# Chapter 12
# Making Chronic Pain Visible: Risks, Mechanisms, Consequences

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## 12.1 Summary Abstract for Presentation Delivered at Uehara Meeting, June 2017

By drawing an analogy between color perception (in the visual system) and pain perception, I highlight the fact that pain states must be considered conscious conditions, and in this sense ultimately our understanding of mechanisms of pain requires elucidation of fundamentals of consciousness. Thus, until we gain such understanding, we need to remember that current knowledge about pain mechanisms remain brain/behavioral correlates for subjectivity (SLIDE 2).

SLIDE 3: The current lecture deals primarily with mechanisms of chronic pain, and we need to differentiate between acute and chronic pain. Acute pain is necessary for avoiding damage based on conscious negative affectively colored states, which give rise to appropriate behaviors, such as avoidance. In contrast, chronic pain is a persistent state of negative affect where appropriate behaviors are no longer available. It is a state of conscious pain perception once the healing process of the initial injury has subsided. Current estimates are that >20% of world population suffers from chronic, proper treatments are missing, and its management imparts a very high cost to society.

SLIDE 4: Descartes' drawing in 1644, illustrates the basic elements that constitute any given sensory system, illustrated specifically for pain. The figure shows transduction, transmission, and cortical representation, which have become the main organizational concepts for each of the sensory systems; and the constituent

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cellular/molecular elements remain a main research direction in all senses. There is now ample evidence that persistence of pain, or transition from acute to chronic pain, is associated with peripheral, spinal cord, and cortical changes in functional and even in anatomical properties.

SLIDE 5: Within this context, this lecture deals with recent advances in our understanding mechanisms of chronic pain. The lecture emphasizes: (1) acute and chronic pain are distinct brain states; (2) recent studies show that we can derive a brain signature for chronic pain; (3) human and rodent-model longitudinal studies show that the limbic brain is critically and causally involved in the transition to chronic pain.

SLIDE 6: The general viewpoint for chronic pain is simply that it must be comprised of four distinct elements: (1) predisposition: necessary as only a minority of subjects with similar injuries develop chronic pain; (2) an injury: often the inciting event is clearly identifiable, but in many cases it may not be; (3) transition: recent evidence shows that both humans and rodent respond differently with treatments and show distinct perceptual properties early after an inciting event, in contrast to later stages of chronic pain. Mechanisms of the transition is a main emphasis of this lecture. (4) The maintenance stage is when the pain persists for long periods (usually years), a stage where treatments are also least effective. The specific mechanisms of maintenance of chronic pain remain minimally understood. The traditional (nociceptive) view has been that all these stages are embedded and thus need to be understood within the properties of the nociceptive circuitry, emphasizing the role of afferent fibers and spinal cord mechanisms of sensitization. Our viewpoint, based on recent advances in the topic instead posit that: (1) Limbic brain properties define risk; (2) the interaction between injury and emotional-learning processes underlie transition to chronic pain; and (3) chronic pain state is a new brain anatomical and functional condition carved during the transition to chronic pain.

SLIDES 7–11: If we compare brain properties between chronic pain patients and healthy controls, then we identify the components that make up the maintenance state of chronic pain. We observe anatomical distortions, and brain activity that seem to uniquely correlate with chronic pain perception.

SLIDE 12: There is also some evidence that when chronic pain is properly treated at least some of the brain anatomy renormalizes to correspond to the healthy brain state.

SLIDES 13–14: Illustrates brain oscillations, recorded in resting state fMRI, in a single subject. These oscillations reflect learning, memory and myriad other properties. Here we use it to derive a signature for the presence of chronic pain.

SLIDE 15: The overall approach is to use brain oscillations to construct an undirected graph of connectivity, and reduce this information to nodal links (degree): the number of nodes (degree, link) any given node communicates with.

SLIDE 16: Healthy subjects group average map for degree is shown. This is a map of the amount of information sharing any given brain location performs with the rest of the brain. If we calculate such a map for a single chronic pain patient, and plot, voxel by voxel, the one subject versus control degree map we can then calculate a distortion index kd.

SLIDE 17: kd provides a whole-brain unitary measure of extent of information sharing distortion a given patient or a group of patients exhibit. We see the index is present in 3 chronic pain conditions, and in all cases individual kd correlate with patients' magnitude of chronic pain. SLIDE 18 shows that we can used kd in a validation data set to predict individual subjects' magnitude of chronic pain, which we can do at an accuracy of about 60–70% correct.

SLIDES 19–28 summarize results from a longitudinal study, where we tracked brain properties of back pain patients, over a 3-year period. These patients entered the study within a few weeks of onset of their back pain (sub-acute stage) and were followed with repeated brain scanning while they transitioned either to recovery or to chronic pain. SLIDE 19 illustrates the general concept of the study, sub-acute back pain patients in time transition into recovering or persistence (based on the level of back pain), and properties that predict long-term outcome identify predispositions, while properties that change in time create the chronic pain state.

SLIDE 20: Brain activity maps are plotted related to the spontaneous fluctuations of back pain, in the recovering group (SBPr), and persistent group (SBPp), over time. We observe that both groups initially show similar brain activity, that matches activity for acute pain, but in time the respective maps diverge. The SBPr brain activity disappears while the SBPp activity moves away from sensory regions and instead engages limbic circuits. Thus, brain activity for back pain shifts in brain location as a function of time.

SLIDES 21–23: Summarize the main functional connectivity that predicts the long-term outcome, namely extent of information sharing between medial prefrontal cortex and nucleus accumbens (mPFC-NAc), which we interpret as a signal of the brain becoming addicted to nociceptive inputs. We suggest that the value of nociceptive afferents is modulated by these connections, which increase their importance to the individual, thus interpreting event small nociceptive inputs as pain.

SLIDES 24–28 summarize our approach to build a comprehensive model for factors that determine risk for chronic pain. SLIDE 24 shows that pain intensity and pain disability begin at equivalent levels but diverge in time between SBPp and SBPr. Thus we try to identify factors that predict these outcomes.

SLIDE 25: We create a brain anatomical network (based on white matter tracks derived from diffusion tensor imaging brain scans, DTI) for the limbic brain, defined as to be composed of amygdala, hippocampus, accumbens, and medial prefrontal cortex. This network was segregated into 3 sub-networks (based on within and across connectivity), one of which (green) had properties predictive of long-term back pain outcomes. This network anatomically and functionally could differentiate between groups, up to 1 year, but only anatomically at 3 years.

SLIDE 26: The volume of the hippocampus (as well as of the amygdala, data not shown) were also distinct between groups and constant over time.

SLIDE 27: The structured approach used to build the model predictive of chronic pain is illustrated. Only parameters that differentiated between the SBPp and SBPr groups were entered into the model.

SLIDE 28: Resultant model is shown. We also performed a limited gene analysis, and identified a single gene mediating contribution of amygdala volume to the model. The model shows three independent parameters all significantly contributing to the prediction of chronic pain, including limbic brain functional properties, anatomy of its connectivity, and the volume of the amygdala (or hippocampus). This result then shows that the limbic brain properties play a critical role in humans transitioning to chronic pain.

SLIDES 29–36 present correlates of the human studies in rodent models for chronic neuropathic pain. SLIDE 29 emphasizes the fact that rodent models provide the opportunity to study injury effects, transition and maintenance of chronic pain, but not predisposition, as these models always exhibit transition to chronic pain. The rest of the slides show the evidence that limbic brain in the rat also undergoes time dependent reorganization, as in the humans. Also, physiological and anatomical reorganization of accumbens indirect pathway is involved in transition to chronic pain.

SLIDE 30: In rats where we perform a neuropathic injury (spared nerve injury model, SNI), resting state fRMI scans show that the brain connectivity remains unchanged at 5 days, but it is reorganized at 28 days after injury. Note the animals show pain-like behavior (data not shown) at both time points. Moreover, the functional connectivity changes are mainly between limbic and somatosensory brain regions.

SLIDE 31: In the same animals as in slide 30, when we specifically examine functional connectivity for nucleus accumbens, again we only observe changes at 28 days, across many brain regions and for different parts of the nucleus.

SLIDE 32: In the same animals as in slide 30, when we examine nucleus accumbens levels of protein expression for various receptors, we observe dopamine receptor type 1 and 2 and kappa opioid receptor levels decreasing in time, which become significant at 28 days after injury.

SLIDE 33: In the same animals as in slide 30, when we examine functional connectivity for 2 sub-regions of the accumbens, we observe that functional connectivity, protein expression for dopamine receptor 2 and pain-like behavior (tactile allodynia) are all inter-related at day 28 after injury.

SLIDES 34–36 are patch recordings from accumbens shell dopamine neurons in mice genetically modified to express dopamine cells with d1 receptor with red and with d2 receptor with green fluorescence. SLIDE 34 shows that 5 days after neuropathic injury, excitability of d2 neurons (but not d1 neurons, data not shown) are increased, their dendritic expanse is shrunk, and afferent inputs are decreased. Moreover, extracellular dopamine levels are decreases and firing frequency of ventral tegmental neurons (the primary source of dopamine to nucleus accumbens) are decreased. Thus, we see both anatomical and functional reorganization of specific cell type in the shell of accumbens, just days after a peripheral neuropathic injury.

SLIDE 35 show that if such animals are treated twice a day either by a combination of L-dopa and naproxen or with pramipexole their tactile allodynia can be decreased together with renormalization of physiology and anatomy of accumbens shell d2 neurons.

SLIDE 36 demonstrates that chemogenetically controlling excitability of accumbens shell d2 neurons can upregulate and downregulate neuropathic pain-like behavior (tactile allodynia). The 5HT3 virus inserts sodium channels, while GLYR virus inserts chloride channels in infected cells. When these proteins are activated with a promoter (PSEM) they increase/decrease d2 neuron excitability and control tactile allodynia. Therefore, the level of excitability of d2 accumbens shell neurons causally controls neuropathic pain.

SLIDES 37–39 summarize the concepts presented in this lecture. SLIDE 37 highlights the circuitry associated with the 4 phases of chronic pain. SLIDE 38 demonstrates the interaction between nociception, limbic circuits and neocortex, pointing the role of limbic modulation of the neocortex to define the chronic pain state.

SLIDE 40 states the main conclusions of the lecture.

SLIDE 41 shows the contribution of Apkarian lab members to our ongoing research, and the 5 NIH institutes that have funded and continue to fund our studies.