Pain and other symptoms of CRPS can be increased by ambiguous visual stimuli – an exploratory study

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Abstract

Background: Visual disturbance, visuo-spatial difficulties, and exacerbations of pain associated with these, have been reported by some patients with Complex Regional Pain Syndrome (CRPS).

Aims: We investigated the hypothesis that some visual stimuli (i.e. those which produce ambiguous perceptions) can induce pain and other somatic sensations in people with CRPS.

Methods: Thirty patients with CRPS, 33 with rheumatology conditions and 45 healthy controls viewed 2 images: a bistable spatial image and a control image. For each image participants recorded the frequency of percept change in 1 minute and reported any changes in somatosensation.

Results: 73% of patients with CRPS reported increases in pain and /or sensory disturbances including changes in perception of the affected limb, temperature and weight changes and feelings of disorientation after viewing the bistable image. Additionally, 13% of the CRPS group responded with striking worsening of their symptoms which necessitated task cessation. Subjects in the control groups did not report pain increases or somatic sensations.

Conclusions: It is possible to worsen the pain suffered in CRPS, and to produce other somatic sensations, by means of a visual stimulus alone. This is a newly described finding. As a clinical and research tool, the experimental method provides a means to generate and exacerbate somaesthetic disturbances, including pain, without moving the affected limb and causing nociceptive interference. This may be particularly useful for brain imaging studies.

Introduction

Complex Regional Pain Syndrome (CRPS) is characterised by sensory, motor and autonomic abnormalities with pain as the central and most distressing feature (de Mos et al., 2009). The signs and symptoms of CRPS demonstrate volatility to a wide range of endogenous and exogenous stimuli (McCabe and Blake, 2008) and pain can be manipulated via cognitive, sensory and motor challenges (Moseley.et al., 2008a,b; McCabe et al., 2003).

Therapies that aim to restore movement via active or cognitive means and sensory desensitisation are reported to give therapeutic relief (McCabe and Moseley,2005; McCabe et al., 2003,2008a,b; Moseley et al., 2008b,c; Harden et al., 2006; Moseley, 2005). Similarly, visual manipulation of the affected part has been shown to induce, exacerbate and ameliorate pain in chronic pain and CRPS patients (Ramachandran and Altschuler, 2009; McCabe et al., 2008a; McCabe et al., 2007; Moseley et al., 2008c). The majority of studies have assessed the sensory consequences of visual manipulation on a moving affected limb. In this experimental pilot study we examined the effects of visual conflict alone using a Necker cube, a well known example of a reversible figure without any obvious contextual features which could evoke an emotional response (Long and Topino, 2004; Gregory, 1998). This was prompted by our patients' reports of visual disturbances which were not related to objective changes in visual performance when assessed by an optometrist. Typically, these visual disturbances occur during normal daily life and include bizarre illusions of seeing tall buildings 'jumping' or 'shimmering,' and difficulties in reading and watching television. Furthermore, and of clinical significance, the visual discord provokes an increase in symptoms (eg, pain, paresthesia, temperature changes). Thus, our exploratory pilot study attempted to establish whether the sensory disturbances reported by our CRPS patients could be replicated in the laboratory setting. We hypothesised that pain and other symptoms would

be exacerbated when people with CRPS viewed the Necker cube; (i) compared to viewing an unambiguous, non-reversible figure and (ii) compared to people with other chronic pain conditions, or healthy controls

Method

The perception of pain is a complex construct, thus a mixed methods study was employed to generate deeper insights than would be possible with a quantitative method alone.

A purposive sample of adult patients who met the IASP diagnostic criteria for CRPS type 1 (Bruehl et al., 1999) were recruited from patients attending the CRPS service at the Royal National Hospital for Rheumatic Diseases (RNHRD), Bath. There were two control groups; patients with general chronic rheumatology conditions recruited from the hospital clinics, and a group of healthy volunteers recruited from staff and visitors. Participants were excluded if they had a concurrent neurological diagnosis, loss of vision or visual disturbances (eg, blurred/double vision) or had viewed the Necker cube during clinical practice. No limitations were placed on routine medication prior to testing. The sample size was based on the number of subjects available within the 6-month time period.

Participants were informed that the purpose of the study was to explore the effects of visual tasks in chronic pain conditions. The rationale provided was that people with chronic pain may differ from healthy controls in processing visual signals due to the attentional demands of pain. Importantly, the participant information sheet stressed that the focus of the study was quantitative (relating to the number of times the percept altered) and there was no mention of potential sensory changes. This explanation met the criteria for informed consent as outlined

by the approving ethics committee (Bath Local Ethics committee, UK) but was considered sufficiently vague not to induce a source of bias.

Procedure

A sequence of three images, each printed on an A4 sized card were shown: these consisted of an ambiguous Duck/Rabbit image, a Necker Cube (RF) and a non reversible figure (NRF) depicting the inner rectangle and dot from the Necker figure, which represented the control condition (Figure 1). The images were placed on a table and the participants seated in a chair at a distance that approximated reading distance, thus the images subtended approximately 4°-10° of the visual arc. This figure is only approximate as the participants were invited to view the images from a comfortable, rather than precisely determined, read position.

Informed consent was taken, in accordance with the Declaration of Helsinki guidance and a short interview to establish demographic and current health status. The Duck/Rabbit was used to illustrate the experimental task and was chosen for this purpose because it lacks the spatial percept inherent in the Necker cube. The bistable nature of the image was pointed out to the participants, who were then asked to confirm that they could see both the Duck and the Rabbit by pressing a digital counter, using their preferred hand. Participants were then informed that they would be shown a series of pictures and again, asked to indicate changes in percept. All participants were cued to focus on the frequency of percept change. Care was taken not to specify the number of pictures to be shown.

The RF and NRF were then shown in sequence, with sequential alteration between participants, for a maximum of 60 seconds each. A rest period of two minutes was given

between each of the figures. At the end of 2 minutes subjects who did not feel ready to continue were given up to 10 minutes before continuing. Before and after each viewing condition patients verbally rated their pain intensity using an eleven point numerical rating pain scale (NRS - where 0 was equivalent to no pain at all, and 10 to the worst pain imaginable (Williamson and Hoggart,2005), and to describe what they saw and what, if anything different they felt, during the viewing. These descriptions were recorded verbatim by the researcher.

Data Analysis and Management

In order to test the hypothesis that the RF condition would increase pain intensity (Numerical Rating Scale) more than the NRF in the CRPS group we undertook repeated measures ANOVA with group as between subjects factor and condition (RF and NRF) and time (pre and post) as within subjects factors. Given the wide variance in pain intensity between patients and healthy controls and the assumption of similar variability between groups required by ANOVA, only the CRPS and rheumatology group data were entered into this analysis. The number of percept changes was analysed by one-way ANOVA to examine for group differences; a paired t-test was used to examine differences between figures.

Qualitative data, generated from the subjects' responses to the open questions was tabulated on MS-Excel and analysed using content analysis (Holsti, 1968; Frankfort-Nachmias and Nachmias, 1992). A process of iterative inductive generation of categories from the descriptive responses generated a number of themes, which corresponded to the diagnostic criteria for CRPS vasomotor, sudomotor and motor symptoms (sensory, pain and paresthesia

were coded separately). Other categories included body perception disturbances (weight/pressure changes, altered sensitivity, loss of limb), affective (feelings of frustration, anxiety, tension) and miscellaneous (disorientation, nausea, eye fatigue, dry mouth). A second independent coder verified category generation; the interrater reliability was found to be Kappa=0.69 ($p < .0.001$).

For statistical testing, these data were summarised by determining the frequency of report of a particular sensation at each stage of the protocol and its reported change. The data were analysed in three categories according to reported change (worse, same, better), and two categories according to type (pain / other somatic sensations).The data were examined using Chi-square test. All statistical tests were performed using SPPS Version 16, a p value ≤ 0.05 was considered significant.

Results

Thirty patients with CRPS (Type I), thirty-three with general rheumatology disease and forty-five healthy controls were studied. Table 1 details the demographics of the participants recruited.

Statistical Analysis

There was main effect on Numerical Pain Rating of group ($F(1, 61=7.33$, $p=0.009$) (Table 2). There were significant "group by time" ($F(1, 61) =8.4$; $p=0.005$) and "condition by time by group interactions" ($F(1, 61) =8.67$; $P=0.005$). This means that pain intensity differed significantly between condition and group such that pain increased in the CRPS group and decreased in the Rheumatology group after viewing the RF (Fig 2). There was, similarly, a

significant difference between the CRPS and Rheumatology groups, for frequency of qualitative pain (x2=19.9, P<0.01) and of other bodily sensation change (x2=17.5; P<0.01) (Table 3). Table 4 defines the type of somaesthetic changes experienced by each of the groups. In addition 37% of patients with CRPS reported increasing somaesthesia during NRF (x^2=17.5; P<0.01).

While there was, as expected, a significant difference between the two visual stimuli in the number of percept changes, there was no difference between groups (Table 5). However, of interest is that four participants in the CRPS group found the RF changed more frequently than the button could be pressed and were unable to complete the task for the full minute.

Qualitative Results

Participants in the rheumatology and healthy control groups reported fewer and more minor sensory disturbances when viewing the figures compared to the CRPS group (Table 4). Most of these sensory effects related to eye fatigue and feelings of slight disorientation ("almost felt a bit wobbly", and "I felt agitated /squiffy"). When viewing the RF and NRF respectively, some participants (12 for RF, 2 for NRF) in the rheumatology group described that their pain diminished and attributed this to "my mind is concentrating on something other than pain".

In the CRPS group eight subjects responded in a similar way to the healthy volunteers in that six reported no change in any sensations to either figure. Of the remaining two subjects, one reported amelioration of their symptoms - attributed to distraction via attention to the figures - and one noted that they felt "a little bit giddy, probably because I was staring at it". The remaining 22 subjects (73%) responded in ways that were different from the healthy and

rheumatology groups. These responses ranged from the mildly to the extremely distressing. Responses at the mild end of the spectrum were isolated or temporary sensations. For example, one subject reported that their pain became more 'nagging'; another reported the onset of 'tingling' on their (affected) forearm, which ceased when the stimulus was removed.

Four subjects with CRPS reported being extremely distressed and were unable to look at the RF for the full minute (mean: 40s, SD: 15.7) due to increases in pain. Furthermore, two of these patients were unable to view the NRF for the full minute (14s and 28s). The symptoms reported included paresthesia ("the tingling has changed to a very deep and irritating feeling"), dizziness, nausea ("don't feel too good……sweaty, feel flushed, sickly, hot, bothered"), temperature changes ("foot is flushed hot now"), perceived weight changes (" right shoulder feels heavy", "entire arm heavy") and disorientation ("feel almost trance-like"). Observation of these subjects showed a characteristic pattern of extreme blinking, looking away, and finally shutting their eyes with head averted and asking for the picture to be removed. No differences between these 4 subjects and others in the CRPS group could be found in relation to baseline pain (NRS), location, symptom duration or medication.

All sensory changes reported by the rheumatology and healthy control groups disappeared rapidly on removal of the stimulus. Whilst this was similar for most of the CRPS group, four of the participants had not returned to their baseline pain values by the end of the 2 minutes rest period and all required the maximum recovery time before proceeding to the next stage of the protocol.

Discussion

The data supports the hypothesis that pain and other symptoms are exacerbated in patients with CRPS, when viewing the RF compared to viewing the NRF but not in other chronic pain patients or healthy controls. Both qualitative and quantitative data supported the hypothesis but the qualitative data was particularly strong with 73% of the CRPS group reporting exacerbation of their pain or other CRPS symptoms on viewing the RF. Furthermore, we identified a small group (13%) who responded with striking worsening of their symptoms, and consequent inability to complete the experimental task. These results differ significantly from rheumatology patients and healthy controls who reported only minor symptoms; in the former group almost half reported improvement in their pain due to attending to the picture. The experimental design does not allow us to attribute the results to the RF alone but it would appear that symptom increase is confined to patients with CRPS.

Our study is limited by the lack of quantitative measures as well as several possible confounding factors. Expectation, suggestion and arousal are possible sources of confounding. The investigators were not blind to the study's hypotheses; however, every attempt was made to use neutral language and to draw subjects' attention to the button count rather than their experiences. Medication may have had an effect on our outcomes as all of the 'severe' responders were on anticonvulsant medication. However, half of the CRPS sample group with mild response were also on similar dosages of psychotropic medication. Furthermore, 24% of the rheumatology group were taking antidepressants also and none of these patients exhibited more than minor symptoms. Nevertheless future studies should include medication and dose as covariates.

Participants with CRPS demonstrated a spectrum of response ranging from none to severe distress which in some cases necessitated task cessation. These participants reported reversal

rates which were too fast to record, suggesting that the speed of reversal was linked to symptom exacerbation. This might be further tested by using two images that are highlighted to draw attention to only one of the two potential visual precepts and these images being alternated in a graded, accelerating manner whilst the subjects' symptom responses are recorded (e.g. a single session of fixed time with the rate of image change controlled at a fixed speed. Escalation of speed of image change in subsequent sessions would allow systematic responses to be measured). Objective evidence of autonomic changes within the affected limb could be captured in this paradigm by adding measures of galvanic skin response and laser Doppler flowmetry.

The switching rate of RF has been used to elucidate the processes underlying perceptual instability and using fMRI, Lumer et al (1998) showed that activity in the visual and frontoparietal cortices was heightened during perceptual transitions (Sterzer et al., 2002; Long and Topino, 2004). It is of note that superior and inferior parietal lobes and anterior intraparietal sulcus are involved in switching as these areas are also activated during hand laterality tasks. The response to such tasks is slower for the affected side in CRPS and suggests disruption of the body schema, the neural correlates of which reside in the parietal cortices (de Lange et al., 2006; Moseley, 2004). Our clinical experience has shown that some patients respond to laterality training in a similar manner to a RF and therefore using a bistable image might provide a rapid clinical assessment to establish suitability for hand laterality training. That perceptual transitions activate the parietal cortices is of particular interest in CRPS aetiology, firstly because of its afferent role in movement via sensory integration and secondly, because it maps for the body schema, disruption of which is reported in CRPS (Lewis et al., 2007; Moseley, 2005; Förderreuther et al, 2004; Galer and Jensen, 1999). Future studies in which the relationships between the response to perceptual

instability, Body Perception Disturbance and vulnerability to sensorimotor disruption are examined may add to the body of literature suggestive of parietal dysfunction in CRPS (Cohen et al., 2009; Schwenkreis et al., 2009; Schwoebel et al., 2001)

Conclusion

This exploratory mixed methods study has shown that the symptoms of CRPS can be exacerbated by viewing ambiguous figures. This phenomenon corroborates anecdotal accounts of the visual disturbances reported by some patients with CRPS. However, further studies which include objective markers of symptom change are required to confirm these initial findings. Our experimental method provides a means to generate or exacerbate somaesthetic disturbances, including pain, without nociceptive interference which could be a useful technique for future studies, particularly those involving imaging. .

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Figure/table Legends

Figure 1. Flow diagram illustrating the sequence of images

Table 1- Participant characteristics.

Figure 2 – Pain intensity on a 10cm Numerical rating scale (mean and SD) before and after each figure

Table 2 – Results from repeated measures ANOVA on Numerical Pain Rating Scale (n=63)

Table 3- number and (%) of participants reporting altered pain and somaesthesia during reversible (RF) and non-reversible figure (NRF) viewing. Pain increased in the CRPS group and decreased in the Rheumatology group during RF ($P<0.01$). A significantly greater proportion of the CRPS group reported somaesthetic disturbance during RF and NRF ($P<0.01$).

Table 4 – number of participants (%) reporting presence, exaggeration or amelioration of somaesthetic experiences, excluding sensory pain, in each of the coding categories.

Table 5. Frequency of button press (mean and SD). Excludes data from 4 subjects in CRPS group as speed of percept change was too rapid to record and subjects were unable to view for full duration.

Figure 1. Flow diagram illustrating the sequence of images

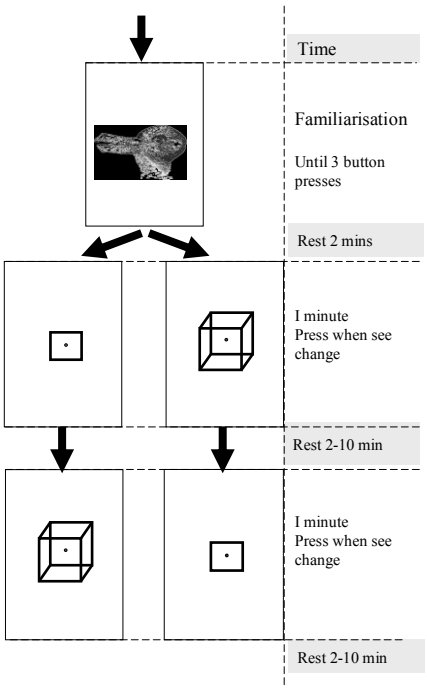

Time
Familiarisation
Until 3 button presses
Rest 2 mins
I minute
Press when see change
Rest 2-10 min
I minute
Press when see change
Rest 2-10 min

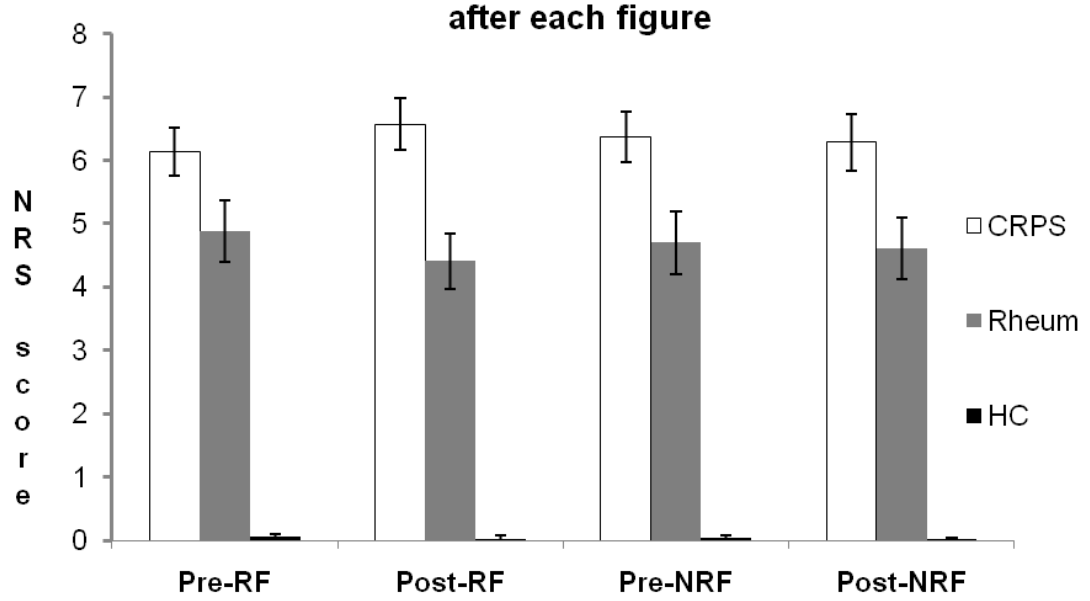
Table 1- Participant characteristics.

Subject characteristics	**CRPS (n=30)**	**Rheumatology (n=33)**	**Healthy Controls (n=45)**
Age (years) [mean& range]	42 (20-63)	63.6(24-88)	46 (22-64)
Male	9	10	4
Distribution of CRPS/ Rheumatology conditions (n=)	UL=13 LL=10 ULLs=4 LT=3	RA=16 OA =13 V=2 AS =1 PsA =1	
Time since diagnosis [median (range)]	16 months (0-9 years)		
Numerical Pain Rating scale (mean&SD)	6.17(2)	5.1(2.7)*	0.044 (0.2)
Frequency of comorbidity	46.6%	59.9%	28.8%
Medication (n)			
DMARDs	0	15	0
Non-opioid analgesic	11	12	1
NSAID	9	13	2
Weak opioid analgesic	17	16	0
Strong opioid	7	5	0
Steroid	0	9	2
Osteoporosis prophylaxis treatment	2	13	0
Gastroprotection	3	16	1
Cardiovascular	6	22	4
Anti-epileptic/anti-depressant	18	8	3
Oral hypoglcaemics	0	5	1
Lipid lowering drugs	0	7	3
HRT	4	2	3
Respiratory medication	5	1	3
Miscellaneous	12	10	3

UL-upper limb, LL-Lower lib, ULLs-Upper and lower limbs, LT-limb and trunk.
RA-Rheumatoid arthritis, OA-osteoarthritis, V- vasculitis, AS-ankylosing spondylitis, PSa-psoriatic arthritis
DMARDs- disease modifying anti-rheumatic drugs
NSAID - Non steroidal anti-inflammatory drug
Cardiovascular (inc. anti-hypertensives, anti-arhythmics, anti-anginal drugs, anti-platelet agents, anticoagulants)

HRT - hormone replacement (inc. thyroxine)
Miscellaneous (vitamin/iron supplementation, antihistamine, night sedation, prostate/bladder medications, antibiotics, antiemetics, quinine)
*There were no significant differences in pain at baseline between patients in the CRPS and rheumatology groups (unpaired t-test).

Fig 2 - Numerical Pain Rating (mean+/-SEM) before and after each figure



Pain increased in the CRPS group and decreased in the Rheumatology group for the RF figure only [F(1,61)=8.67; P=0.005].

Table 2 – Results from repeated measures ANOVA on Numerical Pain Rating Scale (n=63)

Source of Variation	df	Sum of Squares	Mean Square	F	P
Group	1	179.5	179.5	7.33	0.009
Error	61	1492.8	24.5	-	-
Condition	1	0.005	0.005	0.009	0.9
Error	61	31.1	0.509	-	-
Time	1	0.174	0.174	0.45	0.5
Error	61	23.6	0.39	-	-
Group X condition	1	0.017	0.017	0.033	0.86
Group X time	1	3.26	3.26	8.4	0.005
Condition X time	1	0.075	0.075	0.206	0.65
Group X condition X time	1	3.15	3.15	8.67	0.005

Table 3- number and (%) of participants reporting altered pain and somaesthesia during reversible (RF) and non-reversible figure (NRF) viewing. Pain increased in the CRPS group and decreased in the Rheumatology group during RF ($P<0.01$). A significantly greater proportion of the CRPS group reported somaesthetic disturbance during RF and NRF ($P<0.01$).

	RF			**NRF**		
Qualitative Pain	**CRPS (n=30)**	**Rheum-atology (n=33)**	**Control (n=45)**	**CRPS (n=30)**	**Rheum-atology (n=33)**	**Control (n=45)**
Increased	13 (43%)	2(6%)	0 (0)	3 (10%)	2(6%)	0
Same	16 (53%)	18 (54.5%)	44(97.8)	24 (80%)	27 (81.8%)	100 (100%)
Decreased	1 (3%)	13 (39.4%)	1 (2.2)	3 (10%)	4 (12%)	0
Qualitative: somaesthesia						
Increased	15 (50%)	5 (15%)	3 (7%)	11 (37%)	2 (6%)	3 (7%)
Same	12 (40%)	28 (85%)	42 (93%)	14 (47%)	31 (94%)	42 (93%)
Decreased	3 (10%)	0	0	5 (17%)	0	0

Table 4 – number of participants (%) reporting presence, exaggeration or amelioration of somaesthetic experiences, excluding sensory pain, in each of the coding categories.

	Exacerbation of Symptoms						**Amelioration of Symptoms**					
	CRPS		**Rheum**		**HC**		**CRPS**		**Rheum**		**HC**	
	RF	**NRF**	**RF**	**NRF**	**RF**	**NRF**	**RF**	**NRF**	**RF**	**NRF**	**RF**	**NRF**
Sensory-Paraesthesia	7 (23.3)	2 (6.7)	-	-	-	-	1 (2.2)	2 (4.4)	-	-	-	-
Vasomotor	8 (26.6)	2 (6.7)	-	-	-	-	1 (2.2)	-	-	-	-	-
Sudomotor	4 (13.3)	1 (3.3)	-	-	-	-	-	-	-	-	-	-
Motor	3 (10)	2 (6.7)	-	-	-	-	-	-	-	-	-	-
Body Perception change	6 (20)	2 (6.7)	-	-	-	-	2 (4.4)	2 (4.4)	-	-	-	-
Affective	5 (16.6)	2 (6.7)	2 (6.7)	-	-	-	1 (2.2)	-	-	-	-	-
Miscellaneous	9 (30)	7 (23.3)	3 (10)	-	3 (9)	3 (9)	-	-	-	-	-	-

Sensory-Paraesthesia changes: pins and needles, formication.
Vasomotor changes: temperature or colour changes.
Sudomotor changes: sweating changes.
Motor changes: changes in or presence of cramping, stiffness, twitching , tremor.
Body perception changes: weight/pressure changes, altered sensitivity, loss of limb.
Affective symptoms: feelings of frustration, anxiety, tension and well being.
Miscellaneous symptoms: disorientation, nausea, fatigue, eye fatigue and dry mouth.

Table 5. Frequency of button press (mean and SD). Excludes data from 4 subjects in CRPS group as speed of percept change was too rapid to record and subjects were unable to view for full duration.

	CRPS (n=26)	**Rheum (n=33)**	**HC (n=45)**
Reversible Figure	9.7 (6.5)	7.7 (5.1)	8.9 (4.6)
Non-reversible figure	1.2 (2.3)	0.7 (1.5)	0.7 (1.5)