

The Emerging Imaging Science of Chronic Pain: Objectifying the Subjective

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Apart from proving that pain is a brain phenomenon, current neuroscience shows that chronic pain is a disease process in itself. In other words, not only is it a reaction to insult or trauma, but it can cause deleterious brain and body consequences. Neuroscientists can confidently assert that chronic pain damages the body in various ways. It atrophies selective brain regions; can decrease brain volume globally and, thus brain processing capability; adversely alter brain cell connectivity and hence communication; sensitize pain processing, thereby increasing the intensity and frequency of severe spontaneous pain; ramp up activity in brain structures associated with increasing anxiety and depression; and degrade activity in structures associated with emotionally based decision making, moral capacity and judgments, motivation and learning. That is all in addition to its impact in progressively deteriorating the body's entire physiology by disrupting normal functioning of the autonomic nervous system, which among other things regulates cardiac, immune, gastrointestinal and other essential body activities. E.g., Sapolsky, Robert M., Why Zebras Don't Get Ulcers: An Updated Guide to Stress, Stress Related Diseases, and Coping. (3d. Ed. 2004).

Accompanying the scientific explorations leading to these understandings has been a concerted effort to objectively confirm the presence of chronic pain. Two main lines of proof have been pursued: depicting pain-related brain activity and identifying atrophied and/or altered brain anatomy. Although neither litigation nor adjudication have propelled these scientific efforts, it is obvious that objectively confirming pain by proving correlative resultant brain activity and or affected brain anatomy has vast implications for our justice system.

It is no revelation that personal injury and disability cases represent a significant segment of our civil justice system. Almost invariably, these cases turn on findings regarding the reality and/or severity of a plaintiff's pain. Additionally, to the extent chronic pain is shown to impact brain structures responsible for aspects of cognition and psychological function - including the capacity for such things as empathy, moral judgment and guilt - the significance of chronic pain extends to such issues as capacity, competence, intention, *mens rea*, remorse, and mitigation.

Today, pain is almost universally perceived and presented in the courtroom as a purely subjective mental phenomenon, distinct from actual provable body pathology or disease. Yet current neuroscience is increasingly dispelling this notion. Current neuroscience confirms that although chronic pain is indeed subjective, it is a subjective event involving brain activities that have the potential to be objectively shown. Its subjectivity makes it no less real; and increasingly, no less provable. As both a reaction, as well as a disease, chronic pain assumes a life of its own, with its own potentially somatic consequences parallel to other diseases whether they originate bacterially, virally, or malignantly.

As mentioned, this neuroscientific effort to prove chronic pain by depicting its associated brain effects has taken two main forms: 1) identifying related brain activity; and 2) showing associated changes in brain anatomy. fMRI has been the primary vehicle for proving pain through depiction of associated brain activity. For several years, its main application has been with reference to the well-established concept of the “pain matrix”. The pain matrix refers to brain structures correlated with the experience of *acute* pain. Those structures are the frontal cortex cingulate gyrus, insula, and sensorimotor cortex and thalamus.

Guided by the pain matrix, to the extent provocation of a painful limb produced fMRI depiction of recruitment of oxygenated blood to pain matrix structures, confirmation of chronic pain was construed. Reference to the pain matrix as a template for chronic pain was strongly asserted in support of the successful ***Frye*** defenses in ***Koch v. Western Emulsions, Inc.***, (Az. Sup.Ct., Pima Cty. 2008) and ***Danne v. Cushman & Wakefield, Inc.*** (New York S.Ct., Queens Cty. 2008).

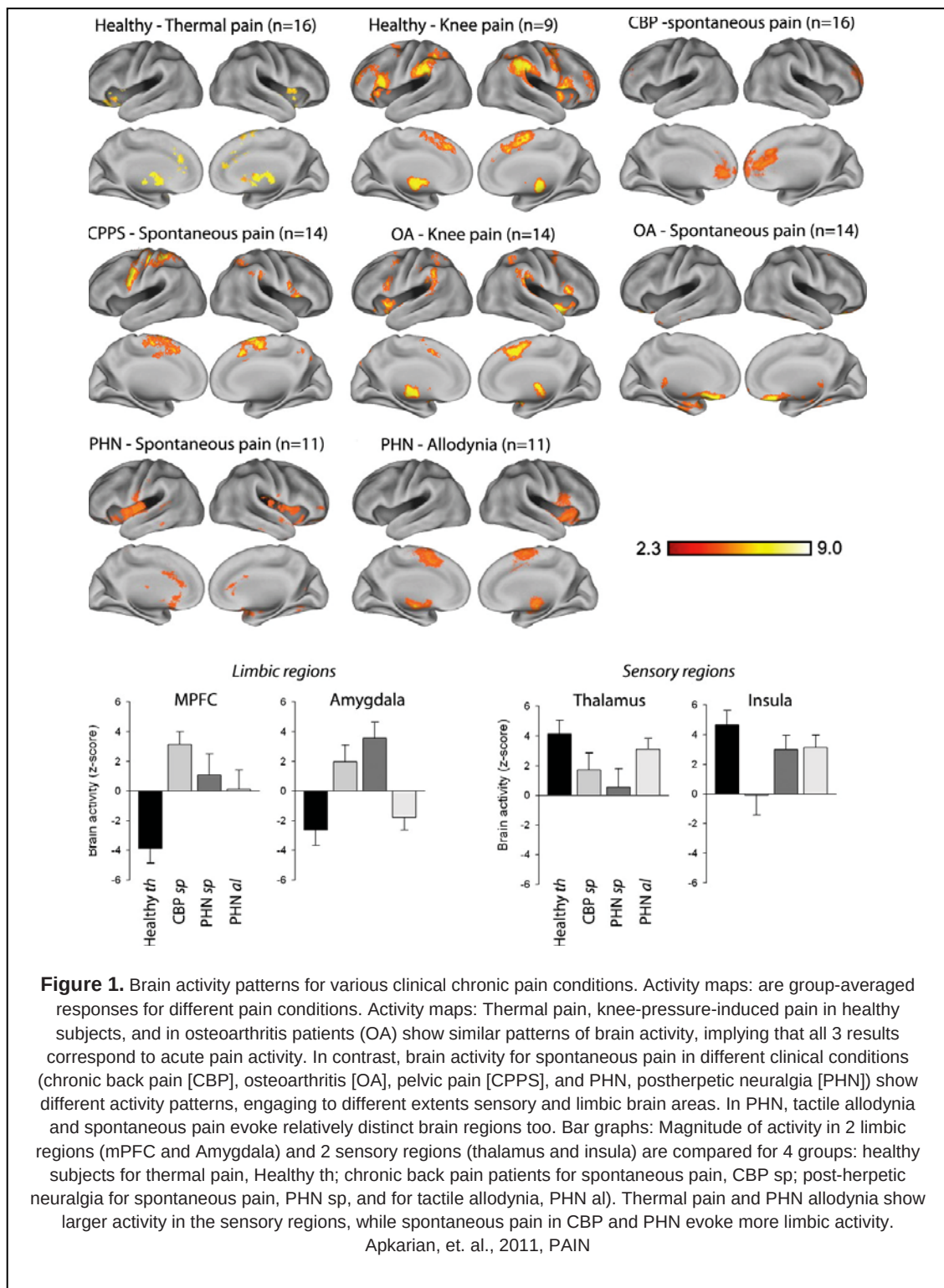
Although the scientific conclusions of chronic pain in those cases were correct, subsequent advances in imaging neuroscience have reconceptualized the brain landmarks for chronic pain. E.g, Apkarian, et. al., Pain and the brain: Specificity and plasticity of the brain in clinical chronic pain, PAIN 152(2011). For although the concept of the pain matrix has become well established in mapping the brain’s activation in *acute* pain, current research now shows that other parts of the brain anatomy largely supplant the pain matrix as acute pain progresses to chronic pain, E.g. Apkarian, et. al., supra.

Although not representative of chronic pain, the pain matrix is nonetheless probative of chronic pain by detecting allodynia. Allodynia

refers to an acute exaggerated pain response to a stimulus caused by sensitization of the central nervous system associated with chronic pain (See pp. 14-15 regarding sensitization). Thus, the detection of allodynia by fMRI visualization of pain matrix activation is important evidence that severe pain has been longstanding.

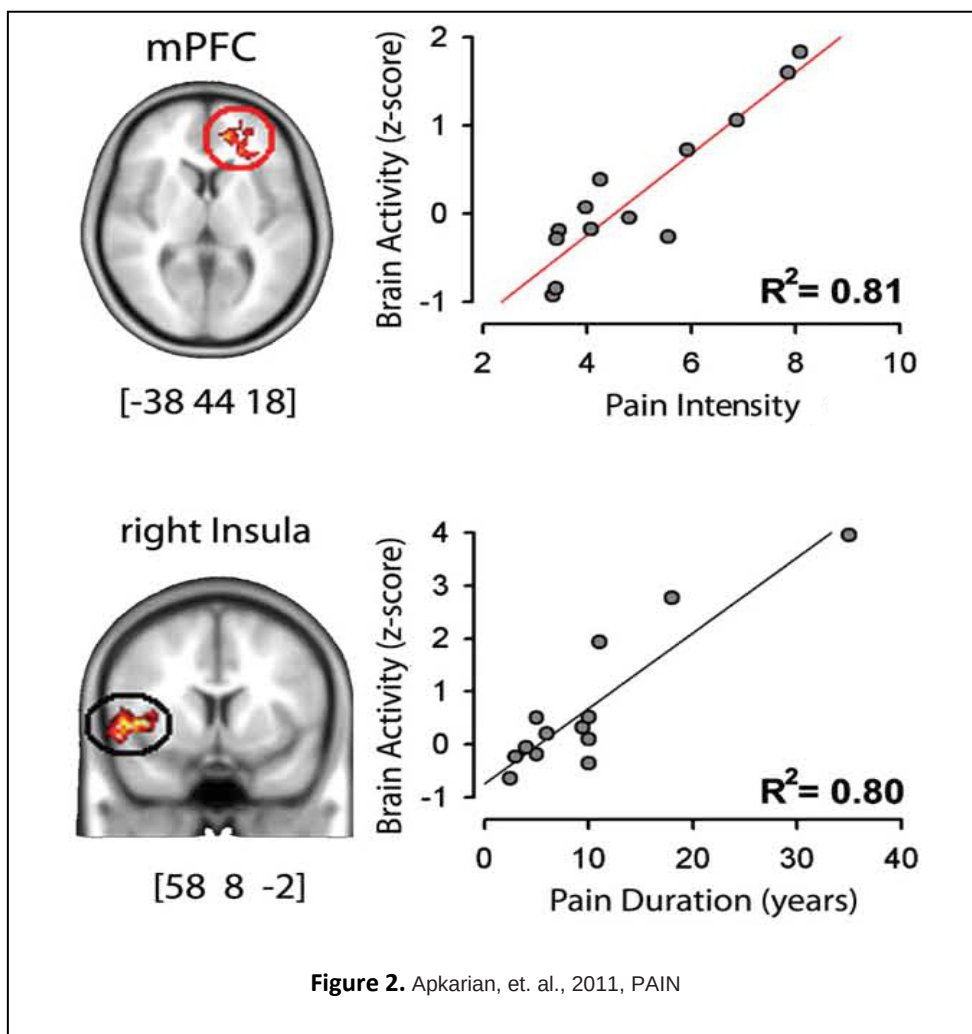
In contrast to acute pain, chronic pain is now understood to be a more complex phenomenon involving issues of anticipation and emotional processes that engage the regions associated with our emotional brain. Apkarian, supra. Moreover, the pattern of the regional engagement associated with chronic pain seems to vary significantly depending upon the pain source. The many and varied brain structures potentially involved in the complex phenomenon of chronic pain include the ventral medial frontal cortex (vmPFC) and subcortical limbic/emotional brain structures, such as the amygdala and hippocampus.

Presented below are fMRI brain activity patterns associated with different pain origins. Additionally, the bar graphs below show that in the examples of *chronic* back pain and *chronic* post herpetic neuralgia the functional activity is much more dominated by the emotional brain structures of the medial prefrontal cortex and amygdala than in the sensory structures, the thalamus and insula, that comprise part of the pain matrix and which predominate in acute pain.



FMRI correlation with chronic low back pain has been the subject of particularly careful study. With this pain, the functional imaging predominance of the medial prefrontal cortex (mPFC) has

been demonstrated. FMRI has displayed close correlation between pain intensity in the medial prefrontal cortex (mPFC) and pain duration with the right insula. The findings support a very high level of predictability of pain magnitude and duration within a 20% error. Indeed, the higher the intensity and duration, the higher the correlation with these particular brain structures and resultant predictability. Apkarian, et al.,supra. The images in Figure 2 show how pain intensity and duration are associated with increased pain activity in the brain structures of the medial prefrontal cortex and insula.



Brain atrophy or volume loss

In addition to using fMRI to confirm pain, scientists can now confidently profile different types of chronic pain through their respective signature gray matter atrophy. Gray matter refers to the brain's neurons or brain cells. Each neuron is tantamount to a powerful computer. Our brain power is exponentially magnified by the connectivity among approximately one hundred million of these computers. This connectivity is obtained from the brain's white matter or axons, representing fibers connecting the brain's neurons to each other, creating a massive multi-processing capability in the process.

Below are examples of different regions of brain atrophy, varying with the type of pain. Chronic back pain, a typical claim in personal injury and other compensation adjudications, appears in A.

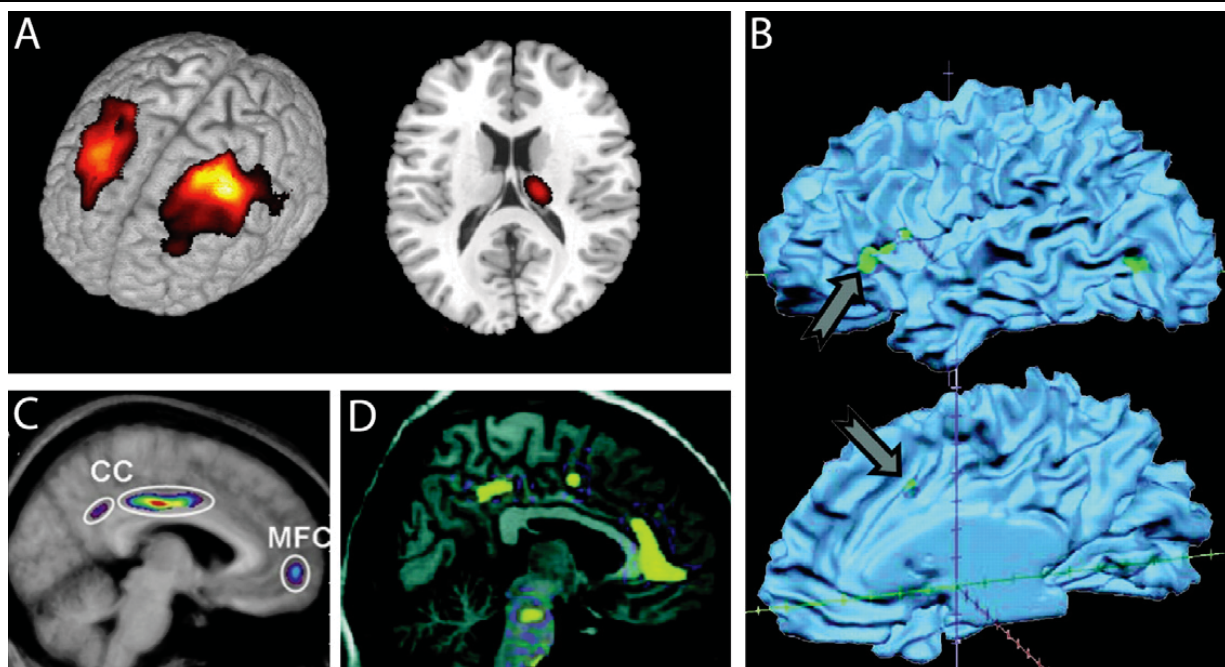


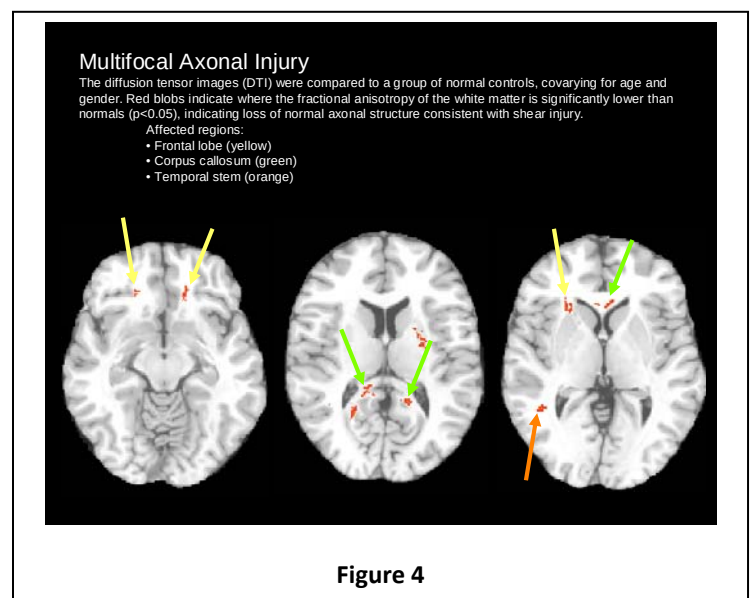
Figure 3. Brain regional gray matter decreases in a number of chronic pain conditions. (A) Bilateral dorsolateral prefrontal cortex and unilateral thalamic gray matter decreases in chronic back pain, from [7]. (B) Insula and cingulate cortex gray matter decreases in irritable bowel syndrome, from [26]. Multiple brain regions show decrease gray matter density in (C) fibromyalgia, from [57], and in (D) tension headache, from [91]. The illustrated data are the earliest reports of brain morphological changes in various pain conditions. The list of additional pain conditions impacting brain anatomy is expanding very quickly. Apkarian, et. al., 2011, PAIN

It is unclear how chronic pain atrophies the brain. Scientists suspect that excitotoxicity - referring to stress-induced dysregulated neurotransmitter activity, resulting in cell deterioration and death - and inflammation are the major factors. With respect to the former, severe chronic pain constitutes a primary excitotoxic stress.

Connectivity and Brain reorganization as biomarkers of chronic pain

At the same time that chronic pain erodes gray matter, it pathologically disrupts and alters the brain's connectivity. Hence, brain mapping for proof of pain also includes investigation of the changed connections between brain regions. Chronic pain disrupts, alters, and diminishes connectivity, and these changes constitute additional brain biomarkers of chronic pain.

The main imaging tool for investigating altered and damaged connectivity is Diffusion Tensor Imaging (DTI). The advent of DTI less than a decade ago has been a boon to exploring injuries to the brain's connectivity that were previously neither evaluated nor diagnosed. In contrast to CT scan and MRI, which are highly insensitive to white matter abnormalities and resultant connectivity loss, DTI discloses white matter abnormalities. This has been particularly important in the realm of traumatic brain injury. Many traumatic brain injuries, including injuries caused by motor



vehicle collisions and shockwaves from bomb blasts, are characterized by minimal, if any, visible gray matter lesions, yet significant white matter (axonal) disruption is present. Consequently, many brain injuries that would be otherwise imaged negatively by CT and MRI and diagnostically discounted are confirmed using DTI modalities.

DTI's modalities are *fractional anisotropy* (FA) (Figures 4,5,6), which measures deviations from normal water molecule alignment as a means of discerning white matter integrity and locating axonal damage, and *tractography* (Figure 7), which delineates white matter pathways, detecting their disruption in the process. Although most institutions interpret fractional anisotropy visually, the images in Figures 4-6 were interpreted quantitatively by reference to a database of normal subjects, which confers a higher sensitivity and objectivity.

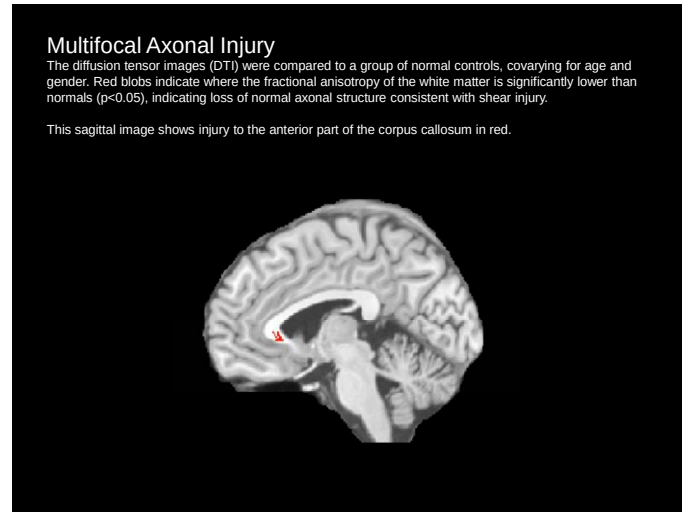


Figure 5

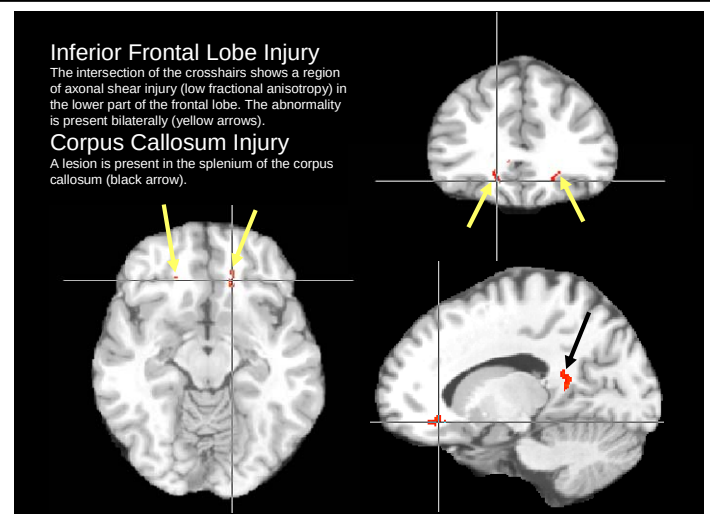
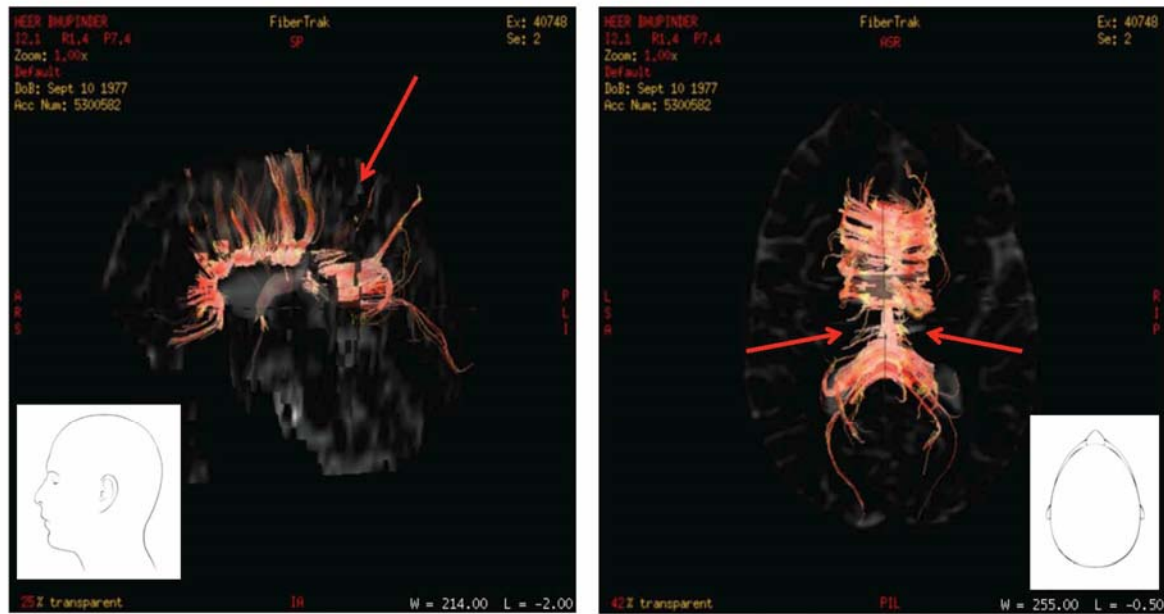


Figure 6

DTI Tractography



Red Arrows: Missing Fibers

Figure 7

Neuroscientists qualitatively assess brain connectivity using brain mapping, which entails computerized processing of digitalized electroencephalographic data known as Quantitative Electroencephalography (QEEG). QEEG depicts in topographic brain maps deviations from normative values in brain connectivity. The blue lines in Figure 8 represent mapping of the corresponding massive loss of brain connectivity in the parietal lobe depicted by the axonal loss shown by the DTI Tractography in Figure 7.

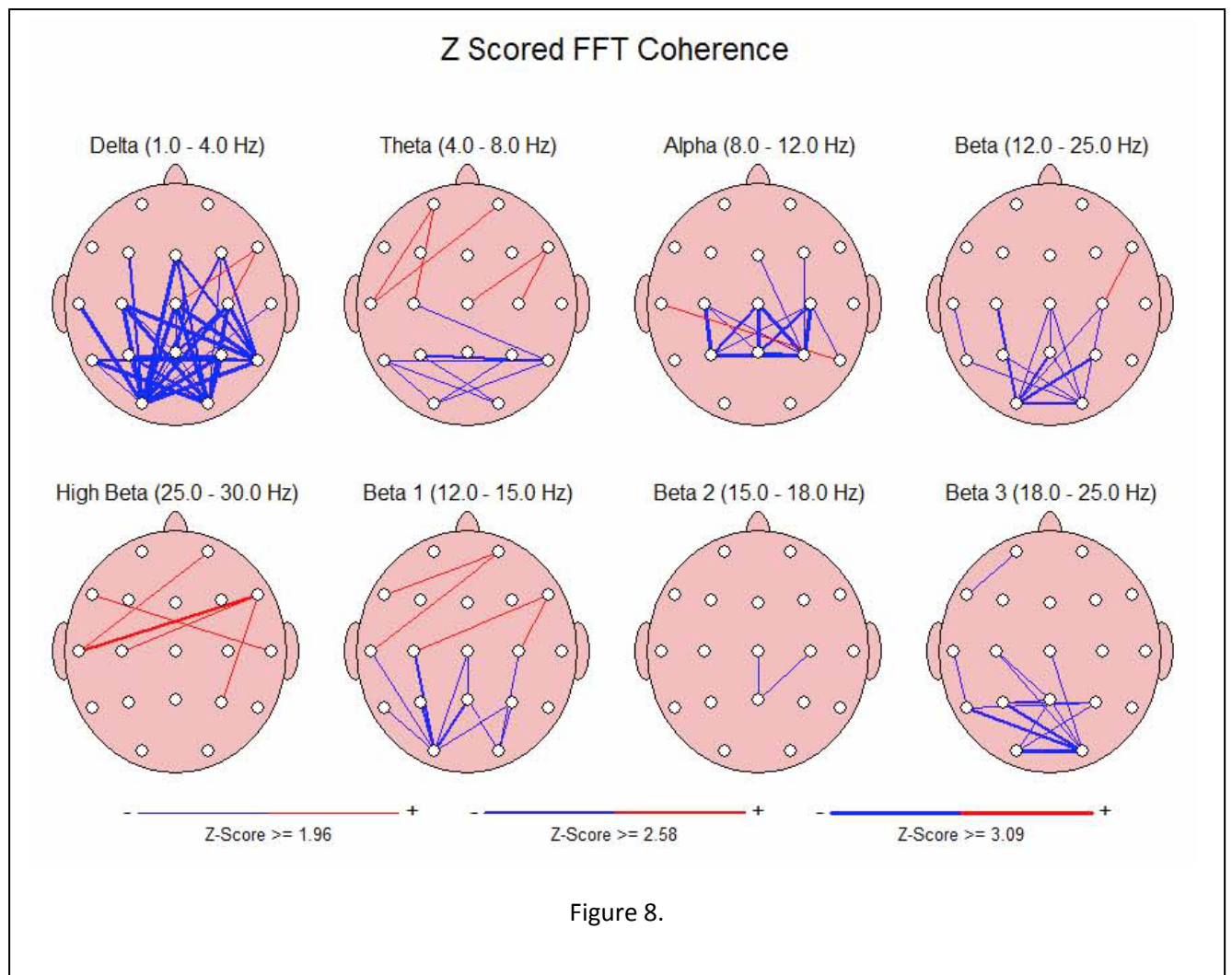
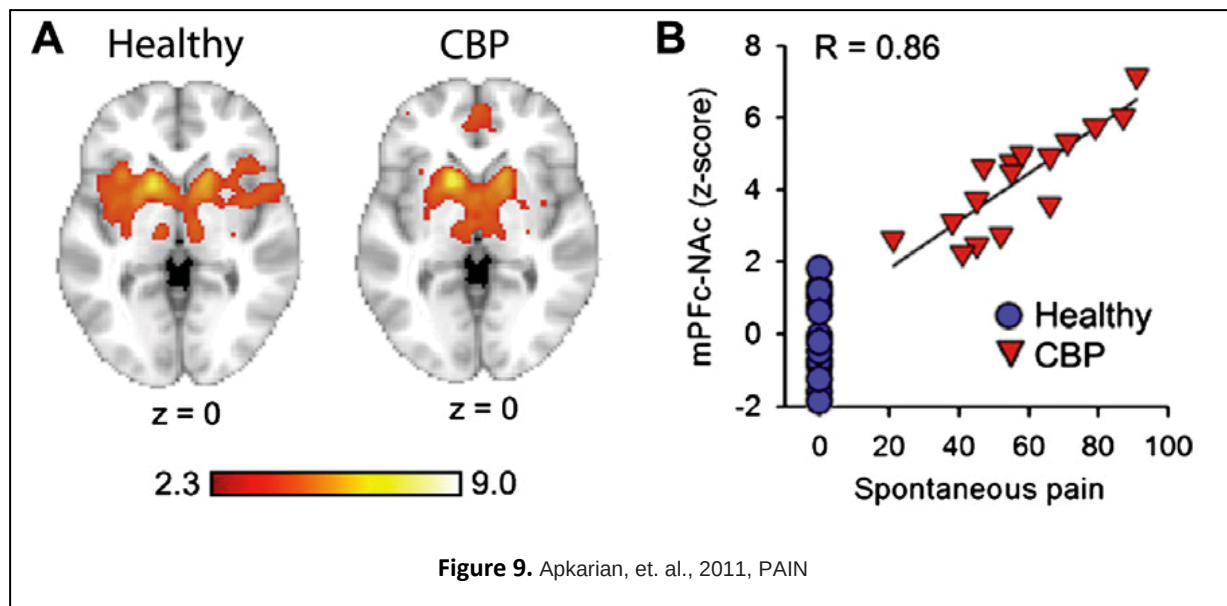
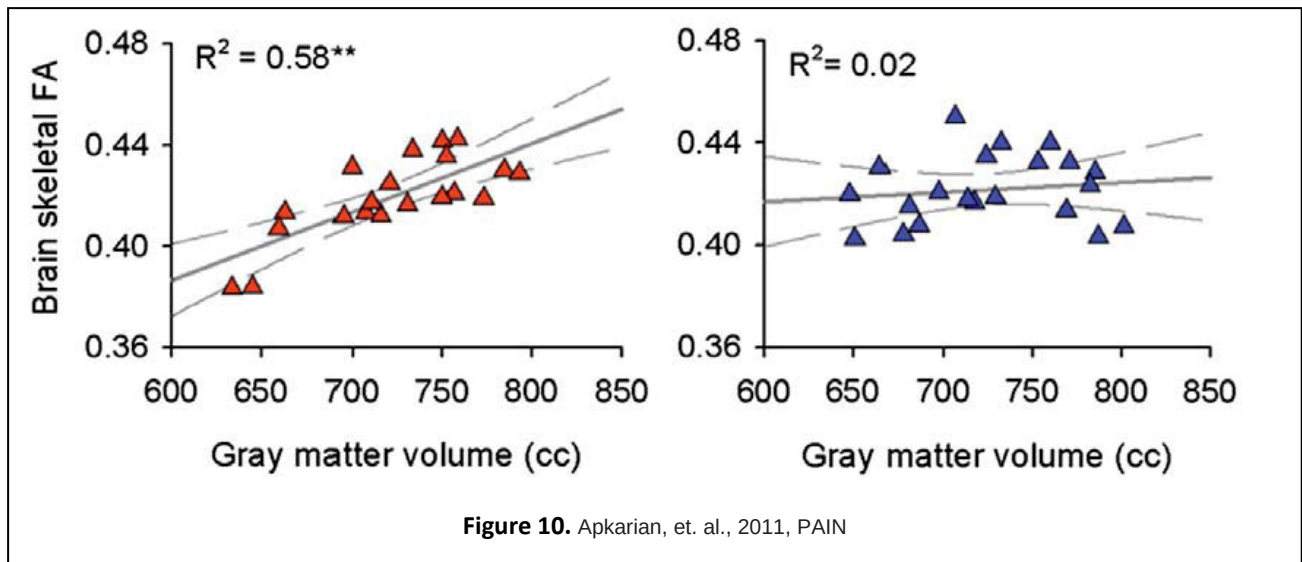


Figure 9 depicts a major change in the brain's wiring in chronic back pain patients. The extent of rewiring is shown as a closely correlated function of pain intensity. In particular, it demonstrates that as back pain increases, the connectivity between the medial Prefrontal Cortex and the nucleus accumbens increases. The increased connection between these structures markedly contrasts with the connectivity in healthy people (blue dots), serving as an additional biomarker for chronic pain.



The chart in Figure 10 shows that in healthy subjects (red triangles on left side) brain connectivity corresponds to gray matter volume: the greater the gray matter, the greater the white matter. This correspondence collapses for patients suffering from Complex Regional Pain Syndrome (CRPS). CRPS signifies a typically traumatically precipitated transformation in peripheral and central nervous system structures resulting in severe debilitating chronic pain greatly disproportionate to the inciting injury. In contrast to the healthy subjects in Figure 10, CRPS patients (who suffer the severe form of neuropathic pain, exhibited in **Koch** and **Danne**) display a marked deficiency in white matter as compared to increases in brain volume. This signifies a major disruption of connectivity caused by the chronic pain associated with CRPS. Apkarian, et. al, supra at 561

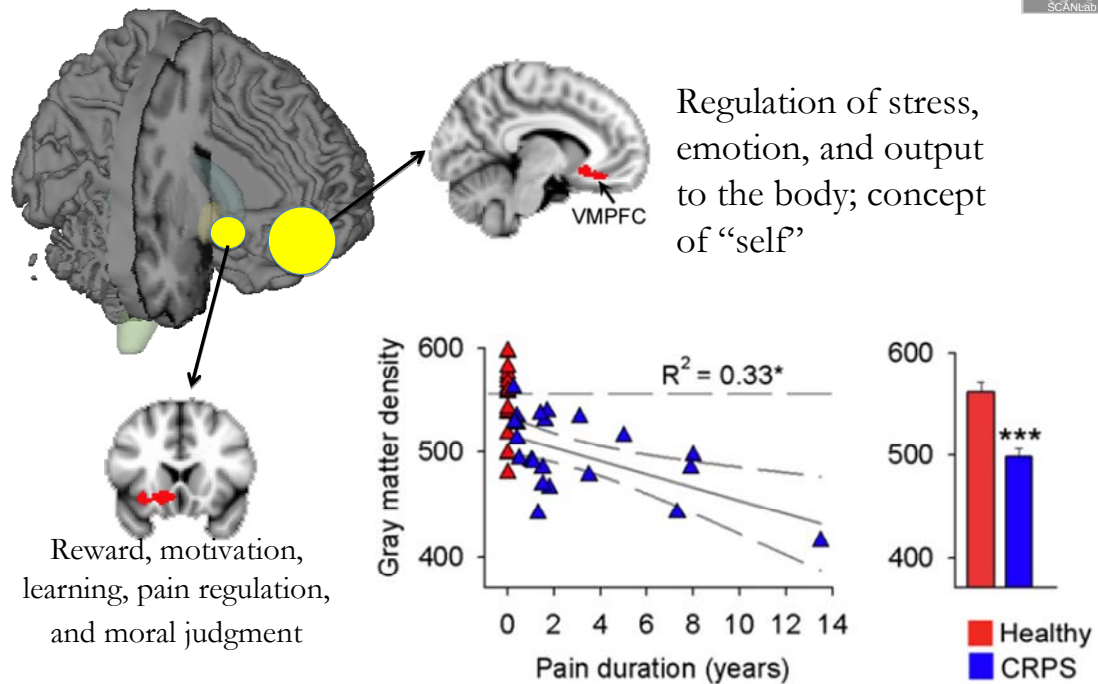
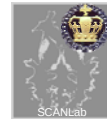


Consequences of brain damage as a result of chronic pain

Chronic pain damages the brain

As shown above, chronic pain atrophies specific regions of the brain, including the ventral medial prefrontal cortex (vmPFC), the frontal location of which is shown in Figures 11 and 14. The chart below shows that the longer CRPS continues, the more brain volume is lost in the vmPFC. This brain structure is closely associated with reward, learning, pain regulation, and moral judgments and behavior.

Chronic pain damages the brain



Geha et al., 2008, Neuron

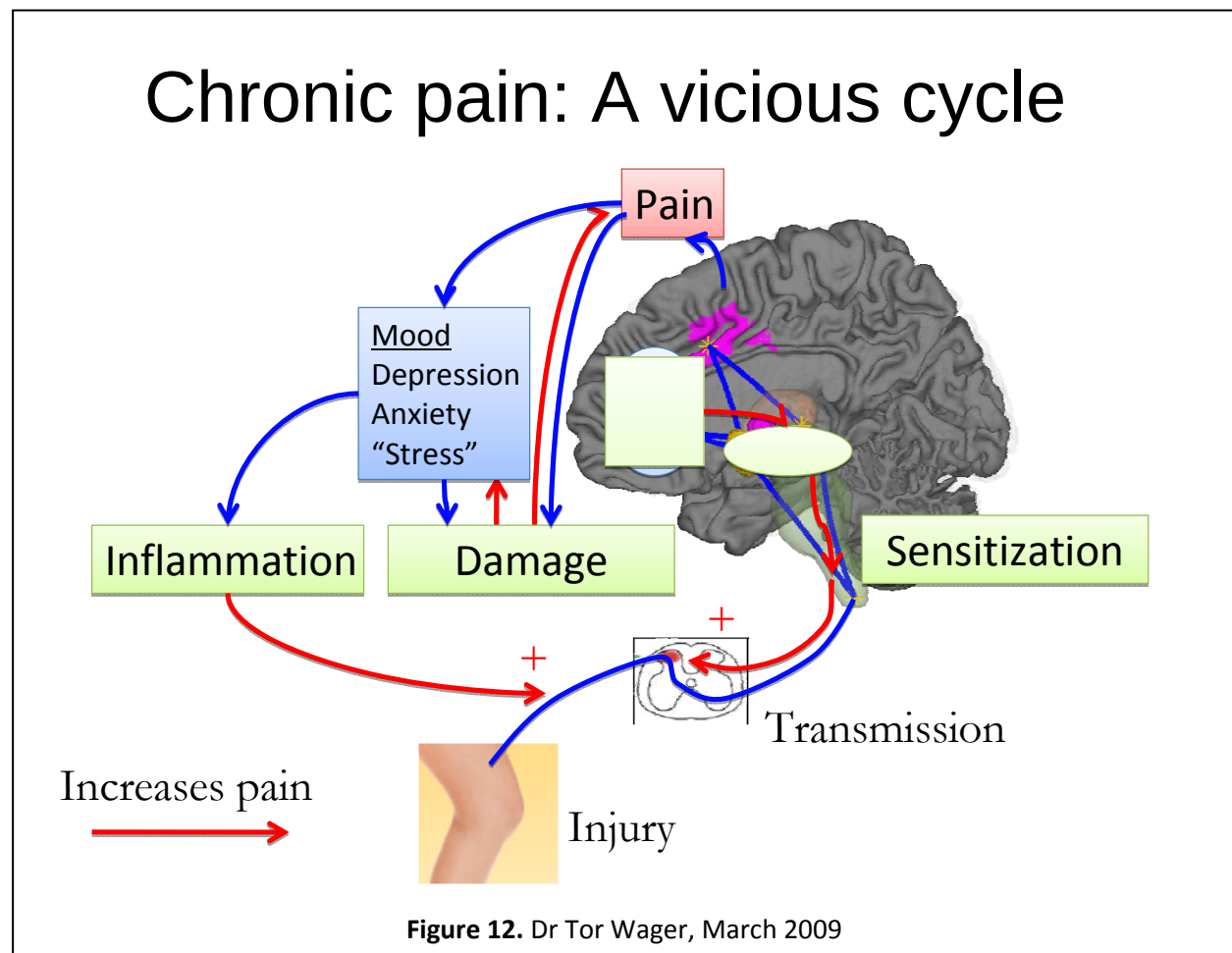
Dr. Tor Wager, March 2009

Figure 11

Sensitization

Pain potentiates pain. In other words, chronic pain alters pain processing structures in the spinal cord and brain in ways which intensify pain, increase pain's spontaneous occurrence, decrease the stimulus necessary for its provocation, and expand its duration. These consequences are associated with the vicious cycle of sensitization, wherein the brain structures associated with the experience of chronic pain produce anxiety, depression and stress that reignites inflammation in the periphery (e.g., arms and legs), bombarding the central nervous structures (spinal cord and brain) with pain signals, and over time,

transforming the central nervous system into an autonomous pain processing generator.



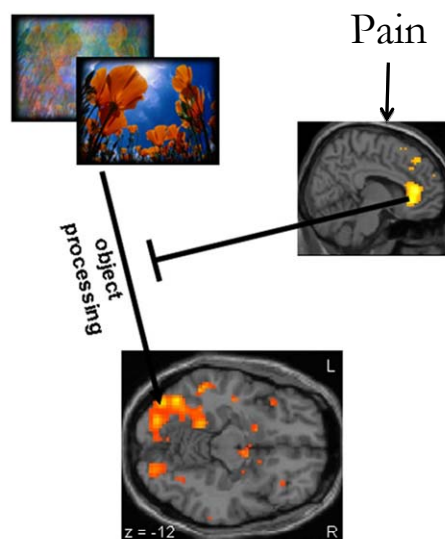
Diminished attention

Pain inflicts significant cognitive deficit by disrupting brain structures involved with attention. When pain is experienced chronically, inattention persistently compromises cognition.

Pain demands attention



- Pain makes it harder to concentrate on other things
- Same brain systems involved in attention and decision-making are co-opted by pain



Pain changes how the visual cortex responds to objects

Bingel et al., 2007, Neuron

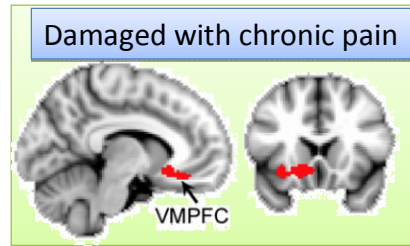
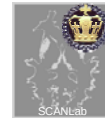
Dr. Tor Wager, March 2009

Figure 13

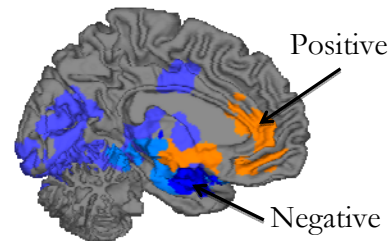
Damaging structures governing emotional regulation

As mentioned, the vmPFC is the major brain structure involved in the experience of chronic pain. It is involved in a wide spectrum of cognitive and emotional experiences depicted in Figure 13 that are subject to progressive disruption as the vmPFC is degraded by chronic pain.

A closer look at emotion regulation



These brain areas are part of the brain's machinery for representing positive value (pleasure) and using it to guide decision-making, learn from experience, and regulate negative emotion, and make moral judgments



Summary of 163 brain imaging studies of emotion

Wager et al., 2008, Handbook of Emotion

Dr. Tor Wager, March 2009

Figure 14

Altered morality

The preferential region for the registration of chronic pain - the ventral medial prefrontal cortex (vmPFC) - is also the subject of dedicated neuropsychological study relating to its role in moral judgment. Various investigators have correlated the vmPFC as an apparent source for our capacity to assign moral blame for failed attempts. In other words, people with vmPFC injury appear to be associated with a diminished ability to perceive the immoral nature of malicious acts, if those acts are not consummated. Hence, for people

with vmPFC lesions, neuropsychological investigations suggest that even a failed murder attempt might not register as a moral violation.

Neuropsychological studies also point to damage to the vmPFC as impairing the ability to discern or evaluate harmful intent, which is crucial for condemning failed attempts. Young et al., Damage to Ventromedial Prefrontal Cortex Impairs Judgment of Harmful Intent, Neuron (2010). As evidence is accumulating that this structure is important to deter moral violations, lesions in this region have been linked with criminal behavior. Damage to this region is also increasingly related to loss of empathy.

Not surprisingly, persons with vmPFC impairment have been observed to display reduced responsiveness to victims and an inability to perceive moral violations as unacceptable. Ciaramelli, et. al. Selective deficit in personal moral judgement following damage to ventromedial prefrontal cortex, Scan (2007). Lesions in this area also show significant correlation with psychopathy, an emotional dysfunction characterized by reduced guilt, empathy and lack of attachment to significant others; and anti-social behavior including impulsivity and poor behavioral control. Blair, R.J.R., The amygdala and ventromedial prefrontal cortex in morality and psychopathy, TRENDS in Cognitive Sciences (2007).

CONCLUSION

Imaging neuroscience and neuropsychological investigations regarding brain activity and responses to severe chronic pain are dissolving the historic dichotomy between the objective and subjective. In turn, a dividing line, often drawn between real and imagined, is

dissolving. Additionally, pain is being increasingly revealed as a brain phenomenon, potentially inextricable from cognitive, emotional and intentional issues, presumed to be independent from the pain experience. Consequently, it can be envisioned that various embedded medical and scientific underpinnings guiding our jurisprudence will be seriously challenged to accommodate these deeper understandings.

In sum, our law has been historically grounded on notions regarding the nature and origins of pain, free will, morality, guilt, and intention that neuroscience is progressively recasting. If truth is to serve as the guidepost of justice, the law will be challenged to integrate these neuroscientific insights and evolve accordingly.