Exploration of the clinical course and longitudinal correlations in frozen shoulder : the role of autonomic function, central pain processing, and psychological variables: a longitudinal multicenter prospective observational study

Exploration of the clinical course and longitudinal correlations in frozen shoulder: the role of autonomic function, central pain processing, and psychological variables. A longitudinal multicenter prospective observational study.

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Abstract

Background: Altered central pain processing (CPP) and dysautonomia might play a role in the clinical course of frozen shoulder and psychological factors, like pain catastrophizing and hypervigilance, might influence clinical variables in frozen shoulder.

Objectives: To explore the clinical course of frozen shoulder regarding CPP, dysautonomia, pain catastrophizing, and hypervigilance and to explore whether longitudinal correlation between these outcomes and pain intensity were present.

Design: prospective longitudinal observational study

Method: Participants with frozen shoulder were recruited at hospitals and general practitioner practices and followed for 9 months. They completed six questionnaires (about demographics, shoulder pain and disability, pain intensity, pain catastrophizing, pain hypervigilance, and autonomic symptoms) and underwent tactile sensitivity (allodynia), pressure pain thresholds (hyperalgesia), temporal summation, and conditioned pain modulation during four timeframes (3-month intervals).

Results: Initially, 149 participants with frozen shoulder were recruited and 88 completed all the measurements. An improvement from baseline to at least one follow-up measurement was found for shoulder pain and disability, pain intensity, pain catastrophizing, hypervigilance, and

dysautonomia. A fair longitudinal correlation was found between pain intensity and catastrophizing and hypervigilance (r = 0.301-0.397). Poor longitudinal correlations were found between pain intensity and allodynia and hyperalgesia (r = -0.180-0.193), between pain catastrophizing and dysautonomia (r = 0.209) and between hypervigilance and hyperalgesia (r = -0.159).

Conclusion: Patients with frozen shoulder showed an early improvement that flattened with time in several pain and psychological variables over the course of 9 months. However, autonomic symptoms rather showed a late improvement over 9 months.

Keywords: central pain processing; autonomic function; psychological factors; frozen shoulder; clinical course.

Introduction

Frozen shoulder is a clinical condition characterized by severe shoulder pain and functional restriction of both active and passive shoulder motion (Abrassart et al., 2020). The prevalence of primary frozen shoulder in the general population is 2-5% (Brue et al., 2007). Duration of this condition has traditionally been estimated between 1 to 3 years (Reeves, 1975), however, recent findings indicate that recovery may be extended and is frequently incomplete (Wong et al., 2017). Multiple factors might contribute to the clinical picture of frozen shoulder thus explaining its variable prognosis (Lyne et al., 2022).

In other chronic musculoskeletal disorders (e.g., osteoarthritis and complex regional pain syndrome), factors like dysautonomia and altered central pain processing (CPP) have been shown to play a role in perpetuating symptoms over time (Lluch et al., 2014; Stanton-Hicks, 2019). Dysautonomia refers to all conditions with altered autonomic activity and is used as an umbrella term for autonomic dysfunction and autonomic imbalance (De Wandele, 2014). Regarding the role of dysautonomia in frozen shoulder, scarce information is available in the literature. Sympathetic dysfunction is suggested to be present in patients with frozen shoulder as reflected by an abnormal temperature control (Jeracitano et al., 1992). Pietrzak (2016) also hypothesized about an autonomic nervous system imbalance in patients with frozen shoulder, which may induce a state of chronic low-grade inflammation and thus trigger the inflammation and capsular fibrosis seen in frozen shoulder. Dysautonomia could be a possible risk factor for the development of frozen shoulder and may influence inflammation and symptom severity, contrary, dysautonomia could arise secondary to the development of frozen shoulder as a result of inflammation (Koopman et al., 2017).

Some non-systematic reviews (Struyf & Meeus, 2014; Mertens et al., 2022a) suggest that altered CPP may play a role in patients with frozen shoulder as it does in other shoulder pain

disorders (Noten et al., 2017). In patients with frozen shoulder, recent studies have shown altered CPP in a subgroup of patients in terms of disrupted tactile acuity and laterality judgement (Breckenridge et al., 2020; Mena-Del Horno et al., 2020) and positive response to central nervous system focused interventions (Sawyer et al., 2018; Mena-Del Horno et al., 2022).

A previous cross-sectional study found medium to large differences in terms of self-reported autonomic symptoms, local and distant allodynia, local hyperalgesia, and psychological variables (i.e., pain catastrophizing and hypervigilance) between patients with frozen shoulder in the early stage and healthy controls (Mertens et al., 2022b). No signs of impaired endogenous pain modulation were found in the frozen shoulder group (Mertens et al., 2022b). The authors argued that it is likely that dysautonomia might have been present before the beginning of frozen shoulder and altered pain modulation had developed once symptoms of frozen shoulder persisted over time. However, due to the cross-sectional nature of this study no conclusion on the clinical course of these variables could be extracted.

Understanding the clinical course of frozen shoulder is key for the management of a clinical condition. Knowledge about the clinical course enables clinicians to provide patients with information related to prognosis and expected time of recovery (Wong et al., 2014) and assists in developing suitable treatment strategies (Tennent & Green, 2020). Information currently available about the clinical course of frozen shoulder indicates, contrarily to what has traditionally been stated, it may not be a self-limiting condition (Wong et al., 2017). Importantly, previous research on the clinical course of frozen shoulder has focused on the behavior of clinical variables such as shoulder pain and disability or range of motion (ROM). The behavior over time of other factors contributing to the pain experienced by this population such as dysautonomia, altered CPP, or psychological factors has been barely explored. De Baets

et al. (2020) explored correlations between perceived stiffness, ROM, and function on the one hand and structural factors (e.g., coracohumeral ligament thickness), pain intensity, and pain-related cognitions (pain catastrophizing and kinesiophobia) on the other hand, at time of diagnosis and at four months follow-up, in patients with frozen shoulder. Interestingly, objectively measured ROM was related to structural factors, while patient-reported outcomes were related to pain intensity and/or pain-related cognitions.

Considering the relationship between autonomic function and pain processing pathways (Chapman et al., 2008), dysautonomia might arise together with altered CPP and evolve in parallel in patients with frozen shoulder. In addition, sympathetic activity might further be enhanced by maladaptive psychosocial factors that are correlated with a delayed recovery (e.g., catastrophizing) (Crofford, 2015) and thus increase autonomic symptoms over time. An exaggerated parasympathetic decline (i.e., enhanced sympathetic activity) was related to negative physical and psychosocial outcomes in a non-threatening situation (Crofford, 2015). When the activity of the sympathetic nervous system is increased, this in turn facilitates the decrease in sensory and nociceptive thresholds (Drummond, 2010). Correlations between static and dynamic psychophysical measures of CPP and psychological factors in patients with chronic musculoskeletal pain including patients with shoulder pain have also been found in cross-sectional studies (Balasch-Bernat et al., 2021; Hirata et al., 2021). If this is the case for frozen shoulder in a longitudinal design is unknown. We are not aware of previous studies that have examined changes in autonomic function, CPP, and psychological factors during the clinical course of frozen shoulder and the relationship between changes in these variables. Moreover, how changes in these variables during the clinical course are correlated with clinical outcomes remains to be determined. If the clinical course of autonomic function, CPP, and psychological variables changes unfavorably (what might be expected based on the long clinical

course of frozen shoulder (Wong et al., 2017)) and this is correlated with changes in clinical variables like pain intensity, this should be considered during treatment in order to optimize outcomes.

The first aim of the current study was to explore the clinical course of frozen shoulder regarding self-reported autonomic symptoms, CPP, and psychological variables (i.e., catastrophizing and hypervigilance). The second aim was to explore potential longitudinal correlations (i.e., including multiple time-points) between these outcomes and clinical variables (i.e., pain intensity).

Methods

Study design

A multicenter prospective longitudinal study was performed in the research laboratories of the authors' affiliated institutions and was reported following the strengthening the reporting of observational studies in epidemiology (STROBE)-checklist (von Elm et al., 2007). This study has been approved by the Human/Clinical Research Ethics Committees of the authors' affiliated institutions. Data were collected between November 2014 and October 2020. Since this was an observational study, the protocol was not registered. This study protocol adhered to the Declaration of Helsinki.

Participants

Participants with frozen shoulder were recruited at the orthopedic departments of different hospitals (three) and through general practitioner practices (three) in cities of the authors' affiliations. Eligibility criteria of participants are presented in Table 1, imaging was not routinely performed. All patients provided written informed consent.

Table 1: Eligibility criteria

Inclusion	Exclusion
• Participants with a maximum of 4 months symptoms related to frozen shoulder were included. • PROM restriction of at least 25% in at least two movement planes and 50% in glenohumeral external rotation compared to the unaffected shoulder (in total 3 movement planes) (Kelley et al., 2013). • Pain and movement restriction present for at least 1 month that reached a plateau or were deteriorating (Kelley et al., 2013). • Able to understand Spanish or Dutch language.	• Symptom improvement during the last month (Kelley et al., 2013). • Pregnant or breastfeeding. • Any shoulder surgery prior to development of frozen shoulder. • Frozen shoulder secondary to humerus fractures, dislocation, or cerebrovascular accident.
AROM: active range of motion; PROM: passive range of motion; ROM: range of motion	

Procedure

First, participants completed six questionnaires at baseline assessment. A description of all questionnaires is presented in Table 2. Secondly, quantitative sensory testing (QST) was performed as a proxy for CPP and included tactile sensitivity, pressure pain thresholds (PPTs), temporal summation (TS), and conditioned pain modulation (CPM). Table 2 provides an overview of all measurements.

All questionnaires and QST measurements were repeated at 3, 6, and 9 months after baseline assessment. Since this was an observational study, no intervention was applied between assessments, however, participants were allowed to receive treatment as needed and the application of treatment was registered at each follow-up measurement. Participants were examined by six physical therapists, all previously trained by two physical therapists with more than 10 years' experience in the examination of shoulder disorders and QST measurements.

Table 2. Overview of questionnaires and quantitative sensory testing measurements.

Measurement outcome		Description
General sociodemographic questionnaire		This questionnaire was used to acquire information about demographics, disease status and course, co-morbidities, work, and sports.
Shoulder pain and disability		
	Visual analogue scale	Patients were asked to rate their pain on a 10 cm line by drawing a vertical mark on that line. The left end of the line represents 'No pain' (0 cm) and the right end 'Most severe pain' (10 cm). The scoring is the distance (in millimeter) from the left end of the line to the vertical mark of the patient (Jensen et al., 1986). Patients had to rate the pain of the shoulder during the last week. The VAS has been found valid and reliable (Boonstra et al., 2008) and has a MCID of 13.7 mm (Hawker et al., 2011).
	Shoulder pain and disability index	This is a self-reported index that consists of 13 items in two domains (pain (5 items) and disability (8 items)) to measure pain and disability associated with shoulder

		disorders (Roach et al., 1991). These 13 items are scored on a 0 to 10 scale, where 0 represents no pain or disability and 10 represents worst pain imaginable/so difficult required help. Each domain score is equally weighted and added to a total percentage ranging from 0 (no pain and disability) to 100 (worst pain and disability). The SPADI has been found valid and reliable in evaluating pain and disability in shoulder disorders (Membrilla-Mesa et al., 2015; Thoomes-de Graaf et al., 2015). The MCID is 8 points (Roy et al., 2009).
Dysautonomia		
	Composite autonomic symptom score	This is a self-assessment that evaluates the autonomic nervous system symptoms and function (Sletten et al., 2012). It consists of 31 questions divided over six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, pupillomotor. The total score ranges from 0 (normal function) to 100 (large dysfunction) (Sletten et al., 2012). This questionnaire has been found reliable and valid (Treister et al., 2015). No MCID is available for this questionnaire.
Quantitative sensory testing		During QST measurement, patients were seated without arm rests with the feet flat on the floor, knees and hips flexed 90° and arms relaxed next to the body. Measurements were performed at the following locations: a) center of the anterior deltoid muscle belly (2 cm below the acromion) at both the affected and unaffected side and b) quadriceps muscle belly (middle point between the anterior superior iliac spine and the superior edge of the patella) at the affected side.
	Tactile sensitivity	Tactile allodynia was assessed by quantifying tactile sensitivity with a Von Frey filament (5.88, North Coast Medical Inc.) at the affected side and quadriceps muscle. Three measurements were performed at each site and patients were asked to rate the pain intensity on a NRS, with 0 representing "No pain" and 10 "Worst imaginable pain". The mean of the three measurements was used for the analysis. The MCID for the NRS is 1.1-2 points (Salaffi et al., 2004; Hawker et al., 2011).
	Pressure pain threshold	PPTs were used to assess hyperalgesia. All PPT measurements were taken at the anterior deltoid (both sides) and quadriceps muscle bellies. The unaffected deltoid and quadriceps muscles were chosen to explore widespread hyperalgesia as an indicator of altered CPP (den Boer et al., 2019). A digital algometer with a rubber tip of 1 cm^2 (Wagner Force Dial FDX 50, Wagner Instruments, Greenwich, USA) was used. The order of PPT measurements was determined based on an Excel-generated random sequence. The assessor applied a gradually increasing pressure at a speed of 1 kg/second until the participant experienced the stimulus as annoying and uncomfortable, which was indicated verbally. Two measurements were performed with a 30 second rest interval between them and the average Was used for analysis (Vanderweeen et al., 1996; Farasyn & Meeusen, 2003; Walton et al., 2011; Lewis et al., 2012; Walton et al., 2014). The test-retest reliability of this method at the shoulder has been found to be excellent (Cathcart et al., 2009). The MDC for the PPT is 1.16kg/cm^2 (converted) (Walton et al., 2011).
	Temporal summation	The efficacy of ascending pain modulation pathways was assessed with TS, based on the procedure described by Cathcart et al. (Cathcart et al., 2009). TS was induced by applying 10 repetitions with a 1-second interstimulus interval with the previously calculated PPT at the quadriceps muscle using a digital algometer. Participants were asked to rate the pain intensity on a NRS (0-10) on the first, fifth and tenth repetition. TS was calculated as the difference between the tenth and first repetition (Cathcart et al., 2009). The test-retest reliability of this method at the shoulder has been found to be high (Cathcart et al., 2009). No MCID value is available for TS, but as the NRS is used to determine the TS-effect, the change in TS with at least 1.1-2.0 points is considered clinically meaningful, as suggested (Salaffi et al., 2004; Hawker et al., 2011).
	Conditioned pain modulation	Efficacy of descending pain modulation pathways was evaluated by assessing CPM, in which the effect of a conditioning stimulus on a test stimulus was assessed. The test stimulus consisted of a pressure as described above in the PPTs section. The conditioning stimulus consisted of ischemic occlusion applied to the unaffected upper arm (i.e., tourniquet test). An inflatable air cuff (Boso Profitest) was positioned just above the cubital fossa of the unaffected side and inflated until the patients perceived the stimulus as annoying and uncomfortable. Thirty seconds after the application of the inflatable cuff, patients were asked to rate the intensity of perceived pain on an NRS. Next, the pressure was adapted (i.e., increased or decreased) until patients experienced a pain intensity of 3 out of 10 on the NRS. PPT measurement was then repeated twice at the affected shoulder with 30 seconds rest interval between them, after whom the cuff was immediately deflated. The mean of the two PPTs taken during cuff inflation was used for analysis (Cathcart et al., 2009). The test-retest reliability of this method at the shoulder has been found to be excellent (Cathcart et al., 2009).

		The relative CPM effect was calculated following the formula: $\frac{(PPT\ at\ baseline - PPT\ during\ CPM)}{PPT\ at\ baseline}$. Positive values were interpreted as a pro-nociceptive CPM effect and negative values as an anti-nociceptive CPM effect. No MCID value is available for CPM, but a change of two standard deviations can be considered a meaningful change (Kennedy et al., 2020).
Psychological variables		
	Pain catastrophizing scale	This questionnaire assesses worrying about pain and catastrophizing. Thirteen items are scored on a 5-item Likert scale ranging from "not" to "always". The total score ranges from 0 to 52, where higher scores are associated with higher levels of catastrophizing. The PCS has been found valid and reliable (Sullivan et al., 1995; Severeijns et al., 2002; Garcia Campayo et al., 2008). The MCID is 10 points (Meyer et al., 2008; Monticone et al., 2012)
	Pain vigilance and awareness questionnaire	This 16-item questionnaire evaluates attention to pain, awareness to pain, vigilance to pain and pain observation. These items are scored on a 6-item Likert scale ranging from "never" to "continuously", resulting in a total score from 0 to 80 (McCracken, 1997). The higher the score, the more the participant is focused on pain. The PVAQ has good reliability and validity (McCracken, 1997; Roelofs et al., 2002; Esteve et al., 2013). The MCID is 8.8 points (Monticone et al., 2016).
SPADI: shoulder pain and disability index; MCID: minimal clinical important difference; VAS: visual analogue scale; PCS: pain catastrophizing scale; PVAQ: pain vigilance and awareness questionnaire; QST: quantitative sensory testing; NRS: numeric rating scale; PPT: pressure pain threshold; CPP central pain processing; MDC: minimal detectable change; TS: temporal summation; CPM: conditioned pain modulation.		

Statistical analysis

Based on the shoulder pain and disability index (SPADI) with a 95% confidence level and 9% error, a sample of at least 118 patients was required.

Mean, standard deviation (SD) and 95% confidence intervals (95%-CI) were calculated for continuous variables and number and percentage for nominal variables.

Negative binomial regression (for all questionnaires, tactile sensitivity and PPT (measurements do not assume negative values)) and linear mixed models (for TS and CPM) were fitted using restricted maximum likelihood to determine the difference over time for pain intensity, shoulder pain and disability, QST measurements, and psychological variables. Individual identifier was entered as random effect to account for the dependence between measurements from the same individual. Treatment received by patients (as a categorical variable) during the 9-month follow-up period was added as a covariate. Pain intensity (VAS), shoulder pain and disability (SPADI), self-reported autonomic symptoms (COMPASS-31), pain catastrophizing (PCS), pain hypervigilance (PVAQ), tactile sensitivity, PPT, TS, and CPM at 9-month follow-up were entered as dependent variables. Tukey post hoc analysis was performed when time-effect was significant ($\alpha < .05$).

Longitudinal correlations were analyzed with multiple regression within subjects, thus removing between-subjects differences and assessing the correlation between pain intensity, self-reported autonomic symptoms, psychological variables, and CPP measurements within participants (Bland & Altman, 1994). Correlation values were interpreted as follows (Chan, 2003): very strong ($r>0.8$), moderately strong ($0.6<r<0.8$), fair ($0.3<r<0.6$) and weak ($r<0.3$). Since we carried out a multitude of longitudinal correlation tests, a multiple testing correction on the p-values is necessary. Therefore, we applied the Benjamini-Hochberg correction on the p-values, which allows for non-independence between the correlation tests. Consequently, significance was set at $\alpha <.015$.

Statistical analysis was performed in R (version 4.1.2, Vienna Austria). Mixed models were fitted using add-on packages lme4 (Bates et al., 2015), pbkrtest (Halekoh & Højsgaard, 2014) and emmeans (Searle et al., 1980). Longitudinal correlation was determined using add-on package rmcorr (Bakdash & Marusich, 2017).

RESULTS

Participant characteristics

Figure 1 shows the flow diagram of this study. A total of 149 participants were initially included and 88 completed all follow-up measurements. Participant characteristics and differences between baseline and 9-month follow-up measurements are presented in Table 3. Baseline differences between the full sample and completers is presented in supplementary Table S1. There were only differences for pain intensity and PPT at the quadriceps at baseline between the full sample and completers.

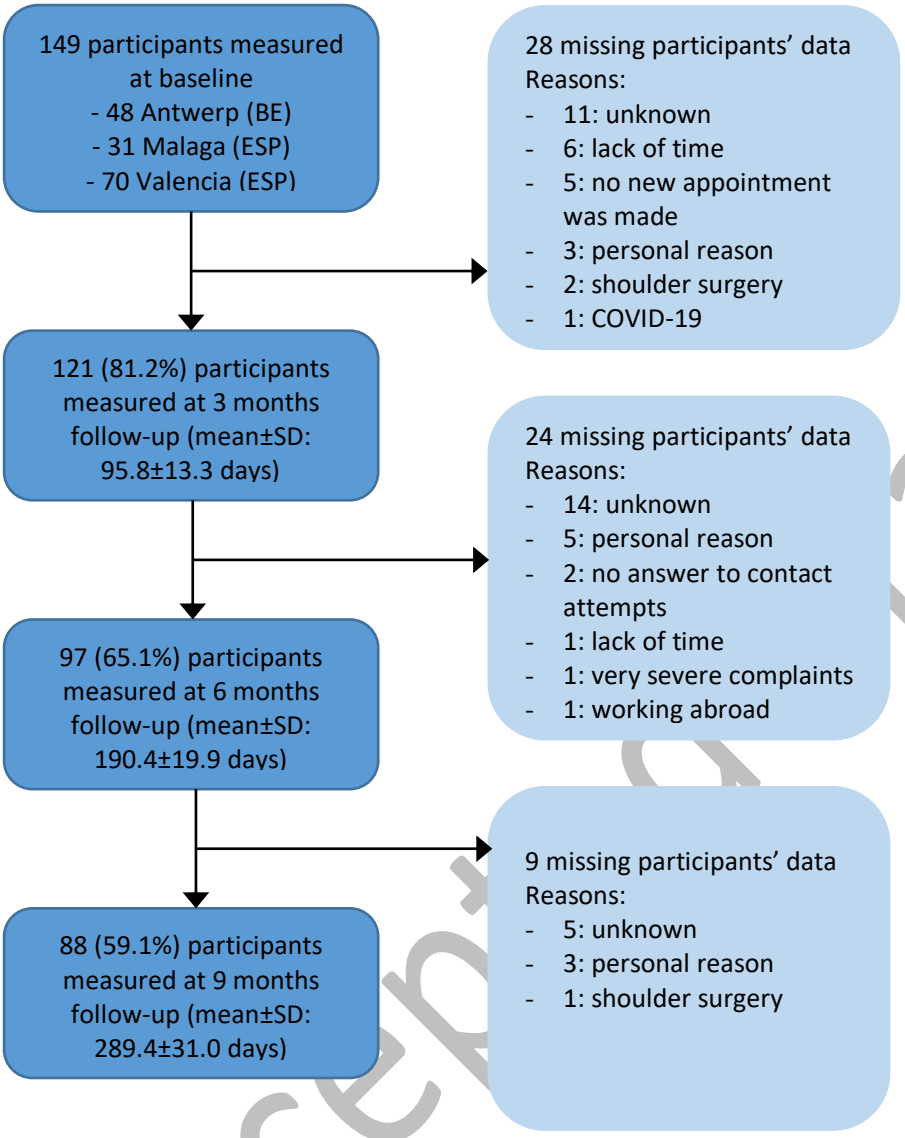

Figure 1. Participant flow during follow-up measurements. BE: Belgium; ESP: Spain.

Table 3. Participant characteristics at all follow-up measurements. Mean±standard deviation [95% confidence interval] or frequencies (percentage) are presented.

	Baseline (n=149)	3 months follow-up (n=121)	6 months follow-up (n=97)	9 months follow-up (n=88)	Mean difference [95%-CI] baseline and final follow-up
Age (y)	52.68±9.35 [51.21;54.14]	52.84±8.12 [51.43;54.25]	53.07±7.86 [51.53;54.62]	52.97±7.89 [51.31;54.62]	-0.29 [-2.58;2.00]
Female sex	98 (65.77%)	76 (63.33%)	64 (64.65%)	57 (64.77%)	NA
Height (cm)	168.13±8.68 [166.77;169.49]	168.71±8.17 [167.28;170.14]	168.15±8.45 [166.49;169.81]	168.52±8.54 [166.72;170.32]	-0.39 [-2.70;1.93]
Weight (kg)	70.60±14.44 [68.27;72.93]	70.62±13.99 [68.10;73.14]	68.68±13.26 [66.05;71.31]	69.11±13.43 [66.28;71.94]	1.49 [-2.19;5.17]
BMI (kg/cm^2)	24.73±3.97 [24.11;25.35]	24.53±3.96 [23.83;25.22]	24.22±3.85 [23.47;24.98]	24.21±3.53 [23.47;24.95]	0.52 [-0.48;1.52]
Hand dominance (right)	121 (82.88%)	97 (82.91%)	80 (83.33%)	72 (82.76%)	NA
Affected side (right)	70 (47.95%)	51 (43.59%)	42 (43.3%)	37 (43.02%)	NA
Dominant side involved (yes)	75 (52.08%)	55 (47.83%)	46 (48.42%)	41 (47.67%)	NA
Cause (idiopathic frozen shoulder)	95 (63.76%)	79 (65.83%)	68 (68.69%)	60 (68.18%)	NA
Diabetes Mellitus (yes)	20 (13.51%)	15 (12.61%)	11 (11.22%)	11 (12.64%)	NA
Thyroid disorder (yes)	13 (8.84%)	12 (10.08%)	11 (11.22%)	11 (12.64%)	NA
Work					
None	70 (47.62%)	54 (45.76%)	41 (42.27%)	34 (39.53%)	NA
Part time	28 (19.05%)	21 (17.80%)	15 (15.46%)	14 (16.28%)	NA
Full time	49 (33.33%)	43 (36.44%)	41 (42.27%)	38 (44.19%)	NA
Sport (yes)	61 (42.07%)	48 (41.38%)	42 (43.75%)	36 (42.35%)	NA
Pain intensity (VAS, 0-100)	48.68±27.77 [44.20;53.16]	31.89±27.96 [27.37;36.48]	20.71±24.28 [16.07;25.35]	13.72±22.14 [9.17;18.28]	34.96 [28.39;41.53]
Shoulder pain and disability (SPADI, 0-100)	60.75±21.16 [57.46;64.05]	40.60±26.37 [36.21;44.99]	27.53±26.06 [22.49;32.56]	22.00±25.68	38.75 [32.14;45.36]
Autonomic symptoms (COMPASS-31, 0-100)	17.40±12.46 [15.45;19.36]	15.85±13.07 [13.70;18.01]	12.55±12.74 [10.09;15.02]	12.73±11.73 [10.31;15.14]	4.68 [1.40;7.97]
Tactile sensitivity shoulder (0-10)	1.32±1.64 [1.05;1.59]	0.94±1.14 [0.74;1.15]	1.05±1.13 [0.84;1.27]	1.01±1.18 [0.77;1.25]	0.31 [-0.06;0.68]
Tactile sensitivity quadriceps (0-10)	1.09±1.34 [0.87;1.30]	0.87±1.00 [0.69;1.04]	0.96±0.97 [0.78;1.15]	0.87±0.82 [0.70;1.03]	0.22 [-0.06;0.50]
PPT affected shoulder (kg/cm^2)	3.97±2.72 [3.53;4.41]	4.38±3.12 [3.82;4.93]	4.17±2.92 [3.61;4.74]	4.40±3.48 [3.69;5.11]	-0.43 [-1.32;0.45]
PPT unaffected shoulder (kg/cm^2)	4.53±2.65 [4.10;4.95]	4.74±3.46 [4.13;5.36]	4.39±2.88 [3.84;4.94]	4.52±3.21 [3.87;5.17]	0.01 [-0.82;0.83]
PPT quadriceps (kg/cm^2)	7.09±5.81 [6.15;8.03]	7.63±8.75 [6.08;9.18]	6.52±7.01 [5.16;7.87]	6.47±8.43 [4.76;8.18]	0.62 [-1.46;2.70]
Temporal summation (difference in NRS, 0-10)	1.50±1.94 [1.19;1.82]	1.70±1.85 [1.37;2.02]	1.89±1.85 [1.53;2.25]	1.56±1.40 [1.28;1.85]	-0.06 [-0.49;0.38]
CPM	-0.15±0.31 [-0.20;-0.10]	-0.12±0.26 [-0.17;-0.08]	-0.10±0.28 [-0.15;-0.04]	-0.17±0.42 [-0.26;-0.09]	0.02 [-0.09;0.13]
Pain catastrophizing (PCS, 0-52)	17.21±11.29 [15.44;18.98]	13.02±11.49 [11.09;14.94]	9.76±9.87 [7.87;11.64]	10.43±10.22 [8.31;12.54]	6.78 [3.88;9.67]
Pain hypervigilance (PVAQ, 0-80)	28.33±12.17 [26.45;30.21]	26.08±12.83 [23.95;28.20]	24.04±13.90 [21.40;26.67]	22.89±14.35 [19.94;25.84]	5.44 [1.71;9.17]
Treatment received					
None	7 (6.36%)				NA
Invasive treatment (including CSI)	11 (10.00%)				NA
Physical therapy	46 (41.82%)				NA

	pharmacotherapy	3 (2.73%)	NA
	Physical therapy & pharmacotherapy	3 (2.73%)	NA
	Invasive and physical therapy	24 (21.82%)	NA
	Invasive and physical therapy & pharmacotherapy	6 (5.45%)	NA
	Alternative treatment (e.g., osteopathy)	2 (1.82%)	NA
	Invasive and physical therapy and alternative treatment	1 (0.91%)	NA
	Physical therapy and alternative treatment	6 (5.45%)	NA
	Invasive and physical therapy and acute pain service	1 (0.91%)	NA
BMI: body mass index; SPADI: shoulder pain and disability index; VAS: visual analogue scale; COMPASS-31: composite autonomic symptom score 31; PPT: pressure pain threshold; CPM: conditioned pain modulation; PCS: pain catastrophizing scale; PVAQ: Pain vigilance and awareness questionnaire.			

Follow-up

Table 4 and Figure 2 show the results of the time analyses for all variables. Statistical analyses showed a significant improvement from baseline to all other follow-up measurements for *shoulder pain and disability, pain intensity, and pain catastrophizing* ($p<0.05$), whereas an improvement was only found from baseline to 6 and 9 months for *hypervigilance and autonomic symptoms* ($p<0.05$). Furthermore, there was a significant improvement from 3 months follow-up to 6- and 9-months follow-up for *shoulder pain and disability and pain intensity* ($p<0.05$) and from 3 months follow-up to 9 months follow-up for *hypervigilance and PPT at the quadriceps* ($p<0.05$). No time-related changes were observed for *tactile sensitivity, PPT (both shoulders), TS,* and *CPM* ($p>0.05$).

Table 4. Analysis for disability and pain, psychological variables, autonomic function, allodynia, hyperalgesia, and pain modulation. Mean and 95% confidence intervals are presented.
All linear mixed models show compliance with assumptions for linear mixed models.

	Fixed effects			
	Baseline	**3 months**	**6 months**	**9 months**
Disability and pain				
Pain intensity (VAS)				
Estimate*	46.16 [27.08;78.69]	27.32 [15.79;47.27]	14.35 [8.27;24.91]	8.88 [5.01;15.74]
Tukey post hoc	Baseline > all other times 3 months> 6 & 9 months			
Disability (SPADI)				
Estimate*	74.00 [50.38;108.69]	38.27 [26.15;55.99]	23.38 [16.93;34.30]	17.81 [12.08;26.24]
Tukey post hoc	Baseline > all other 3 months > 6 & 9 months			
Dysautonomia (COMPASS-31)				
Estimate*	15.38 [9.06;26.11]	13.82 [8.14;23.46]	10.90 [6.41;18.55]	11.61 [6.82;19.76]
Tukey post hoc	Baseline>6 & 9 months			
Allodynia				
Tactile sensitivity shoulder				
Estimate*	0.76 [0.40;1.44]	0.58 [0.30;1.12]	0.61 [0.31;1.18]	0.54 [0.28;1.05]
Tukey post hoc	-			
Tactile sensitivity quadriceps				
Estimate*	1.00. [0.66;1.50]	0.84 [0.54;1.28]	0.86 [0.56;1.32]	0.67 [0.43;1.06]
Tukey post hoc	-			
Hyperalgesia				
PPT affected shoulder				
Estimate*	3.10 [2.32;4.14]	3.15 [2.35;4.21]	3.27 [2.44;4.38]	3.76 [2.82;5.02]
Tukey post hoc	-			
PPT unaffected shoulder				
Estimate*	3.64 [2.84;4.67]	3.36 [2.60;4.34]	3.53 [2.74;4.56]	3.94 [3.06;5.07]

Tukey post hoc	-			
PPT quadriceps				
Estimate*	4.73 [3.62;6.18]	4.54 [3.46;5.95]	4.72 [3.60;6.19]	5.51 [4.21;7.20]
Tukey post hoc	3 months < 9 months			
Endogenous pain modulation				
Temporal summation				
Estimate	2.09 [1.43;2.75]	2.11 [1.45;2.78]	2.28 [1.61;2.95]	1.89 [1.22;2.56]
Tukey post hoc	-			
Conditioned pain modulation				
Estimate	-0.15 [-0.26;-0.03]	-0.12 [-0.24;0.00]	-0.09 [-0.21;0.02]	-0.16 [-0.28;-0.04]
Tukey post hoc	-			
Psychological variables				
Catastrophizing (PCS)				
Estimate*	14.21 [9.42;21.44]	9.24 [6.11;13.98]	7.60 [5.01;11.53]	7.34 [4.85;11.11]
Tukey post hoc	Baseline > all other times			
Hypervigilance (PVAQ)				
Estimate*	26.82 [20.12;35.76]	23.56 [17.63;31.47]	21.86 [16.36;29.20]	19.69 [14.74;26.31]
Tukey post hoc	Baseline > 6 & 9 months 3 months > 9 months			

*: geometric values
VAS: visual analogue scale; SPADI: shoulder pain and disability index; PCS: pain catastrophizing scale; PVAQ: pain vigilance and awareness questionnaire; PPT: pressure pain threshold; CPM: conditioned pain modulation.

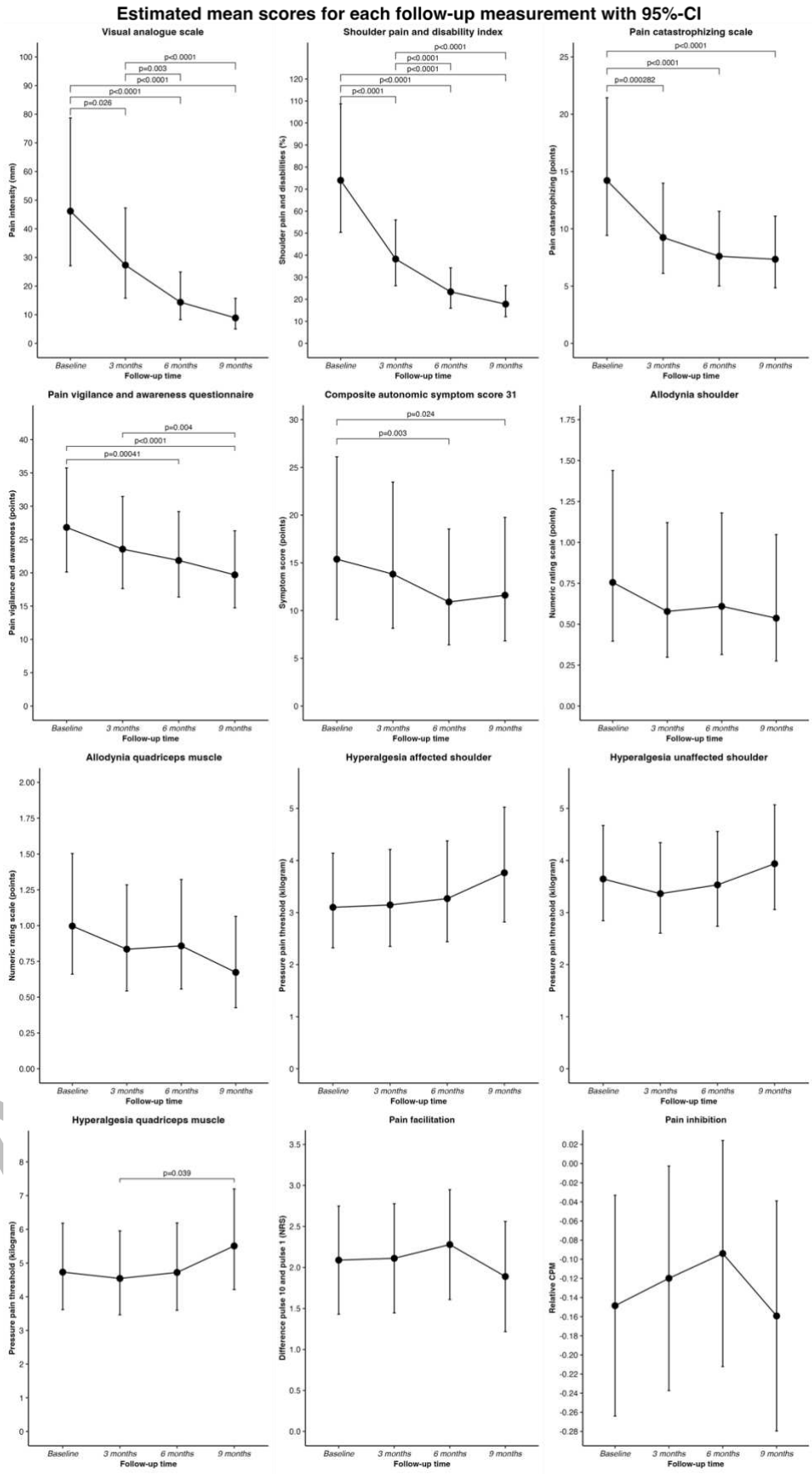

Figure 2. Clinical course of all variables analysed, based on the corresponding models from Table 4.

Longitudinal correlation analysis

The longitudinal correlation coefficients and their corresponding p-values are shown in Table 5. A fair positive correlation over 9 months was found between *pain intensity* and pain catastrophizing and hypervigilance, and between *catastrophizing* and hypervigilance. *Pain intensity* demonstrated a weak positive correlation with tactile sensitivity (both locations), while showing a negative correlation with PPT (affected shoulder). Furthermore, *catastrophizing* demonstrated a weak negative correlation with PPT (affected shoulder) and a positive correlation with self-reported autonomic symptoms. Finally, a weak negative correlation was found between *pain hypervigilance* and PPT at the affected shoulder. No longitudinal correlation was found between self-reported *autonomic symptoms* and any of the other variables.

Table 5. Results of the longitudinal correlation analysis between the different variables, significance level adjusted for multiple correlations with the Benjamini-Hochberg method.

	Pain intensity (VAS)	**Pain catastrophizing (PCS)**	**Hypervigilance (PVAQ)**	**Autonomic symptoms (COMPASS-31)**
Catastrophizing	**r = 0.397** **p < 0.001**			
Hypervigilance	**r = 0.301** **p < 0.001**	**r = 0.354** **p < 0.001**		
Autonomic symptoms	r = 0.019 p = 0.758	**r = 0.209** **p < 0.001**	r = 0.114 p = 0.060	
Tactile sensitivity shoulder	**r = 0.193** **p = 0.002**	r = 0.115 p = 0.065	r = 0.064 p = 0.307	r = -0.041 p = 0.513
Tactile sensitivity quadriceps	**r = 0.171** **p = 0.006**	r = 0.116 p = 0.063	r = 0.077 p = 0.222	r = -0.044 p = 0.484
PPT affected shoulder	**r = -0.180** **p = 0.004**	**r = -0.162** **p = 0.009**	**r = -0.159** **p = 0.011**	r = -0.087 p = 0.163
PPT unaffected shoulder	r = 0.024 p = 0.704	r = -0.072 p = 0.250	r = -0.094 p = 0.134	r = -0.027 p = 0.672
PPT quadriceps	r = -0.117 p = 0.061	r = -0.099 p = 0.111	r = -0.096 p = 0.127	r = -0.039 p = 0.533
Temporal summation	r = 0.012	r = 0.018	r = -0.071	r = 0.068

	p = 0.849	p = 0.772	p = 0.257	p = 0.278
CPM	r = 0.031 p = 0.623	r = 0.108 p = 0.086	r = -0.024 p = 0.706	r = 0.053 p = 0.407

VAS: visual analogue scale; PCS: pain catastrophizing scale; PVAQ: pain vigilance and awareness questionnaire; COMPASS-31: composite autonomic symptoms score; PPT: pressure pain threshold; CPM: conditioned pain modulation.

DISCUSSION

The main findings of this study showed decreased pain intensity, shoulder pain and disability, autonomic symptoms, pain catastrophizing, pain hypervigilance, and increased PPT at the quadriceps throughout a 9-month duration. During this period, no changes were found for tactile sensitivity, PPT (both shoulders), pain facilitation (TS), and pain inhibition (CPM). Furthermore, the findings demonstrated longitudinal correlations with various strengths between pain intensity, self-reported autonomic symptoms, catastrophizing, hypervigilance, tactile sensitivity, and PPT (affected shoulder).

Clinical course of frozen shoulder

To our knowledge, this is the first study examining the clinical course of frozen shoulder in terms of progression over time of self-reported autonomic symptoms, CPP, catastrophizing, and hypervigilance. Previous reports on the clinical course of frozen shoulder were more focused on the course of pain and movement related variables (Vastamaki et al., 2012; Wong et al., 2017). It is difficult to determine the clinical course of frozen shoulder, because of the extensive disease duration. During the study, the treatment participants received was registered and added as a covariate to the mixed model analysis to adjust for this potential influencing factor. We were not interested in the effect of different treatments and therefore, no additional analyses for the effects were conducted.

Pain intensity, shoulder pain and disability, and psychological variables

We found an early improvement in several variables, which is in line with previous research (Wong et al., 2017). However, only the improvement in pain intensity and shoulder pain and disability was clinically relevant since these improvements exceeded the MDC or MCID. Indeed, Wong et al. (2017) concluded with moderate-quality evidence that an early improvement in ROM and disability occurs in participants with frozen shoulder that slows down over time. Similarly, the improvement we observed in pain intensity, shoulder pain and disability, catastrophizing, and hypervigilance slowed down from the 6-month follow-up measurement since there were no significant differences in these variables between measurements taken at 6- and 9-months follow-up.

The time-related improvement in pain intensity, shoulder pain and disability, and autonomic symptoms in the current study might be related to patients moving across the different stages of frozen shoulder from inflammation to fibrosis (Kraal et al., 2020). The initial phases of frozen shoulder have shown to be associated with an overexpression of inflammatory mediators (e.g., cytokines) (Kraal et al., 2020) and alarmins (e.g., high-mobility group protein B1 (HMGB)) (Cher et al., 2018), which are considered to have a central role in high patient-reported pain during the early stages of the disorder. If the condition progress over time, inflammation gives way to other cellular processes responsible for stiffening and thickening of the capsule, characteristic of the later stages of frozen shoulder and less pain (Kraal et al., 2020), as reported in the current study.

Autonomic symptoms

Our results indicate that the level of self-reported autonomic symptoms in participants with frozen shoulder changes over time and might be related to the inflammatory state as explained above. A recent case-control study found more self-reported autonomic symptoms in

participants with frozen shoulder compared to healthy controls (Mertens et al., 2022b). The change in autonomic symptoms does not unravel whether dysautonomia was already present before the development of the frozen shoulder or develops in the early stages of the disorder. To assess autonomic nervous function, we used the COMPASS-31. Results may have been different with other valuable tools related to autonomic function, such as the Composite Autonomic Scoring Scale (CASS) (Novak, 2011). However, these tools reflect end-organ function (like smooth and cardiac muscle or glandular organs), rather than pure neural activity in the autonomic nerves (Nahm & Freeman, 2007).

QST measurements

The scores for allodynia at baseline were so low that improvement could not have occurred and indicate that neuropathic pain is not likely and thus at group level not a feature of this population. The improvement of hyperalgesia at the quadriceps from 3 to 9 months was unexpected, since this seem to be similar as in healthy people (Mertens et al., 2022b). Because hyperalgesia at the other locations remained the same, this improvement is obscure, and we have no explanation for it. Apparently, impaired pain modulation seems not to play a central role in the clinical course of frozen shoulder as it did not show time-related changes. Previous studies have reported that endogenous pain facilitation (measured with TS) and inhibition (measured with CPM) is normally functioning in patients with frozen shoulder (Aguilar-Rodriguez et al., 2021). Consequently, altered CPP mechanisms may thus not be a characteristic of this population.

<u>Longitudinal correlation analysis</u>

To our knowledge, this is the first study examining longitudinal correlations including multiple time-points, as previous studies established correlations only in a cross-sectional way.

Potentially, these findings may be used to identify treatment targets, e.g., improvement in pain catastrophizing will result in improvement of pain intensity or vice versa.

Comparison with other studies

A similar study analyzed correlations between the spatial extent of pain and pain intensity, catastrophizing, and some measurements of altered CPP in participants with frozen shoulder (Balasch-Bernat et al., 2021), but this was cross-sectional. A more widespread distribution of pain was correlated with higher levels of pain, catastrophizing, and altered CPP in participants with frozen shoulder. Another cross-sectional study by Hirata et al. (Hirata et al., 2021) found a correlation between pain intensity and catastrophizing in participants with frozen shoulder and the authors suggested that a reduction in pain intensity would improve catastrophizing. Interestingly, in their model, catastrophizing inversely did not affect pain intensity. Our results are in line with these results, but in a longitudinal manner and without an established direction (catastrophizing improves pain intensity or vice versa).

Possible explanations for correlations

There is a well-known relationship between the autonomic and nociceptive system, so it could be expected to find a correlation between autonomic function activity and nociception (Martinez-Lavin, 2007). However, we did not find any correlation over time between pain intensity and self-reported autonomic symptoms. Cognitive and emotional control is important for stress-regulation and recovery (De Raedt & Hooley, 2016) and autonomic nervous system activity reflects the psychophysiological control of stress-regulation (Lampert et al., 2016). Although the longitudinal correlation between catastrophizing and altered autonomic function in the current study is weak, it might partly explain the demonstrated correlation, similarly to that reported in other pain populations such as chronic whiplash associated disorder (Koenig et

al., 2016). Other factors that might contribute to stress-regulation include anxiety and depression.

Clinical implications

Our results indicate that the largest improvements in pain intensity and shoulder pain and disability occur in the first months after the introduction of the movement restriction and slows down with time. Therefore, it may be important to initiate treatment (i.e., education) as soon as frozen shoulder is diagnosed. Unfortunately, the early diagnosis of frozen shoulder remains currently a challenge (Millar et al., 2022).

The role of the autonomic nervous system in participants with frozen shoulder is still obscure. Differences in baseline self-reported autonomic symptoms between participants with frozen shoulder and healthy controls were observed (Mertens et al., 2022b), but it is unknown whether the time-related change in autonomic function is clinically relevant due to the lack of MDC and MCID values. Furthermore, altered CPP seems not to have a central role in patients with frozen shoulder since no or controversial time-related changes were observed in allodynia, widespread hyperalgesia, TS, and CPM. Nevertheless, altered CPP might be present in a subgroup of patients and should not be underestimated.

Strengths

The main strength of the current study is its longitudinal design. By assessing the outcomes at multiple time points, it was possible to get an overview of the development of CPP measurements and related psychosocial (dys)function (Katz & Seltzer, 2009). Another strength is the biopsychosocial assessment used in this study, both physical and psychological measurements were used to investigate the clinical course of participants with frozen shoulder. The use of an easily applicable assessment protocol, which is convenient for use in clinical

practice, is another strength of the current study. Furthermore, the multi-center design, with different geographic locations is important to emphasize. This design provides multiple benefits over a single center design (e.g., large sample size, decreased personal bias, and larger generalizability of the results). Finally, although there is no gold standard for diagnosing frozen shoulder (Millar et al., 2022), we standardized the stage of the frozen shoulder with strict eligibility criteria, minimizing the influence of symptom duration.

Limitations

The results of this study need to be interpreted considering some limitations. First, there was a relatively low adherence to the research protocol, with only 59% of the sample completing all the assessments. There was already low adherence in the early phase of the project and therefore a higher number of patients were included (149 instead of 118) than initially intended. However, a total of 88 patients finally completed the study, which is a big sample for a so low prevalent condition as frozen shoulder is. Supplementary Table S1 shows barely differences in baseline variables between the full sample and completers. There was only a difference for pain intensity and hyperalgesia at the quadriceps. However, based on the reasons for dropouts (Figure 1), we assume the higher pain intensity was not the main reason for dropout, since only three participants dropped out for shoulder surgery and only one for severity of complaints. Interpretation of the results of TS may be limited due to reliability issues. The pressure stimuli should be identical, which is difficult to achieve manually with an algometer and a computerized approach would increase reliability. However, the method used has been found reliable in a previous study (Cathcart et al., 2009).

Conclusion

Our results showed an early clinically relevant improvement (first 3 months) in pain intensity, and shoulder pain and disability in participants with frozen shoulder, which slows over time. It is unknown whether the improvement in autonomic symptoms is relevant. Additionally, a clinically irrelevant improvement in pain catastrophizing, hypervigilance, and widespread hyperalgesia at the quadriceps was found. No time-related changes in pain sensitivity, local hyperalgesia, TS, or CPM were demonstrated. Several longitudinal correlations (with fair to weak strength) indicated a correlation between psychological and some altered CPP variables and between autonomic function and psychological variables, but the direction and clinical implications of these correlations are unclear and need further investigation.

REFERENCES

Abrassart, S., Kolo, F., Piotton, S., Chih-Hao Chiu, J., Stirling, P., Hoffmeyer, P., & Ladermann, A. 'Frozen shoulder' is ill-defined. How can it be described better? *EFORT Open Rev 2020; 5*(5): 273-279.

Aguilar-Rodriguez, M., Duenas, L., Balasch, I. B. M., Meeus, M., Struyf, F., & Lluch, E. Conditioned Pain Modulation Is Not Impaired in Individuals with Frozen Shoulder: A Case-Control Study. *Int J Environ Res Public Health 2021; 18*(23): 123-130.

Bakdash, J. Z., & Marusich, L. R. Repeated Measures Correlation. *Front Psychol 2017; 8*45-46.

Balasch-Bernat, M., Duenas, L., Aguilar-Rodriguez, M., Falla, D., Schneebeli, A., Navarro-Bosch, M., Lluch, E., & Barbero, M. The Spatial Extent of Pain Is Associated with Pain Intensity, Catastrophizing and Some Measures of Central Sensitization in People with Frozen Shoulder. *J Clin Med 2021; 11*(1): 154.

Bates, D., Mächler, M., Bolker, B., & Walker, S. Fitting Linear Mixed-Effects Models Usinglme4. *J Stat Softw 2015; 67*(1): 1-48.

Bland, J. M., & Altman, D. G. Correlation, regression, and repeated data. *BMJ 1994; 308*(6933): 896.

Boonstra, A. M., Schiphorst Preuper, H. R., Reneman, M. F., Posthumus, J. B., & Stewart, R. E. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. *Int J Rehabil Res 2008; 31*(2): 165-169.

Breckenridge, J. D., McAuley, J. H., & Ginn, K. A. Motor Imagery Performance and Tactile Spatial Acuity: Are They Altered in People with Frozen Shoulder? *Int J Environ Res Public Health 2020; 17*(20): 7464.

Brue, S., Valentin, A., Forssblad, M., Werner, S., Mikkelsen, C., & Cerulli, G. Idiopathic adhesive capsulitis of the shoulder: a review. *Knee Surg Sports Traumatol Arthrosc 2007; 15*(8): 1048-1054.

Cathcart, S., Winefield, A. H., Rolan, P., & Lushington, K. Reliability of temporal summation and diffuse noxious inhibitory control. *Pain Res Manag 2009; 14*(6): 433-438.

Chan, Y. H. Biostatistics 104: correlational analysis. *Singapore Med J 2003; 44*(12): 614-619.

Chapman, C. R., Tuckett, R. P., & Song, C. W. Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. *J Pain 2008; 9*(2): 122-145.

Cher, J. Z. B., Akbar, M., Kitson, S., Crowe, L. A. N., Garcia-Melchor, E., Hannah, S. C., McLean, M., Fazzi, U. G., Kerr, S. C., Murrell, G. A. C., & Millar, N. L. Alarmins in Frozen Shoulder: A Molecular Association Between Inflammation and Pain. *Am J Sports Med 2018; 46*(3): 671-678.

Crofford, L. J. Chronic Pain: Where the Body Meets the Brain. *Trans Am Clin Climatol Assoc 2015; 126*167-183.

De Baets, L., Matheve, T., Dierickx, C., Bijnens, E., Jans, D., & Timmermans, A. Are clinical outcomes of frozen shoulder linked to pain, structural factors or pain-related cognitions? An explorative cohort study. *Musculoskelet Sci Pract 2020; 50*102270.

De Raedt, R., & Hooley, J. M. The role of expectancy and proactive control in stress regulation: A neurocognitive framework for regulation expectation. *Clin Psychol Rev 2016; 45*45-55.

De Wandele, I. *Dysautonomia in the hypermobility type of Ehlers-Danlos Syndrome.* Unpublished Doctoral, Ghent University, Ghent;2014.

den Boer, C., Dries, L., Terluin, B., van der Wouden, J. C., Blankenstein, A. H., van Wilgen, C. P., Lucassen, P., & van der Horst, H. E. Central sensitization in chronic pain and medically unexplained symptom research: A systematic review of definitions, operationalizations and measurement instruments. *J Psychosom Res 2019; 117*32-40.

Drummond, P. D. Sensory disturbances in complex regional pain syndrome: clinical observations, autonomic interactions, and possible mechanisms. *Pain Med 2010; 11*(8): 1257-1266.

Esteve, R., Ramirez-Maestre, C., & Lopez-Martinez, A. E. Empirical evidence of the validity of the Spanish version of the pain vigilance awareness questionnaire. *Int J Behav Med 2013; 20*(1): 59-68.

Farasyn, A., & Meeusen, R. Pressure pain thresholds in healthy subjects: influence of physical activity, history of lower back pain factors and the use of endermology as a placebo-like treatment. *J Bodyw Mov Ther 2003; 7*(1): 53-61.

Garcia Campayo, J., Rodero, B., Alda, M., Sobradiel, N., Montero, J., & Moreno, S. [Validation of the Spanish version of the Pain Catastrophizing Scale in fibromyalgia]. *Med Clin (Barc) 2008; 131*(13): 487-492.

Halekoh, U., & Højsgaard, S. A Kenward-Roger Approximation and Parametric Bootstrap Methods for Tests in Linear Mixed Models - TheRPackagepbkrtest. *J Stat Softw 2014; 59*(9): 32.

Hawker, G. A., Mian, S., Kendzerska, T., & French, M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken) 2011; 63 Suppl 11*S240-252.

Hirata, J., Tomiyama, M., Koike, Y., Yoshimura, M., & Inoue, K. Relationship between pain intensity, pain catastrophizing, and self-efficacy in patients with frozen shoulder: a cross-sectional study. *J Orthop Surg Res 2021; 16*(1): 542.

Jensen, M. P., Karoly, P., & Braver, S. The measurement of clinical pain intensity: a comparison of six methods. *Pain 1986; 27*(1): 117-126.

Jeracitano, D., Cooper, R. G., Lyon, L. J., & Jayson, M. I. Abnormal temperature control suggesting sympathetic dysfunction in the shoulder skin of patients with frozen shoulder. *Br J Rheumatol 1992; 31*(8): 539-542.

Katz, J., & Seltzer, Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Rev Neurother 2009; 9*(5): 723-744.

Kelley, M. J., Shaffer, M. A., Kuhn, J. E., Michener, L. A., Seitz, A. L., Uhl, T. L., Godges, J. J., & McClure, P. W. Shoulder pain and mobility deficits: adhesive capsulitis. *J Orthop Sports Phys Ther 2013; 43*(5): A1-31.

Kennedy, D. L., Kemp, H. I., Wu, C., Ridout, D. A., & Rice, A. S. C. Determining Real Change in Conditioned Pain Modulation: A Repeated Measures Study in Healthy Volunteers. *J Pain 2020; 21*(5-6): 708-721.

Koenig, J., De Kooning, M., Bernardi, A., Williams, D. P., Nijs, J., Thayer, J. F., & Daenen, L. Lower Resting State Heart Rate Variability Relates to High Pain Catastrophizing in Patients with Chronic Whiplash-Associated Disorders and Healthy Controls. *Pain Pract 2016; 16*(8): 1048-1053.

Koopman, F. A., van Maanen, M. A., Vervoordeldonk, M. J., & Tak, P. P. Balancing the autonomic nervous system to reduce inflammation in rheumatoid arthritis. *J Intern Med 2017; 282*(1): 64-75.

Kraal, T., Lubbers, J., van den Bekerom, M. P. J., Alessie, J., van Kooyk, Y., Eygendaal, D., & Koorevaar, R. C. T. The puzzling pathophysiology of frozen shoulders - a scoping review. *J Exp Orthop 2020; 7*(1): 91.

Lampert, R., Tuit, K., Hong, K. I., Donovan, T., Lee, F., & Sinha, R. Cumulative stress and autonomic dysregulation in a community sample. *Stress 2016; 19*(3): 269-279.

Lewis, G. N., Heales, L., Rice, D. A., Rome, K., & McNair, P. J. Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. *Pain Res Manag 2012; 17*(2): 98-102.

Lluch, E., Torres, R., Nijs, J., & Van Oosterwijck, J. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. *Eur J Pain 2014; 18*(10): 1367-1375.

Lyne, S. A., Goldblatt, F. M., & Shanahan, E. M. Living with a frozen shoulder - a phenomenological inquiry. *BMC Musculoskelet Disord 2022; 23*(1): 318.

Martinez-Lavin, M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Res Ther 2007; 9*(4): 216.

McCracken, L. M. "Attention" to pain in persons with chronic pain: A behavioral approach. *Behav Ther 1997; 28*(2): 271-284.

Membrilla-Mesa, M. D., Cuesta-Vargas, A. I., Pozuelo-Calvo, R., Tejero-Fernandez, V., Martin-Martin, L., & Arroyo-Morales, M. Shoulder pain and disability index: cross cultural validation and evaluation of psychometric properties of the Spanish version. *Health Qual Life Outcomes 2015; 13*(1): 200.

Mena-Del Horno, S., Balasch-Bernat, M., Duenas, L., Reis, F., Louw, A., & Lluch, E. Laterality judgement and tactile acuity in patients with frozen shoulder: A cross-sectional study. *Musculoskelet Sci Pract 2020; 47*102136.

Mena-Del Horno, S., Duenas, L., Lluch, E., Louw, A., Luque-Suarez, A., Mertens, M. G., Fuentes-Aparicio, L., & Balasch-Bernat, M. A Central Nervous System Focused Treatment Program for People with Frozen Shoulder: A Feasibility Study. *Int J Environ Res Public Health 2022; 19*(5): 2628.

Mertens, M. G., Meeus, M., Verborgt, O., Vermeulen, E. H. M., Schuitemaker, R., Hekman, K. M. C., van der Burg, D. H., & Struyf, F. An overview of effective and potential new conservative interventions in patients with frozen shoulder. *Rheumatol Int 2022a; 42*(6): 925-936.

Mertens, M. G., Struyf, F., Lluch Girbes, E., Duenas, L., Verborgt, O., & Meeus, M. Autonomic Nervous System Function and Central Pain Processing in People With Frozen Shoulder: A Case-control Study. *Clin J Pain 2022b; 38*(11): 659-669.

Meyer, K., Sprott, H., & Mannion, A. F. Cross-cultural adaptation, reliability, and validity of the German version of the Pain Catastrophizing Scale. *J Psychosom Res 2008; 64*(5): 469-478.

Millar, N. L., Meakins, A., Struyf, F., Willmore, E., Campbell, A. L., Kirwan, P. D., Akbar, M., Moore, L., Ronquillo, J. C., Murrell, G. A. C., & Rodeo, S. A. Frozen shoulder. *Nat Rev Dis Primers 2022; 8*(1): 59.

Monticone, M., Ambrosini, E., Rocca, B., Nava, T., Terragni, E., Cerri, C., & McCracken, L. M. Development of the Italian Version of the Pain Vigilance and Awareness Questionnaire in Subjects with Chronic Low Back Pain: Cross-cultural Adaptation, Confirmatory Factor Analysis, Reliability and Validity. *Int J Behav Med 2016; 23*(2): 214-223.

Monticone, M., Baiardi, P., Ferrari, S., Foti, C., Mugnai, R., Pillastrini, P., Rocca, B., & Vanti, C. Development of the Italian version of the Pain Catastrophising Scale (PCS-I): cross-cultural adaptation, factor analysis, reliability, validity and sensitivity to change. *Qual Life Res 2012; 21*(6): 1045-1050.

Nahm, F., & Freeman, R. (2007). Autonomic testing. In B. AS & R. SB (Eds.), *The clinical neurophysiology primer* (1st ed., pp. 447-460). Totowa, New Jersey: Humana press.

Noten, S., Struyf, F., Lluch, E., D'Hoore, M., Van Looveren, E., & Meeus, M. Central Pain Processing in Patients with Shoulder Pain: A Review of the Literature. *Pain Pract 2017; 17*(2): 267-280.

Novak, P. Quantitative autonomic testing. *J Vis Exp 2011;* (53).

Pietrzak, M. Adhesive capsulitis: An age related symptom of metabolic syndrome and chronic low-grade inflammation? *Med Hypotheses 2016; 88*12-17.

Reeves, B. The natural history of the frozen shoulder syndrome. *Scand J Rheumatol 1975; 4*(4): 193-196.

Roach, K. E., Budiman-Mak, E., Songsiridej, N., & Lertratanakul, Y. Development of a shoulder pain and disability index. *Arthritis Care Res 1991; 4*(4): 143-149.

Roelofs, J., Peters, M. L., Muris, P., & Vlaeyen, J. W. Dutch version of the Pain Vigilance and Awareness Questionnaire: validity and reliability in a pain-free population. *Behav Res Ther 2002; 40*(9): 1081-1090.

Roy, J. S., MacDermid, J. C., & Woodhouse, L. J. Measuring shoulder function: a systematic review of four questionnaires. *Arthritis Rheum 2009; 61*(5): 623-632.

Salaffi, F., Stancati, A., Silvestri, C. A., Ciapetti, A., & Grassi, W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain 2004; 8*(4): 283-291.

Sawyer, E. E., McDevitt, A. W., Louw, A., Puentedura, E. J., & Mintken, P. E. Use of Pain Neuroscience Education, Tactile Discrimination, and Graded Motor Imagery in an Individual With Frozen Shoulder. *J Orthop Sports Phys Ther 2018; 48*(3): 174-184.

Searle, S. R., Speed, F. M., & Milliken, G. A. Population Marginal Means in the Linear-Model - an Alternative to Least-Squares Means. *Am Stat 1980; 34*(4): 216-221.

Severeijns, R., van den Hout, M. A., Vlaeyen, J. W., & Picavet, H. S. Pain catastrophizing and general health status in a large Dutch community sample. *Pain 2002; 99*(1-2): 367-376.

Sletten, D. M., Suarez, G. A., Low, P. A., Mandrekar, J., & Singer, W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. *Mayo Clin Proc 2012; 87*(12): 1196-1201.

Stanton-Hicks, M. D. CRPS: what's in a name? Taxonomy, epidemiology, neurologic, immune and autoimmune considerations. *Reg Anesth Pain Med 2019; 44*(3): 376-387.

Struyf, F., & Meeus, M. Current evidence on physical therapy in patients with adhesive capsulitis: what are we missing? *Clin Rheumatol 2014; 33*(5): 593-600.

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. The Pain Catastrophizing Scale: Development and validation. *Psychol Assess 1995; 7*(4): 524-532.

Tennent, D., & Green, G. Partial articular supraspinatus tendon avulsion: Should we repair? A systematic review of the evidence. *Shoulder Elbow 2020; 12*(4): 253-264.

Thoomes-de Graaf, M., Scholten-Peeters, G. G., Duijn, E., Karel, Y., Koes, B. W., & Verhagen, A. P. The Dutch Shoulder Pain and Disability Index (SPADI): a reliability and validation study. *Qual Life Res 2015; 24*(6): 1515-1519.

Treister, R., O'Neil, K., Downs, H. M., & Oaklander, A. L. Validation of the composite autonomic symptom scale 31 (COMPASS-31) in patients with and without small fiber polyneuropathy. *Eur J Neurol 2015; 22*(7): 1124-1130.

Vanderweeen, L., Oostendorp, R. A., Vaes, P., & Duquet, W. Pressure algometry in manual therapy. *Man Ther 1996; 1*(5): 258-265.

Vastamaki, H., Kettunen, J., & Vastamaki, M. The natural history of idiopathic frozen shoulder: a 2- to 27-year followup study. *Clin Orthop Relat Res 2012; 470*(4): 1133-1143.

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med 2007; 147*(8): 573-577.

Walton, D. M., Levesque, L., Payne, M., & Schick, J. Clinical pressure pain threshold testing in neck pain: comparing protocols, responsiveness, and association with psychological variables. *Phys Ther 2014; 94*(6): 827-837.

Walton, D. M., Macdermid, J. C., Nielson, W., Teasell, R. W., Chiasson, M., & Brown, L. Reliability, standard error, and minimum detectable change of clinical pressure pain threshold testing in people with and without acute neck pain. *J Orthop Sports Phys Ther 2011; 41*(9): 644-650.

Wong, C. K., Levine, W. N., Deo, K., Kesting, R. S., Mercer, E. A., Schram, G. A., & Strang, B. L. Natural history of frozen shoulder: fact or fiction? A systematic review. *Physiotherapy 2017; 103*(1): 40-47.

Wong, J. J., Cote, P., Quesnele, J. J., Stern, P. J., & Mior, S. A. The course and prognostic factors of symptomatic cervical disc herniation with radiculopathy: a systematic review of the literature. *Spine J 2014; 14*(8): 1781-1789.