

COMPLEX REGIONAL PAIN SYNDROME

COMPLEX REGIONAL PAIN SYNDROME: ADVANCING REHABILITATION
THROUGH BETTER EVALUATION AND TREATMENT

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LAY ABSTRACT

Complex regional pain syndrome: advancing rehabilitation through better evaluation and treatment

Complex regional pain syndrome (CRPS) is a painful collection of symptoms that can develop after trauma. Why it happens is not well understood, but most scientists and health care providers agree that rehabilitation should be the primary focus for managing the painful consequences of this condition. There is a need for simple and accurate ways to assess CRPS, as well as to treat it. Better assessment will support treatment that is more targeted to the symptoms of the individual. One of the very challenging symptoms experienced by persons with CRPS is painful sensitivity of the skin, also known as allodynia. This thesis describes the development and testing of several new patient-reported assessments for CRPS and allodynia, as well as two studies on a new method of treatment for allodynia.

**Complex regional pain syndrome:
advancing rehabilitation through better evaluation and treatment**

ABSTRACT

Introduction: Complex regional pain syndrome (CRPS) is a form of neuropathic pain that sometimes develops after trauma or surgery. While diagnostic criteria have been debated, there is agreement participation in rehabilitation should be the primary management. However, there are gaps in the evidence guiding assessment and treatment choices for individuals with CRPS. The purpose of this thesis was to advance the rehabilitation of CRPS by 1) ongoing development and refinement of evaluations for the specific symptoms of CRPS, and 2) to investigate effectiveness of a new treatment (somatosensory rehabilitation) posited to address allodynia associated with CRPS.

Methods: We conducted a series of 4 studies addressing various aspects of CRPS assessment and the somatosensory rehabilitation method: a) a cognitive debriefing study for content validation of the Patient-Reported Hamilton Inventory for CRPS; b) English translation and cultural validation of the Radboud Evaluation of Sensitivity; c) a retrospective cohort study of the effectiveness of somatosensory rehabilitation for allodynia in the upper limb; and d) a pilot study of the somatosensory rehabilitation method to consider the measurement properties of the embedded evaluation tools of allodynography and the rainbow pain scale, and to provide estimates for future controlled trials of effectiveness.

Results: The cognitive debriefing study identified potentially problematic items, and constructs which needed enhancement in future versions of the PR-HI-CRPS assessment. The second paper reported the translation and cultural validation of the RES-E, finding support for test-retest reliability, internal consistency, and preliminary evidence for construct validity and reproducibility. The third paper presented preliminary evidence of a strong effect size for the SRM in an uncontrolled consecutive cohort. Finally, the fourth paper provides an interm analysis of the psychometric properties of allodynography and the rainbow pain scale, and estimates large sample sizes will be required for future trials.

Discussion and Conclusion: None of the assessment tools described herein is ready for unrestricted use in clinical practice or research. Although the effect size estimates for somatosensory rehabilitation from the retrospective cohort are encouraging, the incomplete pilot data suggests large, multi-site trials and careful selection of the primary outcome measures will be required for future, rigorous trials of this method.

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This thesis is dedicated to the memory of my father, Reginald Deagle Windatt, whose kind and generous nature would have gone to great lengths to relieve the suffering of another creature. Dad, I'm not sure I would have made to this point without your giant Mickey Mouse mug to keep me sufficiently caffeinated, and having inherited your wonky sense of humor to keep me sane.

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ABBREVIATIONS AND SYMBOLS

CI – confidence interval

CRPS – complex regional pain syndrome

CNS – central nervous system

COMPACT – Core Outcome Measures for complex regional Pain syndrome
Clinical Trials

COSMIN - Consensus-based Standards for the selection of health status
Measurement Instruments

DVCS – distant vibrotactile counter stimulation

HI-CRPS – Hamilton Inventory for CRPS

IASP – International Association for the Study of Pain

ICC – intra-class correlation coefficient

ICF – International Classification of Function

ITC – item-total correlations

MPQ – McGill Pain Questionnaire

NeP – neuropathic pain

PCS – Pain Catastrophizing Scale

PNI – peripheral nerve injury

PR-HI-CRPS – Patient-reported Hamilton Inventory for CRPS

PROs – Patient reported outcomes

PRWHE – Patient-Rated Wrist and Hand Evaluation

QDSA – *Questionnaire Douleur St. Antoine* (French version of the McGill Pain Questionnaire)

RES – Radboud Evaluation of Sensitivity

RES-E – Radboud Evaluation of Sensitivity, English version

SARA – Somatosensory assessment and rehabilitation of allodynia

SMA – static mechanical allodynia

SRM – somatosensory rehabilitation method

VAS – visual analogue scale

α – alpha, used to represent Cronbach's alpha

p – statistical symbol representing the probability threshold for significance
($p=0.05$, unless otherwise noted)

r – statistical symbol representing the correlation coefficient

CONTRIBUTIONS

This thesis follows a sandwich thesis style. It consists of four separate papers; each one is presented in the format of the target journal for publication.

I, Tara Packham, am the first author for all of the papers herein. All aspects of the study including study design, data collection, data analysis, and manuscript preparation are primarily my own work.

The co-authors on all four papers include my supervisor (Dr. Joy C. MacDermid), and committee member Dr. Susan Michlovitz. Committee member Dr. D. Norman Buckley contributed to three of the manuscripts. Authorship for the second paper includes the original developers of the Radboud Evaluation of Sensitivity from Holland, Lucelle Van de Ven Stevens and Edith Cup, who generously shared their assessment and development work, and offered comment on the manuscript. The author team for the third paper also includes Claude J. Spicher, a collaborator from Switzerland who graciously supplied access to his clinical records for this retrospective review, and contributed to the introduction and methods section of the manuscript to ensure accuracy of the terminology and methodology descriptions. The target journal and publication status is noted for every paper in context.

Chapter 1. INTRODUCTION

Background

Complex regional pain syndrome (CRPS) is a pain condition characterized by a constellation of sensory, autonomic, motor and trophic symptoms (Harden et al., 2010). It can affect a single limb, or in some cases, contribute to widespread neuropathic pain (Borchers & Gershwin, 2014). The etiology is usually associated with some form of trauma or insult to the body (including stroke and spinal cord injury), although not all persons are able to directly associate the onset of pain with a specific event (Schwartzman, Erwin, & Alexander, 2009). While the nomenclature endorsed by the International Association for the Study of Pain (IASP) includes the subtypes of CRPS I and CRPS II, distinguished solely by the presence of a known nerve injury to a major nerve in CRPS II (Galer, Bruehl, & Harden, 1998), this classification and its clinical relevance has been contested (Oaklander & Fields, 2009; Van der Veen, 2015). CRPS I could be considered a form of internal or indirect nerve lesion from inflammation, while CRPS II follows a direct, external trauma to the axon (Wang, Stefano, & Kream, 2014). As the clinical presentation for both CRPS I and CRPS II are essentially identical, the remainder of this thesis will not distinguish between these subtypes, and will refer to the condition as a whole.

Estimates of the incidence and prevalence of complex regional pain syndrome are heterogeneous across geographic regions and diagnostic criteria (de Mos et al., 2007; Sandroni, Benrud-Larson, McClelland, & Low, 2003), and clinical populations such as post-stroke or post-fracture: general population estimates range from 20.6/100,000 to 26.2/100,000. The onset is most commonly associated with trauma such a fracture or ligament injury (Rockett, 2014) although the degree of injury may be relatively minor (Bruehl, 2010). Across adult populations, CRPS is seen more often in women than men, and more often in the upper limb than in the lower (de Mos et al., 2007); it is also associated with increasing age (Bruehl, 2010) or postmenopausal status in females (Pons, Shipton, Williman, & Mulder, 2015). However, the condition also exists in the pediatric population, generally not appearing until after the age of six, and

most commonly seen between the ages of 12 and 13 (Borucki & Greco, 2015). A stronger female predisposition is seen in children, and the presentation is far more common in the lower extremity (Borucki & Greco, 2015; Logan et al., 2013).

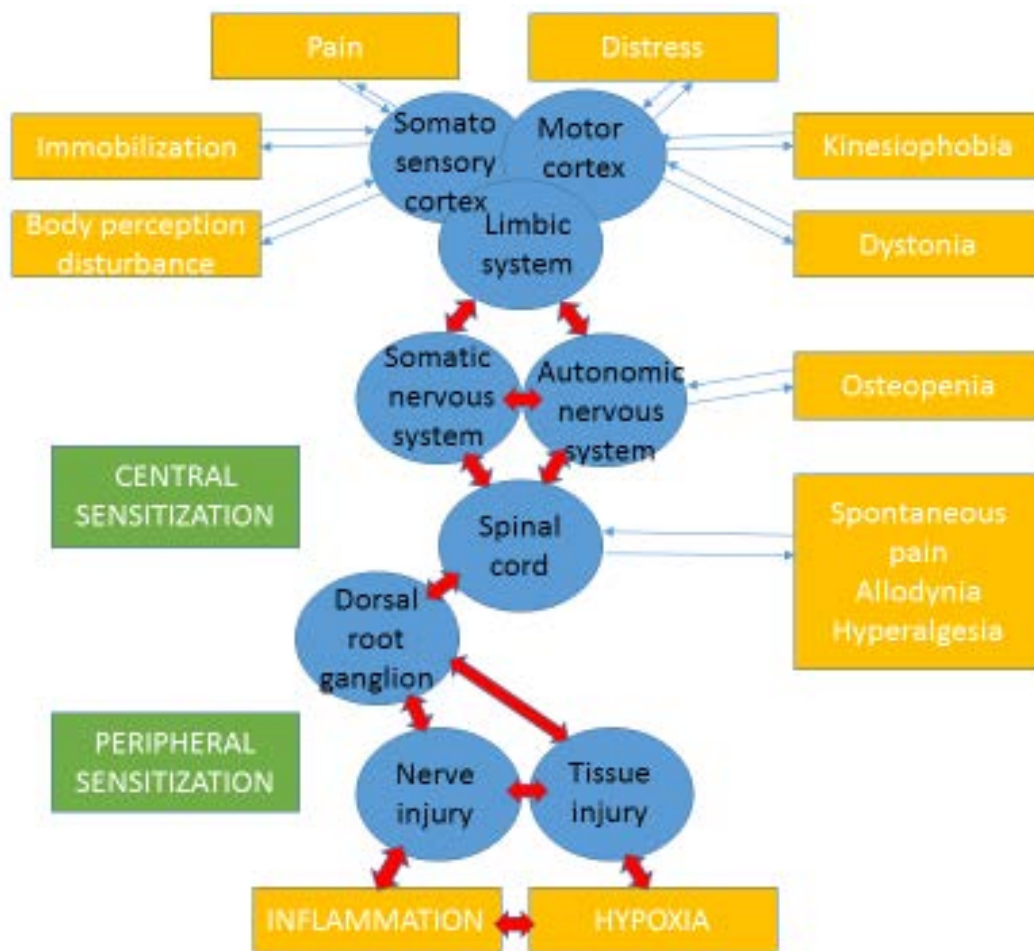
Since Weir-Mitchell's descriptions of exquisite burning pain (termed causalgia) in soldiers after the American Civil War (Oaklander & Fields, 2009), there have been many theories proposed for the underlying mechanisms generating the variable symptoms of CRPS. The many names given the syndrome, such as reflex sympathetic dystrophy, algoneurodystrophy and Sudeck's atrophy reflect these theoretical postulates (Borchers & Gershwin, 2014). Contemporary theories on the etiology of CRPS generally eschew a singular mechanism and often propose multiple contributions from peripheral mechanisms, central mechanisms and genetics (see Figure 1). Overlapping hypotheses include:

1. Local and/or neurogenic inflammation involving cytokines, peptides, neurotransmitters and hormones in the periphery (Hauser, Hsu, & Nader, 2013; Van der Veen, 2015); their responses may be compounded by repeated trauma or insult (Van der Veen, 2015)
2. Hypoxic effects of free radicals after trauma and inflammation (de Mos, Sturkenboom, & Huygen, 2009)
3. Small fibre pathology (Oaklander & Fields, 2009)
4. Autonomic dysregulation: increased sensitivity to the chemical activity of the autonomic nervous system (Bussa, Guttilla, Lucia, Mascaro, & Rinaldi, 2015)
5. Peripheral changes may both induce and maintain pain (Baron, Hans, & Dickenson, 2013)
6. Endothelial dysfunction may result in 'cold' CRPS (Kortekaas, Niehof, Stolker, & Huygen, 2015); this may occur in at onset or reflect the chronification of the condition (Bruehl et al., 2016)
7. Glial activation in the spinal cord (Baron et al., 2013)
8. Sensory cortices shrink; motor cortices enlarge bilaterally; decreased functional connectivity between sensory and motor areas; diffuse increase

in connectivity in other areas (i.e. affective) (Di Pietro et al., 2013; Pleger et al., 2014; Schweinhardt & Bushnell, 2012)

9. Genetic predisposition: specific human leukocyte antigen (HLA) subtypes are more common in CRPS than general population and/or seen in persons who develop dystonia after CRPS (Bussa et al, 2015)
10. Epigenetic changes in gene expression of pro-inflammatory cytokines (Wang et al, 2015)

Figure 1. Schematic representation of proposed mechanisms and relationships in CRPS (adapted from de Mos, Sturkenboom, & Huygen, 2009; Gierthmuhlen, Binder, & Baron, 2014)



At present, the diagnosis of CRPS is on the basis of clinical evaluation, with the most commonly used criteria reflecting a combination of objective assessment of signs

by the clinician, and symptom report by the subject (Perez, Collins, Marinus, Zuurmond, & de Lange, 2007). Although work is currently underway to identify a core set of outcome measures for use in all clinical trials for CRPS (Grieve, Perez, et al., 2015), there is little consensus on how to best measure changes in this condition given its variable nature. Further, there are few psychometrically sound tools developed specifically for this population upon which to draw (Packham, MacDermid, Henry, & Bain, 2012b). Much of the literature is populated with small psychometric studies for limb-specific assessments of pain and disability: my master's thesis included a systematic review of the measurement properties of outcome measures designed for or testing specifically in persons with CRPS. Of the 19 different tools identified, six were specific to the upper extremity, and five focused on the lower extremity. Of the eight remaining tools that were not limb-specific, most focused on a single construct such as skin temperature asymmetry, brush-evoked allodynia, or pain qualities (Packham, MacDermid, Henry, & Bain, 2012a). Further, the Cochrane systematic review of interventions to address pain and disability published by O'Connell et al. (2013) illustrates the narrow range of validated pain and disability outcomes reported in rehabilitation trials. This was echoed for the broader field of CRPS trials in a second recent systematic review (Grieve, Jones, Walsh, & McCabe, 2015). Taken together, these findings support the need for a condition-specific assessment to address both the spectrum of symptoms seen in complex regional pain syndrome, and the impact of these symptoms on activities, participation, and health-related quality of life.

Central sensitization

Central sensitization is the umbrella term that has come to represent amplified sensory signalling in the central nervous system (CNS) occurring independent of input from the periphery (Woolf, 2012; Yunus, 2015). In clinical populations, it is associated with many chronic pain conditions and syndromes demonstrating pain hypersensitivity, including a) exaggerated responses to a painful stimulus (hyperalgesia), b) a painful response to a stimulus that is normally below the threshold for inducing pain (such as cold allodynia), c) increasing pain perception with repeated stimuli (temporal summation) and d) painful responses localized to a larger and larger territory with

repeated stimulation (spatial summation) (Butler, 2000; Woolf, 2012). Central sensitization is considered a form of neuroplastic response at the level of the synapses; whether it is activity or stimulus dependent remains a topic of debate (Bennett, 2012). Plasticity implies the potential for change: and while the effects of central sensitization induced in healthy volunteers may last for hours beyond the inciting event, it is completely reversible (Woolf, 2012). Despite the clinical association of central sensitization with chronic pain, the central nervous system continues to be modifiable, offering the hope of addressing this form of pain by identifying and treating the specific peripheral, spinal and/or central mechanisms contributing to the painful alternations in CNS function (Gierthmühlen, Binder, & Baron, 2014; Vaso et al., 2014; Woolf, 2012). As illustrated in Figure 1, central sensitization is an important contributor to pain in CRPS.

Allodynia

Allodynia is formally defined as a painful response to a stimulus that would not normally be perceived as painful: these may include mechanical (light touch or pressure) or thermal (hot or cold) stimuli (Merskey & Bogduk, 1994). As described above, it is considered a cardinal sign of both peripheral and central sensitization (Gierthmühlen et al., 2012). In complex regional pain syndrome, allodynia is a key sensory sign for diagnosis (Harden, Bruehl, Perez et al., 2010) and has been associated with poorer outcomes in the literature (Wertli, Bachmann, Weiner, & Brunner, 2013). Clinicians also associate allodynia with poorer outcomes (Brunner, Lienhardt, Kissling, Bachmann, & Weber, 2008) and the severity of allodynia has been suggested to predict non-response to certain forms of treatment (Backonja et al., 2013; van Eijs et al., 2010).

Outcome measurement in CRPS

Work by the COSMIN (Consensus-based Standards for the selection of health status Measurement Instruments) group has established a taxonomy for clinical measurement to underpin their goal of developing tools for evaluating the study quality

of psychometric reports for instrument development and validation (Mokkink et al., 2010). This taxonomy identifies reliability, validity, responsiveness, and interpretability as the key considerations in outcome measurement: the COSMIN consensus definitions are seen in Table 1.

Table 1. COSMIN taxonomy for measurement properties (adapted from Mokkink et al, 2010)

Domain	Category	Subcategories	Definition
Reliability	Internal consistency	--	The strength of interrelatedness among the items
	Reliability	Test-retest	The proportion of the total variance in measurements attributed to “true” differences among patients
		Inter-rater	
		Intra-rater	
	Measurement error	Test-retest	The systematic and random error of a patient’s score that is not attributed to true changes in the construct to be measured
		Inter-rater	
Intra-rater			
Validity	Content validity	Face validity	The degree to which the items and related constructs are an adequate reflection in scope and scaling of the construct to be measured
	Criterion validity	Concurrent	The extent to which an instrument agrees with scores of a comparative ‘gold standard’
		Predictive	
	Construct validity	Structural	The degree to which the scores of the instrument adequately reflect the dimensions of the construct to be measured
		Cross-cultural	The degree to which a translated or culturally adapted instrument adequately reflects the performance of the items of the original version
		Hypothesis testing	The degree to which the scores of an instrument are consistent with hypotheses about relationships (i.e. between target groups, scores of other assessments) assuming the instrument validly measures the construct to be measured
Responsiveness	Responsiveness	--	The ability of an instrument to detect change over time in the construct
Interpretability	Interpretability	--	The degree to which one can assign qualitative meaning i.e. clinical or commonly understood connotations, to an instrument’s numerical scores or change in scores.

This framework and definitions provide a template for the evaluation of existing measures, and to guide the development of new tools. Previous work has been completed to systematically review the reported measurement properties of outcome measures developed and/or tested in the complex regional pain syndrome population. Insufficient evidence was found to endorse the use of any existing measures at that time (Packham et al., 2012b). A recent review of the measures used in clinical trials for CRPS also highlighted the heterogeneity of measures employed for this purpose (Grieve, Jones, et al., 2015), reflecting the absence of a gold standard or core measurement set. This underscores the need for condition-specific outcome measures with strong measurement properties demonstrated in rigorous evaluations to address the spectrum of symptoms experienced by persons with CRPS.

Rehabilitation of the upper limb

Historically, rehabilitation of complex regional pain syndrome in the upper extremity focused on maintaining activity despite pain, range-of-motion exercises to reduce edema and prevent the development of contractures, and stress loading to counter the trophic changes seen in this condition (Harden, Swan, King, Costa, & Barthel, 2006; Stanton-Hicks et al., 1998; Walsh & Bannister, 2010; Watson & Carlson, 1987). While several clinical practice guidelines have been published which support the importance of rehabilitation for CRPS (Harden & Oaklander, 2013; Perez et al., 2010; Turner-Stokes & Goebel, 2011), the focus of treatment recommendations remain primarily medical in nature. However, a series of systematic reviews have examined the effectiveness of rehabilitation interventions for CRPS in adults (Cossins et al., 2013; Daly & Bialocerkowski, 2009; Ezendam, Bongers, & Jannink, 2009; O'Connell, Wand, McAuley, Marston, & Moseley, 2013; Rothgangel, Braun, Beurskens, Seitz, & Wade, 2011). Key conclusions include:

- 1) there is a dearth of high-quality powerful trials for rehabilitation interventions
- 2) low quality evidence exists for graded motor imagery and/or mirror therapy

3) low quality evidence supports the benefits of physiotherapy and occupational therapy compared to social work, but does not demonstrate clinical significance (O'Connell et al., 2013)

4) there is not sufficient evidence for stress loading to remain in clinical practice guidelines (Daly & Bialocerkowski, 2009), and

5) more research is needed to guide the selection of clients likely to benefit from mirror therapy, and the utilization of this treatment (Ezendam et al., 2009; Rothgangel et al., 2011).

Objectives of the thesis work

The overarching objective of this thesis is to advance the assessment and rehabilitation treatment options for the management of complex regional pain syndrome. This led to the following specific objectives:

- 1) To explore the content validity of a novel patient-reported, condition-specific outcome measure by conducting cognitive debriefing interviews with persons with CRPS, and identify potential opportunities to improve the reliability and validity
- 2) To translate and culturally validate a patient-reported evaluation of hand sensitivity developed for CRPS from the source Dutch into English, verifying the measurement properties of the translated version
- 3) To report the effectiveness of somatosensory rehabilitation for the treatment of allodynia in a retrospective cohort of persons with CRPS of the upper limb, using existing clinical data; and to consider the predictive value of allodynography and the rainbow pain scale for duration of treatment required for the resolution of allodynia
- 4) To conduct a prospective 8 week pilot study of somatosensory rehabilitation for persons with allodynia after CRPS or peripheral nerve injury in the upper limb to generate preliminary estimates of effect size and sample sizes required in future

controlled trials; and to evaluate the psychometric properties of allodynography and the rainbow pain scale

Summary of the included manuscripts

Chapter 2. Development and content validation of the Patient-Reported component of the Hamilton Inventory for Complex Regional Pain Syndrome: a cognitive interview study.

Work has been undertaken to develop a condition-specific holistic evaluation tool with components for both health professional and patient-reported assessment, the Hamilton Inventory for CRPS (HI-CRPS: Packham, MacDermid, Henry, & Bain, 2012b). This tool is intended to address sensory, autonomic, trophic and motor signs on the clinician component (CB-HI-CRPS) and reported symptoms, daily function, coping and emotional impacts on the patient component (PR-HI-CRPS). While it is condition-specific, the tool is not intended to be limb-specific, and may be used to assess persons with symptoms in either their upper or lower limbs, or with widespread neuropathic pain secondary to CRPS (Carson, Cheng, & Packham, 2007). Higher scores on the PR-HI-CRPS are intended to indicate higher levels of symptoms, poorer daily function, poorer coping, and higher levels of emotional distress. As this tool is intended to provide insight into the patient experience by collecting information about their symptoms, daily function and psychosocial health, we thought it important to validate the questions and the content using the target users: that is, persons living with CRPS. Therefore, the first paper in this thesis describes cognitive debriefing interviews used to explore the content validity of the PR-HI-CRPS.

Chapter 3. Cross cultural adaptation and refinement of an English version of a Dutch self-reported questionnaire for hand sensitivity

The second paper in this thesis describes the translation and cultural validation of a patient-reported outcome measure for hand sensitivity. While the original tool was developed in Holland to measure hypersensitivity related to CRPS, we undertook testing of the measure in a heterogeneous population of persons with pain and/or

sensory changes after trauma, nerve injury and/or CRPS. The mixed examination of both sensory gain (hyperesthesia or allodynia) and sensory loss (numbness or hypoesthesia) is reflective of the spectrum of clinical presentations seen in neuropathic pain. The process of forwards and backwards translation was guided by specific recommendations (Beaton, Bombardier, Guillemin, & Ferraz, 2000), and followed by examinations of reliability, validity and responsiveness.

Chapter 4. *Somatosensory rehabilitation for allodynia in CRPS of the upper limb: a cohort study*

The third paper in this thesis introduces a novel method for the assessment and treatment of allodynia associated with CRPS of the upper limb. Allodynia is defined as a painful response to a stimulus that is not normally perceived as painful (Merskey & Bogduk, 1994), and is considered a poor prognostic factor in CRPS (Wertli et al., 2013). Somatosensory rehabilitation has been proposed as a way to precisely quantify the extent and severity of allodynia using the assessment techniques of allodynography and the rainbow pain scale, respectively. Further, the somatosensory rehabilitation method purports to address the sensitization which underpins the allodynia by inducing positive neuroplastic changes through strategic and graded sensory stimulation and re-education. The retrospective study presented here represents the first report in the English language peer-reviewed rehabilitation literature to specifically address this technique for CRPS of the upper limb.

Chapter 5. *Addressing a sensitive issue: the Somatosensory Assessment and Rehabilitation for Allodynia (SARA) pilot study.*

The final paper describes a prospective pilot study undertaken to 1) examine the psychometric properties of allodynography and the rainbow pain scale for the assessment of allodynia after CRPS or peripheral nerve injury, and 2) to provide preliminary estimates of effectiveness for somatosensory rehabilitation to inform future controlled clinical trials for this treatment method. This is the first formal trial of the somatosensory rehabilitation method, and will lay the foundation for future trials to improve the confidence in evidence for the effectiveness of this novel strategy for the

assessment and treatment of the sensory consequences of neuropathic pain, including complex regional pain syndrome.

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Development and content validation of the Patient-Reported component of the Hamilton Inventory for Complex Regional Pain Syndrome: a cognitive interview study

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Development and content validation of the Patient-Reported component of the Hamilton Inventory for Complex Regional Pain Syndrome: a cognitive interview study**Abstract**

Cognitive interviews can help understand how the target population interpret and respond to questionnaires. This paper describes the use of cognitive interviews to examine content validity of a condition-specific patient-reported outcome currently under development for complex regional pain syndrome (CRPS). Interviews were conducted with 44 persons with CRPS; interviews and questionnaire responses were audio-recorded, transcribed and analyzed to identify problems with wording and to ensure all key areas had been addressed. Item-total correlations were calculated for the proposed subscales, and scores plotted to consider floor/ceiling effects. Interviews identified several questions where respondents consistently provided ratings considering factors unrelated to the construct of interest. Subjects also identified areas they felt were under-addressed by the current version of the questionnaire, including depression and skin temperature asymmetry. The symptoms, daily function, and coping/social impact scales of this iteration of the Patient-Reported Hamilton Inventory for CRPS demonstrated good correlations (Cronbach's alpha 0.73-0.86); while there appeared to be a severity bias, no frank floor/ceiling effects were noted. This study builds a foundation for continuing development and evaluation of the measurement properties of the Patient-Reported Hamilton Inventory for CRPS, including reliability, convergent and divergent validity, and responsiveness.

Keywords: complex regional pain syndrome, content validity, cognitive interviews, patient-reported outcomes

Introduction and Background

Cognitive interviewing is a qualitative approach that can be used to examine how participants interpret and respond to survey questions or self-reported assessments.¹ The methodology is based on Tourangeau's model of response that highlights comprehension, retrieval, judgment, and response as key components of the process of answering questions.^{2,3} The information gathered in cognitive interviews can help developers to discover not only errors made by respondents, but also where those errors arise in the response process, thus facilitating item revision and the development of new items for outcome measures.⁴ Identification and revisions of items or questions that may confuse respondents, prior to full psychometric testing, should improve estimates of reliability and validity.^{3,5}

One of the core forms of validity is content validity, defined as “...*the extent to which an instrument addresses and samples relevant aspects within the concept being assessed.*” (p. 94)⁶ Content validation can take several forms, including examinations of whether theory has informed the choice of items, if experts or members of the target population affirm the relevance of the items, if the study population is well represented, and if the items match the measurement purpose of the tool (i.e. discrimination vs. evaluation).⁷

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is a perplexing neurological condition which may arise following a traumatic injury, and can be associated with a peripheral nerve injury.⁸⁻¹⁰ CRPS, or symptoms consistent with the syndrome, are estimated to affect up to 30% of patients following upper extremity injuries or surgeries, and may become a chronic condition in just under 2% of these patients.^{11,12}

Although consensus-based diagnostic criteria¹³ and assessment recommendations exist,¹⁴ there is as yet no gold standard for diagnosis.^{13,15} The variability of the symptoms in scope, frequency and intensity contribute to the challenge of developing a standard tool.¹⁶ While most patients with CRPS report some form of burning pain, they may also have swelling, circulatory changes, skin changes, sensory complaints, stiffness and altered movement patterns.^{17,18}

Despite these challenges, there have been attempts to quantify some of the symptoms associated with CRPS.^{15,16} For the most part these have focused on specific symptoms and have limited validation;¹⁹ no comprehensive CRPS scale has been accepted into practice or research. Such a scale would be useful in research and clinical practice as the grouping of symptoms, and related treatment strategies, are unique to this pain syndrome. Preliminary work has been undertaken to develop a condition specific outcome measure, the Hamilton Inventory for Complex Regional Pain Syndrome (HI-CRPS).¹⁶

Hamilton Inventory for Complex Regional Pain Syndrome (HI-CRPS)

The HI-CRPS is a multidisciplinary assessment tool originally developed with the goals of developing a condition-specific assessment tool that could 1) be used for evaluation across disciplines 2) be used for both the upper and lower extremities, 3) promote better communication between physicians and therapists by creating a common taxonomy and measurement standard, 4) describe the patient's experience adequately in an effort to guide treatment choices and measure outcomes and 5) allow for wider comparison of research results in an area where little evidence-based progress has been made, and further work is warranted.¹⁹ An initial literature search identified 99 features or constructs associated with this condition; these were compiled and used to formulate items for the HI-CRPS that were reviewed by a small pool of experts and pilot-tested with persons with CRPS,²⁰ representing the first step towards content validation. The current iteration consists of 2 sections: a 15-item clinician-based assessment for health professionals (CB-HI-CRPS), and a 35-item patient self-report (PR-HI-CRPS). Each item is scored 0-6 [with higher scores representing a higher level of dysfunction], using either a frequency or agreement scale (see Fig. 1), and items are both positively and negatively worded. The PR-HI-CRPS is structured with 3 subscales, addressing 1) current symptoms 2) daily functioning and 3) coping and social supports: see Appendix A for a construct map of the scales and questions. These subscales are intended to align with the overall categories of the International Classification of Function (ICF),²¹ with body functions and

structures addressed by symptoms, activities and participation addressed by daily function, and personal and ICF environmental factors represented in the

Figure 1. Scaling used in the PR-HI-CRPS

Agreement scale

<input type="checkbox"/> Strongly agree	<input type="checkbox"/> Agree	<input type="checkbox"/> Slightly Agree	<input type="checkbox"/> Neutral	<input type="checkbox"/> Slightly disagree	<input type="checkbox"/> Disagree	<input type="checkbox"/> Strongly Disagree
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Frequency scale

<input type="checkbox"/> Always	<input type="checkbox"/>	<input type="checkbox"/> Often	<input type="checkbox"/>	<input type="checkbox"/> Sometimes	<input type="checkbox"/>	<input type="checkbox"/> Never
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coping/social supports scale. Cognitive debriefing interviews were previously used to refine and commence validation of the clinician-based component.¹⁶ Our study examines the content validity of the PR-HI-CRPS by conducting cognitive interviews with potential users of the assessment: persons living with CRPS.

Methods

Sampling

For this cross-sectional study, persons with a physician's diagnosis of CRPS of any limb were invited to participate in a one-on-one, semi-structured cognitive interview. Participants were recruited via posters hung in a local pain management clinic and multi-disciplinary outpatient clinic treating upper extremity injuries in a large acute care hospital and trauma centre, and notices posted on the website and in a newsletter for a national CRPS association (PARC/RSD Canada), with email and phone contact information for the primary investigator. All persons who contacted the investigator were provided with an information brochure and informed consent form; signed consents were returned via post,

email or fax prior to conduct of the interview. No verification of the diagnosis of CRPS was made, but all participants were asked to report which category of physician (family doctor, specialist) had diagnosed their symptoms. A single interview was conducted face-to-face where feasible; however, the majority of interviews were conducted via Skype™ or over the phone. Our study was approved by the joint research ethics board at Hamilton Health Sciences/McMaster University in Hamilton, Ontario, Canada.

Data collection

Demographic data were collected on all participants, who then participated in a 'verbal probing' format of cognitive interview. This format uses a combination of established questions and responsive probing to allow the subject to define concepts, express opinions, and examine inherent behaviours and attitudes²² related to each item, as well as to ensure the assessment covered all areas the respondent felt it was important to address. A single interviewer (TP) conducted all interviews, using the questions of the Patient-Reported HI-CRPS and additional probes (see Appendix B for the questions used). Interviews were digitally recorded in an audio format and the responses transcribed for analysis. All participants/transcripts were assigned a pseudonym to allow the use of illustrative quotes. To minimize order bias, which can arise when respondents modify their responses based on a) how they have previously answered other questions, b) fatigue or c) boredom^{23,24} the thirty-five items were presented in a random order for each participant. Interviews that explored the participants' responses to the 35 items on the PR-HI-CRPS ranged in length from 23 minutes

to 2 ½ hours. Additional questions about the questionnaire itself were posed at the end of the interview (i.e. were the response options adequate?); however, not all participants answered these questions as many reported feeling fatigue or pain during or at the conclusion of the main section of the interview.

Statistical and qualitative analysis

Demographic data and actual reported scores for each item of the PR-HI-CRPS were entered into STATA13 for statistical analysis. Descriptive statistics were used to understand the personal characteristics of the participants.

Answers to the PR-HI-CRPS were examined using Cronbach's alpha for item-total correlations across the assessment as a whole and the 3 individual subscales. Total scores and individual subscale scores were also plotted to look for floor or ceiling effects that would suggest a lack of comprehensiveness.⁷

The interviews were initially transcribed as conducted using a word-processing software, then individual answers to each question were imported into Microsoft Excel for a cross-case item analysis,^{25,26} with respondents identified only by numeric code. This facilitated content coding, including item-specific analysis of comprehension and scoring.²⁵ Additionally, general feedback on the overall PR-HI-CRPS, intended to identify participant concerns and suggestions for refinement of existing items and key areas not addressed, was also compiled in the same Excel workbook. Detailed qualitative analysis about the experience of living with CRPS was also undertaken using an interpretive description approach;²⁷ however, those results are beyond the scope of this paper and will be described elsewhere.

Results

Participants

Of the 44 participants who completed an interview, the average participant could be described as a 48 year old female with CRPS in a single upper limb for the past 5 years. Many of the participants had experienced symptoms for less than two years ($n = 18$ or 41%), but duration ranged from four months to over 20 years. Participants were recruited from 11 of the 14 Canadian provinces and territories: two Canadians currently residing in the United States (Connecticut and Arizona) also participated in the study. Recruitment was closed after no new participants were identified in a 2 month period; this decision was further supported by the lack of new findings for problem items in the cognitive debriefing process. Refer to Table 1 for complete summary of the demographic data for participants.

Problem items identified by cognitive debriefing

An important function of cognitive debriefing is to identify items misunderstood by respondents, for reasons of comprehension or misinterpretation.^{4,23} our study identified several problematic items on the current iteration of the PR-HI-CRPS. One of the items under a list of daily activities was “*work*”, and the scoring instructions asked respondents to rate how much difficulty they were experiencing in performing this activity in the past week. The scoring used the frequency scale (see Fig 1), and ranged from *Never* to *Always*, with an additional option to rate the activity as not applicable. However, it became apparent respondents who were not working used very different

Table 1. Participant demographics (n=44)

Variable	Mean	SD	Range
Age	47.8	14.7	15-81
Duration of CRPS symptoms	67.3 months	78.6 months	4 months – 20 years
Variable	Frequency		Percentage
Gender	Female= 40 Male= 4		91 9
CRPS affects	Upper limb= 21 Lower limb = 12 Multiple limbs =11		47 28 26
Precipitating event	Fractures=13 Ligament injury/sprain=9 Surgery= 9 Strain= 8 Can't recall = 3 Other=2		30 20 20 18 7 5
Work status	Unable= 18 Full time= 16 Part time= 6 Not working prior= 4		41 36 13 10
Province	Ontario= 18 British Columbia= 11 Alberta= 5 Manitoba= 4 Quebec= 1 Saskatchewan= 1 Nova Scotia=1 New Brunswick= 1 Northwest Territories= 1 Other= 2		41 25 11 10
Setting	Urban= 29 Rural= 15		66 33

appraisals to score this item. Some used the '*Not applicable*' option to indicate they had not worked in the past week because they were off on long-term disability (as opposed to being retired, or in school); while other respondents rated it as '*Always*' difficult, since they had been unable to work in the past week. Accordingly, this led to revision not of the item itself, but of the scoring

instructions. Respondents of working age who were unable to work in the past week because it was too difficult, were directed to score the item as '*Always*' rather than '*Not applicable*'. Another item on the daily activities list was '*driving*': respondents reported this was difficult to rate, because the amount of difficulty was often dependent on the amount of time spent behind the wheel.

Accordingly, we revised the item to '*driving for an hour*' to include a referent time frame.

Another item frequently misunderstood by participants was '*I need to concentrate to move my affected limb*'. The theoretical construct targeted by this question was to evaluate proprioceptive or perceptual impairments. However, when participants described what information they were considering to select the response category, over 50% of respondents were clearly describing guarding and conscious planning to reduce harm or threat, rather than altered processing of somatosensory inputs impacting on movement planning and execution. When this misunderstanding was identified to participants, they reported the suggested new wording of '*I need to concentrate to make my affected limb move*' was more likely to elicit the intended construct.

Several participants reported they did not like the item '*I am confident I can manage my signs and symptoms*', which was intended to measure the construct of self-efficacy, defined by Bandura as the belief in one's own ability to complete tasks and reach goals²⁸. Responses included "*So when I read [the question], can I manage my symptoms, well how much of that is up to me and how much of that is up to the medications and things that I have been given,*

which is somewhat out of my control? So my managing it, I don't know...." [Cat, 43 year old woman with a 9.5 month history of CRPS in her foot], or "*On my own, no. I would say strongly disagree. No, I want some help from other people, to understand what is going on.*" [Martha, 51 year old woman with 4.5 month history of CRPS in her leg]. However, this item was not altered during the revisions process, as these responses appeared to indicate the item was indeed measuring self-efficacy.

One final item required a complete revision as a result of the cognitive debriefing process. '*My swelling comes and goes*' was intended not only as an indicator of swelling, but to also address symptom variability. Early in the study, it became apparent participants used the associated agreement scale very differently in their responses. Among those participants who agreed, some were agreeing (and thus appropriately receiving a higher symptom score) because it was negative that their swelling kept coming back. However, others agreed (and were thus inappropriately given a higher symptom score) because where they previously had constant swelling, they viewed it as positive since the swelling was now gone at least some of the time. This item was completely deleted, and replaced with "*My symptoms flare even if I am not doing anything*": this new item was also scored using a frequency scale rather than an agreement scale (Fig. 1). For content coverage, it is important to note another item remains on the scale that directly addresses swelling [*I experience swelling in my affected limbs*: rated on the frequency scale].

*Content validity**Item-total correlations*

While item-total correlations (ITC) are often presented as a form of reliability²⁹ they can be considered a form of content validity, as this statistic examines the relationship of each item on a scale to the other items on the scale or sub-scale. The PR-HI-CRPS was developed to have three subscales, addressing the theoretical constructs of symptoms, daily function, and coping/social supports. Item-total correlations for this iteration of the HI-CRPS based on participant responses were above the satisfactory range,³⁰ extending from 0.73 to 0.86 for individual sub-scales (see Table 2), but not so large as to suggest redundancy.²⁹ From a statistical perspective, all items on both the symptom and daily functioning scales appear worth retaining; no increase in α would be obtained by deleting any individual item from its subscale. On the coping and social support subscale, deleting the item “*I am confident I can manage different tasks and activities throughout the day*” would raise α to 0.76.

Table 2. Item-total correlations for the 35 item PR-HI-CRPS

Subscale	Cronbach's alpha α	Number of items on scale
Symptoms	0.83	14
Daily functioning	0.86	12
Coping and social support	0.73	9

Examination for floor or ceiling effects

We generated scatterplots to visually inspect the data for floor or ceiling effects, and examined the endorsement frequencies for evidence the subscales and overall questionnaire are not well targeted for the population or constructs.³¹ Figure 2a illustrates the distribution of total PR-HI-CRPS raw scores (n=44); total possible score is 210. The data suggests a trend towards higher scores (mean score 131.5/210, SD 33.0); however, this should be considered in light of the average duration of symptoms reported as 67.3 months \pm SD=78.6. Figure 2b is composed of overlaid scatterplots for all of the subscales: the symptoms scale had a mean of 49.3/90, SD 13.8; the daily function scale mean 46.8/72, SD 15.1; and coping/social supports mean 30.2/48, SD 9.7. For a simple comparison, the average participant scored 55% on the symptoms scale, 65% on the daily function scale and 63% on the coping/social supports scale: higher scores indicate higher levels of symptoms and greater impacts of those symptoms.

Figure 2a. Total PR-HI-CRPS scores

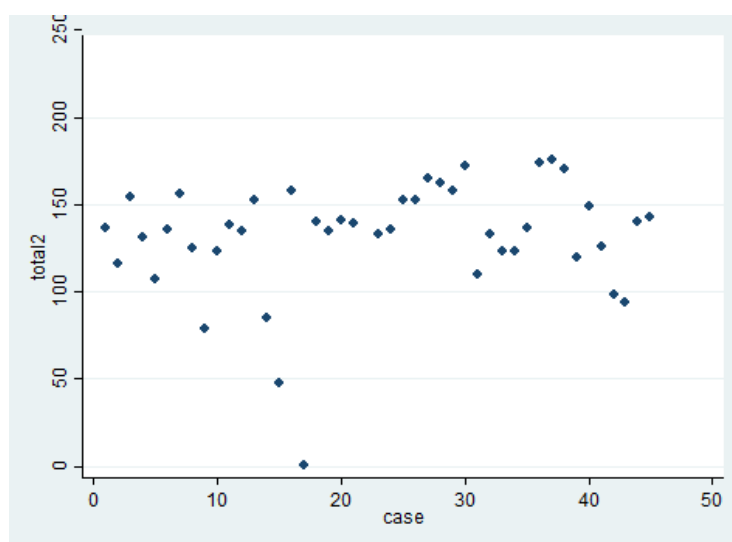
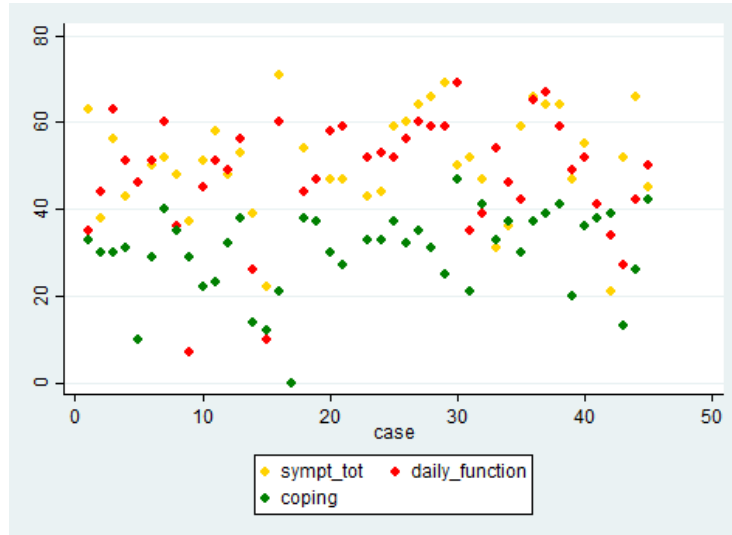


Figure 2b. Overlaid scatterplot of subscale totals

Again, the distribution of the scores visually demonstrates a trend towards higher scores, but does not appear to have a defined ceiling effect. Table 3 illustrates the overall distribution of responses for all items: this does not show overall floor or ceiling effects, but suggests a skew towards higher scores, with individual item variation. For example, the item “*I get tired easily*” may demonstrate a ceiling effect, with 59% of respondents scoring 6/6; however, other items such as “*Getting dressed*” or “*Walking around the home*” from the same daily function scale showed a wider spread across the score categories.

Expert opinion on content coverage

All participants were asked to suggest content areas not addressed by the HI-CRPS; specifically, if there were a) important areas of information they felt their health care team should understand about their daily experience with CRPS and b) if there were other things they would consider to judge if they were getting better or getting worse (see interview guide in Appendix B).

Table 3. Response distribution of endorsements for every level of response option for each item

Item	0	1	2	3	4	5	6
I experience pain that isSharp	7	2	5	6	16	3	5
.....Sensitive	3	1	3	4	6	8	19
.....Throbbing	5	1	4	4	11	8	11
.....Aching	0	1	2	0	8	8	25
.....Stabbing	8	2	5	6	9	7	7
.....Burning	3	1	2	4	8	7	19
I have enough energy to do everything I want to do.	2	5	3	0	4	9	21
I become irritated easily.	3	5	14	4	9	4	5
I am confident that I can manage my signs/symptoms.	5	12	5	4	6	8	4
I feel anxious about my symptoms.	1	6	4	1	10	11	11
Fear of hurting my affected limb prevents me from participating in activities.	3	2	8	0	13	4	14
I have difficulty....Getting dressed	7	3	14	3	4	5	8
.....Taking a bath	9	3	6	4	10	3	9
.....Walking around the home	11	4	5	3	14	2	5
.....Household chores	3	0	3	3	7	7	21
.....Work	14	1	2	3	3	4	17
.....Shopping	3	1	5	3	6	4	22
.....Driving	8	2	5	2	9	2	16
.....Hobbies	3	0	3	2	10	7	19
My pain stops me from sleeping.	6	1	8	0	11	4	14
I get frustrated easily.	2	1	2	5	12	13	9
I feel my symptoms have affected my relationships.	4	1	1	1	5	10	22
I get tired easily.	5	0	0	0	3	10	26
I feel my affected limb is not a part of my body.	18	3	9	5	2	6	1
My symptoms affect my comfort level with intimacy.	6	2	1	1	8	13	13
I need to concentrate in order to move my affected limbs.	9	5	7	2	6	9	6
Pain prevents me from participating in activities throughout my day.	3	0	11	0	9	7	14
I am confident I can manage different activities throughout my day.	6	4	14	2	10	2	6
I experience swelling in my affected limbs.	3	2	2	2	6	9	20
My signs and symptoms embarrass me.	5	9	3	6	4	11	6
I experience muscle cramps or muscle spasms.	3	1	9	2	16	4	9
I worry that people would not believe my symptoms are real.	9	4	1	3	5	7	15
I experience joint stiffness on my affected limb.	3	3	4	3	6	4	21
My swelling comes and goes.	4	4	2	0	2	10	22
The people around me are supportive.	20	7	4	2	2	6	3

The main themes reported by participants are summarized in Table 4; these included depression and thoughts of suicide, need for health care provider education/satisfaction with health care, colour and temperature differences between affected and unaffected limbs, gastrointestinal complaints, and spread

of symptoms beyond the original painful limb. Additional ratings for pain descriptors addressing freezing pain, and cramping or squeezing pain, as well as radiating or electric shock pain were also requested by at least 10% of respondents.

We also asked participants to tell us if the number of response categories were adequate (all 10 respondents to this question affirmed the adequacy of the response options), and if they preferred rating scales using words (8/14), numbers (2/14), or both (4/14).

Table 4. Areas not adequately addressed by HI-CRPS (as reported by more than one participant)

Concept by	Suggested (# of persons)	Concept	Suggested by (# of persons)
Depression	9	Spread, full body impact	2
Suicide	3	Prickling pain	2
		Radiating /electric shock pain	4
Temperature and/or colour differences between limbs	8	Freezing pain	7
		Cramping/squeezing pain	4
Abnormal sweating	3	Satisfaction with health care or need for patient education	8
History of trauma and/or abuse	2	Restorative sleep	2
Gastro-intestinal complaints, diet	5	Ability to participate in/ impact of exercise	3

As a result of the target user feedback, the Patient-Reported HI-CRPS was revised from 35 to 40 items, in addition to the rewording changes already described. These changes included a) adding *cramping* and *radiating* to the list of pain descriptors, b) removing the item on fluctuating swelling from the assessment, and replacing it with “*My symptoms flare even if I am not doing*

anything”, c) adding two additional items to both the symptoms and coping/social supports subscales (see Figure 3).

Figure 3. New items added to the revised PR-HI-CRPS

Symptoms scale:						
I have difficulty concentrating.						
6 Always	5	4 Often	3	2 Sometimes	1	0 Never
My affected limbs are a different temperature (hotter or colder).						
6 Always	5	4 Often	3	2 Sometimes	1	0 Never
Coping and social supports subscale:						
I feel I am a burden to my family.						
6 Always	5	4 Often	3	2 Sometimes	1	0 Never
I still enjoy the things I used to enjoy.						
6 Strongly disagree	5 Disagree	4 Slightly disagree	3 Neutral	2 Slightly agree	1 Agree	0 Strongly Agree

Discussion and Conclusion

The COSMIN guidelines, the current standard for the evaluation of studies of psychometric properties, suggest content validity should address relevance and comprehensiveness,^{7,32} where relevance encompasses applicability to the theoretical constructs, to the study population, and to the stated purpose of the assessment tool. This study used cognitive debriefing interviews to continue the content validation process for a new patient-reported assessment tool for CRPS. Patient-reported outcomes have increased greatly in use, driven by 1) improved rigour in development resulting in strong measurement properties⁶ and 2) increased recognition of the importance and validity of including the patient voice

in evaluation^{33,34} in both medicine and rehabilitation. This has been paralleled by the growth in participatory action research, which values the insights of patient partners as experts in their own health condition and experience.³³ In this study, cognitive debriefing interviews provided a mechanism for generating important insights into perceptions of respondents and new items to address perceived gaps. Further, the interview process identified confusing wording on several items that likely would reduce reliability, and thus by extension, validity. For example, our participants identified depression and suicidal ideation as important concerns not covered by the questionnaire. This led to the inclusion of two additional items on the coping/social supports scale, intended to address both mild depression and more severe depression and feelings of worthlessness (see Figure 3). Additionally, participants expressed concern that temperature and colour differences were not referred to on the patient-reported section of the HI-CRPS. While we had intended this construct would be measured quantitatively on the clinician-based portion, we have now added an item to address this perceived gap to ensure face validity of the patient-reported component.

We examined item-total correlations, represented by Cronbach's alpha,³⁵ and often described as a form of reliability. We would argue this could be considered a form of content validation, as it measures the degree to which each item agrees with the score of the total of its' (sub)scale,²⁹ and thus is an indicator of its relevance to the construct of interest represented by the scale. In our case, the PR-HI-CRPS has 3 proposed scales which all demonstrated good item-total correlations: symptoms ($\alpha=0.83$), daily function ($\alpha=0.86$) and coping/social

supports ($\alpha=0.73$). Not surprisingly, the lowest correlations are seen for the latter scale, which we envisioned to contain 3 related concepts: coping, emotional impacts, and social supports. As we continue with the development and testing of this measure with larger samples, we intend to test our theoretical scale structure using both confirmatory factor analysis and Rasch analysis.²⁹ However, it was not feasible to conduct, transcribe and analyze a larger number of interviews than the $n=44$ represented by this study. Further, we anticipated the scale would be modified in response to the participant feedback, and it was not prudent to conduct a study with the large samples needed for factor and Rasch analysis for this intermediate version of the tool.

We also generated scatterplots of the total raw scores of the PR-HI-CRPS as well as each of the individual subscales to look for floor or ceiling biases suggesting a lack of comprehensiveness.⁷ While scores demonstrated a trend towards the higher values, it must also be considered this severity bias reflects volunteer bias from our sampling methods.³⁵

This study builds on our theoretically derived items and subscales, and is intended to compliment a previous cognitive debriefing study of the clinician-based component.¹⁶ However, we acknowledge this is not the endpoint of the development process, but rather an interim step to inform future studies of the next iteration, including the changes illustrated in Figure 3. Now that we have preliminary support for content validity, future explorations will include address other forms of reliability and validity. This should include validation of the subscale structure (using confirmatory factor analysis and Rasch analysis), and

re-examining internal consistency of the revised PR-HI-CRPS. Estimates of test-retest reliability, responsiveness to change, convergent validity (comparing the scores of the clinician-based and patient-reported sections) and discriminant validity (by administering the PR-HI-CRPS to persons with peripheral nerve injuries) will be generated by an ongoing study of a novel treatment for CRPS (NCT02070367 at www.clinicaltrials.gov).

Appendix A: Concept map for the Hamilton Inventory for CRPS

Category	Construct	Linkages to ICF	Clinician Based HI-CRPS	Patient-Reported HI-CRPS
Sensory signs and symptoms	Pain qualities	Body functions	Allodynia	I experience pain that is: sharp, stabbing, sensitive, throbbing, aching, burning (rated by frequency) [6 items]
			Cold hyperpathia	
	Pain interference		Guarding	My pain stops me from sleeping. My symptoms affect my comfort level with intimacy.
Autonomic signs and symptoms	Autonomic dysfunction		Edema	I experience swelling in my affected limbs.
			Sweating	My swelling comes and goes.
			Mottling	
Trophic signs and symptoms	Trophic changes		Changes in skin quality	
			Changes in hair growth	
			Changes in nails	
Motor signs and symptoms	Stiffness		Movement is less than would be expected for the patient's initial degree of injury	I experience joint stiffness on my affected limb.
			Movement is less than would be expected for the patient's stage of healing/duration of time since injury	
	Dystonia		Abnormal muscle tone (hypo/hyper)	I experience muscle cramps or muscle spasms.
			Incoordination	I need to concentrate in order to move my affected limbs.
	Body perception			I feel my affected limb is not a part of my body.
				Pain prevents me from participating in activities throughout my day.

Impacts on daily function	Pain interference	Activities		I have difficulty: getting dressed, taking a bath, walking around the home, household chores, work, shopping, driving, hobbies [8 items]
	Fatigue			I have enough energy to do everything I want to do. I get tired easily.
	Kinesiophobia			Fear of hurting my affected limb prevents me from participating in activities throughout my day.
Coping	Self-efficacy	Personal factors		I am confident I can manage different activities throughout my day.
				I am confident that I can manage my signs/symptoms.
Emotional impacts	Anxiety			I worry that people would not believe my symptoms are real.
				My signs and symptoms embarrass me.
				I feel anxious about my symptoms
	Emotional regulation			I become irritated easily. I become frustrated easily.
Social impacts	Social impacts	Social environment Personal factors		I feel my symptoms have affected my relationships.
				The people around me are supportive.

Appendix B: Cognitive Interview Script/Questions for the PR-HI-CRPS

Question 1. The type of pain I experience is: (graded 0=never to 6=always)

- **Sharp**
- **Sensitive**
- **Throbbing**
- **Stabbing**
- **Aching**
- **Burning**

Do you feel that each one of those words represents a different type of pain?
What things did you think about to help you decide what word or number best describes what you feel?

Do you think this question is asking you about right now or your experience in general?

Do you need any more information to be able to answer the question?

Do you think there are other important types of pain that are not on this list?

Question 2. I have enough energy to do everything I want to do.

What things did you think about to help you decide what word or number best describes what you feel?

Do you think that your energy level is affected by your CRPS?

Question 3. I become irritated easily.

What things did you think about to help you decide what word or number best describes what you feel?

Do you think that it is important to ask someone with CRPS about feeling irritable?

Question 4. I am confident that I can manage my signs/symptoms.

What things did you think about to help you decide what word or number best describes what you feel?

What types of things do you think might also influence your answer?

Question 5. I feel anxious about my symptoms.

What things did you think about to help you decide what word or number best describes what you feel?

What symptoms in particular were you considering to come up with an answer?

Question 6. Fear of hurting my affected limb prevents me from participating in activities.

Did you feel you understood exactly what this question was asking?

What things did you think about to help you decide what word or number best describes what you feel?

Are there specific activities you were thinking about?

Question 7. Please circle the number in the box that best describes your difficulty doing: (always/often/sometimes/never 6-0)

- Getting dressed
- Taking a bath.
- Walking around the home
- Household chores
- Work
- Shopping
- Driving
- Hobbies

What things did you think about to help you decide what word or number best describes what you are able to do?

What do you think this question was asking?

Question 8. My pain stops me from sleeping.

What things did you think about to help you decide what word or number best describes what you feel?

Is there anything else besides pain that you think has an impact on your sleep?

Question 9. I get frustrated easily.

What things did you think about to help you decide what word or number best describes what you feel?

Do you think living with CRPS has changed how easily you get frustrated?

Question 10. I feel my symptoms have affected my relationships.

What things did you think about to help you decide what word or number best describes what you feel?

What do you think this question was asking?

Do you think that it is important to ask someone with CRPS about their relationships?

Question 11. I get tired easily.

What things did you think about to help you decide what word or number best describes what you feel?

Do you think it would be easier to answer this question using the strongly agree to strongly disagree scale instead of the always to never scale?

Question 12. I feel my affected limb is not a part of my body.

What things did you think about to help you decide what word or number best describes what you feel?

What do you think this question was asking?

Question 13. My symptoms affect my comfort level with intimacy.

What things did you think about to help you decide what word or number best describes what you feel?

What do you think this question was asking?

Question 14. I need to concentrate in order to move my affected limb(s).

What things did you think about to help you decide what word or number best describes what you have experienced?

What do you think this question was asking?

Do you think that having CRPS makes it more difficult to move?

Question 15. Pain prevents me from participating in activities throughout my day.

What things did you think about to help you decide what word or number best describes what you are able to do?

How would you define participating?

Question 16. I am confident that I can manage different tasks and activities throughout the day.

What things did you think about to help you decide what word or number best describes what you feel?

Was that easy or hard to answer?

Question 17. I experience swelling in my affected limb(s).

What things did you think about to help you decide what word or number best describes what you experience?

How would you define or describe swelling?

Question 18. My signs and symptoms embarrass me.

What things did you think about to help you decide what word or number best describes what you feel?

Is there a difference between signs and symptoms?

Was this question easy or hard to answer?

Question 19. I experience muscle cramps or muscle spasms.

What things did you think about to help you decide what word or number best describes what you experience?

Do you think that it is important to ask people with CRPS about muscle cramps?

Question 20. I worry that people will not believe my symptoms are real.

What things did you think about to help you decide what word or number best describes what you feel? Was that easy or hard to answer?

Question 21. I experience joint stiffness in my affected limb(s).

What things did you think about to help you decide what word or number best describes what you experience?

Question 22. My swelling come and goes.

What things did you think about to help you decide what word or number best describes what you feel?

What do you think this question was asking?

Question 23. The people around me are supportive.

What things did you think about to help you decide what word or number best describes what you feel?

Do you feel you had enough rating categories to describe your experience? Were there too many choices? Not enough? Would you rather use a scale of numbers one to 10?

Is there anything about your symptoms that you feel was not covered by these questions today?

Is there anything about living with CRPS that you think it would be important for the health care professionals caring for you to know?

Is there anything else you think would be important to measure to help describe how you might know a new medication is helping or not helping?

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Cross cultural adaptation and refinement of an English version of a Dutch patient-reported questionnaire for hand sensitivity: the Radboud Evaluation of Sensitivity

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Abstract

Introduction

Sensory alterations in the hand can present as both decreased sensation or numbness, and hyperaesthesia, including allodynia and cold intolerance. However, few patient-reported outcomes have been developed and validated for evaluation, particularly for increased sensitivity. The Radboud Evaluation of Sensitivity was developed in the Netherlands for patient-reported evaluation of hand sensitivity in complex regional pain syndrome.

Purpose of the study

The purpose of this study was to translate into English and culturally validate the Radboud Evaluation of Sensitivity for the North American context.

Methods

Forward and backward translation, followed by a psychometric evaluation of the synthesized version of the translated tool, was undertaken in a heterogeneous group of persons after hand injury, including nerve injuries, hand trauma and complex regional pain syndrome.

Results

36 persons completed test-retest reliability testing, yielding an intraclass correlation coefficient of 0.92 [95%CI 0.85 - 0.96] for single measures. Internal consistency was also high at $\alpha=0.96$ in a larger sample ($n=56$). While some support for construct validity was generated, several validity hypotheses were not confirmed. Of interest, there appeared

to be significant differences in the scores between persons with hypoesthesia as compared to those with hyperesthesia.

Conclusions

The RES-E appears to be a reliable tool for the self-reported evaluation of sensory alterations in the hand, including both hypo and hyperesthesia. More research is needed to add to the extent of, and confidence in the validity and responsiveness of this assessment.

Level of evidence: Level II

Keywords: allodynia, patient-reported outcome, translation, cultural validation, psychometrics

Introduction

Painful tactile sensitivity and sensory alterations in the hand can occur after physical damage (i.e. trauma),¹ or chemical insult (i.e. diabetes, inflammation) to the peripheral nerve and/or nervous system.² These may present associated with burns, lacerations, nerve compression syndromes, complex regional pain syndrome, crush injuries, severe post-operative or post-traumatic swelling, and/or the sequelae of infection or metabolic conditions.³ Hand therapists often use the term 'hypersensitivity' as an umbrella term to describe the clinical presentation of abnormal painful sensations.^{4,5} The more precise terminology includes allodynia, hyperpathia, and dysesthesia⁶ as these represent distinct phenomena and can be linked to specific

evaluation tools (See Table 1). Self-reported evaluations or patient-reported outcomes (PROs) have become one of the preferred methods of evaluation in the field of hand rehabilitation.⁷ While a systematic review exists that summarizes the measurement properties of clinician-based sensory evaluation tools,⁸ no synthesis exists for patient-reported outcomes addressing sensation. This group of assessments includes condition-specific PROs such as the Boston Carpal Tunnel Questionnaire⁹ and Patient-Rated Ulnar Nerve Evaluation;¹⁰ and symptom-specific PROs; for example, the Cold Intolerance Severity Scale.¹¹

Although tactile ‘hypersensitivity’ [hyperesthesia, hyperpathia and/or allodynia]¹² is commonly seen, there are few self-reported tools that directly assess this impairment, or address its impact on activity. Since allodynia and hyperesthesia are components of neuropathic pain (NeP),¹³ self-report tools addressing NeP (including the short form of the McGill Pain Questionnaire [SF-MPQ-2],¹⁴ self-reported Leeds Assessment of Neuropathic Signs and Symptoms [S-LANSS]¹⁵ the Neuropathic Pain Questionnaire [NPQ],¹⁶ painDETECT¹⁷ and *Douleur Neuropathic 4* [DN4]¹⁸) may also be considered appropriate assessments. While the DN4, S-LANSS, and NPQ were primarily designed for use as screening tools to differentiate between nociceptive and neuropathic pain, it has been suggested the DN4 also functions as an outcome measure.¹⁹ A single study of the S-LANSS did not find support for outcome measurement on the basis of Rasch analysis;²⁰ however a modified version of painDETECT demonstrated fit to the Rasch model, supporting its ability to measure change.²¹ While several studies of responsiveness endorse the SF-MPQ for prospective evaluation,^{14,22} none of these tools have been evaluated in an upper extremity trauma or post-surgical population.

Table 1. Definitions, descriptors and evaluations for pain and sensitivity

	Definitions from IASP ³	Other clinical descriptors	Standardized sensory evaluations	
			Lab-based ²³	Clinical
Allodynia	painful response to a non-painful or non-noxious stimulus, such as light touch (static or dynamic) or cold	Hypersensitivity, tactile defensiveness, cold sensitivity	Algometer Pressure pain threshold	Brush-evoked allodynia ²⁴ Cold allodynia ²³ TenTest ²⁵
Hyperesthesia	increased sensation	Hypersensitivity to touch and temperature, cold intolerance, heat sensitivity	Thermal evoked pain threshold (hot and cold)	ICE test ²⁶ Cold Intolerance Severity Scale ¹¹
Hyperpathia	increasing pain with repeated stimuli, “Wind-Up” or temporal summation	Hypersensitivity to pain	Pressure pain threshold	Pinprick test ²⁷
Dysesthesia	odd, crude or unexpected sensation; may include paraesthesias such as pins and needles or tingling	Hypersensitivity, pins and needles, tingling, funny feelings, difficulty with discrimination	--	BCTQ symptom severity scale ⁹ PRUNE ¹⁰ STT gnosis test ²⁸
Hypoesthesia	decreased response to any tactile stimulus	Lack of feeling, numbness, crude sensation	Pressure and vibration perception threshold	2 point discrimination ²⁹ Sensory mapping (monofilaments) ²⁹ 10 test ²⁵

Key: IASP = International Association for the Study of Pain; BCTQ=Boston Carpal Tunnel Questionnaire; PRUNE=Patient-Rated Ulnar Nerve Evaluation; STT=Shape Texture Test, ICE=Immersion in Cold water Evaluation

The Radboud Evaluation of Sensitivity (RES) was developed by hand therapists and researchers in the Netherlands to measure hand sensitivity in persons with complex regional pain syndrome.³⁰⁻³² It contains 8 items, scored by the client on a 100 mm visual analogue scale (VAS), comparing the affected hand to the unaffected hand. Standardized instructions are given by the person administering the test. For 6 of the items, the client is presented with tactile media (rice, beans, and a towel) or is asked to touch their own skin, hair, and clothing to make a physical comparison of the sensory

experience, so the evaluation is not entirely a ‘pen and paper’ exercise. The person is asked to rate the differences between hands without specifying the direction of those differences; therefore the assessment could equally be used to rate allodynia, hyperesthesia, hypoesthesia, and dysesthesia. No suggestions are made for the accommodation of bilateral impairments. Ratings of the subjective perception of a standardized stimulus is considered psychophysical testing, which is a common form of sensory testing.^{33,34} Pilot testing of the RES was described by the developers in thesis work and a Dutch publication^{30,35} with measurement properties summarized in Table 2; however, the formal estimates of reliability and validity have not been published in a peer-reviewed journal.

As part of a larger study on assessment and rehabilitation of allodynia (the SARA study: www.clinicaltrials.gov NCT02070367), and to address the need for simple but reliable and valid tools to address the evaluation of hyperesthesia and allodynia, we have undertaken translation and cultural validation of the RES from the original Dutch to English.

Table 2. Reported measurement properties for the Dutch RES N=14 persons with CRPS³⁰

Property	Statistical test	Results	Interpretation
Test-retest	Spearman’s rank correlation coefficients between test 1 and 2 (beginning and end of a single treatment session)	0.74 to 0.98 for individual items, $p < 0.01$ for all	Substantial to excellent test-retest reliability ³⁶
Construct validity	Spearman’s rank correlation coefficients between every question of the RES (8) and every location that was tested with the monofilaments (6)	Out of 48 possible pairings, only 14 were significant at $p < .05$, and 2 were significant at $p < 0.01$	Validity not supported given lack of correlation across multiple comparisons

Cultural validation moves beyond simple translation to consider the cultural factors that may affect how questions are understood and interpreted. Various procedures for cultural validation have been recommended by several authors or organizations.^{37,38} we chose to follow the five steps recommended by Beaton et al.³⁷ Therefore, the purpose of this study was to cross-culturally translate the Radboud Evaluation of Sensitivity into an English version (RES-E); and determine if it is a reliable, valid, and responsive measure of somatosensory impairments for persons after hand trauma.

Methods

Participants enrolled in this study were part of a larger clinical trial on somatosensory assessment and rehabilitation of allodynia (Figure 1). Persons were recruited from the outpatient programs of a large regional trauma centre, including a hand therapy clinic, plastics clinics, and a pain management centre. The target populations were persons with complex regional pain syndrome (CRPS) of the upper limb, persons with a peripheral nerve injury (PNI) in the hand or upper limb, or persons with a recent hand surgery or trauma. Target sample size was calculated for the larger trial using estimates from a previous pilot study addressing measurement and safety issues for a diagnostic sensitivity and discriminative validity of a diagnostic test for CRPS³⁹ and was set at N=90. However, to provide a power of 0.80, at a 'substantial' correlation of at least 0.60³⁶ we relied on Donner's calculations estimating n=35 participants were needed for the 2 administrations planned.⁴⁰ The overall trial with embedded measurement studies was approved by the Hamilton Integrated Research Ethics Board, and informed consent was obtained for all participants.

Study protocol and measurements

Comparison measures for construct validation: To support the validity of the RES-E as a self-reported clinical measure of hand somatosensation incorporating psychophysical elements, we included comparisons of self-reported hand pain and disability, impairment measures, and other psychophysical assessments of sensation.

Patient-Rated Wrist and Hand Evaluation (PRWHE) – The PRWHE is a self-reported measure of pain and disability (a combination of activity and participation elements)⁴¹ with strong clinimetric evidence for reliability, validity and responsiveness.^{42,43}

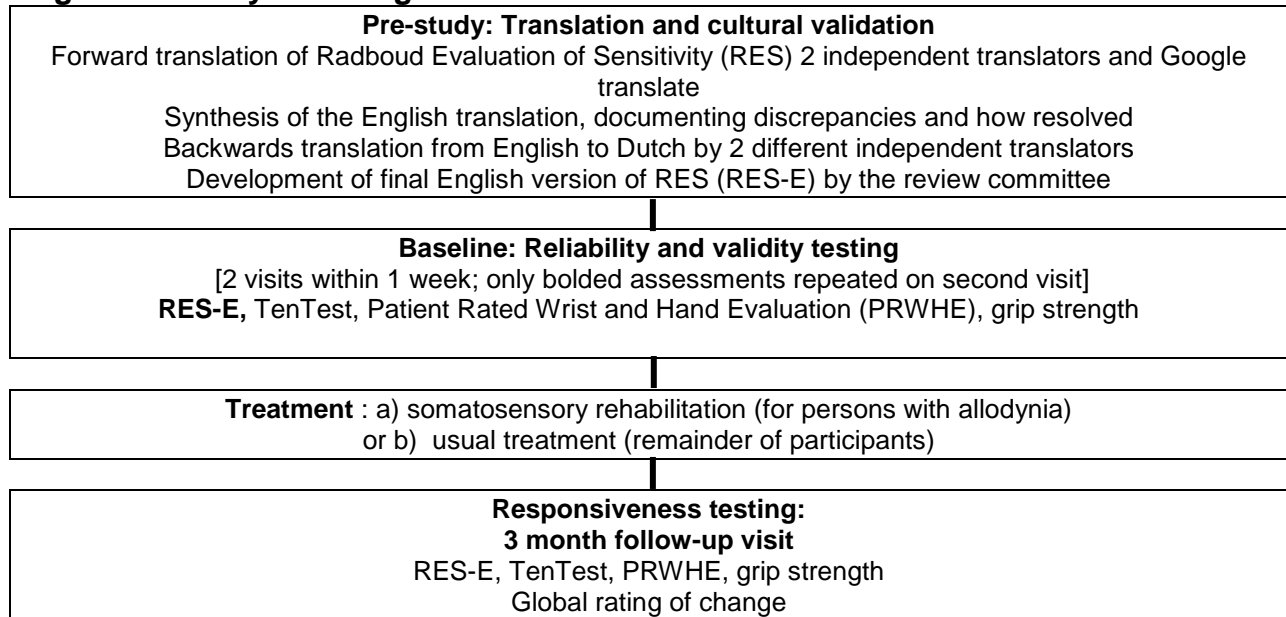
The TenTest – This simple test of light moving touch uses light fingertip stroking simultaneously administered by the tester to bilateral areas representing the same dermatome; the person then rates the hypo or hypersensitivity as a ratio of the area of normal sensation, using a verbal scale with anchors of 1 and 10, with 10 representing normal sensation.^{25,44} It has been shown to have good measurement characteristics, including reliability and responsiveness.^{25,45} In order to compare to the construct of sensory differences captured by the RES-E, we then converted the ratio score to a percentage difference. As sensation was measured in 3 areas of the skin representing the 3 major nerve distributions, the largest percentage difference reported was used for the correlation calculations. Additionally, we recorded whether the person demonstrated hypoesthesia, hyperesthesia, or both.

Grip strength – Power was assessed using a JamarTM dynamometer following standard procedures.^{46,47} The average of the 3 readings was calculated for each hand, and a percentage of normal was calculated based on the score of the uninjured hand,

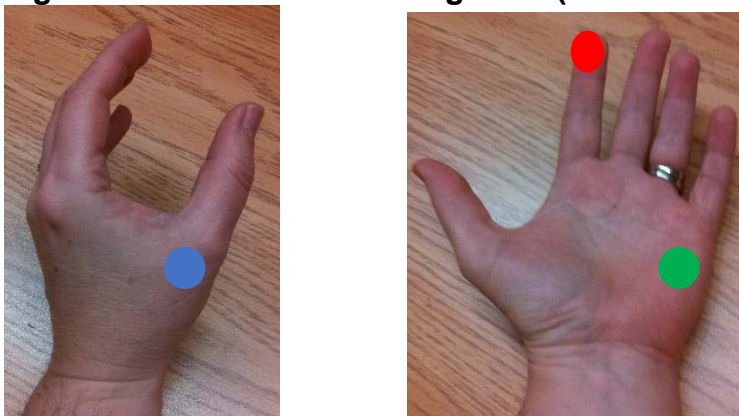
using a predicted pre-injury difference of 10% between the dominant and non-dominant hands.

Cross-cultural validation: We used the five steps recommended by Beaton et al for translation and cultural validation.³⁷ First, forward translation of the RES from the source language of Dutch was completed independently by two native Dutch speakers, a physiotherapist and scientist; both had completed graduate level education in English. It is important to note the translation included the standardized instructions and scoring in addition to the questions answered by the patient on the assessment tool itself. Additionally, Google translate was employed for a literal translation, with minor grammatical editing afterwards by one of the researchers (TLP) to produce three English translations for comparison and to inform the adjudication of the summary. These were compared (see Table 2) and a summary report of the minor differences in grammar was prepared. A composite English version was prepared, and then backwards translation was completed by an occupational therapist and layperson (construction worker); again, both considered Dutch their first language, but had completed their education in English. This was compared to the original document. The forward translation into English and backward translation was then reviewed by a group of 3 expert hand therapists (with an average of 20 years of experience) and 2 of the developers (EC & LVS). This final version (Appendix A) was then employed in the subsequent phases of the study.

Baseline: At their baseline visit, all participants completed the RES-E, TenTest, Patient Rated Wrist and Hand Evaluation (PRWHE) and grip/pinch dynamometry. The test

Figure 1. Study flow diagram

areas for the TenTest were the autonomous territories in the hand for each of the major peripheral nerves (see figure 2),⁴⁸ any other known area of sensory loss (for example, a digital nerve injury) was also evaluated. If the participant identified an area that was painful to touch (confirmed by a painful response to application of a 15g monofilament), then allodyngraphy (a standardized mapping technique for identifying the territory and intensity of allodynia)³ was also completed. 1 week after the baseline visit, all participants completed the RES-E again.

Figure 2. 10 test nerve testing sites (median / ulnar / radial)

Treatment: All participants with an identified area of allodynia were invited to attend 8 weeks of somatosensory rehabilitation. The RES-E was sometimes repeated during this phase at the discretion of the treating therapist to inform progression of the treatment program; this data is captured in the item-total correlation calculations.

Follow-up: At 3 month follow-up, all participants again completed the RES-E, TenTest, PRWHE, dynamometry and an 11 point Likert format global rating of change scale (range -5 =marked decline to 5 =marked improvement).

Statistical analysis

Participant demographics were described using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Internal consistency (or item-total correlation) is traditionally evaluated using Cronbach alpha (α).⁴⁹ We calculated alpha using the baseline measures of all participants combined with the 3 month follow-ups where available; one-week or same day retest data was not included in this analysis to avoid artificial inflation of the reliability coefficients by increasing the sample size without substantially increasing the variability⁵⁰ (on the assumption these would be similar to baseline). Item-total correlations were evaluated for the total RES-E scale, and for the scale if each individual item was deleted. Inter-item correlations were also calculated to inform considerations for reducing the total number of items. Test-retest reliability was evaluated using intra-class correlation coefficients (ICCs) for single and average

measures, comparing the baseline RES-E with one repeated within one week, an interval where we assumed there would not be significant change in sensitivity. A Student t-test was performed to confirm this assumption of no difference in the average scores between testing occasions. Strength of the correlations were interpreted employing Landis & Koch's recommendations, where $r=0$ - .20 is considered slight, $r=$.21 – .40 is fair, $r=$.41-.60 is moderate, $r=$.61 - .80 is substantial, and $r>$.80 is considered excellent.³⁶

Missing items on either the RES-E or PRWHE were addressed the same way. If only a single item was missing, the score was imputed using the average score for that scale. If more than one item was incomplete, then the assessment was excluded. However, because of the direct administration as part of a study, in most cases the examiner immediately identified the missed item to the participant and was able to facilitate completion.

A concern raised by one of our experts in the translation phase was the potential for variability in responses to the clothing item between visits (assuming the participants would be wearing different clothing) that might contribute to inflation of variability, possibly influencing both test-retest reliability and responsiveness. We therefore examined this item individually for test-retest reliability, again using the ICC for single measures. To examine reproducibility, we employed limits of agreement (in the Bland and Altman tradition)^{51,52} to compare the baseline and one-week repeated evaluations; this visually plots the differences between the 2 evaluations against the combined mean score of both occasions, using the mean difference + two standard deviations to set the outer limits.

Validity estimates were explored using Pearson's correlation coefficients to investigate the following hypotheses: a) RES-E scores will be moderately ($r = .41-.60$) correlated to TenTest scores, supporting convergent validity, as both tests are evaluating the construct of sensitivity; b) RES-E scores will have a fair correlation ($r = .21-.40$) to PRWHE total scores and moderately correlated to the PRWHE pain scale score (as both self-report assessments may address the sensation of pain), supporting construct validity; c) RES-E scores will demonstrate a fair negative correlation to grip strength, supporting divergent validity and d) the change scores of the RES-E and PRWHE will be compared to consider longitudinal validity (sometimes also considered external responsiveness).⁵³ Known group validity was also investigated using one-way analysis of variance to explore our hypothesis that RES-E scores will not differ significantly between those participants with sensory loss (numbness) vs. sensory gain (hypersensitivity or allodynia). Finally, responsiveness was evaluated by calculating the effect size using Cohen's d for paired samples, and the standardized response mean was estimated based on a ratio of the mean score change to the standard deviation of the change score.⁵⁴

Results

Translation and cross cultural adaptation

Forward translation of the core questions of the RES produced very similar translations, and required little harmonization. Backward translation produced versions nearly identical to the original Dutch version; the main semantic differences in both translations were found in section B (see Table 3). Review of the harmonized English version by the first author and a group of experienced hand therapists identified a

question was posed in section A as part of the instructions. However, this question was not scored as part of the assessment. We therefore elected to eliminate this question to reduce respondent burden. This was therefore revised to be an introductory statement to indicate the purpose of the assessment. The term ‘maximum difference’ was also replaced with ‘totally different’ as it was thought this idiom would be easier to understand. Further review by the developers yielded minor suggested edits to the standardized instructions; they also endorsed using ‘totally different’ as the upper anchor for the visual analogue scales.

Table 3. Forward and backward translations

	ORIGINAL	Translation 1	Translation 2	Google Translate	Back Translation 1	Back Translation 2
A	Hoe voelt de aangedane hand aan ?	What does the affected hand feel like?	What does the affected hand feel like?	What does the affected hand feel like?	Wat doet de aangedane hand voelen?	Hoe voelt de aangedane hand?
B	Voelt u een verschil tussen uw rechter en uw linkerhand bij:	Do you feel a difference between your right and left hand during	Can you feel a difference between your right and left hand for	Do you feel a difference between your right hand and your left hand with	Voel je een verschil tussen uw rechter en linkerhand tijdens:	Voelt u een verschil tussen uw rechter en linker hand gedurende:
C	geen verschil maximaal verschil	No difference Maximum difference	No difference Maximum difference	No difference Maximum difference	Geen verschil Maximale verschil	Geen verschil Maximale verschil
D	rust	Rest	Rest	Rest	Rust	Rust
E	Bewegen	Movement	Movement	Movement	Beweging	Beweging
F	Aanraken van	Touching of	Touching of	When you touch	als je aanraken	Als u gevoelt
G	Uw haren	Your hair	Your hair	Your hair	Je haar	Uw haren
H	Uw huid	Your skin	Your skin	Your skin	Je huid	Uw huid
I	kleding	Your clothes	Your clothes	Clothing	Je kleding	Uw kleding
J	Rijst	Rice	Rice	Rice	Rijst	Rijst
K	Bonen	Beans	Beans	Beans	Bonen	Bonen
L	handdoek	A towel	A towel	A towel	Een handdoek	Een handdoek
	Translator	MJ	FK	Google	FKP	EDG

Once we started using the RES-E, however, a conceptual issue became apparent. While completing the rating scales for 'Rest' and 'Movement' (see section B for instructions), participants often verbalized they were rating the somatosensation of stiffness rather than numbness, dysesthesias or proprioceptive loss as anticipated. If participants asked for clarification on this, they were directed to consider the latter rather than the former. Clarification from the developers indicated this was the original intent, as persons with CRPS commonly are experiencing both stiffness and sensory change, and these constructs overlap in the perceptual experience.

Demographics

A total of 56 persons participated in this study; however, only n=36 persons completed the test-retest evaluation. While all enrolled participants were asked to complete test-retest measures, not all were seen within the one week window wherein no change was assumed, resulting in the smaller subset for this analysis. A much smaller subset of the participants (n=10) completed the 3 month follow-up evaluations for responsiveness. Demographics are presented here for the larger cohort with differences for the subsets noted in the sections addressing reliability and responsiveness that follow. Our sample included relatively equal numbers of men and women, with a wide range of pain and disability, as represented by the PRWHE scores. Refer to Table 4 for a summary of participant demographic and clinical characteristics. Internal consistency for the 8-item RES-E scale was high at 0.95; see Table 5 for the individual item correlations and alpha estimates if individual items were deleted.

Table 4. Participant demographics (N=56)

Variable	Mean	SD	Range
Age	44.8	15.5	15 – 76
Time since injury (in months)	27.2	61.5	1 – 294
Grip strength (in kgs)	R=28.9 L=26.7	18.4 15.6	0 – 63.3 0 – 60
% of normal grip	44.0	30.2	0 – 100
PRWHE /100	56.3	26.1	0 – 98
RES-E /80	41.8	25.0	1.5 - 80
Variable	Frequency	Percentage	
Gender	M=27 F=29	M= 48.2 % F= 51.8 %	
Diagnosis	Fracture = 19 Tendon = 10 Ligament = 7 Multiple trauma = 6 Nerve = 2 Amputation = 2 Other = 10 **NB n=25 had concurrent CRPS	33.9 % 17.9 12.5 10.7 3.6 3.6 17.9 44.6%	
Dominance	R= 45 L= 11	R= 80.4 % L= 19.6 %	
Side of injury	R= 26 L= 30	R= 46.4 % L= 53.6 %	
Hypoesthesia vs. Hyperesthesia	Loss= 30 Gain= 13 Both= 6	Hypo= 61 % Hyper=27 % Both= 12 %	

PRWHE= Patient Rated Wrist and Hand Evaluation; RES-E= Radboud Evaluation of Sensitivity (English)

Table 5. Internal consistency and item correlations

Cronbach's alpha full scale = 0.95, n= 65		
Item	Item-test correlation	Alpha if item deleted
Rest	0.72	0.96
Movement	0.72	0.96
Hair	0.91	0.94
Skin	0.92	0.94
Clothing	0.92	0.94
Rice	0.91	0.94
Beans	0.93	0.94
Towel	0.89	0.95

Internal consistency and Reliability

Test-retest reliability was calculated on available data for n=36 participants, yielding an ICC (single measures) of 0.92 [95%CI 0.85 - 0.96] and ICC (average measures)= 0.96 [95%CI 0.92 - 0.98] for the entire scale, using a two-way mixed effects model. This can be interpreted as excellent agreement³⁶ for individual or group level measurements. Agreement for the single clothing item was calculated as ICC (single measures)= 0.78, $p < 0.001$. This finding suggests the clothing item may have greater variability, but agreement between measurement occasions still falls within acceptable limits at a 'substantial' rating for individual measurements.³⁶ A paired t-test confirmed no difference in the mean scores between testing occasions ($p=0.85$).

To further explore reproducibility, we also plotted the limits of agreement according to Bland and Altman's recommendations.^{52,55} The range of absolute differences in scores was very large from -22.7 to 13.2, reflecting the large amount of variability in our small sample; this means the limits of agreement ranged from -21.13 to 17.80. However, the mean difference in score was -1.67 (95%CI -4.86 to 1.53). For ideal agreement, this value should be close to zero; the wide confidence interval includes zero but again reflects the variability of a small sample. The limits of agreement are illustrated graphically in Figure 3.

Construct validity

Validity estimates for our *a priori* hypotheses are summarized in Table 6. Figure 4 visually compares the mean scores of persons with hypoesthesia and hyperesthesia, as well as those reporting areas of both.

Figure 3. Limits of agreement plots for the RES-E. The central line on the plot represents the mean difference score between the two moments of administration, while the outer lines represent the 95% limits of agreement. The difference between the first and second RES-E scores is recorded on the y axis, while the x axis records the average of the two scores for each individual.

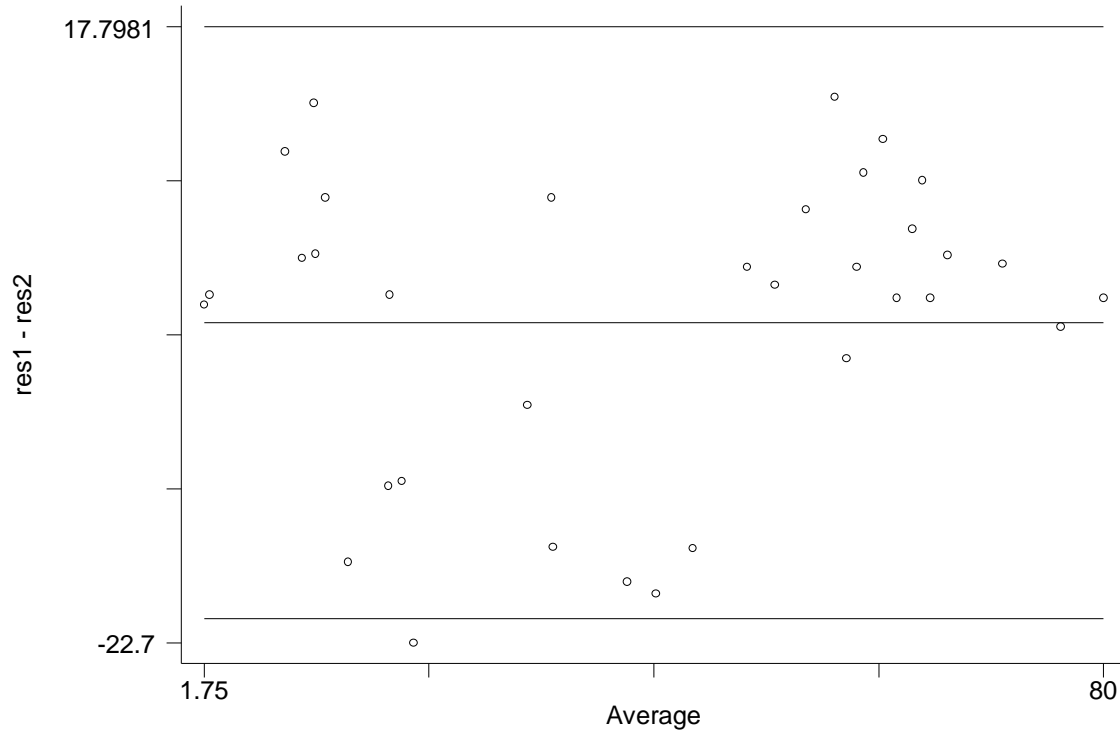
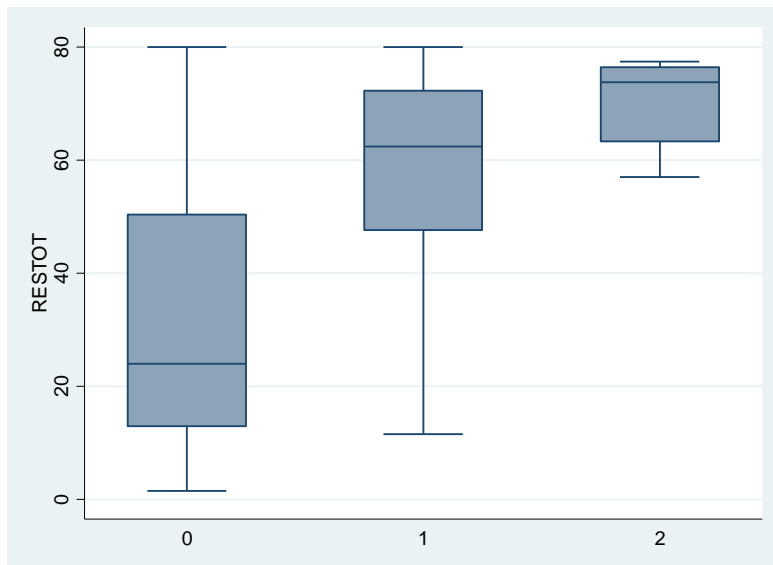


Figure 4. RES-E total scores grouped by sensory loss or gain



Key: 0= hypoesthesia, 1= hyperesthesia, 2= both

Responsiveness

Responsiveness was calculated on a smaller subset (n=10); this was a pragmatic reality as many of the hand injury cohort had completed treatment by 3 months after their initial evaluation, while some of the CRPS cohort dropped out of the treatment study or did not return for follow-up if they were not eligible for the treatment arm.

Table 6. Results of validation hypotheses

Form of validity	Hypothesis	Correlation	Conclusion
Convergent (n=57)	RES-E scores will be moderately correlated to 10 test scores	RES-E $r = 0.55$	Moderate correlation; hypothesis confirmed
Construct (n=49) (n=44) (n=48)	RES-E scores will have a fair correlation to PRWHE total scores	RES-E $r = 0.61$	Strong correlation; relationship much stronger than hypothesized
	RES-E scores will be moderately correlated to PRWHE pain scores	RES-E $r = 0.66$	Substantial correlation; stronger than hypothesized
	RES-E scores will have a fair negative correlation to grip strength	RES-E $r = -0.36$	Moderate negative correlation; relationship stronger than hypothesized
Longitudinal (n=10)	Change scores of the RES-E and PRWHE will be moderately correlated to the global rating of change	RES-E $r = 0.42$	Moderate correlation supports validity
Known group (n=48)	RES-E scores will not differ ($p > 0.05$) between those with sensory loss vs. sensory gain	$F(2,46) = 16.3$, $p < 0.001$	Mean scores differed significantly between the hypoesthesia and hyperesthesia groups

Key: RES-E = Radboud Evaluation of Sensitivity, English version; PRWHE = Patient-Rated Wrist and Hand Evaluation

Cohen's d for paired samples was calculated to be .22 [95%CI -.67 to 1.09], and should be interpreted as a small effect.⁵⁶ However, the wide confidence interval including a zero value also indicates this estimate is not trustworthy because of the small sample

size. The standardized response mean was calculated as $SRM = 0.53$, with the standard error of measurement estimated to be 7 points on the RES-E. Middel et al⁵⁴ have suggested since estimates of responsiveness using effect size are not estimating treatment effects, only the scores of persons who actually consider themselves changed should be used to calculate this effect size. Using this standard, effect size was recalculated on the subset of persons scoring themselves as having some improvement from baseline on the global rating of change ($n=7$). This yielded $ES = 0.36$ [95%CI $-0.70 - 1.41$] and did not alter the conclusion of a small and unstable estimate of effect.

Discussion

This study successfully cross-culturally translated the patient-reported Radboud Evaluation of Sensitivity and found the Radboud Evaluation of Sensitivity-English version had excellent test-retest reliability. The RES-E was also demonstrated to be moderately to strongly related to patient-reported pain and disability in the hand and wrist, and represented a different impairment construct than grip strength. However, we were not able to obtain sufficient evidence to support the responsiveness of this tool in the present study.

There are a dearth of clinical assessment tools to address self-reported tactile sensation or sensory perception of touch. Several important elements have contributed to this challenge: 1) the tension between an objective stimulus delivered to the skin and the subjective perception of the feeling it evokes, creating the experience of sensation, and 2) the complex nature of sensory alterations, in that hypoesthesia, hyperesthesia, and dysesthesia all could be considered 'sensory alterations'. Indeed, all of these 3 forms of sensory alteration could exist simultaneously within the cutaneous surface of a

single functional unit such as the hand, or could be experienced by an individual during the recovery trajectory from a nerve injury.⁴⁴ The ICF codes for sensitivity do not add clarity to this conflict: they address sensitivity as a global construct, and are categorized by the related stimulus (i.e. b2701 Sensitivity to vibration, b2702 Sensitivity to pressure, b2703 Sensitivity to a noxious stimulus x).⁵⁷ The Radboud Evaluation of Sensitivity was developed specifically to address hypersensitivity of the hand after complex regional pain syndrome.⁵⁸ However, there appeared to be an opportunity to explore if indeed this assessment could be used for the broader spectrum of sensory alterations, as a) many of the items were psychophysical in nature, and b) the scales used ask the person to rate the sensory differences (in comparison to the contralateral or unaffected hand) without designating the direction of the differences.

Translation and cultural validation

We undertook translation and cultural validation of the Radboud Evaluation of Sensitivity from the original Dutch language with subsequent psychometric testing of the resultant English version of the assessment (RES-E). Procedural recommendations for forward and backward translation³⁷ were employed to ensure both conceptual and cultural equivalence for each item and the instructions for administration. However, Google Translate was also used to create a literal translation that could be used to identify alternate meanings and synonyms. Although the core items represented basic concepts (e.g. rest, movement, hair, clothing), finding the ideal anchors for the visual analogue scales was more challenging to reach consensus on the translation. Additionally, while we did not undertake cognitive interviews to directly interrogate how respondents understood and interpreted the items,^{59,60} it became apparent from

informal comments by participants that the instruction “*Do you feel a difference between your right and left hand during [Rest or Movement]*” was not always interpreted consistently. Participants would sometimes ask for clarification, as they were not sure if it was asking about tactile sensation or other ‘feelings’ like stiffness or clumsiness. However, this combination of kinesthetic and tactile perception was the target of the original developers, and it appears most participants interpreted the item in this way.

Internal consistency and reliability

Despite the potential inflation of variability from item interpretation, the item-test correlations for the *Rest* and *Movement* items were good, and contributed to the overall rating of excellent internal consistency. Taken together with the strong results for test-retest reliability, this begins to build support for use of the RES-E in clinical practice.

Validity

Of the six *a priori* hypotheses made to explore different aspects of validity, only two were confirmed as being in the direction and strength predicted. Convergent validity was supported by the relationship of the TenTest to the RES-E scores, as was predictive validity as demonstrated by the positive correlation of the change score of the RES-E to the patient’s global rating of change. Three additional hypotheses were confirmed but the relationships were stronger than predicted (see Table 5): 1) the RES-E was moderately negatively correlated with grip strength, when a mild negative correlation had been predicted for divergent validity, 2) the RES-E was moderately correlated to the PRWHE (when only mild correlation had been predicted for convergent

validation), and 3) the RES-E was substantially correlated to the pain subscale of the PRWHE, when only a moderate correlation had been predicted..

Interestingly, our final *a priori* hypothesis for construct validity projected RES-E scores would not differ between those persons with sensory loss (hypoesthesia) and those with sensory gain (hyperesthesia or allodynia). However, analysis of variance demonstrated a significant difference in the mean scores between these two groups. Possible explanations for this finding include the high proportion of persons with CRPS in the hyperesthesia group, or perhaps that hyperesthesia is perceptually more bothersome than sensory loss, resulting in the higher scores.

Limitations

The essential purpose of translation and cross-cultural validation is to establish equivalency of measurement properties in the new language as what have been demonstrated in the original or source language.³⁷ One of the challenges of this study was the limited published literature available to support the original tool. Nonetheless, we felt it worthwhile to pursue this investigation to address the clinical goal of a simple, reliable, and valid measure of either hypo or hypersensitivity. While we have limited evidence to compare against for the original assessment (summarized in Table 2), we were able to provide preliminary evidence for the basic measurement properties of accuracy and stability.

Recruitment of participants from within a clinical trial meant all participants were receiving the same treatment for the estimates of effect size; however, the challenges of trial recruitment and retention are reflected in the small number of datasets available for

the analysis of responsiveness. More study will be required to produce rigorous estimates of responsiveness to support the use of the RES-E for longitudinal monitoring of patient progress and therapy outcomes. Further, the high proportion of persons with CRPS as a sequelae to their hand injury included in our test population represents a recruitment bias and may make the estimates for reliability and validity less generalizable to the cross-section of patients with hand sensitivity seen in a typical hand therapy practice. One of the inclusion criteria for the study was impairment of a single upper extremity. Therefore, a further limitation of this study, and potentially of the RES-E is whether or not it provides useful information in persons with bilateral impairments. Accordingly, we would not suggest the assessment be used for persons with bilateral sensory changes at this time.

A final potential limitation is the validation comparisons for the RES-E and TenTest. This should be considered a ‘bronze standard’ comparison, as most published psychometric data for the TenTest reports its measurement properties for the construct of hypoesthesia, not hyperesthesia.²⁵ Nonetheless, in the absence of any well standardized clinical tests specifically addressing hypersensitivity to light touch and pressure (see Table 1), we elected to use this measure for both hypo and hyperesthesia. Further research is required to demonstrate the reliability of this method of hyperesthesia evaluation; the opportunity remains for the development of simple, cost-effective and standardized tools to capture this construct in the clinical setting. Spicher has proposed the Rainbow Pain Scale using monofilaments to categorize the severity of static mechanical allodynia in the evaluation of neuropathic pain,³ however

estimates for the reliability and validity of this form of evaluation are also currently lacking.

Conclusion

The RES-E appears to be a reliable tool for the self-reported evaluation of sensory alterations in the hand, including both hypo and hyperesthesia. More research is needed to add to the extent of and confidence in the validity and responsiveness of this assessment.

Appendix A

Radboud Evaluation of Sensitivity – English version (RES-E)

Name:

Date:

Injured hand: R / L (please circle) Dominant hand: R / L (please circle)

Please indicate what your affected hand feels like by marking a vertical line on the lines below.

Do you feel a difference between your right and left hands during:

a) Rest
no difference | _____ | totally different
(0%) (100%)

b) Movement
no difference | _____ | totally different

Do you feel a difference between your right and left hands when you touch:

a) Your hair no difference | _____ | totally different

b) Your skin no difference | _____ | totally different

c) Clothing no difference | _____ | totally different

d) Rice * no difference | _____ | totally different

e) Beans * no difference | _____ | totally different

f) Towel * no difference | _____ | totally different

* use samples provided to compare

Score: Total in mm /80

Scoring Instructions: Radboud Evaluation of Sensitivity – English version

The Radboud Evaluation of Sensitivity uses a visual analogue scale, or VAS. The VAS is a horizontal straight line of 100 millimeters, with defined endpoints indicated. The VAS is a simple and frequently used method to measure, for example, the variation in pain intensity.¹⁻⁴ It is important to note that when photocopying the form, care should be taken to ensure the scale remains at precisely 100mm in length. For the evaluation of chronic pain, it is advised to ask the patient to fill in the VAS without having the ability to compare to previous scores.⁵ To increase the reliability, the instructions and scale anchors should clearly specify what dimension of pain is to be evaluated (intensity, or the affective aspects of the pain experience). It should also be clearly established whether the VAS should be in respect of the present pain, average pain, worst pain in last week, etc.⁴

To administer the Radboud Evaluation of Sensitivity- English version (RES-E), the therapist explains the purpose of the test: *“This test is to help us track the sensory changes in your affected hand. Below are eight lines: each one is to help you rate a different part of your sensation. You will be asked to mark a vertical line on each of these lines. If you feel little difference between your hands, you will place a mark somewhere towards the left side of the line. If you feel a great difference, you will put the mark somewhere on the right side. So, the more difference you experience, the further you put your mark to the right. For example, if you touch your hair with both hands at the same time, does the hair feel the same with both hands? If not, how big is the difference? You will make a mark on the line where you think the difference is. Do you understand? Let’s begin.”*

The patient should fill in the VAS scores wherever possible, but may physically require the assistance of the therapist to make the mark. Uncooked long-grain rice, and dried kidney beans (in containers) and a towel are provided so that the patient can actually feel the medium with both hands simultaneously. The score of any item can range from 0 (no difference) to 100 (completely different). To calculate the item score, each line is measured by the therapist in millimeters using a metric ruler. The total score is then summed for total out of 80.

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SOMATOSENSORY REHABILITATION FOR ALLODYNIA IN CRPS OF THE UPPER LIMB: a cohort study

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ABSTRACT

AIMS:

Somatosensory rehabilitation (SSR) is a standardized method of evaluation and conservative treatment of painful disorders of vibrotactile sensation, including the mechanical allodynia and burning pain of complex regional pain syndrome (CRPS). The purpose of this study is to examine the effectiveness of somatosensory rehabilitation for reducing allodynia in persons with CRPS of one upper limb in a retrospective consecutive cohort of patients.

METHODS:

An independent chart review of all client records (May 2004-August 2015) in the Somatosensory Rehabilitation Centre of the Human Body (Fribourg, Switzerland) identified 48 persons meeting the Budapest criteria for CRPS of one limb who had undergone assessment and treatment. Outcomes of interest were the French version of the McGill Pain Questionnaire (QDSA), total area of allodynia as recorded by mapping the area of skin where a 15g monofilament was perceived as painful, and the

allodynia threshold (minimum pressure required to elicit pain within the allodynic territory).

RESULTS:

This cohort was primarily women (70%), with a mean age of 45yrs (range 18-74). Mean duration of burning pain was 31 months (range 1 week – 27.5 years), and baseline QDSA core was 48. The average primary area of allodynia was 66 cm² (range 2.6- 320), and the most common allodynia threshold was 4.0 g. The average duration of treatment was 81 days. At cessation of treatment, the average QDSA score was 20 (Cohen's d ES=1.64). Allodynia completely resolved in 27 persons (56% of the total sample where only 60% completed treatment).

CONCLUSIONS:

Somatosensory rehabilitation appears to be an effective treatment with a large effect size for reducing the allodynia and painful sensations associated with CRPS of the upper limb. More work is in progress to provide estimates of reliability and validity for the measurement tools for allodynia employed by this method.

Keywords: complex regional pain syndrome, allodynia, somatosensory rehabilitation

INTRODUCTION

Complex regional pain syndrome (CRPS) is a neuropathic pain condition; it typically presents with autonomic and inflammatory symptoms accompanying burning pain and sensitivity in a limb.^{1,2} Although there is no defining diagnostic test for CRPS, clinical diagnostic criteria are used to assist in the differentiation of the symptoms from

the normal sequelae of trauma or nerve injury.^{3,2} While it is often associated with an acute injury, it can become chronic in nature.^{4,5} Factors associated with poor prognosis include somatosensory changes such as burning pain and allodynia^{6,7} as well as motor symptoms such as persistent stiffness and contracture.^{5,7} Severe allodynia has been associated with poor response to medical interventions⁸ and is a pragmatic barrier to participation in traditional rehabilitation programs. While physiotherapy and occupational therapy are considered the foundation for management of CRPS,⁹⁻¹¹ there is a need for more evidence-based rehabilitation interventions.¹²⁻¹⁴

Somatosensory rehabilitation is an umbrella term for a standardized method of evaluation and conservative treatment of painful disorders of cutaneous vibrotactile sensation, including mechanical allodynia with or without spontaneous neuropathic pain, as well as the burning or boiling pain of CRPS.¹⁵ The theoretical basis is twofold: neuropathic pain by definition originates from some form of lesion in the nervous system,¹⁶ and somatosensory alterations, including both tactile hypoesthesia and/or mechanical allodynia, cause pain. Altered somatosensory perception of all signals from this area as pain can be explained by peripheral sensitization and/or central sensitization¹⁷⁻¹⁹ First proposed over 16 years ago, the key tenets of the group promoting the concepts of somatosensory rehabilitation for the identification and treatment of static mechanical allodynia include:

- precise psychophysical evaluation of the skin using a 15g monofilament to define the territory that is painful to touch;

- formation of an anatomical hypothesis of the peripheral nerve branch(es) underlying the painful territory and contributing to the aberrant afferent pain signalling and perception
- avoiding reinforcement of the sensitization mechanisms by minimizing evocation of pain by *temporarily* limiting touch (and consequently functional use) of the painful zone; and
- comfortable somatosensory ‘counter-stimulation’ (tactile and/or vibratory) on an anatomically related cutaneous branch (a proximal cutaneous area of the same branch or arising from the same cord of the brachial plexus).¹⁵

While the clinical application of the somatosensory rehabilitation method (SRM) has been well described in non-peer reviewed literature,^{15,20} to date there have only been a few peer-reviewed papers focusing on the effectiveness of the technique with specific populations, addressing both allodynia and hypoesthesia across a spectrum of nerve lesions.^{21–23} Given the need for clinical modalities to address the allodynia that limits both activities of daily living and participation in rehabilitation for persons with CRPS, this study will seek to evaluate the clinical results of SRM for this population.

Purpose of the study

Our primary objective was to answer the research question: Is **somatosensory rehabilitation effective for reducing pain and/or resolving allodynia in persons with CRPS of one upper limb?** However, as this is a novel treatment method, our secondary objective was to explore the theoretical constructs and hypothetical relationships underpinning the method.

METHODS

Design and setting

This retrospective study was based on a chart review conducted at a single centre [the Somatosensory Rehabilitation Centre] in Fribourg, Switzerland by an independent investigator. All files of clients who were no longer receiving treatment at the Centre were reviewed, from its opening in July 2004, to August 2015. Clients were referred by a medical doctor, and assessments and treatments followed a detailed clinical protocol. Clients attended a weekly treatment session and were seen on alternate weeks by two occupational therapists trained in the SRM.¹⁵

Participants

All consecutive patient records identified as a) meeting the Budapest criteria for CRPS²⁴ and b) demonstrating static mechanical allodynia (defined as a painful response to stimulation with a 15g monofilament)²¹ were included in this retrospective cohort, regardless of whether they attended or completed treatment. Persons identified as having CRPS who demonstrated tactile hypoesthesia but no allodynia were not included, as our focus was on allodynia. It is important to note all patients reporting spontaneous neuropathic limb pain are systematically screened using the Budapest criteria as a checklist as part of the initial evaluation at the Somatosensory Rehabilitation Centre, and these results were clearly documented in clinic files.

Outcome measures

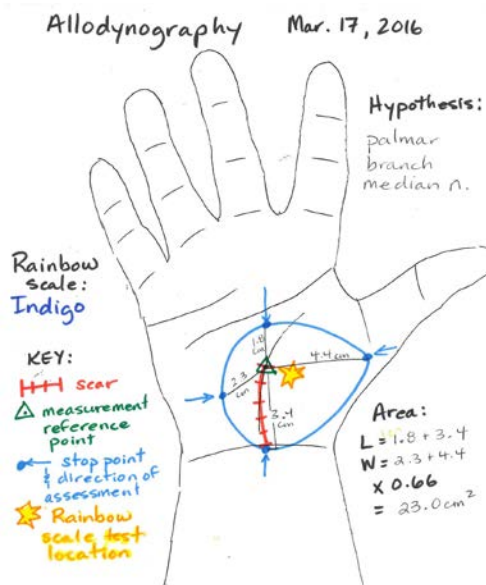
The primary outcome measure was the French version of the McGill Pain Questionnaire (QDSA: *Questionnaire de la Douleur St-Antoine*)²⁵; however, if the client

was unable to complete this assessment because of language barriers, other validated translations of the McGill were employed. The QDSA is comprised of 58 pain descriptors, with sensory (35 word) and affective (23 word) subscales; words are further arranged in construct clusters (temporal, spatial, thermal, etc.).²⁵ The person is instructed to first choose all words that describe their current pain (yielding a total number of words / 58). From these chosen words, the 'best' word from each cluster is rated using a 0-4 scale [0=absent, 1=mild, 2= moderate, 3=strong, 4= very strong] to indicate the severity of this pain at the present time. These ratings are summed and converted to z scores for ease of interpretation, yielding a total score tQDSA /100, as well as sensory pain score (sQDSA) /100, and affective pain score (aQDSA) /100.

In the somatosensory rehabilitation method, allodynia is quantified in 2 ways: allodynography and the rainbow pain scale.^{15,21} Allodynography is a mapping technique using a standard 15g stimulus (Semmes-Weinstein monofilament: mark 5.18) to outline the borders of the territory where application of the stimulus to the skin produces pain (30mm on 100mm visual analogue scale [VAS], or pain at rest + 10mm on a 100mm VAS).²¹ The territory of the allodynography is recorded visually on graph paper: see Spicher et al, 2008²¹ for a detailed description of the technique. However, the mathematical area of the territory can also be estimated from measurements taken relative to invariant anatomical reference points. To account for the reality of a non-rectangular shape of the allodynic territory, we calculated the area of the allodynia as length (most proximal and distal points identified) x width (most lateral points identified) x 0.66; see Figure 1 for an illustrative example. The rainbow pain scale is a categorical scale rating the severity of the allodynia within the allodynic territory. This is tested with

vision occluded by touching the centre of the painful area with a series of monofilaments. Starting with the smallest pressure (0.04 g/2.83 log), a single stimulus is applied for 2 seconds with each monofilament (with a 10 second interval between applications), progressing to greater pressure categories (see Figure 2) until the person being tested indicates the stimulus has become painful (30mm on 100mm visual analogue scale [VAS], or pain at rest + 10mm on a 100mm VAS). As soon as a stimulus is painful, the testing is discontinued, and the rainbow scale category is recorded as the first stimulus perceived as painful. To minimize the effects of summation,¹⁷ the rainbow scale evaluation is not completed at the same time as the allodynography.¹⁵

Figure 1. Sample allodynia map



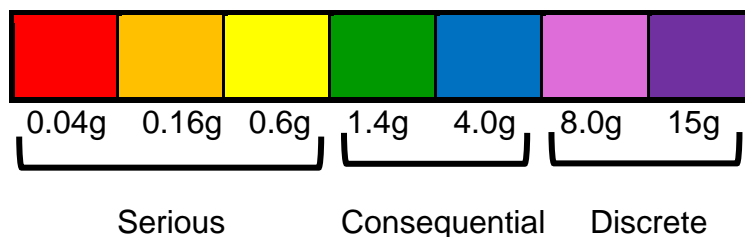
- a) Hypothesis designates the cutaneous nerve branch related to the mapped territory
- b) Arrows indicate the direction of testing, while dot indicates where the person indicated 'STOP'
- c) Green triangle indicates invariant measurement reference point
- d) Star indicates the point where the rainbow scale was tested
- e) Rainbow scale indicates the severity of allodynia

In conjunction with the allodynography, an anatomical hypothesis is formed to identify which cutaneous nerve branch is the primary supplier of the allodynic territory, and therefore potentially the source of the nerve lesion generating the neuropathic pain.^{16,26} This hypothesis is recorded on the allodynia map, and used to inform the

treatment regime. On the initial visit, the primary allodyngography is recorded for only the most painful area. Although the client may have several areas of pain, or may report diffuse pain across an entire limb or hemisphere, they are asked to identify the **most painful area**. As treatment progresses, they may identify additional areas of allodynia, and secondary allodynia maps (and associated cutaneous branches) are recorded for those additional locations.

The assessment protocol was completed as follows: 1) QDSA and allodyngography at the first/baseline visit; 2) rainbow pain scale on first subsequent visit; 3) repeat evaluation of QDSA and allodyngography every 4 weeks, or sooner if indicated;

Figure 2. Rainbow pain scale. The colours represent the severity of allodynia as represented by the smallest amount of pressure which elicits a painful response; they are grouped by severity into discrete, consequential and serious ratings.



and 4) esthesiography [mapping of the underlying area of tactile hypoesthesia],^{21,22} and quantitative somatosensory testing including static two-point discrimination (s2PD), vibration perception threshold (VPT) and pressure perception threshold (PPT) when the allodyngography is negative (15g stimulus to the skin is not perceived as painful) for 2 consecutive visits. The QDSA, s2PD, VPT and PPT were also recorded at discharge. For those clients not completing the recommended course of treatment, the reason for exiting treatment was recorded using the categories a) lack of progress with current

regime (patient perspective), b) other life issues (i.e. moved away, cost barriers), c) other health issues, d) didn't ascribe to the treatment program/dropped out, e) no further recovery expected (therapist perspective), or f) returned to work and unable to continue attending.

Intervention

The treatment regime for the somatosensory rehabilitation method has 3 core elements: distant vibrotactile counter-stimulation (DVCS), application of therapeutic vibration, and avoidance of any touch stimuli that evoke pain. The first element is carried out as a home program where DVCS is applied eight times daily for no longer than one minute. DVCS uses the medium perceived by the client as the most comfortable version of light touch (typically rabbit fur or a plush microfleece), applied in a light stroking motion. It is NOT applied to the painful area; instead, it is applied to an area of the skin with normal sensation that is anatomically related to the sensitized cutaneous branch hypothesized to underlie the allodynic territory. For example, the sensitization hypothesis for the allodynic territory illustrated in Figure 1 is the palmar cutaneous branch of the median nerve. Therefore, DVCS would be applied to the cutaneous territory of a more proximal branch of the same nerve or any nerve joining the same cord of the brachial plexus. In this case, it would be the lateral antebrachial cutaneous nerve, which joins the median nerve in the lateral cord of the brachial plexus.²⁷ If this cutaneous area also demonstrated somatosensory abnormalities or stimulation in this area was not comfortable, then DVCS would be applied on the ipsilateral side in a dermatomal area above or below the nerve roots for the sensitized branch (i.e. in the T1/T2 area just below the collarbone). Vibration stimulation was

applied to the same area as DVCS for 10 minutes during weekly clinic visits, using the Vibradol® (Rehaxone, Sierre, Switzerland). Finally, the occupational therapist reviewed activities of daily living with each individual client, and collaboratively identified sources of evoked pain (such as the rubbing of clothing, tool use) and developed strategies to avoid stimulation and/or delegate provocative tasks until the resolution of the allodynia.

Statistical analysis

Primary objective: After screening for high/low values that might suggest data entry errors, descriptive statistics of demographics and continuous clinical variables were tabulated using means \pm standard deviations (SD), and frequencies/percentages for categorical variables. To address our primary question on effectiveness, QDSA total scores pre and post treatment were compared using 2-sided paired sample student t-tests, with 95% confidence intervals and estimates of effect size using Cohen's *d* (employing an on-line sample size calculator at http://www.psychometrica.de/effect_size.html#dep) to account for the paired or dependent sample).

Secondary objective: To explore and illustrate theoretical constructs within the somatosensory rehabilitation method, we generated eight *a priori* hypotheses (see Table 1). For the regression analyses, normality of the distributions for each variable was assessed statistically and graphically. In multiple regression, we also examined for collinearity using pairwise correlations and scatterplots. For all regression analyses, we followed the analysis with formal regression diagnostics: testing homogeneity of variances, calculating leverage and influence, testing the normality of the residuals, and

plotting residuals against predicted values and leverage, and calculation of the variance inflation factor. In order to develop the ideal model for multiple linear regression, outliers

Table 1. Construct questions and hypotheses

Question		Hypothesis	Variables	Statistical method
1	What is the nature and strength of the relationship between severity of pain and severity of mechanical allodynia at baseline?	There will be a weak positive relationship between these different constructs	QDSA Rainbow scale	Correlation and simple regression
2	What is the nature and strength of the relationship between duration of pain and area of allodynia at baseline?	There will be a weak positive relationship, reflecting the spread of chronic pain beyond the initial noxious event	Duration of NeP Mathematical area of allodynic territory	Correlation and simple regression
3	Is there a difference in duration of pain between different levels of allodynia (severity) at baseline?	There will be a significant positive relationship, with increasing duration seen with increased severity	Duration of NeP Rainbow scale	ANOVA
4	What is the nature and strength of the relationship between the area of allodynia and severity of allodynia at baseline?	There will be a weak positive relationship, as they are unique constructs	Area of allodynia Rainbow scale	Correlation and simple regression
5	Does the severity of allodynia at baseline predict the duration of treatment required to resolve it?	There will be a strong relationship between severity and duration of treatment	Rainbow scale Duration of DVCS	Correlation and simple regression
6	What factors predict change in QDSA scores?	Change in QDSA scores will be multi-factorial	QDSA change, age, rainbow scale, gender, duration of NeP, nerve lesion location, area of allodynic territory, # of nerve lesions	Stepwise multiple regression
7	Do persons with a single nerve lesion report less pain than persons with evidence of multiple lesions?	Persons with multiple lesions will report more pain	# of nerve lesions (coded as single or multiple), QDSA	ANOVA
8	Do persons with a single nerve lesion in the hand (where there is a higher density of nerve endings) report more pain than persons with a single nerve lesion in the arm or trunk?	Persons with lesions in the hand will report more pain than those with more proximal lesions because of the higher density of nerve endings	Nerve lesion location (coded as hand, arm or trunk), QDSA	ANOVA

Key: QDSA=Questionnaire Douleur St. Antoine, NeP=neuropathic pain, DVCS=distant vibrotactile counterstimulation, # = number, ANOVA=analysis of variance

with strong influence were removed, the regression model re-run, and the homogeneity of variances and normality assumptions were checked again. Differences between groups (single nerve lesion vs. multiple, nerve lesion in hand vs. arm vs. trunk) were examined using analysis of variance, with dummy coding for categorical variables.

All analyses were performed with STATA 13, with statistical significance set at $p=0.05$ unless otherwise noted.

RESULTS

Participants

Forty-eight records were identified for persons demonstrating allodynia accompanying CRPS. 70.4% were female, and the average age was 45 years. The average area of allodynia was 65.7 cm² and of 'discrete' severity¹⁵ (35.6% were categorized as purple or indigo on the rainbow scale; see Figure 2). Psychological comorbidities reported included post-traumatic stress disorder (n=1, 2.1% of persons), and anxiety or depression in n=4 or 8.4%. See Table 2 for a summary of demographics and clinical features. Thirty-one different cutaneous nerve branches were identified as underlying the allodynic areas: with the palmar branch of ulnar nerve (n=12, 13.6%) and the palmar branch of median nerve (n=11, 12.5%) being the most common. Overall, more nerve lesions were seen in the hand (70.5% of identified branches) as compared to the arm (23.9%). The average reported duration of neuropathic pain symptoms (not time since CRPS diagnosis) was 31.2 months, but ranged greatly from one month to over 25 years. Baseline QDSA total scores were also highly variable, ranging from 4 to 99 at baseline, with an average score of 48.1 ± 17.7 ; final scores averaged 20.1 ± 20.0 .

However, it is worth noting that ‘baseline’ for identification of the painful area/nerve lesion was not necessarily the first treatment visit for the person: in fact, all QDSA scores below 20 at ‘baseline’ were related to secondary or tertiary lesions, and did not represent the pain score on the client’s first visit.

Table 2. Demographics and clinical features

Demographics & clinical features	Mean	Standard deviation	Range
Age (in years)	45.4	13.4	18-74
Duration of NeP (in months)	31.2	57.5	1–335
Baseline tQDSA (in points)	48.1	17.7	5-99
Final tQDSA score (in points)	20.1	20.0	0-75
Area of allodynia (in cm ²)	65.7	78.6	2.6 – 320.8
Duration of DVCS (in days)	81.0	76.4	5 - 381
Demographics & clinical features	Frequency	Percentage	
Gender	Females=34 Males=14	70.4% 29.6%	
Rainbow pain scale	Violet =12 Indigo=9 Blue=12 Green=7 Yellow=10 Orange=1 Red=8	20.3% 15.3% 20.3% 11.9% 17.0% 1.7% 13.6%	
Cutaneous branch injured or damaged (n=88)* [5 most frequent]	Palmar branch of ulnar nerve =12 Palmar branch of median nerve=11 Dorsal branch of ulnar nerve=8 Superficial branch of radial nerve=7 Superior lateral cutaneous nerve of arm=7	13.6% 12.5% 9.1% 8.0% 8.0%	
Nerve lesion region (n=88)*	Hand=62 Arm=21 Thoracic=5	70.5% 23.9% 5.7%	
Reason for exiting treatment (n=88: recorded for lesion, not for participant)*	Lack of progress=3 Other life issues=4 Other health issues=4 Dropped out=9 No progress expected=2 Completed treatment=51 Not determined=15	3.4% 4.6% 4.6% 10.2% 2.3% 58.0% 17.1%	

*NB some persons had multiple lesions identified

Effectiveness of somatosensory rehabilitation

A paired sample t-test was conducted to compare QDSA total scores at baseline and final evaluations. There was a significant difference in the baseline tQDSA ($x=51.4$, $SD=17.4$) and final tQDSA ($x=20.4$, $SD=20.0$); $t(57)=13.6$, $p < 0.001$. These results suggest somatosensory rehabilitation treatment reduced self-reported pain qualities in this set of 48 patients with 88 nerve lesions. Effect size was calculated at Cohen's $d = 1.64$, using a formula which accounted for the inherent correlation of our paired samples. Of this cohort, reasons for ceasing treatment at final evaluation were reported, with 58% having completed their treatment, 10.2% dropping out of treatment, 3% ceasing treatment because the patient did not see any change, 2% ceasing because the therapist did not feel it was beneficial, and 10% ceasing treatment because of work, health or life issues. Final tQDSA scores were also calculated for the subgroup identified as completing a full course of treatment; these demonstrated lower mean scores ($x=12.3$, $SD 10.2$, range 0-41).

Relationships of clinical characteristics, pain and treatment response

Linear regression was used to investigate the relationship at baseline between the tQDSA and severity of mechanical allodynia as measured by the rainbow scale. There were 54 datasets with this information used for this analysis. The severity of mechanical allodynia required transformation by calculating the square root of each value to normalize the data distribution prior to analysis. This model generated $R^2=0.0004$, $p=0.88$; $F[1,52]=0.02$. Post hoc analyses confirmed the homogeneity of variance, and normal distribution of the residuals. This suggests there is only a weak correlation between the variables, and that the severity of allodynia did not explain any

of the variance in QDSA values at baseline. We then looked to see if there was a correlation between the duration of neuropathic pain at baseline and the (adjusted) area of allodynia. Pearson's correlation was small at $r=0.037$ using the 32 available datasets; further examination of this relationship using transformed data to normalize the distribution (logarithmic transformation applied) was also non-significant at $R^2=0.0455$, $p=0.24$; $F[1,30]=1.43$. Post-hoc tests confirmed the assumptions of regression, meaning we can be confident in the model suggesting there is only a weak correlation between duration of neuropathic pain and the size of the area of allodynia, and the duration of pain did not predict the variability seen in the area of allodynia.

We were also interested in whether the severity of allodynia was influenced by the duration of neuropathic pain. Analysis of variance was therefore conducted to examine whether average duration of pain (transformed logarithmically to normalize the distribution) differed across categories of allodynia severity; this was again non-significant at $F[1, 60]=2.08$, $p=0.06$ based on analysis of 61 available data sets. We then progressed to look at if there was a relationship between the size of the area of allodynia and the severity of allodynia within that territory. Regression analysis of the transformed variables (log transformation of area; squaring of rainbow pain scale values) suggested a small but significant relationship existed, at $R^2=0.1706$, $p=0.02$, $F[1,30]=6.17$. Post-hoc analyses again confirmed the homogeneity of variance, and normal distribution of residuals. Conversion back from the transformed values to the original units of measurement suggests on average, the adjusted area of allodynia increases by 1.25 cm^2 for every increase in the Rainbow Pain Scale severity.

Regression analysis was used to explore the relationship between the severity of allodynia at baseline, and the duration of distant vibrotactile counter-stimulation required to see it resolve. Analysis was based on 36 cases with this data available, however both variables needed transformation to normalize their distribution (using the square root of allodynia severity values, and the log of duration of DVCS values). This generated $R^2=0.23$, $p=0.003$; $\beta_0=2.55$, $\beta_1=0.88$, and met the requisite assumptions of heteroskedasticity, and normality of the distribution of the residuals. After conversion of the beta-coefficients back to the original units, this suggests for every increase in the severity of allodynia, the duration of DVCS necessary to resolve it increases by 24.4 days. Post-hoc power analysis supported this analysis was fully powered to find this relationship; however, it should be noted severity of allodynia only explained 23% of the variation seen in the duration of DVCS required.

We conducted stepwise regression to see what factors would predict change in QDSA scores from baseline to final evaluation (dependant variable). The independent variables of age, gender, nerve lesion location, rainbow scale, area of allodynic territory, number of nerve lesions, and duration of neuropathic pain were introduced into the model (after transformation to normalize distribution if required). Variables were retained if they had a statistical significance of less than $p=0.05$, and were removed if significance was greater than 0.06. This only retained gender in the final model $R^2=0.35$, $p=0.01$, $F(1,15)=8.01$; the coefficients suggested women saw greater reductions in pain than men. Analysis of variance was therefore conducted to look at the difference in change in QDSA scores and gender. Again, there was a significant effect of gender on change in QDSA scores [$F(1,56)=5.88$, $p=0.02$] with a larger sample

Table 3. Summary of results for secondary analyses

Question/Relationship Investigated		Results			Significance
		N=	Coefficients	Meets statistical assumptions	
1	Severity of pain and severity of mechanical allodynia at baseline?	54	$R^2=0.0004$ $F[1,52]=0.02$	✓	$p=0.88$
2	Duration of pain and area of allodynia at baseline?	32	$r=0.037$ $R^2=0.05$ $F[1,30]=1.43$	✓	$p=0.24$
3	Duration of pain between different levels of allodynia (severity) at baseline?	61	$F[1, 60]=2.08$ $R^2=0.22$	✓	$p=0.06$
4	Area of allodynia and severity of allodynia at baseline?	32	$R^2=0.17$ $F[1,30]=6.17$	✓	$p=0.02$
5	Severity of allodynia at baseline predicting the duration of treatment required to resolve it?	36	$R^2=0.23$ $\beta_0=2.55$ $\beta_1=0.88$	✓	$p=0.003$
6	Prediction of change in QDSA scores?	17	$R^2=0.35$ $F[1,15]=8.01$	✓	$p=0.01$
6 b	Gender differences in change in QDSA scores?	58	$F(1,56)=5.88$ $R^2=0.10$	✓	$p=0.02$
7	Pain level and number of nerve lesions (single vs. multiple)?	76	$F[1,74]=4.65$	✓	$p=0.03$
7 b	Pain level and single vs. multiple lesions and duration of NeP	75	Model $R^2=0.10$ β_1 # of nerve lesions β_2 NeP duration	✓	$p=0.03$ $p=0.007$ $p=0.95$
8	Pain level and location of lesion (hand vs. arm vs. trunk)?	76	$F[2,73]=3.72$	✓	$p=0.03$

of $n=58$ observations; the mean difference in QDSA change scores between men and women was 12.4 points, with women achieving greater change in score. However, it is also important to note that based on the R^2 value ($R^2=0.10$), gender only explained 10% of the variance.

Analysis of variance was conducted to examine for differences in baseline QDSA scores between persons with a single nerve lesion or those with multiple nerve lesions. There was a significant effect of the number of nerve lesions on the QDSA total scores [$F(1,74)=4.65$, $p=0.034$]. The average QDSA score for persons with a single nerve lesion was 55.5, while the mean QDSA score for persons with multiple nerve

lesions was 45.6, suggesting that persons with multiple nerve lesions reported less pain than those with a single nerve lesion. This unexpected finding raised the question if the incidence of multiple lesions was related to a longer duration of pain. To explore this hypothesis, we conducted a regression analysis of baseline QDSA scores and introduced the 2 dependent variables of number of nerve lesions (categorized as single or multiple), and duration of NeP (with score conversion to log values for normalizing the distribution). This model confirmed a significant effect of number of nerve lesions, but including duration of NeP did not explain any additional variance [$R^2=0.10$, $p=0.03$ for the total model; but $p=0.95$ for the β_2 value of NeP duration; the β_1 for number of nerve lesions was significant at $p=0.007$. Post hoc analysis confirmed this model met the regression requirements for homogeneity of variances ($p=0.21$, so actual variance was not different than predicted) and normal distribution of residuals ($p=0.38$ is not different from the normal distribution). This means we can be confident in our findings that having more than one nerve lesion predicts a lower QDSA score at baseline, but only explains 10% of the variance seen in those scores.

Analysis of variance was also conducted to see if there was a difference in baseline QDSA scores between persons with nerve lesions in their hand, and those with nerve lesions in the forearm/arm or trunk. There was a significant effect of the location of the nerve lesion on baseline QDSA total for the three locations [$F(2,73)=3.72$, $p=0.03$]. The mean QDSA total score for nerve lesions of the hand was 45.7, for the arm was 57.7, and for lesions on the trunk was 40.2. Post-hoc testing with Bonferroni correction for multiple comparisons shows the significant differences lie between nerve lesions in the hand compared to the arm [$F(1,73)=6.31$, $p=0.03$], while no differences

were found between the scores for nerve lesions in the hand vs. the trunk [$F(1,73)=0.48, p=0.98$], and nerve lesions in the trunk compared to the arm [$F(1,73)=4.04, p=0.10$]. Given the mean score for lesions on the trunk is the lowest of the three mean scores, and the mean score for lesions on the arm is the highest, it is counter-intuitive that no difference would be found when comparing the trunk to the arm; however, due to the high level of variability in the trunk scores, the 95%CI when comparing those 2 values was very large and included 0. Thus nerve lesions of the forearm and arm were reported as statistically significantly more painful than nerve lesions in the hand.

DISCUSSION

This retrospective, uncontrolled cohort study has generated preliminary evidence for the effectiveness of the somatosensory rehabilitation method, and some hypothesized relationships of the supporting constructs. There is a need for mechanism-specific¹⁸ rehabilitation interventions for CRPS to address the burden of pain^{28,29} and the impact on daily activities.³⁰ Somatosensory rehabilitation is a method of assessment and treatment specifically intended to address the sensory aspects of neuropathic pain, including the allodynia frequently seen in CRPS.¹⁵ The theoretical mechanism for the effect of the SRM is the reduction of central sensitization by addressing the altered peripheral signalling. This mirrors the work of others who have demonstrated reduction in pain syndromes with features of central sensitization (such as phantom limb pain) by addressing peripheral pain generators.^{31–33} The treatment target of somatosensory rehabilitation is the skin,²¹ and its rich network of cutaneous nerve endings as the entry point to the nervous system.³⁴ Further, the skin itself has the

ability to produce neurotransmitters and peptides such as serotonin and cortisol, and tactile stimulation can drive the local immune and inflammation regulatory responses.^{35,36} Somatosensory rehabilitation seeks to apply comfortable sensory stimulation to a cutaneous nerve branch anatomically related to the peripheral lesion,¹⁵ where the neurotransmitters generated from this comfortable stimulation have the opportunity to reduce the aberrant signalling.³³ This represents a distinct departure from traditional ‘desensitization’ interventions,^{2,37,38} which seek to flood the area of altered sensation with intense sensory stimuli, with the intent of producing “...sensory accommodation to the stimulus”(p.1715).³⁹ However, the term ‘tactile desensitization’ has also been used to describe sensory-motor re-education programs for CRPS⁴⁰ using conscious attention to direct stimulation of the painful area.^{40,41} In contrast, the SRM seeks to avoid all tactile stimulation to the painful area, and focuses on stimulation to related areas of normal sensation to resolve allodynia, followed by sensory re-education to address the residual hypoesthesia after the allodynia has abated.²¹ This strategy of avoiding tactile stimuli recognizes that only low-level, non-noxious stimuli are required to maintain the modulated neuroplasticity after nerve lesion,⁴² and that simply performing activities of daily living is sufficient to sustain central sensitization.⁴³

This study describes use of the somatosensory rehabilitation method for persons with CRPS of a single upper limb. These patients were identified using the Budapest clinical criteria²⁴ at baseline. However, this evaluation was not repeated at discharge or end of treatment, so it is not known if these persons would have continued to meet the criteria after treatment. Our results demonstrate few patients had zero pain at final evaluation (see Table 2); however, this aligns with the general literature on the

outcomes of CRPS, which reports many people continue to experience pain, stiffness and cold intolerance.^{4,5} Although patients exiting treatment may not have complete resolution of CRPS symptoms, it was often anticipated they would be better able to participate in other forms of treatment like graded motor imagery⁴⁴ to address residual motor symptoms. Additionally, this was reflective of a consecutive cohort where only 58% of participants completed treatment.

We conducted an intention to treat analysis, including any follow-up results available, regardless of if the person had completed the full course of treatment. Despite this, the effect size should be considered large at $d=1.64$.⁴⁵ It is also worth noting the average duration of neuropathic pain symptoms reported at baseline was more than 2 years; however, duration of symptoms was not shown to be predictive of baseline pain or change in pain from baseline to final evaluation.

Nedelec and colleagues recently published their results using the SRM for neuropathic pain in a cohort of 17 burn survivors, an average of 16 months post-burn.²³ In contrast to our CRPS cohort, participants were more likely to be male (71%), and reported a higher level of psychological comorbidities (3/17 had dual diagnoses of depression and PTSD). Of those 6 patients completing the QDSA at baseline and after completing 3 months of treatment, a significant reduction in QDSA scores was reported (22.7% improvement, $p=0.04$); however, no effect size was reported for comparison.²³ Our results in a predominantly female cohort suggest gender is a statistically significant predictor of response to treatment, but the reasons for this are unknown, and 90% of the overall variance in the change in QDSA scores remains unaccounted for. Larger studies are required to build more powerful and stable models to predict treatment

response, and inform the selection of persons likely to benefit from somatosensory rehabilitation.

A unique contribution of this study is the precise identification of the injured or damaged cutaneous nerve branches related to the territory of allodynia. Thirty-eight out of 88, or 43% of the identified painful lesions were in the hand. Branches included the palmar cutaneous branches of both the median and ulnar nerves, the dorsal cutaneous branch of the ulnar nerve, and the superficial sensory branch of the radial nerve. However, despite the abundance of sensory end-organs in the hand, this group of patients reported lower pain scores on the QDSA than did patients with nerve lesions in the forearm/arm, or thoracic regions.

Another interesting finding of this study was the lack of association between overall self-reported pain (QDSA score) at baseline, and the psychophysical measurement of severity of allodynia. This reflects previous research reporting weak correlations between quantitative testing of static and dynamic mechanical allodynia and overall pain scores in persons with CRPS.⁴⁶ In their sample of 145 persons with CRPS, Birklein et al reported average MPQ scores (German version) of 20.4 (range 0-63) and identified the presence of dynamic mechanical allodynia in 26% of this group, but did not rate the severity of allodynia, or compare pain scores for those with and without this symptom.⁴⁷ The statistically significant but weak ($R^2=0.17$) relationship between severity of allodynia (rainbow pain scale scores) and total area of the allodynic territory demonstrated here was not unexpected; this could be interpreted as support for the validity of the measures, as they are intended to measure different constructs.¹⁵ The mean increase in size of the allodynic territory predicted by an increase in the

severity of allodynia as measured by the rainbow pain scale was also statistically significant but not clinically meaningful at 1.25 cm². Although the rainbow pain scale for severity of allodynia was not shown to be related to baseline pain, there was a statistically significant relationship ($p=0.003$) between the rainbow pain score and the duration of distant vibrotactile counterstimulation required to see it resolve. This predicted duration of 24.4 days of treatment for every increase in allodynia severity can be used by therapists for treatment planning, and to provide the client with evidence-informed expectations for outcome.

Limitations and areas for future research

While the main outcome of this study draws on the QDSA, a well-validated self-report measure,²⁵ other analyses drew on measures such as allodynography and the rainbow scale²¹ whose measurement properties are currently unknown (although this work is underway). Mapping techniques for documenting areas of altered sensation have a long history;^{19,48} several other techniques for mapping allodynia have also been recently described for CRPS and post-herpetic neuralgia^{40,49} but without addressing the measurement properties of the technique.

The nature of a retrospective cohort drawn from clinical records has inherent bias. We sought to minimize aspects of this bias by including all available records for our baseline analyses, and records with any follow-up for calculating change scores, regardless of whether the person had completed treatment. Further, all data extraction and statistical analyses were conducted independently by TP, with oversight from the McMaster team, but without involvement of the treating therapists at the Somatosensory Rehabilitation Centre. Because there was no control group, we were only able to

retrospectively compare pre-post measures for the persons in our cohort, which is considered a weak form of support for effectiveness.⁵⁰ Other elements of potential inherent sampling bias are the fee-for-service nature of the treatment facility, and the singular focus of the program on somatosensory rehabilitation, exclusive of other forms of rehabilitation. However, it is important to note the model of alternating therapists for weekly treatment sessions reduces observer bias,⁵¹ and the training in assessment and treatment principles involved in the certification process for somatosensory therapists adds consistency.

This study provides estimates for effect size that will inform future prospective and controlled studies of the somatosensory rehabilitation method for the treatment of allodynia. To achieve the sample sizes necessary to power these more rigorous evaluations, multi-site studies will be required to recruit homogenous populations such as the group with CRPS of a single upper extremity described here. Future studies should include a broader spectrum of validated outcome measures addressing the key domains of pain and pain disability,⁵² and facilitating comparison to other treatment methods that do not employ the SRM-embedded measurement techniques of allodynography and the rainbow pain scale. Other potential populations with high incidence of allodynia include persons with post-herpetic neuralgia,⁴⁹ and women after breast cancer surgery:^{53,54} the potential of somatosensory rehabilitation to reduce pain and disability in these groups should also be explored.

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ADDRESSING A SENSITIVE ISSUE: THE SOMATOSENSORY ASSESSMENT AND REHABILITATION FOR ALLODYNIA (SARA) PILOT STUDY

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Target journal: Journal of Hand Therapy

ABSTRACT

Introduction: Somatosensory rehabilitation is a novel method of assessment and treatment for allodynia that lacks evidence for the reliability and validity of the embedded assessment tools. Further, existing support for effectiveness has a high risk of bias. This pilot study undertook investigation of the measurement properties of the assessments and sought to establish estimates for the sample size required for future controlled trials of this treatment method.

Methods: Persons with pain in one upper extremity after CRPS, a peripheral nerve injury or who had experienced a hand fracture were recruited for assessment; those with identified allodynia were provided with 8 weekly sessions of treatment; participants also attended a one-week and 3 month follow-up visit to generate data to evaluate the outcome measurement tools.

Results: Preliminary estimates did not support the effectiveness of somatosensory rehabilitation ($p=0.15$). However, single measures estimates suggested reliability for allodyniography was excellent at $ICC=0.94$ and was substantial for the rainbow pain scale at $ICC=0.79$.

Discussion: This pilot study has generated preliminary support for the inter-rater reliability of allodynography and the rainbow pain scale. More study is needed to determine test-retest reliability, validity and responsiveness. Estimates of effect size are poor and suggest large trials will be necessary to determine effectiveness of this method; however, given the high variability seen in this small sample, these estimates may not be valid.

Keywords: somatosensory rehabilitation, complex regional pain syndrome, allodynia, effectiveness,

Level of evidence: Level 3 (prospective controlled pilot study).

INTRODUCTION

Allodynia is commonly referred to as hypersensitivity, but is more accurately defined as the perception of a non-noxious stimulus as producing pain.¹ It is frequently associated with neuropathic pain and/or the resultant peripheral and central sensitization.^{2,3} In rehabilitation, allodynia adds to the clinical challenge of effective management for burns, peripheral nerve and plexus injuries, and complex regional pain syndrome.⁴⁻⁶ For research purposes, mechanical allodynia (associated with touch) is often measured dynamically by stroking the sensitive area of the skin with a brush; however this technique is difficult to standardize in the clinical setting.⁷ Furthermore, it is generally used for diagnostic purposes and the responsiveness to change remains to be established.⁸ ‘Desensitization’ is commonly recommended for the rehabilitation of mechanical allodynia⁹⁻¹³ and this technique is often applied in practice on the basis of the gate control theory of pain: the client is encouraged to ‘flood the area with sensory stimuli’ to create sensory accommodation or raise the nociceptive threshold.⁹ However, the gate control theory is now seen as an incomplete model for representing the current understanding of the complex interactions of signal transmission, modulation and perception implicated in the contemporary theories of central sensitization and the accompanying allodynia.^{2,14,15} A need exists for clinically useful but accurate evaluations for both the identification and monitoring of change over time in allodynia, as well as treatments that are both theoretically informed and effective.

Somatosensation has been defined as the “...detection, discrimination, and recognition of body sensations” (p. S41) : it encompasses touch, vibration, pressure,

temperature, and pain sensations.¹⁶ ‘Somatosensory rehabilitation’ is the chosen terminology for a formal method developed by an occupational therapist in Switzerland for the identification and treatment of neuropathic pain and reduced somatosensation following nerve lesion.¹⁷ It is a paradox that an area of reduced sensation may be overlaid with an area of allodynia:¹⁸ simultaneous sensory loss and sensory gain. The somatosensory rehabilitation method (SRM) was developed to apply the principles of sensory re-education based on contemporary understandings of the function and dysfunction of the nervous system.¹⁷ In reference to allodynia, this includes:

a) the need to precisely define the territory that is painful to touch using a standardized method of evaluation, and subsequently avoid touching the area and perpetuating peripheral sensitization, and

b) strategically considering the peripheral nerve branches residing in the painful territory, and applying comfortable tactile or vibratory ‘counter-stimulation’ to a distant (often proximal) site of an anatomically related cutaneous branch.¹⁷⁻¹⁹

This technique is therefore known as distant vibrotactile counterstimulation (DVCS). However, the precisely calibrated equipment used for evaluation of the vibration perception level (to determine the amount of vibration required to generate a comfortable vibration perception for the individual client and cutaneous territory) used in other studies^{18,19} is not widely approved or available in North America. This creates a barrier for use of this technique in wider clinical practice. Therefore, a need exists to evaluate the effectiveness of the SRM without this element.

Somatosensory rehabilitation for allodynia incorporates the unique assessment methods of allodyngraphy and the rainbow pain scale: unfortunately, the measurement properties of reliability, validity and responsiveness for these evaluations have not yet been systematically evaluated. Further, the published research uses the French version of the McGill Pain Questionnaire (*Questionnaire de la Douleur St. Antoine*)²⁰ which has a different number of items, different scaling for pain scores, and cannot be directly compared to the English version. An opportunity exists to evaluate the outcomes of somatosensory rehabilitation in the upper limb using additional measurements for pain, disability and sensibility more common to upper extremity rehabilitation. This will facilitate consideration of the outcomes of the SRM relative to other interventions until a randomized controlled trial is conducted for direct comparison.

Purpose of the study

The overarching purpose of this study was to conduct a pilot study on the effectiveness of a somatosensory rehabilitation protocol for persons with allodynia resulting from CRPS or PNI and to commence concurrent investigation of the measurement properties of the related assessment tools. Therefore, our primary research question was: How effective is somatosensory rehabilitation as part of upper limb rehabilitation for the treatment of allodynia after complex regional pain syndrome or peripheral nerve injury in the upper limb? Secondary questions included:

- 1) Is allodyngraphy a reliable, valid and responsive assessment technique?
- 2) Is the rainbow pain scale a reliable, valid and responsive assessment technique?

- 3) How many persons with allodynia will be required to conduct a fully-powered randomized controlled trial for somatosensory rehabilitation of allodynia?

METHODS

Design and setting

This prospective study was conducted at the outpatient Hand Therapy Clinic at a regional trauma centre and teaching hospital in Hamilton, Ontario: data reported herein was collected between September 2014 and May 2016. Participants attended 8 weekly treatment sessions conducted by an occupational therapist (TP), trained and certified as a somatosensory therapist for pain (CSTP™).¹⁷ Baseline and 3 month follow-up evaluations were conducted by one of two independent assessors who had been trained in the assessment methods of allodyngography and the rainbow pain scale: one physiotherapist, one occupational therapist, and both with over 15 years' experience in hand rehabilitation. All participants gave written informed consent, and the study was approved by the local ethics committee (Hamilton Integrated Research Ethics Board).

Participants

Participants were recruited from local hand therapy facilities and pain programs (the SARA study: www.clinicaltrials.gov NCT02070367). Inclusion criteria were 1) a diagnosis of CRPS meeting the Budapest criteria²¹ in a single upper limb OR 2) a unilateral peripheral nerve injury in the upper limb verified intra-operatively, AND 3) demonstrating static mechanical allodynia (defined as a painful response to stimulation with a 15g monofilament) if the participant were included in the treatment arm. Both criteria 1&2 were confirmed by medical record to ensure eligibility. The screening

process for allodynia is described below. Target sample size for the explorations of reliability was set at $n=35$ using Donner's estimates to achieve substantial reliability at 80% power over 2 test occasions.²²

Outcome measures

Somatosensory assessment

The primary outcome measure was the McGill Pain Questionnaire (MPQ).²³ The MPQ is comprised of 78 pain descriptors, with sensory (54 words) and affective (24 words) subscales; words are further arranged in construct clusters (temporal, spatial, thermal, etc.).²⁰ The person is instructed to first choose all words describing their current pain (yielding a total number of words / 78). From these chosen words, the 'best' word from each cluster is rated using a 0-5 scale [0=absent, 1=mild, 2=discomforting, 3=distressing, 4=horrible, 5=excruciating] to indicate the severity of this pain quality at the present time. These ratings are summed and converted to percentage scores for ease of interpretation, yielding a total score tMPQ /100, as well as sensory pain score (sMPQ) /65, and affective pain score (aMPQ) /35. Additionally, we used the Patient-Rated Wrist and Hand Evaluation (PRWHE) as a more contemporary measure of pain and disability validated for upper extremity outcomes.²⁴

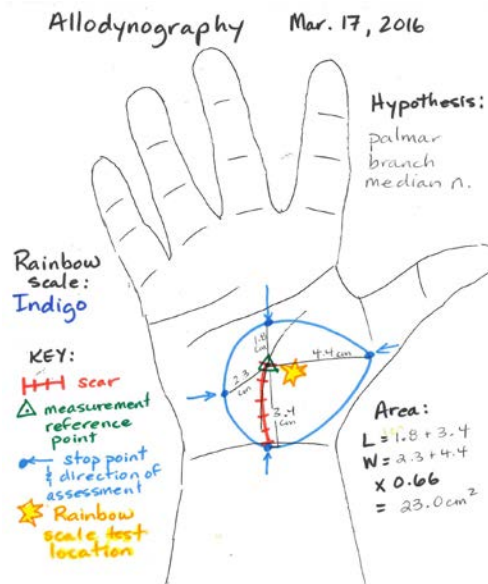
All participants were screened for static mechanical allodynia using a standardized set of questions. First, they were asked to point (but without touching) to indicate their most painful area. Then they were asked to rate (using a 4 point Always/Often/Sometimes/Never scale) if the pain radiated, got worse with movement or touch, or occurred spontaneously. The area was then tested by application of a single 2

second stimulus with a 15g monofilament (after demonstration on their non-painful limb), and the participant asked if it hurt (yes or no). If they answered yes, then the examiner proceeded with further examination to measure allodynia. While the SRM would also encompass assessment of sensation including esthesiography, 2 point discrimination, and vibration perception threshold in persons without evidence of allodynia, this was beyond the scope of the present investigation.

The somatosensory rehabilitation method quantifies allodynia using allodymography and the rainbow pain scale.^{17,18} Allodymography is a standardized technique to map the borders of the territory where application of a 15g pressure stimulus (Semmes Weinstein monofilament mark 5.18) on the skin generates a painful response (defined as 30mm on 100mm visual analogue scale [VAS], OR pain at rest + 10mm on a 100mm VAS).¹⁸ The territory of the allodymography is measured using anatomical landmarks and recorded visually on graph paper: see Spicher et al, 2008¹⁸ for a detailed description of the technique. For added precision, we asked the participant to identify when the stimulus perception started to change, or they experienced dysesthesia. At that point, we would tap the monofilament on a water-based ink pad prior to subsequent application of every stimulus, thus creating an accurate measurement point to record the 'STOP' point when the person indicated a painful response. Four 'STOP' points were identified and measured with a flexible clear plastic ruler held approximately 2 cm above the skin. These were recorded visually on a standardized diagram (front and back of right and left hands) with the measurement indicators (see Figure 1). To pragmatically account for the non-rectangular shape of the

allodynic territory, we calculated the area of allodynia as length (most proximal and distal points identified) *width (most lateral points identified) *0.66; refer to Figure 1.

Figure 1. Sample allodynia map



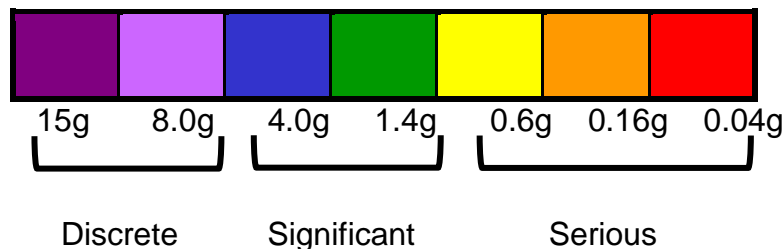
- a) Hypothesis designates the cutaneous nerve branch related to the mapped territory
- b) Arrows indicate the direction of testing, while dot indicates where the person indicated 'STOP'
- c) Green triangle indicates invariant measurement reference point
- d) Star indicates the point where the rainbow scale was tested
- e) Rainbow scale indicates the severity of allodynia

The second step of the allodynography is the formation of an anatomical hypothesis of which cutaneous nerve branch might be implicated as the site of the nerve lesion.^{17,25} This is used to label the allodynia map, and subsequently to develop the treatment plan. For the purposes of our study, a single allodynography map was developed only for the area identified by the participant as the most painful area.

The rainbow pain scale also uses monofilaments, this time to rate the severity of the allodynia within the allodynic territory. With vision occluded, the centre of the painful area (identified through allodynography) is tested by applying a single touch stimulus (0.04 g/2.44 log) for 2 seconds. This process is repeated precisely on the same area of skin with progressively larger filaments (see Figure 2) with a 10 second interval between applications, until the person indicates the stimulus has become painful. As in

allodyngraphy, the standardized definition of pain is 30mm on 100mm visual analogue scale [VAS], or pain at rest + 10mm on a 100mm VAS. Testing is stopped as soon as a stimulus is perceived as painful: and the rainbow scale category is recorded (on the allodyngraphy map) as the first size of filament to produce pain. Contrary to the recommendations of the test developer,¹⁷ it is noteworthy this was completed on the same occasion as the allodyngraphy for pragmatic administration of the study protocol. It is also important to note that if the initial screening for allodynia using the mark 5.18/15 g monofilament was negative, this was recorded as a score of zero on the rainbow scale; the remaining monofilaments were coded from 1 (5.18) to 7 (2.83).

Figure 2. Rainbow pain scale. Colours indicate the rainbow scale category, with the corresponding pressure value designated below. The colour categories are further grouped by severity into discrete, significant and serious ratings.



Evaluations of sensation, pain and disability

In addition to the evaluation measures inherent to the SRM, we also conducted a battery of tests more familiar to occupational and physical therapists for comparison. Active range of motion was recorded bilaterally using standard goniometry guidelines from the American Society of Hand Therapists,²⁶ grip strength was measured using a Jamar dynamometer, also following standard guidelines.²⁷ Sensation was evaluated

using the TenTest; this can be used for areas of hypo or hyperesthesia.²⁸ Pain and disability were reported using the PRWHE,²⁴ and Pain Catastrophizing Scale (PCS).²⁹ Additional testing was also conducted for an embedded translation and cultural validation project for the Radboud Evaluation of Sensitivity³⁰ (English version), the Hamilton Inventory for CRPS³¹ and skin temperature asymmetries;³² these will be described elsewhere. While the initial study outline also called for completion of the Immersion in Cold water Evaluation (ICE),³³ most participants with CRPS declined to participate in this facet of the evaluation, and therefore the evaluation was discontinued as the investigators felt it unethical to continue to ask other participants to complete the evaluation knowing they were unlikely to gather sufficient data to use for analyses.

Assessments were completed at baseline and 3 months by an independent evaluator. For evaluation of inter-rater reliability, the clinician-based section of the Hamilton Inventory for CRPS, and the allodynia screening procedure were repeated by the principal investigator on the same visit. If allodynia was identified, then allodyniography and the rainbow pain scale were also repeated. For evaluation of test-retest reliability, these same evaluations plus the patient-reported section of the Hamilton Inventory for CRPS were repeated one week after baseline.

Treatment

Somatosensory rehabilitation for allodynia traditionally contained 3 core elements: therapeutic vibration in the clinic, and distant vibrotactile counter-stimulation (DVCS) coupled with avoidance of painful touch through activity modification at home.³⁴ Sensory re-education of hypoesthetic areas begins after the overlying allodynia has resolved.^{17,35} However, the more recent recommendations suggest vibration should be

reserved for the treatment of hypoesthesia, and is not used when the client is experiencing allodynia.¹⁷ Further, equipment which delivers adjustable and precisely calibrated vibration stimulation is not currently available for purchase in Canada. Therefore, we elected to use the only the core components of 1) DVCS, 2) ongoing education for adaptive strategies to minimize painful touch, and 3) sensory re-education. DVCS was carried out as a home program, applying comfortable stimulation eight times daily for no longer than one minute, using rabbit fur or a plush microfleece applied in a light stroking motion. This sensory stimulation was applied to an area of the skin with normal sensation that is anatomically related to the sensitized cutaneous branch hypothesized to underlie the allodynic territory, but outside of the painful area. For example, to address allodynia around the base of the thumb following basal joint arthroplasty, the stimulation would not be applied to the painful area of the sensory branch of the radial nerve, but to the area of the skin on the back of the upper arm supplied by the posterior brachial cutaneous nerve.²⁵

At each visit, the area of comfortable stimulation would be reviewed, and the need to avoid touching of the painful area reinforced. The occupational therapist would review activities of daily living, and work with each individual participant to identify potential sources of evoked pain (such as clothing rubbing, tool use) and develop strategies to avoid stimulation and/or delegate provocative tasks until the resolution of the allodynia. However, compromise solutions were often necessary. For example, a compression sock on the hand and wrist was employed to give constant low-level stimulation and some protection from intermittent stimuli. This allowed a participant to engage in a graded return-to-work program, and was preferable to full avoidance of

stimuli and a delay in return to work. Similarly, weaning from splint use was not a priority if the splint limited painful movements; instead, stiffness was monitored for risk of contracture development, but splint wear permitted over the allodynic territory, with splint fit and strapping adjusted to provide maximum contact for consistent light pressure. Other therapy modalities were also adapted to conform to the SRM principles. For example, use of heat, cold or transcutaneous electrical stimulation (TENS) directly on the painful area was not encouraged; instead, participants were taught to apply the modality in a more proximal area, similar to DVCS. Revisiting our previous example of allodynia at the base of the thumb post-arthroplasty, the person would be encouraged to avoid using wax, whirlpool or fluidotherapy; and instead would be instructed to apply a hot pack over the dorsum of the forearm, avoiding any contact with the wrist or thumb area.

Statistical analysis

After data screening, demographics and clinical variables were described with means \pm standard deviations (SD) for continuous variables, and frequencies & percentages for categorical variables. The change in MPQ total scores at 3 months were compared using one-way analysis of variance for those who received SRM treatment vs. those who simply had usual care. Sample size for a future trial was estimated using post-hoc power estimates from this calculation. To calculate inter-rater reliability for allodyngography, and the rainbow pain scale, intra-class correlation coefficients for individual measures were used. Construct validity was estimated by testing *a priori* hypotheses for fair correlations (using Pearson's *r*) between the sMPQ and allodyngography, and between the PRWHE and allodyngography, as well as to look

for moderate correlations between the PRWHE and rainbow pain scale, and TenTest and rainbow pain scale. Strength of correlations was quantified using Landis & Koch's recommendations, where $r=0-.20$ is considered slight, $r=.21-.40$ is fair, $r=.41-.60$ is moderate, $r=.61-.80$ is substantial, and $r>.80$ is considered excellent.³⁶ Longitudinal validity was examined by estimating correlations between the change in tMPQ and a self-reported global rating of change, hypothesizing a fair relationship. Responsiveness was estimated using Cohen's d for effect size accounting for the paired comparisons and the standardized response mean (calculated as a ratio of the mean change to the standard deviation of the change scores).³⁷

All analyses were performed with STATA 13, with statistical significance set at $p=0.05$ unless otherwise noted.

RESULTS

The results reported here represent an interim analysis based on a pragmatic cut-off point to support the on-time completion of the PhD work of the first author. Thus, the sample size is $n=29$ (see Table 1 for a summary of the participant demographics and characteristics). It is interesting to note the rate of catastrophization (considered to be a score of above 30 on the PCS)³⁸ among persons with CRPS was higher than for other participants: 43% of persons with CRPS appeared to demonstrate catastrophic thinking, while only 15.4% of the other participants met this threshold.

Effectiveness of the Somatosensory Rehabilitation Method

The primary question for this study was one of effectiveness for this novel method of treatment. Analysis of variance did not support effectiveness at $F_{1,7}=2.56$, $p=0.15$.

Albeit, with only 8/29 cases attending for the 3 month follow-up, this interim analysis was woefully underpowered. Post-hoc power calculations suggest we would need at least 200 participants to be confident in our estimates of effectiveness. Conducting the analysis of variance using PRWHE data did not change the conclusion: this was also not statistically significant at $F_{1,8}=0.04$, $p=0.84$. The impact of variability is magnified in small samples; this is illustrated visually in Figure 3, which uses a box and whisker plot to compare the change in tMPQ and PRWHE scores between the control and treatment groups. It is important to note negative change scores indicate participants reported more pain and disability at the 3 month follow-up; and the mean change score for both tools was a negative value; however there was a very wide range of change reported.

Measurement properties of allodynography and the rainbow pain scale

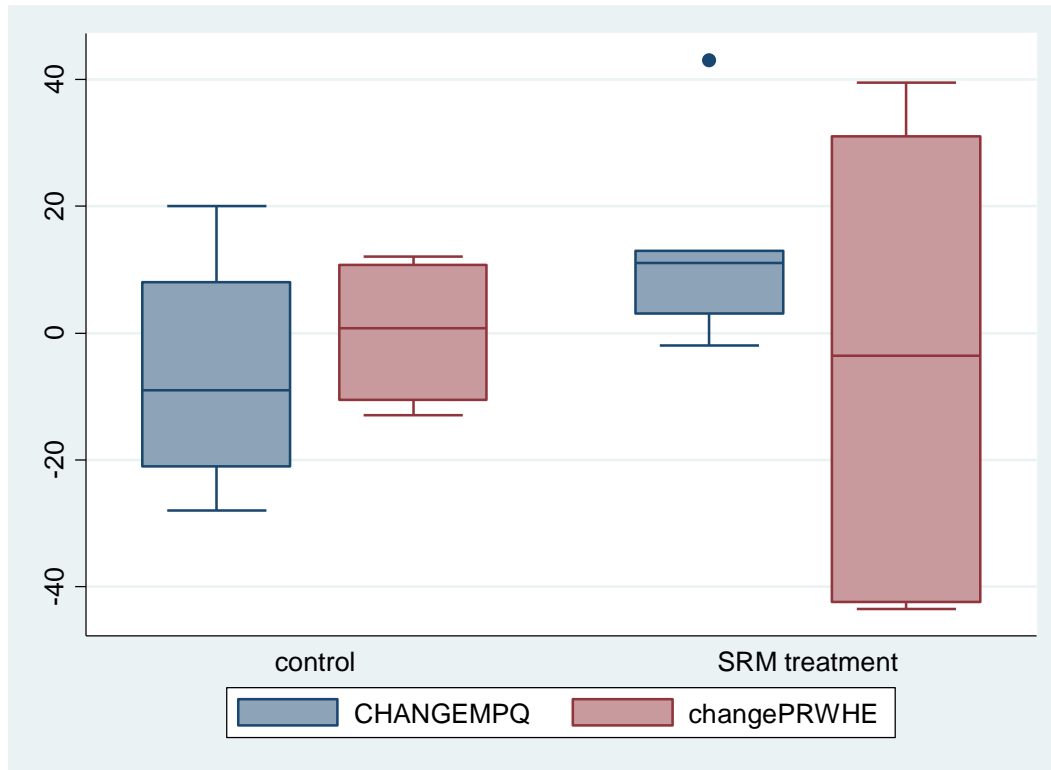
For examining the inter-rater reliability of allodynography, we had 12 cases with repeated measures at baseline representing those participants who had allodynia according to our definition of pain with a static touch of 15 g (or a score of at least 1 on the rainbow pain scale), and therefore were eligible for mapping, and who consented to the procedure. In those persons, we found an excellent intraclass correlation coefficient (ICC) of 0.94 for single measures [95%CI 0.81 – 0.98] and for average measures 0.97 [95%CI 0.90 – 0.99]. Calculating the inter-rater reliability of the rainbow scale, we had 25 cases with complete data, reflecting participants either declining to be tested a second time or altogether with the monofilaments. This yielded an ICC for single measures of 0.79 [95%CI 0.57 – 0.90], and for average measures = 0.88 [95%CI 0.73 – 0.95], $p<0.001$ for both. These could be interpreted as substantial for single measures, and excellent for average measures.

Table 1. Participant demographics and baseline characteristics (N=29)

Characteristic	Mean	SD	Range
Age	45.0	14.4	15 - 76
Duration of injury or pain (in months)	17.9	38.5	1-168
Grip strength (in kgs)	R=26.9 L=27.4	19.1 16.0	0 – 63.3 0 – 54.7
% of normal grip in affected hand	40.7%	29.7	0 – 100%
Total # of words from MPQ (/78)	23.7	16.2	2 - 64
Total MPQ score (tMPQ / 100)	35.3	24.4	2 - 86
PRWHE /100	56.2	25.7	0 – 90.5
PCS /52	19.8	14.6	0 - 44
Allodymography (area in cm ²) (n=7 persons)	160.8cm ²	167.0	16.3 - 483.6cm ²
Characteristic	Frequency	Percentage	
Gender	M=15 F=14	M= 51.7% F= 44.3%	
Diagnosis	CRPS = 16 PNI = 7 Fracture = 6	55.2% 23.1% 21.7%	
Dominance	R= 25 L= 4	R= 86.2% L= 13.8%	
Side of injury	R= 18 L= 11	R= 62.1% L= 37.9%	
Allodynia present	Yes= 13 No= 15 Unable to test = 1	44.8% 51.7% 3.4%	
Catastrophizing present (PCS>30)	Yes = 9 No = 20 CRPS + Yes = 7/16	Yes = 31.0% No = 67.0% (43.8% CRPS; 15.4% other)	
Rainbow pain scale (n=13 as scored by CSTP)	Red = 1 Orange = 5 Yellow = 1 Green = 1 Blue = 1 Indigo =1 Violet = 4	8% 38% 8% 8% 8% 8% 31%	serious] significant] discrete

Key: tMPQ= McGill Pain Questionnaire total score, PRWHE= Patient-Rated Wrist and Hand Evaluation, PCS= Pain catastrophizing scale, CRPS=complex regional pain syndrome, PNI= peripheral nerve injury

Figure 3. Box and whisker plot of change in MPQ and PRWHE scores between baseline and 3 month follow-up



Construct validity hypotheses for allodyngography and the rainbow pain scale were largely not confirmed (see Table 2 for a summary of the results). The sole hypotheses confirmed was the expected fair relationship between the PRWHE and allodyngography; however a stronger than expected relationship was also found between the change in the size of the allodyngography and the patient's global rating of change.

Responsiveness for allodyngography was calculated on the 6 persons with allodynia who returned for 3 month follow-ups at $ES= 0.08$, with a standardized response mean (SRM) of -0.28 . Responsiveness data for the rainbow pain scale was available for 7 persons, and was calculated at $ES= 0.28$, with a $SRM= -0.45$. To

Table 2. Validity hypotheses and results

Construct	Hypothesis	Results	Confirmed
Construct validity	sMPQ and allodynography r 0.21 - 0.40 ³⁶	r=0.05 (n=10)	X
	PRWHE and allodynography r 0.21 - 0.40	r=0.23 (n=11)	✓
	PRWHE and rainbow pain scale r 0.41 - 0.60	r=0.28 (n=11)	X
	TenTest and rainbow pain scale (negative direction) r 0.41 - 0.60	r=-0.26 (n=11)	X
Longitudinal validity	Change in allodynography and GROC r 0.21 - 0.40	r=0.78 (n=5)	✓
	Change in rainbow pain scale and GROC r 0.21 - 0.40	Unable to calculate	--

Key: sMPQ=sensory subscale of the McGill Pain Questionnaire; PRWHE= Patient-rated Wrist and Hand Evaluation; tMPQ=McGill Pain Questionnaire; GROC= global rating of change

consider whether this reflected meaningful change, we conducted paired t-tests of baseline and follow-up scores; both found the changes were not statistically significant ($p=0.59$ for allodynography, and $p=0.50$ for the rainbow pain scale).

DISCUSSION

This pilot study of the somatosensory rehabilitation method is ongoing, and the findings presented here represent an interim analysis. Our preliminary estimates did not support the effectiveness of somatosensory rehabilitation, with $p=0.15$ for the mean difference in total scores on the McGill Pain Questionnaire between the treatment and control groups at 3 months. Consideration of change as measured by the Patient-Rated Wrist and Hand Evaluation also did not support effectiveness at $p=0.84$. Despite the small sample sizes, we were able to find support for the inter-rater reliability of the

assessment tools. Our single measures estimates suggested the reliability for allodynography was excellent at $ICC=0.94$ and was substantial for the rainbow pain scale at $ICC=0.79$. However, Donner's estimates for the minimum number of participants required to achieve 0.80 power for inter-rater reliability based on single ratings by 2 raters²² suggests 12 persons as adequate to demonstrate only slight reliability; and 25 participants would support fair reliability. Validation of allodynography and the rainbow pain scale was limited, with unstable estimates of correlations based on small samples. Responsiveness estimates were similarly poor, reflecting the small amount of available follow-up data.

Beyond illustration of the need for sufficient samples to power meaningful analyses, this interim analysis provides several points of consideration. First, as paired t-tests did not find a statistical difference in the scores between baseline and 3 months, it is difficult to find the estimates of effect size credible. Effect sizes to estimate responsiveness, as with all psychometric properties, should be considered relative to clinically meaningful change for the population under study.³⁹ this study was not able to recruit and retain sufficient numbers of participants to estimate statistically or clinically significant effects. Future studies should not rely only on the embedded outcome measures of allodynography and the rainbow pain scale to determine the effectiveness of somatosensory rehabilitation, but should continue to include validated and responsive measures of pain and disability. Second, estimates of effect size are based on the assumption that the changes are measured over an interval where sufficient time has elapsed to see measureable change in a phenomenon where change is anticipated, often on the basis of implementation of an effective treatment. However, in this study,

we may have failed to meet either of these assumptions. While no estimates for the mean duration of treatment required to change allodynia in CRPS of the upper limb existed at the time this study was designed, based on retrospective clinical data we have recently reported the average treatment duration required for the resolution of allodynia using the SRM is 3 months, and on average requires about a month for each level of the rainbow scale.⁴⁰ This suggests the treatment duration of 8 weeks provided in this study may have been insufficient to change the severity of allodynia seen in this sample. However, the nature of the clinical data upon which that analysis was based precluded examination of the responsiveness of the allodynography and rainbow pain scale tools.

Other differences between the current study and previous reports on the effectiveness of the SRM are also worthy of attention. The retrospective cohorts previously reported in the peer reviewed literature are more heterogeneous in either the forms of neuropathic pain¹⁸ and/or in the anatomical locations of the pain.^{18,19} We chose to focus on complex regional pain syndrome resulting in allodynia of the upper limb: the unique features of this syndrome may reflect a severity bias in our sampling. Patients in both these groups accessed somatosensory rehabilitation under the referral of a physician, while our study did not require physician referral for participation. This may have subtle positive influences in the expected outcomes of treatment that is assumed to be endorsed by the medical profession as compared to participation in a study investigation where the informed consent process clearly indicates the benefits are unknown. Further, the primary outcome measure used in both of these cohorts was the French version of the McGill Pain Questionnaire, the *Questionnaire Douleur de St.*

Antoine. While this has been reported to be a valid measure,²⁰ the agreement between this version and the original MPQ is unknown, as it was not intended to be a parallel translation.⁴¹ Finally, the use of vibration stimulation as part of the clinic visits was described in both of the earlier investigations:^{18,19} however, we chose to not include this element as a) it would be difficult to translate into clinical practice because of equipment issues; and b) recent revisions to the SRM suggest it is not necessary for the treatment of allodynia.¹⁷ Future investigations should consider whether there is a benefit to the use of vibratory stimulation as part of the SRM. It is also critical to note the complete SRM also is intended to address the painful consequences of hypoesthesia, and not simply allodynia. For the purposes of this trial, we chose to limit our investigations to the treatment of allodynia in order to focus on distant vibrotactile counter-stimulation treatment as an alternative to traditional desensitization,⁹ and validation of allodynography and the rainbow pain scale. However, there are other assessment and treatment methods in somatosensory rehabilitation that were simply beyond the scope of this evaluation: the findings of this study should not be considered a complete investigation of SRM.

Limitations and recommendations for future research

While Spicher advocates completing the rainbow scale evaluation on a separate visit from the allodynography¹⁷ to avoid the effects of summation,² this was not feasible given the additional inter-rater reliability demands of the study. Despite this, the inter-rater reliability estimates for the rainbow pain scale reflect substantial correlation.³⁶ To reduce participant burden, we also did not collect test-retest data for either

allodynography or the rainbow pain scale, therefore stability of these assessment results (based on tests by the same rater) between visits is unknown.

The high proportion of persons identified as having an important level of catastrophizing (scoring above 30 on the PCS)³⁸ could be considered a potential sample bias, as catastrophizing after hand injury or surgery has been suggested to be a predictor for poor treatment responses.^{42,43} This may be a confounder for estimates of effectiveness and responsiveness. Future trials in CRPS may wish to stratify their results according to the presence of catastrophizing, and/ or should evaluate the potential for confounding effects.

As previously discussed, the short treatment interval of 8 weeks offered by this pilot study may not have been sufficient to change the effects of longstanding sensitization in this client group. Further, while participants were provided with education on counter-stimulation and educated on the importance of avoiding painful touch activities, we did not measure adherence to these core elements of the SRM. Co-intervention may also have been a source of bias, as participants were allowed to continue to participate in any pre-existing medical and rehabilitation management. Future studies of somatosensory rehabilitation should strive for increased rigor by monitoring adherence and controlling for co-interventions.

CONCLUSION

The somatosensory rehabilitation method for the assessment and treatment of allodynia after CRPS requires more study before it can be endorsed for widespread

implementation into clinical practice. The results presented in this pilot work can inform the rigor and scope of those investigations.

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DISCUSSION AND CONCLUSION

The overarching theme of this thesis was the advancement of assessment and treatment methods for complex regional pain syndrome. To meet this goal, I have presented a series of four papers, each with a unique contribution to this theme. The first paper explored the content validity of the Patient-Reported Hamilton Inventory for CRPS. The expert sample targeted for this task was persons with CRPS, employing the methodology of cognitive debriefing interviews (Ojanen & Gogates, 2006; Willis, 1999). This work identified items of potential conceptual confusion for respondents, and topic areas that participants felt were not adequately addressed in this iteration of the assessment tool. The results informed the subsequent version of the assessment, and should contribute to reliability and validity of this revised version. The second paper reported the translation and cultural validation of another patient-reported assessment tool, the Radboud Evaluation of Sensitivity. This study generated evidence for substantial test-retest reliability and internal consistency of this measure; and also provided preliminary evidence for construct validity and reproducibility. However, estimates for responsiveness were underpowered and not dependable. The third paper presented preliminary evidence for the effectiveness of the somatosensory rehabilitation method, a novel treatment for allodynia related to CRPS of the upper extremity. This retrospective consecutive cohort study was uncontrolled: so while a strong effect size was demonstrated, the influence of time and the efficacy in comparison to other interventions remains unknown. Finally, the fourth paper described the results of pilot work necessary to set up future prospective and controlled trials for somatosensory rehabilitation. The psychometric properties of the embedded measurements of allodynography and the rainbow pain scale were explored, and estimates of sample size requirements for future trials were generated.

This body of work will advance the field of rehabilitation science on several fronts. In the area of clinical measurement, I have reported the refinement of two patient-reported outcomes, intended to be freely available in the public domain. The first of these, the Patient-Reported Hamilton Inventory for CRPS will provide a condition-specific measure of the symptoms and social, emotional, and functional

consequences of this syndrome. While work is currently underway to develop a core measurement set for all clinical trials in CRPS (COMPACT: Grieve et al., 2015) drawing on the Patient-Reported Outcome Measurement Information System (PROMIS) measures, there will still be a need for a more detailed exploration of the complexity of the patient experience beyond this core. Future research on the HI-CRPS should seek to contrast the results from this tool with the COMPACT measures to confirm the unique contributions. The second patient-reported measure reported in this thesis is the Radboud Evaluation of Sensitivity (English version). This tool provides therapists and other health professionals with a patient-reported option for the assessment of either reduced or painful sensitivity. While further psychometric testing is required for both of these measures, this work continues a trajectory of careful development and evaluation to meet the recommended standards for the COSMIN domains of reliability, validity, responsiveness and interpretability (Mokkink, Terwee, Patrick, et al., 2010) for clinical practice as well as research settings. Additionally, this work also included the first explorations of the measurement properties for two novel psychophysical evaluations of allodynia. These tools will provide needed precision to the evaluation of an important feature of neuropathic pain and central sensitization that are often currently dichotomously described as present or absent. All of these evaluation techniques, both individually and collectively, also have the potential to contribute to the development of symptom profiles that may be used in future to predict treatment response, and guide personalized treatment choices for complex regional pain syndrome and other forms of neuropathic pain in both medicine and rehabilitation. Further, expanding the toolkit of psychometrically sound evaluations for pain which can provide a common metric for both medicine and rehabilitation will support communication between disciplines, and ultimately benefit client care.

Finally, two of the papers contained herein represent some of the first English language reports of effectiveness for the somatosensory rehabilitation method for the treatment of the painful consequences of allodynia in CRPS affecting the upper limb. While modest evidence exists for other treatment methods such as graded motor imagery and tactile localization (O'Connell, Wand, McAuley, Marston, & Moseley, 2015) effective rehabilitation treatments specifically targeting allodynia have not been

described. There is a great need to address this feature of complex regional pain syndrome, given the association with poor prognosis (Brunner, Lienhardt, Kissling, Bachmann, & Weber, 2008; Wertli, Bachmann, Weiner, & Brunner, 2013). Further, this fits with the move towards mechanism-based treatments to address the complex symptom presentation of this syndrome (Gierthmuhlen, Binder, & Baron, 2014; Woolf, 2011). The preliminary findings reported here will inform future work to generate high quality and sufficiently powered estimates of effectiveness for this treatment method, and either support or challenge the diffusion of this treatment innovation. If support is generated, there will be an important role for knowledge translation to support fidelity to the assessment and treatment methods (Berwick, 2003), and address the learning needs of professionals seeking to incorporate and sustain their use in clinical practice (MacDermid & Graham, 2009).

Limitations

While limitations of the individual studies have been described within the bodies of the respective papers, it is important to identify some overall limitations of this work. First, none of the assessment tools described herein should be considered ready for widespread and unrestricted use in clinical practice. All have important limitations in the extent of psychometric data available to support the spectrum of measurement properties. Measure development is a complex and iterative process, moving from concepts to items or testing procedures, and then often to scales (Streiner & Norman, 2008). The COSMIN criteria (Mokkink, Terwee, Knol, et al., 2010) have created a standard for which to strive, while providing a useful gauge of progress in measure development. A second key limitation is the confidence we can have in the estimates of effect size for the examinations of the somatosensory rehabilitation method. In the Swiss cohort, the estimates were based on the French version of the McGill Pain Scale, and are not equivalent to the English version. Further, it is not clear if this is indeed the ideal outcome measure to determine change in allodynia and the other sequelae of CRPS. In the pilot study, estimates of effect size were presented using both the MPQ and Patient-rated Wrist and Hand Evaluation; however both of these tools also have limitations. The MPQ is heavily reliant on command of the English language and is

time-consuming to complete. Additionally, given the limb-specific nature of the PRWHE, this would only be useful in trials addressing CRPS of the upper limb, which limits recruitment in a population that is already challenging to both recruit and retain. To have optimal generalizability, measures such as the proposed COMPACT battery (Grieve et al, 2015) should be included along with the embedded measures of allodyngraphy and the rainbow pain scale. However, these tools are intended only to address static mechanical allodynia (Spicher, Mathis, Degrange, Freund, & Rouiller, 2008); it may also be important to include other forms of quantitative sensory testing to address cold and heat allodynia and hyperalgesia.

Two final limitations which merit discussion are the focus of the thesis work on a) the attempted quantification and measurement of pain, a multi-dimensional and contextual experience, and b) the narrow neurobiological lens of rehabilitation presented in the discussions of the somatosensory rehabilitation method. The empirical language of measurement, including terms such as validity and accuracy, suggests there are aspects of truth for any dimension or variable that can be directly measured and understood (Streiner & Norman, 2008). However, even measurement theory acknowledges there are 'latent' constructs, such as the emotional aspects of pain, which cannot be directly measured, and therefore are only estimated in surrogate form (Lovejoy, Turk, & Morasco, 2013). This form of measurement is further constrained by the inherent epistemology, as items are sought which demonstrate statistical relationships to each other (internal *consistency*) to represent a singular reality for a population. This positivist view is in contrast to the ontological philosophy there are multiple contextual aspects of individual experience, and that this *variability* is critical to the understanding of the phenomenon (Avis, 2003). The tension between these two viewpoints is reflected in Chapter 2: the cognitive debriefing interviews collected individual experiences and understandings, but focused on the commonalities rather than seeking out the unique aspects of their lived history.

Secondly, while the mechanisms explored in the introduction acknowledge the potential role of psychological distress in the evolution of CRPS, my professional lens as an occupational therapist also demands an accounting of the contributions of the

socio-cultural environment, both in the development and maintenance of chronic pain. From the lens of the International Classification of Functioning, Disability and Health (ICF: World Health Organization, 2002), healthy function is seen as the result of the dynamic interactions between the elements of the body structures and their associated functions, the activities and life roles of the individual, and their environment. Thus, rehabilitation programs for CRPS should not be focused solely on addressing the body structures and functions, but should also address the contributions of stressors such as i) dealing with an invisible disability, ii) navigating complex systems such as health care and injured worker supports or disability insurance, iii) re-negotiation of household roles and responsibilities, iv) the impact of changing function on participation in social activities and leisure pursuits, and v) the spiritual and cultural meanings and expressions of pain and suffering. Somatosensory rehabilitation should therefore be viewed as only one potential modality within a holistic treatment program delivered by an occupational therapist or other rehabilitation professional.

Future directions

While many areas for future research have been addressed in the context of the individual papers, there are several considerations for future work related to this overall program of research. First, while allodynia has been identified as a poor prognostic indicator (Wertli et al., 2013), very little work has been completed to understand the specific impact of allodynia on function and quality of life. The qualitative analysis of the data from the cognitive debriefing study should add insights into the far-reaching impacts of allodynia on such diverse areas as a) difficulty in finding clothing and shoes appropriate to the climate and societal expectations for professional dress at work when these touch or rub painful areas, b) the challenge of maintaining intimacy in a relationship when it hurts even to be hugged, and c) the physical energy costs of vigilance to guard painful limbs during movement and/or social situations (Packham, unpublished data). There is also a need to quantitatively examine the relationship of allodynia to other established constructs in chronic pain, such as kinesiophobia (Roelofs et al., 2011), pain catastrophizing (Sullivan, 1995), body perception (Lewis, Kersten, McCabe, McPherson, & Blake, 2007), and occupational performance (Brincat, 2004).

This would benefit from a mixed methods sequential explanatory approach (Creswell, 2015), where an in-depth qualitative exploration of these relationships would expand the understanding of allodynia, and could inform a theoretical framework to elucidate both the mechanisms and impacts on health-related quality of life. The expanded understanding of this phenomenon generated by such an approach would assist therapists to appropriately assess the full impact, educate patients and families, and select the most appropriate interventions based on evidence and the unique needs of their individual clients.

The second direction for future research that must be considered is the rigorous examination of the somatosensory rehabilitation method by comparisons to other forms of treatment proposed both for general CRPS pain, and allodynia specifically. We chose to limit our focus to the treatment of allodynia; however sensory profiles suggest allodynia is not seen in all persons with CRPS (Gierthmühlen et al., 2012; Spicher et al., 2016). Indeed, the somatosensory rehabilitation method is proposed to also address the painful sequelae of hypoesthesia, which may be apparent on initial evaluation, or may present after the resolution of allodynia (Spicher, Quintal, & Vittaz, 2015). Future randomized controlled trials for persons with complex regional pain syndrome should compare somatosensory rehabilitation to the treatments with a) the highest levels of current evidence (O'Connell, Wand, McAuley, Marston, & Moseley, 2015), and b) with treatments recommended in current clinical practice recommendations (Perez et al., 2010; Turner-Stokes & Goebel, 2011). These comparisons should include: 1) somatosensory rehabilitation to traditional desensitization (Lewis, Coales, Hall, & McCabe, 2011; Walsh & Muntzer, 2002) for persons with allodynia, 2) somatosensory rehabilitation to tactile localization augmented with mirror visual feedback (Moseley & Wiech, 2009) for persons with allodynia or hypoesthesia, and 3) somatosensory rehabilitation to graded motor imagery (Moseley, 2006) for persons with hypoesthesia. The research reported here would suggest that such trials would need to be multi-centre to support recruitment of the critical mass of patients to fully power such comparisons.

Much work remains to be done to meet the challenge of complex regional pain syndrome. This thesis work contributes small but important advances for the

assessment and treatment options in rehabilitation, and lays out options for future explorations and collaborations to advance the field.

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