Computational AnalySiS of functionAl Neuroimaging and Drug Response in pAinful Diabetic Neuropathy (CASSANDRA-DN)

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Abstract

One in 16 people in the UK has diabetes and half of these develop nerve damage. This can cause severe pain in the feet and legs. Unfortunately, current medications provide only partial benefit in some, with many enduring inadequate pain relief. Part of the problem is that a 'one-size fits all' 'trial and error' approach is used hoping to achieve meaningful pain relief. Current treatments at best achieve partial pain relief in only one in three patients. Hence, a new, more personalised approach is needed where the right treatment is given to the right patient first time. Patients with painful diabetic nerve damage (DPN) can be broadly divided into two main groups. The first group comprises of patients with numbness (dead feeling) in the feet yet who have nerve pain in their feet (painful insensate group) and the second group of patients have feet which are sensitive to light touch and/or mild heat (painful sensate group). More recent studies have suggested that some treatments work better in one group compared to the other. Hence, if we can reliably determine which group individual patients belongs to, we might then be able to offer them the right treatment for their pain. Over the last 10 years, we have performed specialised brain imaging studies known as functional magnetic resonance imaging (fMRI) in patients with painful DPN and identified a number of fMRI measures that can tell these two groups apart. The main objective of this application is to determine if and how fMRI measures can be used to predict the treatment response of an individual patient. We will recruit 40 patients who had previously received lidocaine treatment, 20 whom had responded to treatment and 20 who hadn't. We will use this group of patients to examine if fMRI can be used to identify patients who had responded to treatment.

Research Plan

Recent advances in functional neuroimaging provide us with unique insights into the human central nervous system in chronic pain conditions. We now have a better understanding how the brain processes and modulates nociceptive inputs to produce the pain experience [1]. Despite this, neither the US FDA nor the EMA have recommended the use of neuroimaging as a biomarker for pain [2]. However, there is now growing evidence that advanced magnetic resonance (MR) neuroimaging can be utilised not only as a pain biomarker [3] but also a predictor of treatment response [4]. If confirmed, this will enable future patient stratification and advance the development of personalised medicine. This would herald a major advance in the management of chronic pain.

THE PROBLEM BEING ADDRESSED

Diabetes affects around 4 million people in the UK [5] and half of whom have distal peripheral

neuropathy (DPN) [6]. DPN mostly causes sensory loss that can result in inadvertent injury and foot ulceration/amputations. DPN can also cause disabling neuropathic pain in the lower and upper limbs in around a quarter of all patients with diabetes. The main stay of treatment is pharmacotherapy but the best we can hope for is 50% pain relief in only a third of patients [7]. The current approach assumes that all patients respond similarly to a given drug when in fact there is a wide variability in response. Thus, there is a need to move away from this 'one size fits all' (trial and error) approach, to a more efficient one which tailors treatment to the individual patient in a rational way [8].

Evidence suggests that, even among individuals with the same neuropathic pain condition substantial diversity exists in their clinical manifestations [8]. Each patient has a unique sensory profile based on quantitative sensory testing using the German Network on Neuropathic pain (DFNS) protocol [9]. On this basis, a new approach of subgrouping patients into 1) non-irritable (NIR) nociceptor phenotype (painful insensate phenotype dominated by loss of small and large sensory nerve fibre function) and 2) irritable (IR) nociceptor phenotype (painful sensate phenotype dominated by thermal and/or mechanical hyperalgesia) has been proposed. [9] Recent studies have suggested that some treatments work better in patients with the IR compared to the NIR nociceptor phenotype. (for a review see [2]; for examples see [10-12].

Despite this, sensory profiling is not routinely used in clinical practice. Whilst it has significant appeal, in practice, QST is time consuming and difficult to implement in the context of a busy clinical practice. Furthermore, these are subjective psychophysical measures that rely on a patient's responses which may be subject to bias. Crucially, sensory profiling methods do not capture the complex multifaceted experience of pain which not only affects sensory but

also emotional/cognitive processing. A new approach is therefore required to overcome these limitations.

INNOVATION

To address these limitations, we have used advanced MR neuroimaging and demonstrated altered brain structure [13], metabolic activity [14], cerebral perfusion [15] and resting state (RS) functional connectivity [16] in the pain processing regions of the brain. More specifically, patients with the NIR nociceptor phenotype, have the greatest reduction in somatosensory (S1) cortical thickness which is accompanied by a remapping of the functional organisation [17]. These alterations are strongly related to measures of pain and DPN severity. Furthermore, functional connectivity within the S1 and insula cortices showed a significant correlation with measures of neuropathy severity and behavioural/psychological factors, respectively [17]. Taken together, these assessments could serve as a possible Central Pain Signature (CPS) for painful DPN. The challenge now, is to apply this potential pain biomarker at an individual level that can be used to predict response to treatment. To this end, we will use innovative approaches to image analysis such as Multi Variate Pattern Analysis (MVPA) methods to develop and validate the CPS in order to accurately classify individual patients and their response to treatment.

BENEFITS TO THE NHS

There is clear evidence that poorly managed chronic pain results in increased healthcare utilisation [23]. In 2001, the annual costs of managing painful DPN in the US ranged between $4.6-13.7 billion [24]. In 2003 the likelihood of a hospital admission for painful DPN patients was more than 2.5 fold higher relative to non-painful DPN patients [25]. Thus relieving pain effectively will reduce health care utilisation benefitting the NHS. There is increasing evidence that treatment response may be predicted by the use of advanced functional neuroimaging [2]. If our study confirms this in painful DPN, which is the leading cause of neuropathic pain in the Western world, it will pave the way to more efficient treatment strategies that will benefit sufferers, carers, healthcare professionals, the NHS and society at large.

PROJECT PLAN

OBJECTIVE: To derive, refine and validate a neuroimaging based model which is capable of determining treatment response. Based on our recent studies, we hypothesise that functional neuroimaging is capable of determining responses to neuropathic pain treatment.

DESIGN: Cohort, observational study of 40 patients (20 responders/20 non-responders) who have received IV lidocaine. Forty five patients will be recruited to account for an attrition rate

of 12.5%. Responders are defined as patients whose pain scores at the time of maximal treatment effect are relieved by at least 30% on an 11-point NRS or pain scores fall below 4.
TARGET POPULATION: Patients currently receiving IV lidocaine, database of patients who have previously received IV lidocaine (for non-responders) and all new treatment referrals.
RECRUITMENT PLAN: 43 patients attend every 8 weeks for IV lidocaine. 85% of patients surveyed would be willing to participate in research studies. From our database, 89 potential non-responders are also eligible. On average of 3-4 new patients per month are referred for treatment. Hence, there is a sufficient pool of patients for this study. Non-responders will not be required to have further IV lidocaine treatment.
INCLUSION: Type 1 or 2 diabetes (>18 yo) with painful DPN based on the Toronto Consensus [31], HbA1c <93mmol/mol
EXCLUSION: Non-diabetic neuropathies, major psychiatric disorders, contraindications to lidocaine or MRI, moderate-severe pain form other causes that may confound pain assessment
SETTING: Royal Hallamshire Hospital, Sheffield.

STUDY ASSESSMENTS:
All study visits will be performed before patients receive IV lidocaine treatment. To minimise additional inconvenience, we will arrange study visits on the day patients attend for treatment. If this is not possible, study visits will be done within 2 weeks of lidocaine treatment. This will not apply to non-responders to treatment, when study visits will be booked at their convenience.

VISIT 1:
<u>Clinical and Neurophysiological Assessments</u>
Clinical assessments: demographics, past medical history, alcohol and smoking consumption Family history and other data relevant to peripheral neuropathy
Drug history (past and present): All current drug therapy, current and analgesic/neuropathic pain treatment, previous drug treatment with potentially neuropathy inducing agents: e.g. isoniazid, antiretroviral drugs or cancer chemotherapy.
No blood or urine tests will be performed as part of this study. These results will be obtained from routine clinical testing of urine (albumin:creatinine ratio) and blood (full blood count, urea and electrolytes, liver function tests, glycosylated haemoglobin A1c, thyroid function tests, vitamin B12 serum levels) samples.
Basic pain/neuropathy symptomatology:
• Duration of neuropathy symptoms.
• Duration of pain symptoms.

• Location of pain and neuropathic symptoms on separate body maps.

Neuropathy Screening tools/questionnaires:

• DN4 [21] (Bouhassira et al., 2005)

• Assessment of neuropathic pain symptoms: Neuropathic Pain Symptom Inventory [22-24] (Bouhassira et al., 2004), NPS [REF] and NTSS-6 [REF]

• Mood, anxiety and pain related behavioural assessments: Beck's pain inventory [25], State and Trait Anxiety Inventory [26], Pain Catastrophising Scale [27] and Pain Acceptance [28] questionnaires.

• Brief Pain Inventory-Modified Short Form (BPI-MSF) [29]

• Neurological examination assessed using the Toronto Clinical Scoring System (TCSS) [30]

Nerve conduction studies:

• Surface stimulation and recordings of nerve conduction studies (NCS) will be obtained from the sural, peroneal and tibial nerves. Amplitude, distal latency of compound muscle action potentials, sensory nerve action potentials, and F-wave latency will be measured. Conduction velocities will be calculated from these measurements using standard methods. All nerve conduction studies will be performed at a stable skin temperature of 31^{o}C and a room temperature of 24^{o}C, using a Medelec Oxford Synergy electrophysiological system. A composite score derived from these assessments (Neuropathy Impairment Score of the Lower Limbs plus seven tests of nerve function – NISLL+7+VDT) will be calculated as defined by Dyck et al. [31].

Autonomic function tests:

• Cardiac autonomic function tests performed according to the O'Brien's protocol using a computer assisted method [32].

Quantitative sensory assessments

Quantitative sensory testing will be performed according to the protocol of the German Research Network on Neuropathic Pain [33]. In brief, cold and ward detection thresholds, cold and heat pain thresholds and thermal sensory lime to ascertain any paradoxical heat sensations will be determined using the Thermal Sensory Analyser (Medoc, Israel). Mechanical detection threshold will be assessed with a set of standardized von Frey filaments (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, and 256 mN (Nervtest, Marstock, Germany) using a modified method of limits. Mechanical pain threshold will be assessed with a set of 7 metal probes with standardized stimulus intensities (8, 16, 32, 64, 128, 256, and 512 mN; MRC Systems GmbHl Medizintechnische Systeme, Heidelberg, Germany) with uniform skin contact area of 0.25 mm, using a modified method of limits. Mechanical pain sensitivity of the skin and dynamic mechanical allodynia will be determined by the same set of 7 metal probes with standardized stimulus intensities and in addition by a set of 7 light intensity stimuli: a cotton wool ball with a force of 3 mN, a Q-tip (fixed to a plastic stick) with a force of

100 mN, and a paintbrush with an applied force of between 200 and 400 mN. These stimuli will be applied 50 times (5 runs of 10 stimuli per test site in different pseudo-randomized sequence), and the patients will be asked to rate the intensity of each stimulus on 0–100 NRS. Wind-up ratio (WUR), as a measure of enhanced temporal summation, will be examined by a pinprick stimulus with standardized intensity (256 mN). The stimulus is first applied singularly, and then in a series of 10 stimuli with a frequency of 1 Hz within an area of 1 cm^2. Patients are asked to rate the intensity of the first and mean of 10 stimuli on a 0–100 NRS. The ratio between the 2 measures is calculated as WUR; a WUR of >1 indicates enhanced temporal summation. Vibration detection threshold is examined with a tuning fork (64 Hz, 8/8 scale) at the (lateral or medial) malleolus area. Muscular pressure pain threshold is examined by applying mechanical pressure at 0.5 kg/s rate (Algometer, Somedic AB, Sweden) at the abductor halluces muscle. Except for the vibration detection threshold and pressure pain threshold, all sensory tests are performed in the S1 dermatome bilaterally (unless defined by the distribution of symptoms). Finally, brush evoked dynamic mechanical allodynia with AUC VAS scale/time and suprathreshold warm stimuli dose response curves; determination of ED50 to compare with earlier studies will also be performed. Data analysis of QST measures will be undertaken within the facilities of the German DFNS database which holds a large archive of QST data performed both in normal volunteers and patient populations.

VISIT 2:
Brain volume/structural (T1 and T2 weighted) MRI scan will be acquired. This will be followed by a resting state fMRI scan acquired while patients are resting comfortably in the scanner with eyes open and focused on a cross for 6 minutes. Patients will be asked to discontinue neuropathic pain treatment for 48hours prior to this study visit. If required, patients can take paracetamol for rescue pain relief. Medication can be restarted following this study visit.

All study visits will be performed before patients receive IV lidocaine treatment. Over the past 25 years, we have been using this treatment for intractable painful DPN that does not respond to standard oral agents. . As part of usual clinical practice, patients who have received IV lidocaine treatment will either be contacted by phone or seen in clinic to assess treatment response. Non-responders to IV lidocaine will only attend study Visits 1 and 2. They will not receive further IV lidocaine treatment.

ANALYSIS PLAN: We will classify patients into responders and non-responders to intravenous lidocaine treatment using a machine-learning algorithm [hyper-parameter tuned

support vector machine classifier (SVM)]. Sources will be chosen a-priori and extracted from the structural and volumetric analysis. Of these the most relevant features from both the resting state and the T1 image analysis were chosen using a cross validated recursive feature elimination (RFE-CV) method. Lastly, a 10-fold cross-validation will also be implemented to reduce out of sample bias. All analyses will be performed using the Scikit-learn package in Python [34]. The performance of the machine-learning algorithm will be determined by the area under the receiver-operating-characteristic curve (AUC). Finally, we will develop a machine learning algorithm to stratify painful DPN patients for lidocaine treatment using two threshold values: one that maximises sensitivity and the other maximises specificity, such that the negative likelihood ratio would approach 0.1 while the positive likelihood ratio would approach 10.

SAMPLE SIZE: We ran a simulation learning curve to model the predicted performance of different sample sizes. A learning curve is used in machine learning algorithms to determine how much improvement in classification accuracy is gained by increasing the sample size. Sample size of 40 (20 responders and 20 non responders) yields a predicted mean cross-validated classification accuracy score of 0.78(standard deviation 0.067). In comparison, a 30-subject study is predicted to yield a classification accuracy of 0.77(0.07) and 60 subjects increases classification accuracy to 0.80(0.07). Hence, in order to maximise value for the funding available we propose to examine 40 subjects. 45 subjects to be recruited to allow for 12.5% attrition.

DISCLAIMER

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