

PAIN

Is number sense impaired in chronic pain patients?

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Editor's key points

- Chronic pain may affect brain areas involved in number processing.
- Several different approaches were used here to assess if such changes could be detected.
- Translation of numbers into spatial representation differs between acute and chronic pain patients.
- Prefrontal and parietal brain circuits may function differently in chronic pain.
- Altered number sense may change how patients report their pain, using numerical rating scales.

Background. Recent advances in imaging have improved our understanding of the role of the brain in painful conditions. Discoveries of morphological changes have been made in patients with chronic pain, with little known about the functional consequences when they occur in areas associated with 'number-sense'; thus, it can be hypothesized that chronic pain impairs this sense.

Methods. First, an audit of the use of numbers in gold-standard pain assessment tools in patients with acute and chronic pain was undertaken. Secondly, experiments were conducted with patients with acute and chronic pain and healthy controls. Participants marked positions of numbers on lines (number marking), before naming numbers on pre-marked lines (number naming). Finally, subjects bisected lines flanked with '2' and '9'. Deviations from expected responses were determined for each experiment.

Results. Four hundred and ninety-four patients were audited; numeric scores in the 'moderate' and 'severe' pain categories were significantly higher in chronic compared with acute pain patients. In experiments ($n=150$), more than one-third of chronic pain patients compared with 1/10th of controls showed greater deviations from the expected in number marking and naming indicating impaired number sense. Line bisection experiments suggest prefrontal and parietal cortical dysfunction as cause of this impairment.

Conclusions. Audit data suggest patients with chronic pain interpret numbers differently from acute pain sufferers. Support is gained by experiments indicating impaired number sense in one-third of chronic pain patients. These results cast doubts on the appropriateness of the use of visual analogue and numeric rating scales in chronic pain in clinics and research.

Keywords: acute pain; chronic pain; hemi-spatial neglect; mild cognitive impairment

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Recent advances in imaging techniques have led to the rise of a new era in pain research.¹ One of the most important results so far is the association of chronic pain with functional (reorganization)² and structural (reduced grey matter density)³ alterations in specific brain regions such as the thalamus, anterior cingulate, insular, and motor cortices.^{3–6} Similar results have been obtained for the prefrontal (PFC)³ and parietal (PC)⁶ cortices which are thought to accommodate the 'number-sense', our intuitive skill of understanding numbers and dealing with sizes and proportions.^{7–9} Clinically, number sense is important when patients are faced with tasks requiring numerical–spatial transformations, for instance, while using assessment tools such as visual analogue and numeric rating

scales.¹⁰ Based on the emerging evidence about pain-induced structural changes in the brain, it is feasible to suggest that chronic pain patients might present with an altered number-sense.

The first aim of this study was to elucidate clinically, through analysis of audit data, whether patients with chronic pain use number-based assessment tools differently from acute pain patients. The second aim was to investigate experimentally if patients with chronic pain are more inaccurate when faced with numerical–spatial tasks compared with controls. The third aim was to explore if the inaccuracy was associated with the presence of spatial neglect-like symptoms, a clinical sign of PC and PFC dysfunction.

Methods

Audit

An audit registered with the Clinical Governance Support Team at Chelsea and Westminster Hospital, London, UK (reference number 793), was conducted between October 2011 and April 2012. Patients were asked either in pain clinics (chronic pain) or during ward rounds (acute pain) to self-complete a questionnaire, providing information about age, gender, and pain intensity at rest. Questionnaire-based pain intensity assessments used both an 11-point numeric rating scale (NRS-11) anchored with 0 ('no pain') and 10 ('worst pain imaginable') and a four-item verbal rating scale (VRS-4) using 'no pain', 'mild', 'moderate', and 'severe pain' as descriptors.

Experiments

Participants

Experiments were conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki, 1964, and later revisions. Ethical approval was obtained from the National Research Ethics Service Committee North West—Greater Manchester West (12/NW/0108). All subjects gave written informed consent.

Between February and March 2012, participants were recruited into three groups: controls (C), acute pain (AP), and chronic pain (CP), respectively. Recruitments took place in Chelsea and Westminster Hospital, London, UK. Participants were approached during pain clinics (CP) and in the day surgery unit (AP). Volunteers for the healthy control (C) group were enrolled from hospital staff.

Only adults with the ability to communicate in English fluently, were suffering with chronic pain for at least 12 months (CP), or had an operation within the last 24 h (AP) were included.

Patients were excluded if they refused to participate, had a history of major neurological disease, cancer, substance abuse, chronic renal or liver failure, were pregnant, or presenting with an acute infection. To be eligible for the AP or control group, participants had to have no history of ongoing pain.

There being no previous results on which to base effect size calculations, the decision to use $n=50$ for each experimental group was made, drawing comparison from similar work in developmental and psychological research.^{11–13} In this regard, *post hoc* power calculations have been found to be unnecessary,¹⁴ adding little to the knowledge provided by the *P*-value, especially when complemented by confidence intervals (CIs).¹⁵

Conduct of experiments

Before the start of experiments, participants were assessed for pain intensity at rest (NRS-11), educational level, handedness, and sedation (Ramsay score).

Number line experiments (Experiment 1) were designed to test participants' abilities to translate abstract numbers into spatial representations on straight lines similar to what is required when using visual analogue scales (VAS).

In part 1a (number marking), participants were shown a 23 cm long number line centred on an A4 paper.¹¹ The line was anchored left and right with '0' and '100', respectively.

Participants were presented eight different numbers (6, 17, 29, 43, 52, 61, 84, 96) in random order. They were asked to mark on separate lines where they thought those numbers lay on the lines. The distances of their responses from the left line endings were measured in centimetres. Since on the used number lines, each discrete number is 0.23 cm apart, the measured distances had to be divided by 0.23 to obtain the final number values. From these, the expected numbers were subtracted to obtain the 'deviation from the expected response'.

As the PC is also involved in motor tasks,¹⁶ Experiment 1b (number naming) was conducted to exclude motor dysfunction as cause for deviations potentially observed in 1a. Participants were presented eight number lines in random order that were pre-marked with vertical lines each representing one of the aforementioned numbers. Participants were asked to indicate what number they thought each individual mark denoted. The deviation from the expected was determined by subtracting the expected number values from the participants' responses.

Line-bisection experiments (Experiment 2) test subjects' abilities to correctly judge spatial–numerical interactions. They are used clinically to diagnose spatial neglect, a condition characterized by disrupted functional integrity of PFC and PC.^{17–20}

Participants were shown two separate 8 cm long horizontal lines each centred on an A4 paper.¹² In an adaptation of experiments by de Hevia and Spelke,¹² lines were anchored with the numbers '2' or '9' on either side. Experiments were conducted first showing a line flanked with '2' on the left and '9' on the right and secondly, with '9' on the left and '2' on the right. Each time participants were asked to mark where they thought the middle of the respective line was. Distances of the marks from the left line endings were measured in centimetres. From these results, the expected midline value (4 cm) was subtracted and defined as the 'deviation from the expected response' for Experiment 2.

Outcomes for Experiments 1 and 2 were the 'Mean Absolute Deviation from the Expected Response' (MADER). Additionally, for Experiment 2, the number of deviations to one side from the midline were determined.

Statistical analysis

Audit

Based on their corresponding VRS-4 scores, results for NRS-11 were categorized into 'mild', 'moderate', and 'severe' and comparisons made in each subgroup between AP and CP using the non-parametric Mann–Whitney *U*-tests with the Bonferroni corrections.

Experiments

Differences between pooled MADERs of Experiments 1a were compared with pooled data of 1b with a paired samples *t*-test. A χ^2 test was used in Experiment 2 to explore differences in direction of responses.

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