Central Mechanisms in Complex Regional Pain Syndrome (CRPS)

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CRPS is poorly defined and usually occurs as a pathological response to injury. Established diagnostic criteria are listed in Table 1.[1] CRPS type 1 (no underlying neural injury) occurs with an incidence of 8-25 / 100,000 with about 75% of cases spontaneously resolving within 1 year.[2,3] CRPS type 2 may result from any neural injury, but is seen in the UK most commonly in patients with diabetes, stroke and traumatic nerve injury. Efficacious treatments include steroids, bisphosphonates, nerve-altering adjunct analgesics (e.g. gabapentin), physical and desensitisation therapies. Nerve blocks help some patients. Many patients, despite these treatments, have intractable pain with associated loss of functioning and quality of life. Novel therapies are used including intravenous ketamine, intravenous immunoglobulin, tumour necrosis factor (TNF) blockers, thalidomide and intrathecal baclofen. Innovative rehabilitation techniques such as motor imagery programmes, mirror visual feedback and sensory discrimination techniques may also help.[4,5] Several mechanisms, both peripheral and central, are thought to contribute to the development and propagation of pain in this condition. This review focuses on the brain in patients with CRPS, in particular the symptoms and signs most likely due to brain changes; functional imaging studies to support this; and finally putative mechanisms contributing to the propagation of pain.

Table 1: International Association for the Study of Pain's (IASP) Diagnostic Criteria for CRPS.[1]

1. Presence of an initiating noxious event, or a cause of immobilisation*.
2. Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event.
3. Evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain.
4. This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction.

*Not required for the diagnosis

Clinical findings to suggest brain involvement in patients with CRPS

Patients with chronic (typically more than 1 year) CRPS1 have disorders in their body perception.[6] It is unknown how prevalent these clinical features are in patients with CRPS of shorter duration or how frequently they occur in other diseases of the nervous system or chronically painful conditions such as arthritis. The main features are summarised in Table 2.

Most frequently patients with CRPS demonstrate macro- and microsomatognosias (distorted body part size when asked to draw or match a visual image). The majority of chronic cases also have digit misperception (finger agnosia) when they cannot identify correctly a touched finger with their eyes closed.[7] Finger agnosia was originally described by Gerstmann in 1924 in a group of patients who also had dyscalculia, left-right confusion and agraphia. They all had lesions in the dominant parietal lobe involving the angular gyrus. Finally, patients with CRPS1 demonstrate somatoparaphrenia or a 'neglect-like' state: they have fixed negative beliefs towards their limb; dissociation and depersonalisation (they assign ownership elsewhere ("my hand's not mine", "my leg feels like an alien"); and an autotomy-wish where they desire it to be removed.

Body scheme is an "organised model of ourselves".[8] It is a sub-conscious representation of the body's position in space. It is related to, but different from, body image which is a conscious representation of the body's position from the outside. Body scheme may be understood as part of a neuropsychological theoretical model of 'executive action' whereby non-routine tasks that

Table 2: Symptoms and signs suggesting brain involvement in patients with CRPS.[6,7]

- Hostile feelings directed towards the limb, including a desire to get rid of it
- Dissociation from the limb (not feeling as if it belongs to them)
- Disparity between what is apparent and what is felt
- Altered awareness of limb position
- Changes in conscious attention
- Distorted mental image of affected parts
- Digit misperception

require decision-making and self monitoring are performed – i.e. the Supervisory Attentional System.[9] It receives contributions from touch, proprioception, vision and motor commands. The body scheme has seven properties.[10] It is spatially coded, modular, updated with movement, interpersonal and supramodal, i.e. integrates the different inputs from primary processing. It is adaptable. For example, in monkeys using tools, visual receptive fields of bimodal neurons that previously were linked to hand position become active when vision is directed towards the tip of a tool, or even the visual representation of the tool on a video monitor.[11] Finally the body scheme is internally coherent to ensure a continuity of body experience. For example, an illusory extension of the elbow is experienced when the biceps tendon is vibrated while the forearm is held at a fixed angle. If a blindfolded subject holds his nose during this procedure, the nose is perceived to grow in length (Figure 1).[12] Associative cortex, particularly the parietal lobes, is involved in this representation of the body scheme.

Brain changes in patients with CRPS

Functional imaging studies provide evidence for cortical reorganisation in the primary somatosensory (S1) and motor cortex of patients with CRPS1. The extent of functional activity in these areas is correlated with the severity of the pain. Functional activity normalises following successful treatment and pain resolution. For example, Maihofner et al. (2004) found that the extent of the S1 cortex representing the painful upper limb differed to that for the contralateral cortex representing the pain-free side in patients with unilateral upper limb CRPS1.[13] Symmetry of these magnetoencephalographic functional maps was restored following successful treatment measured by pain reduction (Figure 2). Such cortical reorganisation has an important role in maintaining pain memories suggested by the fact that the amount of cortical reorganisation is correlated with the chronicity and severity of pain in conditions such as fibromyalgia and chronic low back pain.[14]

Central mechanisms

As pain is reported as a conscious experience it is helpful to understand the complex nature of consciousness. It is proposed that consciousness is an 'emergent property' of the brain's functioning.[15] The brain may be thought of as a complex system that is composed of separate parts, each of which has a set of internalised rules. The interaction of these separate parts occurs in a non-linear fashion and generates emergent properties that are best studied at a systems level. Another example of a complex system is the combustion engine, each part having a separate function. Linking the separate parts together generates the emergent property of power. Any change to an individual part of the engine may have unexpected effects on power output. In the brain, perceptual categorisation of sensory information combined with value-category memory may change the emergent property of conscious 'qualia-space'.[15] It is within this conceptual framework that the sensation of pain may be understood.

The distributed neural matrix active during the experience of pain is summarised in Figure 3. This has been mapped under experimental conditions and is based on neurophysiological, neuroanatomical and functional imaging studies.[16,17] Nociceptive input is processed by the brain in at least two parallel pathways simultaneously. In general, the lateral pathway (shown in red) contains sensory discriminatory information allowing localisation and characterisation of the nociceptive stimulus. This pathway therefore processes the sensory-discriminative components of pain. The evolutionary older medial pathway

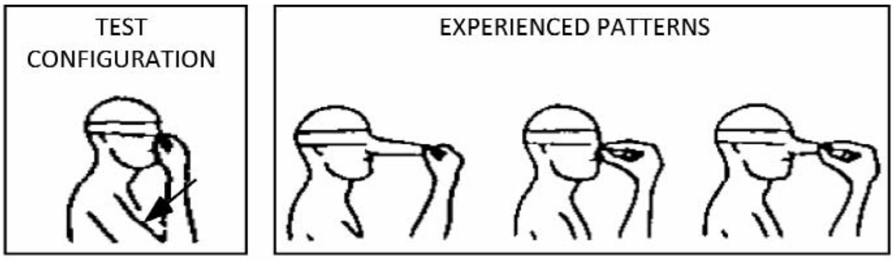

Figure 1: The arrow in the left figure indicates the placement of the vibrator in the physical test situation. Blindfolded subjects experienced their arms extend. In the right, cartoons illustrate the subjective experiences. Most felt their nose elongating, others experienced their fingers elongating but not their noses; a few experienced both elongating (Adapted from Lachner).[12]

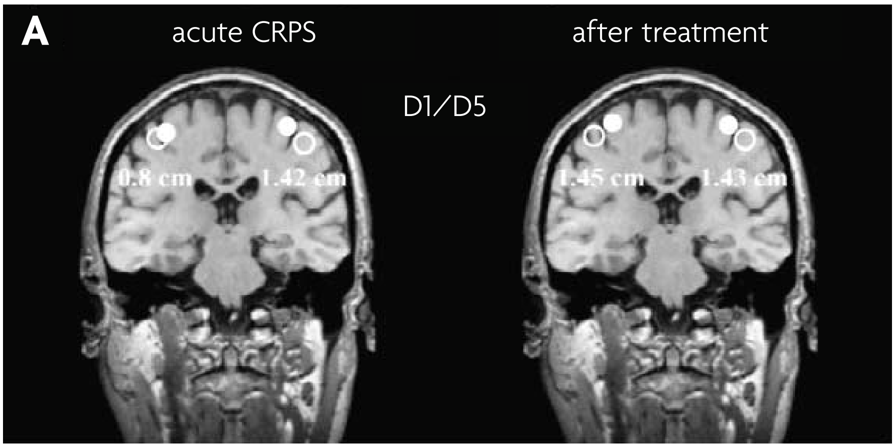

Figure 2: Cortical reorganisation in the primary somatosensory area (S1) in patients with upper limb CRPS. Overlapping representations of thumb (D1) and little finger (D5) resolve following successful treatment.[13]

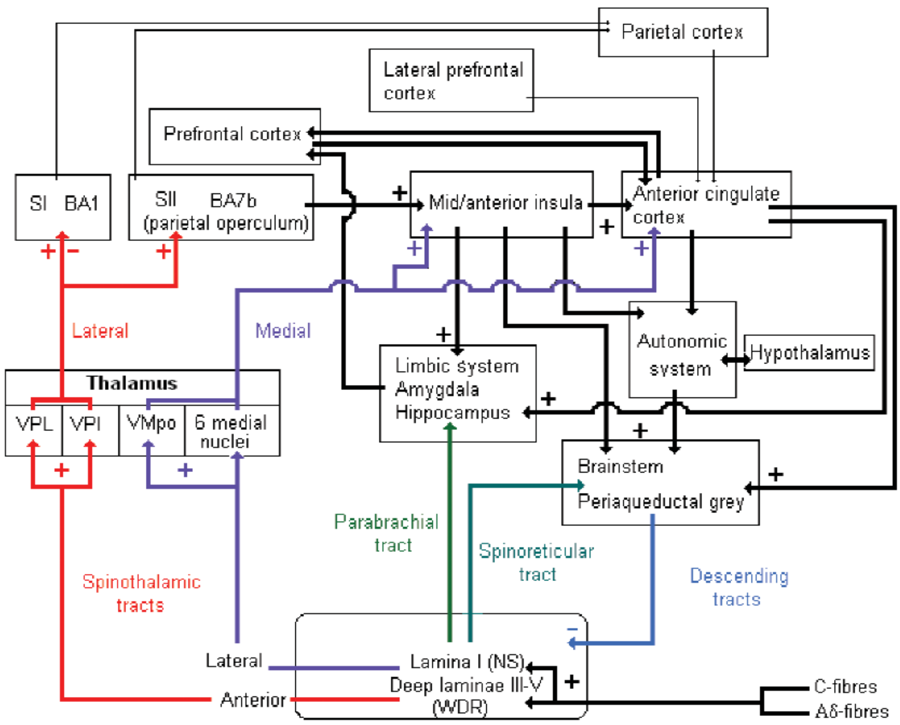

Figure 3: Pathways illustrating neuromatrix representing pain in humans.[16,17]

(shown in purple) processes affective information and has influence on cognitive functions concerning pain such as attention. It also has obvious effector pathways enabling both rapid and prolonged changes in the periphery via the sympathetic nervous system and hormonal release via the hypothalamus. This pathway therefore processes the affective-motivational components of pain.

What are the mechanisms for pain in patients with CRPS? Monitoring for incongruence between predicted and actual body states is an important function of the adaptive central nervous system. It has been hypothesised that sensorimotor incongruence involving vision, proprioception, touch and motor programmes generates pain in an analogous fashion to seasickness where incongruent vestibular, proprioceptive, visual and motor programmes generate nausea and even vomiting.[18] By generating such somaesthetic incongruence using a mirror and mismatched bilateral movements in healthy volunteers, a proportion (66%) described uncomfortable feelings including pain.[19] Pain is relieved for some patients with CRPS by placing their affected limb behind a mirror and performing congruent bilateral movements while looking at the reflection of their unaffected limb.[4] It has been demonstrated that sensorimotor incongruence activates an area in the right dorsolateral prefrontal cortex.[20] However, verbal semantic, visual and auditory congruence monitoring consistently involves the anterior cingulate cortex (ACC), albeit different areas within the ACC depending on experimental conditions.[21]

CRPS is associated with a neglect-like syndrome and neurological signs

The connectivity neuromatrix (Figure 3) demonstrates that both the lateral prefrontal cortex and parietal cortex have input to the ACC. This provides an anatomical opportunity for potential disruption to sensorimotor congruence monitoring, body scheme and autonomic outflow in the same location.[22] ACC activation is important in modifying autonomic outflow responses, particularly the sympathetic nervous system, enigmatically linked to CRPS, a condition previously known as reflex sympathetic dystrophy. Furthermore, the ACC is involved in motor selection responses for noxious stimuli and learning associated with the prediction and avoidance of noxious stimuli.

Case reports of patients with lesions involving the ACC illustrate contralateral hemibody neglect that can be corrected when the affected side is placed in the unaffected visual field.[21] Monkeys with unilateral cingulate lesions demonstrate motor neglect.[21] Performing cingulumotomies in patients with chronic pain produces a loss of emotional distress, even though the patients still reported that they were in pain – its meaning did not distress them.[21] Further research into the specific role of the ACC, particularly Brodmann area 24, in the generation of pain, and pain-associated or learned behaviours may allow a better understanding of the neural basis for the bizarre, but consistent, clinical findings in patients with CRPS. Data from such research may illuminate potential therapeutic targets to allow extinction of maladaptive learning and normalisation of cortical function with the associated benefit of pain relief.

Conclusion

Patients with CRPS have abnormalities in body scheme and perception in addition to abnormalities in their peripheral tissues, nociceptive nerves and psychologic functioning when compared to healthy controls. Imaging studies demonstrate cortical reorganisation in areas involved in body perception. In combination these abnormalities may generate brain states that patients report as pain. Potential central mechanisms include sensorimotor incongruence and neuroplasticity and it is likely that the ACC has a pivotal role in this condition. ◆

REFERENCES

1. Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2nd ed.* Seattle: IASP Press; 1994.
2. De Mos M, de Bruijn AG, Huygen FJ et al. *The incidence of complex regional pain syndrome: a population-based study.* Pain 2007;129:12-20.
3. Sandroni P, Benrud-Larson LM, McClelland RL et al. *Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study.* Pain 2003;103:199-207.
4. McCabe CS, Haigh RC, Ring EF et al. *A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1).* Rheumatology (Oxford) 2003;42:97-101.
5. Moseley GL. *Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial.* Pain 2004;108:192-8.
6. Lewis JS, Kersten P, McCabe CS et al. *Body perception disturbance: a contribution to pain in complex regional pain syndrome.* Pain 2007;133:111-9.
7. Forderreuther S, Sailer U, Straube A. *Impaired self-perception of the hand in complex regional pain syndrome (CRPS).* Pain 2004;110:756–61.
8. Head, H, Holmes G. *Sensory disturbances in cerebral lesions.* Brain 1911;34:102-254.
9. Shallice T. *Specific impairments of planning.* Phil Trans R Soc Lond B 1982;298:199-209.
10. Haggard P, Wolpert DM. *Disorders of body scheme. In "Higher-Order Motor Disorders" Edited,* Freund HJ. OUP 2005. Derbyshire SWG. *Exploring the pain 'neuromatrix'.* Curr Rev Pain 2000;4:467-77.
11. Iriki A, Tanaka, Obayashi S, Iwamura Y. *Self-images in the video monitor coded by monkey intraparietal neurons.* Neurosci Res, 2001.40:163-173.
12. Lachner JR. *Some proprioceive influences on perceptual representation of body shape and orientation.* Brain 1988.11:281-297.
13. Maihöfner C, Handwerker HO, Neundorfer B et al. *Patterns of cortical reorganisation in complex regional pain syndrome.* Neurology 2003;61:1707-15.
14. Flor H. *Cortical reorganisation and chronic pain: implications for rehabilitation.* J Rehab Med 2003;S41:66-72.
15. Edelman GM. *Naturalizing consciousness: a theoretical framework.* PNAS 2003;100:5520-4.
16. Schnitzler A, Ploner M. *Neurophysiology and functional neuroanatomy of pain perception.* J Clin Neurophys 2000;17:592-603.
17. Apkarian AV, Bushnell MC, Treede R et al. *Human brain mechanisms of pain perception and regulation in health and disease.* Eur J Pain 2005;9:463-84.
18. Harris AJ. *Cortical origin of pathological pain.* Lancet 1999;354:1464-66.
19. McCabe CS, Haigh RC, Halligan PW, et al. *Simulating sensory-motor incongruence in healthy volunteers: implications for a cortical model of pain.* Rheumatology 2005;44:509-516.
20. Fink GR, Marshall JC, Halligan PW, et al. *The neural consequences of conflict between intention and the senses.* Brain 1999;122:497-512.
21. Devinsky O, Morrell MJ, Vogt BA. *Contributions of anterior cingulated cortex to behaviour.* Brain 1995;118:279-306.
22. Ward AA. *The cingular gyrus: area 24.* J Neurophys 1948;11:13-23.