Title: Divergent sensory phenotypes in non-specific arm pain: comparison with cervical radiculopathy

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ABSTRACT

Objective: The primary research question under review was whether distinct sensory phenotypes were identifiable in individuals with non-specific arm pain (NSAP) and if they differed from people with cervical radiculopathy. A secondary question considered whether the frequency of features of neuropathic pain, kinesiophobia, high pain ratings, hyperalgesia and allodynia differed according to sub-groups of sensory phenotypes.

Design: A cross sectional study

Setting: Higher education institution

Participants: Forty office people with NSAP, 17 with cervical radiculopathy, and 40 age-gender-matched healthy controls.

Interventions: Nil

Main Outcome Measures: Participants were assessed using quantitative sensory testing (QST) comprising thermal and vibration detection thresholds, and thermal and pressure pain thresholds; clinical examination and relevant questionnaires. Sensory phenotypes were identified for each individual in the patient groups using z-score transformation of the QST data.

Results: Individuals with NSAP and cervical radiculopathy present with a spectrum of sensory abnormalities; a dominant sensory phenotype was not identifiable in individuals with NSAP. No distinct pattern between clinical features and questionnaire results across sensory phenotypes was identified in either group.

Conclusion: When considering sensory phenotypes, neither individuals with NSAP nor cervical radiculopathy should be considered homogenous. Therefore, people with either condition may warrant different intervention approaches according to their individual sensory

phenotype. Issues relating to the clinical identification of sensory hypersensitivity and the validity of QST are highlighted.

Abbreviations: QST: quantitative sensory testing; NSAP: Non-specific arm pain; LANSS: Leeds assessment for neuropathic symptoms and signs

Keywords: Sensory threshold; pain threshold; non-specific arm pain (repetitive strain injury); cervical radiculopathy; musculoskeletal arm pain.

INTRODUCTION

Work related upper limb disorders are a significant public health problem with a prevalence of 29% (Eurostat),[1] 50% of which are described as non specific.[2] Non-specific arm pain (NSAP) commonly affects computer users and is frequently associated with poor prognoses.[3] The absence of consistent information regarding the pathology and pathophysiology underlying NSAP has obvious implications for clinical decision making. Given growing computerisation of the global workforce as well as the intensification of work, improving our understanding of work related non-specific conditions is imperative for improving intervention selection and outcomes.

Quantitative sensory testing (QST) is a non-invasive means of assessing sensory and pain perception, which potentially provides insights into underlying pathophysiological mechanisms of a condition,[4] and has seen growing use in the investigation of patient populations such as complex regional pain syndrome, whiplash and neuropathic pain.[5-10] In studies of NSAP, the presence of hypoaesthesia to vibration has previously been recorded,[11-13] which may suggest the presence of a minor neuropathy[11 12] and/or altered central processing,[13] possibly secondary to pain.[14] Furthermore, we recently reported the presence of sensory hypersensitivity to pressure, cold and heat as characteristic of NSAP, while hypoaesthesia to vibration explained a small percentage of the variance (11%).[15] In addition, in comparison to people with cervical radiculopathy and healthy controls, people with NSAP had normal thermal detection thresholds, whereas sensory hypoaesthesia, to both thermal and vibration stimuli, was evident in people with cervical radiculopathy.[15]

The German Research Network on Neuropathic Pain has suggested that detailed analyses of sensory profiles may yield information regarding the underlying sensory phenotype in individuals and within patient populations and that this may help to direct clinical decision making.[16] They presented data from a large group of people with various neuropathy and neuropathic pain conditions with key sensory phenotypes identified i.e. sensory loss, sensory hypersensitivity, both sensory hypersensitivity + sensory loss and no abnormality.[6] Each of the phenotypes was represented both within each patient population and across the different conditions studied.[6] A further study by Gierthmühlen et al.[5] identified the presence of different sensory phenotypes in people with complex regional pain syndrome, with some people exhibiting increased sensitivity while others demonstrated decreased sensitivity to

thermal and mechanical stimuli; thus, comparison of mean values may not thoroughly represent sensory findings in patient groups. Therefore, while results from between group comparisons identified the presence of sensory hypersensitivity as well as hypoaesthesia to vibration in NSAP, the presence of various sensory phenotypes or indeed a dominant sensory phenotype is not yet known in this group.

The use of QST in clinical practice has limitations in that equipment is not widely available and as such, understanding the relationship between QST findings and clinical features of pain and clinical signs of sensory loss or sensory hypersensitivity is important. Previous reports suggest that pain and disability ratings are poorly correlated with QST findings;[17] however, data on the relationship between clinical features of pain in study populations sub-grouped according to sensory phenotype is lacking and warrants further investigation.

The primary research question under review in this study was whether distinct phenotypes are identifiable in NSAP and if they differ to cervical radiculopathy, a known neuropathic disorder. A secondary question considered whether the frequency of features of neuropathic pain, kinesiophobia, high pain ratings, hyperalgesia and allodynia differed according to sub-groups of sensory phenotypes. We hypothesised that individuals with NSAP would present with a spectrum of sensory phenotypes within the group and that group sensory phenotypes would differ between NSAP and cervical radiculopathy. We also hypothesized that people with sensory hypersensitivity on QST would present with higher pain ratings, clinical features of hyperalgesia and higher scores on kinesiophobia and neuropathic pain screening scales.

METHODS

Design

A cross-sectional observational study investigating sensory profiles in participants with NSAP, cervical radiculopathy and healthy controls was undertaken. Volunteers were screened for inclusion criteria for each particular group, the criteria for which have been previously reported.[15] Subsequently, participants underwent a physical examination and QST and were asked to complete a series of questionnaires for self-reported pain features and kinesiophobia. All aspects of group allocation and data collection were performed by one investigator (NM). The order of QST testing was randomized. The study was approved by the Human Research Ethics Committee for Life Sciences in University College Dublin and the

involved hospitals. All participants were unpaid volunteers and all provided written informed consent before inclusion.

Participants

In relation to NSAP, volunteers with arm pain, aged between 18-65 years old that were recruited from metropolitan hospitals, medical and physiotherapy practices and via a multi-media campaign were screened for inclusion in this study (through a medical history and physical examination). Participants were assigned to the NSAP group if they had pain in the arm in the absence of a specific diagnosis,[18] were office workers who had significant upper limb pain as defined by a numerical pain rating of ≥3/10,[19 20] for longer than 3 months, who spent more than 40% of their working week using desktop equipment,[12] and who had been employed using desk-top equipment for at least two years.[21]

Participants with possible cervical radiculopathy were recruited from metropolitan hospitals as well as medical and physiotherapy practices. They were assigned to the cervical radiculopathy group if they had *all* of the following: radicular pain in the upper limb (≥3/10),[19 20] a positive upper limb neurodynamic test, a positive Spurling's test, MRI confirmation of nerve compression,[22-24] as well as at least one concordant clinical sign of conduction loss[25] (i.e. one of diminished/absent reflexes, myotomal weakness or sensory loss in a dermatomal pattern).

Control participants were included if they did not have a history of significant neck, scapular or shoulder pain over the previous 12 months and did not use desktop equipment for more than 40% of their working week.[12] As participants from the cervical radiculopathy group were older than the non-specific arm pain group, control participants were age- and gender-matched to each group.

Volunteers were excluded from the study if they had any of the following: generalized neurological disorders, generalized musculoskeletal/inflammatory disorders, a history of low back pain and/or low back related leg pain over the previous six months, a history of migraine over the previous six months, previous trauma to the upper quadrant, diabetes, endocrine disorders, epilepsy or if they had been diagnosed with any mental health / psychiatric disorders.

Measurements

Sensory assessment

A previously published QST protocol was undertaken[26] measuring the following parameters: cold, warm and vibration detection thresholds; cold, heat and pressure pain thresholds. All measures were recorded on three sites on each upper limb. Thermal and vibration tests were performed using a NeuroSensory Analyser (TSA 2001 II Medoc, Israel). For thermal testing, a Peltier thermode (16 x 16mm) was attached directly over sites in the hand innervated by C6, C7 and C8. A Vibrameter (VSA 3000 II 2001 Medoc, Israel) was used to measure vibration thresholds with readings taken over sites of the hand innervated by C6, C7 and C8. Pressure pain thresholds were determined using a hand held pressure algometer with a probe size of 1cm² (Somedic AB, Farsta, Sweden) and an application rate of 40 kPa/s over the median nerve (cubital fossa), ulnar nerve (between olecranon and medial epicondyle of the humerus) and radial nerve (mid-lower third of the humerus). Triplicate recordings were taken at each site for all QST parameters and the mean values used for analyses. In order to assess the presence of widespread sensitivity, thermal testing and pressure pain thresholds were recorded at a site remote from the upper quadrant, in this case, unilaterally over Tibialis anterior muscle. All aspects of QST have been found to have acceptable reliability.[27-29]

Hyperalgesia to pin prick was assessed by recording pain responses to a pin-prick stimulus applied in the affected area compared to an unaffected area i.e. the contralateral limb where possible, otherwise the nearest pain-free area was used. The presence of hyperalgesia was determined if the response in the affected area was more painful than in the unaffected area.[30] Allodynia was assessed by moving a brush over the affected area and comparing the response to that in an unaffected area. The stimulus was applied with a single light stroke of at least 2cm in length. Brush stroke allodynia was considered present if the participant reported the stimulus as painful.[30]

Self-reported measures of pain and fear avoidance

All participants in the patient groups completed the following questionnaires: the Leeds Assessment for Neuropathic Symptoms and Signs (LANSS) questionnaire with a score of ≥12 (out of 24) indicating the possible presence of neuropathic pain;[31] the Tampa Scale of Kinesiophobia [32] with a score of ≥37 (out of 68) considered to indicate the presence of significant fear-avoidant pain beliefs,[33] and all provided an average numerical pain rating (NPRS) for the previous 24 hours.

Data Analysis

Data were analysed using SPSS software, version 19.0 (SPSS, USA).

Preliminary data management

QST data were log-transformed before statistical analyses in order to achieve normal distribution of the data,[4] which subsequent analysis revealed was successful. Friedman's tests were used to assess the effect of test site between upper limb sites (C6, C7 & C8 dermatomes or median, ulnar & radial nerves) for QST parameters. As no significant differences were identified for QST parameters between these sites, data were averaged and the resultant value used for subsequent analyses.

Z-transformation

To compare sensory phenotypes of individuals with NSAP or cervical radiculopathy with age-matched healthy controls, QST data were z-transformed to generate z-scores, which allows scores from individuals with a condition to be directly compared to 'normals' in order to identify any abnormality in that individual, as has been previously advocated for assessment of individual sensory profiles.[6 16] QST data were z-transformed using the mean (SD) of their respective control group as reference data i.e. control participants were divided into two groups; one group of 40 participants matched, according to age and gender, to the 40 participants with NSAP and a further group of 14 participants matched to the cervical radiculopathy group. The formula used for z-transformation was: Z-score = (X single participant – Mean controls) / SD controls.[4] For clarity of data presentation, the algebraic sign of the resulting z-score was adjusted appropriately so that it reflected patients' sensitivity for each parameter i.e. values above zero indicated increased sensitivity to the tested stimuli; values below zero indicated reduced sensitivity to the tested stimuli.

Sensory phenotypes for each participant were assessed by generating sensory phenotype graphs using resultant z-scores. *Z*-scores of > 1.96 was considered indicative of increased sensitivity to the tested stimuli compared with controls (hyperalgesia/allodynia), while z-scores of < -1.96 was considered indicative of sensory loss.[6] Each individual was classified according to their sensory phenotype into one of six possible phenotypes: (1) sensory $loss_{small}$ i.e. small fibre sensory loss as determined in this study by the presence of cold and/or warm hypoaesthesia; (2) sensory $loss_{large}$ i.e. large fibre sensory loss as determined by the presence of vibration hypoaesthesia; (3) sensory $loss_{mixed}$ i.e. a combination of small and large fibre sensory loss; (4) sensory hypersensitivity as determined by the presence of hyperalgesia in response to cold pain, and/or heat pain and/or pressure pain thresholds; (5) a combination of

sensory hypersensitivity + sensory loss, and (6) no abnormality.[6] When sensory hypersensitivity was recorded, data were inspected to see if hypersensitivity was localised to upper limb sites or if it was widespread i.e. included sensory hypersensitivity at the Tibialis Anterior site.

The frequencies of different sensory phenotypes in each patient group were recorded and between-group comparisons of sensory phenotypes were conducted using percentage risk difference with 95% confidence intervals.

Sample size:

The sample size was calculated based on mean and standard error vibration threshold data from a study by Greening et al., (2003). A sample of size of 40 participants with NSAP, 40 participants with cervical radiculopathy and 40 matched control subjects was required to detect a medium effect size (0.5) with 0.8 power and 0.05 two tailed significance level.

RESULTS

Characteristics of NSAP and cervical radiculopathy groups

The baseline characteristics of participants are presented in Table 1. The groups were similar with regards to pain duration; however, the cervical radiculopathy group were older ($p<0.001$) and more disabled ($p=0.002$) than the NSAP group. The cervical radiculopathy sample was smaller than anticipated (n=17), primarily due to the strict inclusion criteria. The control group for the NSAP group comprised of 40 age- and gender- matched healthy people, while the control group for the cervical radiculopathy group comprised of 14 age- and gender- matched healthy people.

Individual sensory phenotypes are presented in Table 2. Overall, both groups presented with divergent sensory phenotypes; 45% of the NSAP group and 35% of the cervical radiculopathy group presented with the phenotypes ‘sensory hypersensitivity’ and ‘sensory hypersensitivity + sensory loss’. A further 30% of both groups had evidence of ‘sensory loss’. No sensory abnormality was evident in 25% (n=10) of the NSAP group and 35% (n=6) of the cervical radiculopathy group.

Results from risk difference analyses revealed no significant differences between the groups with respect to the frequency of sensory phenotype. Equal numbers of participants presented with localised and widespread sensory hypersensitivity in both groups.

Clinical features and questionnaire results across sensory phenotypes

The frequency of LANSS scores ≥12, Tampa scale of kinesiophobia scores ≥37, pain >/<5/10, hyperalgesia and allodynia across each sensory phenotype in both patient groups is depicted in Table 3. No distinct pattern was evident with respect to the representation of questionnaire results, high pain levels or clinical measures of hypersensitivity across sensory phenotypes in either patient group. Those with widespread sensory hypersensitivity did not present with higher scores on any clinical measure than those with localised or no sensory hypersensitivity.

DISCUSSION

Sensory phenotypes in NSAP and cervical radiculopathy

The results of this study provide evidence of bi-directional sensory abnormalities in individuals with NSAP with evidence that a distinct sensory phenotype is not evident in these individuals. While bi-directional sensory abnormalities were also evident in individuals with cervical radiculopathy, it was notable that 35% of the cervical radiculopathy group presented with no sensory abnormality using QST. The presence of bi-directional sensory abnormalities in both groups in this study is consistent with data from a similar cohort of people with neck and arm pain,[34] as well as other cohorts with neuropathies and complex regional pain syndrome.[5 6] This further supports the argument for assessment of sensory phenotypes in patient populations on the basis that heterogeneity with respect to sensory phenotypes exists within patient cohorts; hence, people with the same condition could warrant different approaches to assessment and treatment.[6 35]

The identification of different sensory phenotypes within NSAP is an important finding. Whilst we previously reported group data indicating that sensory hypersensitivity was a key characteristic in this group,[15] the current findings indicate that just over 50% of the NSAP group did not have signs of sensory hypersensitivity and presented with either sensory hypoaesthesia or no sensory abnormality. The identification of the absence or presence of sensory hypersensitivity is important as the presence of sensory hypersensitivity has been shown to be a predictor of poor prognosis and poor treatment response in other musculoskeletal populations, [7 38 39] and thus, may be an important consideration in NSAP and cervical radiculopathy. Further, the presence of sensory hypersensitivity is important clinically in considering appropriate interventions in order to prevent acute exacerbations of symptoms. For example, people with sensory hypersensitivity have previously been shown to have less effective descending pain modulation in response to exercise;[40] therefore, selected

exercise dosages would need careful consideration in a patient with a dominance of sensory hypersensitivity. However, for those identified with sensory hypoaesthesia or no sensory abnormality, it is possible that their prognosis is more favourable, although prospective studies are required to elucidate this further.

Almost half of the NSAP group and 35% of the cervical radiculopathy group in this study presented with sensory hypersensitivity, which likely reflects mechanisms of peripheral and central sensitisation. In addition, 27% of the NSAP group presented 'sensory loss + sensory hypersensitivity'. This may reflect the interplay between the mechanisms of hypoaesthesia and hypersensitivity. The presence of pain has been shown to cause an increase in detection thresholds;[14] in contrast, the presence of neuronal insult, as has been suggested in NSAP[36] may lead to sensitisation of peripheral and central pathways.[37] Both scenarios could explain the presentation of sensory hypersensitivity in addition to sensory loss.
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Clinical features and sensory phenotypes

How to identify sensory hypersensitivity in clinical practice is an important consideration. Currently, there are neither established guidelines nor validated measures to do this and whether QST could fill this void is hampered by the limited availability of equipment in clinical practice, as well as the large variability in normative data and lack of established cut-off values. Recent guidelines for the assessment of neuropathic pain recommend that if QST is used in clinical practice, it should only form part of an overall clinical assessment.[42] This raises the question whether self-reports of pain intensity and features of bedside examination are valid means of assessing sensory hypersensitivity. Previous meta-analysis indicated that QST measures of sensory hypersensitivity and self-reported pain and disability were poorly correlated; [41] however, it was highlighted in that study that many of the study participants included in the analysis may not have been sensitised, in which case a strong relationship between QST and self-reports of pain and disability would not be expected.[41] In the current study, we aimed to investigate whether particular clinical features would be more frequent among sub-groups of sensory phenotypes. Specifically, we hypothesized that higher levels of pain, higher scores on neuropathic pain and kinesiophobia questionnaires and clinical features of hypersensitivity (pin-prick hyperalgesia and allodynia) would be more evident in those with the phenotype 'sensory hypersensitivity'; however, we did not find a distinct pattern in

either the NSAP or cervical radiculopathy groups, even when comparing those with a sensory abnormality to those without a sensory abnormality.

Relatively few people with NSAP in this study (28%) presented with kinesiophobia with no demonstrable pattern noted across different phenotypes. The cervical radiculopathy group presented with kinesiophobia more frequently (59% of participants), with 24% of those with kinesiophobia demonstrating sensory hypersensitivity as their dominant sensory phenotype. Both groups had over 60% of participants presenting pain rating ≥5, but no discernible pattern was evident regarding which sensory phenotypes presented with higher pain ratings. Indeed, nine of the 13 people with no sensory abnormality in the NSAP group had a pain rating of ≥5. In considering these findings, it is important to note that the small sample size and particularly the small numbers in each subgroup, mean these data should be considered preliminary and as such, further studies on larger sample sizes are warranted.

Nonetheless, the challenge of how to assess the presence of sensory hypersensitivity in clinical practice without using QST remains. One reason for the poor relationship between QST and clinical measures may be that the clinical measures tested to date against QST are not measuring the same construct. Two clinical measures that may be useful are pin-prick hyperalgesia and brush stroke allodynia[43] but these measures were rarely positive in this study, despite the frequent presence of sensory hypersensitivity to other measures e.g. heat and cold. Recently, stronger correlations were identified between pain ratings on application of ice versus cold pain thresholds;[44] therefore, this may be a better clinical measure of cold sensitivity. A final consideration is that, QST, which quantifies responses to experimentally induced pain may evoke different central nervous system responses than spontaneous pain, normally experienced by patients, as has been demonstrated by brain imaging studies.[45] Therefore, the development of better clinical tools for the assessment of sensory hypersensitivity is needed. The recommendation that assessment of descending pain modulation and pain magnitude rating for a suprathreshold stimulus might facilitate a better understanding of a sensitized nociceptive system rather than threshold measures may also hold validity.[46]

Study Limitations

Due to the relatively small sample size of this study, particularly for cervical radiculopathy, and the small numbers in each sensory phenotype group, these results should be considered as preliminary findings.

Conclusion

The results of this study demonstrate divergent sensory phenotypes in NSAP as well as in cervical radiculopathy with implications for clinical decision making. NSAP and cervical radiculopathy should not be considered homogenous groups and individuals may warrant different intervention approaches according to their sensory phenotype. Researchers should also consider this when stratifying people for intervention studies. Identifying the presence of sensory hypersensitivity is difficult in clinical practice and while some studies have reported criteria for classifying pain;[47-49] validated tools are still lacking with further research needed in this regard.

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