File Cover Sheet
On this sheet, please complete **all** shaded areas

Short Title:	
Project Title:	**Mechanisms of neuropathic pain following spinal cord injury: role of the spinothalamic tract**
Date approved	
Date not approved	

CONTACT DETAILS:

Principal Investigator:	Dr John Riddell	Tel:	0141 330 4495
Institution	University of Glasgow	Fax:	
Department	Institute of Neuroscience & Psychology, College of MVLS	email	John.Riddell@glasgow.ac.uk

2nd Grant holder:	Dr Jozien Goense	Tel:	0141 330 3948
Institution	University of Glasgow	Fax:	
Department	Institute of Neuroscience & Psychology, College of MVLS	email	Jozien.Goense@glasgow.ac.uk

3rd Grant Holder:	Dr Guillaume Rousselet	Tel:	0141 330 6652
Institution	University of Glasgow	Fax:	
Department	Institute of Neuroscience & Psychology, College of MVLS	email	Guillaume.Rousselet@glasgow.ac.uk

4th Grant Holder:	Dr Aleksandra Vukovic	Tel:	0141 330 3251
Institution	University of Glasgow	Fax:	
Department	Biomedical Engineering, College of Engineering	email	Aleksandra.Vukovic@Glasgow.ac.uk

5th Grant Holder:	Professor Bernard Conway	Tel:	0141 548 3316
Institution	University of Strathclyde	Fax:	
Department	Biomedical Engineering	email	b.a.conway@strath.ac.uk

6th Grant Holder:	Dr Margaret Purcell	Tel:	0141 201 2555
Institution	Queen Elizabeth University Hospital, Glasgow	Fax:	
Department	Queen Elizabeth National Spinal Injuries Unit	email	Margaret.purcell@ggc.scot.nhs.uk

7th Grant Holder:	Matthew Fraser	Tel:	0141 201 2539
Institution	Queen Elizabeth University Hospital, Glasgow	Fax:	0141 201 2778
Department	Queen Elizabeth National Spinal Injuries Unit	email	Matthew.Fraser@ggc.scot.nhs.uk

PROJECT:

Start Date:	October 2017	End Date:	March 2021	Duration in months:	42
Does the project involve clinical research?			yes		
Does the project involve NHS services or resources?			yes		
Location of Project	University of Glasgow &Queen Elizabeth National Spinal Injuries Unit				
Amount Requested	£ 100,116				

FOR OFFICE USE						
Amount of award	£		Start date for award		End date	
Number of Payments						
Distribution of Payments						
	Year 1		Year 2		Year 3	
Month 1						
Month 2						
Month 3						
Month 4						
Month 5						
Month 6						
Month 7						
Month 8						
Month 9						
Month 10						
Month 11						
Month 12						

For Office use Project Reference No

INSPIRE

Improving the Quality of Life of the Spinal Cord Injured

Application for an INSPIRE grant

Notes:

a. Please read the covering notes before proceeding with your application.
b. Please follow the format of this form.

1. Applicants

NAME	APPOINTMENT	DEPARTMENT/INSTITUTION
John Riddell	Senior Lecturer	Inst. of Neuroscience & Psychology, College of MVLS, University of Glasgow
Jozien Goense	Senior Res Fellow	Inst. of Neuroscience & Psychology, College of MVLS, University of Glasgow
Guillaume Rousselet	Senior Lecturer	Inst. of Neuroscience & Psychology, College of MVLS, University of Glasgow
Aleksandra Vukovic	Lecturer	Biomedical Engineering, College of Engineering, University of Glasgow
Bernard Conway	Professor	Biomedical Engineering, University of Strathclyde
Margaret Purcell	Consultant	Queen Elizabeth Spinal Injuries Unit, Queen Elizabeth University Hospital, Glasgow
Matthew Fraser	Consultant	Queen Elizabeth Spinal Injuries Unit, Queen Elizabeth University Hospital, Glasgow

2. Address and telephone number of the institution accommodating the project:

University of Glasgow
University Avenue
Glasgow
G12 8QQ
Tel: 0141 330 2000

3. Title of project: Mechanisms of neuropathic pain following spinal cord injury: role of the spinothalamic tract

4. Abstract of research - in not more than 150 words:

Central neuropathic pain is a particularly nasty chronic pain condition that affects about 50% of spinal cord injured patients. It seriously impacts quality of life and is frequently difficult to control. The mechanisms underlying this form of pain are poorly understood and this hampers development of therapies. The aim of this project is to investigate the mechanisms of below-level pain in SCI patients by comparing pain pathways in patients that have developed neuropathic pain with those that are pain free. We will investigate whether sparing of the spinothalamic tract is necessary for development of pain after neurologically complete injuries using sensitive tests based on laser stimuli. We will also investigate supraspinal mechanisms using EEG and functional brain imaging (fMRI) to investigate activity and connectivity that is specific to the brains of patients with neuropathic pain. These approaches will provide mechanistic information and quantitative methods of assessing pain essential for drug discovery.

5. Key words (no more than six): neuropathic pain, spinal cord injury, laser stimulation, spinothalamic tract, perceptual thresholds, evoked potentials

6. Summary of support requested:

The main support requested is for the stipend of a PhD student, who will receive training while working on this project, and the cost of MRI scanning. In addition some small items of equipment, consumables costs and travel and fees for training courses that would be a valuable part of the student's training are requested.

7. Total cost of application: £100,116

8. Proposed starting date: October 2017 **Proposed duration:** 42 months

9. Finance requested: £100, 116

Salary Studentship: Stipend £51,388 + £12,738 fees

Describe proposed appointment with salary scale, grade, and, where known, the name of the individual research worker undertaking the project.

Please complete this section for each proposed employee.

PhD studentship on a Stipend commensurate with that of Research Council UK PhD studentships. Approx. £14,700 per annum for 3.5 years. The last 6 months will be writing up only. This will enable the student to work for a full 3 years on the project with the final 6 months of the grant requiring only stipend support (£7,588) as fees and project running costs will not apply. Fees for 3 years are £12,738.

10. Expenses

Detail of all materials and consumables required, with estimated costings for each year requested.

Cables, electrode repairs, signa gel, blunted needles, syringes, measuring tape, adhesive electrode rings, prep pad alcohol wipes, blenderm tape, Q tips, safety pins, stationary etc: £3000
1% capsaicin for sensitization (The Specials Laboratory Ltd): £2,100

Apparatus

Detail of any essential apparatus or other non-recurrent expenses required to support the project.

MRI scanning time, 40 subjects @ £366 per scan = £14,640
2 pairs of laser safety goggles: £500
EEG caps, small, medium and large, with electrodes (Easy Cap) 3 X £2350 = £7050
Laptop for acquisition and logging of data in the unit including EEG data, QST data, pain questionnaire data, ISNCSCI data: £850
Matlab for EEG analysis (with FieldTrip or EEGLAB EEG freeware): £500
PC for post-grad student: £850

Travel

Reimbursement of travel for SCI subjects attending the unit for participation in tests. Assuming 50% of patients request travel assistance averaging £20 per patient. £1500
PhD student attendance at an EEG analysis training course in FieldTrip or EEGLAB: £1000
PhD student attendance at quantitative sensory testing training course (Mannheim): £1500 course fee and travel (this may be combined with visit to Heidelberg for ISNCSCI training)
PhD student attendance at a meeting of the ISRT: £500

NHS Service Support Costs. *As INSPIRE has met the criteria for National Institute for Health Research (NIHR) Partner Organisation status, any studies funded by INSPIRE will be eligible for inclusion in the NIHR Clinical Research Portfolio and hence access to infrastructure support through UKCRNs.* **Please list below what NHS services and resources you will need to access in pursuit of this project:**

Costs are requested for adaptation of a room in the Queen Elizabeth National Spinal Injuries Unit to provide the necessary safety features for use of class IV laser equipment: £2000 (NB pilot laser studies have so far been performed in the PI's labs in the Institute of Neuroscience & Psychology).

11. **The Award of the Grant** *Should you be successful, the grant will be apportioned and paid out 4 times a year in arrears but only after previously agreed key milestones have been successfully achieved.* **Please submit on a separate sheet a simple Gantt Chart showing these milestones which will form the basis upon which the grant will be made.**

12. Proposed Research Project - please describe the project in clear simple terms, covering no more than four sides of A4 paper, under the following sub-headings:

1. Title: Mechanism of neuropathic pain following spinal cord injury: role of the spinothalamic tract

2. Background information

The problem of neuropathic pain following spinal cord injury: Pain can be a severe complication after spinal cord injury. Chronic pain in body regions below the injury ('below-level central pain'; Siddall et al. 2000, Widerstrom-Noga et al. 2008) has an estimated prevalence of between 35 and 70% (Siddall et al. 1999, 2003; Finnerup et al. 2001). This type of pain is frequently excruciating and seriously impacts the quality of life. It may disrupt sleep, prevent participation in everyday activities and preclude gainful employment. It may cause depression and in extreme cases can become an overriding concern, driving sufferers to contemplate suicide. Neuropathic pain is poorly controlled with current available therapies and normally persists throughout life so that there is a major unmet clinical need amongst the spinal cord injured population for better methods of pain relief and management.

Mechanisms underlying neuropathic pain: The neural mechanisms underlying the development and maintenance of neuropathic pain are poorly understood and this is one reason for slow progress in developing novel therapies. It is thought to arise from an increase in the excitability of the nervous system which may occur at different levels (Defrin et al. 2001; Finnerup & Jensen, 2004). One prevalent view for which there is increasing evidence is that damage to the spinal cord leads to an inflammatory response and activation of glia (microglia and astrocytes) and that consequent neuron-glia crosstalk triggers the hyperexcitable state (Hains & Waxman, 2006).

Role of the spinothalamic tract: The spinothalamic tract (STT) is the main ascending pain pathway in primates. Below-level pain can occur following both incomplete and complete injuries. Its existence after complete injuries, its spontaneous nature and reports of abnormal patterns of activity in sensory structures of the brain has led to the idea that this type of pain may be generated by a supraspinal mechanism (Boord et al. 2008; Jensen et al. 2011). However, there is also some evidence that a degree of sparing of the STT tract may be necessary for the development of below-level pain. Wasner et al. (2008) studied patients with chronic complete (ASIA-A) injuries of the spinal cord, half of whom suffered from below-level pain and half of whom were pain-free. They reported that heat stimuli applied to sensitized (capsaicin) areas of skin below the injury were perceived as painful by 7 of 12 patients suffering central pain but not by any of the pain-free patients. These observations suggest that sparing of the STT is closely associated with development of below-level pain. Heat stimuli appear to be a more sensitive test than pinprick for spared STT function and it has been reported that contact heat evoked potentials can be elicited by stimulation of dermatomes where pin prick sensation is absent, providing further evidence that minor STT sparing may be more common than previously appreciated and significantly underestimated by the pin prick discrimination test (Haefeli et al. 2013). In animal models of SCI, spontaneous activity develops in sensory neurons below the injury level and this may in turn drive spontaneous activity in spared STT neurons (Yang et al. 2014). The role of the STT in below-level pain following incomplete injuries has also yet to be clearly established. Quantitative sensory testing suggests that below-level neuropathic pain of greater severity is associated with greater sensitivity to thermal stimuli below the level of injury and that greater sparing of the STT therefore leads to more severe pain symptoms (Cruz-Almeida et al. 2012). However, there are also studies that suggest that damage to the STT may be necessary for the development of below-level pain (Defrin et al. 2001, discussed by Finnerup et al. 2007).

Role of supraspinal structures in chronic pain states: Identifying the supraspinal structures responsible for pain processing and understanding how pain perception emerges from neural activity is of immense interest because of the enormous implications it has for drug discovery (Hu & Iannetti, 2016; Wanigasekera et al. 2016). Non-invasive recordings of brain activity by EEG, MEG or functional neuroimaging are powerful approaches for investigating this problem. Noxious stimuli are associated with changes in gamma band oscillations over the primary somatosensory cortex (Gross et al. 2007) and there is evidence that this reflects cortical processing involved in pain perception as their magnitude correlates with the intensity of pain (evoked by laser stimuli; Zhang et al. 2012). More recently, an increase in gamma activity has been described over the prefrontal cortex in normal subjects in which heat was used to induce periods of tonic nociceptive pain (Schulz et al. 2015). The findings in this study suggest that gamma-band oscillations may provide a biomarker for pain which relates to subjective pain intensity. Studies based in the Spinal Unit in Glasgow show that oscillatory activity during imagined movement differs between SCI patients with and without pain (Vukovic et al. 2014) and a therapy aimed at modulating activity in supraspinal structures based on this approach is being developed. However, it remains to be established whether resting state gamma band activity or other oscillatory activity is correlated with chronic central neuropathic pain conditions in SCI patients and whether such changes correlate with particular aspects of pain or can be used to predict the development of pain. Functional magnetic resonance imaging (fMRI) of human subjects during the perception of pain has identified consistent activation of interconnected regions including the anterior cingulate cortex, insula, and thalamus (the so called 'pain matrix') and other structures involved in the emotional aspects of pain (e.g. nucleus accumbens, amygdala) or modulation of pain (e.g. the brainstem PAG)(Melzack 1990, Tracy 2011, Apkarian 2015). However, simply detecting

activity in a brain area during pain is not sufficient, as illustrated by individuals with a congenital insensitivity to stimuli that normally cause pain, who show activation of these same pain matrix structures (Salomons et al. 2016). It is therefore necessary to establish that activity is linked to perceptual qualities unique to pain. The dorsal posterior insular cortex is suggested to be one area that may sub-serve a fundamental role in pain perception. Cerebral blood flow in this region is correlated with pain ratings in individual subjects (Segerdahl et al. 2014), stimulation in this region in epilepsy patients triggers pain (Mazzola et al. 2009) and lesions in this area alter pain perception in man (Garcia-Larrea et al. 2013). Studies specific to spinal cord injury pain are limited and most have focused on whether maladaptive brain plasticity in response to deafferentation contributes to the development of pain states. However, even here, only a small number of studies have rigorously addressed this question (Jutzeler et al. 2015, 2016). The ability to study sets of patients with similar injuries, some of whom develop pain and some of whom do not, provides the opportunity to interpret differences in fMRI activity in terms of pain perception and thereby illuminate supraspinal mechanisms of chronic neuropathic pain.

3. Aims and purpose of the proposed investigation

Part 1. Laser stimulation and tests of perception. Is sparing of the spinothalamic tract necessary for the development of below-level neuropathic pain?

- To determine whether sensitization and/or laser stimulation can reveal minor sparing of the spinothalamic tract, not disclosed by pin prick tests, in patients with complete injuries.
- To determine whether perception of laser stimuli below-level is specific to individuals with neuropathic pain and whether perception of these stimuli is restricted to the 'painful' body part.
- To determine whether perceptual thresholds for pinprick sensation evoked by laser stimuli below-level in incomplete patients are increased or reduced compared to normal subjects and how these changes relate to the absence, presence or qualities of pain.

Part 2. Laser evoked potentials and EEG. Is increased gamma band activity a consistent and specific feature of the EEG in patients suffering from neuropathic pain? (to be performed on selected patients from Part 1.)

- To test whether LEPs can be evoked from test locations below-level where sensitization and/or laser stimuli are perceived but pin prick sensations are absent and if they are reduced in incomplete patients with pain.
- To determine whether resting state EEG shows differences in oscillatory brain activity in the gamma band (or other frequencies) in pain-sufferers versus pain-free SCI patients.
- To determine whether oscillatory brain activity is altered differently in response to provocation with sensitization and/or laser stimuli in pain-suffering versus pain-free patients.

Part 3. Can fMRI detect areas in which functional activity or connectivity is altered specifically in spinal cord injured patients with neuropathic pain and do these fMRI changes correlate with features of pain? (selected patients from Part 1.)

- To investigate differences in resting state brain connectivity in SCI patients suffering ongoing spontaneous pain compared to pain-free patients and to able bodied control subjects.
- To investigate differences in the processing of responses to sensitization and/or laser stimuli applied below-level in SCI patients suffering ongoing spontaneous pain compared to pain-free patients and able bodied controls.

4. Detailed plan of investigation and scientific procedures

Part 1. Is sparing of the spinothalamic tract necessary for the development of below-level neuropathic pain?

Patients will be selected from a database of more than 2000 patients who have passed through the unit over the last 20 years. We aim to recruit 25 patients with complete injuries who suffer from below-level neuropathic pain and 25 patients who are pain-free. Exclusion criteria will be applied to avoid unreliable subjects (e.g. known history of drug or alcohol abuse), subjects with conditions that would complicate interpretation of results (e.g. musculoskeletal pain, other neurological conditions) or are unsuitable for laser stimulation (e.g. skin lesions). Inclusion criteria will consider level of injury, time since injury, age, pain symptoms, accessibility of 'painful' areas, geographical location and reliability. Patients with severe pain will normally be taking analgesics but pain control is rarely fully effective. Assessment of the severity and characteristics of pain will be based on that whilst on normal medication. Patient notes and a questionnaire (postal/telephone) designed to obtain updated information on inclusion/exclusion criteria, the existence of spontaneous pain, and the body areas from which the pain arises will be used in the first stage of selection. Results from the sensory part of the ISNCSCI exam together with a map of painful areas will be particularly important in informing patient selection because of their relevance to test locations (see below). Both the ISNCSCI exam and pain questionnaire will be repeated at the first test session at the Spinal Unit. We will use laser stimulation to look for spared STT function. Contact heat with Medoc pathway equipment has already been shown to reveal such sparing where pin-prick does not (Haefeli et al. 2013), probably because the rapid heating it achieves induces a synchronous discharge in nociceptors. Since laser stimuli heat the skin even more rapidly (1000^{o}/s compared to 70^{o}/s) these should be even more effective and there is evidence from a side by side comparison that this is indeed the case (Iannetti et al. 2006). Laser stimuli, kept within safe maximal limits, will be applied below-level to test for perception.

In the study of Wasner et al. (2008), sensitization with capsaicin was used to increase skin sensitivity. Since rapid contact heating alone is sufficient to detect sparing in dermatomes where there is no pin-prick discrimination (Haefeli et al. 2013), sensitization may not provide any advantage over laser stimulation alone. Nevertheless, given the importance of using the most sensitive test available, in the first set of patients we will investigate this by comparing heat stimuli alone and after sensitization with capsaicin (1% applied to the skin, Wasner et al. 2008; Shenoy et al. 2011; Segardahl et al. 2015). We aim to test at least two, and up to four sites, below the injury level, in each patient using the selected stimulus paradigm (sensitization and/or laser stimulation). For cervical level injuries, sites will be selected from the hand (C6, 7, 8) and trunk at T4 (nippleline), T6 (xiphisternum), T8 and T10 (umbilicus). For thoracic level injuries additional sites on the mid-thigh (L2), the medial knee (L3) and ankle (L4) will be considered. In addition C3 or C4 (above-level) will be used to educate the subjects to the sensations evoked by laser stimuli. These sites are readily accessible with the subject lying on a couch (and at least some while in the MRI scanner). The choice of sites will depend on the levels at which sensation is entirely absent (according to ISNCSCI tests) and the areas from which patients 'feel' pain as indicated on a standard drawing of the body (obtained before recruitment and repeated on day of test). Participants will be selected so that their 'painful area' overlaps with the intended test sites. For some individuals, one or more of these test locations may be outside the area of the referred central pain, enabling us to ask whether sensation produced by sensitization and/or laser stimulation is specific to the painful area or also extends into non-painful areas (i.e. is spinothalamic sparing specific to the painful body region). We hypothesise that in pain free individuals there will be an absence of sensation while others will report a sensation, even where pin prick could not be detected.

Depending on progress we aim to extend this part of the study to an investigation of individuals with incomplete injuries. We aim to include at least 15 patients with below level pain, 15 pain free patients and 15 able bodied controls. STT function will be investigated by measuring perceptual thresholds. In preliminary experiments in normal individuals we have shown that laser stimuli can be used to investigate pin prick heat thresholds (see Figs. 1 and 2). We have now combined laser stimulation with thermal imaging so that perceptual thresholds can potentially be determined using both laser power and the peak skin temperature produced. In preliminary investigations in normal individuals we have obtained average values for warmth perception of 34.5^{o}C and for pin prick heat of 41.2^{o}C. These are comparable to those obtained by contact heat (Rolke et al. 2006). The same test locations will be investigated as for complete patients but in addition, standard quantitative sensory testing (Rolke et al. 2006, Cruz-Almeida et al. 2012) will be performed to characterise other pain modalities and sensory functions. We will look for increased laser perceptual thresholds indicative of STT damage and aim to correlate these with reduced laser evoked potentials (see Part 2, below). We will examine whether these indicators of STT damage differ between the pain-suffering and pain-free groups, and whether they correlate with qualities of central and evoked pain.

Part 2. Are specific patterns of EEG activity associated with SCI pain? Patients for this part of the study will be selected from those investigated in Part 1. We aim to investigate 20 subjects with pain, 20 that are pain-free (10 each with complete and incomplete injuries) and 20 normal subjects. The synchronous activation of nociceptors by laser stimulation produces laser evoked potentials (LEPs, seen in EEG as event related potentials) recordable over the sensory cortex. These have been extensively studied in the context of both nociceptive pain and in different pain states (though not pain after SCI) and found to reflect mainly the integrity of the pain pathway rather than pain perception (Garcia-Larrea et al. 2002). We will therefore use LEPs to assess the integrity of the STT and look for LEPs evoked by stimuli applied below-level within selected test locations based on information obtained in Part 1 (see Fig. 3). We hypothesise that in ASIA-A patients, LEPs will be detectable following stimulation at sites corresponding to those where stimuli are perceived but not where there is no perception of the stimulus. In incomplete patients we will look to confirm that increased pin prick thresholds correlate with smaller LEPs. We will also use EEG recording to look for altered oscillatory activity that might be specifically associated with aspects of the pain condition by comparing resting state EEG recorded from each of the patient groups and normal subjects. We will then investigate whether EEG is modified differently in each of the subject groups in response to painful stimuli (sensitization and/or laser stimulation).

Part 3. Can fMRI reveal activity specific to the brains of SCI patients suffering neuropathic pain? A subset of the patients investigated in Parts 1 and 2 will be selected for fMRI based on their suitability for scanning, the nature and characteristics of their pain and their response to sensitization and/or laser stimuli below-level. We aim to scan 13 patients with complete injuries and below-level pain, 13 patients with complete injuries and no pain and 13 normal subjects. Injured patients with and without pain will, as far as possible, be matched for level of injury, time after injury and age. Selected patients will be asked to keep a pain diary for the week prior to scanning and the pain they are experiencing during scanning will be documented. Scanning will be performed using a Siemens 3T Prisma research-dedicated scanner located in the QEUH. For anatomical reference we will use a high-resolution T_1-weighted scan, 3D-MPRAGE, 1x1x1 mm^3. For stimulus-driven and resting state fMRI we will use a T_2^*-weighted EPI with spatial resolution of 3x3x3 mm^3, sufficient slices to cover the entire brain, echo time (TE) of 30 ms, and repetition time (TR) of 2000 ms. We will look for differences in resting-state connectivity between patients with and without below-level

pain and normal subjects in order to identify areas and connections specifically active in those with pain. If we are able to identify individuals with spontaneous pain which waxes and wanes with a suitable frequency, we will take advantage of this to scan during and between their painful episodes. This will enable us to compare resting state connectivity in the same patient under these different conditions and may enable us to pinpoint areas of activity specific to the spontaneous pain condition. We will follow the resting state scans with a stimulus paradigm involving sensitization and/or laser stimulation applied as in Part 1. We will pilot a block design (e.g. 20s of stimulation and 40s off) and event-related design and choose the most suitable approach. This will enable us to look at functional connectivity and pain-induced activation in the same individual. A comparison will be made between those patients in which sensitization and/or laser stimulation evokes a pain sensation, those patients in which such stimuli evoke no sensation and normal subjects. If during the tests in Part 1, we find that some patients perceive pain following sensitisation and/or laser stimulation only in areas corresponding to their central (spontaneous) pain, then we will compare brain activity inside and beyond this area in these individuals. We anticipate that those SCI patients that perceive increased pain in response to sensitization and/or laser stimulation will show an increased BOLD response in pain-related brain areas (which may correspond to areas showing altered resting state connectivity), while those that are unable to perceive such stimuli will not. We will evaluate whether the strength of the BOLD response correlates with the reported level of pain. Comparison of scans from pain perceiving and non-perceiving SCI patients should allow identification of structures specifically engaged in the processing of painful stimuli, while comparison with normal individuals will allow distinction between acute nociceptive processing of laser-evoked pain and the differences that occur in chronic pain. We would expect to see changes in connectivity specific to the pain matrix in patients perceiving pain. Of particular interest will be whether the dorsal posterior insular cortex emerges as a region specifically activated in chronic pain (Segerdahl et al. 2014).

6. Expected outcome to benefit the Spinal Cord Injury Community

Improved understanding of mechanisms and therapeutic strategy: The project will provide a better understanding of the mechanisms underlying neuropathic pain. Part 1 will provide evidence of the origin(s) and therefore therapeutic target(s) for below level pain. Establishing a close correspondence between perception of below-level laser stimuli and the presence of central pain would indicate that treatments that can interfere with signaling in primary afferent fibres (including spontaneous activity), processing in the spinal cord and transmission along the STT should be effective in preventing the induction and or maintenance of pain, even in patients classified as neurologically complete. The development of new therapies should therefore target peripheral, spinal as well as supraspinal mechanisms. The project will also provide a better understanding of the supraspinal mechanism of neuropathic pain. EEG (Part 2) and fMRI (Part 3) analysis of patients, in addition to providing further information on spinothalamic sparing, may reveal specific signatures of oscillatory brain activity or activity in particular brain structures or networks that are associated with pain perception in SCI patients. This may lead to tools for the objective assessment of pain that would be of significance in the development of analgesic therapies (see below).

Development of prognostic tests: If sensations elicited by sensitization and/or laser stimulation are shown to be closely associated with the development of neuropathic pain in patients with a complete injury then this would indicate that laser stimulation examined acutely could be a prognostic test for development of pain in this patient group. A follow-on study of acutely injured patients, investigating the ability of perceptual tests with laser stimuli to predict those ASIA-A patients developing neuropathic pain in the months and years after injury would then be warranted. Perceptual testing with laser stimuli will likely have greatest prognostic value for patients with complete injuries but EEG and fMRI features may be more widely applicable to SCI patients destined to develop central pain and thus usefully investigated in a wider cohort of patients with incomplete injuries.

Developing prophylactic treatments for neuropathic pain: The ability to predict those patients that will develop neuropathic pain would be of great benefit in the development of a prophylactic approach to the treatment of SCI related pain (Zeilig et al. 2012). Current treatments are aimed at symptomatic relief but therapies that aim to block induction of a chronic pain state before it has developed may be more effective. However development of a pre-emptive strategy will require a means of reliably predicting those patients in which pain will develop because success can only be recognized if the probability of a prophylactically treated patient going on to develop pain is known. A predictive test will also be essential for targeting treatment since side effects and cost considerations mean that treatment would only be indicated in those at high risk for the development of neuropathic pain. The potential of this approach and the need for further research in this area was recognised in a draft report on Spinal Cord Injury therapies from NICE.

Facilitation of further research: Being able to predict which patients have a high probability of developing neuropathic pain would facilitate further investigation of mechanisms and treatments. A longitudinal fMRI study of SCI patients developing neuropathic pain would be extremely valuable as it would allow changes in the brain that correlate with the onset and progression of pain symptoms to be investigated and followed in the same individual. This approach would be particularly powerful as it removes variability due to patient heterogeneity. However, the inability

to predict those SCI patients who will develop neuropathic pain currently makes this approach costly. EEG and fMRI also have the possibility to lead to objective, quantitative assessments of pain which could circumvent reliance on pain reporting by patients, difficulties of quantifying pain severity and the problem of the placebo effect when assessing new analgesics. Identifying brain activity indicative of pain would therefore be extremely valuable in the development and testing of new analgesic treatments (Wanigasekera et al. 2016).

5. Justification for support requested

Staff: Assistance with recruitment, consenting, co-ordination of the project, conduct of testing and analysis will be essential. Preliminary work with laser testing has established that it is most efficiently performed by two persons, one holding the laser hand piece to ensure safe targeting of the laser beam and another operating the laser and recording responses. In practice it will be essential to conduct the tests this way to keep patient testing time within acceptable limits. The proposal would form an excellent PhD project and we are requesting a stipend and fees to cover 3 years with a further 6 months of stipend-only support for writing up. **Equipment:** Laser, EEG, thermal camera and QST equipment has been supplied by the Institute of Neuroscience and Psychology. Some smaller items of equipment and accessories are requested including EEG caps and electrodes and a laptop/software for data acquisition and analysis. The room in the Spinal Unit identified for this project will require minor safety modifications to limit access and prevent reflection of stray laser beams. **Consumables/running costs:** MRI scanning costs are requested. Current scanning charges represent excellent value for money compared to other centers because NHS R&D are in an interim period and have yet to finalize a system for costing scanner time for research purposes. A few essential consumables, mainly for EEG recording, are also requested. **Travel:** Travel, subsistence and some course fees are requested to enable the student to attend training courses (e.g. specialized EEG analysis course and QST course run by German Neuropathic Pain Group in Mannheim which it may be possible to combine with attendance at an ISNCSCI training workshop in nearby Heidelberg).

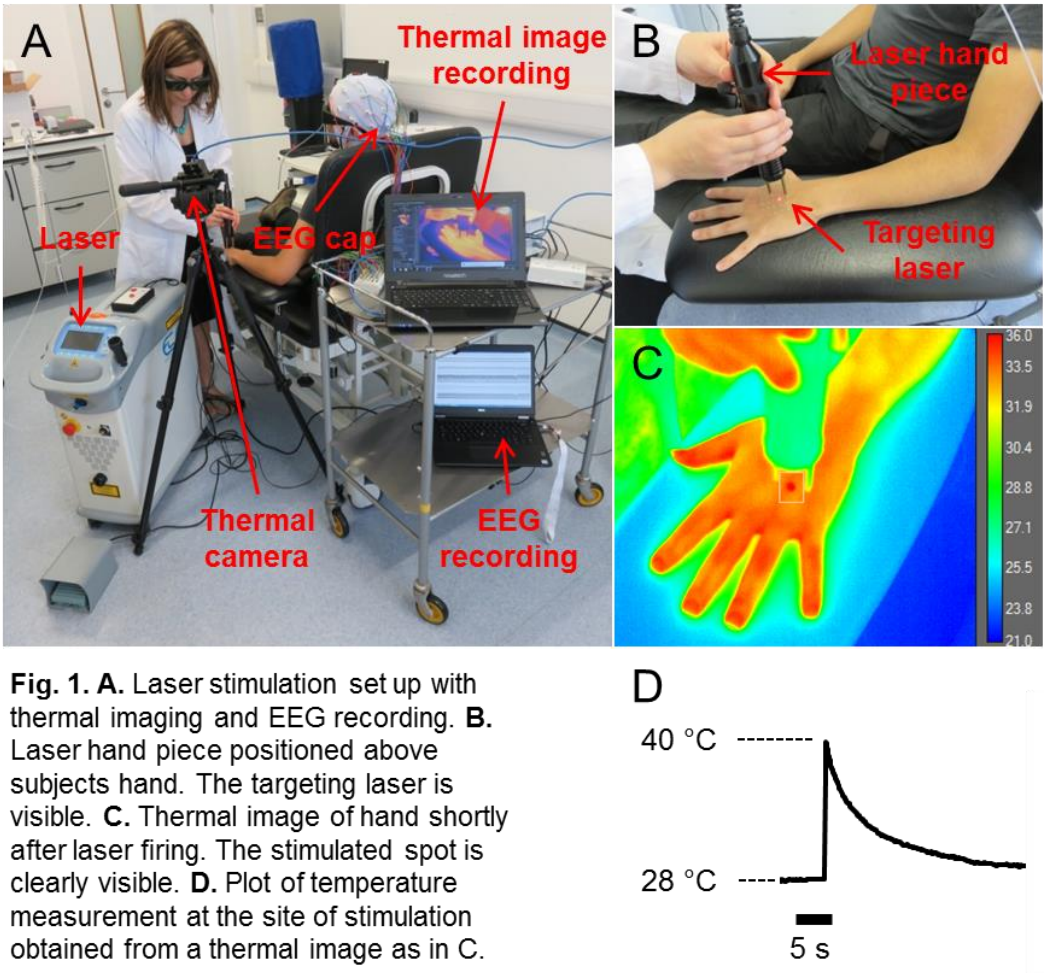

Fig. 1. A. Laser stimulation set up with thermal imaging and EEG recording. **B.** Laser hand piece positioned above subjects hand. The targeting laser is visible. **C.** Thermal image of hand shortly after laser firing. The stimulated spot is clearly visible. **D.** Plot of temperature measurement at the site of stimulation obtained from a thermal image as in C.

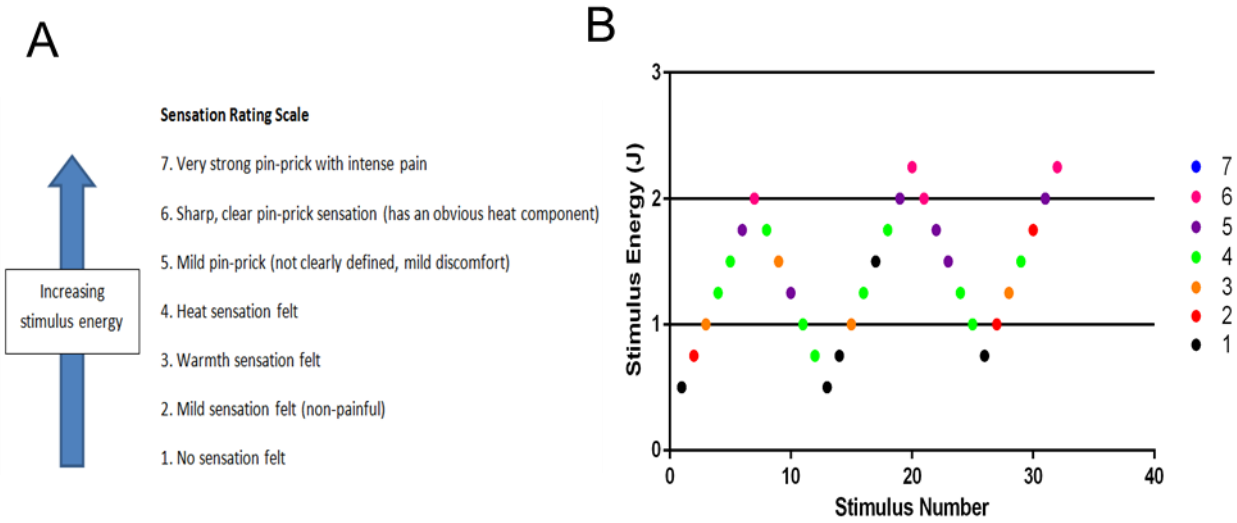

Fig. 2. Procedure for testing perceptual threshold in response to laser stimuli. **A.** Scale for perceived sensation associated with progressively increasing stimulus energy levels. **B.** Results obtained from a subject while applying laser stimuli over a range of intensities to the hand. Starting with a laser energy setting below perceptual threshold, the intensity was increased in 0.25 J steps until a sharp, clear pin-prick sensation was reported. Laser intensity was then reduced until no sensation was reported and the process repeated. Alternative strategies including random presentation of stimuli with different energies proved less suitable.

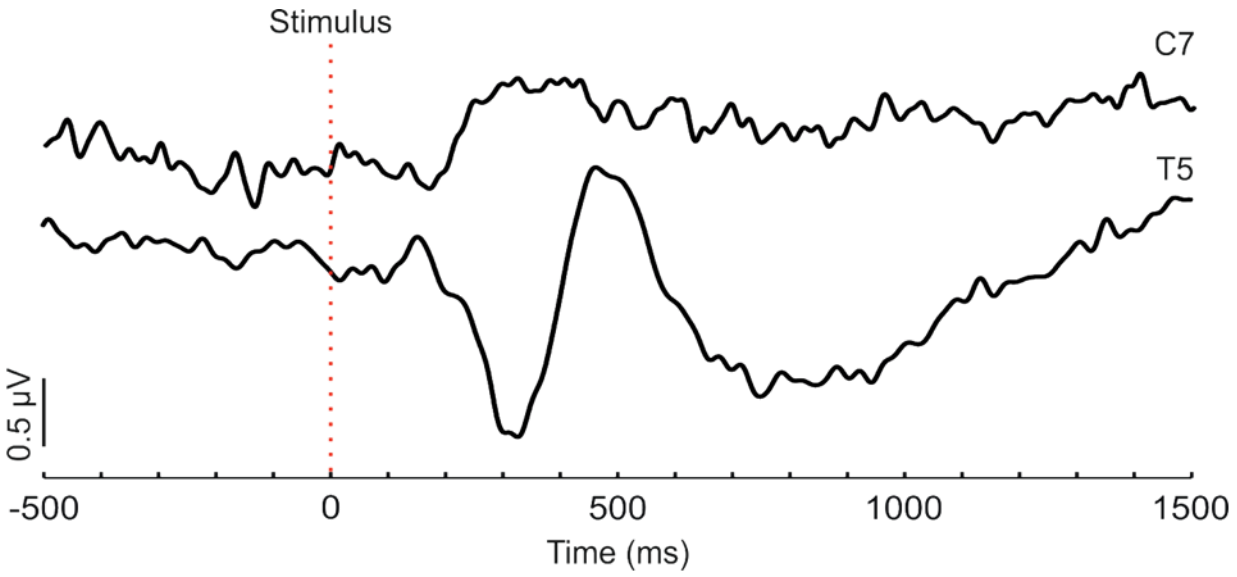

Fig. 3. LEPs recorded during laser stimulation of the C7 (hand) and T5 (back) dermatomes. Stimulus parameters: 5 ms pulse length, 6 mm spot diameter, 2.75 J (C7), 1.75 J (T5). Signals were band-pass filtered from 0.1-40 Hz. Trials contaminated with blink artefacts were manually removed. The traces are averages of 80 potentials (C7) or 138 potentials (T5).

APPENDIX I

Scientific references to the application:

Agostino, R., Cruccu, G., Iannetti, G., Romaniello, A., Truini, A. and Manfredi, M. (2000). Topographical distribution of pinprick and warmth thresholds to C02 laser stimulation on the human skin. Neuroscience Letters 285: 115-118.

Baliki, MN., Mansour, AR., Baria, AT. & Apkarian, VA. (2014). Functional reorganization of the default mode network across pain conditions. Plos One; 9 e06133

Boord, P., Siddall, P. J., Tran, Y., Herbert, D., Middleton, J. & Craig, A. (2008). Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury. Spinal Cord, 46, 118-123.

Cruz-Almeida, Y., Felix, E.R., Martinez-Arizala, A. & Widerstom-Noga, E.G. (2012) Decreased spinothalamic and dorsal column medial lemniscus-mediated function is associated with neuropathic pain after spinal cord injury. Journal of Neurotrauma 29: 2706-2715.

Defrin, R., Ohry, A., Blumen, N. & Urca, G (2001) Characterisation of chronic pain and somatosensory function in spinal cord injury subjects. Pain 89:253-263.

Finnerup, NB., Johannesen, IL., Sindrup, SH., Bach, FW & Jensen, TS. (2001) Pain and dysesthesia in patients with spinal cord injury: apostal survey. Spinal Cord 39:256-262.

Finnerup, NB & Jensen, TS (2004) Spinal cord injury pain-mechanisms and treatment Eur J Neurol 11:73-82.

Finnerup, NB., Sorensen, L., Biering-Sorensen, F., Johannesen, I.L. & Jensen, TS. (2007) Segmental hypersensitivity and spinothalamic function in spinal cord injury pain. Experimental Neurology 207: 139-149.

Garcia-Larrea, L., Convers, P., Magnin, M., Andre-Obadia, N., Peyron, R., Laurent, B and Mauguiere, F. (2002) Laser-evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain. Brain 125: 2766 – 2781.

Garcia-Larrea, L., Perchet, C., Creach, C., Convers, P., Peyron, R., Laurent, B., Mauguiere, F & Magning, M. (2010) Operculo-insular pain (parasylvian pain): a distinct central pain syndrome. Brain 133: 2528-2539.

Gross, J., Schnitzler, A., Timmermann, L. & Ploner, M. (2007) Gamma oscillations in human primary somatosensory cortex reflect pain perception. Plos Biology 5: 1168- 1173

Haefeli, J., Kramer, J.L., Blum, J. & Curt. A. (2013) Assessment of spinothalamic tract function beyond pinprick in spinal cord lesions: A contact heat evoked potential study. Neurorehabil. Neural Repair 30: 494-503.

Hains, BC. & Waxman, SG. (2006) Activated microglia contribute to the maintenance of chronic pain after spinal cord injury. J. Neurosci. 26:4308-4317.

Hu, L. & Iannetti, GD. (2016) Painful issues in pain prediction. Trends in Neuroscience 39:212-220.

Iannetti, G.D., Zambreaunu, L. and Tracey, I. (2006) Similar nociceptive afferents mediate psychophysical and electrophysiological responses to heat stimulation of glabrous and hairy skin in humans. J. Physiol. 577: 235 – 248.

Jensen, M. P., Moore, M. R., Bockow, T. B., Ehde, D. M. & Engel, J. M. (2011). Psychosocial Factors and Adjustment to Chronic Pain in Persons With Physical Disabilities: A Systematic Review. Archives of Physical Medicine and Rehabilitation, 92, 146-160.

Jutzeler, C.R., Curt, A. and Kramer, J.L.K. (2015) Relationship between chronic pain and brain reorganization after deafferentation: A systematic review of functional MRI findings. Neuroimage 9: 599-606.

Jutzeler, C.R., Huber, E. Callaghan, M.F., Luechinger, R., Curt, A., Kramer, J.L.K. and Freund, P. (2016) Association of pain and CNS structural changes after spinal cord injury. Scientific Reports, 6. DPI: 10.1028/srep18534

Mazzola L., Isnard, J., Peyron, R., Guenot. & Mauguiere, F. (2009). Somatotopic organization of pain responses to direct electrical stimulation of the human insular cortex. Pain 146: 99-104

Melzack, R. (1990) Phantom limbs and the concept of neuromatrix. TINS 13:88 - 92

Rolke, R., Baron, R., Maier, C., Tolle, T.R., Treede, R.-D., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Botefur, I.C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G.B., Magerl, W., Maihofner, C., Rolko, C., Schub, C., Scherens, A., Spenger, T., Valet, M. and Wasserka, B. (2006) Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 123: 231-243.

Salomons, TV., Iannetti, GD., Liang, M. & Wood, JN. (2016) The pain matrix in pain-free individuals. JAMA Neurology 73:755-756

Segerhahl, AR., Mezue, M., Okell, TW., Farrar JT. & Tracey, I. (2015) The dorsal posterior insula subserves a fundamental role in human pain. Nature Neuroscience, 18:499.

Shenoy, R., Roberts, K., Papadaki, A., McRobbie, D., Timmers, M., Meert, T. and Anand, P. (2011). Functional MRI brain imaging studies using the contact heat evoked potential stimulator (CHEPS) in a human volunteer topical capsaicin pain model. Journal of Pain Research 4;365-371.

Schulz, E., May., Postorino. M., Tiemann., Nickel., Witkovsky, V., Schmidt, P., Gross, J. & Ploner, M. (2015) Prefrontal gamma oscillations encode tonic pain in humans. Cerebral Cortex 25: 4407-4414.

Siddall, PJ, Yezierski, RP & Loeser, J.D. (2000) Pain following spinal cord injury: clinical features, prevalence and taxonomy. IASP Newsletter 3:3-7.

Siddall, P.J., Taylor, D.A., McLelland, J.M., Rutkowski, S.B. & Cousins, M.J. (1999). Pain report and the relationship of pain to physical factors in the first 6 months following spinal cord injury. Pain 81: 187-197.

Siddall, P.J., McLelland, J.M., Rutkowski, S.B. & Cousins, M.J. (2003). A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. Pain 103:249-257.

Tracey, I (2011) Can neuroimaging studies identify pain endophenotypes in humans. Nature Reviews 7:173 – 181.

Wasner, G., Bonne Lee, B., Engel, S. and McLachlan, E. (2008). Residual spinothalamic tract pathways predict development of central pain after spinal cord injury. Brain 131: 2387-2400.

Wanigasekera, V., Mezue, M., Andersson, J., Kong, Y. & Tracey, I. (2016) Disambiguating pharmacodynamic efficacy from behaiour with neuroimaging.: implications for analgesic drug development. Anasthesiology 124: 150-168.

Widerstrom-Noga, E., Biering-Sorensen, F., Bryce, T., Cardenas. DD., Finnerup, NB., Jensen, MP et al. (2008). The international spinal cord injury pain basic data set. Spinal Cord 46: 818-823.

Vukovic, A., Hasan, M.A., Fraser, M., Conway, B.A., Nasserolesami, B and Allan, D.B. (2014). Dynamic oscillatory signatures of central neuropathic pain in spinal cord injury. The Journal of Pain 15: 645-655.

Zhang, Z.G., Hu, L., Hung, Y.S., Mouraux, A. and Iannetti, G.D. (2012) Gamma-band oscillations in the primary somatosensory cortex-a direct and obligatory correlate of subjective pain intensity. The Journal of neuroscience 32: 7429 – 7438.

Zeilig, G., Enosh., Rubin-Asher, D., Lehr, B. and Defrin, R. (2012). The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain. Brain 135: 418-430.

Yang, Q., Wu, Z., Hadden, J.K., Odem, M.A., ZUo, Y., Crook, R.J., Frost, J.A. and Walters, E.T. (2014) Persistent pain after spinal cord injury is mediated by primary afferent activity. The Journal of Neuroscience 34: 10765 – 10769.

APPENDIX II

Details of facilities available and other support:

1. Facilities available to support the proposed project:

The application is underpinned by the facilities and specialized equipment contributed by the Institute of Neuroscience and Psychology University of Glasgow, the Departments of Engineering at Glasgow and Strathclyde and the Queen Elizabeth National Spinal Injuries Unit, NHS Greater Glasgow and Clyde and by the combined expertise of the applicants drawn from these Institutes.

The Queen Elizabeth Spinal Injuries Unit will accommodate the clinical work with spinal cord injured patients. A Model Spinal Injuries Unit opened in 1992 to provide both acute and long-term care to the spinal cord injured community throughout Scotland, the Unit provides a comprehensive clinical service (all aspects of treatment, rehabilitative training and health and wellbeing from acute care through to life-long follow-up) for 100+ new admissions per year. 47% of patients are admitted within 48 hours and the mean length of stay is 130 days for paraplegics and 150 days for tetraplegics. This provides good patient access for research studies and there is a strong research ethos within the Unit driven by productive interactions between clinicians and academics. Academic input is cross Institute and includes the Universities of Glasgow, Strathclyde and Stirling and the Glasgow School of Art incorporated within an Umbrella group, the Scottish Centre for Innovation in Spinal Cord Injury. The Centre conducts fundamental & applied clinical research in all disciplines relevant to the treatment and quality of life of people with spinal cord injury (Rehabilitation Engineering, Bioengineering, Biomedical Sciences, Health and Social Care, Psychology) and these activities are embedded within the clinical service. Direct and frequent interaction between academics and clinicians ensures that research is informed by real clinical and patient need and a bench to bedside approach ensures patients benefit at the earliest possible stage from the outcomes of research work. Research activities are coordinated from a purpose build Research Mezzanine within the QENSIU funded by £1.2 million from the SRIF infrastructure scheme. The facilities provide a base for Lecturers, Clinical Scientists, Postdoctoral staff and PhD students and their research in the Unit is funded by the ISRT, MRC, EPSRC, AHRC, CSO and INSPIRE (http://www.spinalunit.scot.nhs.uk/wp-content/uploads/2015/05/Annual-Report-2014-15.pdf). A suitable room adjacent to the high dependency ward and associated nurse's station has been identified and will be modified to incorporate safety features necessary for the operation of class IV laser equipment. The clinical applicants will participate fully in discussions on the study design and provide advice and support on practical aspects of working with patients. They will also identify and make initial contact with patients potentially suitable for recruitment to the study. Clinical and Physiotherapy/Occupational therapy staff will provide access to data obtained as part of the standard care of patients in the unit.

Institute of Neuroscience and Psychology/Biomedical Engineering, Universities of Glasgow and Strathclyde

The Institute of Neuroscience and Psychology at Glasgow will provide major items of equipment required for the project. This includes laser stimulation equipment (Stimul 1340) specifically designed for clinical use and of a type widely used in published clinical and basic research work in the pain field (e.g. Hu et . 2014; Machini et al. 2012; Ronga et al. 2013). The Institute will also provide the use of portable EEG equipment (Brainamp). Applicants Rousselet, Vukovic and Conway have extensive experience of recording EEG including from spinal cord injured patients in the clinical setting. Further specialist advice particularly on analysis relating to gamma band activity is available in the Institute of Neuroscience and Psychology (Prof Joachim Gross, http://www.gla.ac.uk/researchinstitutes/neurosciencepsychology/staff/joachimgross/).

MRI facilities, Imaging Centre of Excellence

The College of Medical, Veterinary and Life Sciences, University of Glasgow, has been awarded £16M by the MRC to fund an Imaging Centre of Excellence (ICE) on the new £1B Queen Elizabeth University Hospital site (http://gtr.rcuk.ac.uk/projects?ref=MR/N003403/1). The facility will accommodate state of the

art 7 T and 3 T MRI scanners together with a high resolution CT scanner and other imaging modalities for translational and clinical research as part of a stratified and precision medicine initiative. The imaging centre is immediately adjacent to the Spinal Injuries Unit and linked by a corridor for patient access. The 7T Scientific Strategy Team is comprised of staff from the Institute of Neuroscience and Psychology (Prof Keith Muir, Dr Jozien Goense, Prof Lars Muckli). We are therefore ideally placed, both geographically and in relation to collaborators with expertise in imaging, to capitalize on this opportunity. The 3 T scanner that is already commissioned will be used for this project. Dr Goense (Applicant 2) has extensive experience in fMRI and Dr Celestine Santosh (a NHS GGC neuroradiologist with research interests in MRI) will collaborate on the MRI part of the project to provide further practical help and expert advice.

Overall this funding will enable us to bring to bear on the problem of neuropathic pain, a range of state of the art investigative approaches that capitalize on the unique opportunities provided in Glasgow which include 1) a unique combination of clinical and academic expertise, 2) access to sophisticated equipment and facilities 3) access to an extensive patient list for recruitment of subjects optimal for the study.
The project will provide excellent training for a PhD student in a range of complimentary techniques highly relevant to research on spinal cord injury and will be an excellent opportunity for a young researcher at the start of their career.

2. Grants and financial support currently held by the applicants:

Dr John Riddell
MRC Project grant £438,889 for 3 years (as co-applicant with Professor AJ Todd) (Oct 2013-Sep 2016) "Spinal inhibitory interneurons that suppress itch"
BBSRC Project grant £680,496 for 3 years (as co-applicant with Prof AJ Todd (Apr 2016-Mar 2019) "The role of NPY-containing inhibitory interneurons in spinal pain pathways"
Neurosciences foundation. With Dr. Jozien Goense & Prof Andrew Hart. Development of resting state fMRI and investigation of plasticity of cortical networks after peripheral nerve injury. £10,107

Dr Jozien Goense
Neurosciences foundation. With Dr. John Riddell & Prof Andrew Hart. Development of resting state fMRI and investigation of plasticity of cortical networks after peripheral nerve injury. £10,107
MRC. The UK7T Network; developing the ultra-high field MRI platform for biomedical research. 2016 – 2019. £1,050,000. PI Richard Bowtell with other UK7T network co-Is

Dr Aleksandra Vukovic
EPSRC Impact Acceleration Account funding for technical development of the system 'Mobile Brain-Train System' in collaboration with a company 'Abelon' £20K, till October 2016
INSPIRE £16048 Brain-Train portable neurofeedback system for treatment of central neuropathic pain following spinal cord injury 2015- 2016

Professor Bernard Conway
Scottish Government Health Directorates. Centre for Excellence in Rehabilitation (PI). Apr 2013-2018. £2.4M.
EPSRC. Centre for Doctoral Training in Medical Devices and Health Technologies. (Co-I) Apr 2014-2022. £4.1M

Dr Margaret Purcell
ISRT £10,000 Early interventions to reduce bone loss after spinal cord injury. 2015 – 2017
AHC £50,000 Revisiting spinal cord injury rehabilitation through applications of contemporary design approaches 2014 - 2016
INSPIRE £16048 Brain-Train portable neurofeedback system for treatment of central neuropathic pain following spinal cord injury 2015- 2016

Mr Matthew Fraser

3. Has this or a related application currently or previously been submitted elsewhere? YES/NO (if yes, please give details)
No

4. Is this proposed project likely to lead to patentable or commercially applicable data or apparatus? YES/NO (if yes, please give details)
No

5. Has Ethical Committee approval been obtained? YES/NO/NOT APPLICABLE

The PI is in the process of preparing applications forms via IRAS for ethical approval for the project

APPENDIX III

Grant Conditions. Should your application be successful, the grant would be conditional upon:

Ethics Approval, where appropriate, being obtained.

A sponsor, if necessary, as defined in the Department of Health's Research Governance, agreeing to sponsor the project.

Half yearly reports (maximum 250 words) being made available (January and June) for the INSPIRE Board of Trustees.

An end of trial report being made available for the INSPIRE library.

A paper, if published, in a medical/scientific journal such as *Spinal Cord* giving credit to INSPIRE.

In addition, should you publicise your work either in the press, on TV, radio or you produce a film, you are asked to give credit, where it is due, to INSPIRE.

APPENDIX IV

To be recruited
The position will be advertised and informal enquiries made amongst the wide network of colleagues with which the applicants are acquainted to identify an appropriately experienced individual with personal qualities suitable for the post

Curriculum Vitae of proposed research staff - please use a separate sheet for each person (if known).

1. Surname Forename(s) Date of Birth

2. Degrees (subject, class, university and date):

3. Current Post (please give present source of funding):

4. Summary of previous posts (with dates)

5. List your most important recent research publications (up to a maximum of 10):

6. Number of hours per working week to be spent on this project:

7. Name and address of two referees:

a. **b.**

APPENDIX V

Full contact addresses of all applicants:

APPLICANT A

Title: Dr **Initials J.S.** **Designatory Letters: BSc PhD**

Surname: Riddell **Department Institute of Neuroscience & Psychology**

Institution and address:

University of Glasgow
Post town: Glasgow Post code: G12 8QQ

Dept Tel No: 0141 330 4495 **Personal Tel No:**
Dept Fax No: **Personal Fax No:**
Dept email: John.Riddell@glasgow.ac.uk **Personal email:**

APPLICANT B

Title: Dr **Initials J** **Designatory Letters: Ir, PhD**

Surname: Goense **Department Institute of Neuroscience & Psychology**

Institution and address:

University of Glasgow
58 Hillhead St **Post town: Glasgow Post code: G12 8QB**

Dept Tel No: 0141 330 3948 **Personal Tel No:**
Dept Fax No: **Personal Fax No:**
Dept email: Jozien.Goense@glasgow.ac.uk **Personal email:**

APPLICANT C

Title: Dr **Initials G** **Designatory Letters: BSc, PhD**

Surname: Rousselet **Department Institute of Neuroscience & psychology**

Institution and address:

University of Glasgow
58Hillhead St **Post town: Glasgow Post code: G12 8QB**

Dept Tel No: 0141 330 6652 **Personal Tel No:**
Dept Fax No: **Personal Fax No:**
Dept email: Guillaume.Rousselet@glasgow.ac.uk **Personal email:**

APPLICANT D

Title: Dr **Initials A** **Designatory Letters: MSc, PhD**

Surname: Vukovic **Department Biomedical Engineering**

Institution and address:
University of Glasgow

Post town: Glasgow Post code: G12 8QQ

Dept Tel No: 0141 330 3251 **Personal Tel No:**
Dept Fax No: 0141 330 4885 **Personal Fax No:**
Dept email: aleksandra.vukovic@glasgow.ac.uk **Personal email:**

APPLICANT E

Title: Prof **Initials B.A.** **Designatory Letters: PhD, FIPEM**

Surname: Conway **Department Biomedical Engineering**

Institution and address:
Wolfson Centre
University of Strathclyde

Post town: Glasgow Post code: G4 0NW

Dept Tel No: 0141 548 3316 **Personal Tel No:**
Dept Fax No: 0141 552 6098 **Personal Fax No:**
Dept email: b.a.conway@strath.ac.uk **Personal email:**

APPLICANT F

Title: Dr **Initials M** **Designatory Letters: MBCHB BAO**

Surname: Purcell **Department Queen Elizabeth National Spinal Injuries Unit**

Institution and address:
Queen Elizabeth University Hospital

Post town: Glasgow Post code: G514TF

Dept Tel No: 0141 201 2555 **Personal Tel No:**
Dept Fax No: **Personal Fax No:**
Dept email: Margaret.purcell@ggc.scot.nhs.uk **Personal email:**

APPLICANT G

Title: Mr **Initials M** **Designatory Letters: MBCHB**

Surname: Fraser **Department Queen Elizabeth National Spinal Injuries Unit**

Institution and address:

Queen Elizabeth University Hospital

Post town: Glasgow Post code: G51 4TF

Dept Tel No: 0141 201 2539
Dept Fax No: 0141 201 2541
Dept email: matthew.fraser@ggc.scot.nhs.uk

Personal Tel No:
Personal Fax No:
Personal email:

For Office use
Project Reference No

APPENDIX VI

For 'user review' by the Executive Committee

On **one side of A4**, please describe in *lay terms* what it is you are trying to achieve for the benefit of the spinal cord injured.

TITLE OF PROJECT: Mechanisms of neuropathic pain following spinal cord injury: role of the spinothalamic tract

Most spinal cord injured patients suffer from pain at some point after their injury. Some of this is musculoskeletal in origin and caused, for example, by overuse of particular limbs. However, in about 50% of patients pain also results from damage to the nervous system itself. This type of pain is called neuropathic pain and it has particularly unpleasant qualities. Neuropathic pain frequently has a serious impact on quality of life: it disrupts sleep, it may lead to reluctance to get out of bed, it reduces the capacity for daily activity, it reduces the capacity to participate in rehabilitative training and consequently slows functional recovery. The intense nature of the pain can make it a constant and overriding concern and it may be so distracting that it prevents gainful employment even where capacity for movement is no impediment. The constant nasty nature of neuropathic pain frequently leads to a depressed mood and in extreme cases patients express the desire, or even attempt, to end their lives. The problems posed by neuropathic pain are exacerbated by the fact that it is notoriously difficult to control with current medications. There is therefore a major unmet clinical need amongst the spinal cord injured population for better pain relief and management.

We do not fully understand how pain develops over time though it is clear that it is due to progressive maladaptive changes in signaling in the nervous system and likely involves an increase in excitability at different levels of the nervous system. In addition, there is no way to predict those individuals in which pain will develop and as a result treatment is entirely symptomatic i.e. analgesics are provided only once the pain has already become established. It is likely that we would be able to develop better analgesic strategies if we had a clearer picture of how the nervous system generates pain. In addition, we might be able to control the pain more effectively if treatment could be given before the changes in the nervous system occur and the pain is fully established. However, to make this practicable, we would need to be able to predict, soon after injury, those individuals likely to develop pain. The aim of this project is to investigate the mechanism underlying central neuropathic pain in order to inform the development of treatment strategies and the development of prognostic approaches that would pave the way for pre-emptive therapeutic approaches.

Below level neuropathic pain might arise in two ways. Because it is frequently seen in individuals with a neurologically complete injury (ASIA-A) and because abnormal patterns of activity can be seen in the brain, one theory is that the pain arises in the brain. However, there is increasing evidence that the usual methods of testing for the completeness of an injury are not reliable. More sensitive methods using heat stimuli reveal minor sparing of the spinothalamic tract (the main spinal cord pain pathway) which may correlate with the existence of neuropathic pain. There is also evidence from animal studies that spontaneous activity may arise in sensory neurons below the injury and this may drive the development of abnormal activity in pain pathways. This project will use laser stimuli to investigate whether in patients with complete injuries sparing of the spinothalamic tract is specifically seen in those that have developed neuropathic pain. If so, then this will suggest that interference with peripheral and spinal cord pain processing offers an effective therapeutic strategy. It would also suggest that laser stimulation should be investigated in a study on acute patients as a potential means of predicting those patients that will go on to develop pain, thus paving the way for a prophylactic treatment strategy.

The project will also investigate supraspinal mechanisms of pain processing in spinal cord injured patients using advanced methods for recording (electroencephalography) and imaging (functional magnetic resonance imaging) brain activity. The aim will be to identify patterns of activity that are specific to the experience of central type pain in the brains of spinal cord injured patients by comparing patients with pain with those that have similar injuries but are pain-free and with able bodied individuals. The hope is that this would not only improve understanding of brain mechanisms of pain perception but also lead to ways of assessing more objectively the efficacy of potential analgesics and so advance the drug discovery process.