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Van Bogaert, Wouter; Coppieters, Iris; Nijs, Jo; Buyl, Ronald; Ickmans, Kelly; Moens, Maarten; Goudman, Lisa; Putman, Koen; Huysmans, Eva

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Influence of preoperative pain, cognitions, and quantitative sensory testing measures on the effects of perioperative pain neuroscience education for people receiving surgery for lumbar radiculopathy: secondary analysis of a randomized controlled trial

Van Bogaert Wouter PT, MSc[1-3]; Coppieters Iris PT, PhD[1,4,5]; Nijs Jo PT, MT, PhD[1,4,6]; Buyl Ronald PhD[2,7]; Ickmans Kelly PT, PhD[1,4,8]; Moens Maarten MD, PhD[1,9-12]; Goudman Lisa PT, PhD[1,3,9-11]; Putman Koen PhD[2 †] & Huysmans Eva PT, PhD[1,2,4 †]* ([†]shared last author)

[1] Pain in Motion Research Group (PAIN), Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Brussels, Belgium;
[2] Department of Public Health (GEWE), Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium;
[3] Research Foundation – Flanders (FWO), Brussels, Belgium;
[4] Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Brussels, Belgium;
[5] The Laboratory for Brain-Gut Axis Studies (LaBGAS), Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium;
[6] Department of Health and Rehabilitation, Unit of Physiotherapy, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden;
[7] Department of Biostatistics and Medical Informatics, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium;
[8] Movement & Nutrition for Health & Performance research group (MOVE), Department of Movement and Sport Sciences, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Brussels, Belgium;
[9] Department of Neurosurgery, Universitair Ziekenhuis Brussel, Brussels, Belgium;
[10] STIMULUS research group (reSearch and TeachIng neuroModULation Uz bruSsel/VUB), Vrije Universiteit Brussel, Brussels, Belgium;
[11] Center for Neurosciences, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium;
[12] Department of Radiology, Universitair Ziekenhuis Brussel, Brussels, Belgium.
* Corresponding author

Address of correspondence: Eva Huysmans, Vrije Universiteit Brussel, Campus Jette, EhB-Building KINE, Laarbeeklaan 121, BE-1090 Brussels, Belgium

E-mail: Eva.huysmans@vub.be

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ABSTRACT

Objective: To explore whether preoperative pain intensity, pain cognitions, and quantitative sensory measures influence the established effectiveness of perioperative pain neuroscience education (PPNE) on health-related quality of life at 1 year after surgery for lumbar radiculopathy.

Design: Secondary analysis of a triple-blinded randomized controlled trial.

Methods: Participants (n=90) were Dutch-speaking adults (18-65 years) who were scheduled for surgery for lumbar radiculopathy in 3 Belgian hospitals. They were randomized (1:1) to receive PPNE (n=41) or perioperative biomedical education (PBE; n=49). Linear mixed models were built for health-related quality of life (i.e., SF-6D utility values, Physical, and Mental Component of the Short-Form 36-item Survey) using the following independent variables: therapy, time, and preoperative scores for back, and leg pain intensity, pain catastrophizing, kinesiophobia, hypervigilance, and quantitative sensory measures.

Results: The impact of PPNE on SF-6D utility values over time was influenced by kinesiophobia (F=3.30; p=.02) and leg pain intensity (F=3.48; p=.02). Regardless of the intervention, back pain intensity negatively influenced SF-6D values over time (F=3.99; p=.009). The Physical Component scores were negatively impacted by back pain intensity (F=9.08; p=.003) and were influenced over time by leg pain intensity (F=2.87; p=.04). The Mental Component scores were negatively impacted by back pain intensity (F=6.64; p=.01), pain catastrophizing (F=5.42; p=.02), as well as hypervigilance (F=3.16; p=.03) and leg pain intensity (F=3.12; p=.03) over time.

Conclusion: PPNE may be more effective than PBE in improving postoperative health utility values in patients who reported higher kinesiophobia and leg pain intensity before surgery for lumbar radiculopathy.

Keywords: Lumbar surgery, kinesiophobia, pain catastrophizing, pain intensity, pain neuroscience education, quality of life

INTRODUCTION

In the past ten years, the benefits of perioperative pain neuroscience education (PPNE) for lumbar radiculopathy have been established.[18,24,36] Patients who received one preoperative session of PPNE reported more favorable surgical experience, short-term disability, and kinesiophobia and used fewer medical services in the year following surgery.[24,36] Adding a postoperative education session to a PPNE protocol for people undergoing surgery for lumbar radiculopathy was cost-effective when considering healthcare and productivity loss costs, and improve health-related quality of life (HRQoL) and pain cognitions following surgery.[18] However, the effect sizes were limited for PPNE on postoperative HRQoL.[18] Therefore, introducing this educational therapy to a select group of patients at risk for unfavorable outcomes following lumbar surgery may have merit.[18]

Patients with modifiable risk factors, such as high levels of maladaptive cognitions (e.g., pain catastrophizing, kinesiophobia) or indications of symptoms of central sensitization, might benefit more from PPNE.[4,8,12,16,18,21] Although potential moderators for the treatment success of pain neuroscience education (PNE) have been investigated in other populations, the factors that influence the effectiveness of PPNE in people with lumbar radiculopathy are currently unknown.[5,17,26,27,39]

Therefore, we aimed to explore the potential influence of preoperative pain intensity, pain cognitions, and quantitative sensory testing (QST) measures on the PPNE treatment effect on postoperative HRQoL 1 year following surgery for lumbar radiculopathy. We hypothesized that patients who reported high scores of the preoperative factors would have a greater improvement in their postoperative HRQoL following PPNE than those who reported low preoperative scores.

METHODS

This study was a retrospective secondary analysis of a multicenter randomized controlled trial comparing the treatment effect of PPNE versus perioperative biomedical education (PBE) in people

undergoing surgery for lumbar radiculopathy.[18,19] Data for the trial were collected between June 2016 and March 2020 at the University Hospital Brussels, and the general hospitals of AZ Sint-Dimpna (Geel), and AZ Sint-Maarten (Mechelen), Belgium. Ethical approval was granted by the Commissions for Medical Ethics of all participating hospitals. The trial protocol was prospectively registered at ClinicalTrials.gov (NCT02630732) and has been published elsewhere.[19] No changes to the protocol were made following the start of the trial.

Participants

The original trial included 120 participants who fulfilled the following inclusion criteria: 18-65 years old; able to read and speak Dutch; continuing usual care 3 weeks pre-surgery; and scheduled to undergo surgery for lumbar radiculopathy. Participants were excluded if they were pregnant or gave birth during the year preceding surgery; scheduled for surgery for another condition; or diagnosed with a rheumatoid, endocrinological, neurological, psychiatric, or other chronic disorder or illness characterized by uncontrolled pain. Following inclusion, all participants gave written informed consent and were randomized to one of two treatment groups using a parallel allocation ration of 1:1. Participants, assessors and statisticians were blinded for intervention allocation. Though participants were aware of the type of education they received, they did not know whether it was the experimental (PPNE) or control (PBE) intervention. Further details regarding the sample size calculation, blinding, and randomization can be found in the protocol published elsewhere.[19]

Participants who were uncomfortable with the electric QST protocol did not participate in the complete data collection procedure, leaving some missing data. Consequently, missing QST data were considered to be Missing Not At Random. Therefore, people with missing QST data were excluded from the analysis, resulting in 90 included participants (control group n=49; experimental group n=41).

Outcome measures

<u>Dependent variables</u>

HRQoL was assessed using the 36-item Short-Form Health Survey (SF-36) before surgery (baseline) and at 6 weeks, 26 weeks, and 52 weeks following surgery. Both the Physical (PC) and Mental Component (MC) scores were calculated.[42] Validity and reliability for the Dutch SF-36 were satisfactory.[2] Health utility values (SF-6D) were calculated, though transforming multidimensional SF-36 scores to a single index SF-6D score results in a small loss in discriminative and evaluative properties.[7,29]

Moderating variables

Mean pain intensity was assessed for both leg and back pain via a Visual Analogue Scale (VAS).[44] Evaluated pain cognitions included kinesiophobia (i.e., fear of movement), pain catastrophizing (i.e., catastrophic thoughts and feelings regarding pain), and hypervigilance (i.e., attention to, and awareness, vigilance, and observation of pain) which were assessed using questionnaires validated for the Dutch-speaking population.[32-34,37,38,40,43] The Tampa Scale for Kinesiophobia (TSK), Pain Catastrophizing Scale (PCS), and the Pain Vigilance and Awareness Questionnaire (PVAQ) were used to measure kinesiophobia, pain catastrophizing, and hypervigilance, respectively.[32-34,37,38,40,43] QST measures were evaluated at both ankles (N. suralis) and the wrist ipsilateral to the symptomatic leg (N. medianus). An electrical pain threshold was determined, and a Temporal Summation protocol (i.e., a correlate for nociceptive facilitation) and Conditioned Pain Modulation paradigm (i.e., a correlate for the level of endogenous nociceptive inhibition) were performed.[10,15,41,45,46] For the latter two, absolute and relative (percent change) differences were calculated, with more positive values indicating stronger facilitation and more negative values indicating stronger stimulus inhibition.[45,46] Details regarding the QST measures can be found in the published protocol.[19] All secondary outcome measures, together with demographic variables (i.e., age, sex, educational level, equivalent income category), were assessed at baseline in the week before surgery.

Intervention

The experimental group received PPNE, which aimed to address potential maladaptive pain cognitions by informing participants about what to expect from their surgical experience and recovery and

98 educating them on the neurophysiology of pain and potential sustaining factors of central
99 sensitization.[22,23] The control intervention (PBE) focused on educating participants on the anatomy and
100 biomechanics of the lumbar spine and providing ergonomic advice on participants' activities of daily
101 living.[13,31] Both intervention arms included 1 preoperative educational session, an educational booklet,
102 and 1 postoperative educational session. Each session was provided by a physiotherapist, lasted
103 approximately 1 hour, and was tailored to the participants' situation. More information regarding the
104 interventions can be found in **Table S1** and has been published elsewhere.[14,19]

105 ***Statistical analysis***

106 First, data from the QST measures were standardized, and a principal component analysis with
107 VARIMAX-rotation was used to reduce the number of measures.[11,20,30] The principal component
108 analysis included the QST results of all 3 tests for the 3 test sites. Absolute difference scores were used
109 for the Temporal Summation protocol, while relative difference scores were included for the
110 Conditioned Pain Modulation paradigm. Relevant QST components were selected via a scree plot.[20]

111 Following analysis, the 9 included QST measures were reduced to 3 components. Next, linear mixed
112 models were built for the SF-6D, the SF-36 PC, and the SF-36 MC using the following independent
113 variables: therapy (PPNE or PBE), time (in weeks), and baseline scores for VAS_{Leg}, VAS_{Back}, TSK, PCS,
114 PVAQ, and QST components. Additionally, age, sex, educational level, and equivalent income category
115 were included as control variables. Each base model consisted of the control variables, and the three-
116 way interaction effects of VAS_{Leg}, VAS_{Back}, TSK, PCS, PVAQ, and QST components with time and therapy.
117 Random intercepts and slopes were evaluated for each model and only included when they improved
118 the model's fit. A backward elimination procedure was used to omit the least significant interaction or
119 main effect from the model at each step. Only the two-way therapy*time interaction effect was forced
120 in each model. All analyses were performed in R Studio Version 1.4.1717 (R version 4.1.1, Boston, MA,
121 USA).

122

RESULTS

After excluding participants with missing QST data, this secondary analysis included data from 90 participants (**FIGURE S1**). Demographic and baseline characteristics are shown in **TABLE 1**. For the 30 excluded participants, demographic and baseline characteristics are shown in **TABLE S2**.

Following the principal component analysis, the 9 included QST measures were reduced to 3 components. The cumulative explained variance was 75.1%, with the first to third components capturing 27.0%, 26.7%, and 21.4%, respectively. All variables and their loadings are presented in **TABLE S3**.

Linear mixed models

The final model for the SF-6D included a random intercept with an estimate of variance in intercept across participants (Var_{Int}) of 0.003 (standard deviation (SD_{Int})=0.05) and residual variance (Var_{Res}) of 0.004 (SD_{Res}=0.06). Details regarding the full model are presented in **TABLE 2.a**. There were significant three-way interaction effects for preoperative TSK scores (therapy*time*TSK; $F_{3,\ 226.28}$=3.30; p=0.02) and leg pain intensity (therapy*time*VAS_{Leg}; $F_{3,\ 224.88}$=3.48; p=0.02). The effect sizes were -0.004, -0.011, and -0.002 for the three-way interaction effect between therapy, time, and TSK for the 6-week, 6-month, and 1-year follow-up, respectively. Per point reported on the TSK at baseline, people who received PPNE scored 0.004, 0.011, and 0.002 points less on the SF-6D on the respective follow-up times compared to those who received PBE.

The results of the full model indicated that in people with high baseline TSK scores, PPNE was more effective than PBE in improving SF-6D values over time. Also, in people who reported higher preoperative VAS_{Leg} scores, PPNE led to a greater improvement in SF-6D values than PBE. Specifically, patients who received PPNE increased their SF-6D values with 0.0006, 0.0021, and 0.0021 per point they reported extra on the VAS_{Leg} for the 6-week, 6-month, and 1-year follow-up, respectively, compared to those who received PBE. There was a significant two-way interaction effect of time*VAS_{Back} ($F_{3,\ 229.22}$=3.99; p=0.009) suggesting that back pain intensity negatively influenced SF-6D

values over time regardless of the received education. The three-way and two-way interaction effects are presented in **FIGURES 1, 2** and **S2**, respectively.

In the final random-intercept model for the SF-36 PC (Var_{Int}=2784; SD_{Int}=52.77; Var_{Res}=2566; SD_{Res}=50.66), there was significant two-way interaction effect for time*VAS_{Leg} ($F_{1, 226.37}$=2.87; p=0.04). Following both interventions, people who reported higher baseline VAS_{Leg} scores had a greater increase in SF-36 PC scores over time than those who reported lower baseline VAS_{Leg} scores. Also, a main effect of VAS_{Back} ($F_{1, 96.86}$=9.08; p=0.003) was found, indicating that back pain intensity negatively influenced the SF-36 PC scores regardless of time and therapy (**TABLE 2.b** and **FIGURE S3**).

For the SF-36 MC, the final model included a random intercept (Var_{Int}=2088; SD_{Int}=45.70; Var_{Res}=2948; SD_{Res}=54.30) and significant two-way interaction effects for time*PVAQ ($F_{3, 226.36}$=3.16; p=0.03) and time*VAS_{Leg} ($F_{3, 227.39}$=3.12; p =0.03). The overall improvement in SF-36 MC scores for both intervention groups was greater in those who reported higher preoperative VAS_{Leg} and PVAQ scores than those who reported lower scores. There were significant main effects of preoperative PCS ($F_{1, 91.11}$=5.42; p=0.02) and VAS_{Back} scores ($F_{1,96.45}$=6.64; p=0.01) with both factors negatively influencing the SF-36 MC scores, regardless of time and therapy. **TABLE 2.c** and **FIGURE S4** present the SF-36 MC model.

DISCUSSION

We explored the potential influence of preoperative pain intensity, pain cognitions, and QST measures on the treatment effect of PPNE on postoperative HRQoL 1 year following surgery in people with lumbar radiculopathy. Specifically, we hypothesized that patients who reported high scores of the preoperative factors would show a greater improvement in their postoperative HRQoL following PPNE than those who reported low preoperative scores.

Our results support the hypothesis of a moderating influence of preoperative kinesiophobia levels on the treatment effect of PPNE on postoperative SF-6D scores. Given that the minimal important

difference (MID) for SF-6D scores was 0.027, we suggest that a difference of 3 points on the TSK at baseline leads to a clinically meaningful difference at 6 months following PPNE.[25] Though patients who reported the highest TSK score of our sample (i.e., 55) still reported lower SF-6D values compared to those who reported the lowest TSK scores (i.e., 28), PPNE seemed to minimize this difference as the former group nearly reached identical 1-year follow-up values as the latter following PPNE (see **FIGURE 2**). Earlier studies that identified kinesiophobia as a moderator for PNE therapies in non-surgical populations suffering from chronic pain support out results.[27,39] For example, a study in people with chronic spinal pain reported a similar finding for PNE combined with cognition-targeted exercises.[39] However, kinesiophobia only moderated the treatment effect on the SF-36 MC score.[39] Nevertheless, PPNE, compared to PBE, seems better equipped to limit the unfavorable influence of preoperative kinesiophobia on postoperative health utility scores in people undergoing surgery for lumbar radiculopathy.

There were also significant effects for preoperative pain catastrophizing and hypervigilance on postoperative mental health, irrespective of the treatment received. People who reported higher preoperative pain catastrophizing levels also reported lower SF-36 MC scores following surgery. Due to the significant time-interaction effect, the influence of preoperative hypervigilance is more complex. In patients with higher preoperative hypervigilance, the SF-36 MC scores improved more compared to those with lower preoperative hypervigilance levels (see **FIGURE S4.b**). Though the former start with lower mental health scores, they end with similar scores as the latter group at 1-year follow-up. The lack of a moderating influence of these cognitive factors on the therapy effect agrees with the conclusion of a similar study in people undergoing total knee arthroplasty.[6] However, literature on this topic is still limited, underscoring the importance of the present work and future studies that address moderating effects on PPNE.

Remarkably, though SF-6D utility scores are often regarded as a single utility measure that accounts for both physical, mental, and social health, hypervigilance and catastrophizing did not show a

significant influence on these scores, while they did influence postoperative mental health scores. It is possible that the moderating effect of kinesiophobia was stronger and thus overpowered the individual effects of catastrophizing and hypervigilance on the SF-6D scores. On the other hand, as kinesiophobia was present in the final SF-6D model, we might expect it to influence either SF-36 Component scores. However, no effect of kinesiophobia was found for the models of the Component scores. Kinesiophobia might moderate the influence of PPNE on an underlying concept related to different subscales but which is not present to that extent in the Component scores. Further research is needed to explore the potential interaction between all three cognitions while influencing the treatment effect of PPNE in people receiving surgery for lumbar radiculopathy.

We found significant effects for pain intensity. For preoperative back pain intensity, only time-interaction and main effects were found for all three models. Patients with higher levels of back pain intensity report lower scores for their postoperative HRQoL than those who reported lower preoperative values of back pain intensity, regardless of the received intervention. Our work agrees with earlier studies discussing unfavorable surgical outcomes in patients with increased preoperative back pain intensity.[1,3,28]

There was a moderating effect for leg pain intensity in the final model for SF-6D. In patients who received PPNE compared to those who got PBE, the more leg pain intensity they reported before surgery, the better their SF-6D values were following surgery. The SF-6D scores improved so well in patients who reported the maximum VAS_{Leg} score (i.e., 100) that their 1-year scores were comparable to those of the participants who reported no preoperative leg pain. This indicates that PPNE is more effective than PBE for improving postoperative SF-6D scores in people who reported high preoperative leg pain intensity. In particular, the effect sizes for this three-way interaction effect (0.0006, 0.0021, and 0.0021) show that a difference of 13 points on the VAS_{Leg} at baseline can result in a clinical difference in SF-6D scores (MID=0.027) at 6 months and 1 year following PPNE.[25] Also, significant two-way time*leg pain intensity interaction effects were found for both SF-36 Component models. Thus,

preoperative leg pain intensity influences patients' postoperative physical and mental health, regardless of the received education.

No significant interaction or main effects were found for the QST measures. This result contradicts the findings of an earlier study evaluating a similar intervention in people scheduled for total knee arthroplasty, which reported QST measures as moderators for the treatment effect of PNE.[17] However, the assessment method of QST measures was also different. Whereas we focused on electrical stimuli, mechanical stimulation via pressure algometers was used to determine the QST measures in the earlier study.[9] Indeed, as different modalities for QST (e.g., electrical or mechanical stimuli) engage different nervous system pathways, this difference in assessment method might explain the discrepancy in results between both studies. Endogenous modulation (i.e., pain thresholds, facilitations, and inhibition) of electrical stimuli did not significantly impact the effectiveness of PPNE, while the earlier study concluded a significant moderating effect of the various measures related to the endogenous modulation of mechanical stimuli. We presume that QST measures, as assessed by electrical QST, do not moderate nor influence the treatment effect of PPNE on patients' HRQoL following surgery for lumbar radiculopathy.

Our findings are clinically relevant and provide novel insights into the moderating effect of preoperative kinesiophobia and leg pain intensity on the treatment outcome of PPNE in this population. Indeed, PPNE specifically targets patients' fears and beliefs; thus, more fearful patients might relate more to the given information than those with less kinesiophobia. This finding, combined with the knowledge that PPNE also decreases patients' kinesiophobia, provides further motivation to investigate whether changes in kinesiophobia levels mediate surgical outcome following PPNE.[18] Furthermore, both education programs focused mostly on lumbar radiculopathy, in other words, leg pain radiating down from the lower back. Consequently, patients who experienced more leg pain might identify more with the education focusing on pain (i.e., PPNE) rather than the one detailing the anatomical structure (i.e., PBE), compared to those patients who were less troubled by it.

Lumbar surgery provides an immediate reduction in leg pain intensity.[35] Thus, patients who experience this following surgery may be more susceptible to the information provided in the postoperative education session. A potential next step in research is to evaluate the effectiveness of PPNE in a prospectively group of at-risk patients undergoing surgery for lumbar radiculopathy in which kinesiophobia and leg pain intensity are considered risk factors.

We provide further evidence for the importance of preoperative pain intensity and pain cognitions for postoperative health-related quality of life in people undergoing lumbar surgery. However, our results regarding the moderating effects of leg pain intensity and kinesiophobia on PPNE cannot easily be extrapolated to other surgical populations, as the PPNE offered to the participants was specifically tailored to lumbar radiculopathy. Despite this, our findings motivate similar analyses exploring the moderating role of pretreatment pain intensity and pain cognitions for other PPNE-based therapies in similar surgical populations.

Strengths and Limitations

Study strengths include the multicenter, randomized nature of the study design, the a priori clinical trial registration and trial protocol publication, the balanced treatment arms, blinded outcome assessment, and 1-year follow-up. Our work also has some limitations. First, this is a secondary analysis of an earlier RCT, meaning the data were not intended to evaluate a potential moderating effect. Thirty participants were excluded due to missing QST data, which might have further limited the statistical power. As 1 in every 4 participants in the original trial were excluded from this analysis due to the missing QST data, the analysis should be considered per-protocol, limiting the external validity of our conclusions. Given the exploratory nature of the current analysis, there is a higher potential for bias. These limitations underscore the need for future studies to continue exploring such moderators, as these findings should still be confirmed in a study powered and designed to examine moderating effects. Next, as a principal component analysis reduced the number of included QST measures, some information might have been lost due to this analysis. However, as no relevant principal components

were included in the final models, this information loss would likely have been redundant to forming our conclusions.

CONCLUSION

Perioperative pain neuroscience education may be more effective than perioperative biomedical education in improving postoperative HRQoL in patients who reported higher preoperative scores of kinesiophobia and leg pain intensity than in those who reported lower scores. Regardless of the education program, both back and leg pain intensity significantly influenced patients' postoperative physical health, while pain catastrophizing, hypervigilance, back and leg pain intensity influenced postoperative mental health scores.

KEY POINTS

Findings

- Preoperative pain intensity and cognitions were important factors that influenced patients' health-related quality of life following surgery for lumbar radiculopathy.
- Preoperative kinesiophobia and leg pain intensity were moderators for the treatment effect of perioperative pain neuroscience education on health utility values in people with lumbar radiculopathy.

Implications

- Perioperative pain neuroscience education will be more effective for improving postoperative physical health-related quality of life in patients with high scores for kinesiophobia and leg pain intensity before undergoing surgery for lumbar radiculopathy.

Caution

- Given our limited sample size, further research is needed to confirm these exploratory findings in a study that is sufficiently powered and prospectively designed to examine moderating effects.

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TABLE 1. Characteristics of participants with lumbar radiculopathy (n=90)

	Mean (SD)	Median (IQR) [Min; Max]
Age (yrs)	46.71 (11.89)	48.00 (20.00) [20; 65]
SF-36 PC (/400)	142.17 (63.38)	123.00 (54.50) [62; 339]
SF-36 MC (/400)	222.16 (83.03)	232.50 (135.79) [11; 383]
SF-6D (/1)	.54 (.09)	.54 (.09) [.38; .78]
TSK (/68)	42.56 (5.91)	42.00 (9.00) [28; 55]
PCS (/52)	25.17 (9.52)	25.00 (12.00) [5; 46]
PVAQ (/80)	39.59 (10.91)	39.00 (15.50) [19; 68]
VAS_{Back} (/100)	43.01 (26.90)	44.50 (48.50) [0; 99]
VAS_{Leg} (/100)	53.22 (27.04)	53.00 (43.75) [0; 100]
EPT (mA)		
Median nerve	5.22 (3.32)	4.25 (3.79) [1.17; 17.50]
Symptomatic Sural nerve	7.92 (3.99)	7.00 (4.46) [2.00; 23.00]
Asymptomatic Sural nerve	7.79 (3.55)	6.92 (4.79) [2.17; 19.33]
TS absolute (/10)		
Median nerve	1.52 (2.16)	1.00 (3.00) [-5; 6]
Symptomatic Sural nerve	2.16 (2.36)	2.00 (4.00) [-4; 9]
Asymptomatic Sural nerve	2.08 (2.20)	2.00 (4.00) [-6; 8]
CPM relative (%)		
Median nerve	-12.67 (28.11)	-15.48 (33.33) [-66.67; 100.00]
Symptomatic Sural nerve	-5.80 (66.12)	-14.29 (33.33) [-100.00; 500.00]
Asymptomatic Sural nerve	-20.31 (37.74)	-20.00 (40.00) [-100.00; 133.33]
	N (%)	
Therapy		
PPNE	41 (45.56)	
PBE	49 (54.44)	
Symptom duration		
< 3 months	25 (27.78)	
≥ 3 months	65 (72.22)	
Symptomatic side		
Right	43 (47.78)	
Left	47 (52.22)	
Sex		
Male	48 (53.33)	
Female	42 (46.67)	
Education level		
Primary/low secondary school	26 (28.89)	
High secondary school	35 (38.89)	
High education	29 (32.22)	
Equivalent income category		
No data	5 (5.56)	
Low equivalent income	25 (27.78)	
Moderate equivalent income	39 (43.33)	
High equivalent income	21 (23.33)	

N= Number of participants; SD= Standard deviation; IQR= Interquartile range; yrs= years; SF-36= Short Form 36-item Health Survey; PC= Physical Component; MC = Mental Component; SF-6D= Short Form Health Utility Score; TSK= Tampa Scale for Kinesiophobia; PCS= Pain Catastrophizing Scale; PVAQ= Pain Vigilance and Awareness Questionnaire; VAS= Visual Analogue Scale; EPT= Electrical Pain Threshold; mA= milliamps; TS= Temporal Summation, the effect is calculated as the absolute difference between the Numeric Rating Scale scores of the 20th and 1st stimulus of the TS-protocol; CPM= Conditioned Pain Modulation, the effect is calculated as the relative difference between the Numeric Rating Scale scores of the first and second part of the CPM-paradigm; PPNE= Perioperative Pain Neuroscience Education; PBE= Perioperative Biomedical Education.

TABLE 2.a Results of the linear mixed model analysis showing the estimates of the fixed effects and their confidence intervals for the final model for the Short Form-6 Dimensions Health Utility Values in people undergoing surgery for lumbar radiculopathy (n=90).

Independent variables	Estimate	SE	95% CI	p-value	Type III test
(Intercept)	0.83	0.09	0.66 to 1.00	≤.001***	
Therapy	-0.30	0.13	-0.55 to -0.04	.026*	F=1.97; p=.16
Time [6]	0.05	0.10	-0.14 to 0.25	.579	F=3.81; p=.01**
Time [26]	-0.01	0.10	-0.21 to 0.19	.918	
Time [52]	0.22	0.10	0.03 to 0.42	.026*	
TSK	-0.006	0.002	-0.010 to -0.002	.005**	F=6.38; p=.01**
VAS_{Back}	-0.0005	0.0003	-0.0012 to 0.0001	.115	F=16.46; p≤.001***
VAS_{Leg}	-0.0002	0.0004	-0.0011 to 0.0007	.635	F=0.82; p=.37
Therapy * Time [6]	0.15	0.15	-0.15 to 0.45	.331	F=2.36; p=.07
Therapy * Time [26]	0.39	0.16	0.08 to 0.69	.013*	
Therapy * Time [52]	0.05	0.16	-0.25 to 0.36	.735	
Therapy * TSK	0.008	0.003	0.002 to 0.014	.013*	F=2.03; p=.16
Time [6] * TSK	-0.000	0.002	-0.005 to 0.004	.966	F=0.62; p=.60
Time [26] * TSK	0.003	0.002	-0.001 to 0.008	.132	
Time [52] * TSK	-0.001	0.002	-0.005 to 0.004	.734	
Time [6] * VAS_{Back}	-0.0011	0.0004	-0.0018 to -0.0003	.009**	F=3.99; p=.009**
Time [26] * VAS_{Back}	-0.0001	0.0004	-0.0010 to 0.0007	.718	
Time [52] * VAS_{Back}	-0.0011	0.0004	-0.0020 to -0.0003	.008**	
Therapy * VAS_{Leg}	-0.0011	0.0007	-0.0025 to 0.0002	.094	F=0.01; p=.93
Time [6] * VAS_{Leg}	0.0006	0.0005	-0.0004 to 0.0016	.238	F=2.41 p=.07
Time [26] * VAS_{Leg}	-0.0002	0.0005	-0.0012 to 0.0009	.747	
Time [52] * VAS_{Leg}	-0.0007	0.0005	-0.0017 to 0.0004	.205	
(Therapy * Time [6])* TSK	-0.004	0.004	-0.011 to 0.004	.318	F=3.30; p=.02*
(Therapy * Time [26])* TSK	-0.011	0.004	-0.019 to -0.004	.003**	
(Therapy * Time [52]) * TSK	-0.002	0.004	-0.010 to 0.005	.513	
(Therapy * Time [6])* VAS_{Leg}	0.0006	0.0008	-0.0009 to 0.0022	.422	F=3.48; p=.02*
(Therapy * Time [26])* VAS_{Leg}	0.0021	0.0008	0.0005 to 0.0037	.010**	
(Therapy * Time [52]) * VAS_{Leg}	0.0021	0.0008	0.0005 to 0.0037	.009**	

95% CI= 95% Confidence Interval; n= Number of participants; SE= Standard error; Therapy= Perioperative Biomedical Education (reference category), Perioperative Pain Neuroscience education; Time= Baseline (reference category), 6 weeks follow-up [6], 26 weeks follow-up [26], 52 weeks follow-up[52]; TSK= Tampa Scale for Kinesiophobia; VAS= Visual Analogue Scale. Significant fixed effects for independent variables are shown with an asterisk. (*:p≤.05; **:p≤.01;***:p≤.001).

TABLE 2.b Results of the linear mixed model analysis showing the estimates of the fixed effects and their confidence intervals for the final model for the Physical Component Score of the Short Form 36 item Health Survey in people undergoing surgery for lumbar radiculopathy (n=90).

Independent variables	Estimate	SE	95% CI	p-value	Type III test
(Intercept)	215.57	20.14	175.94 to 255.20	≤.001***	
Therapy	-19.41	15.49	-49.89 to 11.08	.211	F=0.29; p=.59
Time [6]	3.04	18.88	-34.12 to 40.19	.872	F=13.34; p≤.001***
Time [26]	53.88	18.97	16.54 to 91.22	.005**	
Time [52]	71.69	19.02	34.26 to 109.12	<.001***	
VAS_{Back}	-0.74	0.25	-1.23 to -0.26	.003**	F=9.08; p=.003**
VAS_{Leg}	-0.61	0.29	-1.18 to -0.04	.035*	F=0.32; p=.57
Time [6] * Therapy	22.61	16.09	-9.06 to 54.28	.161	F=3.72; p=.01**
Time [26] * Therapy	26.53	16.66	-6.27 to 59.32	.112	
Time [52] * Therapy	56.16	16.83	23.03 to 89.29	.001***	
Time [6] * VAS_{Leg}	0.73	0.30	0.14 to 1.33	.016*	F=2.87; p=.04*
Time [26] * VAS_{Leg}	0.78	0.31	0.18 to 1.38	.011*	
Time [52] * VAS_{Leg}	0.39	0.31	-0.22 to 1.00	.208	

95% CI= 95% Confidence Interval; n= Number of participants; SE= Standard error; Therapy= Perioperative Biomedical Education (reference category), Perioperative Pain Neuroscience education ; Time= Baseline (reference category), 6 weeks follow-up [6], 26 weeks follow-up [26], 52 weeks follow-up[52]; VAS= Visual Analogue Scale. Significant fixed effects for independent variables are shown with an asterisk. (*:p≤.05; **:p≤.01;***:p≤.001).

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TABLE 2.c Results of the linear mixed model analysis showing the estimates of the fixed effects and their confidence intervals for the final model for the Mental Component Score of the Short Form 36 item Health Survey in people undergoing surgery for lumbar radiculopathy (n=90).

Independent variables	Estimate	SE	95% CI	p-value	Type III test
(Intercept)	406.86	30.88	346.08 to 467.64	≤.001***	
Therapy	-2.75	15.08	-32.43 to 26.92	.855	F=2.71; p=.10
Time [6]	-82.55	33.95	-149.37 to -15.72	.016*	F=1.48; p=.22
Time [26]	-48.12	34.66	-116.33 to 20.09	.166	
Time [52]	-44.62	34.89	-113.30 to 24.06	.202	
PCS	-1.82	0.78	-3.35 to -0.28	.021*	F=5.42; p=.02*
PVAQ	-2.23	0.78	-3.77 to -0.69	.005**	F=2.26; p=.13
VAS_{Back}	-0.61	0.24	-1.08 to -0.14	.010**	F=6.64; p=.01**
VAS_{Leg}	-0.44	0.30	-1.02 to 0.15	.142	F=0.01; p=.94
Time [6] * Therapy	32.74	17.19	-1.09 to 66.56	.058	F=2.88; p=0.04*
Time [26] * Therapy	9.36	17.79	-25.66 to 44.39	.599	
Time [52] * Therapy	47.19	17.97	11.81 to 82.56	.009**	
Time [6] * PVAQ	0.80	0.82	-0.81 to 2.41	.330	F=3.16; p=.03*
Time [26] * PVAQ	2.42	0.85	0.76 to 4.09	.005**	
Time [52] * PVAQ	1.80	0.86	0.11 to 3.49	.037*	
Time [6] * VAS_{Leg}	1.02	0.33	0.36 to 1.68	.003**	F=3.12; p=.03*
Time [26] * VAS_{Leg}	0.38	0.34	-0.29 to 1.05	.267	
Time [52] * VAS_{Leg}	0.42	0.35	-0.26 to 1.11	.228	

95% CI= 95% Confidence Interval; n= Number of participants; SE= Standard error; PCS= Pain Catastrophizing Scale; PVAQ= Pain Vigilance and Awareness Questionnaire; Therapy= Perioperative Biomedical Education (reference category), Perioperative Pain Neuroscience education ; Time= Baseline (reference category), 6 weeks follow-up [6], 26 weeks follow-up [26], 52 weeks follow-up[52]; VAS= Visual Analogue Scale. Significant fixed effects for independent variables are shown with an asterisk. (*:p≤.05; **:p≤.01;***:p≤.001).

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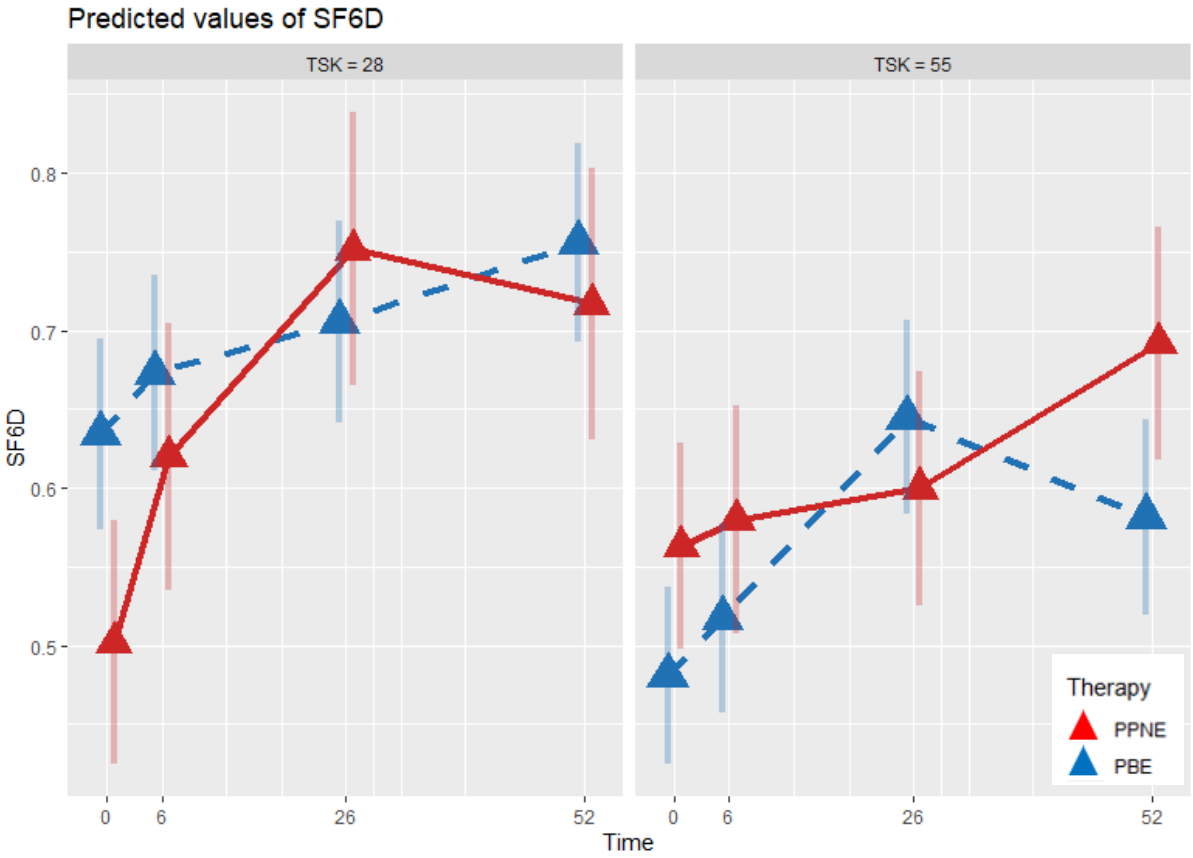
FIGURE 1. Results of the linear mixed model analysis showing the three-way interaction effect with 95% confidence intervals for therapy*time*preoperative leg pain of the final model for the Short Form-6 Dimensions Health Utility Values (SF6D) in people undergoing surgery for lumbar radiculopathy. The predictive values are presented over time per therapy group, Perioperative Pain Neuroscience Education (PPNE) versus Perioperative Biomedical Education (PBE), for patients with minimum (0) and maximum (100) scores on the Visual Analogue Scale (VAS) for leg pain intensity (n=90).



462 **FIGURE 2.** Results of the linear mixed model analysis showing the three-way interaction effect with 95% confidence intervals
463 for therapy*time*preoperative levels of kinesiophobia of the final model for the Short Form-6 Dimensions Health Utility
464 Values (SF6D) in people undergoing surgery for lumbar radiculopathy. The predictive values are presented over time per
465 therapy group, Perioperative Pain Neuroscience Education (PPNE) versus Perioperative Biomedical Education (PBE), for
466 patients with minimum (28) and maximum (55) scores on the Tampa Scale for Kinesiophobia (TSK) (n=90).

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