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Clinical Investigation

CLINICAL INVESTIGATION

# Disambiguating pharmacological mechanisms from placebo in neuropathic pain using functional neuroimaging

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## Abstract

**Background:** A lack of objective outcome measures and overreliance on subjective pain reports in early proof-of-concept studies contribute to the high attrition of potentially effective new analgesics. We studied the utility of neuroimaging in providing objective evidence of neural activity related to drug modulation or a placebo effect in a double-blind, randomized, placebo-controlled, three-way crossover trial.

**Methods:** We chronically administered pregabalin or tramadol (first-line and second-line analgesics, respectively), recommended for neuropathic pain, in 16 post-traumatic neuropathic pain patients. We measured subjective pain reports, allodynia-evoked neural activity, and brain resting state functional connectivity from patients during the three sessions and resting state data at baseline from patients after washout of their current medication. All data were collected using a 3 T MRI scanner.

**Results:** When compared with placebo only, pregabalin significantly suppressed allodynia-evoked neural activity in several nociceptive and pain-processing areas of the brain, despite the absence of behavioural analgesia. Furthermore, placebo significantly increased functional connectivity between the rostral anterior cingulate and the brainstem, a core component of the placebo neural network.

**Conclusions:** Functional neuroimaging provided objective evidence of pharmacodynamic efficacy in a proof-of-concept study setting where subjective pain outcome measures are often unreliable. Additionally, we provide evidence confirming the neural mechanism underpinning placebo analgesia as identified in acute experimental imaging studies in patients during the placebo arm of a clinical trial. We explore how brain penetrant active drugs potentially interact with this mechanism.

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Clinical trial registration: NCT0061015

Key words: analgesics; magnetic resonance imaging; neuralgia; placebos; randomized controlled trial

**Editor's key points**

- A lack of objective outcome measures contributes to the high attrition of potentially effective new analgesics.
- Non-invasive functional magnetic resonance imaging was used to measure brain activity and connectivity in chronic pain patients treated with pregabalin, tramadol or placebo.
- This proof-of-concept study demonstrates the utility of this noninvasive neuroimaging approach to provide objective evidence of analgesic efficacy and placebo effect on patients with neuropathic pain.

Existing analgesics provide 50% pain relief in only a third of patients, with significant individual and societal costs.[1 2] Many promising new compounds fail to reach the market as effective analgesics in patients because potentially effective compounds are discarded in early drug development due to a lack of statistically significant reductions in pain reports in randomized placebo-controlled trials (RPCTs).[2] Pain relief in the placebo treatment arm—which is often large—can confound potentially valuable, mechanistic and pharmacodynamically produced analgesic effects of the study drug.[3] Further, subjective pain reports during drug-induced analgesia are significantly influenced (negatively and positively) by the expectation of treatment out-come.[4] Therefore there is a clear need for additional objective outcome measures of pharmacodynamic efficacy that can demonstrate target engagement and analgesic drug modulation of relevant neural activity in early patient studies so that effective analgesics reach chronic pain patients.

Non-invasive functional magnetic resonance imaging (FMRI) is a useful method for characterizing central nervous system (CNS) activity in chronic pain and for objectively demonstrating analgesic drug modulation of such activity.[5 6] Using a doubleblind RPCT design and a healthy volunteer model of central sensitization, FMRI was used to demonstrate that gabapentin suppressed neural activity in relevant brain areas irrespective of behavioural pain reports.[7 8] We aimed to establish this principle in post-traumatic neuropathic pain patients using pregabalin and tramadol as the study drugs, chronically administered at the proposed clinical dose, as these are recommended first- and second-line therapies, respectively, for neuropathic pain.[9]

The assumption that in RPCTs expectation-driven placebo analgesic effects are non-specific, and therefore equal in both the drug and placebo arms, is now being questioned[10] because placebo analgesic responses have distinct neural mechanisms that CNS-acting drugs can interact with.[11] Therefore we hypothesized that brain networks underpinning placebo analgesia would be measurable in the placebo arm (to date, not shown in a patient study with chronic dosing) but not during active treatment.

## Methods

### Participants

The study was approved by the Oxford Research Ethics Committee C (08/H0606/5) and registered with ClinicalTrials.gov (NCT00610155). Subjects were enrolled from three study centres in the UK after obtaining written informed consent. Neuroimaging was performed at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB). Patients between the ages of 18 and 75 years with a confirmed diagnosis of post-traumatic neuropathic pain associated with brush allodynia that has persisted for at least 3 months with at least moderate-intensity daily and allodynic pain were included in the study. Patients with other neuropathic pain conditions; a history of failure to respond to gabapentin, pregabalin or tramadol; contraindications for MRI scanning; and patients with any medical, psychological or social condition that would interfere with study participation were excluded (inclusion and exclusion criteria details are in the Supplementary Material).

### Study design and procedures

This was a double-blind (patients and investigators), third-party open (sponsor), three-way crossover RPCT. Patients were randomized to receive 7 days of dosing with pregabalin [75 mg on day 1, 75 mg twice a day (BID) on day 2, 150 mg BID on days 3-7, and 150 mg on the morning of the FMRI visit], tramadol sustained-release tablets (50 mg on day 1 and morning of day 2, 100 mg on evening of day 2 and morning of day 3, 200 mg on evening of day 3, and 200 mg BID on days 4-7 and 200 mg on the morning of the MRI visit), or placebo. Paracetamol and codeine were permitted as rescue medication. An overview of the study procedures is shown in Figure 1 (study procedure and randomization details are in the Supplementary material).

### Data collection

During visits 4-6, we collected averaged pain scores (DPS) from daily pain diaries, including the morning of the scanning day summarized as the past 1 (DPS1), 3 (DPS3) and 7 days (DPS7), and scores from several validated questionnaires (listed in Table 1).

DPS7 and the Neuropathic Pain Symptom Inventory (NPSI)[13] were also collected during visit 3. During visits 3-6, we collected the following measures: present pain intensity (PPI) of the ongoing background pain at the beginning of the scanning session and pain intensity when brushing the affected site (DMAa) and the unaffected control site (DMAc). For all pain ratings we used an 11-point numeric rating scale, with 0=no pain and 10=worst pain possible.

Allodynia was elicited outside the scanner during visit 3 and inside the scanner during visits 4-6 while obtaining functional scans. Body sites were brushed using a Somedic brush for 10 min on each side. Subjects rated the average pain