Cortical function and sensorimotor plasticity are prognostic factors associated with future low back pain after an acute episode

the Understanding persistent Pain Where it ResiDes prospective cohort study

Jenkins, Luke C; Chang, Wei-Ju; Buscemi, Valentina; Liston, Matthew; Humburg, Peter; Nicholas, Michael; Graven-Nielsen, Thomas; Hodges, Paul W; McAuley, James H; Schabrun, Siobhan M

Published in:
Pain

DOI (link to publication from Publisher):
10.1097/j.pain.0000000000002684

Publication date:
2023

Document Version
Accepted author manuscript, peer reviewed version

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000002684

Cortical function and sensorimotor plasticity are prognostic factors associated with future low back pain after an acute episode: the UPWaRD prospective cohort study

Luke C Jenkins,[1,2] Wei-Ju Chang,[1,2] Valentina Buscemi,[1,2] Matthew Liston,[1,2] Peter Humburg,[1, 7] Michael Nicholas,[3] Thomas Graven-Nielsen,[4] Paul W Hodges,[5] James H McAuley,[1, 6] Siobhan M Schabrun[1]

[1]Centre for Pain IMPACT, Neuroscience Research Australia (NeuRA), Randwick, New South Wales, Australia,

[2]School of Health Sciences, Western Sydney University, Penrith, New South Wales, Australia,

[3]Pain Management Research Institute, University of Sydney at Royal North Shore Hospital, Sydney, New South Wales, Australia,

[4]Center for Neuroplasticity and Pain (CNAP), Department of Health Science and Technology, Aalborg University, Aalborg, Denmark,

[5]The University of Queensland, School of Health and Rehabilitation Sciences, Brisbane, Queensland, Australia,

[6]University of New South Wales, Neuroscience Research Australia, Sydney, New South Wales, Australia,

[7]Mark Wainwright Analytical Centre, University of New South Wales, Sydney, New South Wales, Australia

Corresponding author: Dr. Siobhan Schabrun Neuroscience Research Australia, 139 Barker St, Randwick NSW 2031, Australia Phone: +61 421568494 Email: s.schabrun@neura.edu.au

ABSTRACT

Predicting the development of chronic low back pain (LBP) at the time of an acute episode remains challenging. The Understanding persistent Pain Where it ResiDes (UPWaRD) study aimed to identify neurobiological and psychological risk factors for chronic LBP. Individuals with acute LBP (N=120) participated in a prospective cohort study with six-month follow-up. Candidate predictors were selected from the neurobiological (e.g. sensorimotor cortical excitability assessed by sensory and motor evoked potentials, Brain Derived Neurotrophic Factor genotype), psychological (e.g. depression and anxiety), symptom-related (e.g. LBP history) and demographic domains. Analyses involved multivariable linear regression models with pain intensity or disability degree as continuous variables. Secondary analyses involved a multivariable logistic model with presence of low back pain at six months (thresholding pain intensity and disability degree) as a dichotomous variable. Lower sensory cortex and corticomotor excitability, higher baseline pain intensity, higher depression, stress and pain catastrophizing were the strongest predictors (R^2=0.47) of pain intensity at six months. Older age and higher pain catastrophizing were the strongest predictors (R^2=0.30) of disability at six months. When LBP outcome was dichotomised, sensory cortex and corticomotor excitability, BDNF genotype, depression and anxiety, LBP history and baseline pain intensity, discriminated between those who did and did not report LBP at six months (c-statistic 0.91). This study identifies novel risk factors for the development of future LBP. Neurobiological risk factors, when added to a multivariable linear regression model, explained a further 15% of the variance in six-month pain intensity.

Keywords: Low back pain; Prognostic model; Sensorimotor cortex excitability; plasticity; BDNF; Transcranial magnetic stimulation, Somatosensory evoked potential

INTRODUCTION

Low back pain (LBP) is the leading cause of years lived with disability worldwide [97] with approximately 40% of people experiencing pain for longer than three months after onset (termed 'chronic LBP') [20]. Clinical strategies designed to 'treat' LBP once it has become chronic show at best, modest effect sizes regardless of intervention type [1; 66; 68; 75]. An alternative approach for a condition with variable prognosis and treatment response such as LBP, is stratification of individuals by outcome and targeted treatment [27; 36; 55; 67; 83]. A key step in implementing this approach is the identification of relevant risk factors [72].

Risk factors are often used as building blocks for prognostic models [72]. Currently, the models used in clinical practice to determine an individual's risk of developing chronic LBP (e.g. STarT Back Screening Tool [34], and the short-form Orebro Musculoskeletal Pain Screening Questionnaire [54]) rely on self-report psychosocial and symptom-related factors. Although these models allocate higher predicted risk scores to individuals who develop chronic pain, their ability to discriminate between those who will, and will not, develop chronic pain remains limited [42; 43]. Risk models that integrate psychological (e.g. depression and coping strategies) and symptom-related factors (e.g. baseline pain intensity, history of prior LBP), explain up to 46% of the variance in LBP outcome [45]. Together these data suggest that although psychological and symptom-related risk factors are associated with the development of chronic LBP, a large proportion of variation in outcome is due to risk factors that are currently unmeasured or unknown [30; 45].

Emerging evidence suggests several neurobiological risk factors with a putative link to LBP outcome that are yet to be evaluated as risk factors in longitudinal studies. These include altered sensory and anterior cingulate cortex excitability [11; 26], altered corticomotor excitability [12; 78; 89], Brain Derived Neurotrophic Factor (BDNF) genotype [5; 15; 46; 81] and BDNF serum concentration [24; 51]. Prior studies have shown altered excitability in the primary sensory (S1) and primary motor (M1) cortices that is associated with the development and maintenance of chronic pain [23; 26; 77]. Further, a single nucleotide polymorphism in the human BDNF gene is associated with decreased behavioural driven changes in corticospinal output and cortical organization [4; 13; 24; 29; 46; 69]. As serum BDNF concentration is associated with BDNF genotype [49] both measures are considered markers of neuroplastic potential [5; 22].

The Understanding persistent Pain Where it ResiDes (UPWaRD) study aimed to recruit and follow a cohort of adults living in Australia who experienced an acute episode of LBP. The primary aim as reported 'a priori' in the study protocol [38] was to use this cohort to identify biological (with an emphasis on neurophysiological factors), psychological and sociodemographic risk factors of worse LBP outcome at six-month follow-up. The neurobiological risk factors selected for investigation in the protocol were those with a putative link to the development of aberrant cortical and spinal neuroplasticity, hypothesized to explain why some individuals develop chronic pain after an acute episode.

1. METHODS

1.1. Study population

Details of the participants, recruitment and procedures for this study are reported in the study protocol [38]. In brief, participants were eligible for inclusion if they had experienced acute LBP, reporting pain of at least 2/10 (Numerical rating scale [NRS], 0 = “no pain” and 10 = “worst pain imaginable”) at any time during the 7 days preceding initial screening [62]. Pain must have been present for more than 24 hours and less than six weeks duration following a period of at least one month without pain [21; 62; 82; 99]. Acute LBP was defined as pain in the region of the lower back, superiorly bound by the thoracolumbar junction and inferiorly by the gluteal fold. Participants remained eligible if they had pain referred beyond this region that was not caused by lumbosacral radiculopathy. Radiculopathy was suspected if participants reported a history of pain with dermatome-associated distribution, leg pain worse than back pain, worsening leg pain during coughing, sneezing or straining, a positive straight leg raise test or if the participant presented with neurological signs such as dermatome-associated sensory loss, impaired motor function or attenuated reflexes. Participants who presented with suspected lumbosacral radiculopathy during the clinical examination were excluded from the study and referred to their general practitioner for further assessment. Any individual who presented with suspected serious spine pathology (e.g. fracture, tumour, cauda equina syndrome), other major diseases/disorders (e.g. schizophrenia, chronic renal disorder, multiple sclerosis), a history of spine surgery, presence of active (i.e. being treated) chronic pain conditions or contraindications to the use of transcranial magnetic stimulation (TMS) were excluded [44]. Four assessors performed all study related procedures at laboratories located at Western Sydney University or Neuroscience Research Australia, Sydney, New South Wales, Australia. All procedures were approved by Western Sydney University (H10465) and Neuroscience Research Australia (SSA:16/002) Human Research Ethics Committees and conducted in accordance with the Declaration of the World Medical Association [2]. All participants gave written informed

consent. Pre-planned methodology was published [38] and the study registered (ACTRN12619000002189; Pre-results), adhering to recommendations of the PROGRESS initiative and TRIPOD statement [72; 85].

Important demographic and clinical data were collected at baseline for the UPWaRD LBP participants and reported in **Table 1**. Participants reported their age, sex, height, and weight which was converted into their body mass index (BMI). Participants were considered to have no inciting event for their LBP episode if they selected "no obvious cause" from a list of statements including "other". Participants were asked to report if they had experienced LBP in the past and completed the STarTBack Risk Screening Tool [35]. Other clinical data reported by participants were the presence of comorbid health conditions selected from a list including "other" (e.g. hypertension) and any current medications (e.g. Acetaminophen). Participants also reported how many times in the past three months they had visited their general practitioner, allied health practitioners, or completed diagnostic tests in relation to their pain. Participants completed the Brief Pain Inventory (BPI) that was used to rate their average and worst pain intensity, and the degree pain was interfering with their life over the previous seven days using an 11-point numerical rating scale (NRS). Low back related disability during their acute LBP episode was measured using the Roland-Morris Disability Questionnaire (RMDQ), and measures of psychological function were obtained including the 21-item Depression, Anxiety and Stress Scale (DASS-21), Pain Catastrophizing Scale (PCS) and Pain Self-Efficacy Questionnaire (PSEQ), that are described in more detail below.

1.2.Candidate predictors recorded at baseline

Fifteen candidate predictors were selected *'a priori'* based on a theoretical association with the development of chronic pain and supporting evidence from cross-sectional studies [5;

26; 31; 53; 76; 89]. Justification for each variable and specific methodology is provided in the study protocol [38]. In brief:

1.2.1. Sensory and anterior cingulate cortex excitability

Participants were seated comfortably in a chair with feet on the floor and arms relaxed. Participants were asked to sit still, keep their eyes closed and not to fall asleep for the duration of the test procedure. A bipolar electrode (silver-silver chloride disposable electrodes, inter-electrode distance 2.0 cm; Noraxon USA, Arizona, USA) was positioned 3 cm lateral to the L3 spinous process, ipsilateral to the side of the worst LBP and a constant current stimulator (Digitimer Ltd, Hertfordshire, UK DS7AH) delivered non-noxious electrical stimuli (single stimulus; pulse width 1 ms). The testing intensity was set at three times the perceptual threshold. If this testing intensity evoked pain, it was decreased in 1 mA increments until the stimulus was reported as non-noxious.

Sensory evoked potentials (SEPs) were recorded in response to two blocks of 500 non-noxious electrical stimuli (~2 Hz, with random interval schedule of 20% to decrease accommodation), using gold plated cup electrodes positioned over S1 (3 cm lateral and 2 cm posterior of Cz) on the hemisphere contralateral to the side of worst LBP and referenced to Fz using the International 10/20 System [37]. Electrode impedance was maintained at <5 kΩ. EEG signals were amplified 50,000 times, band pass filtered between 5-500 Hz, and sampled at 1,000 Hz using a Micro1401 data acquisition system and Signal software (CED Limited, Cambridge, UK).

Individual SEP traces were inspected and those with eye movements, muscle artefacts or electrical interference were rejected. Less than 15% of all SEP traces were excluded. Remaining traces from the two SEP blocks were averaged for each participant and used for analysis [10]. The averaged wave form was full-wave rectified and the area under the rectified

curve (μV) determined for the N_{80} (between the first major downward deflection of the curve after stimulus onset and the first peak, N_{80}), N_{150} (between the first and second peak, N_{80} and N_{150}, respectively) and P_{260} (between the second negative peak, N_{150} and the positive deflection of the curve starting around 150 ms after stimulus onset, P_{260}) time epochs [23]. **Figure 1** displays a rectified trace with time epochs used for analysis. The SEP area measurement was chosen for analysis as it is less susceptible to signal-to-noise ratio concerns [17], and considered superior to peak-based measures for assessing event-related potentials [23; 41; 70; 100].

1.2.2. Corticomotor excitability

Participants underwent a standardised TMS mapping procedure as described in the study protocol and in previous studies [38; 65; 80; 89]. Single-pulse, monophasic stimuli (Magstim 200 stimulator, 7 cm figure-of-eight coil; Magstim Co. Ltd. Dyfed, UK) were delivered over the primary motor cortex (M1) contralateral to the side of the worst LBP. The coil was positioned tangential to the skull with the handle pointing posterior-laterally at 45 degrees from midline [6; 40; 59]. Electromyography (EMG) was recorded from the paraspinal muscles 3 cm lateral to the spinous process of L3 and 1 cm lateral to the spinous process of L5 on the side of the worst LBP using disposable Ag/AgCl surface electrodes (Noraxon USA Inc, Arizona, USA) [50; 64]. Ground electrodes were placed over the anterior superior iliac spine bilaterally. EMG data were amplified 1000x, filtered between 20-1000 Hz and sampled at 2000 Hz using a Micro1401 data acquisition system and Spike2 software (CED Limited, Cambridge, UK). As 120% of active motor threshold often exceeds the maximum stimulator output [89], all stimuli were delivered at 100% of stimulator output while participants activated the paraspinal muscles to 20 ± 5% of their EMG recorded during a maximum voluntary contraction (MVC; determined as 20% of the highest root mean square [RMS] EMG averaged over 1 s during three, 3-s maximal muscle contractions performed against

manual resistance in sitting) [78; 79; 89]. Real-time feedback of time paraspinal muscle RMS EMG and the target level was displayed on a monitor for the duration of the test procedure [91]. All TMS procedures adhered to the TMS checklist for methodological quality [14].

TMS motor evoked potentials (MEP) were analysed using MATLAB 2019a (The MathWorks, USA). Onset and offset of the MEPs in each individual trace were visually identified then averaged at each scalp site. Paraspinal MEP amplitudes were normalized to the largest MEP amplitude across sites and superimposed over the respective scalp sites to generate a topographical map. A scalp site was considered active if the normalised MEP amplitude was equal to or greater than 25% of the peak response [10]. Normalised values below 25% of the peak response were removed and the remaining values rescaled from 0 to 100% [80; 90].

Two parameters were calculated from the normalised motor cortical maps. First, L3 and L5 map volumes were calculated as the sum of normalized MEP amplitudes recorded at all active scalp sites [98]. Second, the centre of gravity (CoG), defined as the amplitude weighted centre of the map, was calculated for the M1 cortical representation of L3 and L5 paraspinal muscles using the formula: $CoG = \Sigma Vi \cdot Xi/\Sigma Vi, \Sigma Vi \cdot Yi/\Sigma Vi$ where: Vi=mean MEP response at each site with the coordinates Xi, Yi [92; 98]. Distance between the L3 and L5 CoG (L3/L5 CoG overlap) was calculated as the Euclidean distance (ED) using the formula: $ED = \sqrt{((Y_{L3} - Y_{L5})^2 + (X_{L3} - X_{L5})^2)}$, where Y = anterior-posterior coordinates; X = medial-lateral coordinates of L3 and L5 [94; 95].

1.2.3. BDNF genotyping

Buccal swabs were taken on the day of baseline testing (Isohelix DNA Isolation Kit) [15]. Samples were immediately frozen and stored at −80°C. Genomic DNA samples were polymerase chain reaction amplified and sequenced by the Australian Genome Research Facility (AGRF). Genotyping was performed as recommended by the manufacturer with

reagents included in the iPLEX Gold SNP genotyping kit (Agena) and the software and equipment provided with the MassARRAY platform (Agena) [16]. Consistent with prior investigations [5; 48; 57], the BDNF gene was coded as a dichotomous variable (AA/AG or GG). The more common G allele encodes Valine (Val), while the A allele encodes Methionine (Met).

1.2.4. BDNF serum concentration

Peripheral venous blood was drawn into serum tubes (BD, SST II Advance) through venepuncture of the median cubital vein at baseline. The sample was clotted (30 min, room temperature) then separated by centrifugation (2500 rpm, 15 min). The samples were pipetted into 50 µL aliquots and stored at -80°C. After thawing, the Simple plex Ella™ platform was used to analyse the specific expression of BDNF. Briefly, 10 µL samples were diluted with 90 µL of sample diluent then added to the cartridge, according to the standard procedure provided by the manufacturers (Protein Simple, CA, USA). All steps in the immunoassay procedure were carried out automatically and scans were processed with no user activity. Cartridges included built-in lot–specific standard curves. Single data (pg/mL) for each sample were automatically calculated and converted to ng/mL for statistical analysis. The limit of detection was 5.25 pg/mL. Fifteen randomly selected samples were analysed in duplicate and demonstrated near perfect correlation ($r = 0.98$, $P = < 0.001$).

1.2.5. Psychological status

Three questionnaires were used to assess specific aspects of psychological status known to be of relevance to the development of chronic LBP [38]: depression and anxiety [8], pain catastrophising [7] and pain beliefs [52]. The DASS-21 was used to assess depression, anxiety and stress. The 13-item PCS assesses distressing thoughts related to painful experiences [86]. A total score between 0 and 52 was calculated, where higher scores represent more severe catastrophic thoughts about pain [86]. The 10-item PSEQ was used to assess an individual's

beliefs in their ability to perform a range of functional activities while in pain. The DASS-21 (Cronbach's $\alpha = 0.88$), PCS (Cronbach's $\alpha = 0.87$) and PSEQ (Cronbach's $\alpha = 0.92$) have all demonstrated high degrees of reliability (internal consistency) [32; 63; 86].

1.2.6. Symptom-related factors

Baseline pain intensity was drawn from the Brief Pain Inventory (BPI) administered on the day of baseline testing. Participants rated their pain on average over the previous week using an 11-point NRS [18]. Participants were considered to have a previous history of LBP if they answered "yes" to the question: "Have you experienced low back pain in the past"?

1.2.7. Demographics

Age and sex were collected from all participants on the day of baseline testing.

1.3. Primary and secondary outcomes recorded at six-month follow-up

The primary outcome was average pain intensity over the past week, assessed using the NRS at six-month follow-up. The secondary outcome was disability assessed using the 24-point Roland Morris Disability Questionnaire (RMDQ) at six-month follow-up [74]. The primary and secondary outcomes were combined to distinguish between those who did and did not report LBP at six months, defined as an NRS score ≥ 2 on average over the previous one-week or ≥ 7 on the RMDQ scale at six-month follow-up [35; 88]. This dichotomised outcome measure was used in the secondary analysis, described in detail below.

1.4. Sample size

Sample size was calculated *'a priori'* and is described in detail in the study protocol [38]. Briefly, we assumed that at least five variables would show no association with the outcome and be excluded from analysis, and 20% of participants would be lost to follow up. Therefore, 120 participants were required to ensure at least ten subjects per variable within linear regression models (95). Sample size for the logistic regression model was calculated using the

rule of thumb that five events per candidate variable (EPV) are required for adequate statistical power (96).

1.5. Statistical Analyses

All analyses were conducted with the statistical programming language R, version 4.0.3 (R Development Core Team, Vienna, Austria) [19]. Statistical significance was accepted at $P \leq 0.05$. Continuous data are presented as mean ± standard deviation (SD) and categorical data as frequency and percent (%). Candidate predictors measured on a continuous scale were not dichotomised as this can increase risk of bias in regression models [60; 61]. Categorical candidate predictors were coded as follows: sex [male or female], previous history of LBP [yes or no] and BDNF genotype [AA/AG or GG].

All missing data were imputed using the multiple imputation by chained equations (MICE) procedure and thirty imputed data sets were generated [93]. Missing data within the candidate predictors are described in **Table 2**. Comparisons were made between participants who did or did not complete follow-up using independent samples t-test and Fisher's Exact test for continuous and categorical data respectively. Spearman's rank correlation coefficients were used to determine whether there was any evidence of collinearity between measures of cortical excitability [28].

Next, the remaining candidate predictors underwent a variable selection procedure using the least absolute shrinkage and selection operator (lasso) technique [87]. This is a variation from the variable selection procedures described in the published study protocol [38]. For a detailed description about lasso variable selection procedure used in this study please refer to Supplemental File 1 (available at http://links.lww.com/PAIN/B648). For the primary analysis, outcome variables of pain and disability were treated as continuous data and the strongest risk factors were selected using the lasso variable selection procedure. The results of

the primary analyses are presented using hierarchical linear regression. Goodness of fit for the linear models was assessed using the R^2 and adjusted R^2 value.

In the secondary analysis the lasso variable selection procedure was repeated within a logistic regression model to determine the strongest risk factors of future LBP at six-months (dichotomized outcome: NRS $\geq$ 2 or RMDQ $\geq$ 7). The goodness of fit for the final logistic regression model was estimated following ten-fold cross-validation as described in **Supplemental File 1** (available at http://links.lww.com/PAIN/B648) and reported as the c-statistic (i.e. area under the receiver operating characteristic curve).

3. RESULTS

3.1. Participant characteristics

Between 14 April 2015 and 23 January 2019, 498 participants presented with an acute episode of LBP for screening and 120 were included in the study sample (**Figure 2**). Two hundred and seven participants (41.5%) were ineligible because they had chronic LBP, two were ineligible because they had previous spinal surgery and three were ineligible because physical examination by the study investigator suggested a diagnosis of lumbosacral radiculopathy. Of the 286 eligible participants, 94 (32.9%) failed to respond to contact attempts to organise baseline assessment and 72 (25.2%) declined participation after reviewing the study information sheet. The date of the final participant's six-month follow up was 25 July 2019. Baseline data were obtained on average 2.4 weeks (SD 1.4, range 1 day to 6 weeks) after the onset of an acute LBP episode. Seventy-two participants (60%) were coded GG and 48 (40%) were coded AA/AG for BDNF genotype. According to the Hardy–Weinberg Equilibrium, this observed distribution does not differ significantly from the expected rate (χ^2 = 1.27, df = 1, P = 0.26). **Table 1** shows baseline demographic and clinical characteristics. Participants with LBP at six-months were more likely at baseline assessment

to have pain referred below the level of the gluteal fold and consult more frequently with general practitioners. These participants also had higher levels of psychological distress, lower pain self-efficacy, higher average and worst pain intensity and experience more disability and pain interference. There were no other statistically significant differences at baseline assessment between participants who did or did not experience LBP at six-months.

Follow-up at six months was completed in 96 participants (80%). Missing follow-up cases were due to the participant failing to respond to multiple contact attempts. The intention was to determine the presence of LBP at six-months (183 days), in practice, follow-up occurred a mean 194 (SD = 20) days after entering the study with an acute episode of LBP. Baseline candidate predictors and their univariable association with chronic LBP are provided in **Table 3**. Individual participant data for normalised motor cortical maps and sensory evoked potentials are displayed in **Figure 3 and 4**.

3.2. Incidence of chronic LBP

Analysis of complete cases revealed that 54% of participants reported LBP at six-month follow-up (average pain intensity 3.9 [SD = 1.7], average RMDQ score 4.8 [SD = 5.4]) and could be considered to have persistent or recurring LBP. This is comparable to the incidence of chronicity in previous Australian estimates [33]. Of the 52 participants deemed to have LBP, only 12 participants (23%) had an RMDQ score ≥ 7. The remaining 46% of participants were classified as recovered (average pain intensity 0.3 [SD = 0.5], average RMDQ score 0.9 [SD = 1.6]).

3.3. Continuous data distribution and collinearity

All variables were normally distributed except the N_{80}, N_{150} and P_{260} SEP area and these variables were log-transformed. Baseline characteristics were then compared between participants who did (N=96), and did not (N=24), complete follow up at six months (**Table 4**).

Apart from N_{150} and P_{260} SEP area measures, no statistically significant differences at baseline were identified between participants who did, or did not, complete follow-up, however, the N_{80} SEP area did demonstrate a strong tendency (P = 0.06). Next, spearman's correlation coefficients were calculated between all measures of cortical excitability (**Table 5**). No strong correlation was identified between SEP and TMS measures. The N_{80} and N_{150} (r_s = 0.84, P = < 0.001), and N_{80} and P_{260} (r_s = 0.85, P = <0.001) SEP area values were strongly correlated. As the N_{150} and P_{260} SEP area measurements may have impacted the missing at random assumption and demonstrated collinearity with the N_{80} SEP area they were excluded from further analyses. The remaining thirteen candidate predictors were subjected to the λ-1se variable selection procedure to identify relevant risk factors.

3.4. Risk factors associated with pain intensity at six months

Higher baseline pain intensity (P = <0.001), higher depression and anxiety (DASS-21: P = 0.31), higher pain catastrophizing (PCS: P = 0.39), lower N_{80} SEP area (P = 0.01) and lower L3 map volume (P = < 0.01) were the risk factors demonstrating the strongest association with pain intensity over the previous week (continuous outcome) at six months and thus were entered into a hierarchical regression model**.** The results of hierarchical regression modelling are presented in **Table 6**. Baseline pain intensity explained 22% of the variance in pain intensity at six-months. Addition of the DASS-21 and PCS instruments explained a further 10% of the variance ($F_{[2,88]}$ = 4.99, P = 0.01) and the addition of novel neurobiological risk factors (N_{80} SEP area and L3 map volume) explained a further 15% of the variance in six-month pain intensity ($F_{[2,76]}$ = 8.61, P = < 0.001). In combination, these five variables explained 47% (R^2 = 0.47 95% CI = 0.31 – 0.60) of the total variance in six-month pain intensity.

3.5. Risk factors associated with disability at six months

Higher pain catastrophizing (PCS: B = 0.47, 95% CI = 0.30 to 0.64, *P* = < 0.001) and older age (B = 0.24, 95% CI = 0.08 to 0.42, *P* = < 0.01) were the strongest risk factors associated with disability over the previous week (continuous outcome) at six months. These two factors explained 30% of the variance in disability outcome at six months (R^2 = 0.30, 95% CI = 0.14 to 0.46).

3.6. Risk factors associated with the presence or not of LBP at six months

When the dichotomous variable of LBP at six-months was designated on the basis of pain or disability above a threshold value (NRS ≥ 2 or RMDQ ≥ 7), six risk factors remained in the multivariable logistic regression model following λ-1se variable selection and ten-fold cross-validation **(Table 7)**. Lower primary sensory cortex excitability (N_{80} SEP area: P = < 0.01), lower corticomotor excitability (L3 map volume: P = 0.07), BDNF genotype MET allele carriers (P = 0.18), higher depression and anxiety (DASS-21 score: P = 0.01), no prior history of LBP (P = 0.11) and higher baseline pain intensity (P = < 0.01). The c-statistic for the multivariable model was 0.91 (95% CI 0.84 to 0.95).

3.7. Sensitivity analysis

A sensitivity analysis was conducted to explore the effect of imputing missing six-month outcome data on study results. Participants who did not return for follow-up at six months were removed from the dataset and the analysis repeated. Risk factors included in the multivariable regression models following λ-1se variable selection were identical for all outcomes. The multivariable linear model predicting six-month pain intensity had a R^2 value of 0.45 (95% CI = 0.29 – 0.60) and the linear model predicting six-month disability score had a R^2 value of 0.32 (95% CI = 0.17 – 0.47). Goodness of fit for the multivariable logistic regression model was also comparable, demonstrating a c-statistic of 0.88 (95% CI = 0.81 to 0.95).

4. DISCUSSION

This prospective longitudinal cohort study is the first to investigate biological measures of sensorimotor cortical function and neuroplasticity as risk factors of six-month outcome after an acute episode of LBP. A novel finding was the identification of lower primary sensory cortex excitability (N_{80} SEP area) and lower corticomotor excitability (L3 map volume) in the acute stage of LBP as risk factors for higher pain intensity reported at six months. When these variables were combined with psychological factors (higher emotional distress) and symptom-related factors (no prior LBP history, higher baseline pain intensity), they explained a similar percentage of the variance in six month pain intensity (47%) as earlier models that integrate psychological and symptom-related factors (46%) [45], but uniquely, addition of the novel neurobiological risk factors explained a further 15% of the variance in six-month pain intensity. These findings provide further support for the importance of assessing diverse phenotypic traits, across a range of neurobiological, psychological, symptom-related, and demographic domains, when attempting to predict LBP outcome. Previous studies utilising cluster analyses have shown stronger associations between LBP outcome and psychological factors when relevant biological factors are considered in tandem [47;48]. For example, in a longitudinal study using cluster analyses, individuals with the worst recovery from acute LBP at six-month follow-up displayed higher depression-like symptoms in conjunction with higher serum concentrations of tumor necrosis factor [47]. We caution readers not to infer causal relationships between any of the risk factors identified in this study and six-month LBP outcome. No attempt was made to identify, or control for, relevant confounders as the aim of this study was to identify novel risk factors of six-month LBP outcome, with a clear emphasis on neurobiological variables. As stated within the PROGRESS Initiative, prognostic factor research has many uses in healthcare and clinical

research [73]. The study data we report here identifies for the first time novel neurobiological risk factors of future LBP outcome. Future studies should assess their predictive value over established prognostic factors.

The primary analysis aimed to the candidate predictors most strongly associated with pain intensity and disability at six months as continuous outcomes. These analyses revealed largely discrete risk factors for the outcomes of pain (strongest risk factors of lower sensory cortex excitability [N_{80} SEP area], lower corticomotor excitability [L3 map volume], higher baseline pain intensity with a lesser contribution from higher emotional distress and higher pain catastrophising) and disability (older age, higher pain catastrophizing), with no neurobiological risk factors identified for disability following the lasso variable selection procedure. Patient-reported outcomes of pain (e.g. NRS) and disability (e.g. RMDQ) are known to be weakly correlated with each other when LBP is chronic [47] and previous research has shown that disability is more closely aligned with psychological risk factors than is pain intensity. For example, in a large cohort study of people with chronic LBP, psychological questionnaires thought to assess 'pain-related distress' explained 51% of the variance in disability, but only 35% of the variance in pain intensity [8]. The absence of a relationship between sensorimotor cortex excitability and disability suggests other factors predict this outcome. This is an important consideration when interpreting the current findings. People who develop pain-related disability account for a significant proportion of the total healthcare costs associated with LBP, thus identifying risk factors of LBP-related disability is of critical importance [25; 30]. Previous studies have suggested a link between pain-related neurobiology (e.g. neuro-endocrine responses to pain [58]), pain-specific neurophysiological and psychological processes that may in turn, drive pain-related disability. Future research should seek to identify and validate neurobiological risk factors for LBP-related disability.

Our findings on the psychological and symptom-related risk factors for chronic LBP are consistent with prior work [31; 53; 71]. We confirm previous findings that show higher emotional distress and higher pain in the acute stage of LBP are risk factors for the development of persistent or recurring LBP. The discovery that lower sensory cortex excitability and lower corticomotor excitability are risk factors for future LBP is novel. When N_{80} SEP area, L3 map volume and BDNF genotype were combined with psychological (higher emotional distress) and symptom-related (no prior LBP history, higher baseline pain intensity) factors, the multivariable logistic regression model could discriminate between those with and without LBP at 6-months follow-up (c-statistic 0.91 [0.84 to 0.95]).

The discovery that low primary sensory cortex excitability and low corticomotor excitability in the acute stage of LBP are risk factors for worse LBP outcome at six-months builds on a growing body of evidence that suggests measures of brain structure and function are important risk factors of LBP outcome. For example, in sub-acute LBP, greater functional connectivity of corticostriatal circuitry is associated with chronic LBP at 1-year [3; 56]. Using causal inference analyses, we have shown that low sensory cortex excitability (N_{80} SEP area) in acute LBP is a cause, and not an epiphenomenon, of chronic pain [39]. Further research is required to determine if these neurobiological risk factors are modifiable.

Despite a robust and rigorous approach to data collection and analyses, this study has some limitations. First, MEPs used to quantify corticomotor excitability were obtained by delivering TMS at 100% of stimulator output over the M1 during a sub-maximal paraspinal muscle contraction. Although this methodology has been reported previously [78; 79; 89], recent methodological developments have shown that pseudo-randomly delivering 90 stimuli over a 5 x 7 cm grid with a high-intensity coil reliably maps the M1 paraspinal muscle representation and minimises acquisition times (ICC = 0.82 [95% CI 0.66 – 0.91]) [9]. This approach should be considered in future studies and may decrease participant attrition and

missing data. Second, despite some evidence suggesting as few as five EPV may provide adequate statistical power for logistic regression [96], the most commonly accepted rule for minimising overfitting encourages EPV of twenty or more and our sample size does not achieve this [61]. As recommended by the TRIPOD statement, penalized regression was applied to address this limitation of the study, and results of the logistic model underwent ten-fold cross-validation to minimise optimism [60; 61]. However, additional, large-scale studies are needed to confirm and validate our findings. Third, missing data were present within some candidate predictors and no outcome data were available for 24 participants. To limit the impact of missing data on our findings, missing values were imputed using the MICE procedure [84] and a sensitivity analysis identified no differences between models developed with or without imputed outcome data. Fourth, the outcome measures for pain and disability asked participants to report these features over the past week, and we cannot determine whether LBP had persisted since the acute episode (i.e., defined as chronic) or had reoccurred as a new discrete episode (i.e., defined as recurrent). For this reason, we refer to our dichotomised results as risk factors for future LBP and cannot determine whether risk factors differ between chronic or recurring LBP. Finally, the dichotomous outcome of future LBP was based on a threshold value of ≥ 2 on the NRS or ≥ 7 on the RMDQ scale, as used in prior studies predicting LBP outcome [35; 88]. There remains no widely accepted cut-off for classifying LBP outcome based upon subjective pain and disability scores and transforming a continuous subjective measure into discrete categories remains challenging [6]. The arbitrary cut-off chosen in this study to define recurrent or future LBP may not optimally reflect the experience of individuals with LBP and continuous outcomes remain preferable, consistent with our primary analysis [82]. Finally, 0.8 percent of individuals who presented for screening in the UPWaRD study were deemed ineligible due to the presence of radiculopathy. This figure is similar to that reported by a large-scale inception cohort of 973 individuals with

acute, non-specific low back pain presenting to Australian primary care (1.2 % of screened participants excluded due to radiculopathy) [33]. The relatively low prevalence of radiculopathy in these studies is likely explained by the recruitment process. Referring healthcare practitioners were provided with information on study inclusion criteria and thus, participants with suspected radiculopathy were unlikely to have been referred for screening.

4.1 Conclusion

This study identified novel risk factors relating to cortical function and neuroplasticity for the development of future LBP. Neurobiological risk factors, when added to a multivariable linear regression model, explained a further 15% of the variance in six-month pain intensity. Future research should seek to determine whether the neurobiological risk factors identified in this study are modifiable causal mechanisms.

Acknowledgements:

We thank the patients who participated in the study. We thank Dr Valerie Wasinger, Biosciences Precinct Laboratory, Level 2, Biosciences South (E26), UNSW Sydney, NSW 2052 for her expertise and assistance with serum analyses.

Conflict of interest statement:

This work was supported by grant 1059116 from the National Health and Medical Research Council (NHMRC) of Australia. SMS and PWH receive salary support from the National Health and Medical Research Council of Australia (1105040 and 1102905, respectively). TGN is a part of Center for Neuroplasticity and Pain (CNAP) that is supported by the Danish National Research Foundation (DNRF121).

5. REFERENCES

[1] Artus M, van der Windt DA, Jordan KP, Hay EM. Low back pain symptoms show a similar pattern of improvement following a wide range of primary care treatments: a systematic review of randomized clinical trials. Rheumatology 2010;49(12):2346-2356.

[2] Association WM. WMA Declaration of Helsinki-Ethical principles for medical research involving human subjects: Fortaleza, Brazil, 2013.

[3] Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. Nature neuroscience 2012;15(8):1117-1119.

[4] Bath K, Lee F. Variant BDNF (Val66Met) impact on brain structure and function. Cognitive, Affective, & Behavioral Neuroscience 2006;6(1):79-85.

[5] Baumbauer KM, Ramesh D, Perry M, Carney KB, Julian T, Glidden N, Dorsey SG, Starkweather AR, Young EE. Contribution of COMT and BDNF Genotype and Expression to the Risk of Transition from Acute to Chronic Low Back Pain. The Clinical journal of pain 2020.

[6] Brasil-Neto JP, McShane LM, Fuhr P, Hallett M, Cohen LG. Topographic mapping of the human motor cortex with magnetic stimulation: factors affecting accuracy and reproducibility. Electroencephalography and clinical neurophysiology / Evoked potentials section 1992;85(1):9-16.

[7] Burton AK, Tillotson KM, Main CJ, Hollis S. Psychosocial predictors of outcome in acute and subchronic low back trouble. Spine (Philadelphia, PA 1976) 1995;20(6):722-728.

[8] Campbell P, Bishop A, Dunn KM, Main CJ, Thomas E, Foster NE. Conceptual overlap of psychological constructs in low back pain. Pain® 2013;154(9):1783-1791.

[9] Cavaleri R, Chipchase LS, Massé-Alarie H, Schabrun SM, Shraim MA, Hodges PW. Corticomotor reorganization during short-term visuomotor training in the lower back: A randomized controlled study. Brain and Behavior 2020;10(8):e01702.

[10] Chang W-J, Buscemi V, Liston MB, McAuley JH, Hodges PW, Schabrun SM. Sensorimotor Cortical Activity in Acute Low Back Pain: A Cross-Sectional Study. The Journal of Pain 2019.

[11] Chang W-J, Buscemi V, Liston MB, McAuley JH, Hodges PW, Schabrun SM. Sensorimotor Cortical Activity in Acute Low Back Pain: A Cross-Sectional Study. The Journal of Pain 2019;20(7):819-829.

[12] Chang W-J, Buscemi V, Liston MB, McAuley JH, Hodges PW, Schabrun SMJTJoP. Sensorimotor cortical activity in acute low back pain: a cross-sectional study. The Journal of Pain 2019;20(7):819-829.

[13] Cheeran B, Talelli P, Mori F, Koch G, Suppa A, Edwards M, Houlden H, Bhatia K, Greenwood R, Rothwell JC. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. Journal of Physiology 2008;586(23):5717-5725.

[14] Chipchase L, Schabrun S, Cohen L, Hodges P, Ridding M, Rothwell J, Taylor J, Ziemann U. A checklist for assessing the methodological quality of studies using transcranial magnetic stimulation to study the motor system: An international consensus study. Clin Neurophysiol 2012;123(9):1698-1704.

[15] Cirillo J, Hughes J, Ridding M, Thomas PQ, Semmler JG. Differential modulation of motor cortex excitability in BDNF Met allele carriers following experimentally induced and use-dependent plasticity. European Journal of Neuroscience 2012;36(5):2640-2649.

[16] Clarke SM, Henry HM, Dodds KG, Jowett TW, Manley TR, Anderson RM, McEwan JC. A high throughput single nucleotide polymorphism multiplex assay for parentage assignment in New Zealand sheep. PLoS One 2014;9(4).

[17] Clayson PE, Baldwin SA, Larson MJ. How does noise affect amplitude and latency measurement of event-related potentials (ERPs)? A methodological critique and simulation study. Psychophysiology 2013;50(2):174-186.

[18] Cleeland CS, Ryan K. The brief pain inventory. Pain Research Group 1991.

[19] Core Team R. R: A language and environment for statistical computing. R Foundation for statistical computing, Vienna 2013.

[20] Costa LdCM, Maher CG, McAuley JH, Hancock MJ, Herbert RD, Refshauge KM, Henschke N. Prognosis for patients with chronic low back pain: inception cohort study. Bmj 2009;339:b3829.

[21] De Vet CWH, Heymans WM, Dunn MK, Pope PD, Van Der Beek JA, Macfarlane JG, Bouter ML, Croft RP. Episodes of Low Back Pain: A Proposal for Uniform Definitions to Be Used in Research. Spine 2002;27(21):2409-2416.

[22] Deitos A, Dussán-Sarria JA, de Souza A, Medeiros L, da Graça Tarragô M, Sehn F, Chassot M, Zanette S, Schwertner A, Fregni F. Clinical value of serum neuroplasticity mediators in identifying the central sensitivity syndrome in patients with chronic pain with and without structural pathology. The Clinical journal of pain 2015;31(11):959-967.

[23] Diers M, Koeppe MC, Diesch ME, Stolle MA, Hölzl MR, Schiltenwolf MM, Van Ackern MK, Flor MH. Central Processing of Acute Muscle Pain in Chronic Low Back Pain Patients: An EEG Mapping Study. Journal of Clinical Neurophysiology 2007;24(1):76-83.

[24] Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003;112(2):257-269.

[25] Engel CC, Von Korff M, Katon WJJP. Back pain in primary care: predictors of high health-care costs. 1996;65(2-3):197-204.

[26] Flor H, Braun C, Elbert T, Birbaumer N. Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neuroscience Letters 1997;224(1):5-8.

[27] Foster NE, Mullis R, Hill JC, Lewis M, Whitehurst DG, Doyle C, Konstantinou K, Main C, Somerville S, Sowden G. Effect of stratified care for low back pain in family practice (IMPaCT Back): a prospective population-based sequential comparison. The Annals of Family Medicine 2014;12(2):102-111.

[28] Glantz S, Slinker B. Primer of Applied Regression & Analysis of Variance, ed: McGraw-Hill, Inc., New York, 2001.

[29] Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF, Weinberger DR. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. Journal of Neuroscience 2003;23(17):6690-6694.

[30] Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, Hoy D, Karppinen J, Pransky G, Sieper J, Smeets RJ, Underwood M. What low back pain is and why we need to pay attention. The Lancet 2018;391(10137):2356-2367.

[31] Hayden JA, Chou R, Hogg-Johnson S, Bombardier C. Systematic reviews of low back pain prognosis had variable methods and results: guidance for future prognosis reviews. J Clin Epidemiol 2009;62(8):781-796 e781.

[32] Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. British journal of clinical psychology 2005;44(2):227-239.

[33] Henschke N, Maher CG, Refshauge KM, Herbert RD, Cumming RG, Bleasel J, York J, Das A, McAuley JH. Prognosis in patients with recent onset low back pain in Australian primary care: inception cohort study. Bmj 2008;337:a171.

[34] Hill CJ, Vohora MK, Dunn JK, Main MC, Hay ME. Comparing the STarT Back Screening Tool's Subgroup Allocation of Individual Patients With That of Independent Clinical Experts. The Clinical Journal of Pain 2010;26(9):783-787.

[35] Hill JC, Dunn KM, Lewis M, Mullis R, Main CJ, Foster NE, Hay EM. A primary care back pain screening tool: identifying patient subgroups for initial treatment. Arthritis Care & Research: Official Journal of the American College of Rheumatology 2008;59(5):632-641.

[36] Hingorani AD, van der Windt DA, Riley RD, Abrams K, Moons KG, Steyerberg EW, Schroter S, Sauerbrei W, Altman DG, Hemingway HJB. Prognosis research strategy (PROGRESS) 4: stratified medicine research. 2013;346.

[37] Homan RW, Herman J, Purdy P. Cerebral location of international 10–20 system electrode placement. Electroencephalography and Clinical Neurophysiology 1987;66(4):376-382.

[38] Jenkins LC, Chang W-J, Buscemi V, Liston M, Toson B, Nicholas M, Graven-Nielsen T, Ridding M, Hodges PW, McAuley JH. Do sensorimotor cortex activity, an individual's capacity for neuroplasticity, and psychological features during an episode of acute low back pain predict outcome at 6 months: a protocol for an Australian, multisite prospective, longitudinal cohort study. BMJ open 2019;9(5):e029027.

[39] Jenkins LC, Chang WJ, Buscemi V, Liston M, Skippen P, Cashin AG, McAuley JH, Schabrun SM. Low Somatosensory Cortex Excitability in the Acute Stage of Low Back Pain Causes Chronic Pain. J Pain 2021.

[40] Kaneko K, Kawai S, Fuchigami Y, Morita H, Ofuji A. The effect of current direction induced by transcranial magnetic stimulation on the corticospinal excitability in human brain. Electroencephalography and clinical neurophysiology / electromyography and motor control 1996;101(6):478-482.

[41] Kappenman ES, Luck SJ. Best practices for event-related potential research in clinical populations. Biological psychiatry: cognitive neuroscience and neuroimaging 2016;1(2):110-115.

[42] Karran EL, McAuley JH, Traeger AC, Hillier SL, Grabherr L, Russek LN, Moseley GL. Can screening instruments accurately determine poor outcome risk in adults with recent onset low back pain? A systematic review and meta-analysis. BMC medicine 2017;15(1):1-15.

[43] Karran EL, Traeger AC, McAuley JH, Hillier SL, Yau Y-H, Moseley GL. The Value of Prognostic Screening for Patients With Low Back Pain in Secondary Care. Journal of Pain 2017;18(6):673-686.

[44] Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol 2001;112(4):720.

[45] Kent PM, Keating JL. Can we predict poor recovery from recent-onset nonspecific low back pain? A systematic review. Manual Therapy 2008;13(1):12-28.

[46] Kleim JA, Chan S, Pringle E, Schallert K, Procaccio V, Jimenez R, Cramer SC. BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. Nature neuroscience 2006;9(6):735.

[47] Kovacs FM, Abraira V, Zamora J, del Real MTG, Llobera J, Fernández C. Correlation between pain, disability, and quality of life in patients with common low back pain. Spine 2004;29(2):206-210.

[48] Lang U, Hellweg R, Kalus P, Bajbouj M, Lenzen K, Sander T, Kunz D, Gallinat J. Association of a functional BDNF polymorphism and anxiety-related personality traits. Psychopharmacology 2005;180(1):95-99.

[49] Lang U, Hellweg R, Sander T, Gallinat J. The Met allele of the BDNF Val66Met polymorphism is associated with increased BDNF serum concentrations. Molecular psychiatry 2009;14(2):120-122.

[50] Lariviere C, Arsenault AB, Gravel D, Gagnon D, Loisel P. Surface electromyography assessment of back muscle intrinsic properties. J Electromyogr Kinesiol 2003;13(4):305-318.

[51] Laske C, Stransky E, Eschweiler GW, Klein R, Wittorf A, Leyhe T, Richartz E, Köhler N, Bartels M, Buchkremer G, Schott K. Increased BDNF serum concentration in fibromyalgia with or without depression or antidepressants. Journal of Psychiatric Research 2007;41(7):600-605.

[52] Lee LH, Hübscher JM, Moseley CG, Kamper HS, Traeger HA, Mansell HG, McAuley HJ. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. PAIN 2015;156(6):988-997.

[53] Linton JS. A Review of Psychological Risk Factors in Back and Neck Pain. Spine 2000;25(9):1148-1156.

[54] Linton SJ, Boersma K. Early identification of patients at risk of developing a persistent back problem: the predictive validity of the Örebro Musculoskeletal Pain Questionnaire. The Clinical journal of pain 2003;19(2):80-86.

[55] Linton SJ, Nicholas M, Shaw WJP. Why wait to address high-risk cases of acute low back pain? A comparison of stepped, stratified, and matched care. 2018;159(12):2437-2441.

[56] Mansour RA, Baliki NM, Huang ML, Torbey JS, Herrmann AK, Schnitzer AT, Apkarian AV. Brain white matter structural properties predict transition to chronic pain. Pain 2013;154(10):2160-2168.

[57] Mata J, Thompson RJ, Gotlib IH. BDNF genotype moderates the relation between physical activity and depressive symptoms. Health psychology 2010;29(2):130.

[58] McBeth J, Silman AJ, Gupta A, Chiu Y, Ray D, Morriss R, Dickens C, King Y, Macfarlane GJA, Rheumatism. Moderation of psychosocial risk factors through dysfunction of the hypothalamic–pituitary–adrenal stress axis in the onset of chronic widespread musculoskeletal pain: findings of a population-based prospective cohort study. 2007;56(1):360-371.

[59] Mills KR, Boniface SJ, Schubert M. Magnetic brain stimulation with a double coil: the importance of coil orientation. Electroencephalography and clinical neurophysiology / Evoked potentials section 1992;85(1):17-21.

[60] Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Annals of internal medicine 2015;162(1):W1-W73.

[61] Moons KG, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallett S. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. Annals of internal medicine 2019;170(1):1-33.

[62] Müller M, Curatolo M, Limacher A, Neziri AY, Treichel F, Battaglia M, Arendt-Nielsen L, Jüni P. Predicting transition from acute to chronic low back pain with quantitative sensory tests - a prospective cohort study in the primary care setting. European journal of pain 2019;23 (5):894-907.

[63] Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. European journal of pain 2007;11(2):153-163.

[64] O'Connell NE, Maskill DW, Cossar J, Nowicky AV. Mapping the cortical representation of the lumbar paravertebral muscles. Clinical Neurophysiology 2007;118(11):2451-2455.

[65] O'connell NE, Maskill DW, Cossar J, Nowicky AV. Mapping the cortical representation of the lumbar paravertebral muscles. Clinical Neurophysiology 2007;118(11):2451-2455.

[66] Oliveira VC, Ferreira PH, Maher CG, Pinto RZ, Refshauge KM, Ferreira ML. Effectiveness of self-management of low back pain: Systematic review with meta-analysis. Arthritis care & research 2012;64(11):1739-1748.

[67] Patel S, Friede T, Froud R, Evans DW, Underwood MJS. Systematic review of randomized controlled trials of clinical prediction rules for physical therapy in low back pain. 2013;38(9):762-769.

[68] Pereira LM, Obara K, Dias JM, Menacho MO, Guariglia DA, Schiavoni D, Pereira HM, Cardoso JR. Comparing the Pilates method with no exercise or lumbar stabilization for pain and functionality in patients with chronic low back pain: systematic review and meta-analysis. Clinical Rehabilitation 2012;26(1):10-20.

[69] Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR. The brain-derived neurotrophic factor

val66met polymorphism and variation in human cortical morphology. Journal of Neuroscience 2004;24(45):10099-10102.

[70] Picton T, Bentin S, Berg P, Donchin E, Hillyard S, Johnson Jr R, Miller G, Ritter W, Ruchkin D, Rugg M. Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. Psychophysiology 2000;37(2):127-152.

[71] Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine 2002;27(5):E109-E120.

[72] Riley RD, Hayden JA, Steyerberg EW, Moons KG, Abrams K, Kyzas PA, Malats N, Briggs A, Schroter S, Altman DG. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. PLoS medicine 2013;10(2):e1001380.

[73] Riley RD, Hayden JA, Steyerberg EW, Moons KG, Abrams K, Kyzas PA, Malats N, Briggs A, Schroter S, Altman DGJPm. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. 2013;10(2):e1001380.

[74] Roland M, Morris R. A Study of the Natural History of Back Pain: Part IDevelopment of a Reliable and Sensitive Measure of Disability in Low-Back Pain. spine 1983;8(2):141-144.

[75] Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain: an update of a Cochrane review. Spine 2011;36(13):E825-E846.

[76] Schabrun MS, Elgueta-Cancino LE, Hodges WP. Smudging of the Motor Cortex Is Related to the Severity of Low Back Pain. SPINE 2017;42(15):1172-1178.

[77] Schabrun SM, Burns E, Hodges PW. New Insight into the Time-Course of Motor and Sensory System Changes in Pain.(Report). 2015;10(11).

[78] Schabrun SM, Elgueta-Cancino EL, Hodges PW. Smudging of the motor cortex is related to the severity of low back pain. Spine 2017;42(15):1172-1178.

[79] Schabrun SM, Jones E, Elgueta Cancino EL, Hodges PW. Targeting Chronic Recurrent Low Back Pain From the Top-down and the Bottom-up: A Combined Transcranial Direct Current Stimulation and Peripheral Electrical Stimulation Intervention. Brain Stimulation 2014;7(3):451-459.

[80] Schabrun SM, Jones E, Elgueta Cancino EL, Hodges PW. Targeting Chronic Recurrent Low Back Pain From the Top-down and the Bottom-up: A Combined Transcranial Direct Current Stimulation and Peripheral Electrical Stimulation Intervention. Brain stimulation 2014.

[81] Shyh-Yuh W, Hsiang-Tai C, Cheng-Hao T, Ming-Wei L, Wei-Chi L, Intan L, Horng-Der S, Li-Fen C, Jen-Chuen H. The BDNF Val66Met polymorphism is associated with the functional connectivity dynamics of pain modulatory systems in primary dysmenorrhea. Scientific Reports 2016;6(1).

[82] Stanton T, Henschke N, Maher CG, Refshauge K, Latimer J, McAuley J. After an Episode of Acute Low Back Pain, Recurrence Is Unpredictable and Not as Common as Previously Thought. Spine 2008;33(26):2923-2928.

[83] Stanton TR, Hancock MJ, Maher CG, Koes BWJPT. Critical appraisal of clinical prediction rules that aim to optimize treatment selection for musculoskeletal conditions. 2010;90(6):843-854.

[84] Stef van B, Karin G-O. mice : Multivariate Imputation by Chained Equations in R. Journal of Statistical Software 2011;45(3).

[85] Steyerberg EW, Moons KG, van der Windt DA, Hayden JA, Perel P, Schroter S, Riley RD, Hemingway H, Altman DG, Group P. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. PLoS medicine 2013;10(2):e1001381.

[86] Sullivan M, Bishop S, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychological Assessment 1995;7(4):524.

[87] Tibshirani R. Regression Shrinkage and Selection Via the Lasso. Journal of the Royal Statistical Society: Series B (Methodological) 1996;58(1):267-288.

[88] Traeger AC, Henschke N, Hübscher M, Williams CM, Kamper SJ, Maher CG, Moseley GL, McAuley JH. Estimating the risk of chronic pain: development and validation of a prognostic model (PICKUP) for patients with acute low back pain. PLoS medicine 2016;13(5):e1002019.

[89] Tsao AH, Danneels WL, Hodges WP. ISSLS Prize Winner: Smudging the Motor Brain in Young Adults With Recurrent Low Back Pain. Spine 2011;36(21):1721-1727.

[90] Tsao H, Danneels LA, Hodges PW. ISSLS prize winner: Smudging the motor brain in young adults with recurrent low back pain. Spine (Phila Pa 1976) 2011;36(21):1721-1727.

[91] Tsao H, Galea MP, Hodges PW. Driving plasticity in the motor cortex in recurrent low back pain. European Journal of Pain 2010;14(8):832-839.

[92] Uy J, Ridding M, Miles T. Stability of Maps of Human Motor Cortex Made with Transcranial Magnetic Stimulation. Brain Topogr 2002;14(4):293-297.

[93] van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. 2011 2011;45(3):67.

[94] van de Ruit M, Grey MJ. Interindividual variability in use-dependent plasticity following visuomotor learning: The effect of handedness and muscle trained. Journal of motor behavior 2019;51(2):171-184.

[95] Van de Ruit ML. Rapid assessment of corticospinal excitability using transcranial magnetic stimulation: University of Birmingham, 2016.

[96] Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. American journal of epidemiology 2007;165(6):710-718.

[97] Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abdulkader RS, Abdulle AM, Abebo TA, Abera SF. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet 2017;390(10100):1211-1259.

[98] Wassermann EM, McShane LM, Hallett M, Cohen LG. Noninvasive mapping of muscle representations in human motor cortex. Electroencephalography and clinical neurophysiology 1992;85(1):1-8.

[99] Williams CM, Maher CG, Latimer J, McLachlan AJ, Hancock MJ, Day RO, Lin C-WC. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. The Lancet 2014;384(9954):1586-1596.

[100] Woodman GF. A brief introduction to the use of event-related potentials in studies of perception and attention. Attention, Perception, & Psychophysics 2010;72(8):2031-2046.

Figure 1. Example of a sensory evoked potential (SEP) recorded from the paraspinal muscles (average of 500 traces) from a single participant. **Figure 1A** shows the N_{80}, N_{150} and P_{260} SEP peaks. **Figure 1B** shows the area under the rectified curve for each time epoch (N_{80}, N_{150} and P_{260} area) that was used for analysis.

Figure 2. Study flow chart.

*defined as LBP lasting for longer than 6 weeks and/or an LBP episode preceded by a period of less than one-month without pain.

Figure 3. Motor cortical maps for two representative participants at the L3 recording site normalized to peak motor evoked potential (MEP) amplitude. **Figure 3A** displays large volume corticomotor excitability during acute low back pain (LBP) in a participant who was recovered at 6-months. **Figure 3B** displays small volume corticomotor excitability during acute LBP in another participant who experienced chronic/recurrent LBP at 6-months. The dashed lines indicate the location of the vertex (coordinate 0,0). The coloured scale represents the proportion of the maximum MEP amplitude. Warmer colours represent higher excitability.

Figure 4. Sensory evoked potentials (SEP) recorded in response to stimuli to the paraspinal muscles at baseline (average of approx. 500 traces) for two representative participants. The black trace displays high SEP excitability in the acute stage of low back pain (LBP) in a participant who was recovered at 6-months. The red trace displays low sensory evoked potential excitability in the acute stage of LBP in a participant who reported LBP at 6-months.

Table 1. Reporting key clinical characteristics of participants at baseline, compared between those with (N = 52) or without (N = 44) low back pain (LBP) at six months.

	Low back pain present at six months		
Characteristic at baseline	**Yes (N = 52)**	**No (N = 44)**	***P*-Value**
Age, years (mean ± SD)	39 (15)	40 (17)	0.82
Sex: Female, n (%)	30 (57.7)	21 (47.7)	0.3
Body mass index, kg/m^2 (mean ± SD) [#]	26.5 (6.6)	25.3 (4.7)	0.34
Pain below gluteal fold: No, n (%)	31 (62.0)	36 (83.7)	**0.02**
Inciting event: No, n (%)	19 (36.5)	14 (32.6)	0.69
Compensable injury/sickness benefits: No, n (%)	48 (92.3)	44 (100.0)	0.06
Previous history of LBP: No, n (%)	13 (25.0)	9 (20.5)	0.87
STarTBack Risk Score, n (%)			
Low	32 (62.7)	34 (79.1)	0.06
Medium	14 (27.5)	9 (20.9)	
High	5 (9.8)	0 (0.0)	
Comorbid health conditions, n (%)			
None	33 (66.0)	32 (72.7)	0.48
Heart Disease/Hypertension	7 (14.0)	3 (6.8)	0.26
Lung disease	2 (4.0)	1 (2.3)	0.64
Diabetes	2 (4.0)	0 (0.0)	0.18
Ulcer or stomach disease	3 (6.0)	1 (2.3)	0.37
Kidney disease	0 (0.0)	0 (0.0)	NA
Depression/Anxiety	4 (8.0)	5 (11.4)	0.58
Cancer	0 (0.0)	1 (2.3)	0.28
Anaemia or other blood disease	1 (2.0)	1 (2.3)	0.93
Osteoarthritis	3 (6.0)	2 (4.5)	0.75
Inflammatory arthropathy	1 (2.0)	0 (0.0)	0.35
Stroke or other neurological condition	0 (0.0)	0 (0.0)	NA
Other medical problems	4 (8.0)	3 (6.8)	0.83
Medication use, n (%)			
None	26 (50.0)	20 (45.5)	0.66
Not pain-related	14 (26.9)	14 (31.8)	0.60
NSAID	9 (17.3)	4 (9.1)	0.24
Acetaminophen	9 (17.3)	5 (11.4)	0.41

Opioid	4 (7.7)	2 (4.5)	0.53
Benzodiazepine	3 (5.8)	0 (0.0)	0.11
Anti-depressant	3 (5.8)	4 (9.1)	0.53
Anti-convulsant	2 (3.8)	1 (2.3)	0.66
Healthcare Utilization, (mean±SD)			
General practitioner [#]	0.8 (1.6)	0.2 (0.5)	**0.02**
Allied health	1.3 (2.4)	1.4 (2.9)	0.83
Diagnostic tests	0.2 (0.5)	0.1 (0.4)	0.39
21-Item Depression, Anxiety, Stress Scale (mean±SD)			
Depression [#]	8.4 (9.6)	2.5 (3.2)	**< 0.001**
Anxiety [#]	5.5 (5.4)	2.3 (3.0)	**< 0.01**
Stress [#]	13.1 (10.2)	5.2 (5.0)	**< 0.001**
Pain Catastrophizing Scale (mean±SD)			
Rumination [#]	4.4 (4.2)	2.2 (2.5)	**< 0.01**
Magnification [#]	3.2 (3.0)	1.6 (2.0)	**< 0.01**
Helplessness [#]	5.7 (5.3)	3.2 (3.3)	**< 0.01**
Pain Self Efficacy Questionnaire (mean±SD)	43.8 (13.4)	51.9 (10.0)	**< 0.01**
Roland-Morris Disability Questionnaire (mean±SD)	7.0 (4.9)	4.2 (3.5)	**< 0.01**
Average pain intensity past week, NRS (mean±SD)	5.0 (1.9)	3.3 (1.8)	**< 0.001**
Worst pain intensity past week, NRS (mean±SD)	6.7 (2.1)	5.9 (1.8)	0.07
Pain Interference, NRS (mean±SD)			
General activity	5.0 (2.8)	3.7 (2.7)	**0.03**
Mood	4.8 (2.8)	3.0 (2.7)	**< 0.01**
Walking ability [#]	3.7 (3.2)	2.7 (2.5)	0.08
Normal work	4.6 (3.0)	3.2 (2.7)	**0.02**
Relations with other people [#]	2.8 (3.2)	1.3 (1.9)	**0.01**
Sleep [#]	4.9 (3.2)	2.8 (2.4)	**< 0.001**
Enjoyment of life	3.9 (2.8)	2.6 (2.7)	**0.02**

Variable means were compared between participants with, or without LBP at six-months using t tests (continuous variable) or X^2 tests (categorical variables).

[#] Welch's t test was performed. [$] Other comorbid health conditions include Meniere's disease/Vestibular migraine, T5-T8 thoracic compression fracture, endometriosis, hypothyroidism, pituitary microadenoma/prolactinoma, repetitive strain injury wrists, obstructive sleep apnoea.

Statistically significant values are in bold font.

LBP – low back pain; NRS – numerical rating scale; NSAID – non-steroidal anti-inflammatory drug.

Table 2. Missing data within candidate predictor variables.

Candidate Predictor	Number of missing data (%)	Reason
SEP N_{80} component area (μV) SEP N_{150} component area (μV) SEP P_{260} component area (μV)	2 (2%) 2 (2%) 2 (2%)	Equipment failure
L3 map volume (cm^2) L5 map volume (cm^2) L3/L5 centre of gravity overlap (cm)	31 (25.8%) 31 (25.8%) 31 (25.8%)	Unresolvable noise to signal ratio (N = 5) Consent not obtained (N = 13) Participant unable to tolerate (N = 7) Equipment failure (N = 6)
BDNF genotype (0 = AA/AG, 1 = GG) BDNF serum concentration (ng/mL)	0 (0%) 30 (25%)	Researcher error during phlebotomy (N = 10) Consent not obtained (N = 11) Simple plex Ella™ machine error (N = 9)
PCS (0 – 52 scale) DASS-21 (0 – 63 scale) PSEQ (0 – 60 scale)	2 (2%) 7 (5.8%) 3 (2.5%)	Incorrect completion of questionnaire
NRS score at T1 (0-10 scale) Previous history of low back pain (0 = no, 1 = yes)	2 (2%) 4 (3%)	Incorrect completion of questionnaire
Age (years Sex (0 = female, 1 = male)	0 (0%) 0 (0%)	N/A

BDNF, brain-derived neurotrophic factor; DASS-21, Depression, Anxiety and Stress Scale; L3, electrode recording site 3cm lateral to the L3 spinous process; L5, electrode recording site 1cm lateral to the L5 spinous process; PCS, Pain Catastrophising Scale; PSEQ, Pain Self-Efficacy Questionnaire; SEP, sensory evoked potential; T1, within 6 weeks of acute low back pain onset; NRS, 11-point numerical rating scale. All variables were treated as continuous, with the exception of sex, previous history of low back pain and BDNF genotype.

Table 3. Candidate predictors selected 'a priori' and compared between participants, with (N = 52) or without (N = 44) low back pain (LBP) at six months.

Statistically significant values in bold font; Values are numbers (%), means (SD), unadjusted odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs), and p□values from univariable logistic regression models. Values for each baseline characteristic are calculated from raw data. Odds ratio and P-Values are pooled following multiple imputation. The odds ratio is the increase in odds per unit increase in the predictor. AA/AG - G allele encodes Val, A allele encodes Met; BDNF – brain derived

	Low back pain present at six months			
Characteristic at baseline	**Yes (N = 52)**	**No (N = 44)**	**OR (95% CI)**	***P***
Gender: Female (%)	30 (58)	21 (48)	0.73 (0.34 – 1.58)	0.42
Previous history of LBP: No (%)	13 (25)	9 (20)	0.71 (0.27 – 1.86)	0.48
BDNF genotype: AA/AG (%)	23 (44)	12 (27)	0.42 (0.18 – 0.99)	**0.05**
L3 map volume (cm^2)	7.0 (3.0)	9.9 (4.0)	0.88 (0.78 – 1.00)	**0.05**
L5 map volume (cm^2)	7.5 (3.3)	8.3 (3.2)	0.96 (0.85 – 1.08)	0.49
L3/L5 CoG Overlap (cm)	0.5 (0.5)	0.8 (0.6)	0.54 (0.26 – 1.14)	0.10
Log-transformed N_{80} area (μV)	-3.4 (1.4)	-1.9 (1.3)	0.49 (0.35 – 0.68)	< **0.001**
Log-transformed N_{150} area (μV)	-3.2 (1.3)	-1.9 (1.3)	0.50 (0.36 – 0.70)	< **0.001**
Log-transformed P_{260} area (μV)	-3.1 (1.2)	-1.8 (1.4)	0.50 (0.35 – 0.71)	< **0.001**
BDNF serum concentration (ng/mL)	52.1 (12.2)	50.7 (12.5)	1.00 (1.00 – 1.00)	0.39
PCS (0 – 52 scale)	13.6 (11.7)	7.0 (7.0)	1.07 (1.02 – 1.13)	**0.01**
DASS-21 (0 – 63 scale)	26.9 (22.0)	10.1 (8.2)	1.06 (1.02 – 1.10)	**0.01**
PSEQ (0 – 60 scale)	43.5 (13.5)	51.0 (9.1)	0.95 (0.91 – 0.99)	**0.01**
Average baseline pain intensity (0-10 scale)	5.0 (1.9)	3.3 (1.8)	1.57 (1.22 – 2.01)	< **0.001**
Age (years)	39 (15)	40 (17)	1.00 (0.97 – 1.02)	0.92

neurotrophic factor; CoG – centre of gravity; DASS – depression, anxiety, stress subscale; NRS – numerical rating scale; PCS – pain catastrophizing scale; PSEQ – pain self-efficacy questionnaire.

Characteristic	Completed follow-up (N = 96)	Did not complete follow-up (N = 24)	P-value
Gender: Female (%)	53.1	33.3	0.08
Previous history of LBP: No (%)	22.9	12.5	0.32
BDNF genotype: AA/AG (%)	36.5	54.2	0.11
L3 map volume (cm^2)	8.4 (4.0)	10.0 (5.5)	0.13
L5 map volume (cm^2)	7.8 (3.5)	8.5 (4.2)	0.43
L3/L5 CoG Overlap (cm)	0.7 (0.6)	0.5 (0.4)	0.21
Log-transformed N_{80} area (μV)	-1.2 (0.7)	-1.5 (0.6)	0.06
Log-transformed N_{150} area (μV)	-1.1 (0.6)	-1.4 (0.6)	**0.04**
Log-transformed P_{260} area (μV)	-1.1 (0.6)	-1.4 (0.6)	**0.03**
BDNF serum concentration (ng/mL)	52.2 (13.7)	50.9 (13.7)	0.71
PCS (0 – 52 scale)	10.6 (10.3)	12.6 (8.9)	0.35
DASS-21 (0 – 63 scale)	19.1 (19.3)	27.2 (24.7)	0.17
PSEQ (0 – 60 scale)	47.1 (12.1)	42.5 (11.5)	0.10
Average baseline pain intensity (0-10 scale)	4.2 (2.0)	4.6 (1.3)	0.37
Age (years)	40 (16)	40 (12)	0.91

Table 4. Comparison of candidate predictors selected 'a priori' and compared between participants who did, and did not, complete six-month follow-up.

Statistically significant values in bold font; Values are numbers (%), means (SD) compared between low back pain (LBP) participants who did, and did not follow-up, at 6 months follow-up using t tests (continuous data, normally distributed) or Fishers exact test (categorical data). All values are calculated from raw data. AA/AG - G allele encodes Val, A allele encodes Met; BDNF – brain derived neurotrophic factor; CoG – centre of gravity; DASS – depression, anxiety, stress subscale; NRS – numerical rating scale; LBP – low back pain; PCS – pain catastrophizing scale; PSEQ – pain self-efficacy questionnaire.

Table 5. Spearman's correlation coefficients between measures of cortical excitability during acute low back pain.

	L3 map volume (cm^2)	L5 map volume (cm^2)	Log-transformed N_{80} area (µV)	Log-transformed N_{150} area (µV)	Log-transformed P_{260} area (µV)	L3/L5 CoG Overlap (cm)
L3 map volume (cm^2)	-	0.82**	0.02	0.07	0.07	-0.15
L5 map volume (cm^2)		-	-0.05	-0.06	-0.02	-0.29**
Log-transformed N_{80} area (µV)			-	0.84**	0.85**	0.20
Log-transformed N_{150} area (µV)				-	0.90**	0.21*
Log-transformed P_{260} area (µV)					-	0.20
L3/L5 CoG Overlap (cm)						-

All values are calculated from raw data. ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Table 6. Hierarchical linear regression model predicting six-month pain intensity.

Variables entered		**R^2**	**Adjusted R^2**	**Significance of Adjusted R^2 change**	**B (95% CI) (final model)**	**Significance of B**
Step 1	Average baseline pain intensity (0-10 scale)	0.22	0.22		0.33 (0.17 to 0.48)	**< 0.001**
Step 2	DASS-21 (0 – 63 scale)				0.14 (-0.13 to 0.41)	0.31
	PCS (0 – 52 scale)	0.32	0.30	**0.01**	0.10 (-0.13 to 0.35)	0.39
Step 3	L3 map volume (cm^2)				-0.29 (-0.48 to -0.10)	**< 0.01**
	Log-transformed N_{80} area (μV)	0.47	0.44	**< 0.01**	-0.25 (-0.42 to -0.07)	**0.01**

Statistically significant *P*-values in bold font. Hierarchical linear regression was performed with six-month pain intensity as the dependent variable. Predictors identified from the λ-1se variable selection procedure were entered into the model. Step 1 included average baseline pain intensity, step 2 included psychological risk factors and step 3 included measures of sensorimotor cortical excitability. The significance of the adjusted R^2 change was calculated using a one-way ANOVA. All results reported in this table are pooled across the imputed datasets. B – unstandardized beta coefficient; CI – confidence interval; DASS-21 – 21 item depression, anxiety, stress subscale; PCS – pain catastrophizing scale.

Table 7. Multivariate logistic prediction model of risk of low back pain at six months.

Predictor	**B**	**Odds Ratio (95% CI)**	**Significance of B**
Log-transformed N_{80} area (μV)	-0.79	0.45 (0.27 to 0.75)	< **0.01**
L3 map volume (cm^2)	-0.21	0.81 (0.65 to 1.01)	0.07
BDNF genotype (0 = AA/AG, 1 = GG)	-0.87	0.41 (0.10 to 1.69)	0.22
DASS-21 (0 – 63 scale)	0.07	1.07 (1.02 to 1.23)	**0.01**
Average baseline pain intensity (0-10 scale)	0.54	1.71 (1.17 to 2.50)	**0.01**
Previous history of LBP (0 = no, 1 = yes)	-1.29	0.27 (0.05 – 1.61)	0.15

Statistically significant values in bold font. All results reported in this table are pooled across the imputed datasets. The odds ratio is the increase in odds per unit increase in the predictor. AA/AG - G allele encodes Val, A allele encodes Met; B – unstandardized beta coefficient; BDNF – brain derived neurotrophic factor; CI – confidence interval; DASS-21 – 21 item depression, anxiety, stress subscale; GG – G allele encodes Val; LBP – low back pain.

Figure 1.

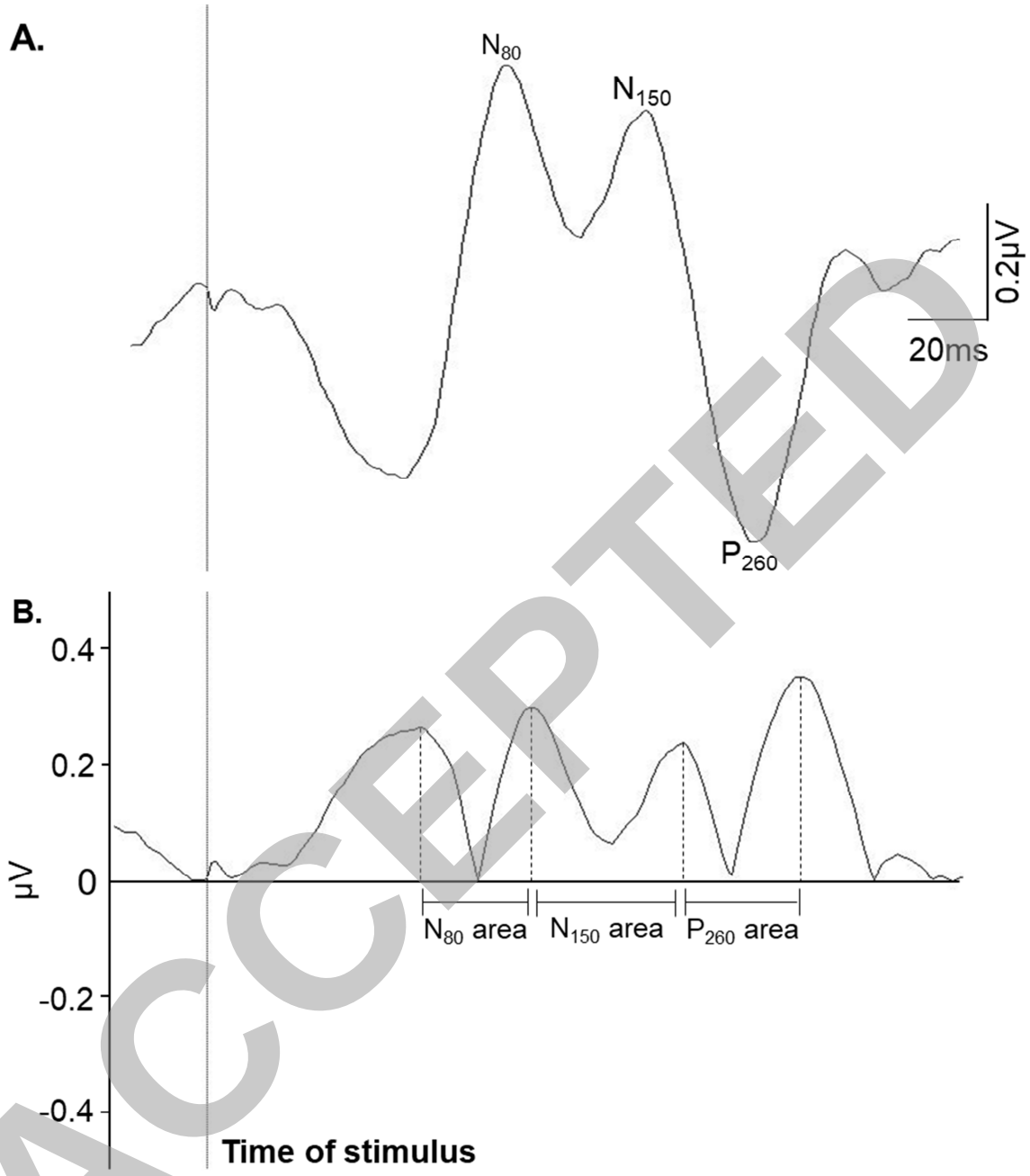

Figure 2.

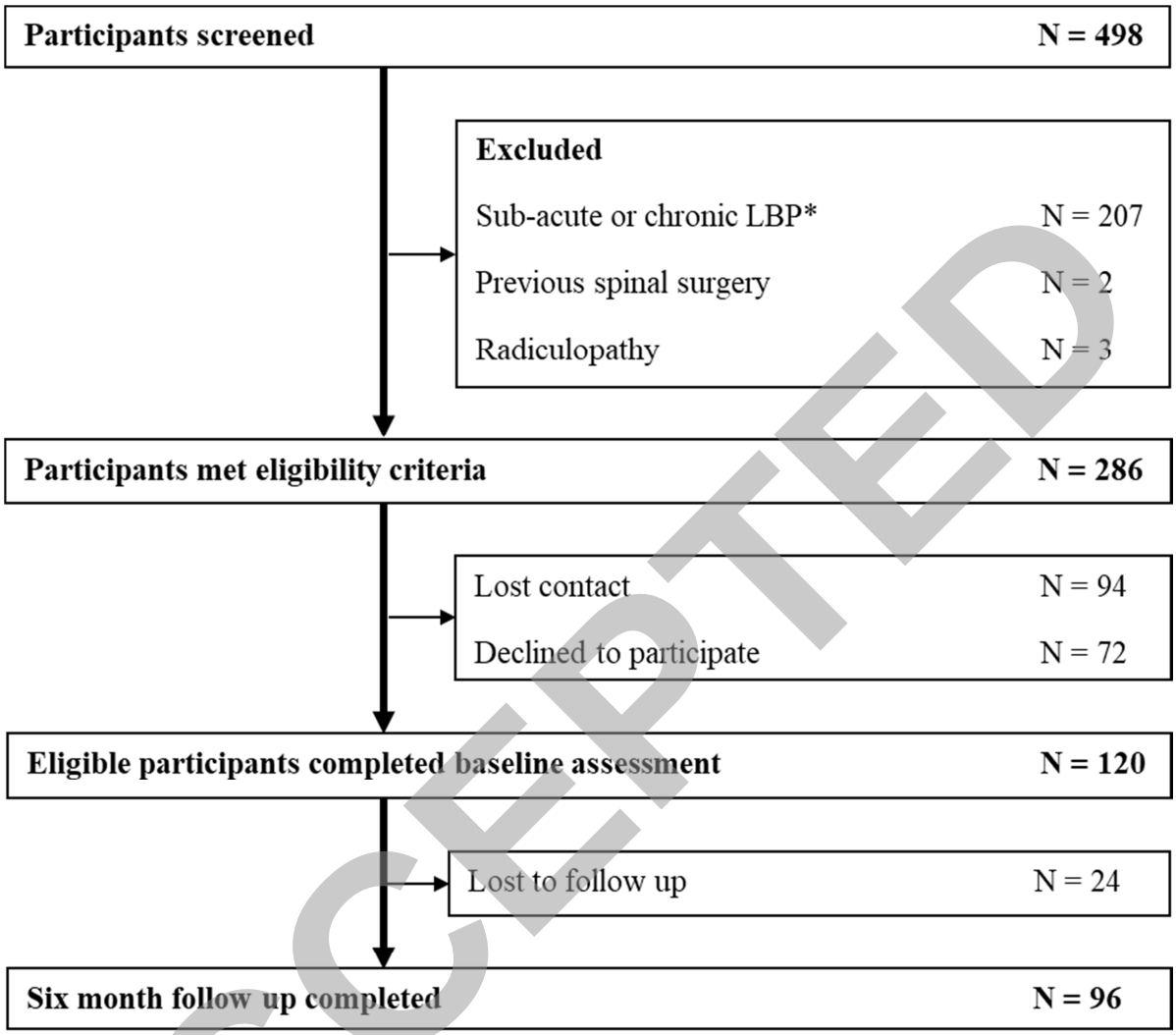

Figure 3.

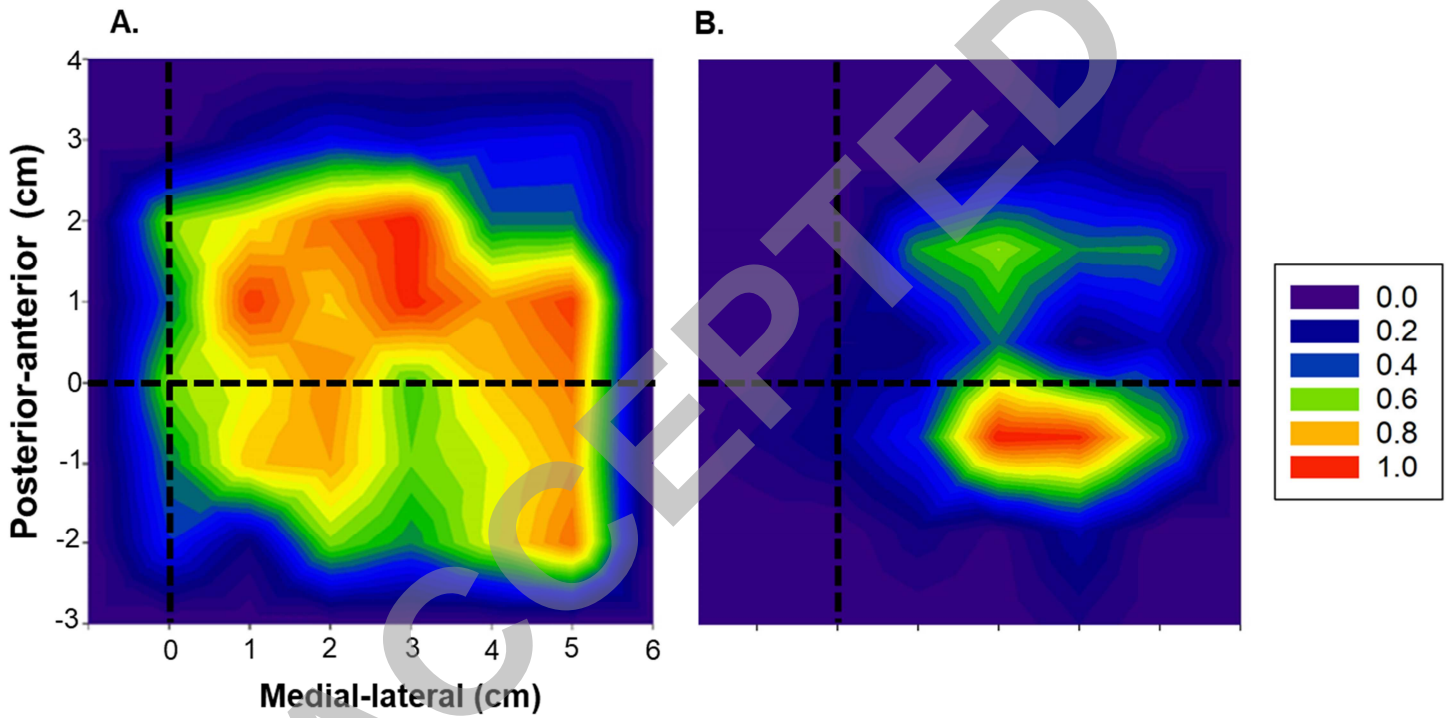

Figure 4.