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Can quantitative sensory tests predict failed back surgery? A prospective cohort study

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Running Head:

Predicting failed back surgery with QST.

Authors contribution: M.M., P.J. and M.C.: conceiving the study. M.M., F.T., P.H. and U.S.: Patient recruitment. M.M. F.T.: Data collection. C.A.: reading out imaging data. M.M., L.A. and P.J.: data preparation and data analysis. M.M. and M.C.: first draft of the paper. All authors: final draft of the paper. MC: takes senior responsibility of the whole research process.

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Abstract

Background: Failed back surgery syndrome (FBSS) is a therapy-refractory pain condition characterized by persistent low back pain after spine surgery. FBSS is associated with severe disability, low quality of life and high unemployment rate. We are currently unable to identify patients who are at risk of developing FBSS. Patients with chronic low back pain may display signs of central hypersensitivity as assessed by quantitative sensory tests (QST). This can contribute to patients' vulnerability to develop persistent pain after surgery.

Objective: We tested the hypothesis that central hypersensitivity as assessed by QST predicts FBSS.

Design and Setting: We performed a prospective cohort study in 141 patients with chronic low back pain scheduled for up to three segmental spine surgery for chronic low back pain due to degenerative changes in three tertiary care centres.

Patients: Chronic low back pain was defined as of at least 3 on a numerical rating scale at most days during the week and with a minimum duration of three months.

Outcomes: We defined FBSS as persistence of pain, persistence of disability or a composite outcome defined as either persistence of pain or disability. The primary outcome was persistence of pain 12 months after surgery. We applied 14 QST using electrical, pressure and temperature stimulation to predict FBSS and assessed the association of QST with FBSS in multivariable analyses adjusted for socio-demographic, psychological and clinical and surgery-related characteristics.

Results: None of the investigated 14 QST predicted FBSS, with 95% confidence intervals of crude and adjusted associations of all QST including one as measure of no association. Results remained robust in all sensitivity and secondary analyses.

Conclusion: The study indicates that assessment of altered central pain processing using current QST is unlikely to identify patients at risk for FBBS and is therefore unlikely to inform clinical decisions.

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Introduction

Failed back surgery syndrome (FBSS) is a therapy-refractory pain condition characterized by persistent low back pain after spine surgery, associated with disability, low quality of life and high unemployment.[1, 2] Twenty-five to 38% of patients develop FBSS.[1, 3-6] Given the high prevalence of chronic low back pain [7, 8], the increase of spine surgery [9, 10] and its high failure rate, the number of patients with FBSS is substantial and expected to rise. Considering this, the high costs of spine surgery [11] and the associated burden of disease, it is important to identify pre-surgical predictors of poor surgical outcome. This would support decision on the indication of surgery, alternative treatments, and preventive measures.

We are currently unable to identify patients at risk of developing FBSS with an acceptable confidence. Evidence on socio-demographic, psychological, clinical and surgery-related predictors is inconclusive.[12, 13] Therefore, investigating other contributing mechanisms is important. Prolonged or intense nociceptive input induces neuro-plastic changes that lead to central nervous system hypersensitivity.[14] This can be assessed using quantitative sensory tests (QST).[15, 16] Previous case-control studies found lower pain thresholds of QST in patients with chronic low back pain, compared to pain-free controls.[17-19] This suggests that central hypersensitivity is involved in chronic low back pain. Theoretically, the surgical trauma may enhance these neuro-plastic changes, thereby canceling out the benefits of surgery and producing persistent pain.

We tested the hypothesis that central hypersensitivity as assessed by QST predicts FBSS and thus QST would be a tool to inform clinical decision making in the patient selection process for spine surgery. Unlike any previous study, we included pain, disability, a composite endpoint of pain and disability [20-22], as well as a comprehensive set of potential pre-surgical predictors.

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Methods

Study population

We included patients undergoing spine surgery for chronic low back pain associated with degenerative changes of the lumbar spine. Patients with planned surgery for lumbosacral radiculopathy due to herniated discs, surgery for cancer or trauma were ineligible because clinical presentation, surgical approach and prognosis after surgery typically differ in these patients, as compared to patients with low back pain associated with degenerative changes.[11] Chronic low back pain was defined as lumbar back pain of ≥3 on a numerical rating scale (NRS) with 0 ”no pain” and 10 “worst pain imaginable” at most days during the week and with a minimum duration of three months, with or without radiation to the leg. We excluded patients with bilateral pain below the knees because of possible interference with QST, patients with rheumatologic inflammatory diseases, neurologic co-morbidities potentially affecting the neurological function of the lower extremity to be tested, psychiatric co-morbidities other than unipolar depressive disorder, previous instrumented spine surgery (previous total disc replacement or spinal fusion with pedicle screws, cages or internal splints), planned surgery of more than three segments, and with multiple somatic co-morbidities. We also excluded patients who could not be contacted by phone or mail before surgery. We chose a pragmatic approach with broad eligibility criteria to best reflect the clinical setting and thus conclusions based on this study population are more likely to inform clinical decision making.[23]

Study setting

We recruited patients for this prospective cohort study at three tertiary care centers in Bern, Switzerland where they underwent a detailed orthopedic and neurologic assessment and received spinal magnetic resonance imaging (MRI). Two assessors performed a repeat clinical examination at study entry to confirm study eligibility and other study-related procedures according to a previously applied, standardized, prospective protocol.[17] We performed all study-related procedures at the Department of Anesthesiology and Pain Medicine of the University Hospital of Bern. The protocol was approved by the Ethics Committee of the Canton of Bern, Switzerland (application number 176/11, Committee President Prof. Niklaus Tüller) and conducted in accordance with the Declaration of Helsinki.[24] We obtained written informed consent from all participants. This manuscript adheres to the applicable STROBE guideline.[25]

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Quantitative Sensory Tests

We performed QST according to a previously applied prospective protocol [17] in a quiet room to avoid patient distraction. Participants were lying in a bed with a leg rest placed under the knees to obtain a 30° semi-flexion for testing. All patients received identical instruction regarding the testing session and underwent a training session to familiarize with the procedure before data collection was initiated. This is common practice of testing protocols. [17, 26] We performed tests at the most painful area at the lower back (regional hypersensitivity) and the contralateral extremity (widespread hypersensitivity). In case of bilateral back pain, the testing extremity was randomly selected according to a computer-generated list. We made two measurements and considered the mean value for data analysis, except for the cold pressor test and the assessment of conditioned pain modulation, for which only one measurement was taken. We randomly assigned the sequence of testing modalities according to a computer-generated list to avoid bias as a result of testing order. [27] Supplemental digital text 1 includes details of the QST assessment.

Baseline assessment

Socio-demographic predictors included age, gender, education (higher/lower), working status (regular work including houseworkers/no regular work) and civil status (married/not married). We considered patients with high school or university degree as having higher education. We administered the Beck Depression Inventory version 2 [28], the State-Trait-Anxiety-Inventory [29] and the Pain Catastrophizing Scale.[30] The clinical assessment included Body-Mass-Index (BMI), smoking (yes/no), finger ground distance (>10 cm/≤10 cm), positive Lasègue sign (yes/no), previous non-instrumented back surgery (yes/no), pain radiating to the leg (yes/no), pain duration (>5 years/ ≤ 5 years), pain intensity, disability, intake of non-opioid and opioid analgesics (yes/no). We used the maximum NRS during seven days preceeding baseline assessment for pain intensity and the Oswestry Disability Index for disability.[31] We chose these socio-demographic, psychological and clinical characteristics because of their potential prognostic value for FBSS per previous studies.[12, 13]

Radiologic assessment

All MRIs were read by an independent radiologist at Balgrist University Hospital in Zurich, Switzerland, blinded to type of surgery, spinal levels operated and surgical outcome. He evaluated degenerative changes of the spine by characterizing: spinal stenosis, spondylolisthesis, endplate changes, scoliosis, facet joint degeneration, disc degeneration and

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fatty degeneration of paraspinal muscles. He first rated each segment between L1 and S1 according to these features. We then identified the worst segment for each feature in each patient and considered degenerative changes of the worst segment as co-variate for further statistical analysis. Supplemental Digital Text 2 describes in detail the classification criteria.

Surgery and post-surgical care

All surgeries were performed by senior surgeons under standard general anesthesia (combined volatile anesthetics an intravenous opioids). The surgeons based the decision on the type of surgery and the number of segments to be operated upon clinical reasoning and radiologic findings.[6, 32] Post-surgical treatment was standardized for all patients and included intravenous patient-controlled analgesia (morphine as routine, fentanyl in case of renal insufficiency or intolerance to morphine), prescription of post-discharge non-opioid analgesics and stepwise rehabilitation. Rehabilitation consisted of stabilizing muscle exercises for trunk muscles in supine position. Patients were encouraged to walk as much as tolerated. The rehabilitation training begun two months after surgery. Evidence on type of surgery (instrumented/non-instrumented surgery) and number of segments to be operated (multi-segmental/uni-segmental) [33, 34] as predictors of FBSS is inconclusive. We therefore adjusted our analyses for these procedural characteristics. We recorded maximum pain intensity at the first day after surgery and at the last in-hospital day using the NRS, and considered the average value for analysis. Acute post-surgical pain is an important predictor for FBSS [35] but also an intermediate outcome potentially lying on the causal pathway. We did not include it in the main model but performed a sensitivity analysis adjusting for this variable.

Definition of FBSS

We performed follow-up assessments 6 and 12 months after surgery to determine the presence of FBSS. We defined FBSS as less than 30% reduction in maximum pain intensity during the last seven days as compared to baseline and less than 30% reduction in disability from baseline.[20-22] Additionally, we used a composite endpoint and defined FBSS as persistence of either pain or disability to integrate both outcomes as recommended.[20-22] The primary outcome was persistence of pain at 12 months. We considered all other outcomes as secondary outcomes.

Statistical analysis

We expected a frequency of FBSS of 30%.[3-5] We estimated that a sample size of 155 patients detects a dichotomized predictor that is approximately twice as frequent in patients with FBSS

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as compared to patients without FBSS, if the frequency of the predictor was at least 25%. For continuous predictors, this sample size would detect a difference between patients with and without FBSS of 0.5 standard deviation (SD) units. We considered a power of 80% and a two-sided alpha of 0.05. A sample size of 155 patients allowed the inclusion of approximately nine variables in multivariable models.[36]

To determine pre-surgical predictors of FBSS, we calculated odds ratios (ORs) for socio-demographic, psychological, clinical and radiologic characteristics, as well as QST, using logistic regressions based on multiple imputations.[37] As pre-specified, we dichotomized education, working conditions, civil status, pain radiating to the leg and all radiologic variables to facilitate clinical interpretation. We dichotomized finger-ground distance and pain duration at baseline because these variables were neither normally nor log-normally distributed. QST data with electrical or pressure stimulation were normally or log-normally distributed. Heat and cold pain detection thresholds and hand withdrawal time of the cold pressor test were truncated and neither normally nor log-normally distributed. Therefore, we dichotomized these variables using the maximally attainable stimulus as cut-off. To ensure comparability of regression coefficients for continuous and binary covariates, we expressed the effect for all continuous variables per 2 SD change on the normal or logarithmic scale.[38] For continuous socio-demographic, psychological and clinical variables, the effect was expressed per 2 SD increase. For continuous QST, it was expressed per 2 SD decrease. ORs above one imply that pathological values of QST (i.e. lower thresholds after pressure, electrical and heat stimulation, higher thresholds after cold stimulation, shorter hand withdrawal time of the cold pressor test and impaired CPM) are associated with an increased risk of FBSS.

We imputed predictors and outcomes using chained equations with predictive mean matching for continuous variables and logistic regression for binary variables generating 15 multiply imputed datasets. We performed stepwise imputation, first imputing psychological, clinical, radiological and procedural characteristics, then values of QST, and finally all outcome variables.

In our main analysis, we calculated crude, partially and fully adjusted ORs of all predictors and persistence of pain at 12 months. We included type of surgery and number of segments operated as procedural characteristics in partially adjusted analyses. We estimated fully adjusted ORs including socio-demographic, psychological, clinical and radiologic characteristics that were associated with the primary outcome at $p \leq 0.10$ in partially adjusted analyses and forced procedural characteristics and gender into the models. We performed four sets of fully adjusted sensitivity analyses of the association between QST and the primary outcome. First, we

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included acute post-surgical pain for the reason mentioned above. Second, we restricted the analysis to patients with complete follow-up at both time points, using multiple imputation only for missing covariate data. Third, we performed a linear regression with pain intensity at 12 months as continuous outcome variable. Fourth, we conducted a subgroup analysis including only patients with no previous surgery to rule out the possibility that FBSS at baseline would influence the results. We conducted several secondary analyses exploring the fully adjusted associations of QST and FBSS according to different outcome definitions and follow-up time points, including the same set of co-variates as in the main analysis. P-values are two-sided and confidence intervals (CI) refer to 95% boundaries. We performed all analyses with Stata (Version 12.1, StataCorp, College Station, TX).

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Results

Study Flow

We screened 958 patients with chronic low back pain undergoing spine surgery between 2012 and 2015, found 392 patients (41%) to be eligible, and tested 141 patients (Figure 1). Time and resource constraints led us to close the study 14 patients (9%) short of the planned 155. Ninety-six (68.1 %) patients were operated at a single, 34 (24.1 %) at two and 11 (7.8 %) at three segments, respectively. Twenty-eight (19.9%) patients had a previous non-instrumented back surgery. In 49 (34.8 %) patients, decompression without additional instrumental stabilization was performed. We did not encounter any surgical complications. Treatment of patients developing FBSS was left to the treating surgeon and not monitored by the study team. Eleven (7.8 %) patients were re-operated during the follow-up period as a result of incident FBSS. 140 patients (99%) and 137 patients (95%) presented for the 6 and 12 months' follow-up, respectively.

Patients with FBSS according to definition of outcome and follow-up time point and completeness of data

Table 1 shows the frequency of FBSS depending on outcome definition and time of assessment. Forty-four patients (31.2%) developed FBSS, defined as persistence of pain 12 months after imputing missing data. The frequency of FBSS, as defined by persistence of pain or by persistence of disability, was around 30% at both follow-ups. Forty% of all patients presented with FBSS if defined according to the composite endpoint. The frequency of FBSS remained robust per outcome if we based the calculation on data as observed, on patients with complete follow-up data or on data after multiple imputation. Supplemental Digital Table 1 shows details of data completeness and distribution of all predictors. Data on heat and cold pain detection thresholds, hand withdrawal time of the cold pressor test and CPM were missing due to logistic reasons and were thus considered as completely missing at random. Data completeness of these QST ranged from 82% to 97%. We were able to evoke a nociceptive withdrawal reflex (NWR) in only 67% of patients, since painful stimulation became intolerable before a NWR could be elicited. We already encountered this issue in a previous study [39]. We cannot rule out that the inability to evoke a NWR is the result of normal central pain processing. Therefore, the assumption of missing at random for multiple imputation was likely to be violated and we refrained from analyzing NWR threshold.

Sociodemographic, psychological, clinical and radiologic predictors of FBSS

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Table 2 presents crude and partially adjusted associations of socio-demographic, psychological, clinical and radiologic predictors of FBSS, defined as persistence of pain after 12 months. Socio-demographic and radiologic predictors were similarly distributed in both patient groups. We found equal scores of depression and anxiety in patients with and without FBSS. However, higher scores of catastrophizing, increased BMI, larger finger-ground distance, positive Lasègue sign, higher baseline disability, intake of non-opioid analgesics and intake of opioid analgesics were associated with an increased risk for FBSS, with ORs ranging from 1.85 and 2.44 and p-values from 0.02 to 0.10 in partially adjusted models. We included these predictors along with procedural characteristics and gender in all fully adjusted models. Procedural characteristics were not associated with FBSS. Instrumented surgery as compared to simple decompression showed an OR of 0.80 (95% CI 0.40-1.64, p=0.54) and multi-segmental as compared to uni-segmental surgery showed an OR of 0.94 (0.43-2.04, p=0.87). After full adjustment, we did not find any significant association for gender (OR 0.59, 95% CI 0.26-1.34, p=0.21), catastrophizing (OR 1.58, 95% CI 0.66-3.79, p=0.31), BMI (OR 1.73, 95% CI 0.77-3.93, p=0.19), finger-ground distance (OR 1.42, 95% CI 0.55-3.66, p=0.47), Lasègue sign (OR 1.85, 95% CI 0.75-4.56, p=0.18), baseline disability (OR 1.13, 95% CI 0.46-2.77, p=0.78), intake of non-opioid analgesics (OR 1.95, 95% CI 0.83-4.54, p=0.12) and intake of opioid analgesics (OR 1.35, 95% CI 0.46-3.94, p=0.58).

Quantitative Sensory Tests as Predictors of FBSS

Table 3 and figure 2 show crude and partially adjusted associations as well as fully adjusted associations of QST with FBSS, defined as persistence of pain 12 months after surgery. All point estimates appeared randomly scattered around one and all 95% CI included one as measure of no association. We found none of the QST to be associated with the primary outcome in any fully adjusted sensitivity analyses (Supplemental Digital Table 2). OR and corresponding 95% CI of all QST remained similar to the main analysis after including acute post-surgical pain (sensitivity analysis a) and after restricting the analysis to patients with complete follow-up at both time-points (sensitivity analysis b). Except for cold pain detection threshold at the leg, none of the p-values of showed a statistical trend or a significant association between QST and pain intensity after 12 months as continuous outcome (sensitivity analysis c). Table 4 shows fully adjusted secondary analyses of the associations between QST and FBSS, defined as persistence of disability and persistence of pain or disability after 12 months. Supplemental Digital Table 3 shows association of QST and FBSS after six months (secondary

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outcomes). Results were similar to the main analyses, with no statistically significant associations and point estimates randomly scattered around one.

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Discussion

Main findings

In this prospective cohort study of 141 patients with chronic low back pain undergoing up to three level spine surgery, none of the investigated 14 QST at baseline showed a statistically significant association with FBSS at 12 months. The negative conclusion of our study remained robust to three sets of sensitivity analyses and five sets of secondary analyses with only one statistically significant association across clinical outcome definitions, time points and analytical strategies. Therefore, the potential association of cold pain detection threshold at the leg analyzed as continuous outcome with persistence of pain after 12 months (sensitivity analysis) is likely a chance finding in view of a total of 126 statistical tests performed.

Context

We are aware of a single study linking QST with pain and disability after spinal surgery in 38 patients with lumbar disc herniation.[40] QST parameters showed low or no correlation with pain and disability. The study was limited by its small sample, no standard definition of FBSS, and lack of including a comprehensive set of socio-demographic, psychological, clinical and surgery-related predictors. Two previous cohorts included patients with other musculoskeletal pain syndromes.[41, 42] Petersen and colleagues examined the prognostic value of 7 QST for persistent pain after total knee replacement.[41] Only pressure pain detection threshold at the leg was associated with pain at 12 months.[41] Wylde and colleagues used only pressure pain detection threshold at the forearm in over 400 patients with total knee or hip replacement, and found a statistically significant association with persistent post-surgical pain after 12 months.[42]

Strengths and limitations

To our knowledge, our study is the first to prospectively assess a comprehensive number of QST testing different pain modalities as pre-surgical predictors for FBSS in a large sample. We did not limit our outcome assessment to pain intensity, but also included disease-specific disability and a composite endpoint of pain and disability. The higher incidence of the composite outcome defined as persistence of pain or disability after surgery as compared to the single component outcomes reflects the lack of consistent association between pain and disability. Still, the definition of FBSS followed established concepts [20-22] and the incidence of FBSS of 30% for the primary outcome was concordant with previous studies.[1, 3-6] Other strengths include the long follow-up period with near complete follow-up at 6 and 12 months. A limitation was the difficulty in recruiting, partly due to the large number of ineligible patients and to 46% of eligible patients

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who refusing participation. This might have compromised the generalizability of our results. Time and resource constraints led us to close the study 14 patients (9%) short of the planned number of 155. This decreased statistical precision slightly. However, it is extremely unlikely that the negative conclusions are merely due to limited statistical precision because the results remained robust to several secondary and sensitivity analysis including exploring associations between QST the primary outcome as continuous variable. A major strength of our study was the application of an extensive, multimodal QST protocol using 14 tests to assess different dimensions of nociception and pain processing. Due to the consistent evidence for central hypersensitivity in chronic low back pain, we did not include a control group of pain-free subjects. [17-19] We also included type of surgery and number of operated segments as co-variates in all multivariable analyses, in view of the potential variation of clinical outcome associated with these factors.[33, 34] We did not see any relevant differences in effect estimates of the associations between QST and FBSS before and after adjusting for procedural characteristics. To account for missing data, we used multiple imputation.[37]

Implication for further research

Our negative findings do not necessarily imply that central hypersensitivity is not involved in FBSS. First, the present study assessed the association of QST with persistence of pain at distinct time-points after surgery, rather than with clinical course over time. Different, yet unknown phenotypes of patients may experience distinct patterns of pain or disability over time. These time-depending patterns are commonly referred to as trajectories.[43] Future research should investigate if patients belonging to different trajectories may have different prognosis after surgery. Second, current QST may be limited in detecting clinically relevant central pain processes. Future research should aim at identifying biomarkers of central hypersensitivity that are better linked to patient-relevant outcomes.

Conclusion

The study indicates that assessment of altered central pain processing using current QST is unlikely to identify patients at risk for FBBS and is therefore unlikely to inform clinical decisions.

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Conflict of interest: None.

Presentation: None.

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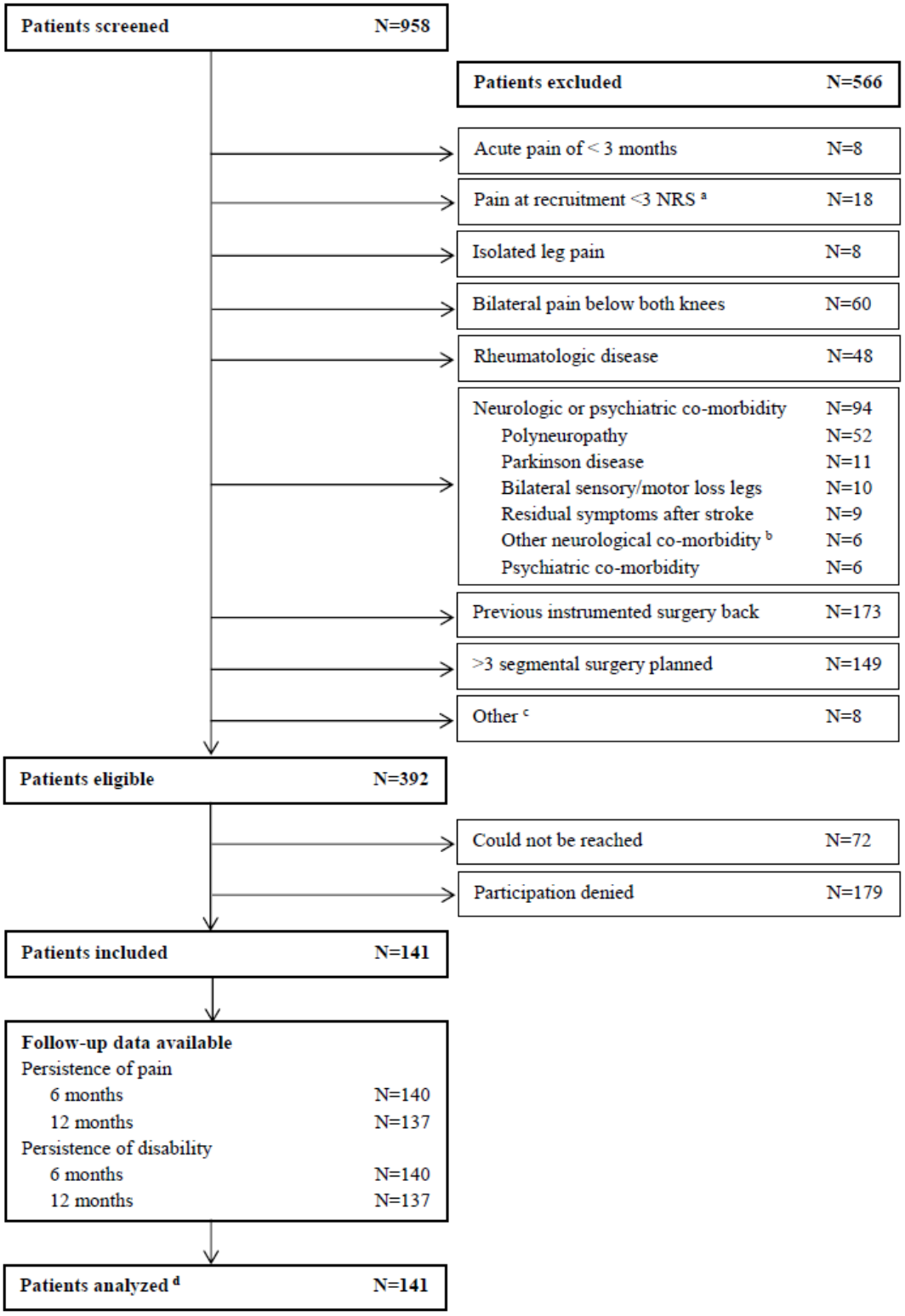
Legends of figures

Figure 1: Flow chart of study participant recruitment and follow-up.



[a] NRS: Numerical Rating Scale from 0 (no pain) to 10 (worst pain imaginable).

[b] 2 Multiple Sclerosis, 2 Dementia, 1 Post-polio-Syndrome, 1 epilepsy.

[c] Other: 2 withdrew consent, 6 had poly-morbidity.

[d] After multiple imputation.

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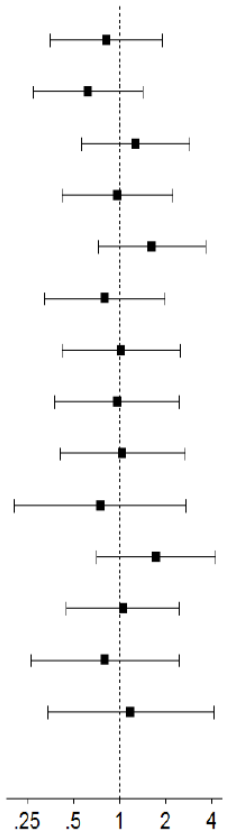
Figure 2: Fully adjusted associations between quantitative sensory tests and failed back surgery syndrome, defined as persistence of pain at 12 months. Values are odds ratios (OR) with corresponding 95% confidence intervals (CI) of multivariable regression models based on multiple imputation. N total =141.

Quantitative sensory test	Adjusted OR (95% CI)	p-value
Electrical pain detection single stimulation (mA) [a]	0.82 (0.35 to 1.91)	0.64
Electrical pain detection repeated stimulation (mA) [a]	0.62 (0.27 to 1.41)	0.26
Pressure pain detection threshold 2nd toe (kPa) [a]	1.28 (0.57 to 2.88)	0.55
Pressure pain tolerance threshold 2nd toe (kPa) [a]	0.97 (0.42 to 2.22)	0.94
Pressure pain detection threshold 2nd finger (kPa) [a]	1.63 (0.72 to 3.67)	0.24
Pressure pain tolerance threshold 2nd finger (kPa) [a]	0.80 (0.32 to 1.98)	0.62
Pressure pain detection threshold back (kPa) [a]	1.02 (0.42 to 2.48)	0.96
Pressure pain tolerance threshold back (kPa) [a]	0.96 (0.38 to 2.46)	0.94
Heat pain detection threshold leg (cut-off < 50.5 °C) [b]	1.05 (0.41 to 2.68)	0.92
Heat pain detection threshold back (cut-off < 50.5 °C) [b]	0.75 (0.21 to 2.71)	0.66
Cold pain detection threshold leg (cut-off > 0.0 °C) [b]	1.73 (0.71 to 4.20)	0.23
Cold pain detection threshold back (cut-off > 0.0 °C) [b]	1.05 (0.45 to 2.46)	0.90
Hand withdrawal time cold pressor test (cut-off < 120 sec) [b]	0.80 (0.26 to 2.45)	0.70
Conditioned pain modulation: % without increase of pressure pain detection threshold 2nd toe [b]	1.18 (0.34 to 4.09)	0.80



Adjusted for type of surgery, number of segments operated, gender, catastrophizing, Body-Mass-Index, lasègue sign, finger ground distance, disability at baseline, intake of non-opioid analgesics, intake of opioid analgesics.

OR>1.0 means less pathological values of QST are associated with increased risk for failed back surgery syndrome (i.e. low thresholds after pressure, electrical and heat stimulation, high thresholds after cold stimulation, short hand withdrawal time and impaired CPM).

[a] OR per two standard deviation decrease.

[b] Quantitative sensory tests with missing data.

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Legends of supplemental material

Supplemental Digital Text 1: Detailed description of the assessment methods of Quantitative Sensory Tests. (word file)

Supplemental Digital Text 2: Detailed description of radiologic assessment of degenerative changes of the lumbar spine. (word file)

Supplemental Digital Table 1: Baseline characteristics and Quantitative Sensory Test results, as observed in patients with and without failed back surgery syndrome according to primary outcome defined as persistence of pain at 12 months. (word file)

Supplemental Digital Table 2: Fully adjusted sensitivity analyses of associations between Quantitative Sensory Test and failed back surgery syndrome defined as persistence of pain at 12 months. (word file)

Supplemental Digital Table 3: Fully adjusted secondary analyses of associations between Quantitative Sensory Test and failed back surgery syndrome at 6 months according to different outcome definitions. (word file)

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Table 1: Impact of different definitions of Failed Back Surgery Syndrome (FBSS) according to pain or disability at 6 or 12 months after surgery.

	Patients with FBSS as observed	**Patients with FBSS complete case**	**Patients with FBSS multiple imputation**
Persistence of pain at			
6 months	50/140 (35.7%)	47/137 (34.3%)	50/141 (35.5%)
12 months [a]	*42/137 (30.7%)*	*42/137 (30.7%)*	*44/141 (31.2%)*
Persistence of disability at			
6 months	41/140 (29.3%)	39/137 (28.5%)	41/141 (29.1%)
12 months	38/137 (27.7%)	38/137 (27.7%)	39/141 (27.7%)
Persistence of pain or disability at			
6 months	60/140 (42.9%)	57/137 (41.6%)	61/141 (43.3%)
12 months	51/137 (37.2%)	51/137 (37.2%)	53/141 (37.6%)

[a] primary outcome

Persistence of pain: failure if < 30% reduction of baseline pain measured using Numerical Rating Scale (0: no pain to 10: worst pain imaginable)

Persistence of disability: failure if <30% reduction of baseline disability measured using Oswestry Disability Index (0: no disability to 100: maximum disability)

Persistence of pain or disability: failure if <30% reduction in pain or disability

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Table 2: Baseline characteristics in patients with and without failed back surgery syndrome according to primary outcome defined as persistence of pain after 12 months. Values are mean (standard deviation), numbers (percentages), odds ratios (OR) with corresponding 95% confidence intervals (CI) and p-values from logistic regression models after multiple imputation. N total = 141.

	Failed back surgery syndrome		**Unadjusted**		**Adjusted for procedural characteristics ***	
	Yes (N=44)	No (N=97)	OR (95% CI)	p-value	OR (95% CI)	p-value
Socio-demographic characteristics						
Age [a]	60.7 ± 14.2	61.3 ± 13.7	0.91 (0.44 to 1.90)	0.81	0.82 (0.36 to 1.87)	0.64
Female	21 (48%)	60 (62%)	0.57 (0.28 to 1.18)	0.13	0.58 (0.28 to 1.21)	0.15
Higher education	11 (25%)	23 (24%)	1.08 (0.46 to 2.52)	0.86	1.12 (0.48 to 2.61)	0.80
Regular work [c]	15 (34%)	40 (41%)	0.79 (0.37 to 1.67)	0.54	0.82 (0.37 to 1.81)	0.62
Married	26 (59%)	66 (68%)	0.68 (0.32, 1.43)	0.31	0.67 (0.31 to 1.41)	0.29
Psychological characteristics						
Depression (BDI-ll) [a]	11.3 ± 6.0	11.2 ± 6.9	1.02 (0.49 to 2.10)	0.97	1.02 (0.49 to 2.27)	0.96
Anxiety (STAI Trait) [a, b]	55.4 ± 6.6	53.8 ± 8.5	1.52 (0.73 to 3.16)	0.27	1.51 (0.72 to 3.17)	0.28
Catastrophizing (PCS) [a, b]	19.8 ± 11.8	16.5 ± 10.6	1.85 (0.87 to 3.90)	0.10	1.85 (0.87 to 3.93)	0.10
Clinical characteristics						
Body-Mass-Index (kg/m^2) [a]	29.3 ± 4.6	27.8 ± 4.4	1.94 (0.95 to 4.00)	0.07	2.03 (0.94 to 4.34)	0.07
Smoking [b]	13 (30%)	26 (27%)	1.21 (0.54 to 2.72)	0.64	1.21 (0.54 to 2.72)	0.64
Large finger ground distance (cut-off >10cm) [b]	31 (70%)	49 (51%)	2.39 (1.08 to 5.30)	0.03	2.40 (1.05 to 5.45)	0.04
Lasègue positive [b]	28 (64%)	40 (41%)	2.43 (1.15 to 5.13)	0.02	2.44 (1.15 to 5.16)	0.02
Previous back surgery	11 (25%)	17 (18%)	1.55 (0.65 to 3.66)	0.32	1.57 (0.65 to 3.78)	0.31
Low back pain with irradiation to leg [b]	35 (80%)	86 (89%)	0.51 (0.19 to 1.38)	0.19	0.47 (0.17 to 1.33)	0.15
Long pain duration (cut-off > 5 years) [b #]	13 (30%)	23 (24%)	1.41 (0.61 to 3.27)	0.42	1.49 (0.63 to 3.51)	0.37

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Maximum pain intensity at baseline (NRS last 7 days) [a]	7.7 ± 1.4	7.8 ± 1.4	0.87 (0.42 to 1.78)	0.70	0.88 (0.43 to 1.81)	0.73
Disability at baseline (ODI) [a]	43.1 ± 12.3	39.1 ± 13.0	1.91 (0.91 to 4.02)	0.09	1.92 (0.91 to 4.04)	0.09
Intake of non-opioid analgesics [##]	25 (57%)	38 (39%)	2.17 (1.04 to 4.53)	0.04	2.20 (1.05 to 4.61)	0.04
Intake of opioid analgesics [b]	12 (27%)	14 (14%)	2.21 (0.90 to 5.47)	0.09	2.21 (0.89 to 5.48)	0.09
Radiologic characteristics (classification system)						
Spinal stenosis (Schizas B, C or D) [b]	24 (55%)	53 (55%)	1.02 (0.49 to 2.14)	0.96	0.89 (0.36 to 2.24)	0.81
Spondylolisthesis (Meyerding I-IV) [b]	24 (55%)	66 (68%)	0.55 (0.26 to 1.15)	0.11	0.57 (0.27 to 1.20)	0.14
Endplate changes (Modic 1-3) [b]	32 (73%)	75 (77%)	0.78 (0.34 to 1.79)	0.55	0.80 (0.34 to 1.85)	0.60
Scoliosis (cobb angle > 10°) [b]	4 (9%)	17 (18%)	0.42 (0.11 to 1.59)	0.20	0.43 (0.11 to 1.62)	0.21
Severe facet joint degeneration (Weishaupt 3) [b]	18 (41%)	49 (51%)	0.69 (0.33 to 1.44)	0.32	0.63 (0.28 to 1.38)	0.25
Severe or extreme disc degeneration (Pfirrmann 4 and 5) [b]	36 (82%)	85 (88%)	0.68 (0.24 to 1.88)	0.46	0.69 (0.25 to 1.94)	0.49
≥ 50% fatty degeneration muscles (Goutaillier 3 and 4) [b]	3 (7%)	14 (14%)	0.49 (0.13 to 1.88)	0.30	0.48 (0.12 to 1.87)	0.29

* adjusted for type of surgery and number of segments operated

[#] median pain duration (IQR) in patients with and without FBSS was 36 months (IQR 18 – 96 months) and 24 months (IQR 10 – 60 months)

[##] No. patients (%) taking antiepileptic drugs among patients with and without FBSS was 5 (11%) and 9 (9%)

[a] OR per two standard deviation increase; OR>1.0 means increased risk for failed back surgery syndrome

[b] predictors with missing data

[c] includes houseworkers

BDI-ll: Beck Depression Inventory Version 2 (0: no depression to 63: maximum depression)

STAI: State Trait Anxiety Index

PCS: Pain Catastrophizing Scale (0: no catastrophizing to 52: maximum catastrophizing)

NRS: Numerical Rating Scale (0: no pain to 10: maximum pain)

ODI: Oswestry Disability Index (0: no disability to 100: maximum disability)

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Table 3: Quantitative Sensory Tests at baseline in patients with and without failed back surgery syndrome according to primary outcome defined as persistence of pain at 12 months.Values are mean (standard deviation), numbers (percentages), odds ratios (OR) with corresponding 95% confidence intervals (CI) and p-values from logistic regression models after multiple imputation. N total =141.

	Failed back surgery syndrome		**Unadjusted**		**Adjusted for procedural characteristics ***	
	Yes (N=44)	No (N=97)	OR (95% CI)	p-value	OR (95% CI)	p-value
Electrical pain (mA)						
detection single stimulation [a]	10.1 ± 6.4	9.2 ± 3.8	0.82 (0.39 to 1.73)	0.59	0.81 (0.38 to 1.72)	0.59
detection repeated stimulation [a]	7.0 ± 3.4	6.3 ± 2.4	0.66 (0.32 to 1.37)	0.26	0.65 (0.31 to 1.36)	0.26
Pressure pain (kPa)						
detection 2nd toe [a]	263 ± 114	270 ± 107	1.15 (0.56 to 2.40)	0.70	1.13 (0.53 to 2.41)	0.74
tolerance 2nd toe [a]	472 ± 157	478 ± 163	1.08 (0.52 to 2.22)	0.84	1.06 (0.50 to 2.23)	0.88
detection 2nd finger [a]	304 ± 155	331 ± 156	1.66 (0.80 to 3.45)	0.17	1.66 (0.79 to 3.47)	0.18
tolerance 2nd finger [a]	633 ± 190	630 ± 192	0.97 (0.48 to 1.98)	0.94	0.98 (0.47 to 2.02)	0.95
detection site most pain back [a]	307 ± 143	345 ± 188	1.32 (0.64 to 2.74)	0.45	1.36 (0.66 to 2.84)	0.41
tolerance site most pain back [a]	560 ± 231	602 ± 268	1.40 (0.68 to 2.89)	0.37	1.44 (0.69 to 2.99)	0.33
Heat pain (cut-off < 50.5 °C)						
detection leg [b]	33 (75%)	68 (70%)	1.24 (0.55 to 2.81)	0.61	1.29 (0.56 to 2.97)	0.57
detection site most pain back [b]	39 (89%)	86 (89%)	0.96 (0.31 to 2.99)	0.94	0.96 (0.31 to 3.01)	0.95
Cold pain (cut-off > 0.0 °C)						
detection leg [b]	20 (45%)	29 (30%)	1.88 (0.89 to 3.99)	0.10	1.93 (0.91 to 4.11)	0.09
detection site most pain back [b]	24 (55%)	45 (46%)	1.45 (0.70 to 3.00)	0.32	1.45 (0.70 to 3.01)	0.32
Cold pressor test (cut-off < 120 sec)						

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hand withdrawal time [b]	37 (84%)	82 (85%)	0.87 (0.32 to 2.35)	0.78	0.90 (0.33 to 2.48)	0.84
Conditioned pain modulation (CPM)						
% without increase of pressure pain detection threshold 2nd toe	7 (16%)	16 (16%)	0.96 (0.33 to 2.83)	0.95	0.92 (0.31 to 2.77)	0.89

* adjusted for type of surgery and number of segments operated

OR>1.0 means more pathological values of QST are associated with increased risk for failed back surgery syndrome (i.e. low thresholds after pressure, electrical and heat stimulation, high thresholds after cold stimulation, short hand withdrawal time and impaired CPM)

[a] OR per two standard deviation decrease

[b] quantitative sensory tests with missing data

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Table 4: Fully adjusted secondary analyses of associations between quantitative sensory tests and failed back surgery syndrome defined as persistence of pain and persistence of pain or disability at 12 months. Values are odds ratios (OR) with corresponding 95% confidence intervals (CI) and p-values from multivariable logistic regression models after multiple imputation. N total =141.

	Persistence of disability		**Persistence of pain or disability**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Electrical pain (mA)				
detection threshold single stimulation [a]	0.84 (0.34 to 2.09)	0.71	0.78 (0.33 to 1.83)	0.56
detection threshold repeated stimulation [a]	0.87 (0.37 to 2.07)	0.76	0.54 (0.23 to 1.25)	0.15
Pressure pain (kPa)				
detection threshold 2nd toe [a]	1.66 (0.67 to 4.11)	0.28	1.59 (0.71 to 3.60)	0.26
tolerance threshold 2nd toe [a]	1.14 (0.46 to 2.82)	0.77	1.16 (0.51 to 2.64)	0.72
detection threshold 2nd finger [a]	1.88 (0.77 to 4.58)	0.17	2.24 (0.97 to 5.14)	0.06
tolerance threshold 2nd finger [a]	1.42 (0.51 to 3.93)	0.50	1.20 (0.48 to 2.99)	0.69
detection threshold site most pain back [a]	1.33 (0.51 to 3.47)	0.57	1.32 (0.54 to 3.21)	0.54
tolerance threshold site most pain back [a]	1.17 (0.42 to 3.29)	0.76	0.98 (0.39 to 2.47)	0.96
Heat pain (cut-off < 50.5 °C)				
detection threshold leg [b]	1.07 (0.36 to 3.19)	0.90	1.11 (0.44 to 2.79)	0.83
detection threshold site most pain back [b]	0.41 (0.10 to 1.70)	0.22	1.02 (0.28 to 3.76)	0.98
Cold pain (cut-off > 0.0 °C)				
detection threshold leg [b]	2.47 (0.91 to 6.66)	0.08	2.38 (0.97 to 5.83)	0.06
detection threshold site most pain back [b]	0.93 (0.35 to 2.45)	0.88	1.17 (0.51 to 2.71)	0.71
Cold pressor test (cut-off < 120 sec)				
hand withdrawal time [b]	0.68 (0.19 to 2.35)	0.54	1.16 (0.37 to 3.57)	0.80

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Conditioned pain modulation (CPM)				
no increase of pressure pain detection threshold 2nd toe [b]	1.40 (0.35 to 5.62)	0.64	1.09 (0.33 to 3.65)	0.89

adjusted for type of surgery, number of segments operated, gender, catastrophizing, Body-Mass-Index, lasègue sign, finger ground distance, disability at baseline, intake of non-opioid analgesics, intake of opioid analgesics

OR>1.0 means more pathological values of QST are associated with increased risk for failed back surgery syndrome (i.e. low thresholds after pressure, electrical and heat stimulation, high thresholds after cold stimulation, short hand withdrawal time and impaired CPM)

[a] OR per two standard deviation decrease

[b] quantitative sensory tests with missing data