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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 cingulated, 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 abstracts 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.

More detailed analyses of results of Experiments 1 and 2 were done using univariate general linear models (GLM) with MADER as dependent variable and 'group', 'pain at rest', 'duration of pain' (CP only), 'gender', 'highest level of education', 'age', and the interaction term 'group × pain' as independent variables. Since only 13 out of 150 of all participants were left-handed, handedness was excluded from further analysis.

Statistical analysis was performed with Prism 5 for Mac (Graph-Pad Software, La Jolla, CA, USA) and SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Non-parametric data were presented as median with 25th and 75th percentiles and parametric data as mean with 95% CIs; $P<0.05$ was considered significant.

Table 1 Details of patients included in the audit

	Chronic pain	Acute pain	Total
Number of patients approached	275	318	593
Number of patients excluded	44	55	99
Number of patients included	231	263	494
Age (yr), mean (95% CI; range)	53 (51–55; 16–100)	54 (52–56; 16–86)	53 (52–55; 16–100)
Gender (m/f)	90/141	98/165	188/306

Results

Audit

Details of patients and pain scores are shown in Table 1 and Figure 1, respectively.

Frequency distributions of NRS-11 scores revealed that 61% ($n=140$) of patients with CP and 22% ($n=58$) of AP patients chose numbers ≥7 to describe their pain intensity (Fig. 1A and B). Similar results were found for VRS-4: in the CP cohort, 88% ($n=203$) of subjects described their pain as moderate or severe, whereas in the AP group, this was true for 46% ($n=122$) (Fig. 1C and D).
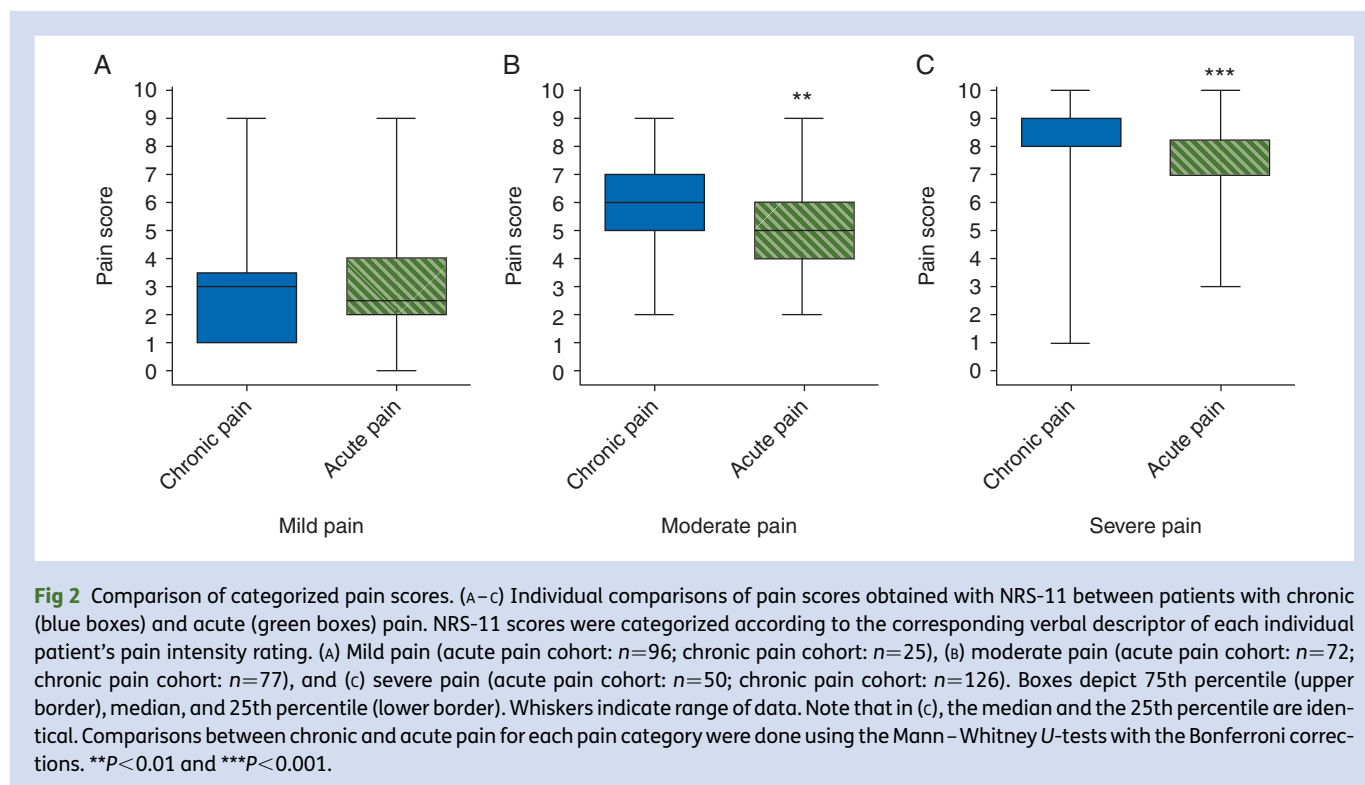
These findings might simply reflect differences in pain intensities or in the effectiveness of used analgesics in both patient groups. However, if numeric scores were categorized according to the respective verbal descriptor as given by each patient, an additional picture unfolded. The numeric score for both groups was similar for mild pain [median AP: 3 (2; 4); median CP: 3 (1; 4); $P=0.839$; Fig. 2A]. However, it was significantly different for moderate [median AP: 5 (4; 6); median CP: 6 (5; 7); $P=0.007$; Fig. 2B] and severe pain [median AP: 7 (7; 8); median CP: 8 (8; 9); $P<0.001$; Fig. 2C], indicating that CP patients used higher numbers to describe their pain.

Experiments

Experimental group characteristics are shown in Table 2. In Experiment 1a (Fig. 3A and B), MADER was greater ($P<0.001$) in CP
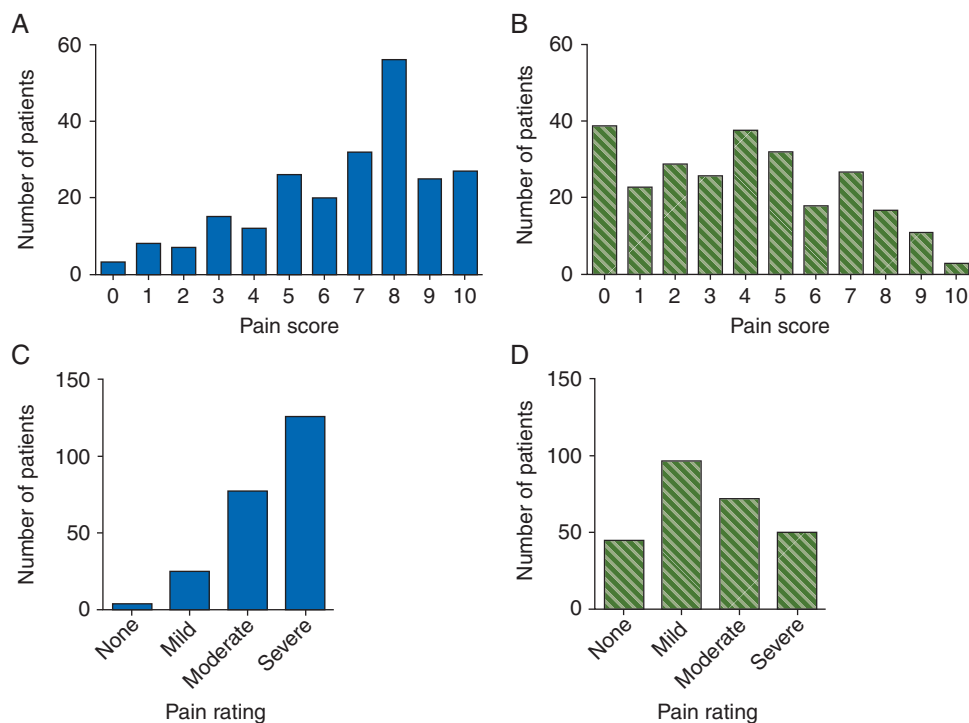
Fig 1 Frequency distribution of pain scores obtained through the audit. (A and B) Frequency distributions of pain scores obtained with 11-point numeric rating scales. (A) Chronic pain patients and (B) acute pain patients. (C and D) Frequency distributions of pain ratings obtained with four-point verbal rating scales. (C) Chronic pain patients and (D) acute pain patients.

Fig 2 Comparison of categorized pain scores. (A–C) Individual comparisons of pain scores obtained with NRS-11 between patients with chronic (blue boxes) and acute (green boxes) pain. NRS-11 scores were categorized according to the corresponding verbal descriptor of each individual patient's pain intensity rating. (A) Mild pain (acute pain cohort: $n=96$; chronic pain cohort: $n=25$), (B) moderate pain (acute pain cohort: $n=72$; chronic pain cohort: $n=77$), and (C) severe pain (acute pain cohort: $n=50$; chronic pain cohort: $n=126$). Boxes depict 75th percentile (upper border), median, and 25th percentile (lower border). Whiskers indicate range of data. Note that in (C), the median and the 25th percentile are identical. Comparisons between chronic and acute pain for each pain category were done using the Mann–Whitney U-tests with the Bonferroni corrections. **$P<0.01$ and ***$P<0.001$.

(mean 4.81; 95% CI: 4.18–5.45) compared with both controls (3.22; 95% CI: 2.90–3.55) and AP patients (3.51; 95% CI: 3.16–3.85).

GLM further revealed that pain intensity significantly ($P=0.016$) contributed to the results. Because CP patients reported higher median pain scores [6 (4; 8)] compared with AP patients [1 (0; 4)], the interaction of 'pain×group' also significantly influenced the degree of MADER ($P=0.029$).

Results of Experiment 1b (Fig. 3c and d) were similar to those of 1a: MADER of CP patients (4.85; 95% CI: 4.18–5.51) was greater ($P=0.009$) than that of controls (2.84; 95% CI: 2.59–3.10) and AP patients (2.96; 95% CI: 2.77–3.25). Nevertheless, pain intensity ($P=0.059$) and the interaction 'pain×group' ($P=0.071$) only showed a trend in contribution to MADER.

Age, education, gender, and sedation did not significantly affect results of Experiment 1a and b. A subgroup analysis of CP indicated the duration of pain did not influence MADER in both experiments (Supplementary Table S1).

The reason for conducting Experiment 1b was to exclude motor dysfunction as cause for group differences observed in 1a. For analysis, data of all groups were pooled for Experiment 1a and compared with the pooled data of Experiment 1b. A paired samples t-test showed no difference between MADERs of pooled groups of both experiments ($P=0.904$), hence excluding motor dysfunction. Results of Experiment 1 therefore suggest an altered number-sense in CP but not AP patients.

Not all CP patients were equally affected by number-sense changes. To assess the magnitude of the phenomenon in the study population, all data of Experiment 1a and b from AP and C were pooled into a new control (NC) group based on the finding that MADERs of AP and C were not different (Fig. 3).

The mean and standard deviation for the NC data were calculated. A 'mean expected response' (MER) was defined in this group by adding 2 standard deviations to the group mean. Finally, the frequency of occurrence of MER in both NC and CP was determined and analysed using a z-test. Results showed significantly ($P<0.001$) more CP patients (36%) than NC participants (8%) exceeded MER.

MADERs for line-bisection experiments (Experiment 2) defined as the magnitude of departure from the midpoint were statistically not different between the groups. MADER for CP patients was 0.18 cm (95% CI: 0.15–0.21), whereas it was 0.12 cm (95% CI: 0.10–0.14) and 0.14 cm (95% CI: 0.11–0.16) for controls and AP patients, respectively. Age, education, gender, pain intensity, and sedation did not influence the results of Experiment 2, nor did the duration of pain in the CP group (Supplementary Table S1).

When in Experiment 2, the direction of deviation was analysed instead of its magnitude, differences between cohorts indicated right-sided bias in the pain groups that was independent of the flanking number. When '9' was presented on the right, 54% ($n=27$) healthy volunteers crossed the midline towards the right (Fig. 4a and b) and 56% ($n=28$) controls favoured the left, when '9' was shown on the left (Fig. 4c and d). This was different to the response pattern observed in patients with pain. When '9' was shown on the right, 72% ($n=36$) and 70% ($n=35$) AP and CP patients, respectively, tended also towards the right (Fig. 4a and b). However, if '9' was shown on the left, 46% ($n=23$) of AP and only 34% ($n=17$) of CP patients followed the large number (Fig. 4c and d). A χ^2 test indicated the differences between the groups were statistically significant ('9' on right: $P<0.001$; 2 d.f.; '9' on left: $P=0.04$; 2 d.f.).

Table 2 Characteristics of participants recruited for the experiments. *Other types of pain: bone, dysuria, stomach, temporal arteritis. N/A, not applicable; pain intensity at rest was assessed using an 11-point numeric rating scale; sedation was assessed using the six-point Ramsay score (1 representing anxious/restlessness; 2 cooperative/orientated; and scores from 3 to 6 increasing levels of sedation)

	Healthy	Acute pain	Chronic pain
Group size (*n*)	50	50	50
Gender (m/f)	23/27	26/24	19/31
Age (yr), mean (95% CI; range)	37 (33–41; 20–75)	40 (36–44; 19–77)	51 (46–55; 20–90)
Duration of pain (yr), mean (95% CI)	N/A	N/A	7.3 (5.7–9.0)
Educational status (*n*)			
Entry level	3	3	5
GCSE	6	11	10
A-level	7	7	8
Higher education	11	7	13
Higher degree	23	22	14
Handedness (R/L)	48/2	44/6	45/5
Pain intensity, median [25th; 75th percentile (range)]	0 [0; 1 (0–3)]	1 [0; 4 (0–9)]	6 [4; 8 (0–9)]
Sedation score, median [25th; 75th percentile (range)]	2 [2; 2 (2)]	2 [2; 2 (2)]	2 [2; 2 (1–2)]
Type of pain			
Back	N/A	N/A	28
Joint	N/A	N/A	5
Muscular	N/A	N/A	4
Neck	N/A	N/A	3
Neuropathic	N/A	N/A	2
Scar	N/A	N/A	4
Other*	N/A	N/A	4
Type of surgery			
General surgery	N/A	14	N/A
Gynaecology	N/A	9	N/A
Orthopaedic	N/A	11	N/A
Plastic	N/A	11	N/A
Urology	N/A	5	N/A

Discussion

Audit data presented here indicate that CP patients use number-based pain assessment tools differently from AP patients. The reasons for this observation are likely to be manifold. They might for instance represent differences in psycho-social pain communication[21] or stimulus intensities between cohorts. However, results could also indicate alterations in number-sense on the bases of pain-induced morphological and re-organizational changes in the brains of CP patients.

Number-sense and brain dysfunction

Evidence suggests chronic pain-induced morphological and plastic changes in the brain.[3 4 22] However, so far only scarce data exist linking these changes to clinically relevant functional alterations such as short-term memory changes, enhanced sense of taste, or neglect.[23–25]

Therefore, this study adds to our knowledge of pain-induced alterations of brain function. Increased errors in number marking and naming in patients with chronic pain strongly suggest impairment of number-sense in this group in contrast to patients with AP and controls. Interestingly, not only was the

absolute degree of inaccuracy greater in chronic pain so was its rate of occurrence. One-third of patients with CP compared with 1/10th of patients with AP and controls showed a magnitude of error that was more than 2 standard deviations away from control means.

The hypothesis that these changes may result from alterations in prefrontal and parietal circuits was tested with line bisection experiments. Here, healthy volunteers normally deviate to the left,[26] except when lines are flanked with numbers. This leads to deviation towards the higher number regardless of whether it is shown on the left or right.[27] Results from healthy controls in this study confirm previous findings. However, patients with chronic pain showed right-sided deviation bias, which is reminiscent of the left-sided neglect of patients with right parietal stroke.[20 26 28] Yet, the magnitude of 'pain-related neglect-like symptoms' is less compared with the neglect of stroke patients, possibly because grey matter changes described in pain are considerably smaller than they are in stroke.[3] In keeping with studies linking PC and PFC to numero-spatial tasks, and grey matter reductions in chronic pain,[6 7 18] results of line bisection experiments suggest pain-induced functional alterations in both areas. Consequently, it might be hypothesized that spatial memory circuits have been
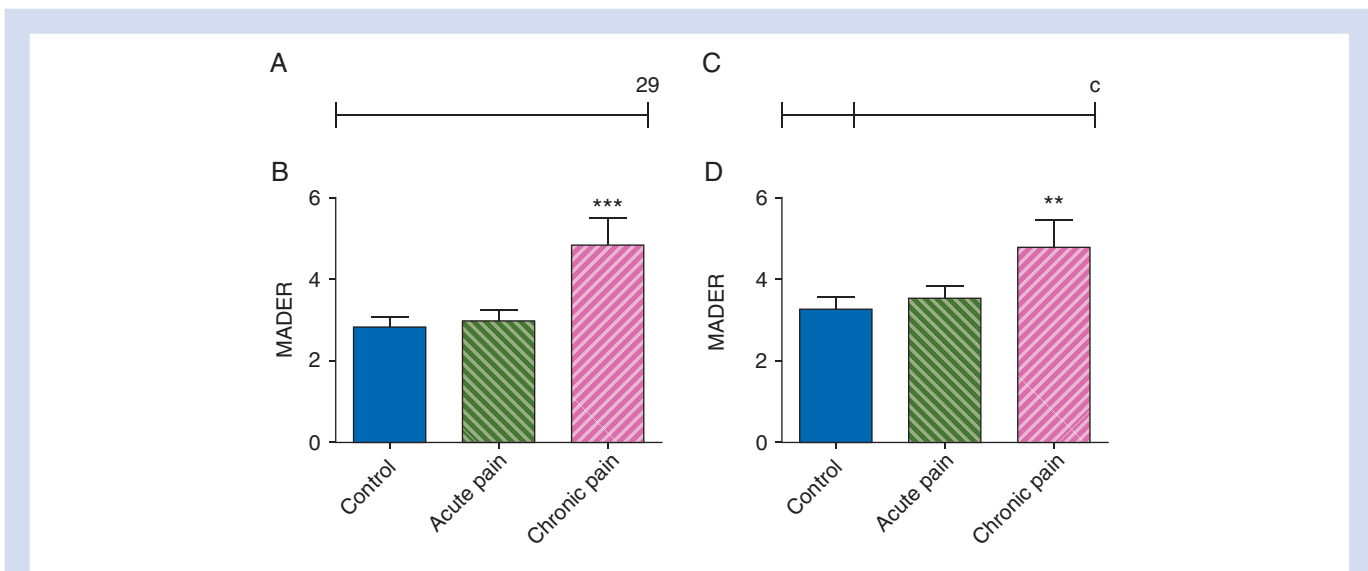
Fig 3 Results from Experiment 1 (number marking and naming). (A) Example of a number line for number marking experiment (Experiment 1a) as presented to participants. Right corner shows the number which representation the subject was expected to mark on the line. (B) Bar chart of MADER for Experiment 1a (number marking) against group. Shown are means and 95% CIs. Differences between the groups were determined using univariate GLM. ***$P<0.001$. (C) Example of a number line for number naming experiment (Experiment 1b). Participants were asked to name the number represented by the vertical mark. (D) Bar chart of MADER for Experiment 1b (number naming) against group. Shown are means and 95% CIs. Differences between the groups were determined using GLM. **$P<0.01$.
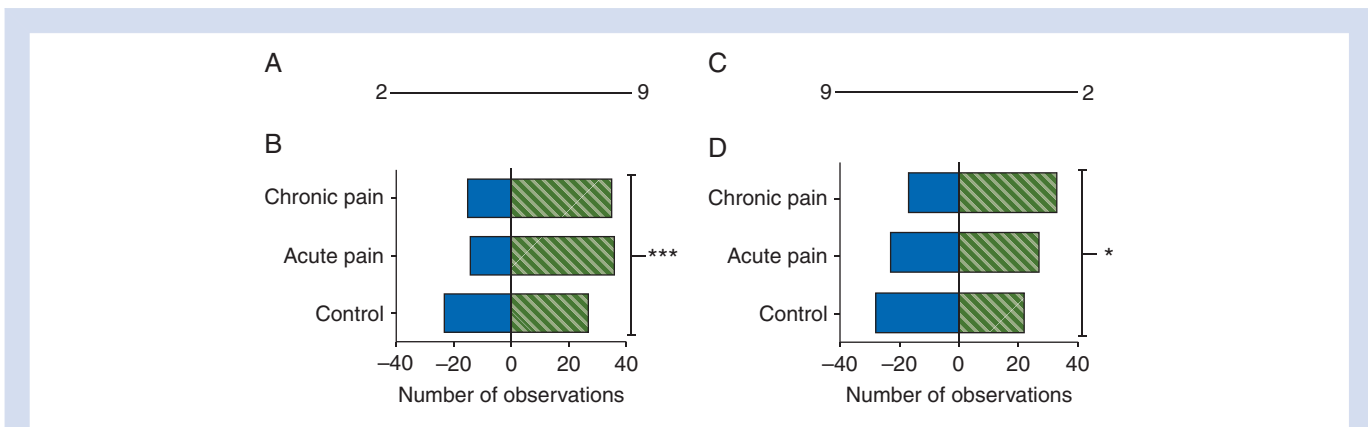
Fig 4 Results from Experiment 2 (line bisection). Bar charts depict the number of deviations from the exact midline to the right (green bars; positive numbers) and to the left (blue bars; negative numbers). Each observation represents the result of a single participant. (A) Example of a number line for line bisecting experiment. Line flanked with the big number (9) on the right. (B) Results from lines flanked with '2' on the left and '9' on the right. (C) Example of a number line for line bisecting experiment. Line is flanked with the big number (9) on the left. (D) Corresponding results obtained from experiments with lines as depicted in (C). Comparisons between the groups were made with the χ^2 tests. ***$P<0.001$; *$P<0.05$.

disrupted, similar to descriptions in right hemispheric strokes[20] or in volunteers after right parietal transcranial magnetic stimulation.[29]

Interestingly, we found that number-sense dysfunction was not related to pain duration. As only patients with an at least 1 yr history of pain were included into the study, it is possible that at the time of experimentation, underlying cortical changes were already fully established. Hence, changes of number-sense are likely to occur early in patho-mechanisms of chronic pain. This is supported by the subtle changes in line bisection experiments of AP patients; like patients with

chronic pain, they also showed right-sided bias in deviation from midline. Because the AP group consisted exclusively of patients who recently had surgery and anaesthesia but no history of pain, it might be argued that residual drug actions rather than genuine pain mechanisms were responsible for the results. Support for this notion is provided by studies demonstrating deleterious effects of general anaesthesia on cognitive function in patients after surgery[30 31] and from *in vitro* studies attributing neurotoxicity to anaesthetics.[32] Although sedation scores as indirect measures for residual anaesthetic actions were not different between groups, an adverse effect

of medications on cognitive function could not be entirely ruled out. Nonetheless, the results of the number marking and naming experiments, and that no differences between the AP and control groups were found, seem to contradict this idea of drug-induced decline in number sense in CP patients. It seems more likely that acute insults initiate mechanisms that have an immediate small effect on cerebral function.[33] If mechanisms persist, they might then lead to sustained morphological and functional changes.[3 22]

Practical consequences of number-sense impairment

Gold standard for assessing pain intensity in clinics and research are VAS and NRS,[10 34] but they are also used in psychology, psychiatry, or for quality-of-life assessments.[35–37] To generate valid results, they require recipients to have intact cognitive function[38] defined as absences of reduced level of consciousness, learning difficulties, or dementia.[39 40] Yet results presented here suggest that a refinement of current practice might be needed, as reduced number-sense is observed in one-third of CP patients and audit data indicate the clinical relevance. An alternative could be the employment of VRS as a gold-standard test. This is supported by findings that elderly patients prefer VRS to VAS.[41] However, evidence also suggests that even verbal descriptors are used differently depending on the pain entity.[42] Thus, an entirely novel approach might be necessary, for example, the employment of images to depict pain characteristics.[43] In any case, more research is needed to optimize assessment for CP.

Study limitations

Since pain is complex, no construct can represent it completely; the main mathematical models used here do not fully explain the variability observed (R^2 values of 0.473 and 0.385). Factors that might contribute, but were not included, are the degree of grey matter density reduction, visual acuity, cultural background, employment status, psychological factors, and co-morbidities. Further, pain entities other than the predominant back pain of this study might also influence MADERs differently. Future work needs to determine how those variables might improve the models.

However, because age, duration of pain, education, and gender were not found to influence results, it is feasible to suggest that the changes in MADERs are caused by mechanisms genuine to pain.

Finally, it could be argued the data shown here are biased because of discrepancies of pain intensities between AP and CP. Owing to ethical concerns that prevent delay of pain treatment, however, matching pain intensities of patient cohorts is sometimes difficult if not impossible. Employment of appropriate statistical tests can help at least partially to overcome this dilemma. GLM-based interaction analysis used for this study for instance found a modulatory effect of pain intensity on number naming but not on number marking (Supplementary Table S1).

Although, pain intensity thus might have affected part of the results, it cannot explain all differences between AP and CP. This adds credibility to the hypothesis that number sense indeed can be impaired in chronic pain.

Conclusion

This study demonstrates impaired number-sense in one-third of chronic pain patients, possibly linked to functional alterations in the right PC and PFC. Audit data revealed that the usage of number-based pain assessment tools is different between acute and chronic pain patients, indicating that number-sense impairment is clinically relevant. Since intact number-sense is essential for the use of VAS and NRS, it can be inferred that results generated with these tools should be used with caution in those patients, not because they are not in pain but instead due to the possibility of increased measurement inaccuracy. Further work is needed to directly verify the suggested link between pain-induced cerebral changes and the observed altered number-sense.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

C.B., A.S.C.R., and J.W. contributed to the study design. B.M.K. and J.W. were responsible for patient recruitment. A.S.C.R. conducted the pilot experiments and audit. J.W. collected the data. J.W., A.J.P., and C.B. analysed the data and wrote the manuscript. All authors discussed the results presented here and commented on the manuscript. This article presents independent research commissioned by the National Institute for Health Research (NIHR) under the Collaborations for Leadership in Applied Health Research and Care (CLAHRC) programme for North West London. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

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Declaration of interest

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