# Title page

**Title:**

Mechanisms-based classifications of musculoskeletal pain: Part 1 of 3: Symptoms and signs of central sensitisation in patients with low back (± leg) pain.

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**Manuscript**

## 1. Introduction

As a mechanisms-based classification of pain, where pain is classified according to the dominant neurophysiological mechanisms responsible for its generation and/or maintenance, 'central sensitisation' pain (CSP) has been proposed as a category of pain distinct from other mechanisms-based classifications, such as 'nociceptive' pain (NP) and 'peripheral neuropathic' pain (PNP) (Lidbeck, 2002; Smart et al. 2008). Central sensitisation pain has been operationally defined as an amplification of neural signalling within the central nervous system (CNS) that elicits pain hypersensitivity (Woolf, 2011).

Central sensitisation refers specifically to those neurophysiological processes occurring at a cellular level throughout a widely distributed CNS, including the spinal cord and/or supraspinal centres (brainstem, thalamus, limbic system and cerebral cortex) that contribute to up-regulation of the nociceptive system, i.e. enhanced synaptic excitability, lowered thresholds of activation and expansion of receptive fields of central neurons that process nociceptive inputs (Latremoliere and Woolf, 2009).

The pathophysiological mechanisms underlying central sensitisation are potentially numerous and complex, a review of which is beyond the scope of this paper. Briefly however, as well as up-regulation of nociception from enhanced synaptic efficacy secondary to processes such as 'classic central sensitisation' 'long-term potentiation' and 'transcription-dependent central sensitisation' (Woolf and Salter, 2006), additional mechanisms may also contribute to an enhancement of nociceptive transmission including loss of spinal cord inhibitory inter-neurones, enhanced

facilitatory and/or loss of inhibitory descending pain control mechanisms, facilitatory cognitive-affective mechanisms and altered cortical processing of nociceptive inputs (Latremoliere and Woolf, 2009; Woolf, 2011). The net effect of these processes is that noxious input may now become magnified, more intense and longer lasting, and normally non-noxious inputs may initiate central nociceptive transmission.

A growing body of experimental and clinical data, although not always consistent, has provided some evidence suggesting that processes associated with central sensitisation may underlie some commonly encountered clinical presentations of musculoskeletal pain including chronic low back pain, whiplash associated disorders, rheumatoid arthritis and fibromyalgia (Nijs et al. 2010; Woolf, 2011).

Mechanisms-based classifications of pain, such as CSP, might optimise clinical outcomes by inviting clinicians to select treatments known or hypothesised to target the dominant neurobiological mechanisms underlying patients' pain (Woolf, 2004). However, before this assertion can be tested diagnostic or classification criteria with which to identify the phenomenon of CSP in patients must be established (Woolf, 2011).

Widespread pains, pain persisting beyond expected tissue healing times, inconsistent and/or disproportionate responses to clinical examination testing, the presence of tactile allodynia and hyperalgesia, pain in association with cognitive, affective and behavioural dysfunction as well as hypersensitivity to various sensory stimuli (e.g. light, sound and temperature) have all been proposed as symptoms and signs

suggestive of a dominance of CSP (Butler, 2000; Clauw, 2005; Smart et al. 2008; Nijs et al. 2010; Woolf, 2011) although their validity as diagnostic criteria is not known.

A recent Delphi-type survey of pain consultants and musculoskeletal physiotherapists identified a consensus-derived list of thirteen symptoms and four signs suggestive of a dominance of CSP (see Figure 1) (Smart et al. 2010).

The symptoms and signs associated with a clinical classification of CSP in patients presenting for physiotherapy have not been widely studied. The purpose of this study was to identify a cluster of symptoms and signs associated with a clinical classification of CSP in patients with low back (± leg) pain presenting for physiotherapy assessment. Data related to the identification of symptoms and signs associated with CSP have previously been reported in the wider context of the discriminative validity of mechanisms-based classifications of pain (Smart et al. 2011). The following paper, derived from the same study, provides an expanded analysis and allows for the presentation of additional results as well as a more detailed discussion of the underlying biological plausibility of those symptoms and signs associated with a clinical classification of CSP.

## 2. Methods

### 2.1 Study design

This study employed a cross-sectional, between-subjects design.

### 2.2 Setting

This study was carried out at four hospital sites, 1) The Adelaide and Meath Hospital, Dublin, 2) Waterford Regional Hospital, Waterford, 3) St Vincent's University Hospital, Dublin (all Ireland) and 4) Guy's and St Thomas' NHS Foundation Trust, London (United Kingdom); and two private physiotherapy practices in Dublin. Ethical approval for this study was granted by the Ethics and Medical Research Committees of each Irish institution and the National Research Ethics Service (UK). Data was collected between March 2008 and September 2009.

### 2.3 Participants

Fifteen experienced musculoskeletal physiotherapists (mean number of years since qualification = 12 (SD: 5.2, Range: 5-21)), participated in data collection; thirteen were based in public hospital settings, one of whom was the primary investigator (KMS) and two in private practices. Thirteen clinicians held 'masters' level qualifications in physiotherapy and one clinician had a postgraduate diploma.

Eligible patients included those of 18 years of age or over with low back (± leg) pain referred for physiotherapy assessment and/or treatment. Patients with a history of diabetes or central nervous system injury, pregnancy or non-musculoskeletal low back pain (LBP) were excluded. Patients were recruited by physiotherapists working in various outpatient services including back pain screening clinics, general

physiotherapy departments and pain clinics. All patients gave signed informed consent prior to their inclusion. The process of patient recruitment and exclusion is presented in Figure 2.

**2.4 Instrumentation and Procedures**

A standardised form was used to collect patient demographics**.** Patients were assessed using a standardised clinical interview and examination procedure (Petty and Moore, 2001). During the clinical interview patients were encouraged to disclose details of their current low back (± leg) pain/symptoms, including aggravating and easing factors, diurnal variations and sensory disturbances as well as their LBP history. The clinical examination included postural, movement and neurological assessments.

After examining each patient clinicians completed a 'Clinical Criteria Checklist' consisting of two parts. 'Part 1' invited clinicians to classify each patient's pain presentation on the basis of experienced clinical judgement regarding the likely dominant mechanisms assumed to underlie each patient's pain. Patients were classified in to one of three categories of pain mechanism (i.e. NP, PNP, CSP) or one of four possible 'mixed' pain states derived from a combination of the original three categories (i.e. Mixed: NP/PNP, Mixed: NP/CSP, Mixed: PNP/CCP, Mixed: NP/PNP/CSP). In the absence of a diagnostic gold standard from which to infer a dominance of CSP the best alternative 'reference standard' – operationally defined as, *'…the best available method for establishing the presence or absence of a condition of interest'* (Bachman et al. 2005), may be expert clinical judgement (Streiner and Norman, 2003). Using this approach the development of classification criteria is

based on a determination of which symptoms and signs match the impression of an experienced clinician (Katz et al. 2000).

In 'Part 2', clinicians completed a 38-item clinical criteria checklist, consisting of 26 symptoms and 12 signs (see Table 1), derived from an expert consensus list of clinical criteria suggestive of a dominance of NP, PNP and CSP mechanisms (Smart et al. 2010). Response options for each criterion included 'Present', 'Absent', or 'Don't know'. Clinicians were provided with practical training together with an 'Assessment Manual' with written instructions on how to undertake the patient examination and interpret and document findings in order to ensure that symptoms and signs were assessed consistently.

**2.5 Sample size requirements.**

The sample size required for this study was based on guidelines for the use of logistic regression which recommend a minimum of 10 subjects per criterion (Hosmer and Lemeshow, 2000). The 38 items on the clinical criteria checklist (see Table 1) together with the variables 'age' and 'gender' provided 40 predictor variables necessitating a minimum sample of 400 patients.

**2.6 Data analysis.**

Data screening and univariate analyses ($\chi^2$, one way analysis of variance) were performed initially in order to exclude non-discriminatory symptoms and signs (Hosmer and Lemeshow, 2000). A subsequent analysis using binary logistic regression (CSP versus non-CSP, i.e. patients classified with NP and PNP) with Bayesian model averaging (BMA) was undertaken in order to test for and identify a

discriminatory cluster of symptoms and signs associated with a clinical classification of CSP in patients with low back (± leg) pain (Smart et al. 2011). Bayesian model averaging i) generates a number of possible models, i.e. clusters of symptoms and signs, predictive of a disease state (e.g. CSP), ii) estimates the probability that an independent predictor variable (i.e. a symptom or sign) will be present in a given model, providing an indication of the extent to which it contributes to the model's explanatory power, and iii) provides more robust estimates of model parameters by averaging the coefficients across all possible model configurations; thereby accounting, to some degree, for the uncertainty associated with model specification as well as reducing the tendency towards inflated parameter estimates from over-fitting of single models (Montgomery and Nyhan, 2010). It has been suggested that averaging coefficients across all possible models provides better predictive performance. As a statistical procedure, BMA can therefore help to facilitate criteria selection and 'final' model specification, and lessen the uncertainty associated with conclusions regarding model parameters and prediction (Hoeting et al. 1999; Wang et al. 2004).

Symptoms and signs associated with a dominance of CSP identified from a Delphi survey were selected as candidate criteria for inclusion into the model (Smart et al. 2010) (Criteria: 4, 6, 10, 13, 14, 15, 16, 19, 23, 24, 25, 26, 30, 33, 34, 35, 36, and 38; see Table 1). Additional symptoms and signs were included when data screening and univariate analyses identified criteria whose 'absence' also appeared to be associated with a dominance of CSP (Criteria: 1, 5; see Table 1).

The weakest predictive symptoms and signs were excluded from successive models. Selection of the final model was based on considerations of classification accuracy and parsimony, i.e. identifying a cluster comprising the fewest symptoms and signs whilst preserving classification accuracy (Hosmer and Lemeshow, 2000).

Indices of classification accuracy (sensitivity, specificity, positive and negative predictive values (PPV, NPV), positive and negative likelihood ratios (LR+, LR−)) with two-sided 95% confidence intervals (CIs) were calculated in order to assess the classification accuracy of each model.

Univariate analyses were performed using SPSS (SPSS for windows, version 15). The binary logistic regression analysis with BMA was performed in 'R' (2009, version 2.9.2).

## 3. Results

A presenting sample of 551 patients with musculoskeletal low back (± leg) pain was invited to participate in the study. Fifty-one ineligible patients were excluded, and 36 patients with a mixed ($n$ = 35) or indeterminate ($n$ = 1) pain state were excluded on the grounds that any discriminatory clusters of symptoms and signs would be more clearly identified from those patients classified with a dominance of CSP, a practice in keeping with similar studies (Bennett, 2001; Freynhagen et al. 2006). Patient demographics for the final sample ($n$ = 464) are presented in Table 2.

### 3.1 Data screening and Univariate analyses

Age (Browne-Forsythe F-ratio 0.23 ($df$ 2, 463), $p$ = 0.80), gender ($\chi^2$ ($df$ 2, $n$ = 464) = 1.59, $p$ = .45) and Criterion 17 ($\chi^2$ ($df$ 2, $n$ = 464) = 2.30, $p$ = .32) were not significantly associated with pain classification and were subsequently excluded from the multivariate analysis.

### 3.2 Regression analysis

Missing values were identified for 12 cases, thus reducing the valid sample size from $n$ = 464 to $n$ = 452 (CSP $n$ = 98, Non-CSP $n$ =354). Model parameters (posterior probabilities, expected values of the regression coefficients) and indices of classification accuracy for successive models are presented in Tables 3 and 4 respectively. 'Model 7' was selected as the 'final' CSP model. Model parameters for each criterion in the final CSP model are presented in Table 5 (where shortened criterion descriptions are given; full descriptions are presented in Table 1).

According to the final model a clinical classification of CSP was predicted by the presence of three symptoms (Criteria 4, 13 and 25) and one sign (Criterion 33). The strongest predictor of CSP was Criterion 13 (OR: 30.69; 95% CI: 8.41-112.03) suggesting that patients with *'Disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors'*, were over 30 times more likely to be classified with a dominance of CSP compared to those with non-CSP, controlling for all other variables in the model.

Patients with *'Diffuse/non-anatomic areas of pain/tenderness on palpation'*, *'Pain disproportionate to the nature and extent of injury or pathology'*, and those whose pain presentation had a *'Strong association with maladaptive psychosocial factors (e.g. negative emotions, poor self-efficacy, maladaptive beliefs and pain behaviours, altered family/work/social life, medical conflict)'* were around 27, 15 and 7 times more likely, respectively, to be classified with a dominance of CSP.

**3.3 Classification accuracy**

The cross-tabulation from which the indices of classification accuracy were calculated are presented in Table 6, as recommended (Bossuyt et al. 2003). Indices of classification accuracy, with 95% confidence intervals, for the final CSP model are presented in Table 7.

The final model had a sensitivity of 91.8% (95% CI: 84.5-96.4%) suggesting that this cluster of symptoms and signs correctly predicted a clinical classification of CSP in 91.8% of patients classified with CSP according to the reference standard of 'expert' clinical judgement, but incorrectly predicted 8.2% of these patients as having Non-

CSP. A specificity of 97.7% (95% CI: 95.6-99.0%) suggests that the final model correctly predicted 97.7% of patients with Non-CSP, but incorrectly predicted 2.3% of patients as having CSP.

The PPV of 91.8% (95% CI: 84.5-96.4%) indicates that a patient with the cluster of symptoms and signs outlined by the model was likely to have been classified with CSP with a 91.8% level of probability. The NPV indicates that the probability of a patient without the cluster having Non-CSP is 97.7% (95% CI: 95.6-99.0%).

The LR+ of 40.64 (95% CI: 20.43-80.83) suggests that the specified cluster of symptoms and signs is around 40 times more likely to be found in patients classified with CSP than Non-CSP. The LR− indicates that the likelihood of the cluster being absent in patients classified with CSP compared to those with non-CSP is 0.08 (95% CI: 0.04-0.16). Negative likelihood ratios ≤ 0.1 may be useful clinically (Jaeschke et al. 1994), indicating the absence of a cluster of symptoms and signs may be accurate at ruling the condition of interest, i.e. CSP, out.

The diagnostic odds ratio of 486.56 (95% CI: 177.74-1331.97) indicated that the cluster was around 480 times more likely to accurately than inaccurately predict a clinical classification of CSP in patients classified with CSP.

The predictive accuracy of the cluster is illustrated by the scatter plot presented in Figure 3. Figure 3 (left) provides an indication of how well the final CSP model ‘fits’ the sample from which it was derived. The clusters in the top right and bottom left quadrant of the graphic represents those patients correctly ‘observed’ (i.e. classified)

and predicted by the model to have a dominance of CSP and Non-CSP respectively. Those clusters in the top left and bottom right represent those patients misclassified. The scatter plot depicted in Figure 4.5 (right) shows the spread of predictive probabilities from the model, which suggest that the model is predicting very well.

## 4. Discussion

This multi-centre study identified a cluster of three symptoms and one sign associated with a clinical classification of CSP in patients with low back (± leg) pain presenting for physiotherapy assessment.

Three of the initial 14 symptoms entered into the first model together with one of the six signs emerged as predictors of CSP, suggesting that symptoms rather than signs may be relatively more predictive of CSP. We speculate that each symptom and sign in the cluster is underpinned by a degree of clinical and biological plausibility.

According to the final model, *'Disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors'* was the strongest predictor of CSP. A distortion in the stimulus-response relationship between movement/mechanical stimuli and pain has been suggested as a possible clinical indicator associated with a dominance of CSP (Butler, 2000). Distortions in this relationship may reflect those alterations in the functional, chemical or structural properties of a widely distributed network of CNS neurones that may lead to excessive neuronal excitability and enable nociceptive inputs to become magnified (hyperalgesia) and/or non-noxious stimuli to initiate or augment nociceptive transmission (allodynia) (Woolf and Salter, 2006; Dickenson, 2007). This symptom could represent one example of the ways in which these phenomena may manifest clinically.

The presence of non-segmental/diffuse areas of tenderness on palpation could similarly reflect disordered pain regulation (Jensen et al. 2010) and specifically the

clinical manifestation of mechanical (touch-evoked) allodynia, a clinical phenomenon considered to reflect some degree of CNS dysfunction (Lidbeck, 2002). For example, enhanced synaptic excitability, lowered thresholds of activation, and/or expanded receptive fields in the dorsal horn of the spinal cord may allow non-nociceptive afferents to activate second order neurones previously only accessible by nociceptive afferents (Vicenzino et al. 2002). The presence of lowered pressure pain thresholds together with altered patterns of neuronal activation in pain-related cortical areas has been demonstrated in patients with non-specific LBP and fibromyalgia suggestive of augmented central pain processing (Giesecke et al. 2004). Furthermore, diffuse non-anatomic pain on spinal palpation is one of the five validated non-organic physical signs often employed as an index of pain-related behaviour in patients with LBP (Waddell et al. 1980). Cortical responses to tactile stimuli in areas thought to be involved in descending modulatory control of nociception are known to differ in those patients with and without significant non-organic signs (Lloyd et al. 2008) raising the possibility that the presence of diffuse tenderness may be associated with alterations in descending pain control mechanisms and/or reflect altered cortical sensory processing whose mechanisms might be considered to sub-serve the phenomenon of central sensitisation.

A pain report disproportionate to the nature and extent of injury or pathology could reflect some of the underlying pathophysiological processes associated with central sensitisation which may ultimately contribute to heightened pain perception (Wand et al. 2011) and consequently to what might ultimately be interpreted by a clinician as a more severe, disproportionate pain report.

And lastly, the presence of maladaptive psychological features as a predictor of CSP could reflect alterations in CNS pain processing (Curatolo, 2008). For example, there is some evidence to suggest that cognitive-emotive constructs such as fear and attention can enhance pain transmission in the dorsal horn of the spinal cord via forebrain mediated activation of facilitatory descending pathways (Zusman, 2002). In addition, the manifestations of emotional distress that a pain experience may evoke, such as fear and anxiety may modulate pain processing in cortical and sub-cortical areas and further contribute to and enhance the intensity and unpleasantness of a patients pain experience (Neugebauer et al. 2009).

Interestingly, a number of symptoms and signs often associated with CSP, such as pain persisting beyond expected tissue healing times and hyperalgesia, did not emerge as predictors of CSP. The reason for this is not known. Future studies in different patient populations may establish the diagnostic validity of such features.

The ability to identify patients with an assumed dominance of CSP could be useful when deciding on management strategies for such patients. Clinicians might select treatments either known or hypothesised to target the neurophysiological mechanisms underlying CSP in an attempt to improve outcomes and provide a rational basis for intervention. For example, there is some evidence to suggest that educating patients about the neurobiology of pain as a therapeutic intervention might improve illness beliefs, movement performance and lessen the threat value of pain (Moseley, 2002; Moseley et al. 2004; Van Oosterwijck et al. 2011). Whilst the mechanism of action is unknown we speculate that neurophysiology pain education might induce cognitive reappraisals that lessen the cognitive-affective contributions to central sensitisation,

perhaps by reducing the descending facilitation and/or enhancing inhibition of pain (Van Oosterwijck et al. 2011). Similarly, centrally acting analgesics might be selected when CSP is suspected (Mease et al. 2011).

At the same time, clinicians might be discouraged from employing interventions targeted towards more peripheral mechanisms thus lessening the use of interventions unlikely to benefit such patients. Such an approach might limit the potential iatrogenic effects of inappropriate or failed interventions and the waste of valuable healthcare resources.

The findings from this study should be interpreted in light of a number of limitations (Smart et al. 2011). Studies that develop classification criteria with small to moderate sample sizes tend to produce individual symptoms and signs with inflated odds ratios and clusters with inflated estimates of classification accuracy since the regression modelling process optimises model fit. Cross-validation of the symptom and sign cluster in separate cohorts of patients in various clinical settings is required in order to provide more accurate model estimates (Tabachnik and Fidell, 2007; Nemes et al. 2009).

In addition, future studies could enhance the robustness and generalisability of their findings by recruiting larger patient samples with varied musculoskeletal disorders from across different healthcare settings (primary versus secondary) in order to obtain alternative and/or more precise model estimates.

Also, the assignment of the reference standard by two independent clinicians and the completion of clinical criteria checklists by clinicians blinded to the patient's clinical classification is desirable in order to improve the robustness and legitimacy of the clinical classification as a reference standard and minimise the potentially confounding influence of 'clinical review bias' whereby a clinicians prior knowledge of the reference standard (i.e. clinical classification) may have influenced completion of the clinical criteria checklist as a consequence of their preconceived ideas about the nature of clinical findings associated with NP (Scott et al. 2008). Furthermore, estimates of classification accuracy derived in the absence of a gold standard method by which to determine the true presence/absence of the target condition (i.e. CSP) should be treated with caution (Jones et al. 2010).

Neuroimaging and/or quantitative sensory testing (QST) techniques could be used to further evaluate the biological plausibility of mechanisms-based pain classifications. Demonstrable evidence of areas of differential brain activation and/or QST profiles associated with CSP compared to NP/PNP could provide additional evidence to support of the validity of CSP as a mechanisms-based classification of pain.

**5. Conclusion**

This study identified a cluster of three symptoms and one sign associated with a clinical classification of CSP in patients with low back (± leg) pain. The cluster was found to have high levels of classification accuracy suggesting it might be useful clinically. Further studies involving larger patient samples with a range of musculoskeletal disorders are required in order to provide more robust estimates of

classification accuracy as well as identify other potential symptoms and signs associated with CSP.

**Conflicts of interest:** None declared.

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**Legends for illustrations:**

Figure 1. Delphi-derived clinical indicators of 'central sensitisation' pain.

**Subjective:**

- Disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors.
- Pain persisting beyond expected tissue healing/pathology recovery times.
- Pain disproportionate to the nature and extent of injury or pathology.
- Widespread, non-anatomical distribution of pain.
- History of failed interventions (medical/surgical/therapeutic).
- Strong association with maladaptive psychosocial factors (e.g. negative emotions, poor self-efficacy, maladaptive beliefs and pain behaviours, altered family/work/social life, medical conflict).
- Unresponsive to NSAIDS and/or more responsive to anti-epileptic (e.g. Lyrica) /anti-depressant (e.g. Amitriptyline) medication.
- Reports of spontaneous (i.e. stimulus-independent) pain and/or paroxysmal pain (i.e. sudden recurrences and intensification of pain).
- Pain in association with high levels of functional disability.
- More constant/unremitting pain.
- Night pain/disturbed sleep.
- Pain in association with other dysesthesias (e.g. burning, coldness, crawling).
- Pain of high severity and irritability (i.e. easily provoked, taking a long time to settle).

**Clinical examination:**

- Disproportionate, inconsistent, non-mechanical/non-anatomical pattern of pain provocation in response to movement/mechanical testing.
- Positive findings of hyperalgesia (primary, secondary) and/or allodynia and/or hyperpathia within the distribution of pain.
- Diffuse/non-anatomic areas of pain/tenderness on palpation.

Figure 1. Delphi-derived clinical indicators of 'central sensitisation' pain (Smart et al. 2010).

Figure 2. Flowchart of patient recruitment.

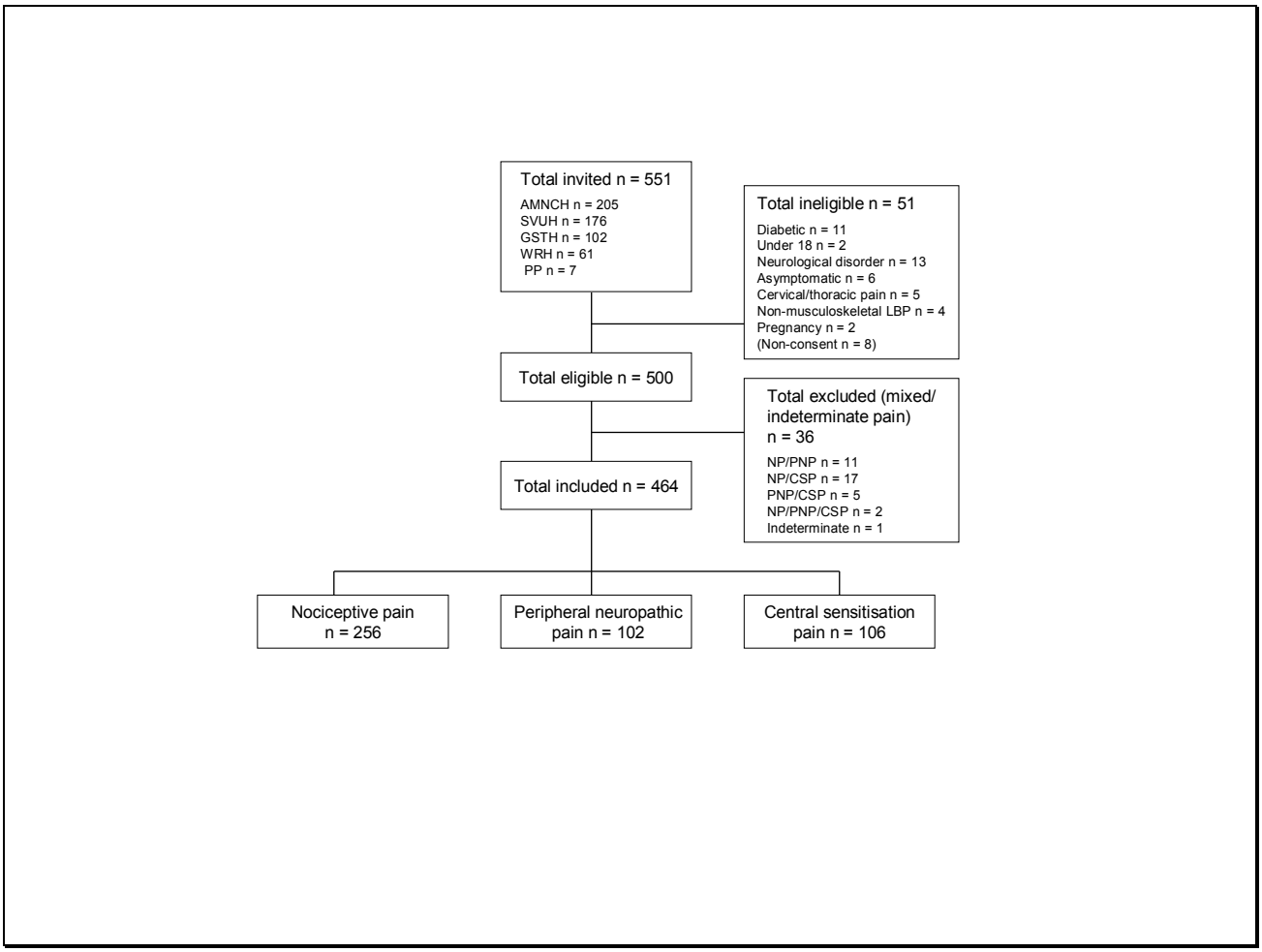


Figure 3. A graphical representation of the discriminatory properties of the final 'central sensitisation' pain model.

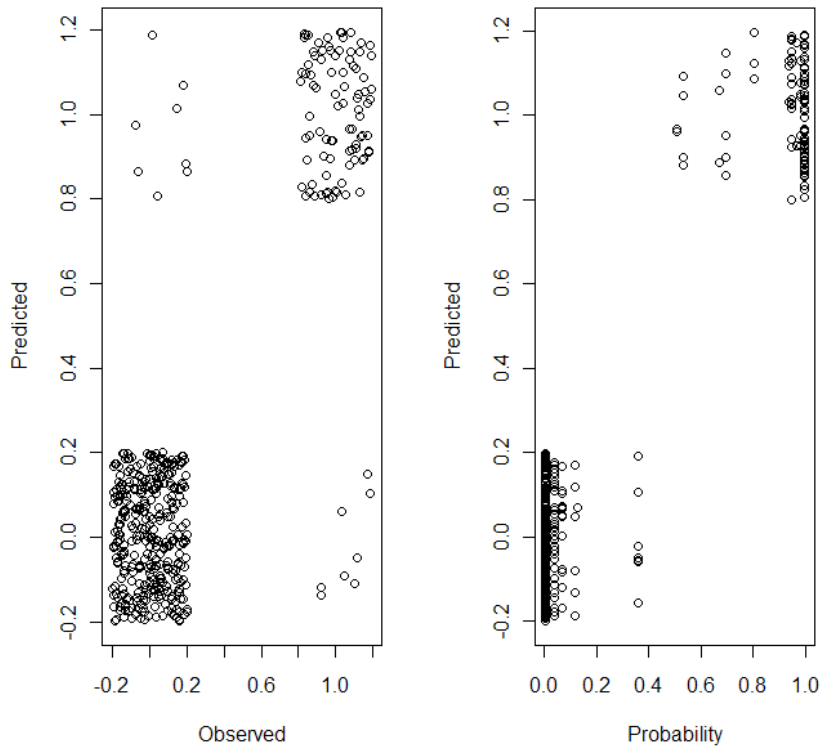


Figure 3. A graphical representation of the discriminatory properties of the ‘final’ ‘central sensitisation pain’ model.