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Sensory profiling in animal models of neuropathic pain: a call for back-translation

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1 Introduction

This Topical Review considers the misalignment between outcome measures traditionally reported in animal models of neuropathic pain* and those employed for estimating pain intensity and the impact/burden of pain in clinical trials. In particular, we propose that traditional methods of assessing rodent sensory thresholds could have predictive utility for the sensory profiling approaches being explored for patient stratification in clinical trials. To initiate this process we propose a “research agenda” to develop and validate a protocol and normative values for sensory profiling in rodents which reflects the best established clinical methods. This could then be used to establish definitive sensory profiles of new and existing rodent neuropathic pain models.

In general, animal modelling of neuropathic pain has two main goals: Firstly, to identify pain mechanisms and thus potential targets for drug development. However, it is difficult to identify clear examples of the success of this approach in delivering new drugs for neuropathic pain, with the exception of high concentration topical capsaicin[20]. Secondly, animal models are used in an attempt to predict the clinical efficacy of a novel therapeutic and thus justify the initiation of clinical trials. We concentrate on the latter aspect and ask whether the drug response associated with specific sensory profiles in animal models might predict the most appropriate patients to examine in exploratory clinical trials?

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**For brevity we will adhere to convention and use the shorthand “animal model of neuropathic pain”. However, we suggest that a more accurate classification is in terms of the disease they purportedly mimic (e.g. traumatic nerve injury, diabetic neuropathy etc) rather than as a model of “pain”.

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2 The problem of homogeneity in current animal models of neuropathic pain

To date, animal modelling of neuropathic pain has been dominated by homogeneity in both the models created and outcomes (behavioural constructs) measured in those models. The predominant animal model reported is of traumatic injury to a rodent sciatic nerve. The predominant “pain” outcome measure is limb withdrawal evoked by applied sensory stimuli. (In passing, we note that experiments are usually conducted in genetically similar animals; although we do recognise that such homogeneity may be of relevance in the specific context of animal genetic studies. There has also been a tradition of homogeneity of sex and age [33], with the use of young male animals predominating). In contrast to the homogeneity of animal modelling, there is emerging evidence of the importance of clinical heterogeneity in neuropathic pain in terms of underlying disease, clinical presentations, pain mechanisms and treatment responses at the individual patient level. Recognising such heterogeneity is fundamental to developing the concept of precision (personalised) medicine for neuropathic pain[7]. Therefore, we argue that refinement of pre-clinical methods is required to achieve alignment with emerging concepts of clinical heterogeneity.

3 Potential biomarkers to reveal clinical heterogeneity in neuropathic pain

There are multiple potential biomarkers that might be hypothesised to predict efficacy of analgesic interventions in neuropathic pain at the individual patient level[54]. One example is the prediction of duloxetine efficacy in diabetic neuropathy by measuring endogenous pain modulation[72]. Others include symptom and epidermal innervation profiling[3], testing nociceptor function with capsaicin[12] and even ascertaining the characteristics of patient-derived stem cells[13]. However, here we focus on aligning sensory measurements made in animal models with current methods of clinical sensory assessment[4; 17; 18; 25]. In this context, we argue that the traditional evoked limb withdrawal outcome measures used in animal models of neuropathic pain should be redeployed as sensory profiling tools. We submit that their use should henceforth be interpreted not as a measure of “pain”, but rather as a sensory profile biomarker of that injury or disease model.

4 Neuropathic pain, associated sensory abnormalities and animal models

Neuropathic pain clinically manifests as spontaneous pain (ongoing or paroxysmal) and/or, more uncommonly, evoked pain. Neuropathic pain is usually accompanied by sensory abnormalities which are broadly categorised into modality-specific sensory gain (allodynia, hyperpathia and/or hyperalgesia) or sensory loss (*anaesthesia dolorosa*). Evoked limb withdrawal measures conventionally reported from animal model experiments reflect only the small group of patients characterised by sensory gain and then only the evoked pain component. Furthermore, these measures resemble a spinal cord reflex activation ignoring all other pain-related phenomena in the neuraxis. There are disparities between simple reflex withdrawal and operant escape responses which measure the cerebral-dependent component of the response in normal animals. In animals with traumatic nerve injury operant behaviours are more consistent with evidence from humans than evoked measures[59; 60].

Hyperpathia is not generally reported for animal models, possibly because of the inherent difficulty of quantifying an explosive pain response as opposed to a simple threshold[27].

5 The proposition

We advocate that animal models should not only be classified by the lesion or disease of the somatosensory system which they purport to reflect, but also by a phenotype-based classification defined by sensory profile. This will align animal modelling with the cross-disease sensory heterogeneity of sensory profiles in patients with neuropathic pain[7; 62] and the associated stratification approaches implicit in precision medicine[6]. Mitchell Max was amongst the first to hypothesise that the efficacy of neuropathic pain treatments might be predicted using measurable characteristics[40]. It was later reported that patients with postherpetic neuralgia could be stratified on the basis of three broad sensory profiles which likely reflect distinct pain mechanisms[19]. Using large multi-aetiology clinical cohorts we have shown that most neuropathic pain patients can be classified, irrespective of underlying disease, into one of these three distinct sensory subgroups[7; 62]. These are strikingly similar to those originally reported in postherpetic neuralgia[19] (Figure 1). There are now encouraging examples of how such sensory profiles can represent heterogeneous pharmacologically tractable pain mechanisms[3; 12; 15; 38; 53]. However, a caveat is that this effect was reported to have only limited usefulness in a retrospective analysis of data from clinical trials of painful polyneuropathy[29]. A strengthening of the clinical evidence is required before definitive statements can be made about the value and robustness of sensory biomarkers for precision pain medicine. Nevertheless, as clinical medicine moves towards stratification of patients based on individual sensory characteristics, we posit that animal modelling be refined to inform that approach. This, in turn, could predict the logical sensory profile to recruit in a sensory profile-stratified clinical trial.

6 Evolution and current status of animal models of neuropathic pain

In one of the first reports of an animal model of neuropathic pain (sciatic nerve axotomy), the importance of reflecting pain occurring in the context of the sensory loss was recognised[64; 65]. This sensory loss profile is reported in the majority of patients with common polyneuropathies for example: diabetic[47; 55], chemotherapy-induced[58] and HIV-associated[46] polyneuropathies, rarer conditions such as non-freezing cold injury[56] and in some patients with spinal cord injury[21] and postherpetic neuralgia[19]. Wall and colleagues also recognised that to assess the impact of pain in such a model required the measurement of complex behavioural paradigms; although the autotomy measure they described is no longer in widespread use for ethical reasons and because of uncertainty about exactly which sensory construct it reflects[64].

Later, the animal modelling of neuropathic pain was refined by a sciatic nerve constriction method[8]. This partial nerve trauma approach has, with many subtle variations, since dominated the literature. Partial nerve trauma models are generally characterised by an ipsilateral gain in sensory function measured as hypersensitivity of reflex limb withdrawal evoked by mechanical and sometimes heat or cold stimuli[8]. This perhaps reflects the mechano- or thermal sensory profile of allodynia observed in some, but by no means all,

patients with neuropathic pain, notably some of those with peripheral nerve injury, Complex Regional Pain Syndrome, inherited channelopathies, postherpetic neuralgia, some aspects of pain after spinal cord injury and the mixed picture reported in epidermolysis bullosa[13; 16; 21; 23; 37; 45; 63]. An important caveat is that sometimes patients can report symptoms of sensory gain, such as allodynia, but it can be difficult to show the corresponding signs by cutaneous quantitative sensory testing in a circumscribed test area[61].

The reporting of sensory gain outcome measures in animal models has become ubiquitous. They are usually, and we suggest incorrectly, described in terms of a “pain” outcome measure. In an ongoing systematic review of animal models of drug-induced neuropathy, 348 (95.6%) of publications report such outcomes (data on file). The reason for the historical focus on such measures might be that they appear robust, reliable and relatively easy to consistently measure[60]. However, is this a case of measuring what *can* be measured and not what *should* be measured? We argue that these measures of sensory gain remain useful, but should be primarily interpreted as reflecting one modality of the model´s global sensory profile and not as implying the presence of non-evoked pain for predicting the efficacy of putative therapeutic interventions.

For many years the neuropathic pain animal model literature has been dominated by traumatic nerve injury (~66% of publications from our ongoing animal models meta-analysis– protocol at www.dcn.ed.ac.uk/camarades/research.html#protocols); a condition examined in only ~8% of clinical trials; the majority of which recruit patients with postherpetic neuralgia or polyneuropathy[20]. Traumatic peripheral nerve injury patients are most often characterised by a loss of sensitivity to non-painful stimuli and moderate gain in sensitivity to painful stimuli[23]. However, recently other relevant disease models have been developed and validated, notable examples being those related to drug-induced neuropathy and diabetic and HIV-associated neuropathy and herpes zoster infection[2; 11; 22; 26; 28; 31; 32; 66; 67]. Establishing a portfolio of diverse disease–based animal models affords the opportunity not only to document a range of sensory profiles, but also to explore heterogeneity in the pathophysiological responses to nerve damage. Examples from our own work reveal that features consistently observed in animal models of traumatic nerve injury are not necessarily prominent in other conditions. These include changes in dorsal root ganglion gene and protein expression[10; 39], spinal cord microgliosis[9] and pharmacological responses[26; 66].

7 The problem of opposing sensory profiles in animal models and patients

Another difficulty with some existing animal models is that the sensory gain reported[31; 35; 66; 67] is the precise opposite of the sensory loss profile described in the corresponding disease,; for example, HIV-associated or diabetic polyneuropathy[46; 47; 55]. This could be related to the fact that the animal models reflect the early initiation phase (up to 28 days) of the neuropathy when sensory gain could conceivably be a clinical feature; whereas the clinical profiles were reported in patients with an established neuropathy, often of several years standing. It is conceivable that if such animal models were followed up for extended

periods then the sensory profile could switch to sensory loss, as has been demonstrated for diabetic neuropathy[11]. It has also been shown that following traumatic nerve injury in animals, alterations in operant behaviours persist beyond the resolution of enhanced limb withdrawal reflexes evoked by sensory stimuli[60]. Another explanation could possibly be that animals with a sensory loss profile are indeed observed in such experiments, but through reporting bias are excluded from the analysis as “outliers” or “non-responders” which did not show sensory gain[30]. It is important that long-term behavioural and other biological outcomes are assessed across multiple time points in both animal models and in patients participating in clinical research.

8 Developing a portfolio of non-evoked pain-related outcome measures for use in rodents

Although evoked limb withdrawal measures will retain utility in the specific scenario of sensory gain, rebadging their use as profiling tools will require alternative measures of the impact of pain in rodents to be developed. Self-evidently, such measures will also be required for assessment of pain in the proposed rodent models of neuropathic pain in the context of a sensory loss profile. This research-active area is now reaching sufficient maturity for this to be plausible – several groups have risen to this challenge and are developing complex behavioural constructs that crucially do not require an evoked response, for example[41; 44; 48; 49]. In doing so it is important to understand the ethological response to pain in a prey species and to avoid anthropomorphising human emotions to rodents[5; 57]. To illustrate this approach we have, for example, shown that animals with purportedly painful surgical, viral or drug induced neuropathies and inflammation show a pharmacologically sensitive increase in a predator avoidance behavioural construct (thigmotaxis)[26; 31; 32; 42; 66–69]. Similarly, an innate rodent social behaviour (burrowing) is pharmacologically-sensitive in pain models[1; 14; 24; 34; 43; 51; 52; 70]. Another approach not requiring evoked responses is pharmacologically induced place preference[36] It will be important to demonstrate that such measures are robust, reliable and reproducible across centres and have face, construct and pharmacological validity. This is not a trivial task and to facilitate this we have demonstrated the value of a prospective multicentre validation approach[71] and advocated the open publication of individual animal level data for further analysis[42].

9 Conclusions

We propose classifying animal models of neuropathic pain by sensory profile. This presents major challenges which will require a collaborative approach. We suggest prioritising the following key aspects of a research agenda to address these:

a. The development and validation of a range of stable, reproducible, ethologically–relevant, and pharmacologically tractable behavioural constructs which can be used to assess the impact of pain, especially in those models characterised by a sensory loss profile[43]. In all likelihood, such behavioural paradigms will reflect the general wellbeing of an animal rather than be pain specific (and thus akin to “global impression” measures used in humans). Their pain relevance in

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any particular situation could be revealed by pharmacological validation using responses to known analgesic interventions. There may also be scope for cross fertilisation with inflammatory pain research, if it can be shown that behavioural findings are consistently replicated between neuropathic and inflammatory pain models because in the latter the presence of ongoing pain can be more reasonably purported[41; 72]. Clearly, developing and validating pain related outcome measures reflecting neuropathic pain in the specific context of sensory loss could also benefit from additional surrogate non-behavioural techniques such as electrophysiology and *in vivo* imaging.

b. The development and validation of multimodal sensory profiling protocols and normative data for use in rodents. These can then be used to establish the definitive sensory profiles of new and existing models of neuropathic pain, including models characterised by sensory loss. Presently the sensory profile of animal models is often only reported by evoking limb withdrawal to one or two sensory modalities, yet clinical research shows the importance of pan-sensory modality profiling[7; 62], especially in conditions such as postherpetic neuralgia and epidermolysis bullosa where differential responses to various sensory modalities are observed within the same patient[19; 63]. The best validated multimodal clinical sensory profiling protocol is that developed by the German Neuropathic Pain Network (DFNS)[50] which was used to define sensory subgroups[7; 62] and demonstrate the heterogeneity of pharmacological responses[15]. To facilitate this discussion, we have suggested (Table 1) aspects of the DFNS Quantitative Sensory Testing protocol and associated measures that might conceivably be deployed for sensory profiling in animals.

c. The development and validation of a portfolio of animal models which accurately reflect at least the three major sensory profiles reported in neuropathic pain patients including, crucially, aspects of sensory loss[8; 60].

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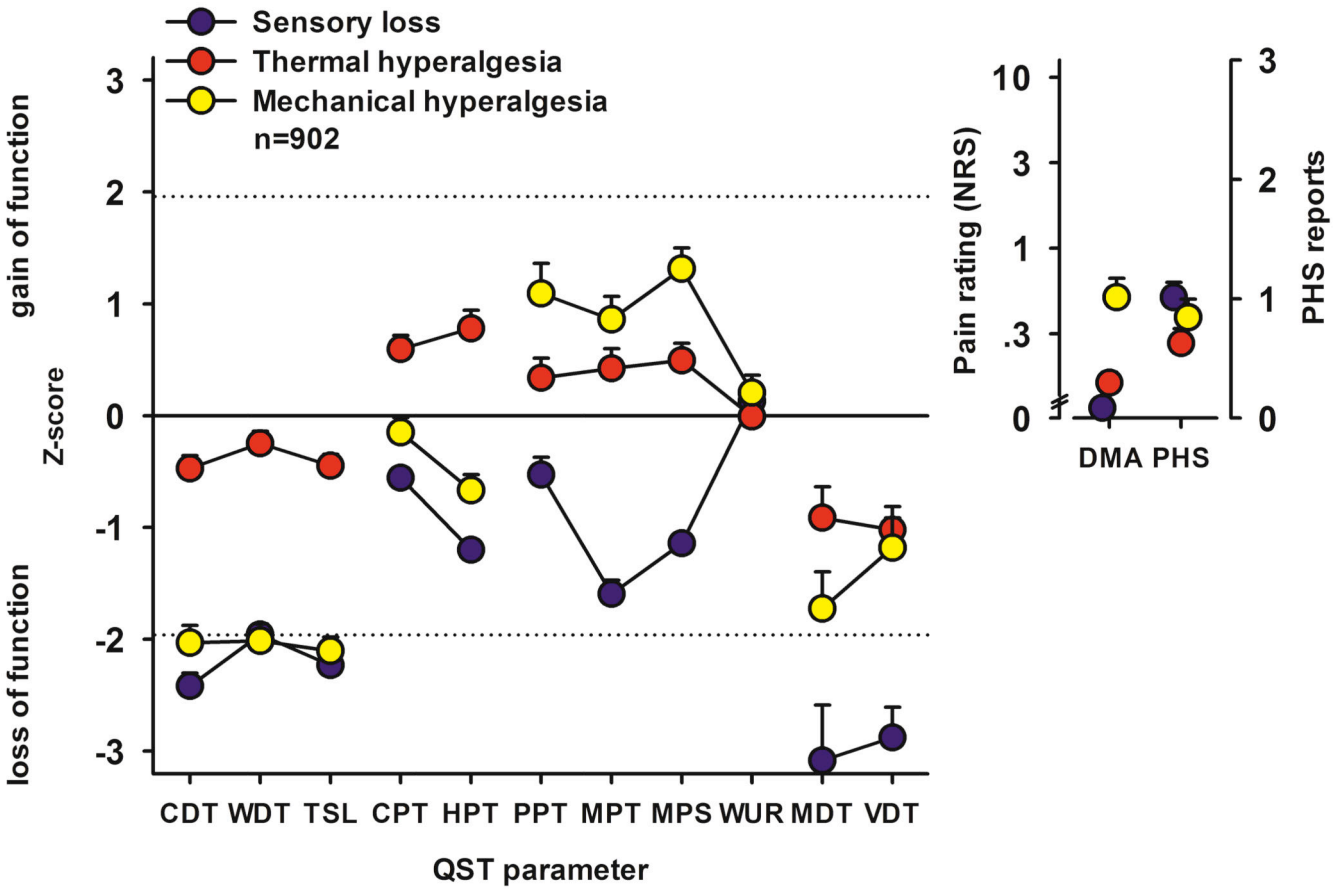

Figure 1.

The three major subgroups of sensory profiles reported in neuropathic pain patients across a range of underlying diseases. Positive z scores indicate positive sensory signs (hyperalgesia), whereas negative z values indicate negative sensory signs (hypoaesthesia and hypoalgesia). Dashed lines: 95% confidence interval for healthy subjects (−1.96 < z < +1.96). The inset graphs represent the reported pain intensity on a 0-10 numerical rating scale for dynamic mechanical allodynia and the number of episodes of paradoxical heat sensations reported during cooling stimulation, respectively. Blue symbols: cluster 1 “sensory loss” (42%) are distinguished by a loss of small and large fiber function in combination with paradoxical heat sensations. Red symbols: cluster 2 “thermal hyperalgesia” (33%) is characterized by preserved sensory functions in combination with heat and cold hyperalgesia and mild dynamic mechanical allodynia. Yellow symbols: cluster 3 “mechanical hyperalgesia” (24%) which is characterized by a loss of small fiber function in combination with pinprick hyperalgesia and dynamic mechanical allodynia.

CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio; DMA, dynamic mechanical allodynia; PHS, paradoxical heat sensations.

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Table 1

Key parameters of the German Network on Neuropathic Pain (DFNS) protocol for Quantitative Sensory Testing[47].

Sensory Stimulus	**Fibre Type**	**Putative Animal Model Correlate**	**Example of Behavioural Method**
-	-		
Cold Detection Threshold (CDT)	Aδ	Electrophysiological surrogate?	
Warm Detection Threshold (WDT)	C	Electrophysiological surrogate?	
Thermal Sensory Limen (TSL) & Paradoxical Heat Sensation	Aδ & C	?	
Cold Pain Threshold (CPT)	Aδ? C?	Established - behavioural	Plantar cold assay (Brenner)[1]
Heat Pain Threshold (HPT)	Aδ? C?	Established - behavioural	Plantar radiant heat assay (Hargreaves)[2]
Mechanical Detection Threshold (MDT)	Aβ	Electrophysiological surrogate?	
Mechanical Pain Threshold (MPT)	Aδ	Established - behavioural	
Mechanical Pain Sensitivity (MPS)	Aδ Stimulus - Response	Electrophysiological surrogate? Behavioural -possible, needs development	Monofilament (von Frey) or pinprick
Dynamic Mechanical Allodynia (ALL)	Aβ Stimulus - Response	Electrophysiological surrogate? Behavioural -possible, needs development	Brush-evoked limb withdrawal[3]
Windup Ratio (WUR)	Aδ or C Temporal Summation	Electrophysiological surrogate	
Vibration Detection Threshold (VDT)	Aβ	Electrophysiological surrogate?	
Pressure Pain Threshold (PPT)	Aδ? C?	Established - behavioural	Randall-Sellito device[4]
Additional items			
Hyperpathia	?	Electrophysiological surrogate?	
Conditioned Pain Modulation	Diffuse Noxious Inhibitory Control	Electrophysiological surrogate	

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Column three indicates the correlate for each parameter that could be measured in an animal model, and the current status thereof. For the purpose of this review, additional domains representing hyperpathia and conditioned pain modulation have been added.