Implicit motor imagery of the foot and hand in people with Achilles tendinopathy: a left right judgement study

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Running title: Left right judgement in Achilles Tendinopathy

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Keywords: Achilles, tendinopathy, left right judgement, pain, motor imagery, foot

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Abstract

Objective: To determine if impairment in motor imagery processes is present in Achilles tendinopathy (AT), as demonstrated by a reduced ability to quickly and accurately identify the laterality (left-right judgement) of a pictured limb. Additionally, this study aimed to use a novel data pooling approach to combine data collected at 3 different sites via meta-analytical techniques that allow exploration of heterogeneity.

Design: Multi site case-control study.

Methods: Three independent studies with similar protocols were conducted by separate research groups. Each study-site evaluated left/right judgement performance for images of feet and hands using Recognise© software and compared performance between people with AT and healthy controls. Results from each study-site were independently collated, then combined in a meta-analysis.

Results: 126 participants (40 unilateral, 22 bilateral AT cases, 61 controls) were include. There were no differences between AT cases and controls for hand image accuracy and reaction time. Contrary to the hypothesis, there were no differences in performance between those with AT and controls for foot image reaction time, however there were conflicting findings for foot accuracy, based on four separate analyses. There were no differences between the affected and unaffected sides in people with unilateral AT.

Conclusions: Impairments in motor imagery performance for hands were not found in this study and we found inconsistent results for foot accuracy. This contrasts to studies in persistent pain of limbs, face and knee osteoarthritis, and suggests that differences in pathoaetiology or patient demographics may uniquely influence proprioceptive representation.

Keywords: Achilles, tendinopathy, left right judgement, pain, motor imagery, foot

Introduction

Achilles tendinopathy (AT) presents as localised pain intimately linked with Achilles tendon loading, without spreading or localised pain at rest.(1) It is often a chronic condition and can be recalcitrant to treatment.(2) AT affects both athletic and sedentary populations throughout the lifespan, making it the most common tendinopathy(3) with a reported incidence of 2.35 per 1000 GP presentations.(4)

Little is known about the nociceptive driver in tendon pain and, like other musculoskeletal conditions, the pain experienced does not correlate well with tissue damage or imaging findings.(5) There is an incomplete understanding of the consequences of chronic AT outside of muscle and tendon changes, and a deeper understanding of any central nervous system changes may improve understanding and outcomes for this condition. The presence of sensory processing deficits in AT are conflicting – reduced tactile discrimination ability(6) and conditioned pain modulation (CPM)(7), but no differences in quantitative sensory testing when compared with pain-free controls.(8) In other chronic pain conditions, impairments in implicit motor imagery (tested via left right judgement [LRJ] tasks) have been observed,(9-12) but this has never been explored in people with AT. The LRJ task requires participants to view an image of a body part and decide whether the image shows a left or right part (or is rotated towards the left or right). This is achieved by mentally manoeuvring the image of the body in the brain to match the position of the body in the image, thus activating movement relevant areas including the supplementary motor and pre-motor area.(13) This task involves visuospatial processing, memory, and integration of sensory information.(14) The two main outcomes of the LRJ task are accuracy and reaction time. Accuracy on the task is thought to represent an intact proprioceptive representation for that body part (i.e., intact function of the cortical maps that coordinate and plan movement).(10) In contrast, reaction time is thought to provide information on the information processing resources delegated to that body part or side of space.(15, 16) Together such information on impairment of task performance is important given past work that has shown that improving LRJ performance via brain-targeted treatment (e.g., graded motor imagery) has positive clinical outcomes in some pain conditions.(17)

The aim of this study was two-fold: first, to investigate implicit motor imagery performance for images of the foot and of the hand (control) using a LRJ task in AT cases compared to pain-free controls; and second, to use a novel approach to combine data collected at three different sites via meta-analytical techniques that allow exploration of site heterogeneity. Given the persistence of pain in AT, we hypothesised that people with AT would be less accurate and slower to make LRJs for images of feet than healthy controls, but that the groups would not differ for images of hands. Further, we hypothesised that in those with unilateral AT, there would be a spatial difference between the affected and unaffected side, with LRJs being slower and less accurate for the images congruent with the foot of the affected side.

Materials and methods

This study collated data from three case-control studies, completed by different research groups. Each of the three studies were independently planned and implemented, but given similarities in objectives and methods identified during collaborative discussion, data were combined into a larger analysis. All studies were designed as case-control studies with an AT group and a pain-free control group. Ethical approval was received at each location: Monash University Research Ethics (ID: CF14/2034-2014001065), University of South Australia Human Research Ethics (ID: 0000034628) and University of Notre Dame Australia Human Research Ethics Committee (ID:011008F).

Participants

English speakers over the age of 18 years were recruited. Cases were required to have a diagnosis of symptomatic mid-portion or insertional Achilles tendinopathy (unilateral or bilateral). Symptomatic AT was defined slightly differently between study-sites:

For study-site 1 (University of Notre Dame), the inclusion criterion for the AT group was a clinical diagnosis based on the following diagnostic criteria: greater than a 6-week history of mid-portion Achilles tendon pain, concordant pain on tendon palpation, pain with or after tendon loading, morning stiffness, and a Victorian Institute of Sport Assessment-Achilles (VISA-A) score of less than 80/100.

For study-site 2 (University of South Australia), the diagnosis of AT was self-reported, as data were collected in an online questionnaire format, with no face-to-face contact with a researcher. Participants were asked whether they had “undertaken activity to elicit Achilles tendon pain in the previous 24 hours.”

Study-site 3 (Monash University) recruited people with localised pain at the AT insertion or mid-portion on a progressive load test of a single leg calf raise or hop with no restrictions on symptom chronicity duration.

Participants with AT at all three study-sites were excluded if they had a history of tendon rupture, previous lower limb surgery or other concomitant lower limb pathologies, were pregnant, or had other metabolic diseases (e.g. diabetes mellitus, rheumatoid arthritis, psoriasis). Study-site 2 also excluded participants if they had a diagnosis or suspected diagnosis of partial tear in the Achilles tendon.

At all study-sites, controls participants were required to have no current or past AT symptoms, no surgery in the preceding 12 months, no other current lower limb disorders and no other medical problems. Participant groups from study-site 3 were matched for age, sex, and activity level.

Recruitment

For study-site 1, cases were recruited via referrals from health professionals and through advertising amongst local sporting communities (Freemantle, Australia), whilst control participants were recruited from the local community (Freemantle, Australia). Study-site 2 recruited through advertisements on pain science websites (bodyinmind.org and noigroup.com), social media, presentations at conferences, and flyers at local sporting clubs in Adelaide. Study-site 3 recruited through social media and contacting physiotherapy clinics and clinicians in the Melbourne region.

Procedures

All three study sites used the experimental protocol for LRJ testing described by Bray & Moseley.(18) LRJ discrimination was assessed using Recognise © (NOI, Adelaide, Australia http://www.noigroup.com/). This program is reliable(10) and has been used previously for assessment of LRJ in a number of conditions.(9, 19) The program presents a series of pictures of body parts (for example, feet) in various positions. Participants are asked to determine whether the pictured feet belong to the left or right side of the body. Images of hands were also used as a control condition.

Three slightly different protocols were used. Study-sites 1 and 3 seated participants comfortably in front of a computer monitor with their forearms resting on the table and feet in a standardised position (figure 1). The “A” key was used to indicate a left hand/foot and the “D” key was used to indicate a right hand/foot. Instructions were not given on which fingers to use. The keyboard was positioned to ensure the A and D keys aligned with the middle of the computer monitor. Each picture was displayed for a maximum of 5 seconds and participants were instructed to identify the pictures as left or right as quickly and as accurately as possible. To eliminate assessor bias, standardised instructions were provided to each participant. Study-site 2 modified the original Recognise program for use in an online survey platform that was delivered to eligible participants at their own convenience. Because it was delivered online, the exact set up of the participant could not be controlled. The “F” and “J” keys were therefore used to encourage centralisation of positioning of the hands and body in front of the computer. The keyboard and computer were placed centrally within the participant mid-line given that bias in the allocation of attention to a spatially-defined location, as seen in many pain conditions, could influence responding(20). No further instructions were provided on how the participants were to position themselves, apart from sitting comfortably with their feet on the floor.

The images used in the judgements tasks for all study arms were comprised of left and right hands and left and right feet against plain backgrounds. Images of hands and images of feet were tested in separate blocks. Assessment sets contained 50 percent left-sided and 50 percent right-sided images. Images of varied magnitude of rotation and 'awkwardness' of limb position were randomly provided during each assessment set. Assessment sets contained 40 images as suggested by Bray & Moseley(18). Study-sites 1 and 2 completed a familiarization of 20 images and then 2 sets of 40 images each for the hand and the foot for formal testing. Study-site 3 completed a familiarization of 20 images and 1 set of 40 images for formal testing. Accuracy results (correct/incorrect) and reaction times (to the nearest tenth of a second) were exported as raw excel spreadsheets.

Approx. location of Figure 1

Data analysis

<u>Primary analysis:</u>

Given differences in recruited populations, inclusion criteria, testing methods, and the timing of when studies were conducted, we decided to separately summarise the results of each individual sub-study , and then collate these sub-study results together in a meta-analysis, allowing for formal evaluation of heterogeneity between study-sites.

Each of the three study-sites collated their own data returned from participants. For each participant, the number of correct responses was calculated and reported as a percentage correct for both hand images and foot images for each side (left/right; affected/unaffected). Average reaction time for hand images and feet images were calculated using trials for which correct responses were given. Any trials with reaction times less than 500ms were excluded, as this is quicker than human processing times and consistent with past protocols.(21, 22) Means and SDs were calculated for each group (control, unilateral AT, bilateral AT) for each outcome (accuracy and reaction time for foot and hand). Left and right values for each outcome were also averaged, and mean and SD calculated. No statistical testing was conducted within study-sites (only group mean and SD was calculated).

Data from all study-sites were then collated and analysed with a random-effects meta-analysis by an independent researcher (MG) who was not involved in any data collection; however the researcher was unblinded to group status. All meta-analyses were conducted in the statistical program R (v. 3.3.3, R Foundation for Statistical Computing, Vienna, Austria) using the 'metafor' package.(23) A random-effects model was used, given the subtle differences in data collection characteristics. Standardised mean differences (SMD) were calculated for all comparisons. Heterogeneity was indicated by the I^2 statistic, with 0-40% indicating heterogeneity might not be important, 30-60% moderate heterogeneity, 50-90% substantial, 75-100% considerable heterogeneity.(24) Separate meta-analyses were planned for outcomes of foot image accuracy, foot image reaction time, hand image accuracy and hand image reaction time, using the following group comparisons:

- *Analysis 1: Cases with AT compared to healthy controls*. Overall reaction time and accuracy values from all cases (unilateral and bilateral AT) were calculated by averaging performance for left and right images. This was completed for images of feet and for images of hands.
- *Analysis 2: Unilateral AT affected side versus healthy controls*. Past work has shown that people with bilateral neck pain are most impaired in LRJ performance (vs left-sided or right-sided pain),(25) thus we aimed to separately evaluate those with unilateral AT to confirm and supplement the above findings. Reaction time and accuracy values from those with unilateral AT (affected side only) were compared to those of healthy controls, separately for hand and feet images. Because not all data-sets provided information on hand dominance, the right side of controls was used for comparison. A sensitivity analysis using the left side of controls was then conducted, and visually inspected to identify any discrepancies.
- *Analysis 3: Unilateral AT – Affected side compared to the non-affected side*. This analysis aimed to determine if within-individual differences existed in LRJ performance, given that this pattern of impairment is seen in some conditions such as complex regional pain syndrome.(11) Such findings would suggest a high somatotopic specificity of impairment.
- Analysis 4: Bilateral AT compared to controls. If sufficient participants, this analysis planned to supplement and confirm Analysis 1 findings, using averaged performance for left and right images.

Exploratory analyses

Due to the inconsistencies in data collection, notably the omission of hand dominance in one dataset, a decision was made to conduct two exploratory analyses to evaluate the effect of 'location [side] of pain' where all data from each study cohort were combined together (without weighting).

First, the influence of pain location was explored for all outcomes, given that previous work has shown that people with left-sided pain (or bilateral) pain have more impaired LRJ performance than those with right-sided pain.(25) Specifically, four groups (Control, R sided AT, L sided AT and Bilateral AT) were compared using a Kruskall-Wallis test to determine if there were differences between group for left and right accuracy and reaction time, at the hand and the foot (8 comparisons). Non-parametric testing was chosen for more conservative estimates, and adjustments for multiple comparisons were made using the Benjamini-Hochberg method.(26)

Second, we explored whether impairment in LRJ performance might relate to the side of space from the mid-line of the body (e.g., altered performance for images of left hands *and* left feet). Stanton et al previously found an interaction effect for the side of pain on image accuracy in knee OA,(9) thus in people with unilateral AT, a 2 (painful side: left side versus right side) x 2 (image side: left sided images versus right sided images) repeated measures ANOVA was conducted. Values for image sides were calculated by summing together the foot and hand value from each side of the body (i.e. left foot accuracy plus left hand accuracy). This analysis was repeated for reaction time values. The alpha level for all testing was set at 0.05.

Results

Study-site 1 recruited 27 people of which 1 was removed due to corrupted data leaving 12 cases and 14 controls. Study-site 2 had 210 participants provide consent, however 103 did not complete the full online questionnaire (i.e., discontinued part-way through leaving incomplete data), and 26 were removed based on exclusion criteria, leaving 84 participants included in final analysis (45 cases, 39 controls). Study-site 3 recruited 8 cases and 17 controls, of which 8 were matched for analysis, and remaining data not used. In total 126 participants (n= 65 AT cases [43 unilateral, 22 bilateral], n=61 controls) were included for analysis (see Table 1, Appendix A).

Approx. location of Table 1

Primary meta-analyses:

<u>Analysis 1: Cases with AT compared to healthy controls.</u> When values for each side (left & right) were averaged (Figure 2 below, n=65 cases, 61 controls), no differences were seen between AT cases and controls in LRJ accuracy or reaction time for either of the images (hand and feet). gHeterogeneity as measured by I^2 was 0.0% in all analyses.

Approx. location of Figure 2

<u>Analysis 2: Control vs unilateral AT affected side</u>

People with unilateral AT (n=43) were significantly less accurate than healthy controls (n=61) for images of the foot only (SMD=0.68, 95%CI 0.05-1.31); see Figure 3. The sensitivity analysis, using the data from the left side of healthy controls, found conflicting results and showed no difference between AT cases and controls for foot accuracy (SMD= -0.06, 95%CI -0.49-0.38); see Supplementary Figure. There was no difference between groups for any other LRJ outcome.

Approx. location of Figure 3

Analysis 3: Unilateral AT Affected versus unaffected

The affected and non-affected side of unilateral AT cases are compared in figure 4 (n=43). No differences were seen between the affected and non-affected side for foot accuracy, foot reaction time, hand accuracy or hand reaction time. Heterogeneity was low (I^2 = 0.0%).

Approx. location of Figure 4

Analysis 4: Bilateral cases versus healthy controls

Due to limited numbers, this planned meta-analysis comparison was not conducted.

We conducted sensitivity power analyses, assuming an alpha level of 0.05 and a power of 0.80, we were powered to detect a moderate effect in the above analyses (SMD = 0.5, 0.56, 0.44 respectively).

Exploratory analyses

Data from each study cohort was combined, which included data from 61 control participants, 24 participants with right sided AT, 19 with left sided AT, 22 with bilateral AT.

Analysis 1: There were no differences between groups based on the location of pain (left-sided AT, right-sided AT, bilateral AT, and controls) for any of the outcomes: left foot accuracy (p=0.38); right foot accuracy (p=0.26); left hand accuracy (p=0.19); right hand accuracy (p=0.29); left foot reaction time (p=0.68); right foot reaction time (p=0.86); left hand reaction time (p=0.68); and right hand reaction time (p=0.68). See Figure 5A and 5B for accuracy and reaction time findings for each side, for accuracy and reaction time, respectively.

Approx. location of Figure 5A & 5B

Analysis 2: There was no spatially based LRJ performance impairment in people with unilateral AT. Specifically, there was no significant interaction effect found for side of pain on accuracy of left or right sided images (n=43, $F_{1,18}$=0.149, p=0.704). There was also no significant interaction effect for side of pain on reaction time of left or right images (n=43, $F_{1,18}$=2.454, p=0.135).

Discussion

This study presents data from three sub-studies evaluating implicit motor imagery performance in participants with AT compared with healthy controls. Foot reaction time, hand accuracy and hand reaction time were no different between unilateral cases and controls. We found inconsistent results regarding foot accuracy for unilateral AT cases compared with healthy controls. The primary analysis comparing unilateral AT performance for foot images (affected side) showed significantly worse performance than controls, which may represent impaired function of the working body schema (i.e.., proprioceptive representation) for the foot. However, this impairment was not found in sensitivity analyses. The unaffected side of AT cases was also not different to the affected side. Last, the exploratory analyses showed that there were no differences between healthy controls, and unilateral or bilateral AT. Together, these findings suggest that motor imagery performance is not impaired at the hand of individuals with AT, and at this stage the data is not sufficiently consistent to support impairment at the foot either.

Given the conflicting findings regarding the accuracy of LRJ in people with unilateral AT for images corresponding to the affected foot, no strong conclusions can be made. We did not observe widespread alterations in LRJ performance, or a spatial (sided) effect in people with AT. This is in contrast with previous work in musculoskeletal pain conditions. For example, people with leg pain (origin unspecified) were found to be significantly slower and less accurate at performing LRJs of feet images compared with healthy controls.(27) Further, Stanton et al(9) found that patients with lower limb pain (i.e., knee osteoarthritis) had impairments in accuracy for LRJ of foot images (compared with controls) but also side-specific impairment, such that performance was impaired for both hand and feet images that corresponded to the side of pain. Cartilage and tendon injury share similarities in pathoaetiology, however this structural approach does not account for the multitude of other factors that influence and contribute to pain experience, notably context, comorbidities, chronicity, socio-economic status and education status. Understanding how alterations in LRJ performance develop, and how these link to other factors (possibly explaining differences between conditions) is not known. Futher work is needed to understand whether there are are differences in the nociceptive drive between AT and OA, which may then also influence cortical representation of the affected limb. For example, given that walking is frequently painful in OA, it may result in long term potentiation and facilitation, demonstrated by studies previously in knee OA.(28, 29) However, only some people with AT have pain with walking – many athletes only have pain with high-level activities such as sprinting. This may lead to differences in the frequency of stimulation of the peripheral nerve and pain experience(8) Immobilisation has also been linked to altered left-right judgement, which could explain differences between different pain states and conditions.(30) Also, participants in the Stanton et al(9) study were significantly older than any of the cohorts in this study, which may have conflated the difference in findings as older age (>50) may lead to a decrease in performance on a left/right judgement task.(14) Increasing age leads to a variety of changes in neurocognition and sensory processing, which may lead to altered embodiment, potentially explaining these differences.(31)

As the left-right judgement task requires participants to mentally manoeuvre the limb to the position seen, proprioceptive input or output may also be linked to any impairments in the task. For example, in healthy participants, impairing proprioceptive input negatively influences performance on a motor imagery task.(32) Thus the findings here of a lack of LRJ task impairment in people with AT raise the possibility that proprioception is intact in this population. No studies to date have investigated proprioception in people with AT, with only two studies evaluating proprioception in surgically managed Achilles rupture patients.(33, 34) Both of those studies found impaired proprioception of the affected limb, but conflicting findings for the unaffected side. However the applicability to AT patients is questionable, given the differing pathoaetiology of rupture, as well as post-surgical effects on proprioception. Future studies to evaluate both proprioception and LRJ performance within AT cases appear warranted to better understand this condition. For example, unique impairment in proprioceptive capacity but not LRJ performance would suggest intact cortical proprioceptive processes but either impaired proprioceptive detection at the periphery or transmission in the spinal cord.

As well as sensory and motor processes, cognitive processes are also key to motor imagery tasks. This has important considerations for movement control and co-ordination, which call upon the same brain regions for motor planning and execution.(35) Studies have shown limited association between pain duration, severity or other measures of disability and left-right judgement task performance, and instead other cognitive factors and sensory integration may be more important.(36, 37) Our results suggest further work is needed in determining whether alterations in these processes are important to the clinical picture in AT, and how they might relate to symptom trajectory. While only a handful of studies have investigated sensory processing in AT to date, they do not support widespread alterations in sensory processing, though some peripheral impairments are seen at the site of pain.(7, 8)

One of the key limitations of this research is that we did not ascertain duration of symptoms, as well as the fact that we did not measure any other key outcomes such as proprioception, strength, sensorimotor processing or cognitive ability. It is possible that symptom duration may have affected findings, as previous work in back and neck pain has shown first time back pain cases did not have impaired LRJ performance compared to controls but more chronic cases did.(21, 25) Further work is required to investigate proprioception in AT, determine whether cognitive, psychological or sensorimotor deficits are present, and how these might relate to motor imagery, movement and disease progression in this condition. For clinicians our findings suggest that measuring left right judgement performance or targeting implicit motor imagery with specific training may not be required as part of assessment or treatment of AT. However, it is important to note that our present meta-analytic findings were powered to detect a moderate effect, meaning that we may have missed detecting differences between groups and/or limbs should the effect be smaller. It is unclear at present whether the size of implicit motor imagery impairment is important to movement dysfunction, pain levels, or response to brain-based treatment, or, whether any impairment might be relevant.

Our study is one of the first to also consider bilateral musculoskeletal presentations separately, and we found no difference between cases and controls, though this was limited by a small sample size. Our findings of a lack of heightened impairment in those with bilateral cases (and if any impairment potentially exists, it occurs in unilateral cases) is not supported by past work evaluating LRJ performance in people with neck pain where bilateral neck pain cases were most impaired.(25) AT often presents bilaterally, and changes in tendon structure are also often seen bilaterally (even in unilaterally symptomatic cases),(38) yet it is not known whether unilateral or bilateral pain states differ in their pathoaetiology or manifestations. Given that no other studies investigating sensory processing have evaluated bilateral presentations of lower limb tendinopathy, it is therefore unclear whether any significant differences in sensory processing exist between unilateral and bilateral cases beyond our findings.

There were additional limitations that should be considered in this study. While this is one of the largest cohort of laterality research to date, this was achieved by combining 3 smaller study-sites in a meta-analysis. Care was taken by each research group to minimise risk of bias and error and use of meta-analysis methodology was purposeful to weight samples based on size. While data collection was conducted in different locations at different times, which could feasibly influence the results, such methodology may also be considered a strength – amalgamating data from two studies based in laboratories and one online study increases the generalisability of results. This novel approach provides opportunity for research groups to combine data to answer research questions, and to limit research waste. Given that complete demographic data were not available for all study participants, our analyses were limited to those of simple pooling. Complete demographic data could not be obtained for one study, however we thought it best to proceed with including the data set as is, with maximum transparency, to avoid any bias by selection of included participants. Several participants did not fully complete data collection at study-site 2, and we could not determine whether these participants were significantly different from those included in the study. Diagnosis of AT was also self-reported at study-site 2, which could lead to population heterogeneity, however the online data collection method allowed for a larger sample size to be recruited to ensure adequate power. There were slight differences in age between study cohorts, the importance of which is unknown in adults (though as accuracy increases with age in children(39), it seems it may decrease again with older age(14)). Given the unique task and technology involved, it is possible that age may impact on laterality recognition, however neither study showed significantly different results between variables analysed. Future studies should investigate, whether activity level and chronicity are important influencers of results, use tighter inclusion criteria and defined diagnosis (though there is no consensus for this in tendinopathy) and standardise protocols. Increased reporting standards have since been recommended in tendinopathy research including more detailed demongraphic details such as athletic status, comorbidities) to facilitate reproducibility of research and clinical translation (40).

Conclusion

This paper evaluated whether people with AT differ in their left/right judgement performance compared with healthy controls by combining three data-sets. Overall, we found no consistent differences in accuracy or reaction time in left-right judgement between limbs in people with AT, or compared to healthy control participants.At this stage, given conflicting findings, it is unclear if AT patients have impaired working body schema (proprioceptive representation) of their affected foot. Further prospectively designed studies are needed to confirm the findings from this paper, and to understand whether pain chronicity, activity level and other demographic factors may influence any findings.

Figure Legend:

Figure 1: Participant positioning for testing of laterality recognition in study-site 1 & 3.

Figure 2: Meta-analysis with values for each side averaged for AT cases compared to healthy controls

Figure 3: Meta-analysis comparing the affected side of unilateral AT cases to controls (Right side)

Figure 4: Meta-analysis comparing the affected and unaffected side for unilateral AT cases

Figure 5A & 5B: Exploratory analysis comparing accuracy and reaction time between the location of pain (left sided, right sided or bilateral AT).

Supplementary Figure: Meta-analysis comparing the affected side of unilateral AT cases to controls (Left side)

Author Declaration: EKR, TRS, BMW, JRD, MJC, JC & GLM. conceived the research project. EKR, KC, TSR, MVW, JDR, BMW, PB, AJM were responsible for data collection. MG was responsible for data collation and analysis. EKR, TRS, MG interpreted the findings. All authors discussed the results and commented on the manuscript.

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Conflicts of Interest: TS received travel and accommodation support from Eli Lilly Ltd for speaking engagements (2014; unrelated to the present topic). In the last 5 years, GLM has received support from: ConnectHealth UK, Seqirus, Kaiser Permanente, Workers' Compensation Boards in Australia, Europe and North America, AIA Australia, the International Olympic Committee, Port Adelaide Football Club, Melbourne Football Club and Arsenal Football Club. Professional and scientific bodies have reimbursed him for travel costs related to presentation of research on pain at scientific conferences/symposia. He has received speaker fees for lectures on pain and rehabilitation. GLM receives book royalties from NOIgroup publications, Dancing Giraffe Press & OPTP. ER is supported by an NHMRC Early Career Fellowship.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration. Ethical approval was received at each location: Monash University Research Ethics (ID: CF14/2034-2014001065), University of South Australia Human Research Ethics (ID: 0000034628) and University of Notre Dame Australia Human Research Ethics Committee (ID:011008F).

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