 2011). From a qualia viewpoint, the classical tautological definition of chronic pain as persistence of pain past the normal healing period (first formulated by Beecher in the 1950s) suggests that pain is simply an enhanced state of nociceptive activity, as conceptualized by peripheral and central sensitization (Woolf 2011). This definition implies that chronic pain will correspond to brain activity that reflects persisting functional changes in brain regions recruited for acute pain. Therefore, the mere fact that brain anatomy and function are distorted in chronic pain already challenges this classic definition. Moreover, brain morphology characterizing different chronic pain populations shows unique patterns of reorganization (Baliki et al. 2011). Similarly, resting state brain activity, which reflects neuronal fluctuations as the mind wanders, establishes that information exchange throughout the brain is distorted with different types of chronic pain (Baliki et al. 2014). These observations strongly suggest that different chronic pain conditions are characterized by distinct brain anatomic and functional states indicative of plastic reorganization of the brain. In the most parsimonious formulation, this reorganization can be envisioned as properties of the nervous system interacting with the specific injury to give rise to a new chronic pain brain state.

Recent evidence suggests that some brain systems that mediate awareness of acute and chronic pain involve circuitry that is unresponsive to noxious stimulation. For instance, variability in the mesolimbic system during acute pain seems sufficient to predict the opioid-induced analgesia (Wanigasekera et al. 2012), and functional connectivity among the components of the mesolimbic system mediates successful self-regulation of acute pain (Woo et al. 2015). Others demonstrate that higher activation in the default mode network, the ventral striatum, and the periaqueductal gray during episodes of mind wandering is associated with analgesia (Kucyi et al. 2013). These studies challenge the intuitive proposition that chronic pain is the result of an increased and/or sustained nociceptive barrage impinging on the cortex, and they identify pain modulation through nonnociceptive circuitry, suggesting that chronic pain is a complex conscious brain state engaging large-scale networks, which is consistent with clinical evidence indicating that psychological and personality traits may also contribute to chronic pain.

The Corticolimbic System as a Predictor and Determinant of Chronic Pain Conditions

The 2 critical questions that the field has yet to address regarding chronic pain are 1) Who is vulnerable to developing it? and 2) What underlies this vulnerability? So far, the interindividual differences in brain properties best predict this pathology. An accumulating body of animal and human literature has identified the corticolimbic system, which is central to reward and motivated behavior, as a modulator for acute pain and as a mediator for chronic pain (Navratilova and Porreca 2014). A longitudinal study has established that functional connectivity between the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) accurately predicts those individuals with subacute back pain who develop persisting pain 1 y later (Baliki et al. 2012). White matter fractional anisotropy (Mansour et al. 2013) also differentiated subacute back pain transitioning to chronic pain. These findings suggest the presence of preexisting functional and morphologic risk factors for the development of chronic back pain, although the preexistence of these factors remains to be proven. It should be noted that earlier clinical studies have identified a long list of risks for chronic pain, such as demographics, affective states, lifestyle, comorbidities, and others (Mayer and Bushnell 2009), yet collectively such parameters account for a relatively small amount of variance for chronic pain (10% to 20%; Hasenbring et al. 2012; Ramond-Roquin et al. 2015). In contrast, the brain's anatomic and functional properties predict development of chronic pain at 80% to 100% accuracy.

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The alternative competing hypothesis derived from the classical viewpoint posits that central sensitization secondary to peripheral injury is the primary determinant of chronic pain (Woolf 2011). This hypothesis is perhaps best tested for orofacial temporomandibular pain disorder (TMD). In a massive undertaking, a multicenter effort was initiated to prospectively follow thousands of healthy subjects, tracking them over 5 y for development of first-onset persistent TMD (OPPERA study). The psychophysical results disprove the central sensitization hypothesis, with the authors stating, "Premorbid PPT [pressure pain thresholds] poorly predict TMD incidence" (Slade et al. 2014). Similar negative results are now also reported for development of chronic tension-type headache (Buchgreitz et al. 2008), for low back pain (O'Neill et al. 2011), and for development of widespread pain (Gupta et al. 2007). Thus, there is a large contrast in predictability of chronic pain by brain parameters from that of peripheral sensitivity.

Corticolimbic Signaling and Transition to Chronic Pain

Value and motivation are encoded in the brain's emotion circuitry (mesocorticolimbic system): a system composed primarily of the mPFC, NAc, amygdala, hippocampus, and ventral tegmentum. The NAc is responsible for coding prediction errors for appetitive (Schultz 1998) and aversive stimuli (Becerra et al. 2001) and, in turn, is important for regulating certain kinds of learning and for driving motivated behavior. Aversive and reward prediction signals are differentially encoded by dopamine responses within the NAc (Bromberg-Martin et al. 2010), and diminished motivation induced by chronic pain seems to be dependent on the indirect dopamine pathway of the NAc (Schwartz et al. 2014). The NAc signaling of salience of impending painful stimuli remains unchanged between healthy subjects and those with chronic back pain, while the reward value of cessation of pain is distorted in those with chronic back pain (Baliki et al. 2010; Baliki et al. 2012).

Persistently enhanced functional connectivity between the mPFC and NAc may be interpreted as an increased emotional salience signal, which distorts dopaminergic outputs from the ventral tegmentum, and may become a critical gating process that controls transition to chronic pain. The abnormal dopaminergic signaling should in turn modulate the thalamocortical circuits, amplifying the value of nociceptive inputs and thus reorganizing cortical circuits, and this process in time would be observed as local gray matter density reorganization. The extent of dopaminergic signaling, its reorganization, and the specific peripheral injury and consequent nociceptive inputs to the cortex as well as to the corticolimbic system from the peripheral injury—coupled with specific behavioral adaptations—provide a unique interaction between brain activity and dopaminergic synaptic adaptations that, we hypothesize, in time carves a chronic pain condition–specific neocortex. This concept is presented in large strokes in Figure 1.

There is now good evidence that all components of the corticolimbic system are either affected by or control or amplify

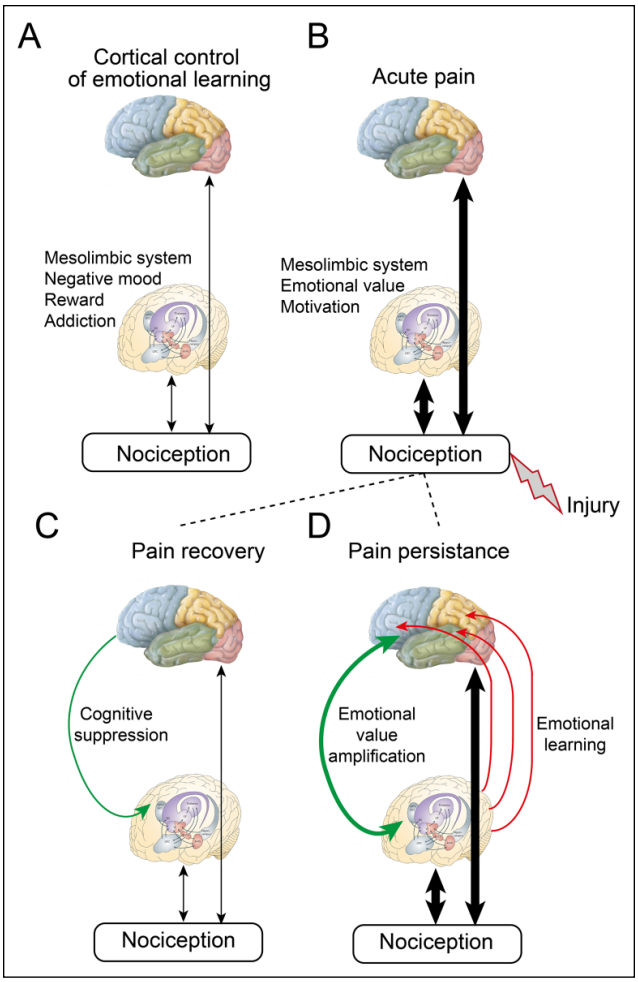

Figure 1. Chronic pain depends on the corticolimbic properties interacting with nociceptive inputs. (**A**) In healthy individuals, afferent signals from the periphery are constantly relayed to the mesolimbic system and the cortex but are rarely brought to awareness because of corticolimbic gating processes. Nociceptive signals unconsciously provide learning and behavior-modifying signals to the limbic cortex but only occasionally evoke conscious perception of pain at the cortex. (**B**) Following an injury that gives rise to a large and persistent increase in nociceptive barrage, the properties of the corticolimbic circuitry dictate long-term outcome. (**C**) Reverberating corticolimbic circuitry can, through interindividual differences in cognitive abilities or anatomic/functional network properties, suppress limbic activity and facilitate recovery from suffering with pain and the diminution of symptom severity coupled with tissue healing. (**D**) Alternatively, a heightened emotional valuation response, driven by predispositions of the corticolimbic anatomic/functional properties, would lead to reorganization of the gating circuitry, which provides a learning signal that in time carves a cortical chronic pain profile. The dynamics of corticolimbic reverberating loops depend both on the preexisting limbic brain circuitry and on the reorganization following the inciting event, and these interactions will determine the likelihood of either recovering from or transitioning to chronic pain.

persistent pain states. In rodent models of persistent pain, amygdala excitability rapidly increases, which increases spinal cord excitability. Moreover, amygdala inputs to the mPFC change the inhibitory drive to the region (Neugebauer et al. 2004; Ji and Neugebauer 2011; Neugebauer 2015). In humans,

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chronic pain or transition to chronic pain activates the amygdala in relation to subjective perception of the chronic pain (Baliki et al. 2006; Hashmi et al. 2013). The mPFC's neuronal activity and morphology change in various animal models of persistent pain (Metz et al. 2009; Kiritoshi and Neugebauer 2015). In humans, the region reflects subjective chronic pain intensity, and its functional connectivity with the NAc is predictive of transition to chronic pain (Baliki et al. 2006; Baliki et al. 2012; Hashmi et al. 2013). Moreover, human evidence now shows that hippocampal intrinsic connectivity and hippocampal cortical connectivity are modified with transition to chronic pain (Mutso et al. 2013). In rodents, hippocampal physiologic properties are consistently altered with persistent pain, and hippocampal adult neurogenesis seems to be causally engaged in the transition to persistent pain and is subsequently depressed following establishment of a neuropathic pain state (Ren et al. 2011; Mutso et al. 2012; Apkarian et al. 2015).

Corticolimbic abnormalities have also been observed in multiple orofacial chronic pain conditions. TMD is associated with a decrease in striatal dopaminergic uptake (Jaaskelainen et al. 2001) and with changes in gray and white matter properties of corticolimbic regions (Younger et al. 2010; Moayedi et al. 2012). Moreover, patients suffering from burning mouth syndrome show structural differences in the hippocampus and mPFC, as well as increased functional connectivity between frontal and limbic regions as the pain increases (Khan et al. 2014). Moreover, sustained pain from postoperative dental surgery is associated with higher cerebral blood flow in the thalamus, frontal regions, and sensorimotor cortex (Newberg et al. 2011). Overall, corticolimbic circuitry seems critical for chronification of orofacial pain. Longitudinal studies, however, are needed to unequivocally establish the concept.

Multiplicity of Mechanisms Underlying the Brain Transitioning to Chronic Pain—Are There Critical Time Windows?

The earliest neuroimaging studies of chronic pain patients provided hints that their brains deviated from the norm (Grachev et al. 2000). The initial propositions advanced by the study have been validated by longitudinally tracking how recurring pain reorganizes the brain circuitry in subacute back pain patients as they transition to chronic pain. In these patients, the early neural representation of spontaneous pain was dominated by somatosensory activity that gradually shifted toward a limbic representation as pain became chronic (Hashmi et al. 2013). An improved understanding of the distinct stages of chronic pain neuroplasticity is therefore critical to identify the optimal timing for therapeutic interventions, including both prevention and management/treatment of existing chronic pain.

We recently proposed a 4-stage model for the transition from subacute to chronic pain (Baliki and Apkarian 2015). The model posits predisposing genetic and brain factors. After an injury occurs, constant nociceptive inputs bombarding the brain are gated, or amplified, by the corticolimbic system. The interaction among the mesolimbic system, other predispositions (including epigenetic factors; Descalzi et al. 2015), and nociceptive inputs determines long-term symptom severity, whereas transition to chronic pain entails reorganization in the limbic-cortical circuitry responsible for encoding new memories, diminishing motivation, and distorting perception and decision making.

The exact timing of these functional and anatomic brain changes remains unclear. In our longitudinal study, individuals recovering from their initial pain showed improvements in both pain intensity and pain disability within 20 wk of onset. After this initial recovery, symptom severity remained stable for years. Similarly, rodent longitudinal studies indicate that functional reorganization of the cortex occurs within a few weeks (Baliki et al. 2014; Chang et al. 2014), during which dopamine and kappa opioid receptor expression levels drop within the NAc (Chang et al. 2014). Therefore, temporal correspondences can also be established between rodent models and human chronic pain conditions.

Learning and Chronic Pain

The amygdala and the hippocampus are central to the consolidation of emotional memories, such as those pertaining to a painful or stressful event (Cahill et al. 1994; Dolcos et al. 2004; Phelps 2004; Richardson et al. 2004). This subcortical circuitry is notably involved in the regulation of the hypothalamic-pituitary-adrenal axis (Snyder et al. 2011), generalized anxiety disorder (Shin and Liberzon 2010), and depression and is suggested to mediate the transition to chronicity through memory consolidation, with persistent physical pain acting as a secondary reinforcer (Apkarian et al. 2009). Animal models of neuropathic pain reveal synaptic plasticity in the amygdala (Neugebauer et al. 2003) and hippocampus (Mutso et al. 2012). Moreover, adult hippocampal neurogenesis plays a role in both emergence and maintenance of postinjury persistent pain (Apkarian et al. 2015). In humans, amygdala and hippocampal volumes have been associated with several psychiatric disorders (Gilbertson et al. 2002; Morey et al. 2012) and chronic pain conditions (Mutso et al. 2012). These volumetric differences likely reflect predispositions that exist before the emergence of psychiatric conditions and before the transition from subacute to persistent pain. We emphasize that while limbic circuitries mediate emotional memory formation of pain at the systems level, the specific processes driving pain chronification remain to be studied at the molecular level.

In humans, functional connectivity between the hippocampus and the rest of the brain is significantly altered in subacute and chronic pain patients compared with healthy controls (Mutso et al. 2012). Diminution of functional connectivity between the hippocampus and the default mode network has been associated with higher transfer of previously learned experiences that guide new decisions and behaviors (Gerraty et al. 2014). In these individuals, symptom severity can be caused by self-reinforcing conditions leading to consolidation

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of maladaptive associative memories and even the generalization of the previous painful experience to innocuous stimuli (Moseley and Vlaeyen 2015). These subcortical limbic circuits are massively interacting with frontal regions responsible for assigning affective meaning to aversive events (Roy et al. 2012). The rodent mPFC has at least 3 components: anterior cingulate, prelimbic (PL), and infralimbic regions. All are now implicated to differing extents in components of chronic pain. Most important, lesions of the PL region or optogenetic activation of the PL region induces analgesic and anxiolytic effects (Wang et al. 2015). Furthermore, activation of GABAergic inhibitory neurons within the PL region decreases pain responses and anxiety behaviors in freely moving mice (Zhang et al. 2015), and optogenetic activation of the PL region produces relief from persistent pain, mediated by projections to the NAc (Lee et al. 2015). Figure 1 illustrates the possibility that the reverberating corticolimbic circuitry could inhibit an enhanced nociceptive signal transmitted from the spinal cord toward the cortex and thus functionally block the nociceptive information flow to nociceptive encoding cortical regions; alternatively, this circuitry could tamper with the transformation of this encoding during its translation to perception.

The overall functional role of the corticolimbic circuit is to preconsciously assign value to the environment within which the organism exists. This process entails learning circuitry based on interactions among all components of this system. The specific learning mechanisms associated with pain transitioning to a chronic condition remains to be established, yet the general idea follows from the extensive research that has unraveled the role of this circuitry in stress, motivation, valuation, behavior, and, especially, addictive behavior (Koob and Volkow 2010; Russo and Nestler 2013). Borrowing from this vast literature, we speculate that 1) the role of the corticolimbic system is to block the transition to chronic pain by inhibiting, through cortical cognitive control, the potential emotional response to an injury (Fig. 1C) or 2) in vulnerable individuals, the inability to actuate this inhibitory control results in an enhanced emotional cascade that in turn reorganizes the cortex through corticolimbic learning processes, thereby carving a brain functionally addicted to pain (Fig. 1D).

A New Hypothesis of Chronic Pain

In accordance with these recent advances, we propose a novel definition of chronic pain. Rather than defining pain by its sensations, we propose a definition that emphasizes the neurobiological mechanisms that control behavioral adaptations, and we hypothesize that persistence of pain is likely mediated through the reorganization of the cortex by corticolimbic learning mechanisms. We therefore posit that chronic pain is a complex web of sensory and emotional experiences, coupled with behavioral adaptations. Specifically, we posit that the chronic pain state is a consequence of a change in value related to nociceptive afferent information impinging on the cortex, with limbic emotional learning mechanisms underlying this shift in value and with little opportunity to extinguish these emotional memories. Subconscious changes in contextual salience and the value of nociceptive inputs are signals that drive cortical reorganization, given that they render the pain more emotional and modify decision making and selection of behaviors. The net outcome is a brain that has learned to filter emotions, actions, and reward through the lens of pain, rendering the brain addicted to pain.

Therapeutic Interventions for Preventing Chronic Pain

D-cycloserine (a partial agonist for the glycine cite of the NMDA receptor) and sarcosine (a glycine transporter blocker) show properties suggestive of their utility in controlling chronic pain (Millecamps et al. 2006; Centeno et al. 2009). We should emphasize the fact that the candidacy of both for relieving chronic pain comes directly from back-translating human brain imaging studies and observing parallels of the circuitry across domains of neuroscience research.

The involvement of corticolimbic circuits in pain chronification itself implies that dopamine may also be important in controlling either transition or management of chronic pain. A cellular/molecular study of NAc shell neurons revealed the mechanistic role of dopamine in the transition to chronic pain (Ren et al. 2016), suggesting therapeutic potential.

The common approach for managing chronic pain is use of nonsteroidal anti-inflammatory drugs (NSAIDs). This is the standard at least for chronic back pain and osteoarthritis, the 2 dominant categories of chronic pain worldwide. Therefore, we examined the efficacy of naproxen (an NSAID) alone and in combination with various potential additional drug therapies. The approach was an effort to identify the long-term efficacy of the treatments, comparing and contrasting dopamine, D-cycloserine, and Marinol (a tetra-hydro-cannabinoid; Fig. 2).

Combining systemic administration of L-3,4-dihydroxyphenylalanine (L-DOPA)—a precursor of dopamine that is well tolerated by humans and gets across the blood-brain barrier—and the NSAID drug naproxen on spared nerve injury (SNI) induced persistent tactile allodynia. These rats received a nerve injury and were treated for 14 d. Only the combination treatment showed a long-term relief from pain behavior (Fig. 2A): a result consistent with evidence showing that dopamine receptor expression decreases in the NAc following an SNI injury (Chang et al. 2014) and with a drop of dopamine concentration in the NAc after SNI injury (Ren et al. 2016). More important, we observed that NAc shell indirect spiny neurons show increased excitability and decreased dendritic fields within days after SNI injury and that oral treatment with L-DOPA and naproxen blocks the effects of SNI on excitability, dendritic architecture, and synaptic connectivity and blunts neuropathic pain (Ren et al. 2016).

Efficacy of this combination treatment was examined acutely and after the SNI pain behavior was established—that is, testing efficacy in a model mimicking an established chronic pain state. These results show that the combination treatment

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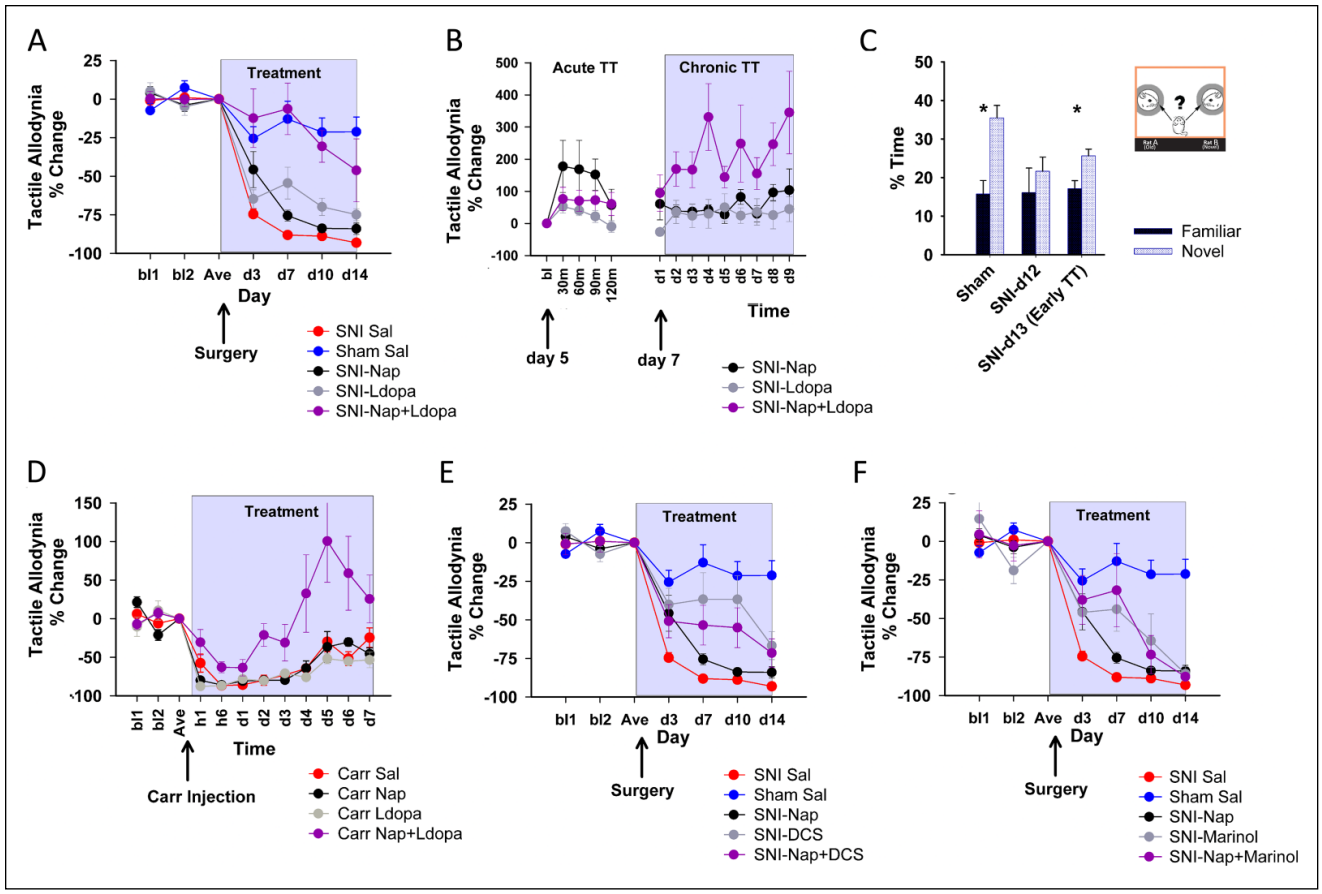

Figure 2. Drug combinations examined in rodent models for neuropathic and inflammatory pain, testing the concept of early combination, peripheral and central, treatment as a strategy for preventing transition to chronic pain. (**A**) Combination treatment with dopamine and nonsteroidal anti-inflammatory drug (NSAID; L-DOPA, 1.5 mg/kg; naproxen, 30 mg/kg) when started at the same time as the peripheral spared nerve injury (SNI) blocks tactile allodynia for 14 d, essentially matching in behavior rats that receive sham injury. Yet, similar treatment with either dopamine alone or NSAID alone shows minimal benefit. (**B**) Acute treatment (TT): A single-dose acute combination treatment in SNI animals 5 d after neuropathic injury is not as efficacious as NSAID alone. Chronic TT: Repeated daily treatment in SNI animals 7 d after neuropathic injury again shows that the combination treatment is superior to either drug alone, although the effect size is smaller than that observed in panel A. (**C**) Sham injured animals show increased time spent exploring a novel rat than a familiar one, expressing heightened curiosity. This behavior is blocked in SNI animals but partially recovered when treated with combination therapy for 13 d that started at the time of incurring neuropathic injury. (**D**) Injecting carrageenan in the paw, an inflammatory persistent pain model, and treating the animals with combination dopamine and NSAID results in faster recovery of tactile allodynia than either treatment alone, when treatment is started at the time of incurring injury. (**E**, **F**) SNI animals treated with combination of D-cycloserine (30 mg/kg) and NSAID (E) or Marinol (2.5 mg/kg) and NSAID (F) show minimal sustained recovery from tactile allodynia. All presented results were performed in rats, and all measures were collected in a blinded fashion. For each average outcome, groups of 7 to 9 animals were used. Also, all drug treatments were administered by oral gavage, twice a day at assigned days, and pain behavior (unless indicated) was measured at least 12 h after gavage—that is, the morning after and just prior to the morning drug administration. Some of these data are reported in Ren et al. (2016), where further experimental details are expounded.

does not potentiate acute analgesia. However, when treatment was started after 7 d from SNI injury and when pain behavior was measured 12 h after drug administration, we again observed that the L-DOPA and naproxen combination was better than either treatment alone (Fig. 2B). Figure 2C illustrates the effect of treatment on SNI-induced deficits in social discrimination that accompany persistent pain, showing that combination therapy alleviates cognitive deficits as well.

Figure 2D examines the efficacy of L-DOPA and naproxen combination treatment on a rat model for persistent inflammatory injury model. We observe that the combination treatment reverses pain behavior within days from carrageenan injection. Figure 2E and F shows results for combining naproxen with D-cycloserine or Marinol. Neither of these combination treatments showed better efficacy. All together, these results, at a minimum, further suggest that central dopaminergic circuits are engaged in transition and maintenance of persistent pain and that the combination of L-DOPA and NSAID treatment needs to be studied in the clinical setting.

Concluding Remarks and Future Directions

Human brain imaging evidence and its back-translation to rodent studies have established a very different view of mechanisms that drive and determine chronic pain. The fact that chronic pain seems to be critically dependent on brain limbic properties expands the general notion of pain, placing it within the proximity of negative

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emotions and negative affective states. Even though chronic pain is commonly assumed to impart stress on the nervous system (Vachon-Presseau et al. 2013), the opposite must also be seriously contemplated—namely, that chronic pain is part of the continuum of brain circuitry controlling affective states of the organism, which raises new questions regarding the interface between early lifetime and environmental factors and epigenetic factors that have been shown to modify stress responses in adulthood, in terms of the extent to which they modify the risk for chronic pain by reorganizing mesolimbic circuitry. It seems that we are at the cusp of a paradigm shift in the concepts and mechanisms of chronic pain. Vast brain circuits, hitherto thought to be irrelevant for pain, are occupying center stage of the research in the field. There is also no doubt that detailed cellular and molecular mechanisms of chronic pain remain mostly unknown and await to be uncovered in the years to come.

Author Contributions

E. Vachon-Presseau, M.V. Centeno, W. Ren, S.E. Berger, P. Tétreault, M. Ghantous, A. Baria, M. Farmer, M.N. Baliki, T.J. Schnitzer, A.V. Apkarian, contributed to conception, drafted the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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