
New Directions for Studying Brain Pathophysiology of Chronic Pain States

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Abstract

The article briefly describes two different directions that we have recently developed for studying brain pathophysiology of chronic pain. The first method uses functional magnetic resonance imaging (fMRI) adapted specifically to understand the neuronal activity of the brain that underlies chronic pain states. The second studies brain biochemistry of chronic pain patients in comparison to normal subjects using in vivo hydrogen magnetic resonance spectroscopy ($^1\text{H-MRS}$). The results we have obtained by both approaches indicate that the brain pathophysiology of chronic pain is very different from normal subjects and seems to be the same mechanisms shared with both technologies used. Both methods, and in two separate chronic pain conditions: patients with chronic reflex sympathetic dystrophy patients and patients with chronic back pain, show that the prefrontal cortex is critically involved in such chronic pain conditions.

INTRODUCTION

Pain can be broadly subdivided into two categories: acute and chronic. Acute pain is the pain experienced in everyday behavior. Acute pain is experienced with environmental stimuli that cause injury or have the potential for causing injury. Temporally it is closely related to the external stimulus and persists only for the duration of healing. It serves to protect the organism from injury and its physiological mechanisms, anatomical pathways as well as peripheral and central receptors and neurotransmitters mediating and modulating such pains are becoming well understood. Drugs acting on peripheral or central receptors, NSAIDs and morphine derivatives, properly treat acute pain.

In contrast pain that persists past the normal time of healing is called chronic pain. This time period may be as short as 1 month, but more conservatively pains persisting for longer than 6 months after the end of healing are classified chronic. Chronic pain results in an enormous medical cost. The National Chronic Pain Outreach Association estimates that chronic pain affects one in every three Americans and costs the US economy \$90 billion every year. It should be emphasized, however, that the precise estimate of the incidence of chronic pains remains unknown, and it may be even higher than the numbers quoted here. It is clearly on the rise in developed countries and highly correlated with technologically advanced lifestyles, where traumatic injuries (especially nerve injuries)

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are caused by sophisticated tools and by surgeons. There is a large medical industry involved in treating chronic pain with a wide spectrum of therapies. The approaches involve using various behavioral modification strategies, such as exercise therapy, social support groups, antidepressants, hypnosis, acupuncture, and other dubious approaches that manipulate the psychological state of the patient, rather than treat the malady. Examples of this attitude permeate the research topics presented on chronic pain at international pain meetings. For example at the 7th World Congress on Pain over a hundred pages of the proceedings were dedicated to the topic, with most attention focusing on: instrumental conditioning, behavioral assessment and therapy, coping strategies, pain beliefs as predictors, and the relation between pain and depression (Proceedings of the 7th World Congress on Pain, pg. 113-212, 1994). Current therapies for chronic pain intend to decrease the magnitude of the pain experienced, thus decreasing the suffering, rather than curing the disease, e.g. anecdotal reports indicate that physical therapy may decrease the magnitude of the spontaneous burning pain in 50% of patients suffering from chronic complex regional pain syndrome (CRPS I or RSD). The primary reason behind these nonspecific approaches to a very debilitating pathophysiological state is the lack of knowledge regarding mechanisms underlying the process and, as a consequence, a lack of effective drug therapies. The problem is complicated since in cases where there is a clearly documented peripheral or central injury most patients recover from the pain soon after the end of healing. Only a small proportion of people precipitate into a chronic pain state (10-20%, the estimate varies by type). Currently there is no scientific knowledge as to the differences between those individuals who progress into a chronic pain state versus those who do not. The primary focus of the research in this laboratory over the last 5 years has been the development of specific methodologies that can be used to study the brain physiology and chemistry of chronic pain patients. Our bias is

that chronic pain states are abnormal brain states that have not been systematically studied primarily because of a lack of adequate technologies. Below is a very brief overview of the technology of functional brain imaging using fMRI, as well as an overview of the technology used in non-invasive measurement of human brain biochemistry using $^1\text{H-MRS}$. Then we briefly describe our approaches for applying these technologies in studying chronic pain, and outline the main conclusions that we have arrived to. It should be emphasized that this work has been done by a number of students and research scientists, and with the help of a large group of collaborators and technical assistants, and normal volunteers and chronic pain patients. The latter group's participations has been instrumental in these studies and they have taken part despite the knowledge that they will experience increased pain during the studies. Also, it is important to point out that this field is moving very fast, as a result we mention here only the broad outlines of our current understanding of brain abnormalities in chronic pain.

1. OVERVIEW OF FUNCTIONAL BRAIN IMAGING USING fMRI:

small case

Functional magnetic resonance imaging is a completely non-invasive method with which scientists can indirectly monitor brain activity in awake humans while the participants are subjected to some stimulus or are instructed to perform some task. Standard MRI is used to examine the anatomy of the brain by documenting differences in magnetization of the tissue, where gray to white matter differences in fat to water ratios are used to examine anatomy. In contrast, functional MRI detects small fluctuations in tissue magnetization properties secondary to neuronal activity. Because fMRI is non-invasive and, as far as is known, totally harmless, there is no limit to the number of studies performed by fMRI, enabling the study of individual subjects and/or patients as many times as necessary. Changes in neuronal activity are accompanied by changes in cerebral blood flow, blood

volume, level of oxygenation, and tissue metabolic rate. Transient changes in these parameters produce differences in the balance between paramagnetic deoxyhemoglobin and diamagnetic oxyhemoglobin in red cells. Changes in this balance results in transient local magnetization changes, monitored directly by fMRI (Kwong, et al. 1992). This method has been used now to visualize brain activations in a very large set of stimulus and task conditions, including for thermal painful stimuli e.g. see (Davis, et al. 1998; Gelnar, et al. 1999). In such studies the participant is subjected to a stimulus-control condition, repeated many times. By assuming that the stimulus and control situations are reproducible and are different brain states, one can determine the brain regions where local magnetization is different between the two states and infer that these regions participate in the perceptual change accompanying stimulus-control sequences. This type of analysis is also used in Positron Emission Tomography (PET) where radionucleotide tagged metabolic markers are injected in the participants and the differential distribution of these radioactive markers between the two states indicate the brain regions that distinguish between the states.

Both fMRI and PET have now been used to identify brain regions involved in acute, or experimental, pain states. The results generally indicate that a number of cortical regions participate in coding acute pain. These regions usually include multiple somatosensory regions, some motor regions, insula, cingulate and prefrontal cortex. The specifics of these patterns depend on stimulus intensity, duration, size, as well as attention and anticipation (Apkarian 1998; Apkarian 1995; Bushnell, et al. 1999; Treede, et al. 1999).

2. APPLICATION OF fMRI TO STUDYING CHRONIC PAIN

There are multiple methods for acquiring functional brain activation information using fMRI. However, the blood oxygenation level-dependent contrast (BOLD-fMRI) remains the

main tool for human brain mapping studies. A number of recent studies have shown that the BOLD-fMRI signal can be treated, within some limitations, as a linear time-invariant system (Friston, et al. 1994; Cohen 1997). The main outcome of such a treatment of the BOLD-fMRI signal is the ability to characterize the hemodynamic response function of the brain. Once the time-course and shape of the brain hemodynamic response is known and assumed constant, then this information can be used to predict the expected brain response functions to arbitrary inputs. The advantage of the latter is that one is no more limited to using fixed repetitive stimulus-control paradigms.

We have taken advantage of this procedure to study chronic pain. Since chronic pain is usually uncontrollable and unpredictable, as to time-course and fluctuations in intensity, we have built a simple gadget with which the patients continuously indicate the level of their pain while we perform fMRI scans of their brain. The patient uses a continuous visual analog scale attached to the fingers, where the finger span indicates the level of pain that they are experiencing at that instant. By collecting the finger span positions together with brain images and by accounting for brain hemodynamics, we can identify the brain regional activations that are specifically involved in the ongoing conscious subjective pain that the patient is experiencing. We recently patented this approach and the New York Times (August 17, 1999) reported on it as the first patent for "an objective measure of pain." We think this approach can be generalized to study all types of chronic pain conditions, although to date we have used it to study a small group of chronic back pain patients. We hope that the patent will help us in using the approach in multiple pain clinics where independent information can be quickly collected across multiple centers regarding the brain physiology of various chronic pain states.

3. SUMMARY OF OBSERVATIONS OF ABNORMAL BRAIN ACTIVITY IN CHRONIC SYMPATHETICALLY MEDIATED CRPS I PAIN PATIENTS

In sympathetically mediated chronic pain (SMP), peripheral sympathetic blockade temporarily relieves this pain, so that related neural activity can be studied without perturbing sensory inputs. We used fMRI and thermal painful stimuli applied to the chronically painful body site, before and after sympathetic blockade, to examine the cortical network of chronic pain in such patients (Apkarian, et al. 1999). The chronic SMP state was associated with a widely spread prefrontal hyperactivity, increased anterior cingulate activity and decreased activity in the thalamus contralateral to the body side suffering from SMP, but was unrelated to sensorimotor activity. Ineffective sympathetic blocks, i.e. blocks that did not diminish the SMP pain, did not change the cortical responses to the painful thermal stimulus; while effective placebo resulted in similar responses to those of effective blocks. When the cortical responses to thermal stimuli in chronic SMP state were compared to the responses to the same stimulus in normal volunteers, the main region distinguishing between the groups was the prefrontal cortical hyperactivity in the patients. These findings provide evidence for abnormal brain responses to pain in patients with chronic SMP, which engages prefrontal/limbic networks far more extensively than in acute pain-states (Apkarian et al. 1999). It should be emphasized that this study used the standard stimulus-control repetition paradigm. Brain responses to this paradigm were compared between the chronic pain state (prior to sympathetic block) to the responses to the same stimulus paradigm, in the same patients, moments after blocking the chronic pain (post sympathetic blocks), and contrasted to responses seen in normal volunteers for the same stimulation, where a subgroup were studied in exactly the same manner as the patients, i.e. pre- and post sympathetic blocks.

4. PRELIMINARY OBSERVATIONS OF ABNORMAL BRAIN ACTIVITY IN CHRONIC BACK PAIN

The approach outlined above in 2 was used to study brain activity for ongoing chronic back pain with radicular involvement. The conscious subjective report of spontaneous chronic back pain was associated with prefrontal activity. In contrast to the CRPS patients, in this group the prefrontal activity was limited to the brain ipsilateral to the sciatic nerve involved in back pain and included mainly the orbital portion of the prefrontal cortex (Krauss, et al. Soc. Neurosci. Abstract 1999; Apkarian, et al. 2000).

5. OVERVIEW OF MEASURING BRAIN BIOCHEMISTRY NON-INVASIVELY

Nuclear magnetic resonance spectroscopy or MR spectroscopy (MRS) is a method used in chemistry and physics laboratories for the analysis of molecular interactions and for the identification of chemical compounds. Recently this approach has been adapted for in vivo spectroscopic analysis of the brain which has direct implications to the clinical assessment of the brain biochemistry non-invasively. The key to this method is to localize MR signals to a specific volume, an approach commonly used in anatomic MRI. Since in all biological tissues including the brain water is the predominant chemical, observing weak signals from metabolites with concentrations tens of thousands of times smaller than water requires methods for suppressing the water signal. Advances in MR technology in automating voxel positioning and suppressing the water signal have made in vivo MRS a relatively simple approach that can be used in studying brain chemistry see (Salibi and Brown 1998). MRS can be viewed as a non-invasive method of performing brain biopsies. MRS can be used to study the spectra of compounds in the brain that contain odd-numbered nuclei, such as ^1H , ^{17}Li , ^{13}C , ^{17}O , ^{19}F , and ^{31}P . This methodology has the potential of revolutionizing our understanding of human pathological brain states.

In this sense it has been adapted and most extensively used in the neurology and psychobiology research e.g. see (Nasrallah and Pettegrew 1995, Salibi and Brown 1998). Spectra obtained with ^{31}P enable the measurement of high-energy phosphates such as adenosine tri-, di-, and monophosphates and creatinine phosphate. ^{31}P measurements have been obtained in patients suffering from stroke, various types of brain tumors, multiple sclerosis, Alzheimer's disease, and epilepsy. Proton spectra enable measurement of concentrations of a large number of metabolites and excitatory and inhibitory neurotransmitters. The latter method also has been used to examine the brain biochemistry of various patient populations similarly to the ^{31}P spectra see (Salibi and Brown 1998).

6. APPLICATION OF ^1H -MRS TO STUDYING CHRONIC PAIN

We have used proton spectroscopy to study the brain chemistry in chronic back pain patients and compare them to age and sex matched normal subjects. Six separate single-voxel measurements were done in 6 different left brain regions (Grachev and Apkarian 2000; Grachev, et al. 2000). The main hypothesis tested in this study was that, in chronic pain patients, brain areas that show hyperactivity in fMRI studies should also show abnormal brain chemistry. This was tested across three brain regions: thalamus, cingulate cortex and dorsolateral prefrontal cortex, where we quantified the concentrations of N-Acetyl aspartate (NAA), choline (Cho), glutamate (Glu), glutamine (Gln), (-Aminobutyric acid (GABA), myo- and scyllo-inositol complex (Ins), glucose (Glc) and lactate (Lac) relative to the concentration for creatine/phosphocreatine complex (Cr), which is commonly used as an internal standard. All chronic back pain subjects underwent clinical evaluation and perceptual measures of pain and anxiety. We show that chronic back pain alters the human brain chemistry. Reductions of N-acetyl aspartate and glucose were demonstrated in the dorsolateral prefrontal cortex. Cingulate,

sensorimotor, and other brain regions showed no chemical concentration differences. In chronic back pain, the interrelationship between chemicals, within and across brain regions was abnormal, and there was a specific relationship between regional chemicals and perceptual measures of pain and anxiety. These findings provide direct evidence of abnormal brain chemistry in chronic back pain, which may be useful in diagnosis and future development of more effective pharmacological treatments. Therefore, this study indicates not only that the brain chemistry is different in chronic pain patients but also that the abnormal changes reflect the specific perceptual parameters that these patients suffer from. These are relatively preliminary results with tantalizing implications. Based on these results we have applied for a patent to use the technique for identifying chronic pain and for tracking changes in pain during therapy. Again we hope that obtaining the patent will greatly expedite the dissemination of the technique to the clinical arena, where multi-center studies can extend these findings and demonstrate the specific use of the method in understanding chronic pain conditions.

7. CONCLUSIONS

Above we briefly outline the methods recently advanced in our laboratory that are enabling the study of the brain pathophysiology of chronic pain. These results have given us a real sense of excitement since for the first time we are able to differentiate between various pathophysiologies of chronic pain based on the functional and chemical state of the brain. We hope that these approaches will very quickly translate into applications in the clinical setting providing objective tools with which patients with chronic pain disabilities may be diagnosed and treated based on solid scientific approaches.

Visit our website (<http://alpha.nmrlab.hcssyr.edu/pain>) for more details regarding the currently ongoing studies in our laboratory, as well as a more detailed meta-analysis

of brain imaging studies of pain.

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