

# Relationship between delayed episodic pain flares and release of stress-related thyroxine in a patient with complex regional pain syndrome- a case report

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## INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic pain disorder characterized by autonomic changes and pain in an extremity which is out of proportion in intensity and duration to the inciting trauma.<sup>1,2</sup> Pain experienced by individuals with CRPS fluctuates over time and manifests episodic peaks.<sup>1</sup> These episodic pain flares are often debilitating and can lead to dramatic changes in lifestyle, activity participation, and fulfillment of life roles. Patients may begin limiting many life activities, uncertain as to which ones are causing the severe flares. Since the antecedents of many pain flares are uncertain, it is a challenge for therapists to help patients understand what factors(s) may have precipitated a particularly painful episode, minimize future pain flares, or distinguish between flares brought on by overly aggressive therapeutic activity and those due to other activities or circumstances.<sup>3</sup> Many factors, such as excessive limb use, maladaptive activity pacing, pain contingent

## ABSTRACT

**OBJECTIVE:** The purpose of this study was to investigate temporal relationships between daily stress, perceived pain intensity, pain-related function, and serum levels of the stress-related hormone thyroxine in a patient with complex regional pain syndrome (CRPS).

**DESIGN:** Case report.

**PARTICIPANT:** The participant was a 54 year-old woman with a five year history of right lower extremity CRPS. She had no history of thyroid pathology and was on stable time-contingent neurontin for pain.

**MEASURES:** Measures for this study included visual analog stress scale (VASS), visual analog pain scale (VAPS), an individualized visual analog function scale (VAFS), the McGill pain questionnaire short form (SF-MPQ), and free serum thyroxine (T4) assays.

**RESULTS:** Over ten weeks, four peak stress episodes and eight significant pain flares were observed. Each stress episode was followed ten days by a significant pain flare and peak free T4 values exceeding the normal adult range (2.4ng/dL). Serial lag correlations were strongest between stress and pain for pain experienced ten days after a stressor ( $r=+0.281$ ,  $p<0.05$ ) and stress and function for function ten days after a stressor ( $r=-0.329$ ,  $p<0.05$ ). Free thyroxine index (FTI) was correlated most highly with stress ten days following a stressful episode ( $r=+0.428$ ,  $p<0.001$ ). Same-day pain and FTI were correlated at  $r=+0.651$ ,  $p<0.001$ . Same-day pain and function were highly correlated ( $r=-0.875$ ,  $p<0.01$ ).

**CONCLUSIONS:** The temporal relationships observed in this study support the hypothesis that increased pain activity following ten days after stressful events may be related to the psychogenic release and activity of the stress-related hormone thyroxine in patients with CRPS.

**Key words:** Complex Regional Pain Syndrome, thyroxine, stress, delayed pain

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exercise/activity, tactile hypothesized to account for contact, temperature changes, the appearance of episodic and stress have been pain flares.<sup>2,3</sup>

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Complex regional pain syndrome (CRPS) is a chronic pain disorder characterized by autonomic changes and pain in an extremity which is out of proportion in intensity and duration to the inciting trauma.<sup>1,2</sup> Pain experienced by individuals with CRPS fluctuates over time and manifests episodic peaks.<sup>1</sup> These episodic pain flares are often debilitating and can lead to dramatic changes in lifestyle, activity participation, and fulfillment of life roles. Patients may begin limiting many life activities, uncertain as to which ones are causing the severe flares. Since the antecedents of many pain flares are uncertain, it is a challenge for therapists to help patients understand what factors(s) may have precipitated a particularly painful episode, minimize future pain flares, or distinguish between flares brought on by overly aggressive therapeutic activity and those due to other activities or circumstances.<sup>3</sup> Many factors, such as excessive limb use, maladaptive activity pacing, pain contingent exercise/activity, tactile contact, temperature changes, and stress have been hypothesized to account for the appearance of episodic pain flares.<sup>2,3</sup>

A number of case studies have reported consistent correlations between peak stress days and pain flares occurring ten days later in patients with fibromyalgia syndrome (FS)<sup>10,12</sup> and CRPS.<sup>3,9</sup> After administering ten weeks of daily stress and pain inventories to two male

patients with type I CRPS, Hulten et al. found correlations of  $r = +0.49$  and  $r = +0.52$  between stress and flares in pain occurring ten days later, compared to same-day stress and pain correlations for the two patients of  $r = +0.04$  and  $r = +0.14$ . Similar results were reported by Harlow, et al. for three patients with fibromyalgia syndrome assessed daily over a ten-week period. For the patients with fibromyalgia syndrome same-day stress and pain intensity correlations ranged from  $r = 0.00$  to  $r = +0.03$ , while correlations between stress and pain ten days later were as high as  $r = +0.70$ .<sup>10</sup> They further reported that of 19 notable peak stress days occurring across all three patients during the ten-week period,<sup>17</sup> of those stress episodes were followed ten days later by pain flares that exceeded the patients' average pain intensity ratings by more than two standard deviations.<sup>10</sup> A case series report quantifying the extent of pain distribution across time found that ten days following significantly stressful days, patients with fibromyalgia syndrome reported an increased extent of their bodies to be in pain, indicating that the latent pain response is not limited to perceived pain intensity, but also influences how much of the body is perceived to be painful.<sup>12</sup> Studying the relationship between stress and delayed pain responses in 38 patients with fibromyalgia syndrome participating in a four-week multidisciplinary pain program, Pyle et al. found "In all statistical comparisons, the

most significant mean elevations in pain responses occurred on day 10 following program intake/initial evaluation. It may be concluded that stress increases are associated with delayed episodic pain flares and pronounced sensory and affective responses to pain occurring ten days later in patients with FS."<sup>11</sup>

Allen and Moe suggest a plausible psychophysiological mechanism that may account for this ten-day delay between the occurrence of a salient stressor and a flare in neuropathic pain involving the hypothalamic-pituitary-thyroid (HPT) axis.<sup>13</sup> In this pathway of the stress response, after their psychogenically mediated release, thyroid hormones thyroxine (T4) and triiodothyronine (T3) are immediately bound to serum thyroxine-binding globulins (TBGs), thus delaying the effects of T4 and T3 until they dissociate from the TBGs.<sup>14</sup> The half-life of this bond is such that free thyroxine is released to produce a well established symptomatic peak approximately ten days after initial secretion from the thyroid.<sup>15-17</sup> Effects of thyroxine include increased peripheral nerve excitability, central nervous system sensitization, and insomnia, which may mediate both nociceptive input intensity and cognitive interpretation of pain.<sup>3,18-20</sup>

Connections between the activity of thyroid hormones via the HPT axis and the experience of pain have been cited in previous literature. Hyperthyroid mice have demonstrated more sensitivity to pain and showed

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decreased analgesia response duration to exogenous morphine.<sup>21</sup> Neeck reports that a factor contributing to a dysfunctional stress response system in FS patients involves alterations in thyroid activity.<sup>22</sup>

While theoretically plausible, there is not yet evidence that the stress-related release of thyroxine is the mechanism responsible for changes in pain intensity occurring ten days after significant stressors for patients with chronic neuropathic pain syndromes.<sup>18</sup>

The purpose of this study was to investigate a hypothesized psychophysiological mechanism for recent findings that psychogenic stress episodes precipitate delayed flares in pain intensity occurring ten days after the stressful event in patients with CRPS. Specifically, this study assessed temporal relationships over a ten-week period between daily stress, perceived pain intensity, pain-related function, and serum levels of the stress-related hormone thyroxine in a patient with CRPS.

### MATERIALS AND METHODS

This study was approved by the University of Puget Sound's Institutional Review Board (IRB protocol #0607-007) and informed consent was obtained from the participant.

Purposive selection identified a participant with CRPS. Inclusion criteria were 1) diagnosis of CRPS for at least one year; 2) over 18 years of age; 3) willing and able to provide a daily blood

sample for ten weeks; 4) willing and able to complete daily stress, pain, and function assessments for ten weeks; 5) normal thyroid function; 6) time contingent medication for pain. Exclusion criteria were: 1) under 18 years of age; 2) cognitive impairment making it difficult to follow directions, complete daily inventories and provide blood samples; 3) history of thyroid disease or thyroidectomy; 4) thyroid supplementation or altering medication; 5) chronic tachycardia; 6) chronic insomnia; 7) treatment for anxiety disorder; 8) blood coagulation disorder; 9) pain contingent (PRN) medication.

The participant was a 54 year-old Caucasian woman with a 5-year history of right lower extremity CRPS following a 1st metatarsal spiral fracture. She had normal thyroid function, no medical history of thyroid-related disease or other thyroid-related disorders, and was on a stable dosage of time-contingent neurontin for pain.

The participant was assessed daily for ten weeks on the dependent measures of stress, pain intensity, pain-related function, free serum thyroxine (T4) levels and thyroxine index. All measures of stress, pain, and function and the blood draw for thyroxine assay were conducted at 9PM daily. The participant's stress, pain, and functional measures represented an average indication of her condition throughout each day. Blood from each daily draw was collected on two separate blotting papers for blind independent analysis and

reliability assessment. Dependent measures used to assess stress, pain, and pain-related function parallel those used in previous investigations into delayed pain responses in patients with fibromyalgia syndrome and CRPS.<sup>3,9-13</sup>

A Visual Analog Pain Scale (VAPS) assessed daily pain intensity by the participant marking on a 10 cm scale to indicate perceived pain intensity. The VAPS is an extensively utilized measure of pain intensity and temporal changes in perceived pain.<sup>23-25</sup> Over short periods of time, the test-retest stability of this single-item measure of pain intensity is reported to often exceed  $r = 0.80$ .<sup>26</sup> It has been employed as a pain intensity measure in numerous studies investigating temporal changes in perceived neuropathic pain.<sup>3, 9-13</sup>

The McGill Pain Questionnaire Short Form (MPQSF) assessed both sensory (MPQSF-S) and affective (MPQSF-A) dimensions of daily perceived pain.<sup>27</sup> Potential daily score ranges are from 0-33 for the sensory subscale and 0-12 for the affective. Previous literature has statistically supported the reliability, factor structure, and concurrent validity of the McGill Questionnaire,<sup>23,28,29</sup> with adequate test-retest stability of the entire scale found to be  $r = 0.83$ ,  $r = 0.76$  for the sensory subscale, and  $r = 0.78$  for the affective component.<sup>30</sup>

Daily stress was quantified using a 10 cm visual analog stress scale (VASS), with low or absent stress to the left and high stress to the right. This single-item scale provides no information

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on specific stressors encountered, however, yields a summary number indicating the cumulative intensity of stress over the course of the day. When used concurrently with the Daily Stress Inventory (DSI)<sup>31</sup>, the VASS correlated very highly with the total stress score from the DSI,  $r = +0.91$ .<sup>9</sup> The determination was made to utilize this single-item VASS because the present study required only a single value to represent daily stress, correlation with a detailed daily stress inventory was quite high, and the participant was being asked to complete multiple assessments and a blood draw every day for ten weeks. The scale has been utilized in all previous studies assessing the temporal relationship between stress and episodic flares in neuropathic pain.<sup>3,9-13</sup>

The impact of pain on daily function was quantified using the Canadian Occupational Performance Measure model for individualized functional assessment.<sup>32</sup> The participant self-selected an activity she needed to perform daily that was impacted by elevations in pain. A 10 cm visual analog continuum format was used, with the extreme left representing complete performance of the activity unhindered by pain and the extreme right representing complete inability to perform the activity secondary to pain. Given her lower extremity pain, this patient selected walking her dog (Buster) as the functional activity to rate each day using this visual analog function scale (VAFS). This pain-related function

rating protocol and scaling method was utilized by prior studies investigating stress and pain temporal relationships.<sup>3,9-13</sup> A case series following patients with CRPS administered a VAFS daily for 70 days along with the 36 item Rand-36 functional measure<sup>33</sup> and reported a correlation of  $r = +0.84$  between the two functional assessments.<sup>9</sup>

Due to possible influences on pain intensity and/or hormone activity, the participant reported daily medication usage and any menstrual activity. Questionnaires were predated, labeled to ensure accuracy of completion, filed in a manila folder upon completion, then mailed to the Department of Physical Therapy at the University of Puget Sound at the end of each week for collection, blind scoring, and analysis.

Throughout the ten-week period the participant submitted daily blood draws for analysis of free T4 and free thyroxine index (FTI). T4 levels were determined using microplate enzyme immunoassay.<sup>34,35</sup> Samples were maintained at 2-8° C until analysis and all assays were conducted within seven days of collection. To assess daily reliability of T4 assays, each daily blood sample was collected on two separate sheets of blotting paper. The split samples were coded and samples from each day were blindly assayed by two independent technicians using reagent kits from separate manufacturers, one from *Diagnostic Automation Immunodiagnostics* of

Calabasas, CA, USA and the other from *MP Biomedicals* of Orangeburg, NY, USA. Correlations between independent T4 tests of split blood samples were quite strong, ranging from  $r = +0.862$  for free T4 interrater comparisons to  $r = +0.996$  for free T4 correlated with FTI. Assay results from coded daily blind split samples were compiled and reported to the investigators weekly for statistical analysis.

### Data analysis

Linear regression relationships between perceived stress, pain, function, and FTI were analyzed using serial lag correlations to determine occurrences of consistently delayed elevations in pain and free T4. Daily stress scores were correlated with pain, function and T4 measures for same-day as well as each consecutive day's pain and T4 scores up to a fourteen-day lag. Same-day Pearson product-moment correlation coefficients were also calculated between pain, function and T4 scores.

### RESULTS

During the ten-week observation period, the participant experienced four peak stress episodes and eight peak episodes of pain intensity. Not all of the participant's pain flares were preceded by a salient stressor ten days earlier; however, every stressful episode was followed by a major pain flare ten days later, as shown in Figure 1. Of the 4 peak pain episodes not preceded by a

FIGURE-1

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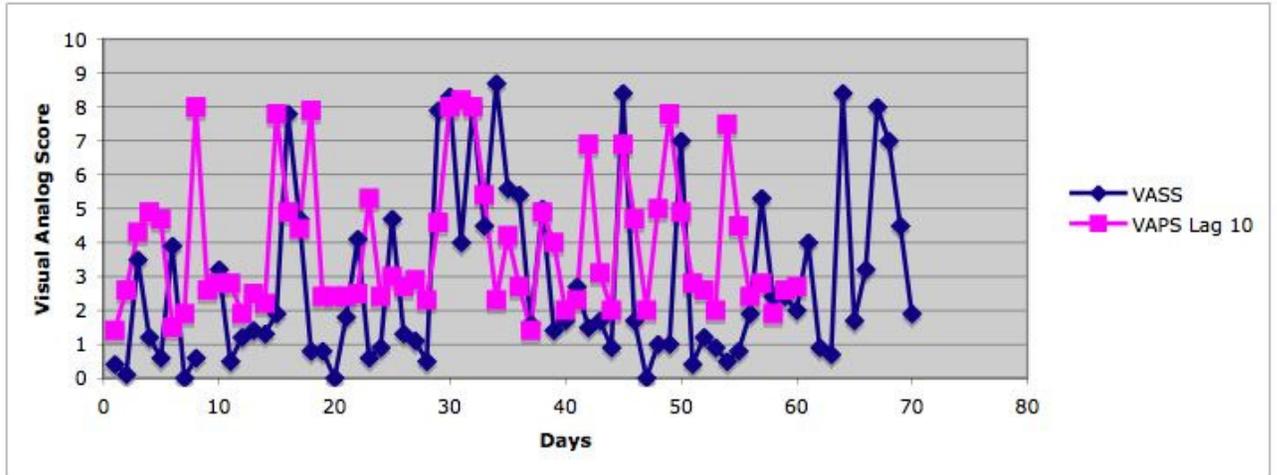


FIGURE-2

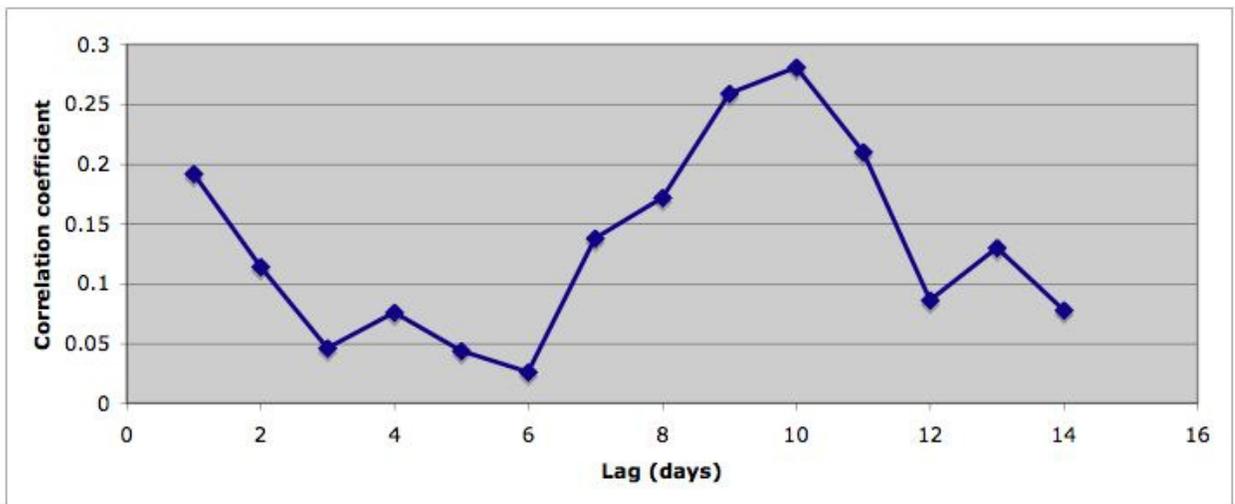
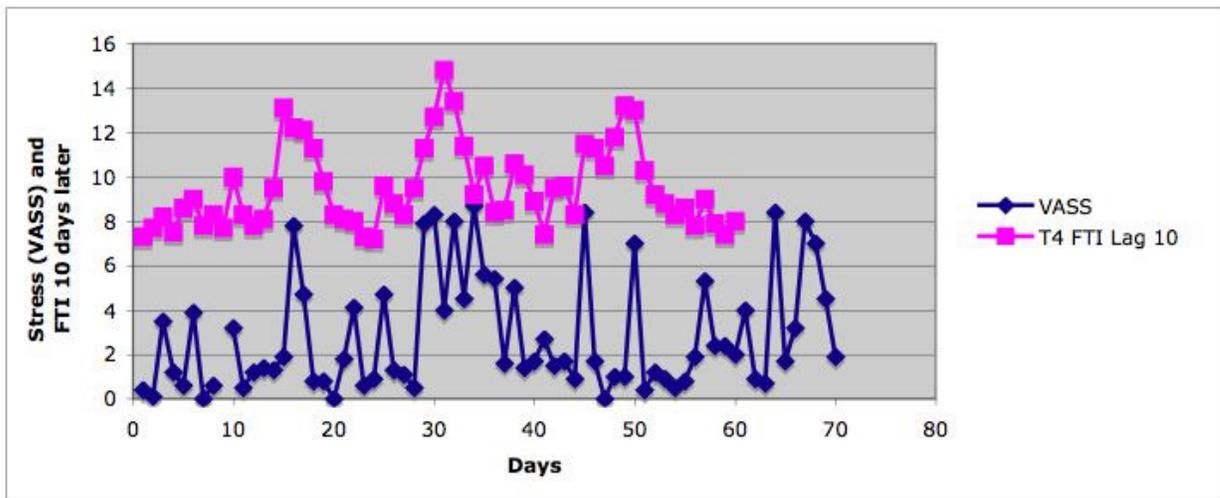


FIGURE-3



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FIGURE-4

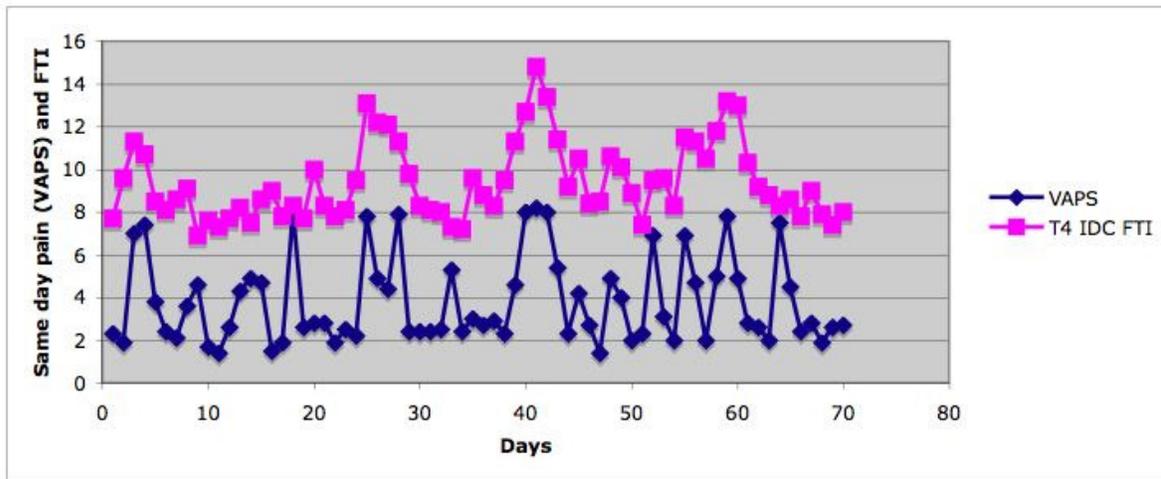
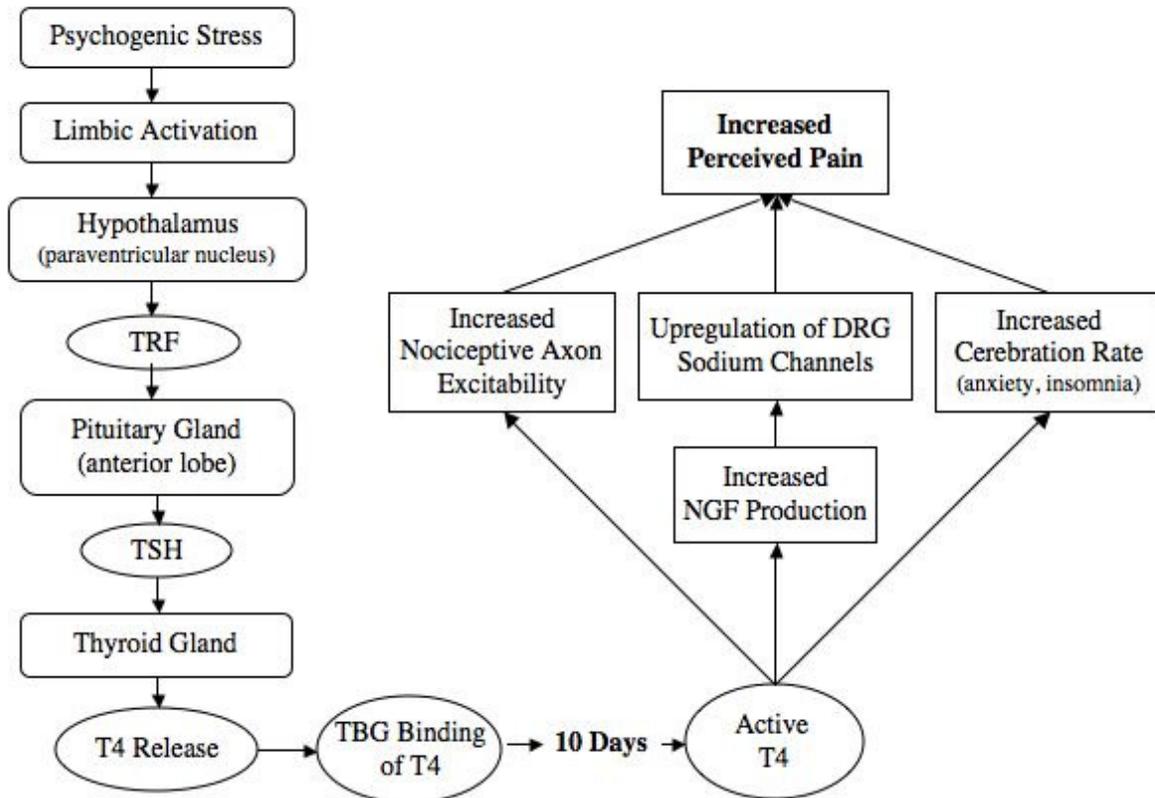


FIGURE-5



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stress episode, 3 were immediately preceded by a day of low stress (rated less than 1cm VASS).

As illustrated in Figure 2, serial lag correlations yielded the strongest relationships between reported stress and pain for pain experienced nine and ten days after a stressor ( $r = +0.259$  &  $+0.281$  respectively,  $p < 0.05$ ).

Pain-related function was similarly influenced by this delayed mechanism. The only significant correlations for stress and individualized function were found for stress followed by decrease functional ability nine and ten days later ( $r = -0.287$  and  $r = -0.329$  respectively,  $p < 0.05$ ). Same-day pain and function were highly correlated ( $r = -0.875$ ,  $p < 0.01$ ).

McGill pain questionnaire short form sensory component was highly correlated with same-day pain ( $r = 0.954$ ,  $p < 0.01$ ) and same-day function ( $r = -0.892$ ,  $p < 0.01$ ). While MPQ-SF affective component was correlated with pain at  $r = 0.354$ ,  $p < 0.01$  and function  $r = -0.274$ ,  $p < 0.05$ , for each of the 4 days that an affective characteristic was marked, function was marked at or higher than 9cm and pain averaged 6.65cm.

Each of the four peak stress episodes can be seen in Figure 3 to be also followed ten days later by peak free T4 values exceeding the upper limit of the normal adult range of 2.4ng/dL (or greater than 12.2 FTI score). Peak free T4 values did not exceed 2.4 ng/dL on any day that was not preceded 9-10 days by a stressful episode.

From Figure 4, the relationship between pain flares and same-

day free T4 values can clearly be discerned ( $r = +0.651$ ,  $p < 0.001$ ).

Free thyroxine index was correlated most highly with stress ten days following a stressful episode ( $r = +0.428$ ,  $p < 0.001$ ). Same-day pain and FTI were correlated at  $r = +0.651$ ,  $p < 0.001$ . Same-day function and FTI were correlated at  $r = 0.697$ ,  $p < 0.01$ .

To summarize the results, this patient with CRPS experienced 4 salient stressful days over ten weeks. Each was accompanied by a notable rise in free serum thyroxine ten days later with a corresponding marked increase in pain on that tenth day.

### DISCUSSION

These findings show that stress and the stress-released hormone thyroxine had a significant relationship with pain flares experienced by this patient with CRPS. Of eight pain flares experienced during this ten-week observation period, four were preceded ten days by stressful episodes. Perhaps the most significant finding is that every peak stress episode was followed ten days later by peak pain with concurrent elevation of free thyroxine beyond normal adult ranges. This finding supports previous reports regarding stress and pain in fibromyalgia<sup>10-13</sup> and CRPS.<sup>3,9</sup>

While each of the four stress-related pain flares was accompanied by a rise in T4 above the upper limit for normal adults, not all pain flares were preceded by a stressful event and these non-stress-related pain flares were

not concurrent with an elevation in free thyroxine levels. It is clear that not all pain flares in this case were related to stress. This supports findings from previous research.<sup>9,10</sup> Interestingly, three of the four non-stress related pain episodes were immediately preceded by a day of low stress. One explanation is that these pain flares are associated with increased activity beyond normal the day before resulting from decreased emotional and psychological stress. This theory is substantiated by known relationships between attitude and exercise participation, indicating that positive cognitive and affective elements of attitude correspond to increased likelihood to participate in physical activity.<sup>20</sup> It is also known that mood and emotional state can have a profound effect on a person's willingness and initiative for physical activity.<sup>36</sup>

The results of the MPQ-SF show that pain flares for this participant were most often experienced in the sensory domain. The patient did, however, report affective responses to pain on four separate occasions, each of which was accompanied by particularly low function (VAFS) ratings indicating inability to perform her functional activity. These results indicate that pain flares for this participant can have both sensory and emotional effects that impact function, which mirrors previous findings that pain can present with both a sensory focus and an emotional focus.<sup>37</sup> Interestingly, average pain

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ratings were not significantly greater than normal for the days on which affective responses were marked on the MPQ-SF. This suggests that the emotional effects of pain may have greater impact on a person's ability to function than on actual pain levels at the involved extremity.

Pain flares delayed by ten days following salient periods of psychogenic stress are consistent with the timing of the binding and release of thyroxine by thyroxine-binding globulins (TBG). However, if the psychogenic release of thyroxine is a mediating factor in significantly delayed pain flares, the question remains as to how the thyroid hormones are impacting pain perception. The theoretical model speculated prior to this investigation suggested two mechanisms.<sup>3,13</sup> First, by elevating peripheral nerve excitability, thyroxine increases peripheral nociceptive input to the dorsal horn without the necessity of an accompanying change at a distal lesion site. Second, via reticular core activation from increased spinoreticular input and direct CNS sensitization, cerebation rates increase, resulting in elevated cortical activity and anxiety. Further, high cerebation rates could lead to episodic insomnia and hence elevated pain perception secondary to sleep loss. Thyroxine could, therefore, increase the perceived intensity of pain by bringing a stronger pain signal into the CNS and ultimately deliver that message to a hyperaroused cortex that is more likely to interpret that message as severe, all without

any change at the distal tissue level.<sup>3,13</sup>

Thyroxine may additionally induce hyperalgesia in patients with neuropathic pain through an indirect pathway, by increasing levels of neurotropic growth factor (NGF) resulting in an upregulation of sodium ion channels in the dorsal root ganglion (DRG).<sup>38</sup> Thyroxine plays a role in protein synthesis, through the stimulation of RNA polymerase. Several studies have shown that there is a relationship between the administration of thyroxine and an increase in NGF production.<sup>39, 40</sup> Thyroxine has been shown to cause increases in NGF in the brains of mice.<sup>39</sup> Walker et al. demonstrated that daily administration of thyroxine in healthy human patients caused a significant increase in liver and submaxillary gland NGF.<sup>40</sup> At the cellular level, NGF increases the expression of sodium gate channels in DRG neurons. *In vitro* studies exhibit that the application of NGF to the soma of the DRG neurons cause a steady level of SNS/PN3 mRNA, which encodes a TTX sodium resistant channel.<sup>41</sup> High levels of SNS/PN3 mRNA have been found after DRG neurons have been axotomized, and in hyperalgesia conditions in mice.<sup>42</sup> A link has also been reported between NGF and gross outward pain. Small doses of NGF have been found to cause pain and hyperalgesia in rats.<sup>43</sup> Additionally, intravenous injections of NGF in human patients have resulted in hyperalgesia and deep tissue pain, which occurs at the site

of injection.<sup>44</sup> Thyroxine's effect on the increase in NGF may, therefore, result in increased expression of sodium gated channels leading to a hypersensitivity to pain. In future studies, it would be enlightening to measure NGF levels, to determine if thyroxine's effect on NGF has implications on the hypersensitivity to pain in patients with CRPS.

Figure 5 summarizes the psychophysiological release of thyroxine and proposed mechanisms by which increased thyroxine levels could intensify the experience of pain ten days following a salient stressful event.

Patients and therapists are frequently at a loss to explain the causes of debilitating CRPS pain flares. Knowing that, via delayed thyroxine activity, stressful episodes may lead to pain flares ten days later, patients could predict particularly painful days, and better plan activity. This may placate some patient fear and anxiety related to pain increases. Therapists can use this information to plan treatment components and distinguish stress-related pain flares from those induced by treatment intensity or poor activity pacing.

Generalizability of these findings is limited by the single participant design. However, further studies into this potential mechanism of delayed pain responses are warranted, using larger samples of patients with CRPS and other chronic neuropathic pain disorders, and investigation into the influence of thyroid hormones on nociceptive pathways.

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### CONCLUSION

The temporal relationships observed in this study support the hypothesis that increased pain activity following ten days after stressful events may be related to the psychogenic release and activity of the stress-related hormone thyroxine in patients with complex regional pain syndrome.

### FINANCIAL SUPPORT

None

### CONFLICTS OF INTEREST

None

### PRIOR PRESENTATIONS

12th World Congress on Pain: Pain, Mind, & Movement II, Dublin, Ireland, August 14, 2008.  
27th Annual Scientific Meeting of the American Pain Society. Tampa, FL, May 8-10, 2008.

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