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Do people with unilateral mid-portion Achilles tendinopathy who participate in running-related physical activity exhibit a meaningful conditioned pain modulation (CPM) effect: A pilot study

Myles C. Murphy

Ebonie K. Rio

Paola Chivers
Edith Cowan University

James Debenham

Sean I. Docking

See next page for additional authors

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ABSTRACT

Objectives: Our primary objective was to report the presence of a conditioned pain modulation (CPM) effect in people with localised mid-portion Achilles tendinopathy and whether changes occur over a 12-week period. Our secondary objectives were to quantify the proportion of participants who present for tendinopathy research with previous interventions or co-morbidities, which may impact the CPM-effect and investigate modulating factors.

Design: Prospective, observational cohort pilot study

Method: 215 participants presented for this Achilles tendinopathy research and were screened for inclusion with nine being included. Included participants had the CPM-effect (cold-pressor test) assessed using pressure pain thresholds at the Achilles tendon and quantified as absolute, relative and meaningful change at baseline and 12-week follow-up.

Results: The most common reasons for exclusion were failure to meet a load-related diagnosis for Achilles tendinopathy (15.5%), presence of confounding other injury (14.1%) and previous injection therapy (13.6%). All participants had a meaningful CPM-effect at baseline and 12-week follow-up. The mean (SD, n) baseline relative CPM effect (reduction in PPTs) was -40.5 (32.7, 9) percent. Moderators of the CPM-effect as well as follow-up changes were not statistically analysed due to a small sample size.

Conclusion: Based on these data, we would suggest that a homogenous population of patients with chronic, unilateral mid-portion Achilles tendinopathy and no other co-morbidities are likely to exhibit a meaningful CPM-effect. Impairments to endogenous analgesic mechanisms seen in people presenting with mid-portion Achilles tendinopathy may be due to other confounding variables.

KEY WORDS

Tendon; descending inhibition; diffuse noxious inhibitory control; methodology

PRACTICAL IMPLICATIONS

- Methodological flaws in existing studies on conditioned pain modulation (CPM) of people with Achilles tendinopathy have resulted in erroneous conclusions of the results.
- All participants with unilateral, mid-portion Achilles tendinopathy presenting with localised tendon pain with a single leg hop had a meaningful CPM effect at baseline and 12-week follow-up.
- Ninety-six percent of people presenting for inclusion to a mid-portion Achilles tendinopathy CPM study were not appropriate for inclusion.
- This study suggests that impaired descending pain inhibition is unlikely to be a key driver in the development of persistent mid-portion Achilles tendinopathy

INTRODUCTION

Pain science is an increasingly popular field within sports medicine and can help explain why different pathologies and clinical presentations behave the way they do. The efficacy of endogenous analgesia in response to a nociceptive stimulus is considered a key factor in understanding musculoskeletal conditions. These endogenous responses may assist in patient-profiling and in turn assist in directing treatment pathways.[1] This is especially relevant for chronic musculoskeletal pain where many presentations demonstrate features of dysfunctional, or absent endogenous analgesic mechanisms.[2]

'Conditioned Pain Modulation' (CPM) is a reliable method to investigate endogenous analgesia.[3] The CPM paradigm involves assessing sensitivity, such as mechanical sensitivity via pressure pain thresholds (PPTs) or thermal sensitivity, before and after the application of an ongoing, tonic painful stimulus, such as ice water bath immersion.[4] The assessment of sensitivity (e.g. PPTs) is referred to as the test stimulus and the painful stimulus (e.g. ice water) is referred to as the conditioning stimulus. A meaningful CPM response is to observe a reduction in mechanical sensitivity after application of the conditioning stimulus. CPM is a well-established paradigm for investigating endogenous analgesia in chronic pain states, such as chronic lower back pain.[2 5] Current recommendations are that the size of the CPM effect (which is the difference in the testing stimulus before and after application of the conditioning stimulus) is reported as both absolute (raw scores) and relative (percentage change from baseline) values[4] and whether a meaningful CPM effect was elicited (CPM effect greater than the standard error of the measurement). Such recommendations recognise that the baseline measure of sensitivity (such as PPTs) likely differs between painful versus pain-free groups due to peripheral/ and or central sensitisation.[6] The use of relative change accounts for this difference.

The causes of tendon pain are not fully understood and little research regarding the role of central pain mechanisms for tendinopathy exist, especially within the Achilles tendon.[7] While widespread mechanical sensitivity (but not temporal summation) has been shown to be a feature in Achilles tendinopathy[8] the CPM effect in people with mid-portion Achilles tendinopathy has been investigated in just one study with a reduction in the *absolute* CPM effect being reported within the painful versus

pain-free group.[9] This study compared the CPM effect in people with mid-portion Achilles tendinopathy to a pain-free control group, finding a reduced CPM effect in the presence of persisting Achilles tendon pain.[9] This result should be interpreted with caution though as the analysis was based on the *absolute* CPM effect. Given the large difference in baseline PPT between groups (Achilles tendinopathy group baseline PPT 253kPa; Control group baseline PPT 671.4kPas ($p<0.001$),[9] the *relative* CPM effect is the appropriate comparison. Importantly, when we calculated the relative CPM effect there was no significant difference between groups (Appendix A).

Basic science research investigating pain phenomena such as endogenous analgesia relies on carefully controlled testing paradigms where confounding factors are minimised.[6] One common confounding factor in musculoskeletal pain research is the presence of co-morbidities and these are common exclusion criteria. In the case of CPM, comorbidities, such as lower back pain or knee osteoarthritis can affect the CPM response.[1] As such, it can be strongly argued that they should be considered exclusion criteria to avoid drawing erroneous conclusions regarding the condition of interest.[6] Studies examining Achilles tendinopathy commonly enrol athletic populations[10 11] who likely have a high incidence of confounding injuries yet the study by Tompra et al. did not report they excluded any participants due to comorbidities such as concurrent pain sites (e.g. lower back pain).[9] For example, up to 65% of running injuries that occur within competition require medical attention[12] and between 34-47% of runners report a time loss injury at short-term follow-up.[12] To generate clean and usable Achilles tendinopathy-related CPM data, it is likely that a number of potential participants would need to be excluded due to comorbidities or participant comorbidities should be recorded and accounted for within statistical analysis.[6]

In addition to concurrent injuries a plethora of other factors have been shown to influence the CPM effect including age,[2] ethnicity[13] and gender.[2] Physical activity levels have also been shown to influence the CPM effect[14] and specifically the magnitude of the CPM effect assessed at the Achilles tendon has been shown to differ between runners and non-runners in healthy controls.[15] Specific to the assessment procedures for CPM the temperature of the conditioning stimulus as well as the induced pain have been theorised to influence the reliability of the CPM effect.[3] Due to the potential influence

of these factors on the CPM effect research reporting the CPM effect should either include a homogenous sample or account for them within statistical analysis.[6]

There are no published studies, to the authors knowledge, on the stability of the CPM effect over time in people with mid-portion Achilles tendinopathy. This is important to quantify as if the CPM effect is not stable over time erroneous conclusions regarding the efficacy of interventions targeted towards addressing impairments to descending inhibition (e.g. exercise rehabilitation or cognitive functional therapy) may be attributed.

OBJECTIVES

Our primary objectives were to:

1. Report the absolute, relative and meaningful CPM effect in people with only localised midportion Achilles tendon pain.
2. Report whether the CPM effect changes over the course of 12 weeks.

Our secondary objectives were to:

1. Quantify the proportion of participants that present for inclusion in Achilles tendinopathy CPM research who are included/ excluded based on study inclusion/ exclusion criteria.
2. Investigate potential modulating factors for changes in the CPM effect over time (such as level of pain and disability or fear of movement).

METHODS

A prospective, observational cohort pilot study was performed with two testing occasions based 12-weeks apart (12-weeks being the most commonly used reassessment point within longitudinal, mid-portion Achilles tendinopathy studies).[10] Due to the outbreak of the Coronavirus COVID-19, recruitment was ceased approximately 10 months prior to the planned final recruitment date.

The XXXX Human Research Ethics Committee (Reference number: XXXX) approved this study. This study was registered with the Australian New Zealand Clinical Trial Registry (ANZCTR): 12617000675325.

All recruitment occurred in XXX with all appointments occurring in a quiet, distraction-free environment within either a biomechanics laboratory at XXXX or a private consulting room of a sports medicine practice, XXXX.

We included participants determined to have mid-portion Achilles tendinopathy who met our inclusion and exclusion criteria (Appendix B). We chose to exclude those participants with insertional Achilles tendinopathy as it is considered a separate condition[16] as well as those participants with bilateral symptoms as this could impact the CPM effect as deficits in the CPM effect have been correlated to the number of painful regions.[17] We also chose to exclude physically inactive people due to the potential influence on the CPM effect.[15] Participants self-reported their age (years), sex (male/female), height (cm), weight (kg) and duration of symptoms (weeks). Valid and reliable outcome measures to assess pain over a specified time, pain with loading, tendon pain related disability, fear of movement, patient perception of improvement and the conditioned pain modulation effect were selected based on recent reviews of appropriate outcome measures within Achilles tendinopathy research and CPM.[3 15 18 19]

Physical activity levels were recorded using an activity diary for the seven days prior to baseline testing. Reports included the type of physical activity, as well as its duration (mins) and intensity (modified CR-10 RPE scale) and is reported as Arbitrary Units (AU)= duration x intensity.

Participants were asked to rate their average pain over the past week when performing Achilles tendon loading exercise on an 11-point numerical rating scale with 0 representing “no pain” and 10 representing the “worst pain imaginable.”

Pain mapping was used to ensure symptoms were localised to the tendon when performing a loading task.[20] After completing a series of five single leg hops, participants were asked to draw the location of their pain on a pain map of the posterior ankle using their finger on a tablet. Each location of pain was then transformed into a round figure and then all figures were superimposed as a single figure within Adobe Illustrator 20.0.3 (Adobe Creative Cloud, Adobe Inc, 2019) to construct a combined pain map of all participants.

All treatments occurring within the past 12 weeks, other than those resulting in study exclusion, were recorded for participants.

Participants were asked to rate their pain with 5 consecutive single leg hops on an 11-point numerical rating scale (NRS) with 0 representing “no pain” and 10 representing the “worst pain imaginable.” Participants were cued to hop on the spot as high as possible at a comfortable pace and to land on the forefoot without the heel touching the floor to maximise the stretch-shorten load through the Achilles tendon.

The Victorian Institute of Sport Assessment – Achilles (VISA-A) was used to assess participants Achilles tendon specific disability.[21] The VISA-A is a reliable and validated patient-reported outcome measure for the assessment of pain and function with a maximum score of 100 representing no tendon related disability.[21]

Fear of movement was assessed using the Tampa Scale of Kinesiophobia (TSK), a patient-reported outcome measure commonly used in chronic lower back pain research[22] that is now being used in other musculoskeletal pain conditions . The TSK has a cut-off of greater than 37 points used to represent maladaptive fear of movement.[23]

Patient perception of improvement over the course of the study was measured via the 7-point Patient Global Impression of Change (PGIC) scale, with options ranging from very much worse to very much improved.[24] The PGIC was only used to assess perceived change at follow-up.

Pressure pain thresholds were used as the test stimulus and determined using a manual algometer with a 1cm diameter, circular tip (Force Ten™ FDX digital force gage, Wagner Instruments, Greenwich, CT; annually calibrated). All assessments were performed by the same examiner (MM), an experienced physiotherapist with over five years of experience and having received training in assessment of the CPM effect using an identical procedure to that previously reported (Appendix C).[15]

The conditioning stimulus used was the cold pressor test and involved a bucket of ice water that was placed next to the participant with the temperature maintained as close to five degrees Celsius as possible (range 3-6 degrees). Participants immersed their hand to the level of the wrist, selected as contralateral to the painful Achilles. Their hand remained immersed until instructed to remove by the examiner (180 seconds) or the participant voluntarily removed the hand as a result of intolerance to cold. However, no participants removed there hand prior to 180 seconds.

The test stimulus was assessed at the Achilles tendon at baseline, 60 seconds and 180 seconds after hand immersion. Mean follow-up PPT was calculated from these values (60 seconds and 180 seconds) and the CPM effect was calculated as the difference between the mean follow-up and baseline PPT values. A negative value (e.g. -25) reflects an increase in the PPT after introduction of the conditioned stimulus (i.e. a reduction in the mechanical sensitivity).[15] The **absolute** CPM effect refers to the difference in N/cm^2 from baseline and after introducing the conditioning stimulus whereas the **relative** CPM effect refers to the percentage difference after introducing the conditioning stimulus.[15] Reliability of the CPM testing procedure for this assessor has previously been reported as ICC (3,1)(95% confidence interval- 95%CI) as 0.99 (0.95-1.00) and 0.96 (0.83-0.99) for parallel and sequential paradigm testing of the Achilles tendon, respectively.[15] This results in a relative CPM effect standard error of the measurement of 2.21% and 3.97% for parallel and sequential paradigm testing, respectively.[15] If the relative CPM effect was greater than the SEM and reduced PPTs it is

187 referred to as **meaningful**, if the relative CPM effect was greater than the SEM but increased PPTs or
188 was not greater than the SEM it is referred to as absent**.** [25]

189 Power calculations were performed in G.Power to determine the sample size needed for within group,
190 single arm pre/post parametric t-tests using the relative CPM effect calculated from the data provided
191 in Tompra et al.[9] (appendix A) With α=0.05 and β=0.8 it was determined a sample size of 25 would
192 be required.

193 All demographic data are presented as mean, median, standard deviation (SD) and range as
194 applicable. Data from outcome measures are presented as count, frequency, mean, SD, median and
195 range as applicable. The effect size (Cohens D) and 95%CI were calculated for all measures assessed
196 at baseline and follow-up (https://www.psychometrica.de/effect_size.html). The influence of potential
197 factors on the CPM effect (participant age, participant gender, duration of the condition, BMI,
198 physical activity levels, Achilles tendon related disability, fear of movement, pain with function/
199 loading, baseline pain over time, pain due to the conditioning stimulus) would be explored using
200 generalised estimated equations however these were not performed due to a small sample size. The
201 relationship between the change in the VISA-A and the relative CPM effect from baseline to follow-
202 up are presented graphically and tests of correlation were not performed due to low numbers.

203

RESULTS

Between 01/06/2017 and 01/03/2020, 215 participants presented for this Achilles tendinopathy research and were screened for inclusion. Of all screened participants, 9 were identified as having no confounders, with only localised mid-portion pain on the loading tests. The reasons for exclusion of remaining participants are presented in Figure 1 with the detailed reasons presented in Appendix D.

Nine participants (4 female, 5 male) were included at baseline. All baseline demographic and outcome measure data are presented within Table 1 as mean, SD, median and minimum to maximum. All participants had a meaningful CPM effect. All participants had pain localised to the Achilles tendon (during tendon loading) with the combined pain patterns depicted in Figure 2. Only 1 of the 9 participants reported having had any previous treatment (not resulting in exclusion) which was a stretching program, which was not considered to have significant influence on our outcome measures.

Six participants (2 female, 4 male) completed both baseline and follow-up testing and were included within analysis of within group change from baseline. The mean (SD) baseline, follow-up and within-group differences for physical activity level, average pain with tendon loading over the past 7 days, pain with tendon loading activity, tendinopathy related disability, fear of movement and the conditioned pain modulation effect are presented within Table 2.

Two participants reported being “minimally worse” after 12 weeks, 3 participants reported being “minimally improved” after 12 weeks and 1 participant reported being “very much improved” after 12 weeks.

While all participants reported being physically active at the time of injury not all were performing physical activity at the time of baseline assessment. Over the course of the 12 weeks there appeared to be an increase in physical activity levels due to a moderate effect size. However, due to the small sample size this estimate is not very precise.

Participants appeared to report relatively low levels of pain with loading over the past 7 days at baseline (mean NRS= 3.2/10), which reduced at follow-up (mean NRS= 1.2/10) representing a large effect size. However, due to the small sample size this estimate is not very precise.

Participants appeared to report relatively low levels of pain with single leg hopping at baseline (mean NRS= 1.8/10) which reduced at follow-up (mean NRS= 1.3/10) representing a small effect size. However, due to the small sample size this estimate is not very precise.

A small improvement in the VISA-A score from baseline to follow-up (mean= 7.7 points) was seen representing a small effect size.

Both baseline (mean=35 points) and follow-up (mean= 32 points) mean TSK scores were less than 37 points indicating no fear of movement. There was a small improvement in these scores over time representing a moderate effect size.

The distribution of the PPTs for both baseline and follow up assessments can be seen within Appendix E showing a decrease in sensitivity at both the 60 second and 180 second follow-up following application of the conditioning stimulus. There was a large effect size for changes in PPTs from baseline to follow-up suggesting a decrease in mechanical sensitivity of the Achilles tendon over time. There were also moderate to large effect sizes for changes in the absolute and relative CPM effect over time indicating a reduction in the size of the CPM effect. However, given the large changes in the baseline PPTs this may be confounded by that change and cannot be accounted for within analysis with our current sample size.

The relationship between change in the VISA-A score and the change in the relative CPM effect is shown in Appendix F and does not appear to demonstrate any association.

DISCUSSION

The present study aimed to quantify the CPM effect in people with mid-portion Achilles tendinopathy, determine if the CPM effect changed over time and to quantify the proportion of potential participants who would be appropriate for inclusion in a CPM study. We sampled a running population and given that between 34-47% of runners report a time loss injury at short-term follow-up,[12] we hypothesised that that we would have to exclude multiple potential participants due to the presence of a co-morbidity. We hypothesised that most of the included participants would demonstrate a meaningful CPM response.

We found that 206 (96%) potential participants who were screened for eligibility were not appropriate for inclusion within our study design. Specifically, 53.5% of participants were excluded as they had a confounder to assessment of the CPM effect meaning that even if they were included they would not have helped answer our research question. We observed that all included participants had a meaningful CPM effect at baseline suggesting that people with chronic, unilateral mid-portion Achilles tendinopathy and no other co-morbidities do not exhibit impaired endogenous analgesic mechanisms.

All nine participants in this study had a meaningful CPM effect at baseline. While the number of overall participants within this sample is low, this suggests it is unlikely that an absent CPM effect is common in people with mid-portion Achilles tendinopathy (when localised, load-related tendon pain is used as the diagnostic criteria).. This is the first study to report a meaningful CPM effect in a sample of individuals with mid-portion AT; whilst Tompra et al. have investigated this phenomenon, they did not report the proportion of participants who had a meaningful CPM effect [9]

The participants who completed the 12-week follow-up (n=6) appear to have a large reduction in mechanical sensitivity (Cohens d (95%CI) = 1.22 (-0.01 to 2.46)) and a large reduction in the relative CPM effect (Cohens d (95%CI) = 1.10 (-0.11 to 2.32)). However, given the large confidence intervals caution should be taken in interpreting these results. Additional caution in interpreting the changes in the relative CPM effect are needed without being able to model to determine the influence of how the

changes in mechanical sensitivity might have influenced the relative CPM effect given mechanical sensitivity is used to calculate the CPM effect.

This study excluded 96% of people presenting for inclusion. The most common reasons for exclusion were; failure to meet diagnostic criteria for Achilles tendinopathy (15.5%), presence of confounding other injury (14.1%), previous injection therapy (13.6%), previous conservative management (11.2%), insertional Achilles tendinopathy (9.2%) and not being physically active (7.3%). Of interest, the original Achilles tendinopathy CPM study had only excluded 33% of people presenting with only the two the following reasons; not Achilles tendinopathy or symptoms of less than 3 months, and included people with heterogenous pain locations.[9] This sample had different inclusion and exclusion criteria to our current study (for example our study excluded all regions of persistent pain, not just lower limb complaints) and this may explain the differences in results (Achilles tendinopathy group baseline mean (SD) relative CPM effect was -24% (12.7) whereas in our study the mean (SD) relative CPM effect was -40.5% (32.7)).

We recognise that the inclusion and exclusion criteria presented within our study may not reflect all people who have Achilles tendinopathy (for example we excluded participants with concurrent lower back pain). However, for basic science research investigating centrally driven pain modulatory mechanisms having a clean sample is vital to understanding the condition and making conclusions from the data specific to the pain condition of interest.[1 6 15] This study design allows us to make the conclusion that it is the condition of interest, Achilles tendinopathy, and not other persistent pain conditions participants may have which is associated with meaningful, or absent, CPM effects.

The most significant limitation of this study is the small sample size (n=9). Given that this study recruited over more than a two-year period with more than 200 people screened for inclusion, our small final sample was homogeneous, including participants with only chronic, unilateral mid-portion Achilles tendinopathy and no other confounders. This strategy removed confounders that may impact our objective of ascertaining whether chronic mid-portion Achilles tendinopathy results in an absent CPM effect. Due to the small sample size we were also unable to perform any statistical analysis or control for confounding variables (e.g. participant gender, physical activity levels)[26 27] which would

303 be suggested in pain science research.[6 15] This study also collected the testing stimulus over the
304 painful Achilles and not in the upper limb which could be viewed as a limitation. However, given the
305 conditioning stimulus was applied to the upper limb (e.g. distal to the Achilles tendon) it is feasible
306 that changes in the PPT are from central processing changes. It has also been previously shown that
307 the CPM effect is not consistent between testing sites which decreases the value of inferences based
308 on comparing different testing regions[15 28 29] but future studies including multiple sites may strengthen
309 any inferences regarding central processing mechanisms.

310 Our recommendations to researchers designing a study investigating endogenous analgesic effects or
311 clinicians interpreting these results would be; 1) Strict screening procedures, ensuring participants
312 with confounding comorbidities are excluded, when undertaking CPM research. 2) analysis of the
313 CPM effect should account for potential confounders which are not excluded (e.g. participant gender,
314 physical activity levels), 3) reporting of the CPM effect should include absolute, relative and
315 meaningful change to avoid making erroneous conclusions about the presence or absence of
316 endogenous analgesic effects, and 4) diagnostic criteria for including participants should be clearly
317 stated to facilitate replication of research and translation.

CONCLUSION

This pilot study was able to demonstrate that of participants with unilateral, mid-portion Achilles tendinopathy included, all had a meaningful CPM effect. Achilles tendinopathy was diagnosed using criteria of localised, load-related tendon pain, and not palpation pain or imaging.[30] Our suggestion to clinicians would be that based on this study and the revised analysis of Tompra et al.[9] the previously held assumption that mid-portion Achilles tendinopathy is associated with altered endogenous analgesia cannot be supported within a sample of participants who did not have confounders to assessment of the CPM effect. This pilot study demonstrated a large reduction in average pain over the last seven days with Achilles tendon loading, Achilles tendon PPTs and the CPM effect over 12-weeks, however caution is needed in interpreting these results due to the small sample size and wide confidence intervals. This pilot study was also able to demonstrate that a large proportion of people presenting for inclusion within mid-portion Achilles tendinopathy research are not appropriate for inclusion if the studies outcome measures relate to basic pain science. Due to the large number of participants presenting who had confounders to the CPM effect (such as chronic lower back pain or patellofemoral pain) it may be that deficient endogenous analgesic mechanisms are present within a clinical sample. However, based on this pilot study deficiencies in endogenous analgesia are unlikely to be primary causative mechanisms to the development of Achilles tendinopathy symptoms.

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437 **Table 1. Baseline variables (n= 9)**

	Mean	Standard deviation	Median	Minimum-maximum
Age (years)	42	9.3	41	30 to 54
Height (cm)	176.7	9.6	179	162 to 186
Weight (kg)	74.8	12.9	75	56 to 95
BMI (kg/m^2)	23.8	2.1	23.4	21.3 to 27.8
Duration of symptoms (weeks)	202.4	204.1	200	12 to 572
Physical activity level (AU)	228.3	378.8	90	0 to 1200
Average tendon pain with loading over past 7 days - NRS	3.3	2.2	3	1 to 7
VISA-A	59.7	13.4	63	44 to 80
TSK	36.8	5.4	37	24 to 43
Pain with single leg hop (NRS)	2.11	1.5	2	0 to 5
NRS- pain from conditioned stimulus	5.14	1.25	5	4 to 7.5
Achilles tendon PPT (n/cm^2)	58.8	23.3	55.5	30 to 106

CPM effect – absolute (n/cm^2)	-20.6	16.3	-14.8	-52.2 to -6
CPM effect – relative (%)	-40.5	32.7	-35.3	-100 to -6.8

438 BMI= Body mass index, AU= Arbitrary units, NRS= numerical rating scale, VISA-A= Victorian
439 institute of sport assessment – Achilles, TSK= Tampa scale of kinesiophobia, PPT= pressure pain
440 threshold, CPM= conditioned pain modulation

Table 2. Within group differences from baseline to follow-up (n= 6)

	Baseline mean (SD)	Follow-up mean (SD)	Mean difference (SD)	Cohens D (95% CI)
Physical activity level (AU)	290 (459.2)	585 (822.2)	295 (888.8)	0.44 (-0.70 to 1.59)
NRS- average tendon pain with loading over past 7 days	3.17 (1.9)	1.17 (1.6)	-2.0 (2.3)	-1.14 (-2.36 to -0.08)
VISA-A	58.8 (13.7)	66.5 (24.5)	7.7 (26.5)	0.388 (-0.75 to 1.52)
TSK	34.8 (5.5)	31.7 (7.3)	-3.2 (5.1)	-0.48 (-1.63 to 0.67)
NRS- pain with single leg hop	1.8 (1.2)	1.3 (1.8)	-0.5 (2.1)	-0.33 (-1.94 to 1.28)
NRS- pain from conditioned stimulus	4.5 (0.58)	5.0 (1.5)	0.41 (1.32)	0.44 (-0.71 to 1.59)
Achilles tendon PPT (n/cm^2)	56.5 (27.5)	91.9 (30.3)	35.4 (40.5)	1.22 (-0.01 to 2.46)
CPM effect – absolute	-18.6 (17.2)	-10.1 (10.3)	8.5 (26.1)	0.60 (-0.56 to 1.76)
CPM effect – relative	-39.3 (33.7)	-10.8 (14.3)	28.5 (43.9)	1.10 (-0.11 to 2.32)

Legend: SD= standard deviation, AU= arbitrary units, NRS= numerical rating scale, VISA-A= Victorian institute of sport assessment- Achilles, TSK= Tampa scale of kinesiophobia, PPT= pressure pain threshold, CPM= conditioned pain modulation.

446 **Figure 1. CONSORT Flow diagram**

447 **Figure 2. Combined pain maps**