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Brain mechanisms of chronic pain: critical role of translational approach

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Abstract

Chronic pain is a leading cause of disability worldwide and its prevalence is likely to increase over the next decades. Treatment for chronic pain remains insufficient and therapeutical advances have not made comparable progress with that for many chronic disorders, thus amplifying the concern on the future burden of the disease. At the same time, and even after decades of intense research, the underlying pathophysiology of chronic pain remains minimally understood. We believe advancing our current understanding of chronic pain requires mechanistically explicit, hypothesis-driven, and clinically focused models. In this review we highlight some of the main findings over the last decades that have contributed to the present knowledge of brain mechanisms of chronic pain, and how such advances were possible due to a reverse translational research approach. We argue that this approach is essential in the chronic pain field, in order to generate new scientific hypotheses, probe physiological mechanisms, develop therapeutic strategies and translate findings back into promising human clinical trials.

1. Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [1]. Chronic pain (CP) is defined as “persistent or recurrent pain lasting longer than 3 months” [2]. Though clinically useful, these definitions

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embrace an important shortcoming: they do not incorporate underlying mechanisms and at least suggest, erroneously, that chronic pain is the temporal extension of acute pain, implying commonly shared mechanisms between both. Chronic pain is now accepted as a disease entity of its own [1]. A large body of evidence, human and animal model observations, distinguish between acute and chronic pain: while acute pain is commonly observed as a sign of tissue insult or of disease related tissue injury, chronic pain is now conceptualized as pathological. Further, it should be emphasized that the strict temporal cut-off (3 months) between acute, subacute, and chronic pain remains uncertain, and it is perhaps dependent on the details of specific clinical conditions.

Chronic pain is both a clinical and scientific challenge. While important advances have been made in the past two decades regarding underlying processes both in peripheral and central nervous system, the scale of the problem continues to increase. Population-based estimates of chronic pain among US adults show 20.4% (50 million) of US adults suffer from chronic pain and 8% (19.6 million) exhibit high-impact chronic pain (unmanageable and debilitating levels of persistent pain) [3]. Similar estimates of prevalence are also reported in Europe (10 to 30% of the adult population[4,5]), and a global burden of disease study in 2016 [6] asserts the high prominence of pain and pain-related diseases as the leading cause of disability and disease burden globally. These numbers show that not only are we failing to combat the condition, but also current concepts and theories that may lead to better strategies to prevent chronic pain remain unsatisfactory.

Management of severe chronic pain remains ineffective, marked by a continuous imbalance between pharmacological analgesia and tolerability, which is a burden to patients and results in poor treatment outcomes. The lack of efficacy in interventions, side effects and drug tolerability often lead to treatment discontinuation[7]. And though there is an extensive collection of non-pharmacological resources to treat people with chronic pain –operative procedures, regional anesthesia, neuromodulation modalities (spinal cord stimulators, implantable drug delivery systems) and comprehensive pain rehabilitation programs - relief remains elusive for many pain patients total elimination of pain is rare, and high quality data on treatment effectiveness is still lacking[8,9]. With continued dispensing of opiates (in the absence of more effective treatments) to a large proportion of chronic pain patients, the iatrogenic effect of treating chronic pain directly contributes to current epidemic of opiate-related deaths in the USA[10], which has been further exacerbated with the Covid-19 pandemic (30% increase in opiate related deaths in the year 2020[11]).

Our viewpoint regarding the roadway to improving patient outcomes is simple. Only mechanistically informed therapy development pathways can change the current situation, and recent basic science advances in the topic are pointing to such opportunities. This review briefly outlines important advances that led to establishing this view, emphasizing human brain imaging and its contribution to translational research. We will explore the advantages that translational research, in particular reverse translation, has to offer to the chronic pain field, how it has helped to advance the field of brain science in chronic pain, in what way these two fields can complementarily progress knowledge, and what new paths such approaches may open.

1.2 A classic approach to studying and managing chronic pain

For most of the twentieth century pain science was studied from the viewpoint of acute injury, examining pathways and responses to minor tissue insults. Starting perhaps with the discovery of a robust rat neuropathic pain model, in late 1980-s [2,3], it was already evident that acute and chronic pain are not equivalent. After testing various classes of medications on several rodent models for chronic pain, the field continues the search for additional models that may better approximate a specific type of clinical chronic pain [4,5]. Importantly, rodent models of chronic pain quickly led to the discovery that spinal circuitry is undergoing rapid changes in circuit properties, leading to the concept of "central sensitization" [6]. The concept of peripherally driven spinal cord reorganization quickly grew and led to the pursue of the idea that reversing these processes should be sufficient to treat chronic pain. The general idea is that pain perception is dictated by labeled-line information transmission through the spinothalamic pathway. Decreasing excitability of spinal cord second order neurons –which mediate the central sensitization –should lead to a decrease in the nociceptive barrage to the thalamus and to thalamocortical projections thus treating chronic pain[7–14]. In fact, there is no lack of evidence concerning nervous system reorganization in chronic/persistent pain in rodent models, which particularly emphasizes changes in peripheral afferent nociceptors, dorsal root ganglia and spinal cord circuitry[12,13,14], as well as descending pain control pathway[15,16]. Despite all these efforts, this approach has been rather insufficient in generating new successful treatment approaches. While the list of potential targets from the periphery and spinal cord is expanding rapidly, researchers continue to struggle in the transition of analgesic efficacy from animal models to humans[17].

Early 1990-s was also the period when non-invasive human brain imaging of physiological activity was developed - functional MRI (fMRI)[15,16]. The method rapidly supplanted the more cumbersome positron emission tomography (PET) and continues to be the primary technology for studying human brain function. fMRI and related measures (T1 for studying brain anatomy, and DTI for studying brain white matter) have had a major impact in unraveling brain circuitry underlying acute and chronic pain. It should be noted that prior to MRI technology we knew virtually nothing about the human brain in chronic pain. It took about another decade for MRI technology to begin to be applied to clinical pain. However, even the earliest studies demonstrated that brain properties were abnormal in humans with chronic pain [17,18]. We now understand that the brain in chronic pain is not simply encoding a nociceptive peripheral input into a perceptual output, but instead is part of a much more complex interplay, relying on distributed brain structures that support diverse functions, such as memory, emotion, and motivation.

Even though mechanistic concepts of chronic pain have dramatically expanded in the last 30 years, unraveling circuit properties and providing novel therapy targets, the lack of clinically important novel treatments for chronic pain remains stark evidence of insufficient progress. One reason might be related to the circumscribed technical fields in pain research –there has been little interaction across topics/disciplines of research: clinical and epidemiology research, human brain imaging, and experimental animal models. But even if the lack of knowledge integration is problematic, another important drawback arises from the mismatch

in conceptual framework. This problem can be expounded with multiple arguments: 1) mechanisms of nociception and acute pain are commonly confounded with that for chronic pain even though there is now ample evidence that knowledge in the former domain is minimally informative and perhaps misleading regarding mechanisms of chronic pain. 2) although there is a biological anatomical and functional parallel between human and rodent nervous systems, the scientific questions tested are not always shaped by the human experience, but instead rely heavily on animal behavior; this often leads to exciting findings but of little direct value to the human clinical condition. 3) additionally, most studies in human conditions and in animal models target either the peripheral or central mechanisms, omitting the interaction between both.

1.3 Moving forward: from humans to animals and back to humans; or how to complete the translational circle in pain research

Animal models for chronic pain have become a fundamental tool to systematically study underlying mechanisms, create potential targets for new drug development, test possible treatments and new modalities of interventional pain management. Nonetheless, pain is a very unique field in what concerns translational research: even the existence of chronic pain relies heavily, if not exclusively, on individual subjective self-reporting, where the pain experience seems to depend on a complex interplay between sensory information, perception and cognitive traits, that are not easily captured in animal studies[18]. It is worth mentioning that while rodent pain studies may provide mechanistic insights that can be probed in humans, they also provide a pathway for back-translation of findings from humans to model preparations, wherein more invasive mechanistic experiments can be performed. Reverse translation –starts with clinical observations especially by examining brain properties in various chronic pain populations, real life patient experiences in the clinic, or during a clinical trial, and works backwards to uncover its mechanistic basis[19], has an important role uncovering pain mechanisms and advancing pain management.

We support the view that reverse translational research is crucial for advancing current knowledge of chronic pain. Our group has been on the forefront of translational pain research for the last 20 years. Starting with a particular question from the human or a finding in a human study, translational research allows us to probe specific mechanisms in the animal model which leads to mechanistic findings and potentially opening the field for new therapeutical approaches (Figure 1.A–C). As an illustrative example, we have found that the extent of information sharing within corticostriatal circuitry predicts transition to a chronic state with high accuracy in humans [20] (Figure 1.A). This finding was then replicated in a longitudinal rodent study[21] (Figure 1.B), and after in-depth characterization of underlying cellular and molecular adaptive mechanisms in the nucleus accumbens (NAc), it was possible to pharmacologically manipulate this system[22]. Subsequently, this approach paved the road to a new therapeutic approach for managing/preventing transition from acute to chronic pain in humans, that was recently tested in a human clinical trial [23](Figure 1.C). The biological similarity between human and rodent, especially regarding brain circuitry between the neocortex and the limbic subcortex, is a powerful concept that we continue to use to interrogate the brain circuitry underlying chronic pain and more recently its overlap with addiction (Figure 2). The precise correspondence in addiction circuitry between human

and rodent allows us to further probe challenging questions regarding the complex interplay between chronic pain and opioid drug effects in the brain. Over the next sections of this paper, we depict some of the most significant findings on brain reorganization in chronic pain and show how the reverse translational research paradigm made it possible.

2. Reorganization of brain circuity in chronic pain: new translational opportunities

Functional brain imaging technology led to exciting new research with significant impact in the field of chronic pain (examining the physiology and anatomy of the human brain in chronic pain was hitherto unavailable). When examining the brains of chronic pain patients, it became evident that pain not only leads to changes in primary nociceptive brain areas but also to a large-scale and widespread functional and morphological reorganization[24,25], and that particular regional changes may be specific for various chronic pain conditions [26,24](Figure 3).

Recent evidence has put forward the idea that chronic pain is associated with a global functional reorganization of brain activity. The concept of global reorganization starts with the hypothesis that chronic pain may be characterized as an abnormal network state[27,23]. Let us break up this concept: brain functions are organized as networks, where multiple brain areas work together in larger communities when engaged in a given mental process[28,29]. Efficient information sharing between these brain regions is necessary to support high-order brain functions (e.g., cognition, perception); pain can be viewed as a major stressor to the brain[30], leading to a series of changes (adaptive/maladaptive) in its structure and function, and impacting such information sharing abilities [6]. In other words, we theorize that pain may alter the homeostasis of normal brain sharing information, since the functional role and relative status of several brain regions is now impacted by what is a new priority: attending to the painful sensation and adjusting behavior accordingly. Importantly, since these changes arguably occur at the network-level, they permeate the whole-brain functional architecture from primary sensory to high-level cognitive systems, leading to a generalized disruption.

One way to query the concept of brain reorganization that has seen a more recent widespread use is the application of properties of graph systems to model brain activity[26]. If we think about the brain as a set of distinct defined regions (nodes) and its relationships –the functional connectivity between regions (edges), we can further study brain's information sharing reorganization. In this context, novel and exciting questions arise: are brain information sharing properties in chronic pain patients different from healthy controls? If so, are these differences at a whole-brain scale, or highly specific within pain-related brain areas? Moreover, do these changes highlight a temporal process of brain reorganization that, ultimately, leads to the emergence of chronic pain? Are there critical processes that lead to a maintenance of this disruption long after tissue heals? And ultimately, can this disruption be reversed?

That chronic pain leads to a reorganization of brain networks is not particularly novel, with several studies showing both anatomical and functional changes in network properties across chronic pain conditions [32,24]. A particular robust finding is that changes in structural and

functional topology permeate across the whole brain, and are characterized by a shift in equilibrium from that of normal subjects: regions that show high-levels of hubness (highly connected, integrative centers in the brain) are downregulated and play a lesser role in sharing and coordinating information with the rest of the brain, and brain regions that are less connected are now upregulated, a phenomenon that is quantifiable by a measure of rank-order disruption (known in the literature as K_D[26], see Figure 3A). This widespread disruption in brain topology is observed in chronic pain at large: this has been demonstrated, so far, in osteoarthritis (OA), chronic regional pain syndrome (CRPS), subacute back pain (SBP) and chronic back pain (CBP) patients [26], and these findings have been replicated in more recent studies, namely patients with LBP and disk herniation[33]and in knee and hip OA patients[34], highlighting its generalizability across clinical pain populations. In line with the previous observation, the latter study further explores brain topology shift in higher detail, showing that the regions that are most impacted show a striking dissociation: sensorimotor brain regions (precentral and postcentral gyrus, typically non-hubs) increase their connectivity to the rest of the brain, while other regions that typically function as brain hubs (i.e., insula, operculum) are downregulated[34]. Another prominent finding is that this shift in brain topology seems to be of a similar magnitude for all pain clinical conditions; moreover, in pain, the higher the disruption, the higher pain intensity is reported [26]. This link between pain and overall extent of shift in connectivity (K_D) further solidifies the evidence that this state is associated with pain and is not a consequence of other trivial epiphenomena.

The rodent's brain obeys to similar organizational principles regarding brain topography and underlying connectivity structure as the human brain. And indeed, given the underlying hypothesis that chronic pain is an abnormal network state, one should be able to replicate the finding in animal models. This is exactly the case: in neuropathic rats (spared-nerve injury model –one of the most popular models of chronic pain in the animal since the injury leads to pain-like behavior that persists), when compared to rats who underwent sham surgery, showed a substantial disruption in network topology 27 days after surgery (Figure 3B). This disruption is again, widespread. Mirroring human findings, this magnitude of disruption (K_D value) was also associated with tactile allodynia in the animal (a pain related behavior where harmless and non-painful touch is perceived as painful)[26].

Above and beyond these large-scale changes in brain connectivity, it is also possible to study how the connectivity of individual brain regions to the rest of the brain are also being affected by chronic pain. Across several chronic pain conditions, we have identified localized functional changes in brain regions typically associated with pain (Figure 3C, upper panel). For instance, the thalamus, an important relay of nociceptive information, and the hippocampus, an important area for memory formation and learning, are more connected to the rest of the brain in chronic pain patients, compared to healthy controls. Importantly, there are also specific changes that accompany certain chronic pain conditions (Figure 3C, bottom panel). It is tempting to put forward the argument that although there is a generic imprint of the chronic pain state in the brain, some changes are indeed specific and may reflect adaptations that are unique to the disease [26,27]. Whether they are caused by pain-related behavior or by primary disease specific adaptations remains speculative and is an outstanding question that needs to be tackled in the future. Similarly, in neuropathic rat model, localized changes in the extent of information sharing (i.e. functional connectivity)

between brain regions can be observed in well-known pain-related brain areas (Figure 3D) such as the primary sensorimotor, the cingulate cortex, thalamus and periaqueductal gray matter[26]. Importantly, such disruption has also been identified in brain regions that have not been traditionally considered important to acute and chronic pain, such as the ventral tegmental area, nucleus accumbens, and in the hippocampus[2426]. There is, noticeably, some degree of overlap between human and rodent regional disruption, but data assessing local mechanisms remains scarce. These regions form optimal candidates for further research, as we highlight in the next two sections.

Human and animal studies clearly show that chronic pain leads important consequences in the brain and imprints the brain function and structure with a unique, adaptive/maladaptive state. We claim that this widespread disruption is a hallmark of chronic pain and may be used as a prognostic and/or diagnostic biomarker (for an in-depth discussion see [35]). Importantly, the widespread disruption in brain's information sharing was found in human and animal models, highlighting the possibility of reverse translating biomarkers to probe into specific mechanisms, and study its progression in time.

3. Regional reorganization –the mesocorticolimbic circuitry and hippocampus as new targets for translational pain research

Classically, chronic pain research has been conceptualized from the viewpoint of nociceptive processing and in its early days, human brain imaging research focused on nociceptive brain circuits and its perceptual output. More recently, the role of emotional limbic brain in bridging nociception and pain perception, as well as in the transition from acute to chronic pain has been exceedingly recognized. Thought the literature remains recent and up to a point fragmented, the complimentary nature between human and animal models in this field of research revealed to be vital. Over the next two sections we discuss the role of the limbic brain in chronic pain and interrelation with memory, emotion, and motivation.

3.1 Reward, motivation and addiction –the role of the mesocorticolimbic circuitry in chronic pain

The mesocorticolimbic system is one of the brain's major dopaminergic pathways and is composed by the ventral tegmental area (VTA), primarily characterized by its dopaminergic projections to the prefrontal cortex (PFC; mesocortical pathway) NAc, amygdala and hippocampus (mesolimbic pathway). Together, these regions are responsible for encoding value, motivation, reward and aversion, and for regulating learning processes[36,37]. Due to its tight link with motivated behavior, this system has been traditionally studied in the reward, motivation, and addiction fields. In the context of chronic pain, this circuitry has been classically neglected. The dorsolateral prefrontal cortex was firstly implicated in humans with chronic back pain in one of the first studies examining anatomic properties of brains of chronic pain patients, showing reduced gray matter density in the region (together with the right thalamus), and these changes were strongly related to both the pain duration, pain intensity parameters, and with sensory and negative-affective dimensions of CBP [38]. Since then, many other studies have highlighted the tight relationship between chronic pain and the mesocorticolimbic system[3940]. This circuit has recently been implicated in

the development, amplification and persistence of chronic pain and its emotional-affective dimension[30]. The underlying hypothesis here is that chronic pain can be seen from the perspective of an addictive behavior: following an injury, a new state of brain plasticity is triggered where the brain engages into emotional learning mechanisms[31]. This new state is largely dominated by reward and learning processes (i.e., ventral striatum, medial prefrontal cortex, amygdala, and hippocampus[20,41,42]). The corticolimbic circuitry is crucial to regulate and assess the salience of impeding pain, as well as the reward for pain relief, and may drive a reorganization process that leads to a new state –a brain in pain –that is not solely dependent on sensory (nociceptive) input but, instead, further regulated by emotional circuitry.

Amongst the areas in the mesolimbic system, the NAc plays an important role in behaviors related to addiction and now, chronic pain. This key structure is involved in mediating motivational and emotional processes, incentive, and reward, behaves as the limbic-motor interface, and mediates the effects of certain psychoactive drugs. It has been implicated in numerous neurological and psychiatric disorders [43]. In contrast to the extensive work on reward-related activity, fewer studies have explicitly addressed the role of mesolimbic motivation/valuation circuitry for aversive events, however, in recent years, ample evidence emerged showing the fundamental role of the NAc in the chronic pain state, and in the transition from acute to chronic pain [20,44]. In fact, in the first study examining the transition from subacute to chronic back pain in humans[20], it was shown that the NAc functional connectivity has strong predictive value for the development of chronic pain: at the subacute stage, the amount of information sharing between the NAc and the mPFC was substantially higher in patients who went on to transition into a chronic state, compared to those who go on to recover (Figure 3A); further, this measure alone was able to predict individuals who transitioned to chronic pain in an independent, new sample of subjects with high accuracy (> 80%). The enhanced functional connectivity between mPFC and NAc may be interpreted as an increased emotional salience signal, which distorts dopaminergic outputs from the VTA, and may become a critical gating process that controls transition to chronic pain[30]. The role of NAc in pain chronification was further explored in a more recent study, which showed that the volume of the NAc is also predictive of pain chronification, and its functional profile is also changed throughout the transition from subacute to chronic pain[44].

If there are multiple evidences pointing to structural and functional changes in the human mesolimbic system and given the well-known parallel between animal and human structures, surely animal models can be used to tap into the underlying mechanisms. In line with a reverse translational approach, this provides ample opportunity to discover mechanisms of pain chronification, can serve as possible therapeutics targets, and its pharmacologic manipulation can be tested in the animal model. Greatly inspired by the human studies reviewed above, the study of the mesolimbic system in rodents has been highly successful since its inception. In fact, studies focusing on the NAc have shown that just 5 days after SNI neuropathy, covariance of receptor gene expression in NAc is upregulated [21], and 28 days after SNI, functional connectivity of the NAc to dorsal striatum and cortex was substantially reduced[21] (Figure 3B). Later studies substantiated the pivotal role of the NAc in chronic pain. For instance, it has been shown that glutamatergic transmission through

AMPA-type receptors in the core and shell of the NAc, known to be important in regulating reward and aversion-type behaviors is increased in a neuropathic pain animal model[45].

Similarly, there is now strong evidence that the PFC is equally affected in chronic pain animal models. For instance, just days after SNI injury in rats, dendritic size and branching of prefrontal pyramidal neurons were expanded [46]; 6 months after neuropathic injury that led to early and sustained hyperalgesia in the rat, PFC cortical gray matter volume was decreased, and these changes were coincident with the onset of anxiety-like behaviors[47] (Figure 4.D). Moreover, it was shown that the optogenetic activation of the PFC produced strong antinociceptive effects in a SNI rat model of persistent neuropathic pain and this activation also reduced the affective symptoms of pain[46].

Other regions within the limbic system are also affected: for instance, Neugebauer et al showed that the amygdala neurons become hyperexcitable hours following induction of arthritis in the rat [48]; on the other hand, bilateral lesions of the basolateral amygdala diminish post-injury tactile allodynia for 28 days after SNI [49]. The amygdala plays a key role in fear learning and extinction, and it was recently shown that the magnitude of neuropathic pain related affective behaviors is predicted by fear extinction learning ability, which is in turn correlated with the amygdala (central nucleus) neuronal activity changes[50].

With accumulating evidence suggesting the implication of mesocorticolimbic influences in chronic pain, it is now necessary to evaluate how targeting these mechanisms fares, against more peripherally centered treatment options. Can we reduce, revert, or impede chronic pain by tapping into this system?

Starting by the PFC, and given its known role in reward and aversion, we studied the drug D-cycloserine (DCS) a centrally acting, partial agonist of the NMDA receptor with known effects in attention, memory [51,52], and most importantly, in conditioned fear extinction[53,54,55]. If chronic pain is indeed potentiated by the inability to extinguish pain-related memories, and driven by reward-based learning, then pharmacological manipulation of this mesolimbic system should enhance extinction of pain and, particularly, its affective component. In fact, infusions of DCS directly into the mPFC (especially within prelimbic cortex), or the amygdala, acutely induced antinociception in SNI rats. Moreover, the mPFC infusions reversed place avoidance behavior induced by mechanical stimulation of the injury paw in SNI rats. There was a cumulative increase in antinociception with continued treatment and long-lasting antinociception after cessation of treatment, which indicate that the antinociceptive effects of DCS are amplified over time[56].

Regarding the NAc, there is now good evidence suggesting that following neuropathic injury, the medial shell portion of the NAc shows decreased concentration of dopamine, changes in excitability of dopamine D2 receptor expressing spiny neurons, shrinkage of dendrites and decreased synaptic inputs, as well as diminished dopamine D1 and D2 receptor expression[22,21]. Most importantly, these adaptations can be blunted either with L-DOPA in combination with naproxen or pramipexole, a D2/3 dopamine receptor agonist there is higher excitability in the msNAc that worsens tactile allodynia. These results

advance specific forebrain circuits involved in the transition to chronic pain and point to a new therapeutic approach[22].

With evidence that drugs like DCS and that L-DOPA can change pain-related behavior in rodent, new efforts at targeting the human chronic pain condition can be attained. The results from such undertaking are both exciting and promising. For instance, DCS was later tested in a randomized placebo-controlled pilot human clinical trial, where a clinically meaningful effect size in the magnitude of pain relief was observed with a consistent pattern across multiple outcome measures with good safety, supporting further research into the effectiveness of DCS for CBP[57]. Similarly, providing L-DOPA to human patients at the sub-acute stage of low back pain blocked the transition for chronic pain in a sex-dependent manner (only females benefited from L-DOPA plus Naproxen)[23].

From this short summary, many more questions arise and plenty stimulating new ideas emerge. For instance, the dysregulation of the mesolimbic pathway and its output neurons in the NAc plays a significant role in the development and maintenance of addictive behavior –including opioid addiction. It is quite striking that there is a clear overlap between the addiction brain circuity and brain circuitry that causally linked to the development of chronic pain (Figure 1B). It is imperative to disentangling the influence of chronic pain and opioid dependence in mesolimbic circuitry, however, such task is not trivial. We remain naïve as to whether opioid usage can lead to brain adaptations in reward circuitry that influence pain chronification, and/or, in the reverse, whether the brain structural and functional adaptations seen in chronic pain place patients at higher risk for opioid abuse and reduced treatment efficacy. These remain outstanding questions will shape the research in chronic pain, and particularly may benefit substantially from the ability to translate findings between human and animal models.

3.2 Memory and learning: the hippocampus and its critical mechanisms in chronic pain.

We have so far reviewed how the mesolimbic system plays an important role for the development and persistence of pain, through processes related to motivation, reward, memory, and emotional learning. Chief among brain structures involved in memory formation and emotional learning is the hippocampus, a part of the mesolimbic system central to human and animal cognition. The hippocampus has been the object of intense study in both human and animal models in clinical conditions such as Alzheimer’s disease and other forms of dementia, post-traumatic stress disorder, chronic stress, depression, and neurological/psychiatric conditions, and has led to many exciting and ground-breaking advances in these fields.

In contrast to the well-known role of the hippocampus in other pathologies, literature implicating the hippocampus in the development and maintenance of chronic pain remains relatively scarce. This is surprising since pain is inherently charged with a strong emotional valence, and when faced with a behavior that induces pain, a set of brain adaptations take place to ensure such behavior is extinguished and future harm is avoided. Similarly, subsequent pain relief should reinforce the protective appropriate response in the brain. One could argue that pain, memory, and emotional learning go hand-in-hand: pain will necessarily be a main driver of plasticity, leading to the consolidation, maintenance

and extinction of pain-related memories[31]. In humans, there is evidence linking the hippocampus and pain-related behaviors. For instance, the hippocampus has been implicated in exacerbation of pain by anticipation anxiety, in predicting and evaluating future pain sensation[58], and in enhanced pain sensation after inducing negative moods[59]. The hippocampal formation is also crucial for the formation of pain-related memories, and, in the context of chronic pain, it has been shown that the shape of the hippocampus is linked to an exaggeration of pain recollection in chronic pain patients [60]. More generally, too, patients with chronic pain have marked deficits in hippocampal-dependent behavior, including poor performance on memory tasks and classical conditioning [61,62,63]. We established the idea that chronic pain can be seen as a continuous state of learning where pain is repeatedly associated with negative mood and aversive emotions leading to plastic changes accommodating new memory traces [21,31]. Chronic pain patients may be unable to extinguish these pain memory traces, and along with the continued reinforcement and learning that is caused by the continuous presence of pain, a maladaptive painful state may arise. This premise is supported by two key lines of evidence. First, studies contrasting healthy subjects and chronic pain patients show that chronic pain leads to structural changes in the hippocampus, including abnormal size [41,64,65] and shape[5]. Patients with chronic pain also show altered hippocampal function[64,65], and in particular how different specialized hippocampal subregions share information between themselves and with other areas of the brain (Figure 5A). Some of these changes are quite dynamic and develop over time as patients transition from subacute to chronic pain[66] (Figure 5A, right panel), hinting again at the tight relationship between the development of chronic pain and hippocampal-dependent memory consolidation. Second, the hippocampus might be a key player for the development of chronic pain in the first place, whereby its structural and functional characteristics may predispose individuals to develop chronic pain. In fact, the volume of the hippocampus, as well as its underlying structural and functional connectivity within the mesolimbic system were proven to be a-priori risk factors for developing CP [47]. Together, these findings clearly place the hippocampus as a central player in chronic pain, and open promising new avenues for research.

We have so far tied together pain perception, memory formation, hippocampal structure and function –but remained agnostic as to what is the underlying pathophysiology causing these changes. These questions are best answered in animal models, and so, we turn again to reverse translational research. Importantly, the hippocampus has a surprising parallel between humans and other mammals, with equivalent neuronal layout and projections, becoming a prime candidate for translational research. In the animal literature, it has been recognized that chronic pain also leads to marked memory deficits [67,68] that are accompanied by structural changes in the hippocampus at the cellular and molecular level, including abnormal cytokine expression[69,70] and deficits in long-term potentiation[71]. Moreover, the impaired memory performance of chronic pain animals associates with disruption of fronto-hippocampal connectivity[72], and the modulation exerted by painful conditions is critical for this network disturbance[73].

One of the remarkable idiosyncrasies of the hippocampus is its ability to generate new neurons in adulthood, a process termed hippocampal neurogenesis. Adult hippocampal neurogenesis is crucial for adaptive behavior and is implicated in learning and memory[74].

Reduced neurogenesis, on the other hand, has been associated with depression[75], anxiety[76], stress[77], and importantly, impairment in fear conditioning[78]. One of the most striking findings in the hippocampus is how neurogenesis is impacted by chronic pain models in mice: two weeks after SNI, marked decreases in hippocampal neurogenesis have been observed [41] (Figure 5B). These mice also develop abnormal pain-related behaviors, including painful sensation where there was none (i.e., mechanical allodynia), inability to extinguish to context when compared with healthy mice. These findings highlight the plastic changes that take place in the hippocampus and have a striking resemblance to the human findings reviewed above –chronic pain leads to reduced hippocampal volume in humans, and to reduced neurogenesis in mice –providing a possible mechanistic understanding to the structural and functional changes observed in the human hippocampus.

Given the clear association between chronic pain, hippocampal neurogenesis, and pain-related behavior, causal studies are now required: can we revert chronic pain, or at least, pain-related behavior by manipulating hippocampal neurogenesis? In fact, in one such study, *Apkarian et al.* [79] performed a series of experiments modulating neurogenesis both pharmacologically, using x-rays, and in transgenic mice with increased and decreased hippocampal neurogenesis. Pharmacological downregulation of neurogenesis following SNI substantially diminished pain-related behaviors, while upregulating neurogenesis led to the opposite pattern. Further, ablation of hippocampal neurogenesis led to a substantial delay in the development of mechanical allodynia following SNI. Finally, transgenic mice with decreased hippocampal neurogenesis did not develop mechanical allodynia after SNI. Together, these findings causally implicate the hippocampus, and specifically, hippocampal neurogenesis in the development of chronic pain.

The finding that plastic changes in the hippocampal network is key for the development and maintenance of pain provides us with room to further experiment novel therapeutical targets with animals. An exciting new study shows how direct glutamate microinjection within the dorsal hippocampus after SNI can completely reverse mechanical allodynia in rodents, (Figure 5C)[80]. In the same study, chemo genetically increasing the excitability of dorsal hippocampus neurons also diminished mechanical allodynia in these animals. Increases in excitability of the dorsal hippocampus neurons further altered the synchrony between the hippocampus and multiple brain regions that are related to neuropathic behavior, including the somatosensory cortex and the thalamus[80]. Additionally, it was recently showed that the disrupted connectivity between the hippocampus (CA1) and infralimbic cortex (IL) in pain animals can be rescued with chemo and optogenetic tools, leading to relief of spontaneous pain in an inflammatory pain animal model[81]. This data puts a clear focus on how pain relief can be triggered by targeting hippocampal circuitry, memory extinction and emotional learning. The hippocampus may pose as a key target for the treatment and management of chronic pain.

We are currently at the frontier of knowledge on how hippocampal modulation can help us develop new treatments, help us characterize chronic pain conditions, or even serve as a predictive biomarker for chronic pain. Recent discoveries point to provocative but exciting new ideas. For instance, just recently a large-scale reanalysis of data in chronic back patients clearly shows how hippocampal shape deformation –that is, how the geometric shape of the

hippocampus is changed in chronic back pain patients compared to healthy volunteers –is a robust diagnostic biomarker[82]. However, this biomarker is only relevant in females, showing a possible gender-specific effect. Considering that up until recently most animal research has been conducted with male animals, this finding shows –yet again –the importance of reverse translation research in guiding animal research hypothesis.

4. Conclusions

In this review we outline brain mechanisms of chronic pain, and how the reverse translational approach provides opportunities to both uncover mechanisms and drive the field into drug development. Chronic pain depends on a complex interplay between sensory information, perception and cognition; although animal models for chronic pain have become a fundamental tool to study underlying mechanisms of pain, its success is potentiated by studying the human experience. By posing scientific questions that arise from human observations and clinical pain, animal models allow us to mechanistically probe pain pathophysiology and create potential new targets for drug development. These, in turn, can lead to new clinical trials, driven by the primary hypothesis devised in the human. As stated by Sydney Brenner, molecular genetics pioneer, and reinforced by Valentina Shakhnovich[19,83], "*we don't have to look for model organisms anymore, because we are the model organism*." We firmly advocate that human and animal research are complimentary fields, and their interaction is necessary to advance the field of pain research and find much needed new pathways for treatment and management of chronic pain.

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Abbreviations:

CBP	chronic back pain
DLPFC	dorsolateral prefrontal cortex
mPFC	medial prefrontal cortex
NAc	nucleus accumbens
PFC	prefrontal cortex
OA	osteoarthritis

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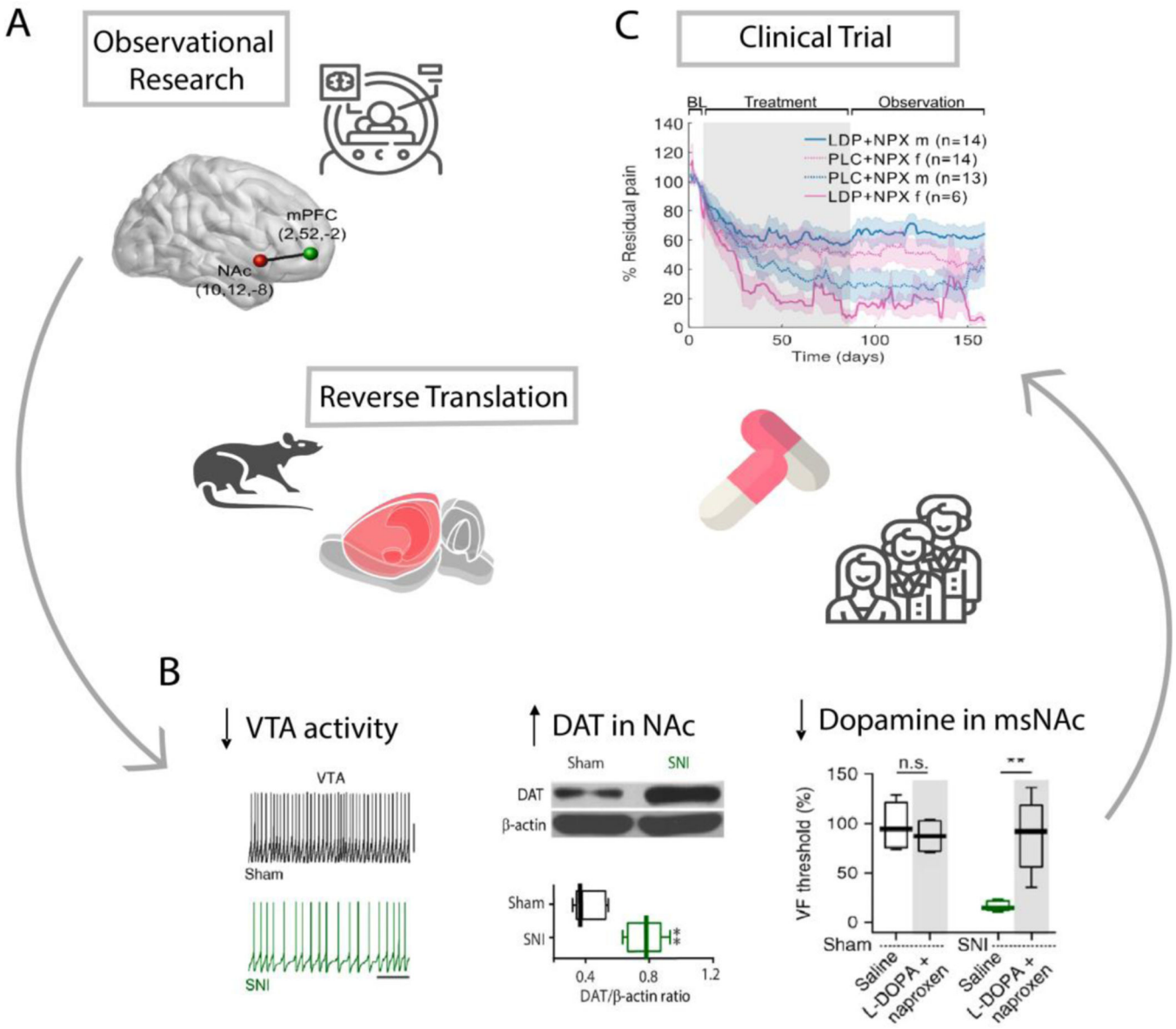

Figure 1.

Reverse translational approach in chronic pain research. Reverse translation research starts with clinical observations, real-life patients experience and observational research studies, and works backwards to uncover the mechanistic basis of the research question. One successful example of this methodology in chronic pain research is depicted in the figure. A. The corticostriatal functional connectivity predicted transition to a chronic state with high accuracy in humans[20]; B. This finding was replicated in a longitudinal rodent study, in-depth characterizing underlying cellular and molecular adaptive mechanisms in the NAc, and further pharmacologically manipulating this system[22]; C. Subsequently, this approach pointed to a new therapeutic approach for managing/preventing transition from acute to chronic pain in humans, that was recently tested in a human clinical trial[23].

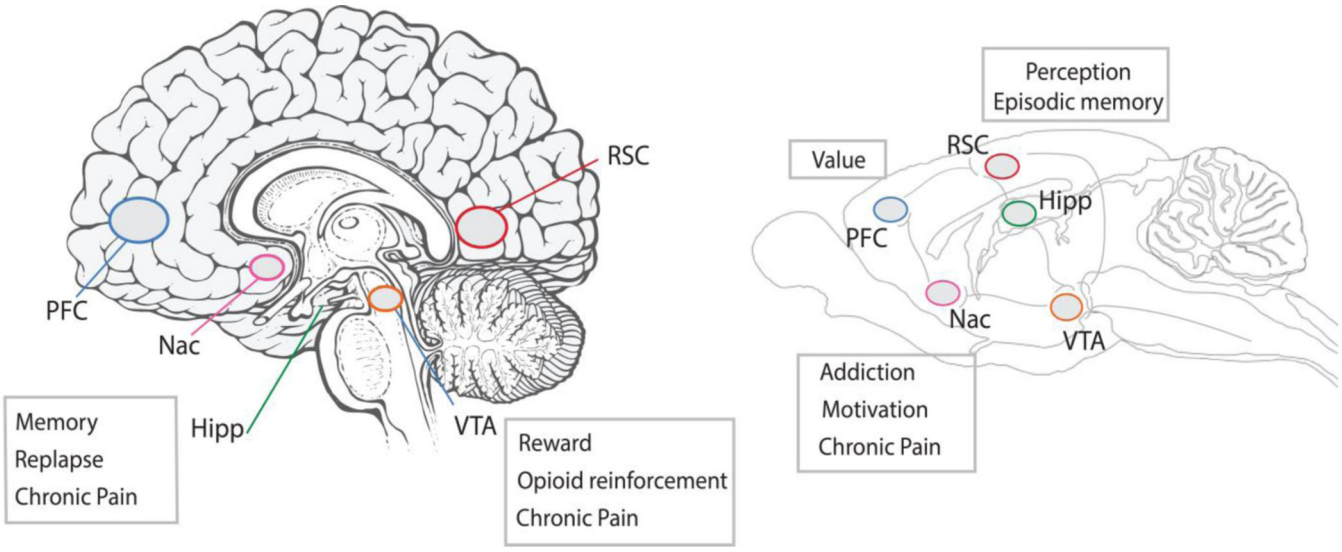

Figure 2.

Mesocorticolimbic circuitry in humans and animal models. The biological similarity between human and rodent is a powerful tool that we use to interrogate the brain circuitry underlying chronic pain and, more recently, its overlap with addiction. Brain areas involved in addiction, as the prefrontal cortex (PFC), hippocampus, nucleus accumbens (NAc), ventral tegmental area (VTA) and retro splenial cortex (RSC) are also associated with chronic pain[84]. Studying neuroadaptations in animal and humans' models of pain and addiction offer a heuristic opportunity to explore its pathophysiology and interactions.

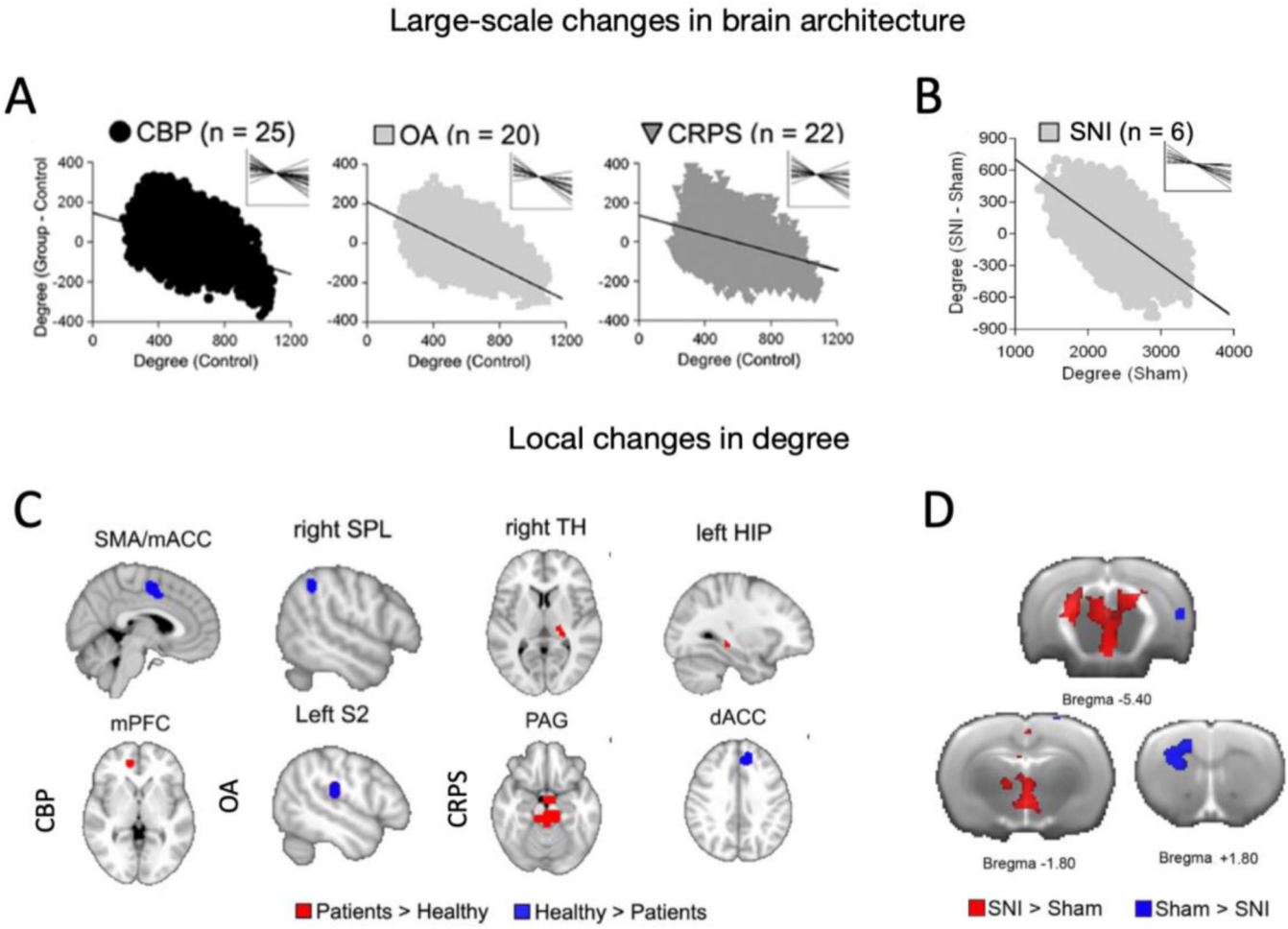

Figure 3.

Chronic pain leads to large-scale and local changes in brain functional connectivity in both humans and rodents. A. Chronic back pain (CBP), Osteoarthritis (OA) and Chronic Regional Pain Syndrome (CRPS) show similar disruption in rank-order that permeates the whole brain architecture[26]. B. SNI rats (27 days after injury) also show rank-order disruption when compared with sham surgery rats[26]. This disruption is again generalized and in similar magnitude to the findings in humans. C. Despite large-scale changes in functional architecture, the connectivity of specific brain regions to the rest of the brain are upregulated (red, upper panel: right thalamus and left hippocampus), or downregulated (blue, upper panel: supplementary motor area, superior parietal lobule) across chronic pain conditions. Some of these changes are specific to the chronic pain condition as illustrated in the bottom panel. D. Similar to human data, SNI rats show localized changes in functional connectivity[26].

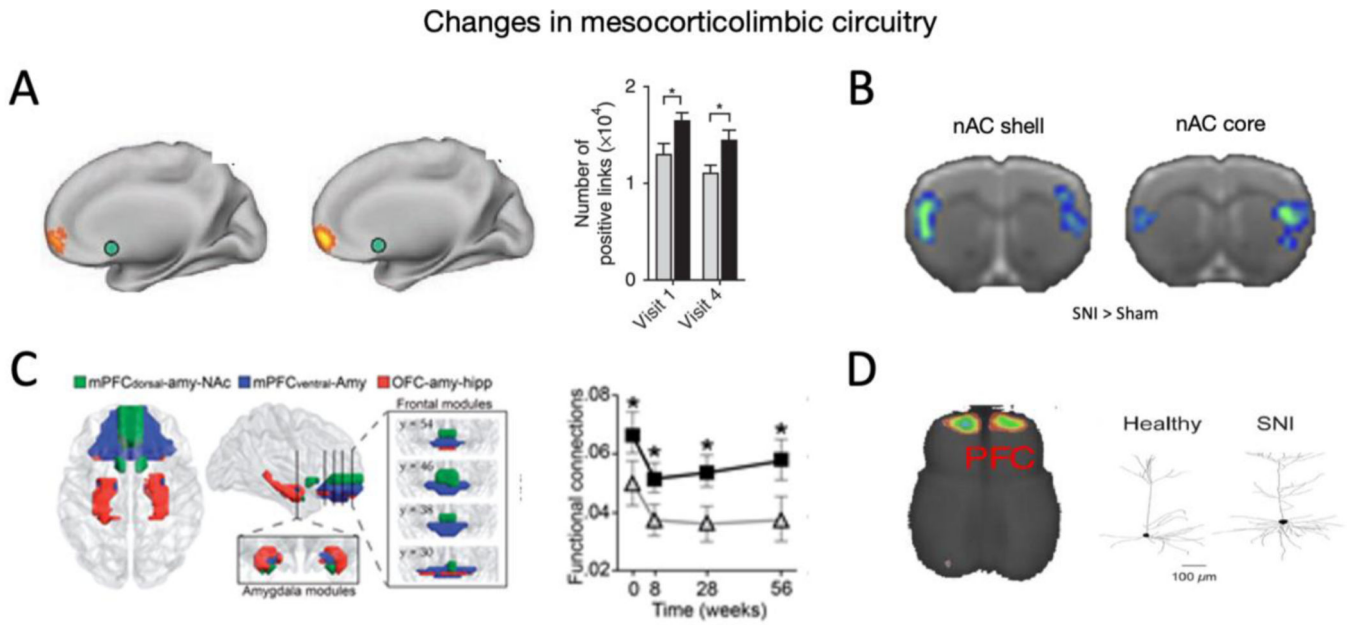

Figure 4.

Mesocorticolimbic circuitry, central to reward and motivation, has been implicated in the development, amplification and persistence of chronic pain, both in animal models and human subjects. A. The strength of information exchange (functional connectivity) between the nucleus accumbens (NAc; green) and medial prefrontal cortex (mPFC) is predictive of the transition from acute to chronic low back pain. B. 28 days after SNI, functional connectivity of the NAc core and shell to Caudate, Putamen, Insula and S1/2 brain areas was reduced, compared to sham animals[21]. C. Intra-corticolimbic white matter connectivity of the medial PFC-amygdala-nucleus accumbens module imparts risk for chronic low back pain in humans[42]. D. In a rat model of neuropathic pain (SNI), prefrontal cortex (PFC) gray matter volume is decreased [47], and 5 days after SNI neuropathy NAc covariance of receptor gene expression is upregulated[21].

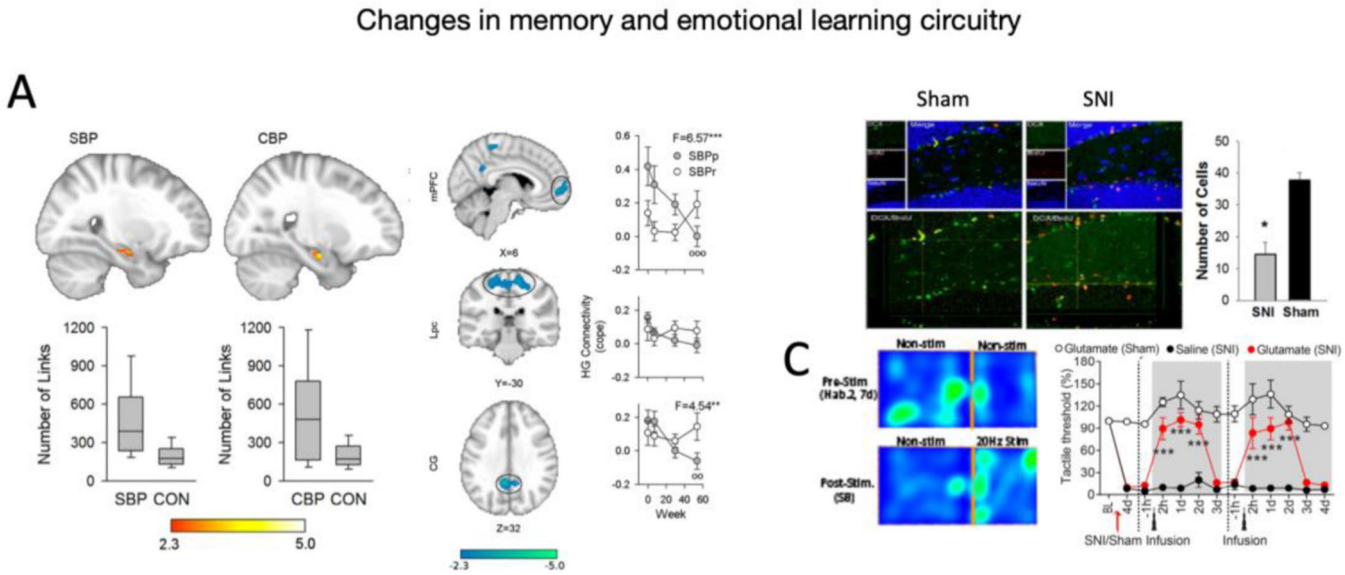

Figure 5.

Hippocampus structure and function is changed in chronic pain, over time. A. Anterior hippocampus functional connectivity is substantially upregulated in subacute, and chronic back pain patients, when compared to controls[66]. Functional connectivity from the anterior hippocampus to the medial prefrontal cortex (right upper panel) and posterior cingulate gyrus (right bottom panel) shifts over time and differentiates patients who develop chronic pain to those who recover[66]. B. Examining how the hippocampus changes with chronic pain reveals that hippocampal neurogenesis is substantially downregulated in SNI animals compared to sham[41] C. Identifying these mechanisms allows to probe for new treatments. In SNI animals, direct stimulation of the dorsal hippocampus leads to changes in behavior (changes in place preference in chambers with optogenetic stimulation, left panel) and a total extinguishment of mechanical allodynia(right panel)[80].