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INVITED REVIEW

Inflaming the Brain: CRPS a Model Disease to Understand Neuroimmune Interactions in Chronic Pain

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Abstract We review current concepts in CRPS from a neuroimaging perspective and point out topics and potential mechanisms that are suitable to be investigated in the next step towards understanding the pathophysiology of CRPS. We have outlined functional aspects of the syndrome, from initiating lesion via inflammatory mechanisms to CNS change and associated sickness behavior, with current evidence for up-regulation of immunological factors in CRPS, neuroimaging of systemic inflammation, and neuroimaging findings in CRPS. The initiation, maintenances and CNS targets implicated in CRPS and in the neuro-inflammatory reflex are discussed in terms of CRPS symptoms and recent preclinical studies. Potential avenues for investigating CRPS with PET and fMRI are described, along with roles of inflammation, treatment and behavior in CRPS. It is our hope that this outline will provoke discussion and promote further empirical studies on the interactions between central and peripheral inflammatory pathways manifest in CRPS.

Keywords CRPS · Cytokine · fMRI · PET · Glia · Astrocyte · Brain · Inflammation

Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic pain syndrome following nerve injury (either defined or subclinical) that may evolve into a number of other manifestations over time that implicate brain changes. These manifestations include hypersensitivity to noxious somatosensory stimuli (hyperalgesia), pain to non-noxious stimuli (allodynia), spreading pain (spontaneous and evoked) (Maleki et al. 2000) that involves undamaged regions in the affected limb to the opposite limb and other parts of the body (e.g., from lower extremities to upper extremities), swelling and skin discoloration, autonomic changes such as coldness, poor circulation, abnormal sweating, hemi-inattention, motor changes (movement disorders including tremor and focal dystonias) as well as changes in emotional and cognitive function. CRPS type 1 occurs without detectable nerve trauma, and minor injuries or a limb fracture often precede the onset. CRPS type 2 CRPS develops following injury of a major peripheral nerve, but the subtype distinction is often not made in the scientific literature (Watts and Kremer 2011). However, even clinically, the differences may be limited because microscopic nerve damage is not possible to detect. The estimated overall incidence rate of CRPS was 26.2 per 100,000 person years with females being affected 3-4 times more than males (de Mos et al. 2007), usually occurring from peripheral nerve injury.

Clinically, CRPS patients are profoundly affected with decreased ability to participate in normal activities of daily living. Following nerve injury a cascade of events is initiated that include peripheral inflammation (Tal 1999) and potentially increased CNS inflammation. The peripheral changes include immune-related genes and members of the complement system (Liang et al. 2012) as well as presence of several pro-inflammatory cytokines (Strong et al. 2012). A number of etiopathophysiological processes have been suggested, including cytokine imbalance and neuroinflammation (Cooper and Clark 2012). Here, we evaluate lines of evidence from animal and human research indicative of focal and disseminated effects of cytokine alterations that may affect *brain circuits* through changes on glia, astrocytes and neurons.

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CRPS the model: from peripheral nerve damage to diffuse CNS changes

The behavior of sick animals and humans is recognized as part of a motivational system that priorities seeking quiescence to facilitate recovery (Dantzer and Kelley 2007; Hart 1988). Cytokines are signaling proteins secreted by peripheral immune cells, microglia, astrocytes and neurons that signal the detection of pathogens (Galic et al. 2012). An overproduction of cytokines may result in disease (Czura and Tracey 2005; Pavlov and Tracey 2006). The inflammatory reflex is "*a physiological pathway in which the autonomic nervous system detects the presence of inflammatory stimuli and modulates cytokine production*" (Czura and Tracey 2005). From a functional perspective, the inflammatory processes in traumatic events induce central and peripheral sensitization to increase pain awareness and limit further injury.

Inflammatory cytokines are associated with common symptoms of sickness including loss of appetite, sleepiness, withdrawal, fatigue and pain sensitivity in both rodents (Maier et al. 1993) and humans (Benson et al. 2012). For example, in the common cold, headaches and sinus pain may originate from nasal congestion and pressure changes, but inflammatory mediators within the sinuses may also trigger sensitization of pain or directly stimulate trigeminal nerves (Eccles 2005). Moreover, muscle aches (myalgia) occurs in around 50% of patients with the common cold (Eccles et al. 2003). Of the possible mechanism for this increase in myalgia, the perhaps most studied is that circulating cytokines increase the production of prostaglandin E2 in muscle tissue, thereby stimulating peripheral sensory neurons and inducing hyperalgesia (Baracos et al. 1983). A second route for increased pain responses is via cytokine activation of microglial cells and/or macrophages in the spinal cord and dorsal root ganglion (Yoon et al. 2012). *A third route is via direct cytokine effects on brain excitability.* In other conditions such as depression it has been postulated that the depressed state may activate peripheral mechanisms resulting in an up-regulation of systemic levels of inflammation and peripheral inflammation may exacerbate depression (Messay et al. 2012). Here, we explore the potential for such a bi-directional process as a model for CRPS.

Evidence for up-regulation of immunological factors in CRPS

There is mixed evidence for pro-inflammatory cytokines profiles in CRPS (Birklein and Schmelz 2008). Van de Beek et al. (2001) found no difference in the production of pro- and anti-inflammatory cytokines when comparing 26 severely affected CRPS patients and 20 healthy controls. However, others have found increased levels of IL-8, IL2, TNF-α receptors and substance P (Maihofner et al. 2005b; Schinkel et al. 2006; Kramer et al. 2011; Uceyler et al. 2007). Case reports of blocking TNF-α with the antibody infliximab have shown success in treatment CRPS (Bernateck et al. 2007), and there is accumulation of TNF-α antibodies in affected hands of patients with early-stage CRPS, but not in clinically unaffected hands or in late-stage CRPS (Bernateck et al. 2010).

Evidence for CNS alterations in CRPS

CRPS is thought to involve peripheral and central sensitization of neuronal function (Janig and Baron 2002), and several recent neuroimaging studies have demonstrated changes in brain function. Table 1 provides an overview of the literature, as per July 2012. We performed an activation likelihood estimate (ALE) of the above studies to provide an overview of CNS structures that have been consistently implicated in CRPS. An ALE analysis determines the convergence of activation foci, providing a quantitative meta-analytical estimate of activation probability in the form of a brain map (Eickhoff et al. 2009). As there are still only a handful of studies on alteration in brain activity in CRPS, the resulting ALE maps should be considered preliminary. Results indicate that CRPS patients commonly display alteration in the bilateral parietal lobe, somatosensory cortex, mid insula, mid cingulate and the superior medial frontal gyrus. See Table 2 for details.

Evidence for inflammation effects on CNS processing

In the last years, several studies have used functional MRI to investigate how systemic inflammation influences brain function. We view this evidence, although not obtained in CRPS patients, as a potential overlapping mechanism:

Typhoid vaccination (Brydon et al. 2008; Harrison et al. 2009a, b), endotoxin administration (Eisenberger et al. 2009, 2010; Inagaki et al. 2012; Kullmann et al. 2012), and psychological manipulations — social stress (Slavich et al. 2010) and grief (O'Connor et al. 2009) — have been used to induce systemic inflammation and determine brain reactivity. Other studies include the effects of interferon-alpha treatment on brain function in in patients infected with hepatitis C virus (Capuron et al. 2005), and the effects of an antigen challenge TNF alpha production and brain responses in asthma patients (Rosenkranz et al. 2005). Moreover, the glucose metabolism of the cingulate and insula is altered by endotoxin administration (Hannestad et al. 2012b). Also for these studies, we performed an ALE analysis, to identify brain regions that have been

Table 1 Neuroimaging studies of CRPS

Reference	Subjects	Modality	Paradigm	Key results
(Freund et al. 2010)	10 CRPS, 15 HC	1.5T fMRI	Electrical pain	increased PCC activation, decreased opercular activation
(Freund et al. 2011)	10 CRPS, 15 HC	1.5T fMRI	Electrical pain + cogn. suppression	PAG and cingulate less active during suppression of pain, regardless of stimulation site
(Gieteling et al. 2008)	8 CRPS, 17 HC	3T fMRI	Motor execution +motor imagining	imaginary, but not actual movement showed reduced premotor, prefrontal cortex, and anterior insula activation
(Gustin et al. 2010)	20 CRPS	3T fMRI	Motor execution and morphine+memantine or morph. + placebo	morphine treatment reduced ACC activation, the addition of memanite further reduced somatosensory activation
(Maihofner et al. 2005a)	12 CRPS	1.5T fMRI	von-Frey hyperalgesia	increased activation of S1 S2, insula, associative-somatosensory, frontal and ACC
(Maihofner et al. 2006)	12 CRPS	1.5T fMRI	Brush allodynia	increased S1, S2, M1, parietal, frontal cortices, aACC, pACC
(Maihofner et al. 2007)	12 CRPS, 12 HC	1.5T fMRI	Finger tapping	reorganization of central motor circuits, increased activation of M1 and supplementary motor areas
(Lebel et al. 2008)	8 pediatric CRPS	3T fMRI	Cold and brush, pre and post recovery	multiple regions of increased CNS activation, functional abnormalities may persist after pain has resolved
(Pleger et al. 2006)	17 CPRS, 17 HC	1.5T fMRI	TENS stimulation	SI and SII were significantly reduced parallel impaired tactile discrimination
Not included in ALE				
(Baliki et al. 2011)	28 CPRS, 46 HC 36 CBP, 20 OA	3T VBM	Structural changes	decreased gray matter in anterior insula and orbitofrontal cortex
(Geha et al. 2008)	21 CRPS, 21 HC		Gray, white matter	decreased gray matter in VMPFC and accumbmens, decrease in fractional in the left cingulum-callosal bundle, and in insula and basal ganglia connections
(Mutso et al. 2012)	30 CRPS 50 HC 38 CBP, 20 OA	3T structural	Hippocampus volume	Reduced hippocampus volume in CRPS, CBP but not OA
(Klega et al. 2010)	10 CPRS, 10 HC	[^{18}F]-diprenorphine		reduced opioid receptor binding potential in amygdala and parahippocampal gyrus, increased in prefrontal cortex

ACC anterior cingulate cortex, CPRS Complex Regional Pain Syndrome, HC Healthy Controls, CBP Chronic back pain, OA osteoarthritis, PAG periaqueductal gray, PCC posterior cingulate cortex, VMPFC ventromedial prefrontal cortex

Table 2 Activation likelihood estimated brain regions implicated in inflammatory responses

Cluster size	Cluster peak MNI_{xyz}	Gray matter regions implicated
528 mm^3	−12, −12, −13	Subthalamic nucleus, Left Parahippocampal Gyrus, Substania Nigra, Globus Pallidus, Uncus
472 mm^3	−44, −5, 9	Left Insula, Left Precentral Gyrus
360 mm^3	−7, −33, −11	Left Anterior and Culmen of the Cerebellum, left brainstem, Left Thalamus
320 mm^3	20, −97, −10	Right Fusiform Gyrus, Right Lingual Gyrus, Right Inferior Occipital Gyrus
304 mm^3	−38, −59, −12	Left Temporal Fusiform Gyrus, Left Declive of the Cerebellum
304 mm^3	−29, −60, 35	Left Middle Temporal Gyrus, Left Precuneus, Left Angular Gyrus
280 mm^3	48, −42, −9	Right Temporal Fusiform Gyrus, Right Occipital Fusiform Gyrus
272 mm^3	−5, 17, −13	Left Anterior Cingulate, Left Caudate Head
200 mm^3	16, 24, 61	Right Superior Frontal Gyrus, Right Middle Frontal Gyrus

consistently linked to systemic inflammation. Due to the relatively few studies, this resulting ALE maps should also be considered preliminary. Nonetheless, the results indicate that the brainstem, amygdala, anterior cingulate, insula and posterior cingulate reliably increase in functional activation as a function of systemic inflammation (see Table 3).

As illustrated in Fig. 1, there is substantial overlap in the brain regions that have been linked to both CRPS and to systemic inflammation independently: notably the middle cingulate, posterior insula, dorsolateral prefrontal cortex and the parietal lobule. Moreover, there may be overlap between inflammatory responses and the structural changes observed in CRPS (Baliki et al. 2011; Geha et al. 2008), i.e. the ventral medial prefrontal cortex and the anterior insula and the nucleus accumbmens.

Another line of (circumstantial) evidence comes from a recent study by Hess and colleagues (Hess et al. 2011) who demonstrated that in rheumatoid arthritis, the rapid clinical effects of TNF-α neutralization affect central nociceptive activity. Specifically, 24 hours after patients received the TNF-α blocker infliximab (Remicade®) at a dose of 3 mg/kg, fMRI BOLD signal evoked by compressing joints showed diminished spatial extent in somatosensory cortex, the parietal cortex, the posterior cingulate cortex and the medial prefrontal cortex. These effects paralleled pain reduction, but preceded reduction in joint swelling, serum C-reactive protein levels and serum IL-6 levels. These findings provide a potential bridge between the fields of neurology and immunology, in that brain regions associated with immune responses may map onto what has been dubbed an "an immunological homunculus" (Diamond and Tracey 2011; Tracey 2007).

To our knowledge, no study has yet investigated how pain processing is altered by experimental induction of systemic inflammation, and no study has linked pro-inflammatory cytokine levels directly to brain function in CRPS. Such an endeavor would be a highly important contribution to the field, as all the regions implicated above play a key role in sensory and affective components of pain processing, as well as potentially in hemi inattention type manifestations of CRPS. The commonly observed alterations in pain processing observed in CRPS may perhaps, in part, be explained by ongoing systemic inflammation.

Nerve damage as an initiator of an inflammatory feedback loop

Below, we present a basic outline for how CRPS may develop, based on a neuro-inflammatory perspective in terms of contributing events, from initiations in a peripheral injury, via an inflammatory reflex to maintenance, specific CNS targets, and the potential plateauing of the disease.

Initiating events – peripheral to CNS activity

Following injury to a nerve (typically by a sprain, fracture, surgery, or other traumatic injury) a cascade of events take place locally and systemically. These processes have been well characterized and are the subject of a number of reviews (Ren and Dubner 2010; Skaper et al. 2012). The nerve injury is a likely primary driver of neurogenic inflammation in CRPS. The inflammation has best been described at the site (Kim and Moalem-Taylor 2011) and in the spinal cord (Clark et al. 2007; Cao and Zhang 2008). Chemokines (e.g., (CCL2, CCL3, and fractalkine) and cytokines (e.g., IL1, IL6, NF-KB, TNF-alpha) are released by neuro-inflammatory immune cells (e.g., leukocytes) that are induced in the injured nerve. Both inflammatory and anti-inflammatory processes are initiated (Austin and Moalem-Taylor 2010). Presumably, a balance between pro- and anti-inflammatory systems, such as IL-10, is lost (Gaba et al. 2012). In some conditions such as CRPS it is assumed that the anti-inflammatory processes may be abnormal or overwhelmed. Recent data show that one-sided inflammation may increase pain systems in the contralateral cord – viz., c-fos activation pattern of spinal Gly/GABA neurons (Hossaini et al. 2011). Such data support a process by which

Table 3 Activation likelihood estimated brain regions implicated in CRPS

Cluster size	Cluster peak MNI_{xyz}	Gray matter regions implicated
1320 mm^3	0, 12, 52	Superior Frontal Gyrus, Medial Frontal Gyrus
832 mm^3	−29, −53, 45	Left Superior Parietal Lobule, Left Inferior Parietal Lobule, Left Angular Gyrus
736 mm^3	0, 6, 36	Cingulate Gyrus
696 mm^3	−31, −32, 48	Left Postcentral Gyrus, Left Inferior Parietal Lobule, Left Precentral Gyrus
648 mm^3	−44, −21, 51	Left Postcentral Gyrus, Left Inferior Parietal Lobule
616 mm^3	−53, −22, 16	Left Postcentral Gyrus, Left Insula, Left Transverse Temporal Gyrus
512 mm^3	30, −52, 43	Right Superior Parietal Lobule, Right Precuneus, Right Cingulate Gyrus
368 mm^3	35, 3, 18	Right Claustrum, Right Insula, Right Precentral Gyrus
224 mm^3	−34, −35, 5	Left Caudate Tail, Left Transverse Temporal Gyrus

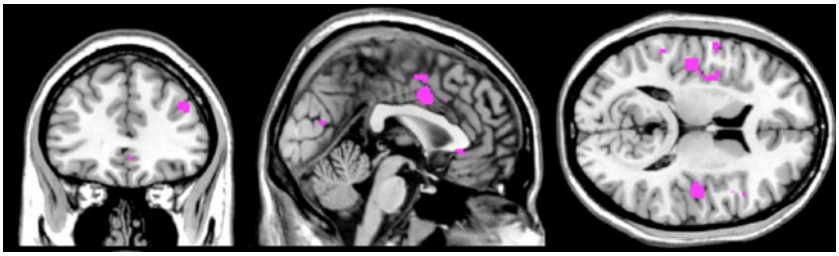

Fig. 1 Shared activation in CRPS processing and cytokine related activation, illustrating the potentially shared networks between the conditions. The Activation Likelihood Estimate (ALE) overlap was created as the conjunction of ALE maps from CRPS and cytokine related fMRI studies, not corrected for multiple comparisons

contralateral pain (Schreiber et al. 2008; Hatashita et al. 2008) may progress to other non-injured sites in CRPS (van Rijn et al. 2011). Finally, prior inflammation may contribute to later pain responses in these patients (Hains et al. 2010; Vega-Avelaira et al. 2012), presumably due to sensitization or alteration of pain networks. While inflammatory pain in preclinical models has been shown to activate microglia and astrocytes in the spinal cord, less information is available on central activation of these systems (Wang et al. 2002).

Contributing events – an inflammatory reflex

Following initiation of peripheral neuroimmune activation by injury to nerves, a cascade involving peripherally activated signals, may confer changes in neuroimmune systems in the CNS, as illustrated in Fig. 2. Microglia are an important source of inflammatory mediators and may have fundamental roles in neuropathic pain (Watkins et al. 2001; Milligan and Watkins 2009) through interactions with mast cells (Skaper et al. 2012). Mechanisms by which this happens is either through direct cytokine passage across the blood-brain barrier (Lossinsky and Shivers 2004) or other processes such as activation of afferent signals by nerves, of which the vagus nerve seems to play a well defined role. This circuit of the inflammatory reflex has also been termed the cholinergic anti-inflammatory reflex because afferent signals in the vagus initiate an efferent output that may inhibit cytokine production. Taken together, the inflammatory reflex constitutes a system that informs the CNS about peripheral stress by then having neuroimmune modulators or chemokines act on neurons in brain regions (Abbadie et al. 2009; Gao and Ji 2010; Thacker et al. 2009) that may produce behavioral manifestations observed in CRPS. The reflex involves immune complexes that drive CNS changes. It is unclear if these drivers are needed to maintain the presumed changes within the brain. An alternative view is that nociceptive drive itself activates a neuroimmune cascade.

An additional feature relates to the direct effects cytokines may have on desensitization of endogenous opioid receptors (Szabo et al. 2002). In one study, morphine administered to CRPS patients reported no difference in pain reduction vs. placebo (Harke et al. 2001). A PET study on opioid binding receptor potential found that CRPS patients have reduced binding potential (indicative of fewer receptors and/or higher endogenous competition) in the amygdala and parahippocampal gyri contralateral to the effected limb, and increased binding potential in the prefrontal cortex (Klega et al. 2010).

Maintenance events – CNS glia/neuronal/astrocyte interactions

Brain cytokines elevated through peripheral nociceptive drive or through activation of systemic inflammatory responses (e.g., IL-1) following nerve damage. Specifically, following nociceptive induced activation by nerve injury the release of neuroimmune modulators activate glia. CNS neuroinflammation may be exacerbated by the recruitment of microglia and astrocytes creating a feed forward cumulative process that may maintain neuropathic pain (Vallejo et al. 2010). Ongoing CNS inflammation is thus a possible contribution to the manifestations and maintenance of the psychophysical/behavioral responses observed in CRPS. In support of this, expression of some neuroimmune drivers such as TNF-a is increased in a chronic constriction injury (CCI) model of neuropathic pain (Covey et al. 2002). Importantly, the increased expression is observed in discrete brain regions.

Furthermore, neuroinflammation can spread from the primary injury site to second order synapses via remote neuroimmune activation (Banati 2003). Evidence for this comes in the form of elevated translocator protein (TSOP) PET ligand binding in contralateral thalamus in patients with ongoing phantom limb pain (Banati et al. 2001), likely indicative of microglial activation spread along "neuro-inflammatory tracts" (Cooper and Clark 2012). While phantom limb pain and CRPS are clinically distinct, recent evidence indicates a similar disruption of body schema (Reinersmann et al. 2010) and mirror box therapy has some evidence for both conditions (Lamont et al. 2011). Moreover, microglial

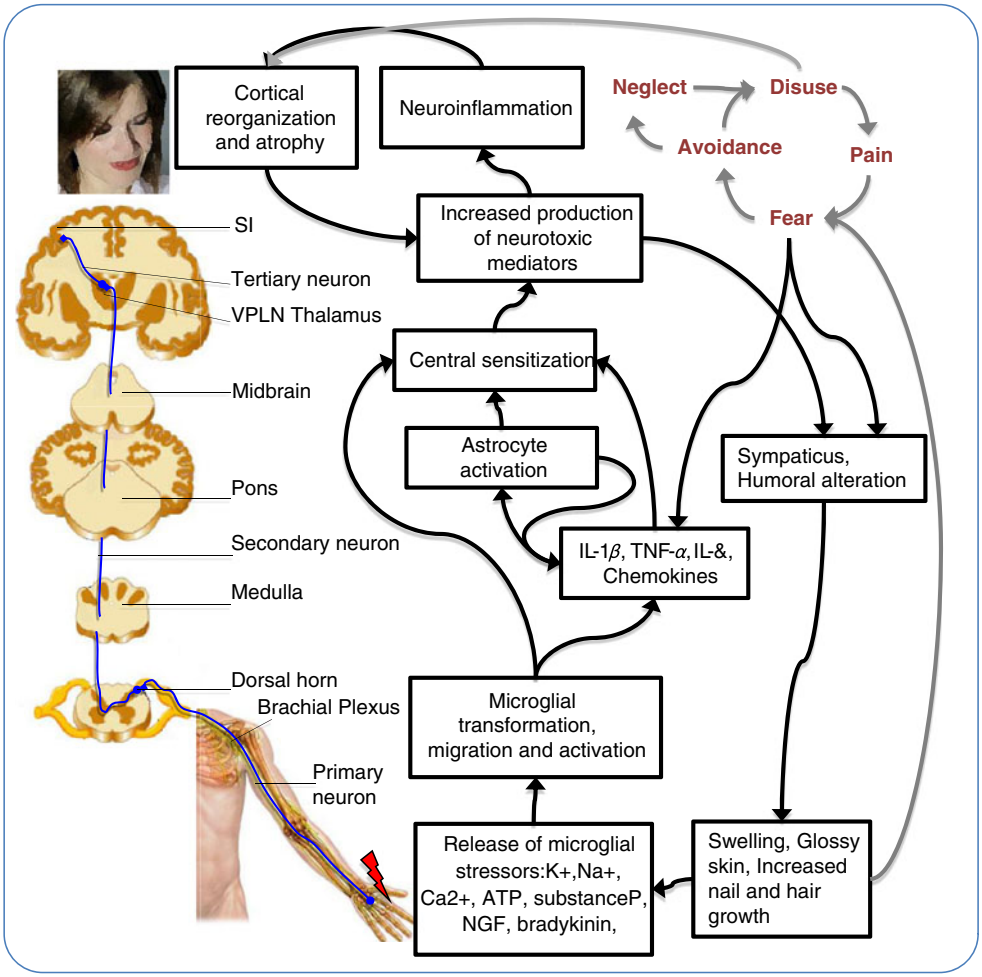

Fig. 2 Cartoon showing CRPS related pathways subsequent to neuronal injury and glial activation. The primary nociceptive pathway is illustrated in blue, biochemical cascades in black, and psychosocial circuits in gray, with potential interactions. Adapted from (Jha et al. 2012; Vlaeyen and Linton 2012; Marinus et al. 2011)

activation as well as neuronal loss in has been reported throughout the entire length of the spinal cord, most prominently at the injury level in the posterior horn (Del Valle et al. 2009). However, the link between phantom limb pain and CRPS, and the possibility of anterograde microglia involvement in both disorders, remains speculative.

Compared with the microglial response to nerve injury, astrocyte proliferation begins relatively late and progresses slowly, but is sustained for more than 5 months, a time frame paralleling the development of chronic pain (Zhang et al. 2012). Unlike microglia, astrocytes form networks with themselves and are closely associated with neurons and blood vessels, a close contact that makes it possible for astrocytes to regulate the external chemical environment of neurons during synaptic transmission. Moreover, there is recent evidence that spinal astrocytes but not microglia contribute to the pathogenesis of painful neuropathy (Zhang et al. 2012). As such, preclinical studies are needed to define whether microglia or astrocytes present a better target for novel CRPS treatments. CRPS is reversible in children (Low et al. 2007; Harris et al. 2012), but more chronic in adults following similar initial injuries. This might suggest that the plasticity and maturation/reorganizing capabilities of the CNS are crucial in responding to a persistent inflammatory response.

CNS targets

Following peripheral nerve injury a number of brain regions are affected by the process. The typical brain regions identified in human neuroimaging studies of pain processing include the anterior cingulate cortex, insular cortex, ventrolateral orbitofrontal area, amygdala, striatum, thalamus, hypothalamus, rostral ventromedial medulla, periaqueductal gray, pons, red nucleus, and medulla oblongata (Apkarian et al. 2005; Geha and Apkarian 2005). As noted by Diamond and Tracey (2011), *"The nervous system is hardwired to monitor the presence of cytokines and molecular products of invaders"*. In recent reviews of this topic, it is suggested that remote neuroimmune signaling after nerve damage may affect CNS processing by amplifying the gain of the pain-processing pathway (Saab and Hains 2009; Zhuo et al. 2011).

Inflammatory processes have also been postulated to contribute to specific syndromes such as depression (Krishnadas and Cavanagh 2012) and other behavioral manifestations common to this syndrome in CRPS (viz., general

malaise, sleep disorders, decreased activity, decreased social interaction). Taken together, these behavioral changes must be driven by altered neural circuits. In CRPS behaviors may be categorized as sensory (pain), emotional (depression or anxiety), cognitive, motor (e.g., movement disorders including dystonia) and other (e.g., hemi-inattention). Thus, a condition expressed following peripheral nerve injury now becomes a disease of the CNS. While immunologic processes are increasingly being described in CRPS (Kramer 2012), little information is available on specific brain targets.

Are some brain regions or circuits simply more susceptible to the inflammatory response in patients who have CRPS? An innate status of "inflammatory disposition" may be present in brain regions in CRPS patients. Although not reported in brains of such patients, preclinical studies have evaluated a number of inflammatory and associated receptors (BDNF, IL-6, IL-1β, IL-18 and NMDA receptors) in different brain regions (thalamus, hippocampus and hypothalamus) of mice with altered reactivity to pain, stress and anxiety related behaviors (Benatti et al. 2011) — indicating that anxiety related behavioral phenotypes constitute intrinsic risk factors for pervasive inflammation. Furthermore, newborn mice exposed to an inflammatory challenge have increased responsiveness to pain and anxiety related behavior (Benatti et al. 2009), further supporting the notion of the peripheral to central inflammatory reflex. Such long-term changes may relate to genetic, epigenetic and environmental processes. Potential interactions with specific brain regions known to confer particular behaviors are summarized below:

CNS inflammation and somatosensory function – thalamus and somatosensory cortex

Simplistically, the somatosensory system involving pain perception includes the thalamus, primary somatosensory cortex and posterior insula (Apkarian et al. 2005; Craig 2003). One of the unusual features of CRPS is the spread of pain from its original location that may envelop the other parts of the limb, other initially uninvolved body regions and extremities. Insights into central sensitization, spreading pain or allodynia have been well documented in other chronic pain conditions including migraine and osteoarthritis albeit not at the same pain intensity (Woolf 2011). Functional imaging studies have implicated anti-inflammatory blockade with TNF-alpha receptor antagonist in diminishing nociceptive CNS activity in the thalamus and somatosensory cortex (Hess et al. 2011). Neuroinflammation as measured by glial cell activation has also been reported in the thalamus in phantom limb pain (Banati et al. 2001). Preclinical studies have further implicated glial activation in a model of chronic neuropathic pain where minocycline injected into the somatosensory thalamus (posterolateral nucleus) reverses both microglial activity and hyperalgesia (LeBlanc et al. 2011). Less is known about neuroinflammation in the somatosensory cortex. A recent paper reports on functional and structural changes in synapses in the somatosensory cortex following peripheral injury but results were not related to alterations in neuroimmune modulators (Kim et al. 2012).

CNS inflammation and autonomic function – hypothalamus

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been observed in multiple chronic pain disorders (Galli et al. 2009) including CRPS (Park and Ahn 2012). One of the commonly observed features in CRPS in autonomic dysfunction manifest as altered temperature regulation, sweating and altered skin color (Marinus et al. 2011), making the hypothalamus a suspect of CNS dysfunction in the disease. In addition, sleep disturbances are present in chronic pain, and thought to be related to hypothalamic (suprachiasmatic) regulation of the sleep-wake cycle, affecting significant (96%) numbers of patients (Sharma et al. 2009). Increased microglial activation is observed in the hypothalamus in rat models of neuropathic pain (Takeda et al. 2009), and increased expression of IL-1 mRNA is observed in the hypothalamus following persistent pain induced formalin injection (Yabuuchi et al. 1996).

Inflammation cognition and memory – hippocampus, frontal lobes

Neonatal inflammation increases neurogenesis in the hippocampus. Other studies have implicated abnormal hippocampal function in chronic pain in both animals (Mutso et al. 2012) and humans (Maleki et al. 2012), and patients with CRPS have reduced hippocampal volumes (Mutso et al. 2012). Following peripheral inflammation, alterations in myo-inositol (a presumed marker of glial activation) were observed in the hippocampus that also correlated with increased measures of anxiety-like behavior (Schneider et al. 2012). In a seminal study be Geha and colleagues (2008), gray matter volume and white matter anisotrphy was determined in CRPS patients and healthy subjects. Results indicate gray matter atrophy in the insula, ventromedial prefrontal cortex and nucleus accumbens. The white matter anisotrophy of the cingulum-calosum bundle was decreased. Further, the strength of connectivity between atrophied regions related to anxiety, suggesting that abnormal anatomy of the CRPS brain may be at play in autonomic and cognitive symptoms in CRPS.

CNS inflammation and motor function – basal ganglia

In CRPS, putative roles for the basal ganglia include motor dysfunction (movement disorders) as well as alterations in

mood including reward dysfunction (Geha et al. 2008). Cytokines and glial mediated changes have been observed in the basal ganglia following inflammation or pain in humans (interferon-alpha therapy) (Capuron et al. 2007). In rats, both the chronic constriction injury and the spared nerve injury models of neuropathy, striatum hippocampus and cigulum levels of IL-1ß and IL6 are elevated (Al-Amin et al. 2011). Microglial activation with dichlorvos (2,2-dichlorovinyl dimethyl phosphate) produces alterations in the nigrostriatal dopaminergic system in part through increased levels of IL-1ß, TNF-α and IL-6 in the midbrain (Binukumar et al. 2011). Interferon-alpha therapy is associated with widespread bilateral increases in glucose metabolism in subcortical regions including the basal ganglia and cerebellum, and decreases in dorsal prefrontal cortex (Capuron et al. 2007) and behavioral symptoms including lassitude, inability to feel, and fatigue.

CNS inflammation and inattention – parietal lobe

Behavioral observations in CRPS patients suggest hemi-inattention to the affected side or limb(Moseley 2004; Frettloh et al. 2006). Functional imaging studies and neuropsychological testing indicate altered parietal lobe function in CRPS (Lebel et al. 2008; Kolb et al. 2012), a region involved in this type of abnormal processing. While higher neglect scores are reported for CRPS patients there does not seem to be a significant difference between CRPS and other pain conditions (Kolb et al. 2012). Other features of parietal dysfunction include impaired hand size estimation (bigger than it is) (Peltz et al. 2011) and agnosia for object orientation (Robinson et al. 2011), suggesting abnormalities in visiospatial information processing. While no information is available on parietal inflammation in CRPS, direct inaction of rTNF into the parietal lobe in animals induces a significant inflammatory reaction mediated by leukocyte invasion into the perivascular space (Wright and Merchant 1992). In neuropsychiatric systemic lupus erythemetosis (NPSLE) patients, a condition thought to be caused by a number of factors including pro-inflammatory cytokines, fMRI shows increased activation in parietal lobe (Fitzgibbon et al. 2008).

CNS inflammation and pain modulation – periaqueductal gray

Endogenous pain modulation is altered in CRPS (Seifert et al. 2009) suggesting abnormalities of pain facilitatory modulation in these patients, possibly through the periaqueductal gray (PAG). Cytokines and other neuromodulators have been implicated in PAG function in a variety of models (Benamar et al. 2008; Heinisch et al. 2011; Hao et al. 2011); for example, elevated cytokines in the PAG result in hyperalgesia (Benamar et al. 2008). Indeed, in CRPS patient the PAG (and cingulate) are significantly less activated during pain suppression, as compared to healthy controls. Notably, this lack of activation was present regardless of stimulating a symptomatic or asymptomatic region, suggestive of a generalized functional change (Freund et al. 2011).

CNS inflammation and bodily experience – insula

The insula has been conceptualized as an interoceptive integration region, where ascending sensory pathways conveying proprioceptive and somatosensory information about the body's internal state, as well as visual and auditory information about the external world, terminate in the posterior insula. This activity is then re-represented in the middle and finally anterior insula, where polysensory integration produces a global meta-representation of the internal feeling state of the individual (Craig 2009). Functional neuroimaging studies indicate the mid-insula region to be involved in pain, interoception, tactile sensation, motion perception and the discrimination between internally and externally generated stimuli (Kurth et al. 2010). Insular lesions may lead to altered pain thresholds and central pain (Garcia-Larrea et al. 2010), and have been associated with a failure to withdraw from and/or absent or inadequate emotional responses to painful stimuli, a syndrome known as pain asymbolia (Berthier et al. 1988). Stroke patients with posterior insula lesions and limb dysfunction may be convinced that their limbs function normally (anosognosia), that their limb does not belong to them (asomatognosia) or attribute their own body parts to other persons (somatoparaphrenia) (Baier and Karnath 2008; Karnath et al. 2005). Such manifestations resemble the estrangement CRPS patients sometimes report to their injured limb. Indeed CRPS patients show alterations in insula structure, connectivity (Geha et al. 2008), and function (Maihofner et al. 2005a, 2006). Thus far, direct evidence for a role of the human insula in the inflammatory response has only been demonstrated in asthma patents exposed to antigens (Rosenkranz et al. 2005; Rosenkranz et al. 2012).

Progressive nature of CRPS central changes – brain cascades

Evolution of CRPS may be defined into "three possible CRPS subtypes: (1) a relatively limited syndrome with vasomotor signs predominating, (2) a relatively limited syndrome with neuropathic pain/sensory abnormalities predominating, and (3) a florid CRPS syndrome similar to "classic RSD" descriptions" (Bruehl et al. 2002). One potential explanation for the subtypes includes progressive involvement of different brain circuits: hypothalamic;

somatosensory; and more florid and integrated circuit involvement – hypothalamic, somatosensory; basal ganglia; hippocampal; frontal and parietal cortices. Many variables worsen over the course of the illness (Schwartzman et al. 2009a) but, in contrast to more devastating neuro-inflammatory disorders such as MS, the disease seems to plateau. How may this occur?

If there were "nodal" regions that are initially involved or activated in the neuro-immune reflex, these would potentially be the thalamus and hypothalamus because of their involvement in nociceptive transmission and the stress response. Changes in other areas may relate to processes that involve consecutive damaging/neuroimmune changes in other brain regions mediated through connections (axonal pathology) or secondary to the neuroimmune onslaught. Such changes may also be secondary to primary sites affected – thus remote changes may occur due to neuronal alterations. Following focal brain lesions or damage there is an associate "spread of death" (Viscomi et al. 2009), that may set up secondary immune responses in diffuse brain regions. In addition, as shown in a model of contralateral spread in mono-arthritic models, antidromic activity of this nature is known to result in the peripheral release of pro-inflammatory and vasoactive neuropeptides (Kelly et al. 2007). Although no large studies have been conducted evaluating the cumulative aggregation of symptoms (and thus putative brain regions) to support such a notion, the evolution of some basic processes would seem to be consistent with this. Thus, for example, the spread of pain from the original site, the evolution of motor changes, the unfolding of depression and other emotional changes would seem consistent with an underlying process that temporally captures involvement of these different regions.

Imaging astrocytes, microglia, peptides and the inflammatory process in CRPS

Human in vivo imaging of glial function is becoming more viable. In response to injury, microglia migrate to the site of injury, and express multiple cell surface proteins, including the translocator protein (18kDa) (TSPO, formerly known as the peripheral benzodiazepine receptor.) This conditional expression makes TSPO a prime target for PET imaging. Microglia responses have been documented in a variety of pain and nerve injury models (Milligan and Watkins 2009). In human studies, increased TSPO expression has been reported in the thalamus after peripheral nerve injuries (Banati et al. 2001) and in widespread cortical regions after traumatic brain injury (Folkersma et al. 2011). There are multiple candidate PET tracers for microglial activity, with PK11195 being most commonly used (Ching et al. 2012). However, several higher affinity TSPO radioligand suitable for imaging of microglial activation are emerging, such as PRB28 (Kreisl et al. 2010). In a very recent study on baboons, lipopolysaccharide administration led to a significant microglial response, most prominently in the accumbmens, insula and frontal cortex (Hannestad et al. 2012a). However, there are several caveats to TSPO imaging, including a common genetic polymorphism that alters ligand binding properties (Kreisl et al. 2012), and recent evidence that also reactive astrocytes can contribute to the signal in addition to reactive microglia (Lavisse et al. 2012).

Astrocytes are the most abundant brain cell type in terms of their number and volume, and they constitute 40% to 50% of all glial cells. Astrocyte reaction has been demonstrated in peripheral nerve injury and in tissue inflammation models. For example, peripheral chronic nerve lesion is associated with breakdown of the blood spinal cord barrier permeability and activation of astrocytes (Gordh et al. 2006). Although most studies have focused on the role of astrocyte activation at the spinal cord dorsal horn level, alterations can occur at supraspinal areas, such as the rostral ventromedial medulla and in the forebrain (Raghavendra et al. 2004). The enzyme MAO-B exists on the outer mitochondrial membrane, occurring predominantly in astrocytes (Fowler et al. 2005). When astrocytes become activated [as customarily defined by their greatly enhanced glial fibrillary acidic protein (GFAP) binding] they express high levels of MAO-B (Ekblom et al. 1993), thereby providing an indirect target for PET imaging. L-deprenyl (Selegeline) is a selective irreversible MAO-B inhibitor that has been carbon-11 labeled, allowing for PET imaging of a proxy to astrocyte activity (Fowler et al. 1987). A deuterium substitution on the L-deprenyl molecule causes a significant reduction in the rate of trapping, thereby further enhancing the tracer's sensitivity to subtle changes in MAO-B concentration (Fowler et al. 1995). Thus far, studies using this deuterium substituted deprenyl (DED) tracer have been performed to asses MAO-B function and astrocytosis in epilepsy (Bergstrom et al. 1998), amyotrophic lateral sclerosis (Johansson et al. 2007), Creutzfeldt–Jakob disease (Engler et al. 2012) and Alzheimer's (Santillo et al. 2011; Carter et al. 2012).

Substance P is a neuropeptide that modulates pain both peripherally and centrally, primarily through the neurokinin-1 (NK1) receptor. Substance P and its primary receptor, NK1, are widely distributed throughout the brain with high density in the striatum, the amygdala and the dorsolateral prefrontal cortex. We have recently demonstrated significant alterations of NK1 receptors using GR205171 PET in chronic neck pain after a whiplash trauma (Linnman et al.

2010) , in epilepsy (Danfors et al. 2011) and between the sexes (Engman et al. 2012). In CRPS, there are multiple lines of evidence implicating the substance P system, including elevated serum levels (Schinkel et al. 2009) and an animal model of CRPS where continuous substance P application caused a significant and long-lasting decrease in paw withdrawal thresholds upon mechanical stimulation, edema and enhanced leukocyte-endothelial interaction (Gradl et al. 2007).

Given the white matter changes associated with CRPS (Geha et al. 2008), a possible avenue of inquiry would be the evaluation of CRPS patients with respect to astocytosis, microglial activity and neurkinin-1 receptors, ideally in a longitudinal study with parallel (PET-MR) assessment of brain structure, function and measurements of immunological components. Substance P is released from the terminals of specific sensory nerves and NK1 receptors are expressed on both neurons and astrocytes, but about 9 times less on microglia. MAO-B expression occurs primarily in astrocytes, while TSPO expression occurs in activated microglia and to a lesser degree in active astrocytes. Thus, the three systems are somewhat orthogonal, and site specific PET probes may be used indicate different pathological mechanisms.

Gender - hormones and immunosensitization

One of the major issues in CRPS is the predominance (3-4 times) of women who have the condition compared with men. Estrogens may play a role in the sex difference observed in neurological diseases with inflammatory components (reviewed in Czlonkowska et al. 2006). However, in a population based case control study, there was no association between CRPS and estrogen exposure (de Mos et al. 2009). fMRI studies on sex differences in pain reactivity in healthy subjects indicate that men have activation of the somatosensory and insular cortex, and that women have higher medial prefrontal activation (Derbyshire et al. 2002; Moulton et al. 2006; Paulson et al. 1998; Straube et al. 2009; Kong et al. 2010). In addition to task related fMRI, resting state functional connectivity studies also indicate sex differences (Biswal et al. 2010; Kilpatrick et al. 2006). Recently, we demonstrated significant sex differences in pain induced functional connectivity of the PAG. In men, higher pain led to an increased functional connectivity between the PAG and the amygdala and also between the PAG and the putamen (Linnman et al. 2012a). A potential link to inflammatory aspects was demonstrated by Eisenberger et al. (2009) in an fMRI study on endotoxin administration and depression: Women, but not men, exposed to endotoxin, showed increases in IL-6 associated with increases in dorsal anterior cingulate cortex and anterior insula activation, mediating the relationship between IL-6 increases and depressed mood. If such differences are also present in clinical pain conditions, and the relation to inflammatory responses, remains to be determined.

Immunomodulatory effects of medications and other treatments

Immunomodulators have been proposed as useful pharmacotherapies for CRPS and include glucocorticoids, tumor necrosis factor-α antagonists, thalidomide, bisphosphonates, and immunoglobulins (Dirckx et al. 2012). More commonly used medications that may be useful in CRPS include gabapentin (van de Vusse et al. 2004), ketamine (Azari et al. 2012), and lidocaine (Schwartzman et al. 2009b). All are reported to have anti-inflammatory responses. Gabapentin modulates immunoreactivity in neuropathic mice (Schwartzman et al. 2009b). Ketamine is reported to have anti-inflammatory effects through interactions with inflammatory cells recruitment, cytokine production, and inflammatory mediators regulation (Loix et al. 2011). Exercise may also enhance anti-inflammatory function (Walsh et al. 2011). Taken together, the data suggests that anti-inflammatory and neuroimmune modulating treatments adjusted to the temporal nature of the CRPS process (duration, intensity, age). With respect to physical exercise (including physical therapy), data is suggestive that patients improve (Smith 2005) through mechanisms yet not defined but may relate to exercise induced neuromodulation of the exacerbated inflammatory process in these patients.

Behavioral aspects

CRPS is often viewed as a biopsychosocial disorder, for which successful treatment must target concurrently the biological, psychological, and social components (Bruehl and Chung 2006). A recent review of the evidence for such treatments found that "*…randomized controlled studies of psychological interventions for CRPS, alone or in the multidisciplinary context, are almost entirely absent from the literature. The clinical studies available, however, do suggest that psychological interventions are likely to be a useful part of a comprehensive multidisciplinary treatment package*" (Bruehl and Chung 2006). Pain related fear might however be a consequence, rather than a cause of CRPS: In early CRPS, pain severity but not fear of movement was related to functional limitations. In chronic patients, however, functional limitations beyond and above the contribution of pain severity were predicted by patients perceived harmfulness of activities (de Jong et al. 2011). Pain exposure

therapies show initial evidence (van de Meent et al. 2011; de Jong et al. 2005). Fear of pain can shape pro-inflammatory immune system responses to noxious stimulation: Experimental pain induced levels of IL-6 were significantly correlated to pain catastrophizing in healthy volunteers (Edwards et al. 2008). In chronic pain patients, particularly in women, focusing on the negative aspects of their pain condition lead to elevated levels of IL-6, indicating that women display an increased and delayed inflammatory responses following negative emotional expression (Darnall et al. 2010).

Specificity and Sensitivity

A major obstacle for the neuroimaging community is defining specificity in results. This is evident in recent reviews indicating that a wide rage of behaviors are processed in similar brain regions, for example the anterior cingulate (Shackman et al. 2011) and the periaqueductal gray (Linnman et al. 2012b). The effective spatial and temporal resolution of fMRI is increasing, 7 Tesla fMRI with submillimeter resolution is in proccess (Polimeni et al. 2010; Linnman et al. 2012b). Simultaneous PET-fMRI (Judenhofer et al. 2008) and ultra high resolution diffusion weighted imaging (Miller et al. 2011) are other emerging technologies. In the case of CRPS, studying more subjects, preferably longitudinally, to define subtypes, cytokine levels and behavioral correlates to CNS function may be a fast route to success. Furthermore, recent studies have begun contrasting CRPS with other pain states (Baliki et al. 2011; Mutso et al. 2012) to define common and specific structural alterations in distinct disease states. With regard to the neuro-inflammation hypothesis presented here, direct comparisons between CPRS patients and other disorders with inflammatory components such as depression, multiple sclerosis and rheumatoid arthritis are on the agenda.

Summary and conclusions

Neuro-inflammation following nerve injury is a potential process or mechanism by which many of the CRPS clinical manifestations may be produced. Changes from pain in the periphery, to spreading pain and more complex processes such as neglect-like symptoms, autonomic changes, and dystonias could all result from the initiation and maintenance of neuroimmune and cytokine induced changes. The evidence reviewed here supports a potential role for these processes that affect brain systems. That said, there is still a paucity of direct evidence for a neuro-inflammatory mechanism in CRPS. We have attempted to provide an overview of the many potential interactions that are ripe for direct tests, and of the multiple avenues of further inquiry. As such, continued translational efforts and the use of neuroimaging techniques such as functional-, morphological- and diffusion-MRI, PET imaging of neuro-receptor and glial systems, can provide further insights into neuro-inflammation at the onset and during the course of CRPS.

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