Published in final edited form as:
J Neuroimmune Pharmacol. 2013 June ; 8(3): 448–451. doi:10.1007/s11481-013-9457-5.

Imaging Biomarkers and the Role of Neuroinflammation in Neuropathic Pain

Linda Chang, MD, MS, FAAN, FANA,
University of Hawaii, Honolulu, HI

Mark S. Cooper, PhD, and
University of Washington, Seattle, WI

Vincent P. Clark, PhD
University of New Mexico, Albuquerque, New Mexico

Abstract

The papers from this thematic issue followed a translational research workshop, *Imaging Neuroinflammation and Neuropathic Pain*, that focused on the search for neuroimaging biomarkers to assess neuroinflammation associated with neuropathic pain. The topics covered in this issue include overviews of the historical and current knowledge regarding neuropathic pain, the potential mechanisms involved, the often under-recognized clinical presentations that can delay diagnosis, the various neuroimaging techniques that have been applied to evaluate neuropathic pain and neuroinflammation, to case series illustrating novel treatments of neuropathic pain. Furthermore, the use of telemedicine to disseminate knowledge and improve the diagnosis and treatment of pain syndromes is also discussed.

The collection of papers in this issue resulted from a translational research workshop on *Imaging Neuroinflammation and Neuropathic Pain*, which was held at the Santa Ana Pueblo north of Albuquerque, New Mexico in October 2011, and was sponsored by the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA). The goals of the workshop were to explore and share knowledge regarding biomarkers using imaging and other techniques that could lead to better understanding of how neuroinflammation and its co-morbidities might contribute to neuropathic pain syndromes, such as Complex Regional Pain Syndrome (CRPS).

Participants included individuals from academic institutions, national research laboratories, pharmaceutical companies, and a number of patient organizations. Seven patient support organizations also were represented at the meeting: RSDSA, American RSD Hope, Power of Pain Foundation, the Southern Kentucky RSD Support Group, TREND (Trauma Related Neuronal Dysfunction Knowledge Consortium), PARC (Promoting Awareness of RSD and CRPS), and the Korean CRPS Association. Also represented was the American Autoimmune Related Diseases Association. The missions of these patient organizations, which represent support networks for tens of thousands of individuals living with CPRS and related neuropathic pain and autoimmune conditions, provided the impetus for this workshop.

Linda Chang, MD, MS, FAAN, FANA - University of Hawaii, Section Editor, Biomarker and Bioimaging, *Journal of Neuroimmune Pharmacology*
Mark S. Cooper, PhD - University of Washington, Board of Directors, Chair Scientific Advisory Committee, RSDSA, Guest Editor
Vincent P. Clark, PhD - University of New Mexico, Scientific Advisory Committee, RSDSA, Guest Editor

The oral presentations at the meeting covered cellular dynamics underlying neuroinflammation, imaging methods that could assess neuroinflammation, pain management, detecting activated glia, functional changes in the brains of patients with chronic pain, and integrating neuroimaging methods to improve diagnosis, treatment, and patient support. An overview of the scientific issues discussed and streaming videos of workshop talks/discussions are available on the workshop website: http://www.rsds.org/imaging_neuroinflammation_conference.html.

Linda Watkins, PhD, from the University of Colorado, delivered a keynote address, entitled Glial and Endothelial Dysregulation of Pain, Opioid Actions, and Drugs of Abuse – the Need for Imaging is Great! Dr. Watkins described how neuroimmune cells, known as microglia, can become ‘primed’ by nervous system injury or stress. When the nervous system becomes assaulted a second time, these cells undergo genetic changes, and become ‘activated’. This is part of a normal defense and repair process in the nervous system. However, in these rodent models, microglial activation in their nervous system leads to aberrant neuronal firing, and the genesis of neuropathic pain.

Dr. Watkins also emphasized that physicians need to think about the cells that line blood vessels in the central nervous system. These endothelial cells release chemical signals that can initiate and sustain neuroinflammation and neuropathic pain. Research is now directed at why glial cells and/or endothelial cells remain activated in certain states of chronic pain. Dr. Watkins emphasized that to develop better therapeutic approaches to attenuate these cellular drivers of neuroinflammation, clinicians and researchers need to visualize what is occurring (structurally and functionally) in the inflamed human nervous system.

Clearly, there is a need to better understand the processes associated with neuroinflammatory lesions, both *in vitro* and *in vivo*. There is also a need to examine and monitor the roles of neuroinflammation at the onset, during progression, maintenance and remission of neuropathic pain, using non-invasive neuroimaging techniques. Changes in cellular processes may lead to changes in behavior, both at the organ and organismic levels. The personal experience of pain is linked to these hidden cellular dynamics. To advance pain medicine, as well as the clinical differential diagnosis of neuroinflammation, these cellular dynamics must become visible and measureable through neuroimaging and other visualization methods.

Dr. Carl Saab, Ph.D., from Brown University School of Medicine, delivered the second keynote talk on Visualizing the Complex Dynamics of Neuropathic Pain. To fully understand the experience of neuropathic pain, Dr. Saab emphasized that we need to think beyond neurons and linear neural pathways, and concentrate on the concept of an altered “neuromatrix”. For instance, dysrhythmias (altered brain oscillations) that may involve the thalamus and the somatosensory cortex have been found in CRPS patients. Timing errors in reciprocal signaling within the brain may be part of the transduction of CRPS pain. Changes in brain connectivity patterns are also part of the functional changes found within the neuraxis. Fortunately, many of these functional changes appear to be reset through medical therapies. Others changes, however, appear to persist.

The majority of the speakers from this workshop contributed to this special issue. In addition to an introductory paper with historical perspectives provided by the Guest Editors, Mark Cooper, PhD, Vince Clark, PhD and Linda Chang, MD, MS (Cooper et al. 2013), three papers provide different overview perspectives on the field of neuropathic pain. Our second keynote speaker Carl Saab, Ph.D., reviews various neuroimaging techniques that documented structural and morphological remapping of brain circuitry under conditions of chronic pain, as well as aberrant neurophysiology in the brain that confirms neuroplasticity

at the cellular and molecular levels (Saab 2013). He also highlights some emerging methods for pain treatment, such as deep brain stimulation. Ukpong Eyo, PhD and Michael Dailey, PhD provide an overview of the pathophysiology from the cellular and preclinical perspectives, including the diverse roles of microglia in neural development and plasticity, behavior, and neuronal-microglia communication, and how imaging will be essential for further understanding of these various mechanisms (Eyo and Dailey 2013). Karen Binkley, MD, FRCPC, is a clinical immunologist who provides an autobiographical account of her journey with CRPS, and describes the need for Improving the Diagnosis and Treatment of CRPS: an Under-recognized Neuroinflammatory Disorder (Binkley 2013).

The next four papers focus on the current knowledge and possible mechanisms associated with neuropathic pain and CRPS. Mark Cooper, PhD and Vince Clark, PhD, provide a theoretical discussion of how neuroinflammatory foci in the CNS can act as both structural and functional lesions (Cooper and Clark 2013). These neuroinflammatory lesions can potentially produce diverse neurological and neuropsychiatric symptoms that have long been considered to be psychosomatic or psychogenic in etiology. The second paper in this set is by Clas Linnman, PhD, Lino Becerra, PhD, and David Borsook, MD, PhD (Linnman et al. 2013). These authors reviewed current concepts in CRPS, including how the neuroinflammatory processes spread from a focal peripheral lesion (e.g., a minor physical injury) to many specific and diverse brain regions, and how the inflammatory feedback loop may perpetuate chronic pain. They reviewed the topic involving each anatomical region based on neuroimaging studies and highlighted potential mechanisms that are suitable for future investigations of the pathophysiology of CRPS. For instance, they described functional MRI studies that showed long-term changes in brain regions associated with pain processing in children with CRPS, even after they were no longer experiencing allodynia. The recurrence of neuropathic pain in certain individuals, even after the pain had ceased with effective treatment, illustrates the importance of understanding long-term impacts of neuroimmune processes. The third paper is by Jacqueline Bailey, PhD, CPsychol, Sara Nelson, PhD, Jenny Lewis, PhD, DipCot and Candida S McCabe, PhD, RGN, who delineated the imaging and clinical evidence of sensorimotor problems in patients with CRPS (Bailey et al. 2013). Specifically, they discussed the clinical syndrome and possible mechanism(s) of altered sensory processing (altered body perception) and cortical reorganization in patients with CRPS, as supported by imaging findings from positron emission tomography (PET) and magnetoencephalography (MEG). They also reviewed current pharmacological and non-pharmacological therapies (e.g., graded motor imagery, mirror visual feedback, and electrical sensory discrimination therapy). The fourth paper that describes possible mechanism(s) for neuropathic pain is by Richard Banati, PhD, who was the first to use PET to demonstrate increased thalamic uptake of carbon-11(R)PK-11195 (which binds to activated microglia) in patients with peripheral nerve injury, even in those who had the injury for many years (Banati 2001). He discussed and reviewed studies that used the peripheral benzodiazepine receptor ligands, including the ligand for the translocator protein (TSPO), which can be used to monitor brain inflammation and reactive gliosis and may be a therapeutic target also (Banati et al. 2013).

Three other papers specifically reviewed different neuroimaging techniques used to evaluate neuroinflammation. Linda Chang, MD, MS, FAAN, Sody Munsaka, PhD, Stephanie Terry-Kraft, PhD and Thomas Ernst, PhD reviewed the clinical applications of MR spectroscopy in various neuroinflammatory disorders, including multiple sclerosis, HIV and other viral infections that affect the brain, neurodegenerative disorders, psychostimulant abuse, traumatic brain injury and neuropathic pain (Chang et al. 2013). Although few studies have used MRS to assess neuropathic pain, the non-invasiveness and accessibility of the technique provide great potential for future investigations of pain syndromes. Karen Davis, PhD and Massieh Moayedi, PhD reviewed findings from functional MRI studies, using

BOLD fMRI (both during activate stimulation and resting state), perfusion MRI, structural MRI and diffusion tensor imaging, that demonstrated altered brain activity and brain structure in different pain states (Davis and Moayedi 2013). Since recent studies indicate that some structural brain abnormalities associated with chronic pain are reversible following effective pain treatment, and changes associated with pain states are highly individualized, these MRI techniques may guide future personalized treatments for patients with chronic pain. How pain is characterized and conceptualized ultimately influences medical therapies, patient-practitioner relationships, as well as societal support of pain management.

Mera Barr, PhD, Faranak Farzan, PhD, Karen Davis, PhD, Paul Fitzgerald, MBBS, MPM, PhD, FRANZCP, and Zafiris Daskalakis, MD, PhD FRCP(C) discussed the use of transcranial magnetic stimulation (TMS) and EEG to examine the contribution of cortical inhibition neurophysiology to chronic pain (Barr et al. 2013). TMS can assess decreased cortical inhibition associated with impaired GABAergic function while EEG may detect abnormal gamma oscillations; both are found in chronic pain patients. Therefore, treatment with repetitive TMS may be useful in these patients, and that the combination of TMS-EEG also may be a potential non-invasive approach to classify, diagnose and treat chronic pain.

Two case series reports illustrate not only the clinical courses of patients with chronic pain syndrome, but also introduce novel treatment approaches for these patients. Anthony Sims, DDS and Gary Demerjian, DDS presented ten case histories that illustrate how customized oral orthotics can be used to realign the maxilla and mandible to provide rapid relief of debilitating sensory and movement disorders, including Tourette's Syndrome, cervical dystonia, blepharospasm, and Parkinson's Disease (Sims and Demerjian 2013). These cases are presented with accompanying video demonstrations in the supplementary material. Decompression of inflamed auriculotemporal nerve endings located in retrodiscal tissues of the temporomandibular joint may underlie part of the therapeutic actions of these oral orthotics. Sims and Demerjian discussed how injury to the auriculotemporal nerve might establish secondary sites of neuroinflammation in the brainstem via remote neuroimmune activation. In another paper, Pradeep Chopra, MD and Mark Cooper, PhD discuss the use of low-dose naltrexone for the treatment of CRPS in two patients who were refractory to multiple other medications and treatment modalities (Chopra and Cooper 2013). Naltrexone is well-known glial attenuator, which is an antagonist of the toll-like receptor, TLR-4, which has already shown efficacy for the treatment of pain in fibromyalgia patients (Younger and Mackey 2009). They described the therapeutic successes of using low dose naltrexone in two CRPS patients, who achieved suppression of allodynia, vasomotor abnormalities, and remission of dermal ulcerations and dystonias.

Lastly, given the complexity of CRPS and other chronic pain syndromes, the diagnoses are often delayed and required validations from multiple specialists and techniques. Therefore, not only would an integrated and multi-disciplinary clinic be needed to assess and treat these patients, the use of modern telecommunications could provide dissemination and sharing of knowledge and expert advice to the community, especially those in the rural settings. Joanna Katzman, MD, MSPH describes how her enormously successful Project ECHO Pain Team leverages tele-health technologies to connect clinician specialists and primary care providers, increase awareness of disease mechanisms and treatment, and to create knowledge networks to improve clinical care for patients with chronic pain conditions, such as CRPS (Katzman 2013).

We thank the numerous contributors to this volume, as well as the private and corporate sponsors of the *Imaging Neuroinflammation and Neuropathic Pain* workshop, which provided the opportunity for the speakers to share their knowledge and ultimately making

this publication possible. We also thank Dr. Howard Gendelman, Editor-in-Chief of this journal, for his continued support and guidance in assembling this thematic issue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

Bailey J, Nelson S, Lewis J, McCabe CS. Imaging and Clinical Evidence of Sensorimotor Problems in CRPS: Utilizing Novel Treatment Approaches. J Neuroimmune Pharmacol. Oct 11.2013 2012 Epub ahead of print.

Banati RB, Cagnin A, Brooks DJ, Gunn RN, Myers R, Jones T, Birch R, Anand P. Long-term trans-synaptic glial responses in the human thalamus after peripheral nerve injury. Neuroreport. 2001; 16:3439–3442. [PubMed: 11733686]

Banati, et al. TSPO Review. 2013.

Barr MS, Farzan F, Davis KD, Fitzgerald PB, Daskalakis ZJ. Measuring GABAergic Inhibitory Activity with TMS-EEG and Its Potential Clinical Application for Chronic Pain. J Neuroimmune Pharmacol. Jun 29.2013 2012 Epub ahead of print.

Binkley KE. Improving the Diagnosis and Treatment of CRPS: Insights from a Clinical Immunologist's Personal Experience with an Underrecognized Neuroinflammatory Disorder. J Neuroimmune Pharmacol. May 16.2013 2012 Epub ahead of print.

Chang L, Munsaka S, Kraft-Terry S, Ernst T. Magnetic Resonance Spectroscopy Studies of Neuroinflammation in Brain Disorders. J Neuroimmune Pharmacol.

Chopra P, Cooper MS. Treatment of Complex Regional Pain Syndrome using Low-Dose Naltrexone: Two Case Studies. J Neuroimmune Pharmacol. 2013

Cooper MS, Clark VP. Neuroinflammation, Neuroautoimmunity, and the Co-Morbidities of Complex Regional Pain Syndrome. J Neuroimmune Pharmacol. Aug 25.2013 2012 Epub ahead of print.

Cooper MS, Clark VP, Chang L. Imaging Neuroinflammation and Neuropathic Pain: Historical Perspectives and Current Knowledge. J Neuroimmune Pharmacol. 2013

Davis KD, Moayedi M. Central Mechanisms of Pain Revealed Through Functional and Structural MRI. J Neuroimmune Pharmacol. Jul 24.2013 2012 Epub ahead of print.

Demerjian GG, Sims AB. Temporomandibular Joint Dysfunction, Trigeminal Nerve Inflammation, and Biomechanical Dental Treatments for the Suppression of Neurological and Neuropsychiatric Symptoms. J Neuroimmune Pharmacol. 2013

Eyo UB, Dailey ME. Microglia: Key Elements in Neural Development, Plasticity, and Pathology. J Neuroimmune Pharmacol. Jan 27.2013 2013 Epub ahead of print.

Katzman JG. Making Connections: Using TeleHealth to Improve the Diagnosis and Treatment of Complex Regional Pain Syndrome, an Underrecognized Neuroinflammatory Disorder. J Neuroimmune Pharmacol. Oct 2.2013 2012 Epub ahead of print.

Linnman C, Becerra L, Borsook D. Inflaming the Brain: CRPS a Model Disease to Understand Neuroimmune Interactions in Chronic Pain. J Neuroimmune Pharmacol. Nov 29.2013 2012 Epub ahead of print.

Saab C. Visualizing the Complex Brain Dynamics of Chronic Pain. J Neuroimmune Pharmacol. Jun 10.2013 2012 Epub ahead of print.

Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. Pain Med. 2009; 10:663–672. [PubMed: 19453963]