SPECIAL REPORT

STROKE, COMPLEX REGIONAL PAIN SYNDROME AND PHANTOM LIMB PAIN: CAN COMMONALITIES DIRECT FUTURE MANAGEMENT?

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Despite being different conditions, complex regional pain syndrome type 1, phantom limb pain and stroke share some potentially important similarities. This report examines experimental and clinical findings from each patient population. It identifies common aspects of symptomatic presentation, sensory phenomena and patterns of cortical reorganization. Based on these common findings, we argue that established principles of stroke rehabilitation are also applicable to rehabilitation of complex regional pain syndrome type 1 and phantom limb pain. In addition, we contend that promising treatment approaches for complex regional pain syndrome type 1 and phantom limb pain may be helpful in stroke rehabilitation. Examples of emerging supportive evidence for these hypotheses are provided and discussed.

Key words: stroke, reflex sympathetic dystrophy, physiotherapy, sensorimotor cortex, cortical reorganization, neurorehabilitation.

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INTRODUCTION

The brain retains the ability to change throughout one's lifespan. This ability is demonstrated by the continually updating nature of neural representations held throughout the brain, including the somatotopic representation of the body in the primary somatosensory cortex (1). Sensorimotor plasticity may be particularly important following nervous system injury, for example during stroke recovery, which depends on coordinated cortical activation of the affected and surrounding areas (2). That principle of recovery may be relevant to conditions such as complex regional pain syndrome type 1 (CRPS1) and phantom limb pain (PLP), which are characterized by pain but also by abnormal organization of the sensorimotor cortex contralateral to the affected side (3, 4). Post-stroke cortical reorganization can be influenced by therapeutic interventions, but may be limited by areas of permanent neuronal damage (2). However, with CRPS1 and PLP, no such permanent neu-

ronal damage is likely. CRPS1, PLP and stroke originate from distinct mechanisms (peripheral trauma, deafferentation and cortical damage); however, each can be investigated with the same clinical, electrophysiological and imaging techniques to determine their clinical presentation and cortical response to treatment. Therefore, although they are different medical conditions, common features can be compared. From this perspective, CRPS1, PLP and stroke share many features, including the following: similar changes in sensorimotor activation patterns; sensibility; and response to attention-based repetitive-training regimes. Here we argue that, on the basis of clinical and cortical similarities, treatments effective in one patient population might be effective in the others. This is important because stroke, CRPS1 and PLP are all debilitating conditions for which successful rehabilitation can be elusive (5, 6). Therefore, we argue that CRPS1 and PLP may respond to interventions that restore normal cortical activity during post-stroke recovery and that effective stroke treatments may benefit patients with CRPS1 and PLP.

CLINICAL PRESENTATION OF STROKE, CRPS1 AND PLP

Each year approximately 0.5% of the population will sustain a cerebrovascular accident, or stroke (7). In each case, signs and symptoms reflect the damaged areas of the brain and may include motor, sensory, language, perceptual and cognitive deficits (7). Some patients subsequently develop shoulder or hand pain, swelling, hypersensitivity and reduced regional bone density in the affected limb; findings for which there is usually no identifiable peripheral cause (8, 9). The pathophysiology of these findings, sometimes referred to as shoulder-hand syndrome or CRPS1, is unclear, but they are not rare; reported frequencies range from 1.5% to 61% (8, 9).

CRPS1 is most common after minor trauma (10, 11), for example in 8–37% of uncomplicated wrist fractures (12). CRPS1 usually involves a single limb, but it has also been reported following minor trauma to the head (13), neck (13) and chest (14), and via psychophysiological mechanisms such as with post-traumatic stress disorder (15). Signs and symptoms include: intense, non-dermatomal pain; altered sweating and blood flow; peripheral oedema; abnormal sensation, including hyperalgesia and allodynia; restricted active and passive move-

ment; reduced regional bone density; tissue hypoxia; reduced muscle strength; and muscle tremor (see diagnostic criteria (10) and review (11)). There is growing evidence that CRPS1 is a centrally-mediated neurological condition (11) involving the central nervous system (CNS) at several integrated levels, including the somatosensory, sympathetic and somatomotor systems (8, 11).

PLP occurs in as many as 80% of amputees. It is characterized by: intense, burning, non-dermatomal pain; warmth or cold; perceived motor disturbances, including cramping and tremor; perceived limitations in active range of motion; and perceived swelling within the phantom limb (see review (16)). The phantom limb can also be perceptually distorted, for example, reports of the phantom limb in sustained uncomfortable positions (17). The pathophysiology of PLP is complex; however, like CRPS1, it appears to be mediated within or by the CNS (4, 16).

CORTICAL CHANGES IN CRPS1 AND PLP – RELEVANT TO STROKE?

The CNS is highly adaptive and dynamic – functional organization and neuronal response profiles change according to use (1). Neuroimaging techniques investigate brain activity in association with tasks and stimuli, which in turn allow evaluation of the relationship between cortical changes and symptoms (2). Alterations in the size, shape, location and activation pattern of individual body-part representations in the sensorimotor cortex can effectively be visualized (18) and these images can suggest possible mechanisms underlying clinical conditions and their recovery. The neuroimaging findings in stroke, CRPS1 and PLP are presented and interpreted from this point of view.

The nature of cortical reorganization in stroke, CRPS1 and PLP

Recovery after stroke is thought to depend on cortical reorganization (2). Treatment generally employs repetitive verbal and manual cues and task-specific component training (5, 19). A number of studies have investigated the pattern of cortical changes post-stroke; one unifying conclusion is that the best motor recovery is associated with the greatest return to a normal state of brain function (2, 20, 21). Specifically, imaging studies performed before and after successful stroke rehabilitation show a variety of altered brain activation patterns including: a change in the location and the size of the affected areas; less bilateral brain activation; more activation along the rim of the damaged area; and some degree of diaschisis, where brain areas spatially distant take over the function of stroke-affected areas (see reviews (2, 21)). Several studies show that, with treatment, motor recovery occurs in parallel with increased motor cortex activity during movement; including possible changes in sensorimotor, pre-motor and supplementary motor cortices (2, 21) and a shift in the sensorimotor cortex representation (2).

In CRPS1 the sensorimotor cortex of the affected body-part changes in activation pattern, and in the size and location of

the body-part's cortical representation (3, 22, 23). It appears that the cortical representation effectively shrinks (e.g. in unilateral upper limb CRPS1, the distance between the centre of the representation for the hand and lip and between digits one and five of the affected limb are smaller than those of the unaffected limb) (23). Interestingly, the extent of shift in representation is correlated with the pain intensity (3, 23), a relationship also reported in people with PLP (4, 24). In addition, following treatment the greatest pain relief is positively correlated with normalization of the body-part representations in the somatosensory cortex (3).

Cortical reorganization is also a feature of PLP; like CRPS1, the shift in cortical reorganization is associated with pain intensity (4, 24). Altered affected body-part cortical representations are not surprising because of the missing limb's lack of sensory input and motor ability. The somatosensory cortex changes to reflect this with an expansion of the adjacent cortical representations into the amputated body-part representation (4, 24). Notably, cortical reorganization is related to PLP, but it seems to be unrelated to phantom limb pain intensity, stump pain, referred sensations and reports of telescoping (24). Further similarities in cortical activation patterns are noted with CRPS1 and PLP treatment. As with CRPS1 (3), reduced PLP in response to treatment correlates with normalization of cortical reorganization (4).

Clinical findings in stroke, CRPS1 and PLP

Synchiria. Synchiria is a clinical phenomenon in which a cutaneous stimulus that is applied to one limb evokes sensation simultaneously in both limbs (25). Synchiria occurs following stroke (26) and in amputees with PLP (27). Synchiria and dysynchiria have been observed in people with unilateral CRPS1 (28). In dysynchiria touch to the asymptomatic limb evokes the sensation of touch in that limb and pain and dysaesthesia at the corresponding site at a mirror-image site on the affected limb (28). Notably, the experience evoked on the affected limb matched that which would be evoked if that limb was actually touched. Synchiria and dysynchiria are assessed while the patient watches the unaffected limb stimulation with a mirror placed between their limbs such that patients can see the unaffected limb and its mirror image. Neither synchiria nor dysynchiria have been reported in healthy subjects and we have not been able to produce it in people with acute localized or radicular pain (28). However, synchiria has been reported in pain-free post-stroke patients (26), which suggests that the phenomena are not evoked solely in association with pain. The mechanisms underlying synchiria and dysynchiria remain to be elucidated, but could include any of the following working alone or in combination: (*i*) changes in spinal dorsal horn function (including central sensitization (29), bilateral sensory interneurones or ganglia (30), spinal cord or brainstem commissural interneurones (31), or glial cell activation (32, 33)); (*ii*) changes in subcortical structures (including changes in thalamic function (34, 35), associative somatosensory cortices, the insula, frontal cortices or the anterior cingulate cortex, each of which are known to change with CRPS1 (34,

36)) or altered communication between both hemisphere via the corpus callosum (37).

Referred sensations. In this type of sensory referral, a cutaneous stimulus is experienced both at the stimulated area (e.g. the face) and at another site that is anatomically remote but adjacent to the stimulated site in either the primary somatosensory cortex homunculus (S1) (e.g. the hand) (17, 38, 39), the secondary somatosensory cortex (SII), the thalamus, the posterior parietal cortex or the right dorsolateral prefrontal cortex (40). For example, touching the cheek can evoke the feeling of touch in the hand in patients with CRPS1 (39) and stroke (38) and in the phantom limb of amputees (17, 24, 40). This type of sensory referral may reflect changes in the response properties of S1 (37), SII, thalamic, posterior parietal or right dorsolateral prefrontal neurons (40) similar to that proposed to explain synaesthesia. In synaesthesia, stimulation of one sensory modality automatically triggers perception in a second modality (such as coloured numbers) and may be related to neuronal firing (37). However, the mechanisms underlying referred sensations may be more complex than a simple shift in neighbouring cortical representations (38). Possible mechanisms include mediation of extensive and interconnecting neural networks with variable synaptic strength (41), or loss of sensory input which may remove tonic inhibition from the affected zone ("disinhibition") such that sensory input from adjacent zones is now sufficient to activate neurons normally responsible for the anatomically remote area (41). That proposal is similar to the one offered for observations in primates, in which cortical synapses normally suppressed by simultaneous input from two connected neurons are thought to become disinhibited when sensory input from one area is removed (42).

IMPLICATIONS FOR TREATMENT

We propose that these neuroimaging and clinical data raise implications for the management of stroke, CPRS1 and PLP. First, it is accepted that stroke involves direct insult to brain tissue. Therefore one goal of stroke rehabilitation is to maximize the return of normal brain and limb function. Secondly, effective treatments that target cortical changes in stroke may be applicable across conditions characterized by cortical reorganization, and vice versa. Viewing the current literature from the perspective that stroke, CRPS1 and PLP may depend on similar cortical networks to attain maximal functional recovery, novel clinical pathways may be elucidated and investigated to foster the greatest cortical reorganization and recovery independent of the inciting condition (e.g. a peripheral injury in the case of CRPS1 and PLP and central brain damage in the case of stroke). This approach advocates an expansion of current management practices to include interventions which are associated with cortical reorganization and improved function. Interventions based on this model have demonstrated positive results (2–4) and raise potential avenues for treatment in other groups, in which cortical mechanisms may be important. Here we discuss 3 types of treatment to illustrate this point:

(*i*) mirror therapy (43, 44) and motor imagery (45–47), (*ii*) constraint-induced movement therapy (CIMT) (48), and (*iii*) sensory discrimination training (4).

Mirror therapy and motor imagery

Mirror therapy involves bilateral limb movement while simultaneously viewing the unaffected hand and its reflected image performing the movement. During mirror therapy, the affected hand remains hidden from view. Mirror therapy has been evaluated for two different purposes: pain relief with PLP and CRPS1, and motor recovery post-stroke. There is evidence that mirror therapy reduces pain in patients with CRPS1 (44) and anecdotal data suggest likewise for amputees with PLP (27, 37). There is also evidence that mirror therapy enhances motor ability over 6 months post-stroke (43, 49). Mirror therapy has been shown to increase ipsilateral primary motor excitability in healthy controls when compared with sham therapy (50), which may account for the improvement in motor function (43, 49). Mirror therapy is currently being evaluated for its ability to enhance motor recovery early post-stroke (51) when cortical reorganization is at its peak (19).

Motor imagery, which includes imagined movements of the affected limb, is effective in motor recovery in chronic (>6 months) post-stroke populations (45, 52). Motor imagery may be effective with both simple (e.g. wrist movement (45)) and complex (e.g. walking (52)) movement patterns. Similarly, graded motor imagery, which involves combining limb laterality recognition (determining limb images as right or left), imagined movements and mirror therapy (46), imparts improvement in pain and disability and functional gains with patients with CRPS1 (46). Because the effect is lost when the components are reordered, it is unlikely to be simply due to increased attention to the limb, but may depend on sequential activation of cortical sensory and motor networks (47).

The mechanisms underlying motor imagery remain unclear. Real and imagined movements activate similar cortical networks (53), and imagined performance is an established strategy in sports and performance psychology (54). Proposed mechanisms for improved motor recovery post-stroke with mirror therapy and motor imagery include: reconciliation of motor output and sensory feedback (44); activation of so-called pre-motor "mirror neurones", which have intimate connections with visual processing areas (55), are thought to prime the primary motor cortex (46) and to be important in imitating motor action (56); and graded activation of cortical motor networks (57). Although empirical data relating to those theories are lacking, mirror therapy and graded motor imagery programmes may be useful treatment with each of CRPS1, PLP and post-stroke patients.

Constraint-induced movement therapy (CIMT)

CIMT aims to effect cortical changes by forcing use of the stroke-affected limb through impeding use of the unaffected limb, for example by immobilizing the unaffected hand by placing it in an oven mitt (48). CIMT has shown promising results in the chronic stroke population, in whom most studies

have demonstrated expansion of the contralateral cortical motor areas corresponding to improved motor performance both after 2 weeks of treatment and at 6 months post-treatment (48). A proportional change in cortical representational and sensory and motor performance has also been demonstrated in healthy subjects given repeated peripheral input (58, 59) and in patients after stroke participation in repetitive-training regimes (60). One goal for CRPS1 treatment is to increase use of the limb through exercise, desensitization (applying gradual and variable sensory stimuli) and a gradual return to activities (61); however, to our knowledge CIMT has not been investigated formally in this population. CRPS1 has been associated with generalized disuse (62); therefore CIMT, used gradually and as pain allows, could produce good results in the treatment of CRPS1 and warrants further investigation.

Sensory discrimination training

Sensory discrimination training involves discrimination of the type and location of stimuli applied to the skin and has been investigated in amputees (4). In that study, patients localized short-duration electrical stimuli (50 Hz) on the affected limb (90 minutes daily for 10 days) and the results demonstrated three important findings: (*i*) patients had reduced PLP intensity; (*ii*) there was normalization of S1 organization; and (*iii*) both of the above correlated with improved performance on the sensory discrimination task (4). The mechanism underlying the effect is not clear. It is possible that active discrimination of the passive electrical stimulus influenced cortical reorganization and pain intensity as per repetitive learning regimes, or that it had a transcutaneous electrical nerve stimulation-like effect in reducing pain (63); or that it had an effect similar to sensory desensitization, which is often advocated for tissue hypersensitivity (8, 64). The neural mechanisms underlying the effects of sensory discrimination training on hypersensitivity are unclear. They may impact symptoms by influencing cortical reorganization of the somatosensory cortex in patients with CPRS1, PLP and stroke in a similar manner to repetitive learning-regimes in healthy individuals (58, 59) via normalization of somatosensory representation (4).

A common element of mirror therapy and motor imagery, CIMT and sensory discrimination training, is that they might target symptomatic and functional improvement by gradually providing adequate and appropriate input to influence cortical reorganization. In that sense, these approaches are akin to tasks such as learning to read Braille or to play a musical instrument, which are associated with altered sensory representation of the area trained in association with improved performance (58, 59).

DISCUSSION

We have proposed that it may be possible to adapt and apply treatments across post-stroke, CRPS1 and PLP patient populations because: (*i*) they share common neuroimaging and clinical findings; and (*ii*) the best recovery seems to be associated with the greatest return to normal brain function. Stroke

rehabilitation is based on the principle that functional recovery is contingent upon appropriate and maximal cortical activation and use-dependent learning. Similar use-dependent strategies might promote CRPS1 and PLP recovery. The proposed model assumes that improved cortical activation patterns underlie recovery in each of stroke, CRPS1 and PLP, and that interventions that promote maximal cortical reorganization may be applicable across conditions. The current review highlights similar neuroimaging, clinical and treatment-responses in the patient populations of stroke, CRPS1 and PLP. Based on these similarities mechanism-driven treatments that are effective in enhancing recovery in one patient population should be assessed for their effectiveness in the other patient populations. We have used the examples of mirror therapy and motor imagery, CIMT and sensory discrimination training to demonstrate the possibility that treatments associated with changes in cortical activation patterns may be effective across the conditions of stroke, CPRS1 and PLP.

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