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Original article

Do features of central sensitisation exist in Greater Trochanteric Pain Syndrome (GTPS)? A case control study.

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A B S T R A C T

Background: Greater Trochanteric Pain Syndrome (GTPS), which is commonly due to Gluteal Tendinopathy, refers to pain over the lateral hip that can become persistent and disabling. Central nervous sensitisation has been implicated in upper limb tendinopathy, but no studies have investigated if it plays a role in GTPS.
Objectives: To investigate if features of central sensitisation were present in people with GTPS.
Methods: Eighteen people with GTPS were matched with 18 healthy controls in this cross-sectional study. The VISA-G and Central Sensitisation Inventory (CSI) self-report questionnaires were completed and pressure pain detection thresholds (PPDTs) at local and remote sites were measured in all participants. Data were analysed for between-group differences using Mann-Whitney U tests. Correlation between CSI and PPDTs were assessed using Pearson correlation co-efficients.
Results: PPDT values were lower at local (symptomatic greater trochanter) and remote sites in the GTPS group, indicative of central sensitisation, resulting in statistically significant between-group differences. 44.4% of the GTPS group were classified as having symptoms of central sensitisation, based on the CSI.
Conclusion: There is preliminary evidence of central sensitisation in people with GTPS. Results need to be validated using other objective quantitative sensory testing measures in larger samples.

1. Background

Greater trochanteric pain syndrome (GTPS) is an overarching term used to describe pain over the greater trochanter of the lateral hip. Whilst this condition traditionally has been considered to be a trochanteric bursitis, in recent years, degenerative changes in the Gluteus Minimus (GMed) and Gluteus Medius (GMed) tendons consistent with gluteal tendinopathy have been observed (Bird et al., 2001; Ruta et al., 2015; Woodley et al., 2008), with trochanteric bursitis less frequently detected on imaging (Bird et al., 2001; Ruta et al., 2015). It affects women more than men by a ratio of 4:1 (Lievense et al., 2005) and is most common in those aged over 40 years (Segal et al., 2007). Symptoms include pain with side lying, walking and other weight-bearing activities (Fearon et al., 2013). Identified risk factors for GTPS include female sex, older age, lower femoral neck angle (Fearon et al., 2012), back pain and increased adiposity (Segal et al., 2007). It can become persistent and disabling, negatively impacting on everyday activities and quality of life (Fearon et al., 2014). Gluteal tendinopathy is recognised as the predominant pathology associated with GTPS (Blankenbaker et al., 2008; Kong et al., 2007). Due to the discordance between changes on imaging and symptoms in tendinopathy (Cook et al., 1998; Fredberg and Bolvig, 2002), the potential role of altered nervous system sensitisation has been a topic of research interest in tendinopathy (Plinsinga et al., 2015; Plinsinga et al., 2018a,b). Whilst nociceptive and neuropathic pain are clearly defined and recognised internationally, it has been recognised that altered nociceptive function can occur in those experiencing pain and hypersensitivity, but is not associated with frank signs of neuropathy (Kosek et al., 2016). This led to the development of the term 'nociplastic pain' in 2017 by the International Association for the Study of Pain (International Association for the Study of Pain (IASP), 2017). This is defined as 'pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain'. This term is intended to describe the pain associated with altered nociceptive processing, such as hypersensitivity, which is commonly associated with central sensitisation, rather than pain associated with a demonstrable lesion of the nervous system (Kosek et al., 2016).

Recent literature has identified evidence for central nervous system (CNS) sensitisation in tendinopathy (Plinsinga et al., 2015; Tompra et al., 2016), with more robust evidence in upper limb lateral elbow tendinopathy, compared with lower limb tendinopathy such as achilles and patellar tendinopathy (Plinsinga et al., 2018a,b). This sensitisation, a manifestation of altered neurophysiological processes, is mediated within the central nervous system (CNS), and can present with features of hyperalgesia and allodynia which are commonly associated with chronic, maladaptive and persistent pain (van Wilgen and Keizer, 2012). Further evidence for CNS involvement in tendon pain has been

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established in a systematic review of 20 studies which found sensory and motor deficits on the non-injured side in people with unilateral achilles, patellar, rotator cuff and elbow lateral epicondyle tendon pain (Heales et al., 2014). No studies have investigated whether such features are present in GTPS.

Central sensitisation can be objectively measured using quantitative sensory testing (QST), which entails testing responses to standardised thermal or mechanical stimuli and recording the point of pain reproduction. Central sensitisation may be present when lower pain thresholds occur either over the site of pain or at remote sites (away from the area of pain or dysfunction). QST has been used to determine the presence of central sensitisation in persistent musculoskeletal pain states such as fibromyalgia (Kosek and Hansson, 1997), chronic low back pain (Correa et al., 2015), knee osteoarthritis (Fingleton et al., 2015) and chronic whiplash (Van Oosterwijck et al., 2013). Therefore, this study aimed to investigate if features of central sensitisation were present in people with GTPS compared with symptom-free controls. Although gluteal tendinopathy is recognised as the predominant pathology associated with GTPS, and has demonstrated tendinopathic changes using MRI or US imaging (Blankenbaker et al., 2008; Kong et al., 2007), in this study we used recognised clinical criteria to diagnose GTPS (Fearon et al., 2013). Due to similar age and gender profile, shared risk factors and a multi-factorial pathogenesis between tendinopathy and osteoarthritis (de Vos et al., 2016), we hypothesised that 20–30% of people with GTPS would report symptoms of central sensitisation as previously determined in OA (Murphy et al., 2011), based on a self-report questionnaire for central sensitisation. We also hypothesised that pressure pain detection thresholds would be lower in the GTPS group, compared with the control group, both at the greater trochanter and one or more remote site, indicating centrally-mediated pain sensitisation. Furthermore, we hypothesised that there would be, at best, a moderate correlation ($r = 0.41–0.61$) (Landis and Koch, 1977) between self-report symptoms of central sensitisation and objective measures of pressure pain detection thresholds.

2. Methods

2.1. Study design and participants

A case-control cross-sectional study design was used. Consecutive patients with a diagnosis of GTPS were recruited from orthopaedic and rheumatology triage clinics and physiotherapy waiting lists in a large teaching hospital in Ireland. Asymptomatic controls were recruited from staff and acquaintances of the Royal College of Surgeons in Ireland (RCSI). Inclusion criteria for the GTPS group included males and females with unilateral lateral hip pain of at least three months duration, age 18 years or more, pain on palpation of the greater trochanter and one or more of the following: lateral hip pain with side lying on the affected side, pain during weight-bearing activities or pain on sitting. Exclusion criteria for both groups included radiographic signs of hip OA, systemic inflammatory disease, lumbar spine related nerve root signs, previous history of spinal or ipsilateral hip surgery, neurological disease, unable to communicate in English or cortico-steroid injection to the affected hip in the last 3 months. Additional exclusion criteria for controls included current low back, hip or groin pain.

As there are no previous studies in GTPS, sample size estimates were based on previous upper limb tendinopathy research (Coombes et al., 2012) that used a case-control design. Effect sizes (ES) varied between 0.8 and 1.6 for pressure pain detection thresholds (PPDTs) measured at local and remote sites. Based on an effect size of 0.9, alpha of 0.05 and 80% power, a total of 18 participants per group were required.

2.2. Ethical considerations

Ethical approval for the study was obtained from Connolly hospital and RCSI Research Ethics Committees.

2.3. Testing procedures

Testing was done by one of two testers (HPF and MM) on one visit at a time convenient to study participants. Both testers assessed participants in either the GTPS or control groups to remove any systematic bias from the physical examination components of the assessment, but testers were not blinded to group allocation.

2.4. Questionnaire-based measures

The VISA-G questionnaire is an 8-item self-report questionnaire which evaluates the severity of disability associated with GTPS. Score range is 0–100, with higher scores indicating greater severity. It has demonstrated high test-retest reliability (ICC = 0.83, 95% CI = 0.64, 0.92), internal consistency (Cronbach alpha = 0.81). Construct validity testing demonstrated that it measured different constructs to measures used in hip OA (Harris hip Score) and low back pain (Oswestry Disability Index) (Fearon et al., 2015).

The Central Sensitisation Inventory (CSI) is a screening instrument designed to help clinicians identify patients with central sensitisation features by measuring a full array of CS-related symptoms (Mayer et al., 2012). It is intended for use as a proxy tool of the constructs it measures, rather than a diagnostic tool (Scerbo et al., 2018). It comprises 25 questions related to symptoms associated with central sensitisation. Scores range from 0 to 100, with higher scores indicating more symptoms of central sensitisation. Analysis found that a cut-off score of “40” of “100” on the CSI yielded good sensitivity (81%) in correctly identifying patients with central sensitisation, as well as good specificity (75%) in ruling out central sensitisation in other populations (Neblett et al., 2015). It has demonstrated high reliability and construct validity for the measurement of symptoms associated with central sensitisation (Scerbo et al., 2018).

2.5. Physical measures

A digital pressure algometer with a probe size of 2 cm^2 was used to test Pressure Pain Detection Thresholds (PPDTs) (Wagner Instruments, Connecticut, USA). The algometer was applied by the tester with increasing ramp of 0.5 kg/sec to the following test sites on both sides for all participants: tip of index finger, 2 cm below the lateral epicondyle of the elbow, 2 cm posterior to the trochanteric prominence of the greater trochanter and tibialis anterior muscle 5 cm below the tibial tuberosity. Participants were instructed to verbally report pain onset as the point when the sensation of pressure became the ‘first sensation of pain’ (Walton et al., 2011). Three PPDT measures were taken at each site and the average used for data analysis. A 20-s rest was provided between each pressure application. Both testers concurrently practiced PPDT testing at the four sites to ensure consistency in application. Inter-tester reliability of eight symptom-free individuals ranged from 0.71 to 0.93 for the PPDT measures.

To confirm clinical findings consistent with gluteal tendinopathy, two pain provocation tests were performed. In the External Derotation Test, the hip was placed in 90° flexion and external rotation. The tester slightly decreased external rotation short of pain (if pain was present). The participant actively returned the leg to neutral rotation against resistance applied by the tester (Lequesne et al., 2008). The test was considered positive if lateral hip pain was reproduced. Sensitivity of this test is 88% and specificity is 97% (Lequesne et al., 2008). FABER (Flexion/Abduction/Extemal Rotation) has been reported (Fearon et al., 2013) to discriminate between GTPS and hip OA. The lateral malleolus of the limb being tested was placed on the opposite thigh, just above the patella. The tester placed one hand on the medial aspect of the knee being tested, and the other hand stabilised the pelvis at the anterior superior iliac spine, whilst the leg was passively brought into end of flexion/abduction/external rotation. The test was considered positive if lateral hip pain was reproduced.

2.6. Statistical analyses

All data were entered into Microsoft Excel for Office 365 (Microsoft Corp, Seattle, USA) and imported into SPSS (v24, IBM Inc, Chicago, USA) for further analysis. Descriptive statistics such as medians and interquartile ranges were used to describe the sample in relation to demographic and clinical continuous variables. As not all variables were normally distributed and due to small sample size, Mann-Whitney U tests were used to compare the questionnaire and physical examination variables between the GTPS participants and healthy controls for continuous data. The symptomatic leg in the GTPS group was matched to the right leg of the control group. Sensitivity analyses demonstrated no statistically significant differences in results when the corresponding limb was matched (e.g. affected left leg in GTPS participant was matched to left leg in control participant). Bonferroni correction for multiple comparison testing was applied (0.05/14) so statistical significance was set at $p < 0.0035$ for between-group comparisons. Fisher's Exact test was used to compare categorical variables between the groups. Participants in the GTPS group were dichotomised into 'low CSI' group (CSI ≤ 40) and 'high CSI' group (CSI > 40), based on the cut-off score of 40, where scores greater than 40 are indicative of central sensitisation (Neblett et al., 2015). Correlation between PPDTs and CSI were conducted using Pearson's correlation co-efficient. The following reliability coefficients as described by Landis and Koch (1977) were used: 0.0 to 0.20 = slight reliability; 0.21 to 0.40 = fair reliability; 0.41 to 0.60 = moderate reliability; 0.61 to 0.8 = substantial reliability; 0.81 to 1.00 = almost perfect reliability. Associations between PPDT and CSI results (as measures of central sensitisation) were made using Fisher's Exact test, using CSI cut-off of 40). Statistical significance was set at $p < 0.05$.

3. Results

Eighteen people with clinical findings of GTPS (age 25–76 years) and 18 healthy controls (age 26–73 years) were recruited to this study. Characteristics of the two groups are shown in Table 1.

The proportion of females was similar (83%) in both groups. The GTPS group had a higher BMI compared with controls (median difference 3.34 kg/m^2; 95% CI 0.20 to 6.30, $p = 0.01$). The External Derotation and FABER tests were positive in 94.4% and 100% of GTPS participants respectively and negative in all controls. The VISA-G and VAS scores, applicable only to the GTPS group, indicate a moderate level of severity. There was a significant difference in the CSI scores between GTPS and control groups (median difference 25; 95% CI 9 to 36, $p < 0.001$). Using the cut-off score of 40/100 on the CSI, a total of eight (44.4%) of the GTPS group were positive for central sensitisation symptoms, compared with none of the control group.

Table 2 shows the PPDT data for both groups. Results show lower values for local (symptomatic greater trochanter) and two remote sites in the GTPS group, which resulted in statistically significant between-group differences. There was no significant between-group difference in index finger PPDT values.

Fig. 1 shows the PPDT data at the four sites on both the symptomatic and asymptomatic sides in the GTPS group only, when dichotomised by the CSI cut-off score. Although PPDT scores on visual inspection were lower in the 'high CSI' (> 40) group indicative of central sensitisation, there was no statistically significant difference in PPDTs between those in the 'low CSI' and 'high CSI' GTPS groups. More detail is provided in Table 3.

Table 4 shows the correlation between PPDT values and CSI. Overall, correlations were low to moderate based on the criteria used by Landis and Koch (Landis and Koch, 1977), thus supporting our third hypothesis.

4. Discussion

The findings of this study identified that 44% of the GTPS group were classified as having symptoms of central sensitisation based on the Central Sensitisation Inventory, a self-report questionnaire, thus supporting our first hypothesis. This percentage was higher than what we hypothesised, but the small sample size can skew these estimates. Results also demonstrated a significant between-group difference in PPDT values measured at the local site (affected greater trochanter) and two remote sites on the upper limb (elbow) and lower limb (anterior shin), indicative of central sensitisation.

The presence of central sensitisation in GTPS needs to have biological plausibility. It is well established that tendon pain is caused by loading and presents with an on/off pattern related to the nature of the loading activity (Rio et al., 2014), whereas central sensitisation results from sustained nociceptive activity from the target tissue causing a sensitisation of the nociceptive neurons in the dorsal horn of the spinal cord. Central sensitisation can be induced by pro-inflammatory cytokines in the spinal cord (Kawasaki et al., 2008) and although tendinopathy is frequently considered a non-inflammatory pathology, inflammatory mediators have been identified throughout the continuum of tendinopathy pathology despite a lack of obvious clinical inflammatory signs (Millar et al., 2017).

Although there is strong evidence for the presence of central

Table 1
Characteristics of study participants (n = 36).

	GTPS (n = 18)	Controls (n = 18)	Diffs between GTPS and Control (n = 36)
	Median (IRQ)	Median (IRQ)	P-Value
Age (years)	54.5 (23)	46.5 (19)	0.29
BMI (kg/m^2)	27.01 (6.6)	23.67 (7.6)	0.01
Number of Co-Morbidities	1.00 (2)	0	NA
Symptom Duration (months)	9.5 (12)	NA	NA
Pain Severity (0–10)	5 (4)	NA	NA
VISA-G (0–100)	56.5 (26)	0	NA
CSI (0–100)	39 (20)	14 (12)	< 0.001*
	Number (Percentage)	**Number (Percentage)**	
Gender, female, n (%)	15 (83%)	15 (83%)	
Side Affected (%)	Left = 8 (44.4%)	NA	NA
	Right = 10 (55.6%)	NA	NA
Positive CSI (CSI > 40/100)	8 (44.4%)	0 (0%)	0.001*
Positive External Derotation Test	17 (94.4%)	0 (0%)	NA
Positive FABER test	18 (100%)	0 (0%)	NA

BMI: Body Mass Index; CSI; Central Sensitisation Inventory; FABER: Flexion/Abduction/External Rotation; IQR; Inter-quartile range; VISA-G: Victorian Institute of Sport Assessment-Gluteal questionnaire.
*significant at $p < 0.0035$.

Table 2
Pressure Pain Detection Thresholds of GTPS and control groups (n = 36).

**Pressure Pain Detection Thresholds (kgf)	GTPS (n = 18)	Controls (n = 18)	Differences between GTPS and Controls (n = 36)
	Median (IRQ)	Median (IRQ)	p-value*
PPDT Index Finger Symptomatic Side	4.04 (1.43)	6.45 (3.39)	0.01
PPDT Index Finger Asymptomatic Side	4.04 (2.74)	6.24 (3.73)	0.01
PPDT Lateral Elbow Symptomatic Side	2.65 (1.10)	4.28 (2.23)	< 0.001*
PPDT Lateral Elbow Asymptomatic Side	2.56 (1.71)	4.15 (3.17)	< 0.001*
PPDT Greater Trochanter Symptomatic Side	3.90 (2.45)	7.10 (3.53)	< 0.001*
PPDT Greater Trochanter Asymptomatic Side	4.96 (3.77)	7.15 (3.77)	< 0.001*
PPDT Tibialis Anterior Symptomatic Side	4.06 (3.77)	6.99 (4.19)	0.003*
PPDT Tibialis Anterior Asymptomatic Side	3.90 (2.81)	7.10 (3.45)	< 0.001*

IQR; Interquartile Range; PPDT; Pressure Pain Detection Thresholds.
*Significant at $p < 0.0035$.
**Symptomatic side in GTPS group matched with right side in control group

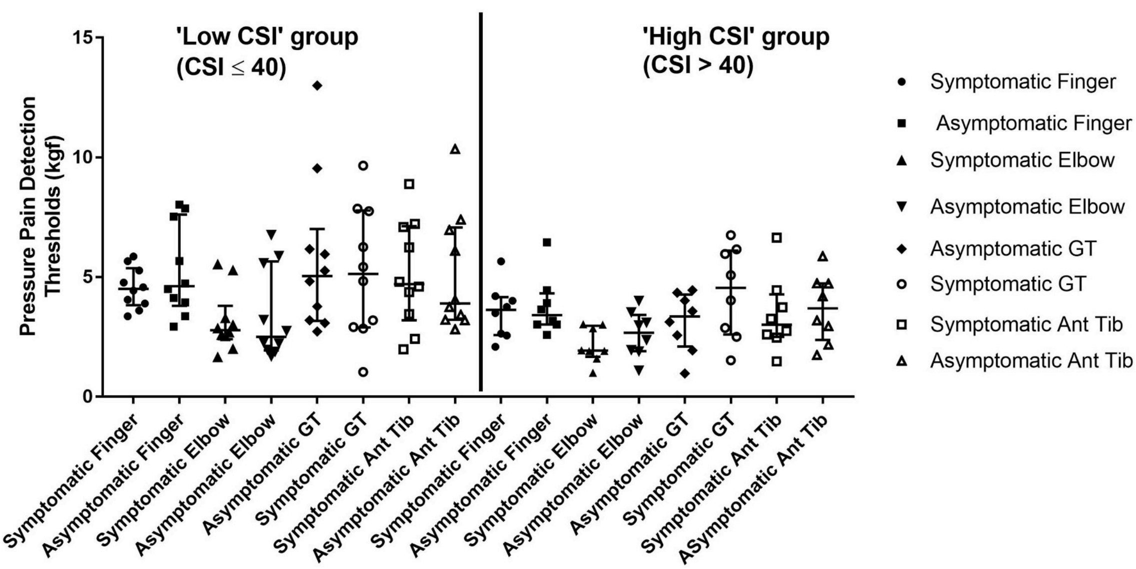

Fig. 1. Pressure Pain Detection Threshold (PPDT) values for GTPS group (n = 18) dichotomised by CSI cut-off score.

sensitisation in upper limb tendinopathy, especially in lateral elbow pain (Plinsinga et al., 2015), the evidence for central sensitisation in other lower limb tendinopathies is conflicting. Reduced conditioned pain modulation using the cold pressor test in achilles tendinopathy, indicative of central sensitisation (Tompra et al., 2016) was demonstrated, whilst pressure, heat and cold threshold changes occurred only at the local tendon site, and not remotely in achilles and patellar tendinopathy (Plinsinga et al., 2018a,b) suggesting local pain sensitisation only. Whilst the argument that findings of central sensitisation in upper limb tendinopathy, particularly lateral epicondylagia, cannot be transferred to lower limb tendinopathy (Mc Auliffe, Whiteley, Malliaras and O'Sullivan, 2018) is reasonable, we would also argue that not all lower limb tendinopathies are the same. Achilles and patellar tendinopathy cannot be compared to gluteal tendinopathy due to differences in tendon anatomy, orientation and effect of adjacent structures on compressive load at the gluteal tendon (Grimaldi and Fearon, 2015). Variation exists in demographic profile, with a higher proportion of women affected by GTPS than achilles or patellar tendinopathy (de Jonge et al., 2011; Lievense et al., 2005; van der Worp et al., 2011). Furthermore, although trochanteric bursitis is present in a minority of people with clinical features of GTPS (Connell et al., 2003; Long et al., 2013), the associated inflammatory process may also contribute to central sensitisation. The PPDT findings suggestive of increased hypersensitivity means that the descriptor of nociplastic pain may be

Table 3
Pressure Pain Detection Thresholds of GTPS group by CSI cut-off score (n = 18).

Pressure Pain Detection Thresholds (kgf)	CSI ≤ 40 (n = 10) Median (IRQ)	CSI > 40 (n = 8) Median (IRQ)	Difference based on CSI cut-off in GTPS group p-value*
PPDT Index Finger Symptomatic Side	4.51 (1.55)	3.63 (1.58)	0.06
PPDT Index Finger Asymptomatic Side	4.62 (3.82)	3.42 (1.31)	0.06
PPDT Lateral Elbow Symptomatic Side	2.79 (1.39)	1.93 (1.29)	0.10
PPDT Lateral Elbow Asymptomatic Side	2.51 (3.72)	2.68 (1.52)	0.70
PPDT Greater Trochanter Symptomatic Side	5.05 (3.84)	3.36 (2.17)	0.04
PPDT Greater Trochanter Asymptomatic Side	5.14 (4.88)	4.56 (3.51)	0.52
PPDT Tibialis Anterior Symptomatic Side	4.71 (3.93)	3.01 (1.78)	0.12
PPDT Tibialis Anterior Asymptomatic Side	3.90 (3.86)	3.70 (2.37)	0.24

CSI, Central Sensitisation Inventory; IQR; Interquartile Range; PPDT; Pressure Pain Detection Thresholds.
*Significant at $p < 0.0035$.

Table 4
Correlation between Pressure Pain Detection Thresholds and Central Sensitisation Inventory scores (n = 36).

Side	PPDT Location	Correlation Co-efficient	P -value
Symptomatic Side	Index Finger	−0.55	0.027
	Lateral Elbow	−0.57	0.02*
	Greater Trochanter	−0.52	0.026*
	Tibialis Anterior	−0.52	0.026*
Asymptomatic Side	Index Finger	−0.54	0.013*
	Lateral Elbow	−0.36	0.15
	Greater Trochanter	−0.27	0.277
	Tibialis Anterior	−0.44	0.007*

*significant at $p < 0.05$; **Symptomatic side in GTPS group compared with right side in control group.
CSI, Central Sensitisation Inventory; PPDT, Pressure Pain Detection Thresholds.

relevant to apply for some people with GTPS, indicating altered nociceptive function (Kosek et al., 2016), however, further validation of presence of nociplasticity would be required through more extensive quantitative sensory testing. The low to moderate correlation between the CSI and PPDT measures in our study suggest that they do not measure the same construct. The CSI was developed as a screening tool to identify symptoms of central sensitisation, rather than as a diagnostic tool (Mayer et al., 2012; Neblett and Mayer, 2017), so caution is advised in solely depending on it to diagnose central sensitisation. Few studies have compared the relationship between the CSI and physical measures of central sensitisation. Coronado and George compared CSI along with the Pain Sensitivity Questionnaire to QST measures such as PPDT, heat pain threshold and suprathreshold pain response in people with shoulder pain (Coronado and George, 2018). Whilst the CSI was positive (> 40/100) in 24.4% of their sample, there was no correlation between CSI and QST measures (r = -0.08 to −0.13), with stronger relationships between CSI and psychological factors such as anxiety, resilience and negative affect (Coronado and George, 2018). This relationship between the CSI and features of psychological distress in people has been shown in other populations with chronic pain (van Wilgen et al., 2018). Conversely, Caumo found a positive relationship between the CSI and serum brain-derived neurotrophic factor (BDNF) (r = 0.52) which has been identified as contributing to both the development and maintenance of central sensitisation in a mixed chronic pain population of fibromyalgia, osteoarthritis, myofascial pain syndrome and chronic tension-type headache (Caumo et al., 2017).

4.1. Study limitations and recommendations for future research

Some limitations should be noted in this study. The two testers were not blinded to group allocation, which could have introduced bias. However, each tester was unable to see the algometer readings during the application of the algometer probe and readings were taken only after the study participant had reported pain and the algometer was removed from the area being tested. Lack of blinding has been reported in other studies of pressure algometry, where pain response is being compared between people with and without pre-existing pain (Correa et al., 2015; van der Heijden et al., 2018). We did not assess psychological status which may account for some of the symptoms associated with central sensitisation in gluteal tendinopathy (Plinsinga et al., 2018a,b) and warrants further investigation to fully understand the pain mechanisms associated with GTPS. Due to the small sample size in this study, caution should be applied in interpreting these results. Although the PPDT values were lower in the GTPS subgroup with higher CSI values (> 40), the possibility of a Type II error should not be out ruled. Therefore, the findings in this study need to be validated in larger samples and as only one QST measure was used, inclusion of more comprehensive objective testing of the nervous system using other QST measures such as conditioned pain modulation, heat and cold threshold pain response may provide further information.

5. Conclusion

This study provides preliminary evidence of central sensitisation in a subgroup of people with unilateral GTPS. Pressure pain detection thresholds at both local and remote sites were lower bilaterally in those with GTPS compared to controls. There was a low to moderate correlation between the Central Sensitisation Inventory and PPDT values. These results require future validation using a battery of recognised objective tests of central sensitisation and should consider other factors such as psychosocial influences.

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