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Loss of Surround Inhibition and After Sensation as Diagnostic Parameters of Complex Regional Pain Syndrome

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ABSTRACT

Complex Regional Pain Syndrome (CRPS) is a severe chronic pain condition. Patients with CRPS experience allodynia, hyperalgesia, autonomic dysfunction, movement difficulties and dystrophic changes. However other characteristics that may be unique to the pain in CRPS require further study. This study evaluated pain parameters in ninety five subjects composed of three groups: healthy pain free controls, patients with radiculopathy and CRPS patients. Healthy subjects were tested in all four extremities, whereas radiculopathy and CRPS patients were tested only on the most affected extremity. All subjects were tested for the following pain parameters: thermal allodynia, mechanical static and dynamic allodynia, windup, and a hyperalgesic mechanical stimulus. All subjects were also evaluated for autonomic dysfunction, movement disorder and dystrophic skin changes. Statistically significant differences were found between both pain groups and the healthy control subjects as well as between the two pain groups. The finding that statistically differentiated CRPS from radiculopathy and normal controls was pain spread following an algesic mechanical and cold stimulus as well as after sensations to these stimuli. The study demonstrated a simple bedside test that discriminated between CRPS, radiculopathy and healthy control subjects.

Keywords: CRPS; Complex Regional Pain Syndrome; Radiculopathy; Pain; After Sensation; Spread; Chronic Pain

1. Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic and often disabling pain disorder composed of a constellation of features that include: pain, autonomic dysregulation, edema, motor dysfunction and dystrophic changes [1-3]. It is most often caused by peripheral soft tissue injury, fracture, or nerve injury [2-5]. Emerging evidence suggests that peripheral small sensory nociceptive afferent fibers are causative when no major nerve injury is detectable [6]. Functional MRI and neuropsychological evaluation have demonstrated changes in the pain matrix, autonomic and motor systems as well as perceptual changes of body image over time and with treatment [7-11]. Although a great deal of progress has been achieved in regard to possible underlying causes, such as central sensitization [12,13], and immune mechanisms of induction and maintenance of chronic pain [14-16], many aspects of its pathophysiology remain unknown.

In our prior clinical observations of patients with CRPS, we noticed that an innocuous or slightly algesic mechanical stimulus, such as a pinprick, was perceived not only as severely painful, but also spread beyond the initial territory of the stimulus. In addition, the perception of the pain was maintained as an after sensation following stimulus removal. This study was undertaken to further evaluate the spread of a mechanical stimulus and its after sensation as a clinical test to differentiate CRPS from radiculopathy and normal sensory function.

2. Methods

2.1. Subjects

Subjects of either gender with a diagnosis of CRPS, cervical or lumbar radiculopathy and healthy and pain-free controls were recruited for this study. The CRPS and some of the radiculopathy subjects were recruited from the neurology clinics of Drexel University School of Medicine. The other radiculopathy subjects were recruited from a neurosurgical practice. Healthy pain-free control subjects were recruited from the general population. All subjects were enrolled after giving informed consent as approved by the Drexel University School of Medicine Institutional Review Boards.

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2.2. Inclusion Criteria

Healthy control subjects were accepted into the study if they did not have any acute or chronic pain and could be tested to all modalities on one extremity. The patients in the radiculopathy group had to demonstrate radiologic MRI and EMG as well as clinical evidence of radiculopathy at the tested segmental level. The CRPS patients met all the IASP criteria for Complex Regional Pain Syndrome [1]. Patients in the radiculopathy and CRPS groups had to have a stable pain greater than 4 on a 0 - 10 Likert numeric rating scale (NRS) where 0 being no pain and 10 the most severe pain imaginable. Subjects eligible for the study had to be between 18 and 65 years of age. They were allowed to continue their pain medication.

2.3. Exclusion Criteria

Subjects were excluded if they had significant comorbidities, which could be causing their pain in addition to radiculopathy or CRPS. They also had to be able to cooperate with quantitative sensory testing and clinical evaluation in all four extremities.

2.4. Pain Parameter Evaluation

The primary end points were after sensation length to an algesic mechanical (pin prick) and a cold stimulus as well as their spread on an extremity surface.

2.5. Thermal Allodynia

The testing of thermal allodynia to cold utilized the metal handle of a standard reflex hammer at room temperature applied to a standard test positions of the forearm (6 inches below the antecubital fossa) and/or mid calf for two seconds. Subjects reported quality of sensation, if it spread and if they continued to feel sensation after stimulus withdrawal. The subjects were asked to describe the sensation of the cold metal in terms of its perception as normal cold, icy cold, burning cold or "paradoxically hot". Spread was measured linearly in centimeters from the sites of application of the stimulus (0 to 10 cm). The after sensation was measured from the end of the stimulus in seconds (0 to 30 seconds).

2.6. Mechanical Allodynia and Hyperalgesia

An algometer with a 1 cm^2 rubber tip FDK 20 (Wagner Insling, Greenwich, CT) was utilized to measure static mechano allodynia. Pressure pain sensitivity was determined in three places in all four extremities in the control subjects or in the most affected extremity in the radiculopathy and CRPS patients. In the upper extremity, subjects were tested supraclavicularly (upper trunk of the brachial plexus primarily C5-C6 roots), 6 inches below the antecubital fossa, and on the middle joint of the third finger. In the lower extremity, measurements were obtained from the posterior popliteal fossa (the bifurcation of the posterior tibial and peroneal nerves, L4-S1 primary roots), the mid calf (6 inches below the popliteal fossa) and the third interphalangeal joint of the great toe. The algometer was pressed until the patient perceived the pressure as painful. The corresponding pressure in kilograms at that point was recorded. Pressure application was stopped at 4 kg/cm^2. It is not clinically possible to distinguish between sensitivity of the skin, muscle or the roots [17] although differences have been demonstrated in these tissues experimentally [17,18]. The measurements in the calf were felt to be a measure of the sensitivity of group III, IV muscle afferents [17,18] (nociceptors) and that from the joints C-fiber and A-δ fiber innervation [19]. Static and mechano allodynia and hyperalgesia elicited with Von Frey hairs were measured in the standard fashion on the extremities at similar locations [20]. A #5.07 von Frey hair was used to measure skin pressure sensitivity. Measurement of pain was recorded when the filament just bent after being pressed and was rated by the 0 - 10 Likert NRS. Also, Wind-up pain was elicited by 6 depressions of a von Frey hair at half second intervals: the duration of the elicited pain was measured for 30 seconds.

2.7. Dynamic Mechano Allodynia

A foam brush (3 inches in diameter) was lightly brushed over the skin at 6 cm/sec on the mid-forearm and/or calf. Subjects were asked to evaluate the sensation on the standard Likert numeric NRS of 0 - 10 in regards to the severity of pain it elicited.

2.8. Algesic Mechano Allodynia

Pinprick was utilized to measure a sharp mechanical (algesic) stimulus. One pinprick stimulus (a 2 inch pin steel safety pin with nickel plating) was applied (deforming but not puncturing the skin) to the standard test sites in all patient groups. The level of pain to the stimulus (Likert NRS), its spread and after sensations was determined. The spread of the stimulus was measured in one plane (linearly in the extremity) by a centimeter tape, up to 10 cm. After sensation was measured from the end of the application of the stimulus to when it could no longer be felt (up to 30 seconds).

2.9. Autonomic Parameters

Dilation of the veins, hyperhidrosis and livedo reticularis (lacy discoloration of the skin in the affected area) were evaluated by observation of the extremities and rated on

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a 0 - 4 scale (0 being normal and 4 being severely affected). Skin temperature was evaluated in the forearm and/or calf (standard positions) with a digital infrared thermometer (DermaTemp DT-1001 Infrared Thermographic Digital Scanner, Exergen Corp.). The average of three values from the same location was recorded as the skin temperature.

2.10. Movement Parameters

Initiation and facility of movement were assessed by asking the subjects to tap accurately and quickly their index finger to their thumb or wiggle their toes. Response was recorded on a 0 - 4 scale: 0 being unable to move the fingers and 4 being normally, accurate and rapid fine finger movement. Spasm, dystonia and tremor were assessed in the affected extremity on a 0 - 4 scale. Spasm was scaled with 0 being normal and 4 being severe involuntary contraction of the muscle. Dystonia was scaled with 0 being no dystonia and 4 being the extremity locked in a fixed position. Tremor of the affected extremity was assessed on a scale of 0 - 4 with 0 being absent and 4 being severe, constant and interfering with the function of the extremity. Muscle weakness in the hands was assessed with a Jamar Hand Dynamometer (measured compressive force to 100 kg). The subjects were required to squeeze the dynamometer with one hand as hard as possible. Strength was recorded in kilograms. Strength in the lower extremities was tested in the extensor hallucis longus and recorded on a scale of 0 - 5 (0 being no muscle contraction and 5 being normal strength). Reflexes were evaluated with a Standard Taylor Diagnostic Percussion Reflex Hammer at the biceps brachii and/or patella on a 0 - 4 scale: 0 is are flexia, 1 is a depressed reflex, 2 is a normal reflex, 3 is hyperreflexia and 4 is clonus.

2.11. Neurogenic and Dystrophic Changes

Neurogenic edema and erythema were evaluated on a scale of 0 - 4 (0 being not present and 4 being severe). All subjects were asked if his or her hair grew too quickly or fell out easily. They were similarly queried in regard to nail growth and integrity (splitting and ridging). Responses were recorded as positive or negative. Subjects were also asked about the presence of skin lesions in affected areas [21]. A brief description of the lesions was recorded.

3. Results

3.1. Demographics

Ninety five subjects were recruited for this study. The number of subjects in each group, their age, gender, duration of illness, overall pain and quality of life evaluation scores are tabulated in **Table 1**. There were no statistically significant differences ($p > 0.05$) in age or gender ratio between any of the three groups. Both pain groups demonstrated significantly ($p < 0.05$) greater pain scores and significantly ($p < 0.05$) lower quality of life scores than the healthy control group. However, there were no significant differences ($p > 0.05$) in overall pain or quality of life score between the CRPS and radiculopathy patients. Previous studies have shown that the ratio of women to men who have CRPS is approximately 4:1 [22]; our study also showed a female predominance in the CRPS group.

3.2. Subject Data

Parameters evaluating allodynia are tabulated in **Table 2**. Thermal allodynia to a cold stimulus was quantitatively different between healthy controls, radiculopathy and CRPS patients. 100% of healthy controls reported the cold metal stimulus to be normally cold. 93% of the radiculopathy patients reported the cold stimulus to be normally cold while 3% reported it as warm and 4% as numb. In the CRPS group, 38% reported the cold stimulus as a burning sensation, 12% as an icy-burn, 19% as icy, 16% as numb, 3% as warm and 12% as normal cold. None of the healthy controls reported spread of the cold stimulus and the average duration of after sensation was 1.46 sec. The radiculopathy group also experienced minimal spread of the cold stimulus (0.13 cm) and a very short duration of after sensation (7.32 sec). The CRPS group had significant spread of the cold stimulus with an average spread of 5.47 cm and an average duration of after sensation that was 24.38 sec.

Table 1. Demographics.

	Healthy Controls, H	Radiculopathy, Rad	CRPS
Number of Patients	35	28 Cervical = 6 Lumbar = 22	32
Males	16	11	9
Females	19	17	23
Age (years)	42.0	47.3	45.4
Duration of Illness (yrs)	NA	4.69	9.67
Overall PainRange P-Value	0 (0 - 1) ≤0.001 (H vs Rad)	8 (4 - 10) =0.936 (Rad vs CRPS)	8 (4 - 10) ≤0.001 (CRPS vs H)
Life Evaluation Score Range P-Value	10 (8 - 10) ≤0.001 (H vs Rad)	5 (0 - 10) =0.153 (Rad vs CRPS)	4 (0 - 6) ≤0.001 (CRPS vs H)

Age is reported as mean value; overall pain and life evaluation score are reported as median values.

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Table 2. Medians and means of allodynia parameters with standard error and range as well as associated p-values.

	Healthy Controls, H	P-Value (H vs. Rad)	Radiculopathy, Rad	P-Value (Rad vs. CRPS)	CRPS	P-Value (CRPS vs. H)
Thermal Allodynia Quality	100% Normal Cold	NA	93% Normal Cold 3% Warm 3% Numb	NA	38% Burn 12% Icy-Burn 19% Ice 3% Warm 16% Numb 12% Normal Cold	NA
Spread (cm) Range	0 (0)	0.980	0.13 ± 0.10 (0 - 2.5)	<0.0001	5.47 ± 0.78 (0 - 10)	<0.0001
Duration (sec) Range	1.46 ± 0.92 (0 - 30)	0.590	7.32 ± 2.23 (0 - 30)	<0.0001	24.38 ± 2.10 (0 - 30)	<0.0001
Dynamic Mechanical Allodynia Range	0 (0)	1	0 (0)	<0.001	6 (0 - 10)	<0.001
Static Mechanical Allodynia (lbs) Range	10.48 ± 0.13 (8.56 - 11)	0.001	8.88 ± 0.44 (2.5 - 11)	<0.0001	3.21 ± 0.31 (2 - 10.75)	<0.0001
Mechanical Joint Allodynia (lbs) Range	10.58 ± 0.12 (7.75 - 11)	0.025	9.38 ± 0.48 (2.5 - 11)	<0.0001	3.63 ± 0.31 (2 - 8)	<0.0001
Tinel's Sign (lbs) Range	10.31 ± 0.18 (7.75 - 11)	0.0004	8.55 ± 0.48 (4.5 - 11)	<0.0001	3.41 ± 0.26 (2 - 7)	<0.0001
Hyperalgesia with Von Frey Hair Range	0 (0 - 2)	1	0 (0 - 3)	<0.001	6 (0 - 10)	<0.001
Von Frey Hair Windup Pain Range	0 (0 - 4)	1	0 (0 - 8)	<0.001	8 (0 - 10)	<0.001

Static mechano allodynia and dynamic mechano allodynia showed similar results with the CRPS subjects reporting pressure turning to pain at much lower pressure values when compared to healthy controls and radiculopathy subjects. In addition, the CRPS group reported the most pain from the von Frey hair when compared to the other two groups.

The healthy controls and the radiculopathy group had no perception of pain from the pinprick stimulus (hyperalgesia). The CRPS group had a median pain level of 8 from the pin prick. The healthy control group had almost negligible spread of the pinprick sensation and no after sensation. The spread of sensation after a pinprick stimulus and the duration of the after sensation differed greatly between radiculopathy patients and CRPS patients ($p < 0.0001$) (**Table 3**, **Figure 1**). The radiculopathy patients had a longer duration of after sensation to pinprick than control patients, but this was four times less than the CRPS patients ($p < 0.0001$). CRPS patients demonstrated significantly longer after sensations and greatly increased spread as compared to control subjects and radiculopathy patients ($p < 0.0001$).

Parameters evaluating autonomic, movement, neurogenic edema and erythema are tabulated in **Table 4**. For autonomic involvement, the healthy controls and the radiculopathy patients both had statistically significantly less ($p < 0.001$) venous dilation and hyperhidrosis than the CRPS group. Skin temperature was found to be significantly increased in the healthy control group compared to the radiculopathy and CRPS patients ($p < 0.0001$; $p = 0.002$ respectively); however there was no difference in skin temperature between the CRPS group and the radiculopathy group ($p = 0.444$). The CRPS group demonstrated significantly more livedo reticularis ($p < 0.001$) than controls and radiculopathy patients.

The movement parameters of initiation, spasm, dystonia and tremor were all significantly more affected in CRPS patients than controls or radiculopathy patients ($p < 0.005$). There was no significant difference ($p = 0.154$) between CRPS and radiculopathy patients in regard to strength of the upper extremities; strength in the lower extremities was significantly different across all three groups with the CRPS patients having the lowest median value ($p < 0.001$). Reflexes were not significantly different across all three groups, as they all had a median value of 2 ($p = 0.318$).

Neurogenic edema and erythema were significantly increased in the CRPS group as compared to the other two groups ($p < 0.001$). Parameters evaluating dystrophic features and skin lesions are tabulated in **Table 5**. Dystrophic features were mixed with radiculopathy patients reporting the most hair growth, but the CRPS patients reported more hair loss. In addition, both the radiculopathy and CRPS groups reported increased nail growth, but the CRPS group reported the most difficulty with nails breaking easily**.** Skin lesions were only reported in CRPS

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Table 3. Median Pain Values and Mean Spread and After Sensation Values for Pinprick Parameters.

	Healthy Controls	P-Value (Controls vs. Rad.)	Radiculopathy (Rad.)	P-Value (Rad. vs. CRPS)	CRPS	P-Value (CRPS vs. Controls)
Pinprick Pain	0	1	0	<0.001	8	<0.001
Range	(0 - 2)		(0 - 8)		(0 - 10)	
Pinprick Spread (cm)	0.01 ± 0.01	0.155	1.35 ± 0.52	<0.0001	5.75 ± 0.73	<0.0001
Range	(0 - 0.25)		(0 - 10)		(0 - 10)	
Pinprick After Sensation (sec)	0	0.019	6.61 ± 2.36	<0.0001	24.22 ± 2.02	<0.0001
Range	(0)		(0 - 30)		(0 - 30)	

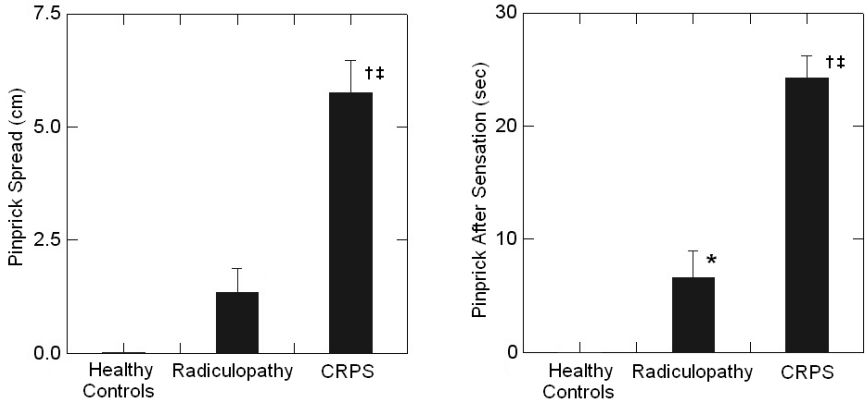

Figure 1. This figure illustrates the differences in pinprick spread (a) and after sensation (b) between the healthy controls, CRPS and radiculopathy groups. The radiculopathy group demonstrated greater pinprick spread (not significant $p = 0.155$) and significantly greater after sensation ($^{*}p < 0.05$) than the healthy controls. The CRPS group demonstrated significantly greater spread and after sensation than the healthy controls ($^{\dagger}p < 0.0001$) and the radiculopathy ($^{\ddagger}p < 0.0001$) groups. The CRPS group overwhelmingly felt more pain with the pinprick stimulus, felt the pinprick stimulus point spread the farthest and felt the pinprick stimulus last for the longest period of time.

Table 4. Medians and means of autonomic, movement and neurogenic parameters with standard error and range as well as associated p-values.

	Healthy Controls, H	P-Value (H vs. Rad)	Radiculopathy, Rad	P-Value (Rad vs. CRPS)	CRPS	P-Value (CRPS vs. H)
Autonomic						
Veins	1	1	1	<0.001	3	<0.001
Range	(0 - 4)		(0 - 3)		(1 - 4)	
Hyperhydrosis	0	1	0	<0.001	3	<0.001
Range	(0 - 2)		(0 - 2)		(0 - 4)	
Temperature (°F)	88.99 ± 0.24	<0.0001	86.31 ± 0.55	0.444	87.02 ± 0.41	0.002
Range	(85.63 - 92.30)		(78.4 - 90.3)		(78 - 90.7)	
Livedo Reticularis	0	0.605	0	<0.001	2	<0.001
Range	(0 - 1)		(0 - 2)		(0 - 4)	
Movement Initiation	4	0.003	3	<0.001	1	<0.001
Range	(3 - 4)		(0 - 4)		(1 - 3)	
Movement Strength Upper Extremity (kg)	35.77 ± 2.24	0.003	18.5 ± 2.32	0.154	8.31 ± 1.80	<0.0001
Range	(14.5 - 66)		(10 - 27)		(0 - 27)	
Lower Extremity (kg)	5	0.001	4	0.001	0.5	<0.001
Range	(3 - 5)		(0 - 5)		(0 - 4)	
Movement Reflexes	2	0.318	2	0.318	2	0.318
Range	(1 - 2)		(0 - 4)		(0 - 4)	
Movement Spasm	0	0.001	1.5	0.004	4	<0.001
Range	(0 - 1)		(0 - 4)		(0 - 4)	
Movement Dystonia	0	0.046	0	<0.001	3.5	<0.001
Range	(0)		(0 - 4)		(0 - 4)	
Movement Tremor	0	0.228	0	<0.001	2	<0.001
Range	(0)		(0 - 4)		(0 - 4)	
Neurogenic Edema	0	0.152	0	<0.001	4	<0.001
Range	(0 - 3)		(0 - 4)		(0 - 4)	
Neurogenic Erythema	0	0.765	0	<0.001	3.5	<0.001
Range	(0 - 1)		(0 - 3)		(0 - 4)	

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Table 5. Percentage of patients with dystrophic changes and presence of skin lesions.

	Healthy Controls	Radiculopathy	CRPS
Dystrophy of Hair Grows Fast	76% No 24% Yes	53% No 47% Yes	66% No 34% Yes
Falls Out	97% No 3% Yes	53% No 47% Yes	16% No 84% Yes
Dystrophy of Nails: Grow Fast	84% No 16% Yes	43% No 57% Yes	41% No 59% Yes
Break Easily	83% No 17% Yes	61% No 39% Yes	34% No 66% Yes
Skin Lesions	None	None	Blisters, Discoloration, Ulcers, Open Sores

patients and were described as blisters, hyperpigmentation, ulcers and open sores [21].

4. Discussion

The most important results of this study are that after sensations and spread of an innocuous and slightly algesic mechanical stimulus clearly discriminate CRPS patients from healthy control subjects and those with radiculopathy. There is an overlap of hyperalgesia as well as mechanical and thermal allodynia among many pain states including neuropathy, plexopathy and radiculopathy so that generalization of these findings to the former two conditions cannot be made [23]. This study also demonstrated significant differences in measures of mechanical sensitivity and motor function but not extremity temperature between CRPS and radiculopathy patients. Autonomic involvement and dystrophic changes in hair and nails were most significant in the CRPS group. Skin lesions were only seen in CRPS patients [21].

The cellular basis of neuropathic pain is incompletely understood. Emerging evidence primarily obtained from experimental pain models demonstrates sensitization of pain transmission neurons (PTNs) following nerve injury [12,24-27]. Physiologic correlates of this sensitization are spontaneous firing, hyperexcitability, enlarged peripheral receptive fields and response to afferents that are usually subthreshold [28,29]. Major physiologic correlates of hyperalgesic states are spontaneous bursts of nociceptive neuronal activity that produce prolonged after discharges (ADs) that out last the period of stimulation [28,30-32].

If spontaneous hyperactivity of wide dynamic range (WDR) PTNs can be modulated, they have an enhanced response to noxious stimuli [33-35]. Non-sensitized WDR and nociceptive specific neurons demonstrate a slow decay of post stimulus discharge following high threshold stimulation [29,36]. In the sensitized state, there is a correlation between action potential wind-up and the onset of spinal "plateau potentials" [31]. The intrinsic membrane properties of neurons that demonstrate these potentials are: 1) auto-regenerative discharges that trigger prolonged rhythmic action potentials that are produced within a restricted range of membrane potentials [27,37]; 2) accelerating discharges during intracellular current injection that "plateau" with prolonged stimulation [37-39]; 3) suppression by hyperpolarization [38]; 4) normal discharge expression occurs in a small number of dorsal horn neurons (DHNs) that increases with activation of metabotropic glutamate receptors or blockade of $GABA_B$ receptors [38]. The correlation of "plateau potentials" with long lasting after depolarizations in PTNs is supported by intracellular recordings obtained from in vitro slice preparations of cervical spinal cord Rexed lamina V WDR neurons. Stimulation of these neurons elicits high frequency responses that sustain a post stimulation discharge for several seconds (*i.e.* ADs) [40]. The initial calcium influx through voltage gated L-type Ca^{2+} channels [41] underlies its initial regulation, depolarization and firing acceleration. Its later component maintains high frequency firing and the expression of prolonged after discharges by a Ca^{2+} activated non-selective Ca^{2+} (I_{CAN}) current [42]. A small percentage of cells that exhibit "plateau" potentials are also capable of rapidly switching activity. Their firing mode may be determined by somatosensory stimuli [36]. These properties would endow this small percentage of DH nociceptive neurons to prolong a short stimulus to a longer lasting one which may be of significance in nociceptive processing [43].

ADs are considered to be a component of pain perception and maybe what was measured as "after sensation" in the present study [33,35,44,45]. A role for calcium currents in the induction and maintenance of neuropathic pain is well documented [46]. Isolated primary sensory neurons from the dorsal root ganglia in rats demonstrating pain behavior following nerve injury have decreased

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endoplasmic reticulum Ca^{2+} stores [47]. Voltage-activated I_{CAN} currents and decreased releasable Ca^{2+} in axotomized nociceptive neurons cause them to fire repetitively during sustained depolarization due to diminished cytoplasmic Ca^{2+} transients. The consequences of diminished intracellular Ca^{2+} concentrations and membrane currents is a decrease of Ca^{2+} activated K^+ currents which results in decreased action potential duration and hyperpolarization resulting in neuronal hyperexcitability [41,46-48].

A large body of evidence supports both synaptic activity and immune dependent mechanisms affected by modulation of microglia, astrocytes and PTNs that could cause after sensations that follow a hyperalgesic stimulus in chronic pain patients [12,15,21,27,47,49,50]. Phosphokinase C (epsilon isozyme) expressing interneurons of Rexed lamina V of the dorsal horn (DH) appear to be particularly important in a subset of NMDA-dependant spinal circuits for maintenance of injury induced chronic pain [51,52] a manifestation of which may be after sensations.

Another mechanism that may account for after sensation in CRPS patients is sensitized peripheral nociceptors recently demonstrated in experimental diabetes [53]. In our study, the other most significant sensory parameter separating control and radiculopathy patients from those with CRPS was spread of a mechanical hyperalgesic stimulus (pin prick). Focus and spatial containment of nociceptive stimuli occur at multiple levels of the neuraxis. At spinal and medullary levels A-δ afferents, $GABA_B$ and glycinergic neurons effect surround inhibition [12, 54,55]. Serotonergic and noradrenergic descending inhibitory fibers from the descending nociceptive inhibitory controls systems further modulate this inhibition [56]. As noted earlier, a manifestation of central sensitization is enlargement of the receptive fields of PTNs and their depolarization from heterotopic afferents that normally would not discharge them [12,28,29,57]. This mechanism could contribute to pain spread in these patients [58, 59].

Neuropsychological studies support plastic changes in both the affective and discriminative components of pain pathways in severe CRPS patients [60]. These patients often describe the affected extremity as feeling smaller or out of place [61]. Stimulating the painful area may be perceived in a different part of the body, such as the face or the contralateral extremity [9]. Proprioceptive deficits occur such that the patient is unaware of the location of the painful part [62]. These psychophysical phenomena have been correlated with dynamic and activity dependent functional MRI changes in the pain matrix [8,63-65]. One patient with generalized CRPS, who was studied with functional MRI, demonstrated false localization from the foot to the face. She demonstrated abnormal activation of the prefrontal cortex neurons that can rapidly shift from low frequency to high frequency firing by stimulation of their receptive fields [66]. This frequency change maybe correlated with spontaneous pain [36]. The prefrontal cortex, primary and secondary somatosensory areas, precuneus, cingulate and insular cortex reverted to normal activation patterns following anesthetic ketamine treatment. She had total relief of pain and false somatotopic localizations to mechanical stimuli [11].

The mechanisms for the greater spread of an algesic mechanical stimulus in CRPS patients as opposed to control subjects and radiculopathy patients are unknown. It is possible that there is a greater immune component in CRPS than radiculopathy. Evidence from the one autopsied patient with CRPS showed generalized (bilateral) spinal cord microglial and astrocytic activation that included the thoracic and cervical cord although the level of injury was at L4-S2 (left gastrocnemius muscle). Neuronal cell loss was seen throughout the spinal cord [50]. Experimental studies in rats with painful mononeuropathy demonstrate primarily segmental spinal level immune activation and loss of DHNs possibly selective for inhibitory GABAergic cells [67-69].

The ease of bedside measurement of both after sensations and spread of an algesic stimulus (pin prick) suggest its use to differentiate radicular from CRPS evoked pain. Prospective blinded studies will be necessary to validate this hypothesis.

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