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ORIGINAL ARTICLE

Prognostic value of preoperative mechanical hyperalgesia and neuropathic pain qualities for postoperative pain after total knee replacement

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Abstract

Background: Total knee replacement (TKR) is the gold standard treatment for end-stage chronic osteoarthritis pain, yet many patients report chronic postoperative pain after TKR. The search for preoperative predictors for chronic postoperative pain following TKR has been studied with inconsistent findings.

Methods: This study investigates the predictive value of quantitative sensory testing (QST) and PainDETECT for postoperative pain 3, 6 and 12 months post-TKR. We assessed preoperative and postoperative (3 and 6 months) QST measures in 77 patients with knee OA (KOA) and 41 healthy controls, along with neuropathic pain scores in patients (PainDETECT). QST parameters included pressure pain pressure threshold (PPT), pain tolerance threshold (PTT), conditioned pain modulation (CPM) and temporal summation (TS) using cuff algometry, alongside mechanical hyperalgesia and temporal summation to repeated pinprick stimulation.

Results: Compared to healthy controls, KOA patients at baseline demonstrated hyperalgesia to pinprick stimulation at the medial knee undergoing TKR, and cuff pressure at the calf. Lower cuff algometry PTT and mechanical pinprick hyperalgesia were associated with preoperative KOA pain intensity. Moreover,

preoperative pinprick pain hyperalgesia explained 25% of variance in pain intensity 12 months post-TKR and preoperative neuropathic pain scores also captured 30% and 20% of the variance in postoperative pain at 6 and 12 months respectively. A decrease in mechanical pinprick hyperalgesia from before surgery to 3 months after TKR was associated with lower postoperative pain at the 12 months post-TKR follow-up.

Conclusion: Our findings suggest that preoperative pinprick hyperalgesia and neuropathic-like pain symptoms show predictive value for the development of chronic post-TKR pain.

Significance Statement: This study's findings hold significant implications for chronic pain management in knee osteoarthritis patients, particularly those undergoing total knee replacement surgery (TKR). Mechanical hyperalgesia and neuropathic pain-like characteristics predict postoperative pain 1 year after TKR, emphasizing the importance of understanding pain phenotypes in OA for selecting appropriate pain management strategies. The normalization of hyperalgesia after surgery correlates with better long-term outcomes, further highlighting the therapeutic potential of addressing abnormal pain processing mechanisms pre- and post-TKR.

1 | INTRODUCTION

Knee osteoarthritis (KOA) affects over 240 million people worldwide (Roth et al., 2018) leading to chronic musculoskeletal pain and disability (Adães et al., 2015). Total knee replacement (TKR) is the gold-standard treatment for end-stage KOA when non-surgical therapies prove ineffective, yet up to 34% of patients experience chronic postoperative pain after TKR (Beswick et al., 2012; Wylde et al., 2011). Efforts have been made to identify risk factors that can predict long-term pain outcomes: meta-analytical evidence supports the role of preoperative pain, widespread pain, pain catastrophizing and mental health as risk factors (Lewis et al., 2015). Nevertheless, the predictive value of clinical and psychological features alone remains insufficient for clinical decision making.

Quantitative sensory testing (QST) has been studied as a possible predictor for TKR success given its ability to quantify aspects related to the pathophysiology of chronic pain, including hyperalgesia, temporal summation (TS) and conditioned pain modulation (CPM), as proxies for sensitization of the nociceptive apparatus (Arant et al., 2022). Many KOA patients present QST abnormalities (Dell'Isola et al., 2016; Wylde et al., 2012), including widespread pressure hyperalgesia, facilitated TS and impaired CPM (Arant et al., 2022; Arendt-Nielsen et al., 2010; Petersen et al., 2017). QST scores have also been suggested to predict outcomes of interventions (Petersen et al., 2023). A recent systematic review shows that preoperative pain pressure threshold (PPT), TS and CPM are most frequently associated with chronic postoperative pain (Petersen et al., 2021). Yet, results are conflicting and difficult to interpret due to heterogeneity in QST methods (Petersen et al., 2021) and arguably due to the existence of multiple OA pain phenotypes (Dell'Isola et al., 2016; Saxer et al., 2024).

The presence of neuropathic pain symptoms prior to surgery has also emerged as a potential predictor of postoperative pain after TKR (Wluka et al., 2020). The PainDETECT questionnaire (Freynhagen et al., 2006) has been used to subdivide patients with KOA into three groups—non-neuropathic, unclear and neuropathic pain-like phenotypes—which have been suggested to differentially respond to treatments (Arendt-Nielsen et al., 2017), with the neuropathic pain subgroup exhibiting widespread pressure hyperalgesia compared to the other groups (Moss et al., 2018). Moreover, higher preoperative PainDETECT scores have also been associated with chronic postoperative pain after TKR (Kurien et al., 2018), above and beyond the predictive ability of TS and hyperalgesia, raising questions about whether TS and hyperalgesia tap into similar mechanisms.

In summary, QST parameters and neuropathic pain-like qualities are promising predictors of TKR outcomes, but more studies are required due to inconsistent findings in the literature. Furthermore, most studies focus only on a single time point, overlooking how preoperative parameters normalize post-TKR, as well as how this

normalization relates to long-term outcomes. Lastly, the relationship between QST and neuropathic pain merits further exploration. The current study aimed to (i) compare QST parameters between KOA patients and healthy controls, (ii) determine if QST parameters and neuropathic pain-like qualities predict post-TKR pain at 3-, 6- and 12-month follow-up and (iii) assess if changes in QST parameters post-TKR relate to long-term pain outcomes.

2 | METHODS

2.1 | Study design and participants

In this observational study, 77 patients (mean age 67.2 years, standard deviation [SD] = 6.9, 70.1% female) with chronic KOA awaiting TKR surgery were recruited from Northwestern Memorial Hospital's Department of Orthopaedic Surgery, between July 2019 and November 2022. Patients invited to participate were older than 40 years, met the American College of Rheumatology criteria for KOA, had KOA for more than 6 months, reported knee pain most days of the week for the past month, had a pain intensity score greater than 4/10 at their preoperative visit, were scheduled to undergo a TKR surgery within 3 months of consent, were able to read and speak English and were in general good health. Of the 77 patients, 14 had a previous TKR surgery on their other knee (18.2%). A second cohort of 41 age- and sex-matched participants with no history of OA or other chronic pain conditions were recruited as a healthy control group (mean age 65.9 years, [SD] = 7.0, 75.6% female). Demographic and clinical details can be found in Table 1. Sample sizes were selected based on an a priori power analysis (see below, section Statistical Analyses).

Participants were excluded if they: (i) had evidence of rheumatoid arthritis, ankylosing spondylitis or other inflammatory arthropathy; (ii) had fibromyalgia; (iii) reported current recreational drug use or history of alcohol or drug abuse; (iv) had chronic neurologic conditions (e.g. Alzheimer's and Parkinson's disease) or psychiatric diseases (e.g. schizophrenia); (v) were not suitable for MRI scanning; or (vi) had other significant medical diseases, such as congestive heart failure or peripheral vascular disease. An additional exclusion criterion for healthy controls was ongoing acute or chronic pain. This study is part of a

TABLE 1 Demographic and clinical characteristics of osteoarthritis patients and controls.

Subjects (*n*)	Controls (41)	Knee OA (77)	*p* value
Age in years, mean (SD)	65.9 (7.0)	64.2 (6.9)	$p = 0.35$[b]
Female, *n*, %	31/10, 68%	54/23, 57%	$p = 0.68$[a]
Race, *n*, %			$p = 0.01$[a]
White	29 (70%)	41 (54%)	
African American	4 (10%)	28 (36%)	
Asian	4 (10%)	2 (3%)	
Other/not disclosed	4 (10%)	6 (8%)	
Previous TKR, *n*, %		5 (17%)	
Pain intensity, NRS, mean (SD)			
Preoperative ($n = 77$)		6.3 (2.1)	
3 Months ($n = 55$)		2.5 (2.1)	
6 Months ($n = 36$)		1.7 (1.9)	
12 Months ($n = 47$)		1.9 (2.4)	
KOOS, mean (SD)			
Symptoms		49.3 (16.7)	
Pain		47.6 (16.8)	
Activities of daily living		55.5 (17.9)	
Sport and recreation		19.8 (20.8)	
Quality of life		25.1 (17.3)	
PainDETECT mean (SD)		9.2 (6.7)	
Beck Depression, mean (SD)	2.4 (3.9)	6.5 (5.2)	$p < 0.001$[b]
Mini-Mental Score, mean (SD)	29 (1.2)	28.7 (1.4)	$p = 0.10$[b]

[a]Chi-square test.

[b]*t*-test.

larger project aimed at studying the brain, psychophysical and psychological predictors, and consequences of chronic pain after TKR; while several psychological parameters, including depression, anxiety, catastrophizing and others, may predict TKR outcomes, in this manuscript, we focus specifically on the predictive ability of psychophysical QST parameters. The study was approved by the Northwestern University Institutional Review Board (STU00207973), and all participants signed a written informed consent.

Baseline visits with initial assessment procedures were conducted within 2 weeks of the KOA patient's TKR surgery. In this first visit, patients consented, completed a series of psychological and clinical questionnaires, underwent a brain scan and performed a QST assessment. Patients were invited to return for a follow-up assessment at 3 and 6 months following TKR surgery to assess their pain and repeat all procedures. Due to COVID-19 pandemic restrictions, not all patients were able to return to the follow-up visits; the full number of subjects per visit and per analysis is reported whenever appropriate, and the full summary can be found in the (Table S1). Patients were contacted at 12 months for clinical pain assessment only. Healthy control participants completed questionnaires and QST assessments once.

2.2 | Pain-related measurements

All patients completed the PainDETECT questionnaire to assess pain intensity and the presence of neuropathic pain-like characteristics. In this questionnaire, KOA patients were asked to report the average pain in the last 4 weeks for their OA knee (VAS, 0–10), which was the main outcome measure at each time point (before TKR, and at 3, 6 and 12 months after TKR). PainDETECT further queries patients regarding their pain pattern, the presence of radiating pain and the frequency at which they feel characteristic neuropathic pain symptoms, such as burning and prickling (Freynhagen et al., 2006). These are quantified to provide a composite score of neuropathic pain profile. If patients did not complete PainDETECT at a given time ($n = 6$, 3 and 3 for 3, 6 and 12 months after TKR, respectively), we instead collected their pain ratings over the phone.

2.3 | Quantitative sensory testing

QST was performed with participants sitting on a reclining chair in a temperature-controlled (21°C), quiet room with their legs extended and slightly bent for comfort. In this study, we used a pinprick stimulator to assess mechanical pain sensitivity and wind-up ratio (WUR) at the affected knee and a cuff pressure algometry device to measure pressure pain threshold, pain tolerance, temporal summation (TS) and conditioned pain modulation (CPM) at the calf of the same leg. Healthy control participants performed the same QST procedures but with the stimulation laterality chosen randomly.

2.3.1 | Pinprick measures of mechanical pain sensitivity and wind-up

Mechanical pain sensitivity and WUR were assessed on the skin adjacent to the affected knee's medial compartment (Figure S1) using a pinprick test. Participants were instructed to close their eyes or look away during the stimulation and rate their pain rating using a 101-point Numeric Rating Scale (NRS, 0–100) following single (prick 1) or repeated (prick 10) stimuli using a weighted-calibrated 25.6 g pinprick stimulator with a 0.6-mm-diameter tip (Aalborg University, Aalborg). Before collecting data on the knee undergoing TKR, a trial test was conducted on the contralateral knee to ensure participants understood instructions and to reduce expectancy effects. Mechanical pain sensitivity in the TKR knee was then assessed. First, a single monofilament stimulation was applied to the skin of the knee, and the corresponding pain was recorded. Subsequently, 10 consecutive monofilament stimulations were applied at one stimulus per second within a 1 cm^2 area of the first stimulation, and participants reported their average pain intensity over the 10 stimuli. After a brief rest interval, the assessments with a single stimulus and 10 stimuli were repeated once more on the same knee. Pain ratings (mechanical hyperalgesia) for a single prick (prick 1) and 10 consecutive pricks (prick 10) were registered as the average across the two respective trials. Prick 1 and prick 10 were used to calculate the so-called WUR, which was averaged across the two trials (see also Statistical Methods below).

2.3.2 | Cuff pressure algometry

To examine dynamic pain responses, TS and CPM, we used a computer-controlled cuff pressure algometer (Cortex Technology and Aalborg University, Denmark) using a 13-cm-wide cuff on the gastrocnemius muscle of each leg. Procedures closely follow previous publications (Kurien et al., 2018; Petersen et al., 2017). For the assessment of pressure pain and tolerance thresholds, the cuff was inflated automatically by a computer at a rate of 30 kPa/s until a maximum pressure of 100 kPa was reached. The participants used an electronic visual analogue scale (VAS) for continuous recording of pain intensity. Participants were instructed to press a pressure

release button when the pain was intolerable. The VAS signal was sampled at 10 Hz, and 0 and 10 cm on the scale were defined as minimum and maximum pain respectively. The pressure value when the subject rated the pain sensation as 1 cm on the VAS was defined as the pressure pain threshold (PPT). When the subject terminated the exam using the pressure release button, the pressure value was defined as the pain tolerance threshold (PTT).

To assess TS, 10 repeated cuff pressure stimulations with a 1-s duration and 1-s interval between stimuli were delivered to the affected leg by inflation of the cuff chamber to the PTT recorded during the previous assessment. In the period between stimuli, the cuff was entirely deflated. Pressure at the PTT intensity was used to ensure that subjects perceived the stimulation as painful but not unbearably painful due to the short stimulation time. Subjects rated their pain sensation on the electronic VAS during the cuff inflations, thus not returning to zero between successive stimulations. The VAS score immediately after each stimulus was extracted for TS calculation. The difference between the average of the last three VAS scores and the average of the first three VAS scores was used to calculate the cuff TS value. Please note that while WUR and TS both characterize a nociceptive gain in response to repeated stimuli, we included both since they were calculated with different methodologies (pinprick and cuff algometry, respectively) and at different locations (the medial patella and calf, respectively).

For the CPM assessment, the cuff on the contralateral leg was inflated to a pressure at 70% of the subject's PTT intensity and held at this constant pressure for the duration of the assessment. The participants were instructed to ignore the stimulus on the contralateral knee and to focus on rating their pain on the electronic VAS for the cuff pressure on their OA knee. Simultaneous reassessment of the subject's PPT of their OA knee was performed. The difference between PPT during and before the conditioned pain was used to calculate CPM.

2.4 | Statistical methods

We specified seven QST variables of interest from the measures described above, in line with previous studies (Izumi et al., 2017; Kurien et al., 2018; Petersen et al., 2021). From pinprick QST measures, we selected prick 1, prick 10 and their WUR; from cuff algometry QST measures, we selected PPT, PTT, CPM and TS. We modelled pain continuously (i.e. through linear modelling) to avoid dichotomizing patients into 'chronic pain' or 'recovered' based on arbitrary criteria (Vigotsky et al., 2021). Linear model residuals were right-skewed, partly because many patients reported relatively minor pain (NRS <3/10, see below) at 6 and 12 months after surgery. Therefore, we log-transformed all pain scores (i.e. $\text{pain}_{\log} = \log_{10}(\text{pain} + 1)$), which yielded normally distributed residuals. In addition, we log-transformed the WUR since it is a ratio, converting it from a multiplicative construct to an additive one. Hence, prick 1 and prick 10 were first log-transformed using the equation above and then differenced ($\log_{10}(\text{prick10} + 1) - \log_{10}(\text{prick1} + 1)$) to calculate WUR. The +1 term enables the calculation of WUR for patients who reported zero pain in prick 1. Admittedly, this is not *exactly* WUR, but it yields results that are largely monotonic with actual WUR while having the advantage of being estimable. We computed correlations between the QST and questionnaire measures using Spearman's ρ.

For cross-sectional comparisons between KOA patients and healthy controls, an analysis of covariance (ANCOVA) was performed by comparing how QST outcomes differed between groups. Sex and age were added to the model as covariates of no interest; we additionally included race as a covariate of no interest for cross-sectional comparisons since we observed differences in proportion of race for healthy versus KOA groups (Table 1). We adjusted the *p*-values to control for the false discovery rate (FDR).

For the longitudinal predictive analyses, we first probed the variables deemed abnormal in the cross-sectional analyses (i.e. compared to healthy controls) and assessed their predictive ability; other variables were tested post hoc. We leveraged the repeated pain assessments by modelling the outcomes across time using generalized estimating equations (GEE)—this estimates 'population effects' (cf. mixed-effects models) while effectively controlling for the covariance between repeated measures. Pain ratings at baseline, 3, 6 and 12 months after surgery were predicted from baseline QST parameters, controlling for age and sex. Since baseline pain was a dependent variable in these models, we did not adjust for it. However, in follow-up models that were specific to the postoperative time points, we included baseline pain as a predictor and assessed its relative importance as compared to other predictors. We adjusted for multiple comparisons across time points using the multivariate *t* approach (i.e. 'mvt' in the R package *emmeans*), which adjusts *p*-values based on the multivariate *t* distribution of the model, hence taking into account the covariance structure of the data. Finally, measures showing statistically significant (adjusted $p < 0.05$) predictive ability were further assessed longitudinally—how they change or normalize after surgery. To do so, we fit a multivariable linear model predicting pain 12 months after TKR with baseline and change in QST scores (i.e. change is 3 months minus baseline or 6 months minus baseline), again with age and sex as covariates of no interest. For these analyses, two models

were run separately for 3 and 6 months due to missing data, as the patients at 3 and 6 months do not fully overlap.

Sample sizes were chosen based on an a priori power analysis; however, the actual numbers collected deviate slightly from initial estimates due to the COVID-19 pandemic restrictions. Power was calculated using G*Power 3.185 and the R package pwd. For the cross-sectional study, it was estimated that a minimum of 30 participants per group was sufficient to detect an effect of $d = 0.8$ at 80% power. For the longitudinal prediction analyses, we initially calculated the power to classify chronic versus recovered patients using logistic regression and estimated the need to collect 105 patients, translating to a statistical power of 82% for variables with odds ratios >2. As pain ratings did not conform to a bimodal distribution (see above) and the numerous previously described issues with dichotomizing outcomes (Rucker et al., 2015), we instead ran linear regressions which also confers more statistical power (Rucker et al., 2015). The power for this analysis was thus not explicitly calculated a priori; post hoc power can be extrapolated from the *p*-values (Hoenig & Heisey, 2001). Finally, we estimated the need to collect 30 subjects for the within-subject comparison at 80% power for the longitudinal change analyses, assuming medium-sized effects (r among repeated measures = 0.6 or 36% shared variance). We initially also planned to have a validation dataset to minimize type I errors, but that proved unfeasible due to the difficulty of recruiting patients during COVID-19 restrictions. Statistical power notwithstanding, here we report *all* results and transparently report measures of uncertainty (CIs) based on which readers can make conclusions about which effects the study could estimate well—if large effects *and* zero are contained within the CI, then no strong conclusions can be made due to the poor precision of the estimate. Standardized effect sizes are also reported whenever appropriate, using R^2 for linear regressions and Cohen's d for group comparisons, that is, the average of one group minus the other, divided by the pooled standard deviation. Whenever analyses are performed on log-transformed data, we calculate $R^2\left(1-\frac{\Sigma\left(\hat{y}_i^{\text{full}}-y_i\right)^2}{\Sigma\left(\hat{y}_i^{\text{null}}-y_i\right)^2}\right)$ and adjusted $R^2\left(1-\left(\frac{\Sigma\left(\hat{y}_i^{\text{full}}-y_i\right)^2}{\Sigma\left(\hat{y}_i^{\text{null}}-y_i\right)^2}\right)\left(\frac{n-k_{\text{null}}}{n-k_{\text{full}}}\right)\right)$ based on y_i and $\hat{y}_i$ transformed back to their raw scales, where n is the number of participants and k is the number of parameters, including the intercept. These R^2 values thus account for any bias associated with fitting models on the log scale.

3 | RESULTS

3.1 | Preoperative QST profiles in KOA and pain-free individuals

For measures collected with the cuff algometer, participants with KOA showed significantly lower PTT compared with healthy controls, yet this did not survive FDR correction ($t(104) = -2.25$, $p = 0.027$, $p_{\text{FDR}} = 0.062$, $d = 0.47$, Figure 1a). All other cuff assessment measures did not statistically significantly differ between groups (all $ps > 0.24$, Figure 1a). For measures collected with the mechanical pinprick stimulator, KOA patients reported higher pain than healthy controls for both the single prick (prick 1, $t(94) = 3.35$, $p = 0.001$, $p_{\text{FDR}} = 0.004$, $d = 0.74$) and the consecutive 10 pricks (prick 10, $t(94) = 3.40$, $p = 0.001$, $p_{\text{FDR}} = 0.004$, $d = 0.75$). WUR did not show statistically significant differences between groups ($p = 0.95$). Together, our findings suggest that KOA patients show mechanical hyperalgesia in the knee—and a smaller effect of pressure pain tolerance at the calf—yet otherwise normal temporal summation and conditioned pain modulation compared to pain-free individuals.

3.2 | Predicting pain after total knee replacement with QST

Of the 77 patients enrolled in the study, 54 patients provided pain ratings at the 3-month mark, 35 patients at the 6-month mark and 46 patients at the 12-month mark—the endpoint of the study.

Patients' pain improved substantially after surgery; however appreciable variability in pain ratings across subjects is observed: at baseline, patients reported an average pain of 6.3/10 ([SD] = 2.1), 2.5/10 at 3 months ([SD] = 2.1), 1.7/10 at 6 months ([SD] = 1.9) and 1.9/10 at 12 months ([SD] = 2.4), see Figure 2a. We first assessed if pain ratings registered during pinprick stimulation and PPT—the three abnormal measures found in the cross-section analysis—were associated with pain before or at 3, 6 and 12 months after TKR. The pain reported with the single prick was associated with baseline pain ($\beta = 0.105$, $p < 0.001$, $p_{\text{mvt}} < 0.001$), and it predicted pain at 12 months ($\beta = 0.243$, $p = 0.002$, $p_{\text{mvt}} = 0.008$). Single-pinprick measures were initially found to be associated with pain at 3 months ($\beta = 0.131$, $p = 0.042$) and 6 months after TKR ($\beta = 0.166$, $p = 0.055$), with confidence intervals largely supporting positive associations with pain (Figure 2b), but these associations did not remain statistically significant after adjusting for multiple comparisons (3 months: $p_{\text{mvt}} = 0.14$; 6 months: $p_{\text{mvt}} = 0.18$). Model fits depict the positive association between baseline prick and clinical

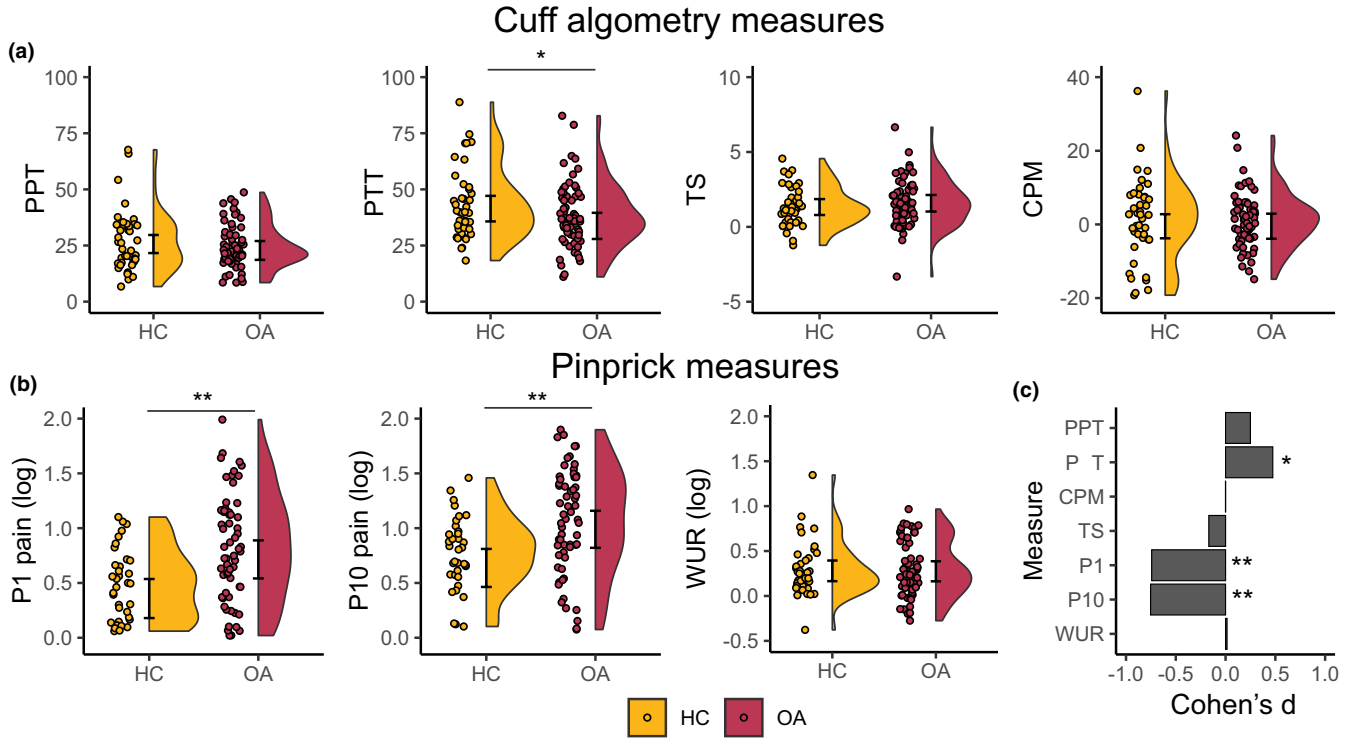

FIGURE 1 Knee osteoarthritis (KOA) patients show pronounced mechanical hyperalgesia before surgery but otherwise similar quantitative sensory testing parameters (QST). (a) For cuff algometry measures, only PTT was significantly different between healthy controls (HC) and knee osteoarthritis (OA) groups, with smaller values for KOA. (b) KOA patients rated both the single pinprick (P1) and the consecutive 10 pinpricks (P10) as more painful than healthy controls (HC). (c) Cohen's *d* effect size for each QST parameter shows large effect sizes for pinprick measures, and small for pain tolerance threshold (PTT). *$p < 0.05$; **$p < 0.01$, after FDR correction. 95% Confidence intervals are reported at the edge of the violin plots. CPM, Conditioned pain modulation; PPT, pressure pain threshold; PTT, pressure tolerance threshold; TS, temporal summation; WUR, wind-up-ratio.

pain preoperative and at later time points (Figure 2c). Baseline prick was able to explain 13% of variance in pain ratings at baseline, 9% at 3 months, 12% at 6 months and 25% at 12 months, thus suggesting that mechanical hyperalgesia may account for a significant portion of the variance in chronic postoperative pain 1 year after TKR, long after the tissue has healed.

Pain ratings for 10 consecutive pinpricks were also significantly associated with baseline pain ($\beta = 0.085$, $p = 0.004$, $p_{mvt} = 0.013$). While this measure also predicted pain at 12 months ($\beta = 0.196$, $p = 0.026$), this result was not statistically significant after adjusting for multiple comparisons ($p_{mvt} = 0.081$, confidence intervals and model can be inspected in Figure S1). Pain ratings for the 10 consecutive pinprick values were not statistically significantly predictive of pain at either 3 months ($\beta = 0.049$, $p = 0.479$, $p_{mvt} = 0.872$) or 6 months after TKR ($\beta = 0.142$, $p = 0.075$, $p_{mvt} = 0.218$).

Finally, baseline PTT values were not statistically significantly associated with pain at any time points: βs = 0 (95% CI: −0.003, 0.003), 0.001 (95% CI: −0.004, 0.007), 0.002 (95% CI: −0.005, 0.008) and 0.001 (95% CI: −0.003, 0.006) for baseline, 3, 6 months and 1 year, respectively, all $ps > 0.50$.

For completion, we also explored, post hoc, the predictive ability of the remaining QST measures. PDT, CPM and WUR were not statistically significantly associated with baseline pain or able to predict pain at future time points (all $ps > 0.42$, see Data S1). TS assessed with cuff algometry was associated with baseline pain ($\beta = 0.025$, $p = 0.021$ $p_{mvt} = 0.072$) yet this result did not survive adjustment for multiple comparisons. Furthermore, TS was unable to predict pain at either of the three postoperative time points (all $ps > 0.196$).

3.3 | Measurement properties of pinprick

We further explored these findings with additional analyses. First, we assessed how prick 1 and prick 10 independently account for variance in 12-month pain outcomes. A Pearson correlation showed that these measures were strongly correlated with each other ($r = 0.85$, $p < 0.001$). When the two were added to a multivariable model, the model favoured prick 1 values ($\beta = 0.35 \pm 0.17$) over prick 10 values ($\beta = -0.11 \pm 0.19$).

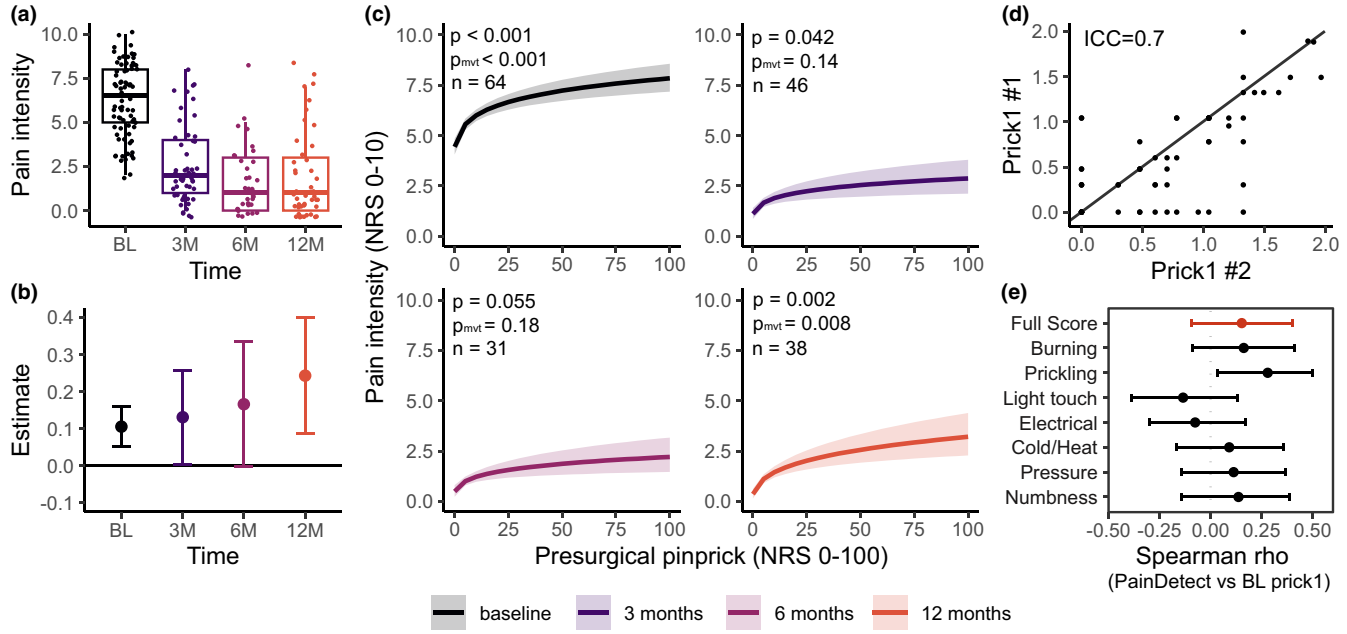

FIGURE 2 Pinprick stimulation predicts long-term pain outcomes. (a) Pain after surgery improves substantially, yet with large variability in outcomes. (b) Higher pinprick pain at baseline is predictive of higher pain at all time points. Solid line reflects the model fits, with corresponding 95% confidence intervals (CIs), with the largest and most significant effect being the prediction of pain at 12 months after TKR. (c) Model predictions and CIs for postoperative pain at each time point for respective single-pinprick values. (d) Pearson correlation shows that the two pinprick trials yield similar results, thus showing robustness of the experimental procedure. (e) Spearman correlations between baseline pinprick measures and pain characteristics as measured with PainDETECT show that subjects with higher pinprick pain more frequently report sensations of tingling and prickling on the affected knee. ICC, intraclass coefficient; NRS, numeric rating scale.

Since prick 1's variance seems to be favoured and prick 10 predictions did not survive adjustment for multiple comparisons, here, we only report the results from prick 1 measures for further analyses. Second, given that pinprick was performed twice (i.e. two trials), we assessed the test reliability of the two pinprick ratings. This entailed calculating the intraclass correlation (ICC, two-way mixed, absolute agreement) between the first and second trials, which showed good test–retest reliability with an ICC = 0.70 (Figure 2d). Since expectancy and anxiety associated with the painful stimulus may contribute to our findings, we separately investigated the predictive abilities of the first and second trials. We surmised that the first trial would be more strongly influenced by anxiety and other effects as compared to the second trial. For each trial, we fit a linear model predicting pain at 12 months from prick 1 adjusted for age and sex. The first pinprick trial explained 19.7% variance in outcomes ($\beta = 0.24 \pm 0.1$, $p = 0.015$), while the second trial explained 25.1% of the variance in the outcomes ($\beta = 0.25 \pm 0.09$, $p = 0.010$). Hence, potential expectancy effects during the first trial are unlikely to drive our findings. Third, since mechanical hyperalgesia and tactile allodynia are hallmark symptoms of neuropathic pain (Woolf & Salter, 2000), we explored associations between baseline pinprick scores and the frequency and characteristics of each painful sensation, as measured by the PainDETECT questionnaire, to assess if patients with higher evoked pain with pinprick also report other abnormal sensations in the knee. For the single-pinprick measures, Spearman rank-based correlations showed that pinprick pain ratings significantly correlated with the frequency upon which patients report 'prickling sensations' in the osteoarthritic knee ($\rho = 0.28$, 95% CI: (0.04, 0.50), $p = 0.028$, Figure 2e). No additional significant associations were found for any other sensation measured with PainDETECT, including the total score ($\rho = 0.15$, $p = 0.24$). For prick 10, we again found associations between pinprick scores and prickling pain ($\rho = 0.27$, $p = 0.03$) and the full PainDETECT score ($\rho = 0.30$, $p = 0.016$). No additional statistically significant associations were found.

3.4 | Predicting pain after total knee replacement with neuropathic pain characteristics

Given previous findings showing that neuropathic pain characteristics predict TKR outcomes (Kurien et al., 2018), we further examined if baseline neuropathic scores provided by PainDETECT could also predict future pain

outcomes. The distribution of PainDETECT scores shows patients have significant variability in neuropathic pain qualities (Figure 3a). PainDETECT scores were associated with baseline pain ($\beta = 0.008$, $p < 0.001$, $p_{mvt} < 0.001$), not statistically associated with pain at 3 months ($\beta = 0.012$, $p = 0.052$, $p_{mvt} = 0.162$) but significantly predictive of pain at 6 and 12 months after TKR ($\beta = 0.024$, $p < 0.001$, $p_{mvt} = 0.002$ and $\beta = 0.021$, $p = 0.004$, $p_{mvt} = 0.014$, respectively, see Figure 3b for confidence intervals and Figure 3c for model predictions). For all time points, higher preoperative PainDETECT scores, which measure neuropathic pain characteristics, were associated with greater pain after TKR. This model was able to explain 16% of variance in pain ratings at baseline, 12% at 3 months, 30% at 6 months and 20% at 12 months. To further explore this finding, we assessed the correlation between each pain characteristic from PainDETECT and pain at 12 months, and we found that higher chronic postoperative pain was correlated with increased frequency of burning sensations ($\rho = 0.46$, 95% CI: (0.17, 0.69), $p = 0.002$), tingling or prickling sensations ($\rho = 0.43$, 95% CI: (0.14, 0.68), $p = 0.004$), pain with cold or heat stimuli ($\rho = 0.31$, 95% CI: (0.002, 0.60), $p = 0.043$) and numbness in the area ($\rho = 0.41$, 95% CI: (0.12, 0.65), $p = 0.006$), see Figure 3d.

3.5 | Modelling hyperalgesia and neuropathic symptoms

Given the previously reported ability of pinprick hyperalgesia and PainDETECT scores to predict postoperative pain, we assessed whether these capture the same or different sources of variation in pain outcomes. Furthermore, we also tested if the predictive ability of these measures is better explained by baseline pain. To do so, the two most significant parameters from the above analyses (prick 1 and PainDETECT score) were singled out and, together with baseline pain, age and sex, added to a single multivariable linear model predicting pain intensity 12 months after TKR. Both prick 1 ($\beta = 0.21$, 95% CI: (0.02, 0.41), $p = 0.030$) and PainDETECT score ($\beta = 0.02$, 95% CI: (0, 0.03), $p = 0.046$) were independently associated with pain at 12 months, while baseline pain ($\beta = 0.14$, 95% CI: (−0.57, 0.80), $p = 0.69$), age ($\beta = 0$, 95% CI: (−0.01, 0.02), $p = 0.71$) and sex ($\beta = -0.07$, 95% CI: (−0.33, 0.19), $p = 0.56$) were not statistically significant. Relative importance metrics (Grömping, 2006) showed that prick 1 accounted for 15% unique variance in pain outcomes (log scale), PainDETECT for 13% of variance, baseline pain 4% and age and sex 0%, thus supporting that prick 1 and

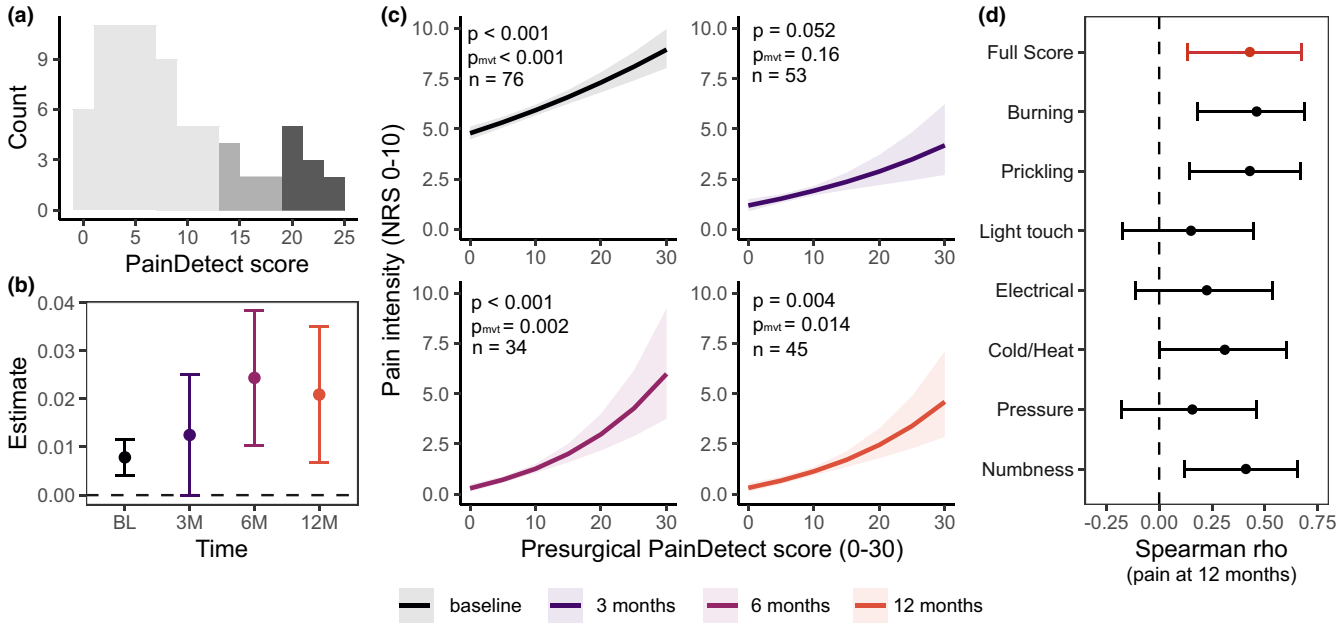

FIGURE 3 Higher PainDETECT scores are also associated with worse long-term pain outcomes. (a) PainDETECT scores show large variability, with 40 subjects falling in the 'unlikely to have a neuropathic component' category, 12 in the 'uncertain' category and 10 likely having a neuropathic pain component. (b) Estimates and confidence intervals for the prediction at four time points show that baseline PainDETECT is significantly predictive of pain at baseline, 6 and 12 months. The results are stronger and less compatible with the null for 6 and 12 months after TKR. (c) Model fits and corresponding 95% confidence intervals for each time point, again supporting that higher neuropathic pain characteristics are associated with higher postoperative pain. (d) Spearman correlations between pain at 12 months and each of the pain sensations assessed with PainDETECT show that prickling and tingling, numbness and burning sensations in the osteoarthritic knee at baseline are correlated with the pain patients report 12 months after TKR surgery.

PainDETECT scores do capture unique sources of variance in clinical pain 1 year after TKR.

3.6 | Changes in hyperalgesia and long-term outcomes

Finally, patients returned for QST assessment 3 and 6 months after surgery. Thirty-six patients returned at 3 months and 25 at 6 months. A linear model with baseline prick values and (i) the change from baseline to 3 months or (ii) the change from baseline to 6 months was used to predict pain at 12 months after adjusting for age and sex. This model aimed to assess if changes in the abnormal QST parameters (i.e. their persistence or reversal) can further relate to long-term outcomes. At 3 months, this two-parameter model shows that both baseline values ($\beta = 0.545$, 95% CI: (0.29, 0.80), $p < 0.001$) and their change ($\beta = 0.38$, 95% CI: (0.11, 0.65), $p = 0.008$) predict the outcome. More specifically, greater preoperative prick pain (Figure 4a) was associated with greater long-term pain, even after adjusting for changes in these parameters. Furthermore, greater decreases in pain reported during pinprick stimulation predicted lower long-term clinical pain after adjusting for baseline pain (Figure 4b). In other words, improvements in mechanical hyperalgesia (i.e. negative change) were associated with less clinical pain after 12 months, and vice versa (Figure 4c). Together, the full model explained 67% of the variance in 12-month pain ($F_{4,19} = 5.50$, $p = 0.004$, $R^2 = 0.67$, adj. $R^2 = 0.63$), although caution is warranted when interpreting this effect size due to the small sample size ($n = 24$). Surprisingly, this result was not observed for the change at 6 months post-surgery: while baseline parameters were still predictive of outcomes ($\beta = 0.39$, 95% CI: (0.03, 0.75), $p = 0.036$), their change from baseline to 6 months was not statistically significant ($\beta = 0.03$, 95% CI: (−0.40, 0.46), $p = 0.89$). The full model at 6 months did not significantly predict pain at 12 months ($F_{4,13} = 2.02$, $p = 0.15$, see Figure 4d–f).

4 | DISCUSSION

The current study found that KOA patients showed mechanical hyperalgesia and decreased PTTs, but otherwise, normal QST parameters compared to healthy controls. Preoperative pinprick hyperalgesia and neuropathic pain-like qualities were predictive of presurgical and 1-year postoperative pain intensities. Furthermore, improvements in hyperalgesia at 3 months predicted less pain 1 year after surgery and together with preoperative hyperalgesia, this model captured 67% of the variance in postoperative pain at 12 months.

4.1 | OA patients show hyperalgesia but otherwise normal QST parameters

A growing body of evidence suggests that OA patients exhibit various site-specific or widespread sensory abnormalities (Arant et al., 2022; Wylde et al., 2012), which are thought to reflect increased gain in nociceptive pathways. In this study, patients with KOA reported higher levels of evoked pain in response to both a single pinprick and a series of 10 consecutive pinpricks and had lower cuff PTT as compared to healthy controls. KOA is often associated with pressure hyperalgesia when compared to healthy pain-free individuals (for a review, see De Oliveira Silva et al. (2019)). Studies using pinprick assessments also find that KOA patients present hyperalgesia at the skin over the affected knee (King et al., 2013; Rakel et al., 2015) and that the magnitude of this hyperalgesia is associated with OA disease severity (King et al., 2013). Hyperalgesia to mechanical stimuli is a common indicator for peripheral sensitization, and potentially also for sensitization at the spinal cord level, given the chronic and ongoing barrage of nociceptive signalling in OA (Reichling & Levine, 2009; Woolf, 2011). We observed significant hyperalgesia at the medial compartment of the knee and, to a lesser degree, at the calf. These areas overlap in their respective dermatomes and correspond to the same spinal segments (Miller et al., 2015), which could indicate the involvement of central sensitization. On the other hand, the differences in effect sizes for prick and pressure stimuli are notable, with more pronounced hyperalgesia near the knee. Besides location, pressure stimuli primarily target C-fibre-rich deep tissue nociceptors, whereas prick stimuli also target skin-level A-delta nociceptors (Beissner et al., 2010; Treede et al., 2002; Ziegler et al., 1999), so further studies are needed to understand the relative contribution of central versus peripheral mechanisms.

No differences were found between KOA patients and healthy controls for all other collected QST parameters, including TS, which is traditionally regarded as a marker of central sensitization, and CPM, here taken as a proxy for descending modulation. Previous studies have shown that KOA patients exhibit facilitated TS and impaired CPM (Arant et al., 2022; Arendt-Nielsen et al., 2010; Kurien et al., 2018). However, findings in this field remain equivocal (Fingleton et al., 2015; Suokas et al., 2012). Our results could suggest that effect sizes for these measures are small; thus, studies with small-to-medium sample sizes may have low power, yielding results that fall on either side of the threshold for 'statistical significance'. Alternatively, it could also suggest that CPM and TS abnormalities are not universally present in OA patients and are only found in a subset of patients, possibly as a consequence of disease severity, duration and other underlying factors, in line with

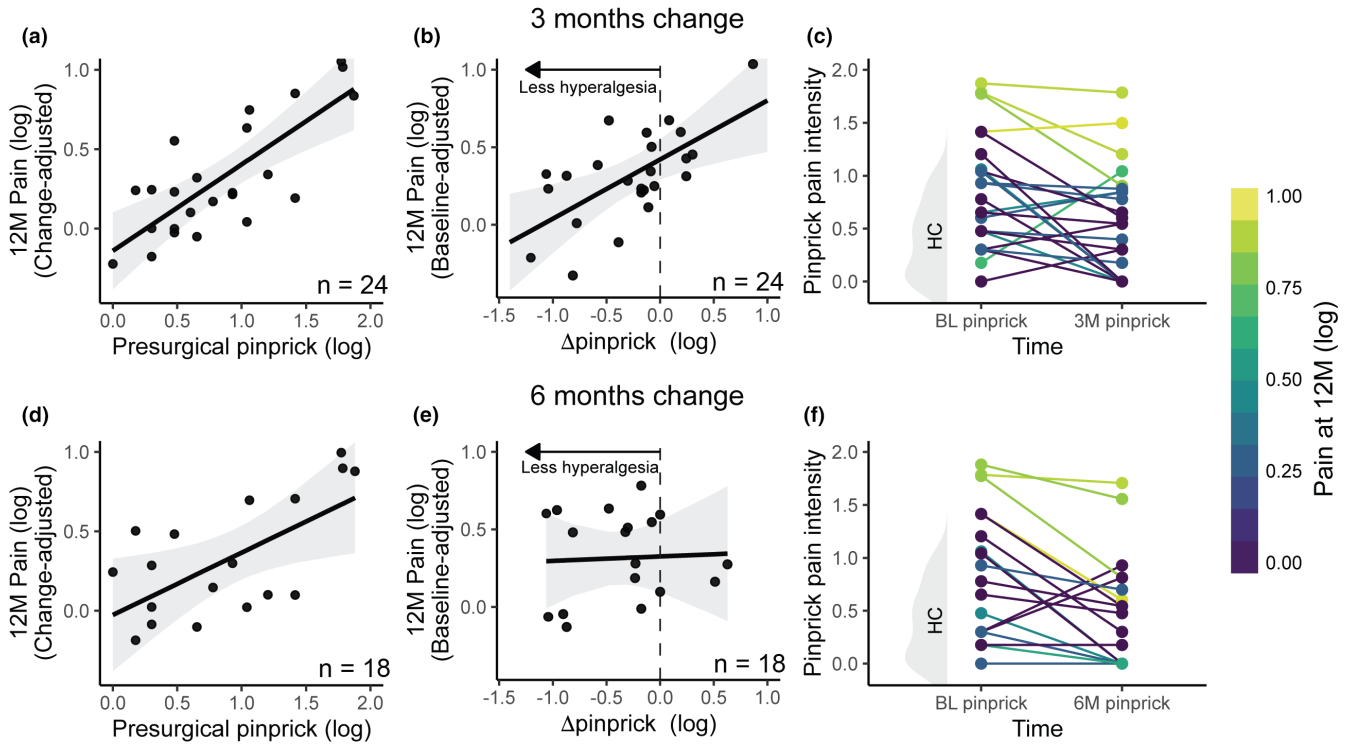

FIGURE 4 Normalization of mechanical hyperalgesia 3 months after TKR is related to long-term outcomes. Mechanical hyperalgesia changes following TKR. For patients whose data were collected preoperatively and at 3 months, baseline pinprick pain is associated with worse outcomes when controlling for the change (a), and change from preoperative to 3-month pinprick pain is also associated with long-term outcomes when controlling for baseline pinprick measures (b). Line plots of repeated measurements illustrate this association, with patients with normative pinprick pain values, or those who return to normative values after surgical intervention. Healthy control (HC) distribution for pinprick pain intensity is highlighted in grey on the left axis. Patients with low preoperative hyperalgesia have low pain 12 months after surgery. In contrast, patients with high preoperative hyperalgesia, or whose hyperalgesia worsened to abnormal states, report the highest pain after 12 months (c). The same analyses for 6 months show again that baseline pinprick pain ratings are associated with pain at 1 year when controlling for the change (d), yet the change in parameters from preoperative to 6-month pinprick pain is not significantly related to 12-month pain (e). Individual subject trajectories for baseline and 6-month pinprick values can be seen in (f).

recent proposals for the existence of multiple osteoarthritis phenotypes (Dell'Isola et al., 2016; Deveza et al., 2019). Finally, it is worth pointing out that there is a large heterogeneity in QST methods (Petersen et al., 2021) with likely consequences in the observed results (Nahman-Averbuch et al., 2013). For instance, in CPM assessment, the conditioned stimuli can be of a different modality (e.g. heat, cold and ischaemic pain) and also applied in distant body sites (e.g. arm). Here, we applied the conditioned stimuli in the contralateral leg, which showed differences between healthy controls and OA patients (Kurien et al., 2018), but whether this methodological choice impacted results remains to be determined.

4.2 | Mechanical pain intensity scores predict long-term pain outcomes

Our study showed that higher mechanical hyperalgesia at baseline, specifically prick 1, is associated with higher preoperative pain and is predictive of postoperative outcomes. This finding has important translational significance, as the prediction is strongest for pain at 12 months after surgery when the healing process should be complete. There is evidence that preoperative PPTs measured at the site of injury can predict long-term pain outcomes (see Paredes et al. (2022)) for a review, supporting the idea that abnormal preoperative nociceptive processing is associated with the persistence of pain after surgery. Comparatively fewer studies have looked at preoperative von Frey or pinprick pain intensity ratings to predict postoperative pain after total joint replacement: one study found that pain intensity reported during von Frey assessment prior to TKR can predict pain 2 days after surgery (Rakel et al., 2012), but not pain with range of motion 6 months after surgery (Noiseux et al., 2014), and for total hip replacement, no associations were found between presurgical pinprick intensity and pain 6 weeks after total hip replacement (Izumi et al., 2017). Future studies are needed to clarify

the generalizability of our findings. Interestingly, the train of 10 stimuli (prick 10) showed poorer predictive ability than a single pinprick. One possible explanation is that asking patients to rate an average pain for 10 stimuli introduces a bias that is not present when subjects focus on one pinprick only. Alternatively, it could also suggest that the average pain rating with repeated stimuli effectively mixes hyperalgesia effects with wind-up, thus confounding the predictive ability of this measure. Lastly, given that pain outcomes at 12 months were better explained by the second pinprick trial than the first, it is unlikely that expectations influenced our findings.

We did not find any other preoperative QST parameters to be statistically significantly associated with pre-TKR pain levels nor predictive of postoperative pain. Other studies have found high TS and impaired CPM to be predictive of postoperative pain intensity after TKR surgery (Bruehl et al., 2022; Dursteler et al., 2021; Edwards et al., 2022; Kurien et al., 2018; Larsen et al., 2021; Petersen et al., 2015, 2016, 2018; Rice et al., 2018; Vaegter et al., 2017). Yet, it is important to note that there are again largely inconsistent results regarding the predictive value of QST (Paredes et al., 2022; Petersen et al., 2021). Furthermore, in our sample, none of the above measures appreciably deviated from the healthy controls in the first place, suggesting they were not 'abnormal'. This could also play a role in our null results—perhaps these measures are only predictive in subgroups of patients showing abnormal CPM or TS.

4.3 | Neuropathic-like symptoms also predict long-term outcomes

It is well-established that sensory abnormalities, including allodynia and hyperalgesia, are hallmark symptoms of neuropathic injury (Decosterd & Woolf, 2000; Obrosova, 2009; Woolf, 2011). Although historically, OA has been regarded as a model of nociceptive pain, extensive data challenge this notion (Adães et al., 2015; Eitner et al., 2017; Miller et al., 2015) and indeed OA patients frequently report neuropathic pain symptoms (Hochman et al., 2013; Moss et al., 2018; Thakur et al., 2014). Furthermore, OA patients with higher neuropathic pain symptoms also present mechanical hyperalgesia (Moss et al., 2018), suggesting a link between the two. Most importantly, the presence of neuropathic pain characteristics has been put forward as a predictor of chronic postsurgical pain after TKR (Barroso et al., 2023; Wluka et al., 2020), and a previous study suggests that PainDETECT scores can predict long-term pain outcomes after TKR above the predictive value of hyperalgesia (Kurien et al., 2018). Our data suggest that preoperative neuropathic pain-like symptoms, as assessed by the PainDETECT score, were predictive of postoperative outcomes at 6 and 12 months after surgery. Importantly, prick 10 pain ratings (and, to a lesser extent, prick 1 pain ratings) were correlated with the PainDETECT scale, which could be construed as pinprick and PainDETECT values tapping into the same underlying mechanisms. To test this explicitly, while also controlling for preoperative pain, we built a multivariable model and found that neuropathic pain qualities and hyperalgesia explain unique variance in pain outcomes, while baseline pain is of lesser importance in the presence of these two parameters. This suggests that hyperalgesia and neuropathic pain reflect synergistic but independent mechanisms.

4.4 | Normalization of hyperalgesia after surgery is associated with long-term outcomes

We followed patients after TKR to understand how abnormal QST parameters at 3 and 6 months after surgery would relate to long-term outcomes. Previous studies have shown that abnormal PPTs to hand-held pressure algometer and abnormal CPM tend to normalize after TKR if the surgery provides pain relief (Graven-Nielsen et al., 2012); this normalization might be associated with better outcomes after surgery (Petersen et al., 2015). Our findings support these notions, with the change in pinprick intensity from baseline to 3 months after TKR correlating with the pain reports at 1 year after TKR, even when controlling for preoperative pinprick scores. Preoperative pinprick pain remained a statistically significant predictor of long-term outcomes when controlling for its change too, possibly due to the fact that patients with high hyperalgesia are also the ones less likely to change. Surprisingly, this result was not consistent when assessing changes at 6 months. While speculatory, this result could suggest an ongoing process where postoperative pain over time is less dependent on peripheral mechanisms and more reliant on distinct neuroplastic properties, particularly in the brain (Hashmi et al., 2013). Future analyses examining brain parameters and their changes at these time points may differentiate between these options.

4.5 | Limitations

This study presents some limitations. Data were collected throughout the COVID-19 pandemic, which impacted retention rates, and might also have played a role in patients' pain outcomes. As a consequence, many patients

were lost to follow-up, decreasing the precision of our estimates. This small sample size also precluded us from developing unbiased predictive models (i.e. out-of-sample prediction) with rigorous validation. Furthermore, we did not instruct our patients with KOA to discontinue their use of analgesic pain medication before the research appointment, potentially impacting their pain thresholds and sensitivity to pain. Finally, our sample was 70% female, in line with the known higher prevalence of knee OA in females; we adjusted for sex in all analyses, but due to lack of statistical power to study sex main effects and interactions (Gelman et al., 2020), we did not study sex-specific effects.

AUTHOR CONTRIBUTIONS

ADV: performed data analyses and drafted, edited and revised the manuscript. OJC: collected data and drafted the original manuscript. CBP: collected data and drafted the original manuscript. JP: collected data. JB, KK and LN: edited and revised the manuscript. DM and KH: performed the surgeries and provided clinical feedback. AVA: designed the study and edited and revised the manuscript. PB: collected data, performed data analyses and drafted, edited and revised the manuscript. All authors discussed the results and contributed to and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REFERENCES

Adães, S., Ferreira-Gomes, J., Mendonça, M., Almeida, L., Castro-Lopes, J. M., & Neto, F. L. (2015). Injury of primary afferent neurons may contribute to osteoarthritis induced pain: An experimental study using the collagenase model in rats. *Osteoarthritis and Cartilage*, *23*(6), 914–924. https://doi.org/10.1016/j.joca.2015.02.010

Arant, K. R., Katz, J. N., & Neogi, T. (2022). Quantitative sensory testing: Identifying pain characteristics in patients with osteoarthritis. *Osteoarthritis and Cartilage*, *30*(1), 17–31. https://doi.org/10.1016/j.joca.2021.09.011

Arendt-Nielsen, L., Jiang, G. L., DeGryse, R., & Turkel, C. (2017). Intra-articular onabotulinumtoxinA in osteoarthritis knee pain: Effect on human mechanistic pain biomarkers and clinical pain. *Scandinavian Journal of Rheumatology*, *46*(4), 303–316. https://doi.org/10.1080/03009742.2016.1203988

Arendt-Nielsen, L., Nie, H., Laursen, M. B., Laursen, B. S., Madeleine, P., Simonsen, O. H., & Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain*, *149*(3), 573–581. https://doi.org/10.1016/j.pain.2010.04.003

Barroso, J., Branco, P., Pinto-Ramos, J., Vigotsky, A. D., Reis, A. M., Schnitzer, T. J., Galhardo, V., & Apkarian, A. V. (2023). Subcortical brain anatomy as a potential biomarker of persistent pain after total knee replacement in osteoarthritis. *Pain*, *164*(10), 2306–2315. https://doi.org/10.1097/j.pain.0000000000002932

Beissner, F., Brandau, A., Henke, C., Felden, L., Baumgärtner, U., Treede, R.-D., Oertel, B. G., & Lötsch, J. (2010). Quick discrimination of Adelta and C fiber mediated pain based on three verbal descriptors. *PLoS One*, *5*(9), e12944. https://doi.org/10.1371/journal.pone.0012944

Beswick, A. D., Wylde, V., Gooberman-Hill, R., Blom, A., & Dieppe, P. (2012). What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open*, *2*(1), e000435. https://doi.org/10.1136/bmjopen-2011-000435

Bruehl, S., Billings, F. T. t., Anderson, S., Polkowski, G., Shinar, A., Schildcrout, J., Shi, Y., Milne, G., Dematteo, A., Mishra, P., & Harden, R. N. (2022). Preoperative predictors of complex regional pain syndrome outcomes in the 6 months following total knee arthroplasty. *The Journal of Pain*, *23*(10), 1712–1723. https://doi.org/10.1016/j.jpain.2022.04.005

De Oliveira Silva, D., Rathleff, M. S., Petersen, K., Azevedo, F. M. D., & Barton, C. J. (2019). Manifestations of pain sensitization across different painful knee disorders: A systematic review including meta-analysis and metaregression. *Pain Medicine (Malden, Mass.)*, *20*(2), 335–358. https://doi.org/10.1093/pm/pny177

Decosterd, I., & Woolf, C. J. (2000). Spared nerve injury: An animal model of persistent peripheral neuropathic pain. *Pain*, *87*(2), 149–158. https://doi.org/10.1016/S0304-3959(00)00276-1

Dell'Isola, A., Allan, R., Smith, S. L., Marreiros, S. S. P., & Steultjens, M. (2016). Identification of clinical phenotypes in knee osteoarthritis: A systematic review of the literature. *BMC Musculoskeletal Disorders*, *17*(1), 425. https://doi.org/10.1186/s12891-016-1286-2

Deveza, L. A., Nelson, A. E., & Loeser, R. F. (2019). Phenotypes of osteoarthritis—current state and future implications. *Clinical and Experimental Rheumatology*, *37*(Suppl 120), 64–72. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6936212/

Dursteler, C., Salazar, Y., Rodriguez, U., Pelfort, X., & Verdie, L. P. (2021). Conditioned pain modulation predicts persistent pain after knee replacement surgery. *Pain Reports*, *6*(1), e910. https://doi.org/10.1097/PR9.0000000000000910

Edwards, R. R., Campbell, C., Schreiber, K. L., Meints, S., Lazaridou, A., Martel, M. O., Cornelius, M., Xu, X., Jamison, R. N., Katz, J. N., Carriere, J., Khanuja, H. P., Sterling, R. S., Smith, M. T.,

& Haythornthwaite, J. A. (2022). Multimodal prediction of pain and functional outcomes 6 months following total knee replacement: A prospective cohort study. *BMC Musculoskeletal Disorders*, *23*(1), 302. https://doi.org/10.1186/s12891-022-05239-3

Eitner, A., Hofmann, G. O., & Schaible, H.-G. (2017). Mechanisms of osteoarthritic pain. Studies in humans and experimental models. *Frontiers in Molecular Neuroscience*, *10*, 349. https://doi.org/10.3389/fnmol.2017.00349

Fingleton, C., Smart, K., Moloney, N., Fullen, B. M., & Doody, C. (2015). Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *23*(7), 1043–1056. https://doi.org/10.1016/j.joca.2015.02.163

Freynhagen, R., Baron, R., Gockel, U., & Tölle, T. R. (2006). painDETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. *Current Medical Research and Opinion*, *22*(10), 1911–1920. https://doi.org/10.1185/030079906X132488

Gelman, A., Hill, J., & Vehtari, A. (2020). *Regression and other stories*. Cambridge University Press. https://doi.org/10.1017/9781139161879

Graven-Nielsen, T., Wodehouse, T., Langford, R. M., Arendt-Nielsen, L., & Kidd, B. L. (2012). Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. *Arthritis & Rheumatism*, *64*(9), 2907–2916. https://doi.org/10.1002/art.34466

Grömping, U. (2006). Relative importance for linear regression in R: The package relaimpo. *Journal of Statistical Software*, *17*(1), 1-27. https://doi.org/10.18637/jss.v017.i01

Hashmi, J. A., Baliki, M. N., Huang, L., Baria, A. T., Torbey, S., Hermann, K. M., Schnitzer, T. J., & Apkarian, A. V. (2013). Shape shifting pain: Chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain*, *136*(9), 2751–2768. https://doi.org/10.1093/brain/awt211

Hochman, J. R., Davis, A. M., Elkayam, J., Gagliese, L., & Hawker, G. A. (2013). Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. *Osteoarthritis and Cartilage*, *21*(9), 1236–1242. https://doi.org/10.1016/j.joca.2013.06.023

Hoenig, J. M., & Heisey, D. M. (2001). The abuse of power: The pervasive fallacy of power calculations for data analysis. *The American Statistician*, *55*(1), 19–24. https://doi.org/10.1198/000313001300339897

Izumi, M., Petersen, K. K., Laursen, M. B., Arendt-Nielsen, L., & Graven-Nielsen, T. (2017). Facilitated temporal summation of pain correlates with clinical pain intensity after hip arthroplasty. *Pain*, *158*(2), 323–332. https://doi.org/10.1097/j.pain.0000000000000764

King, C. D., Sibille, K. T., Goodin, B. R., Cruz-Almeida, Y., Glover, T. L., Bartley, E., Riley, J. L., Herbert, M. S., Sotolongo, A., Schmidt, J., Fessler, B. J., Redden, D. T., Staud, R., Bradley, L. A., & Fillingim, R. B. (2013). Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis. *Osteoarthritis and Cartilage*, *21*(9), 1243–1252. https://doi.org/10.1016/j.joca.2013.05.015

Kurien, T., Arendt-Nielsen, L., Petersen, K. K., Graven-Nielsen, T., & Scammell, B. E. (2018). Preoperative neuropathic pain-like symptoms and central pain mechanisms in knee osteoarthritis predicts poor outcome 6 months after Total knee replacement surgery. *The Journal of Pain*, *19*(11), 1329–1341. https://doi.org/10.1016/j.jpain.2018.05.011

Larsen, D. B., Laursen, M., Edwards, R. R., Simonsen, O., Arendt-Nielsen, L., & Petersen, K. K. (2021). The combination of preoperative pain, conditioned pain modulation, and pain catastrophizing predicts postoperative pain 12 months after Total knee arthroplasty. *Pain Medicine (Malden, Mass.)*, *22*(7), 1583–1590. https://doi.org/10.1093/pm/pnaa402

Lewis, G. N., Rice, D. A., McNair, P. J., & Kluger, M. (2015). Predictors of persistent pain after total knee arthroplasty: A systematic review and meta-analysis. *British Journal of Anaesthesia*, *114*(4), 551–561. https://doi.org/10.1093/bja/aeu441

Miller, R. E., Tran, P. B., Obeidat, A. M., Raghu, P., Ishihara, S., Miller, R. J., & Malfait, A.-M. (2015). The role of peripheral nociceptive neurons in the pathophysiology of osteoarthritis pain. *Current Osteoporosis Reports*, *13*(5), 318–326. https://doi.org/10.1007/s11914-015-0280-1

Moss, P., Benson, H. A. E., Will, R., & Wright, A. (2018). Patients with knee osteoarthritis who score highly on the PainDETECT questionnaire present with multimodality hyperalgesia, increased pain, and impaired physical function. *The Clinical Journal of Pain*, *34*(1), 15–21. https://doi.org/10.1097/AJP.0000000000000504

Nahman-Averbuch, H., Yarnitsky, D., Granovsky, Y., Gerber, E., Dagul, P., & Granot, M. (2013). The role of stimulation parameters on the conditioned pain modulation response. *Scandinavian Journal of Pain*, *4*(1), 10–14. https://doi.org/10.1016/j.sjpain.2012.08.001

Noiseux, N. O., Callaghan, J. J., Clark, C. R., Zimmerman, M. B., Sluka, K. A., & Rakel, B. A. (2014). Preoperative predictors of pain following total knee arthroplasty. *The Journal of Arthroplasty*, *29*(7), 1383–1387. https://doi.org/10.1016/j.arth.2014.01.034

Obrosova, I. G. (2009). Diabetic painful and insensate neuropathy: Pathogenesis and potential treatments. *Neurotherapeutics*, *6*(4), 638–647. https://doi.org/10.1016/j.nurt.2009.07.004

Paredes, A. C., Pinto, J. M., Almeida, A., & Pinto, P. R. (2022). Predictive value of quantitative sensory testing for acute and chronic postsurgical pain after total joint arthroplasty: A systematic review. *Pain*, *163*(3), e385. https://doi.org/10.1097/j.pain.0000000000002385

Petersen, K. K., Arendt-Nielsen, L., Finocchietti, S., Hirata, R. P., Simonsen, O., Laursen, M. B., & Graven-Nielsen, T. (2017). Age interactions on pain sensitization in patients with severe knee osteoarthritis and controls. *The Clinical Journal of Pain*, *33*(12), 1081–1087. https://doi.org/10.1097/AJP.0000000000000495

Petersen, K. K., Arendt-Nielsen, L., Simonsen, O., Wilder-Smith, O., & Laursen, M. B. (2015). Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain*, *156*(1), 55–61. https://doi.org/10.1016/j.pain.0000000000000022

Petersen, K. K., Graven-Nielsen, T., Simonsen, O., Laursen, M. B., & Arendt-Nielsen, L. (2016). Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement. *Pain*, *157*(7), 1400–1406. https://doi.org/10.1097/j.pain.0000000000000531

Petersen, K. K., Simonsen, O., Laursen, M. B., & Arendt-Nielsen, L. (2018). The role of preoperative radiologic severity, sensory

testing, and temporal summation on chronic postoperative pain following total knee arthroplasty. *The Clinical Journal of Pain*, *34*(3), 193–197. https://doi.org/10.1097/AJP.0000000000000528

Petersen, K. K., Vaegter, H. B., Stubhaug, A., Wolff, A., Scammell, B. E., Arendt-Nielsen, L., & Larsen, D. B. (2021). The predictive value of quantitative sensory testing: A systematic review on chronic postoperative pain and the analgesic effect of pharmacological therapies in patients with chronic pain. *Pain*, *162*(1), 31–44. https://doi.org/10.1097/j.pain.0000000000002019

Petersen, K. K.-S., Kilic, K., Hertel, E., Sejersgaard-Jacobsen, T. H., Jørgensen, M. K., Troelsen, A., Arendt-Nielsen, L., & Boye Larsen, D. (2023). Quantitative sensory testing as an assessment tool to predict the response to standard pain treatment in knee osteoarthritis: A systematic review and meta-analysis. *Pain Reports*, *8*(4), e1079. https://doi.org/10.1097/PR9.0000000000001079

Rakel, B., Vance, C., Zimmerman, M. B., Petsas-Blodgett, N., Amendola, A., & Sluka, K. A. (2015). Mechanical hyperalgesia and reduced quality of life occur in people with mild knee osteoarthritis pain. *The Clinical Journal of Pain*, *31*(4), 315–322. https://doi.org/10.1097/AJP.0000000000000116

Rakel, B. A., Blodgett, N. P., Zimmerman, B. M., Logsden-Sackett, N., Clark, C., Noiseux, N., Callaghan, J., Herr, K., Geasland, K., Yang, X., & Sluka, K. A. (2012). Predictors of postoperative movement and resting pain following total knee replacement. *Pain*, *153*(11), 2192–2203. https://doi.org/10.1016/j.pain.2012.06.021

Reichling, D. B., & Levine, J. D. (2009). Critical role of nociceptor plasticity in chronic pain. *Trends in Neurosciences*, *32*(12), 611–618. https://doi.org/10.1016/j.tins.2009.07.007

Rice, D. A., Kluger, M. T., McNair, P. J., Lewis, G. N., Somogyi, A. A., Borotkanics, R., Barratt, D. T., & Walker, M. (2018). Persistent postoperative pain after total knee arthroplasty: A prospective cohort study of potential risk factors. *British Journal of Anaesthesia*, *121*(4), 804–812. https://doi.org/10.1016/j.bja.2018.05.070

Roth, G. A., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, H. T., Abebe, M., Abebe, Z., Abejie, A. N., Abera, S. F., Abil, O. Z., Abraha, H. N., … Murray, C. J. L. (2018). Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: A systematic analysis for the global burden of disease study 2017. *The Lancet*, *392*(10159), 1736–1788. https://doi.org/10.1016/S0140-6736(18)32203-7

Rucker, D. D., McShane, B. B., & Preacher, K. J. (2015). A researcher's guide to regression, discretization, and median splits of continuous variables. *Journal of Consumer Psychology*, *25*(4), 666–678. https://doi.org/10.1016/j.jcps.2015.04.004

Saxer, F., Hollinger, A., Bjurstrom, M. F., Conaghan, P. G., Neogi, T., Schieker, M., & Berenbaum, F. (2024). Pain-phenotyping in osteoarthritis: Current concepts, evidence, and considerations towards a comprehensive framework for assessment and treatment. *Osteoarthritis and Cartilage Open*, *6*(1), 100433. https://doi.org/10.1016/j.ocarto.2023.100433

Suokas, A. K., Walsh, D. A., McWilliams, D. F., Condon, L., Moreton, B., Wylde, V., Arendt-Nielsen, L., & Zhang, W. (2012). Quantitative sensory testing in painful osteoarthritis: A systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *20*(10), 1075–1085. https://doi.org/10.1016/j.joca.2012.06.009

Thakur, M., Dickenson, A. H., & Baron, R. (2014). Osteoarthritis pain: Nociceptive or neuropathic? *Nature Reviews Rheumatology*, *10*(6), 374–380. https://doi.org/10.1038/nrrheum.2014.47

Treede, R. D., Rolke, R., Andrews, K., & Magerl, W. (2002). Pain elicited by blunt pressure: Neurobiological basis and clinical relevance. *Pain*, *98*(3), 235–240. https://doi.org/10.1016/S0304-3959(02)00203-8

Vaegter, H. B., Handberg, G., Emmeluth, C., & Graven-Nielsen, T. (2017). Preoperative hypoalgesia after cold pressor test and aerobic exercise is associated with pain relief 6 months after Total knee replacement. *The Clinical Journal of Pain*, *33*(6), 475–484. https://doi.org/10.1097/AJP.0000000000000428

Vigotsky, A. D., Tiwari, S. R., Griffith, J. W., & Apkarian, A. V. (2021). What is the numerical nature of pain relief? *Frontiers in Pain Research*, *2*, 756680. https://doi.org/10.3389/fpain.2021.756680

Wluka, A. E., Yan, M. K., Lim, K. Y., Hussain, S. M., & Cicuttini, F. M. (2020). Does preoperative neuropathic-like pain and central sensitisation affect the post-operative outcome of knee joint replacement for osteoarthritis? A systematic review and meta analysis. *Osteoarthritis and Cartilage*, *28*(11), 1403–1411. https://doi.org/10.1016/j.joca.2020.07.010

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*, *152*(3), S2–S15. https://doi.org/10.1016/j.pain.2010.09.030

Woolf, C. J., & Salter, M. W. (2000). Neuronal plasticity: Increasing the gain in pain. *Science*, *288*(5472), 1765–1769.

Wylde, V., Hewlett, S., Learmonth, I. D., & Dieppe, P. (2011). Persistent pain after joint replacement: Prevalence, sensory qualities, and postoperative determinants. *Pain*, *152*(3), 566–572. https://doi.org/10.1016/j.pain.2010.11.023

Wylde, V., Palmer, S., Learmonth, I. D., & Dieppe, P. (2012). Somatosensory abnormalities in knee OA. *Rheumatology*, *51*(3), 535–543. https://doi.org/10.1093/rheumatology/ker343

Ziegler, E. A., Magerl, W., Meyer, R. A., & Treede, R. D. (1999). Secondary hyperalgesia to punctate mechanical stimuli: Central sensitization to A-fibre nociceptor input. *Brain*, *122*(12), 2245–2257. https://doi.org/10.1093/brain/122.12.2245

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