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Differences in brain processing of proprioception related to postural control in patients with recurrent non-specific low back pain and healthy controls

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ABSTRACT

Patients with non-specific low back pain (NSLBP) show an impaired postural control during standing and a slower performance of sit-to-stand-to-sit (STSTS) movements. Research suggests that these impairments could be due to an altered use of ankle compared to back proprioception. However, the neural correlates of these postural control impairments in NSLBP remain unclear. Therefore, we investigated brain activity during ankle and back proprioceptive processing by applying local muscle vibration during functional magnetic resonance imaging in 20 patients with NSLBP and 20 controls. Correlations between brain activity during proprioceptive processing and (Airaksinen et al., 2006) proprioceptive use during postural control, evaluated by using muscle vibration tasks during standing, and (Altmann et al., 2007) STSTS performance were examined across and between groups. Moreover, fear of movement was assessed. Results revealed that the NSLBP group performed worse on the STSTS task, and reported more fear compared to healthy controls. Unexpectedly, no group differences in proprioceptive use during postural control were found. However, the relationship between brain activity during proprioceptive processing and behavioral indices of proprioceptive use differed significantly between NSLBP and healthy control groups. Activity in the right amygdala during ankle proprioceptive processing correlated with an impaired proprioceptive use in the patients with NSLBP, but not in healthy controls. Moreover, while activity in the left superior parietal lobule, a sensory processing region, during back proprioceptive processing correlated with a better use of proprioception in the NSLBP group, it was associated with a less optimal use of proprioception in the control group. These findings suggest that functional brain changes during proprioceptive processing in patients with NSLBP may contribute to their postural control impairments.

1. Introduction

Low back pain is a highly prevalent health condition, and the leading cause of disability worldwide (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Approximately 90–95% of patients with low back pain are diagnosed with 'non-specific low back pain' (NSLBP), as their pain cannot be attributed to a specific pathoanatomical cause, such as a vertebral fracture, infection, spondyloarthropathy or radicular pain (Airaksinen, 2006; Koes et al., 2006). This suggests that functional and psychosocial mechanisms (e.g., fear of movement), rather than structural pathology, more likely drive the development and recurrence of NSLBP (Lewis and O'Sullivan, 2018).

Recent reviews have reported that patients with NSLBP show impaired postural control during complex conditions, e.g., during standing on unstable support surfaces with eyes closed (Berenshteyn et al., 2018; Mazaheri et al., 2013). During such complex conditions, proprioceptive reweighting - the process by which the central nervous system (CNS) dynamically adjusts the weight assigned to proprioceptive signals - becomes crucial (Carver et al., 2006; Peterka, 2002). Standing on an unstable support surface, for instance, reduces the reliability of ankle proprioception (Ivanenko et al., 1999; Kiers et al., 2012), forcing the CNS to reduce the weight assigned to ankle proprioception, while increasing the weight given to proprioceptive signals from other body segments including the lower back (Brumagne et al., 2004; Kiers et al.,

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2012). However, studies have demonstrated that patients with NSLBP show a poorer ability for proprioceptive reweighting; they predominantly rely on ankle proprioception, regardless of the postural condition, and are less able to up-weigh back proprioception when needed (Brumagne et al., 2008; Claeys et al., 2011). Interestingly, this dominant use of ankle over back proprioception was identified as a risk factor for the development and recurrence of mild NSLBP in young adults (Claeys et al., 2015). In addition to having a negative influence on static postural control, a reduced ability for proprioceptive reweighting in patients with NSLBP was also demonstrated to affect dynamic postural control; they needed more time to perform five sit-to-stand-to-sit (STSTS) movements (Claeys et al., 2012). Yet, little is known about the mechanisms underlying a reduced ability for proprioceptive reweighting in NSLBP. An optimal ability for proprioceptive reweighting depends on peripheral factors, such as the sensitivity of muscle spindles, and central aspects, more specifically the neural processing of afferent signals from these muscle spindles (Brumagne et al., 2004; Eklund, 1972). In this study, we focused on the latter.

To date, several neuroimaging studies examined neural correlates of postural control impairments in NSLBP. Jacobs et al. (2011) revealed that longer movement times and reduced hip extension during STSTS in individuals with experimentally-induced back pain correlated with the contingent negative variation, a brain potential containing cognitive and motor components. However, neural alterations in individuals with induced back pain may not be generalized to patients with clinical NSLBP. Moreover, previous studies from our research group shed a first light on the relationship between structural brain changes and postural control deficits in patients with NSLBP. Specifically, we demonstrated that a slower STSTS performance in NSLBP correlated with a cortical thinning of the anterior cingulate cortex and a decreased global efficiency of information transfer across white matter pathways (Caeyenberghs et al., 2017; Pijnenburg et al., 2016). Moreover, a poorer ability for proprioceptive reweighting during standing was associated with a reduced microstructural integrity of the superior cerebellar peduncle in subjects with NSLBP (Pijnenburg et al., 2014). However, it remains unclear whether subjects with NSLBP also show functional brain alterations during the 'direct' processing of proprioception.

The neural processing of proprioception can be investigated by applying muscle vibration, a strong proprioceptive stimulus (Roll and Vedel, 1982; Roll et al., 1989), during task-related fMRI. This vibration paradigm has been used extensively to examine ankle proprioceptive processing in healthy young adults (Cignetti et al., 2014; Fontan et al., 2017; Naito et al., 2007) and healthy elderly (Goble et al., 2011; Goble et al., 2012), revealing the involvement of various sensorimotor brain areas (e.g. primary sensorimotor cortices), subcortical regions (e.g., thalamus, putamen), and fronto-parietal cortices (e.g., inferior frontal gyrus (IFG), inferior parietal lobule). Moreover, by using this paradigm, Goble et al. (2011) revealed that healthy individuals showing increased ankle proprioception-related brain activity in the right primary motor cortex (M1), right fronto-parietal cortices and subcortical regions (right putamen and bilateral insula) performed better on a proprioceptively demanding balance test. Yet, so far, no studies investigated brain activity patterns during ankle proprioceptive processing in patients with NSLBP.

Moreover, to our best knowledge, only one research group examined brain activity during mechanosensory stimulation at the lower back, revealing activation in primary and secondary somatosensory cortices (S1, S2), cingulate cortex and anterior cerebellum in healthy individuals (Boendermaker et al., 2014; Meier et al., 2014), and a reduced activation and reorganization of S2 in patients with NSLBP (Hotz-Boendermaker et al., 2016). In these studies, mechanoreceptors within the spine's musculoskeletal structures (e.g., ligaments, muscles, joints) were stimulated by inducing intervertebral movements with manual pressure. However, no correction for the simultaneous activation of tactile receptors was applied. Moreover, the clinical consequences of the observed differences in back proprioception-related brain activity in patients with NSLBP remained elusive, as no associations with for instance postural control were explored (Hotz-Boendermaker et al., 2016).

Therefore, the first aim of this study was to compare brain activity during ankle and back proprioceptive stimulation (muscle vibration) between patients with NSLBP and matched healthy controls. We hypothesized that patients with NSLBP show increased brain activity in sensorimotor (e.g., S1, M1), subcortical (right putamen, thalamus) and inferior fronto-parietal regions (IFG, inferior parietal lobule) during the stimulation of ankle proprioception. Moreover, we expected that patients with NSLBP would show reduced brain activity in S2 during back proprioceptive stimulation compared to healthy controls. Finally, we investigated whether individuals with NSLBP showed increased brain activity in fear-related brain areas, such as the amygdala, during proprioceptive stimulation at the lower back in particular, because pain-related fear of movement is common in patients with NSLBP (Vlaeyen and Crombez, 1999). The second aim of this study was to investigate the relationship between differences in brain activity during proprioceptive processing and postural control (i.e., the use of proprioception during standing, STSTS performance) in patients with NSLBP. This would elucidate whether the hypothesized patterns of increased brain activity during ankle proprioceptive processing in NSLBP reflect (Airaksinen et al., 2006) a generalized, non-functional spread of neural activity due to a loss of neural specialization during proprioceptive processing (i.e., "dedifferentiation") or (Altmann et al., 2007) a compensatory increase in brain activity that supports postural control (Carp et al., 2011; Heuninckx et al., 2008; Ward and Frackowiak, 2003). Moreover, correlation analyses would elucidate whether the expected decrease in brain activity during the processing of back proprioception in S2 in patients with NSLBP is associated with static and dynamic postural control impairments.

2. Materials and methods

2.1. Ethics statement

This study conformed to the principles of the Declaration of Helsinki (1964). The protocol was approved by the Ethics Committee Research UZ/KU Leuven, Belgium (s53802) and registered at clinicaltrials.gov with identification number NCT03097718. All subjects provided written informed consent prior to participation.

2.2. Participants

Twenty individuals with NSLBP and 20 age- and gender-matched healthy individuals, aged 21–39 years, voluntarily participated in this study. Participants were recruited between March 2016 and December 2017 in local private general medical and physiotherapy practices, sport clubs, campuses of the KU Leuven, and the University Hospital Leuven. To be eligible, subjects had to be right-handed and aged 20–45 years. Patients with NSLBP were included if they had experienced NSLBP over a course of ≥ one year, reported ≥ three NSLBP episodes, and were moderately disabled due to their pain (≥18% on the Oswestry Disability Index, Adapted Dutch version 2.1a, ODI-2) (Fairbank and Pynsent, 2000; van Hooff et al., 2015). The ODI-2 is a questionnaire that assesses the perceived level of disability due to low back pain during ten daily life activities, such as walking, sitting, standing and participating in social activities. For each activity, six statements are provided that describe possible scenarios related to the activity, with the first statement indicating the least amount of disability (scored as '0') and the sixth statement representing most severe disability (scored as '5'). Participants indicate which statement resembles their situation the most, after which scores are summed and doubled to attain a percentage score (Fairbank and Pynsent, 2000). Healthy individuals were included if they had no history of low back pain and scored 0% on the ODI-2. Exclusion criteria across groups were:

(Airaksinen et al., 2006) reporting contraindications for fMRI, (Altmann et al., 2007) having a history of major trauma and/or surgery to the spine or lower limbs, (Amemiya and Naito, 2016) having specific vestibular and/or balance problems, significant neck pain and/or acute lower limb problems, (Andersen et al., 1999) having (a history of) neurological or cardiovascular disorders, (Andersen et al., 2003) using opioids or antidepressants and (Ashburner and Friston, 2005) experiencing claustrophobia.

After inclusion, participants completed the Physical Activity Index (PAI), which assessed their physical activity levels during work, sports and leisure time (Baecke et al., 1982). Finally, patients with NSLBP rated their low back pain (i) as experienced on the test day and (ii) on average during the past week on a Numerical Rating Scale (NRS, anchored with 0 = "no pain" and 10 = "worst pain imaginable"). Group differences in participants' characteristics were tested with two-sample *t*-tests and Mann-Whitney *U* tests, depending on the normality of data. A Chi-square test determined group differences in gender distribution. All analyses were performed in SPSS (version 25, IBM, NY, USA) with the significance level set at $\alpha < 0.05$. The results showed that groups did not differ in gender, age, weight, height, body mass index and habitual physical activity ($p > 0.05$) (See Table 1).

Subjects participated in two test sessions. During the first session, proprioceptive use during postural control and STSTS performance were evaluated (See below). Moreover, pain-related fear of movement was assessed in the NSLBP group with the Tampa Scale for Kinesiophobia (TSK, Dutch version). This questionnaire consists of 17 items rated from 1 ("strongly disagree") to 4 ("strongly agree"), with higher values indicating more fear of movement (Kori et al., 1990; Vlaeyen et al., 1995). Healthy individuals completed the TSK-General (Dutch version), a modified version of the TSK developed to assess fear of movement in a general population without low back pain (Houben et al., 2005). The second session took place maximally seven days after the first session (NSLBP: 1.9 ± 2.9 days, healthy: 1.8 ± 2.6 days). During this session, brain activity during proprioceptive stimulation was determined by applying local muscle vibration during fMRI (Cignetti et al., 2014; Fontan et al., 2017; Kavounoudias et al., 2008; Naito et al., 2007; Naito et al., 2005) (See below).

Table 1
Participants' characteristics.

	Patients with NSLBP (*n* = 20)	Healthy individuals (n = 20)	Test statistic	*p*-value
Gender (♂ / ♀)	6/14	6/14		1.000[c]
Age (yrs)	25.0 (23.4–28.0)	24.5 (23.4–27.4)	176.0	0.516[b]
Weight (kg)	72.5 (60.0–78.0)	60.5 (55.3–71.0)	134.5	0.076[b]
Height (m)	1.76 ± 0.11	1.70 ± 0.09	−1.839	0.074[a]
BMI (kg/m^2)	21.7 (20.4–24.1)	21.3 (20.4–22.8)	178.5	0.561[b]
PAI work	2.4 ± 0.6	2.4 ± 0.5	−0.278	0.783[a]
PAI sports	2.8 ± 1.0	3.2 ± 0.6	1.652	0.107[a]
PAI leisure time	3.1 (2.8–3.9)	3.5 (3.3–3.8)	164.5	0.332[b]
ODI-2	18 (18–20)	0 (0–0)	NA	NA
NRSday	2.4 ± 1.9	0 ± 0	NA	NA
NRSweek	4.1 ± 2.0	0 ± 0	NA	NA
Duration of NSLBP (yrs)	6.9 ± 3.7	0 (0–0)	NA	NA

Normally distributed data presented as mean ± SD, non-normally distributed data as median (Q1 – Q3). NSLBP = non-specific low back pain, BMI = body mass index, PAI = physical activity index (0–5), ODI-2 = Oswestry Disability Index (%) (Adapted Dutch version 2.1a), NRSday = back pain score on the Numerical Rating Scale on the test day (0 − 10), NRSweek = back pain score on the Numerical Rating Scale on average during the past week (0–10), NA = not applicable.
The significance level was set at $\alpha < 0.05$.
[a] Two-sample *t*-test.
[b] Mann-Whitney *U* test.
[c] Chi-square test.

2.3. Behavior

2.3.1. Proprioceptive use during postural control

The test procedure, materials, and outcome measures used to assess proprioceptive use during postural control were identical to previous studies (Brumagne et al., 2004; Brumagne et al., 2008; Claeys et al., 2011; Claeys et al., 2015; Kiers et al., 2014; Pijnenburg et al., 2014). For a detailed description, see supplemental content (Supplement 1). In short, participants stood on a six-channel force plate (Bertec Corp., OH, USA) with occluded vision and with two muscle vibrators (Maxon Motors, Switzerland) strapped bilaterally over the triceps surae ('ankle') muscles and the lumbar paraspinal ('back') muscles. Four trials were performed. During the first two trials, participants stood on the force plate ("stable support surface). During the last two trials, they stood on a foam pad placed on top of the force plate ("unstable support surface"). After 20 s of usual standing, local muscle vibration (60 Hz, 0.5 mm, 15 s) was applied at the ankle muscles (trial 1-stable, trial 3-unstable) or back muscles (trial 2-stable, trial 4-unstable) to stimulate muscle spindle Ia afferents and evoke a muscle lengthening illusion (Cordo et al., 2005; Goodwin et al., 1972; Roll and Vedel, 1982; Roll et al., 1989). If an individual used proprioceptive inputs from the vibrated muscle to maintain postural control, an unconscious corrective postural sway would occur (Barbieri et al., 2008; Eklund, 1972). This vibration-induced postural sway (i.e. displacement of center of pressure (COP)) was measured with the force plate and represented the extent to which one uses proprioceptive signals from the vibrated muscle for postural control (Brumagne et al., 2004). Positive COP displacements reflect anterior sways, negative COP displacements represent posterior sways. Please note that the vibration-induced movement illusion during standing constitutes an unconscious illusion, to which the CNS quickly responds by inducing a COP displacement in opposite direction. Hence, this illusion differs from the conscious illusion of movement questioned after fMRI-scanning. Finally, the Relative Proprioceptive Weighting (RPW) ratio was calculated by dividing the absolute COP displacement during ankle muscle vibration by the sum of the absolute COP displacements during ankle and back muscle vibration (Brumagne et al., 2008). This RPW ratio reflects proprioceptive dominance, with values of 0% indicating 100% use of back proprioception, and values of 100% representing 100% use of ankle proprioception. Previous research demonstrated that the COP displacement during muscle vibration and the RPW ratio are reliable measures to quantify the postural response on muscle vibration (Kiers et al., 2014).

2.3.2. Sit-to-stand-to-sit task

The test procedure, materials, and outcome measures used to evaluate the performance on the STSTS task were identical to previous studies (Caeyenberghs et al., 2017; Claeys et al., 2012; Pijnenburg et al., 2015; Pijnenburg et al., 2016). Participants sat on a stool that was placed on the six-channel force plate, with their arms hanging along their body and their vision occluded with non-transparent goggles. The height of the stool was adjusted to create a 90° angle in hips and knees. After 20 s of usual sitting, participants performed five successive STSTS movements as fast as possible, with a full range of motion in hips and knees. After the fifth repetition, participants remained seated for an additional 30 s. This task was performed with the feet on the force plate ("stable support surface") and with the feet on a foam pad placed on top of the force plate (Airex Balance Pad Elite, 50x41x6 cm, "unstable support surface"). A research assistant stood next to the participant to prevent potential falls. The mean COP position during the 15 s of sitting before and after the task were used to define the starting and endpoint of the task. The total duration to perform five successive STSTS movements was used as outcome measure. This measure shows good test-retest reliability (Denteneer et al., 2018).

2.4. Statistical analysis

Group differences in fear of movement (TSK scores) were determined with a two-sample *t*-test. Differences in the COP displacement during muscle vibration were analyzed using a 2 × 2 × 2 mixed-design ANOVA with within-subject factors 'support surface' (stable, unstable) and 'muscle' (ankle, back) and between-subjects factor 'group' (NSLBP, healthy). Because ankle muscle vibration was expected to evoke posterior COP displacements (i.e., negative values), and back muscle vibration anterior COP displacements (i.e., positive values), the signs of the COP displacements during ankle muscle vibration were reversed. Differences in RPW ratio and STSTS performance were analyzed with two 2 × 2 mixed-design ANOVAs, with 'support surface' (stable, unstable) as the within-subjects factor and 'group' (NSLBP, healthy) as the between-subjects factor. Post-hoc tests with Bonferroni correction were performed to explore significant interaction effects. Partial eta-squared (η_p^2) was used to report effect sizes. Finally, Pearson correlation coefficients between fear of movement and postural control measures were calculated. Based on the outliers labeling rule (Hoaglin, 1987), no outliers were found. The statistical analyses were performed with SPSS (version 25, IBM, NY, USA), with the significance level set at $\alpha < 0.05$.

2.5. Brain activity during proprioceptive stimulation

2.5.1. Experimental procedure

Participants were placed head first in a 3 T MRI scanner (Achieva, Philips, The Netherlands), equipped with a 32-channel standard head coil. Subjects lied supine on pillows that were adjusted so that pneumatically driven muscle vibrators could be strapped over the triceps surae ('ankle muscles') and lumbar paraspinal muscles ('back muscles') (See Fig. 1). These muscle vibrators were designed by our research group and show good fMRI-compatibility and good to excellent concurrent validity compared to classical electromagnetic muscle vibrators, implying that these devices can be used interchangeably (Goossens et al., 2016). The participants' bare feet were placed with a ~90° ankle angle against a flexible wooden board that allowed small sagittal ankle movements (See Fig. 1). Participants wore ear plugs to protect their ears from the scanner noise, and headphones to allow communication with the researchers. Finally, vision was occluded by means of non-transparent goggles.

Three fMRI runs with ankle muscle vibration and three fMRI runs with back muscle vibration were acquired in alternating order (whole-brain, T2*-weighted, FE-EPI gradient echo sequence, voxel size: 2.5 × 2.5 × 2.5 mm^3, FOV: 210 × 210 mm^2, 53 slices, slice gap: 0.2 mm, flip angle: 90°, TR: 3000 ms, TE: 30 ms, TA: 4.20 min per run, 84 volumes per run). Four dummy scans were acquired at the beginning of each fMRI run to allow time for reaching signal equilibrium. These dummy scans were automatically discarded after scanning.

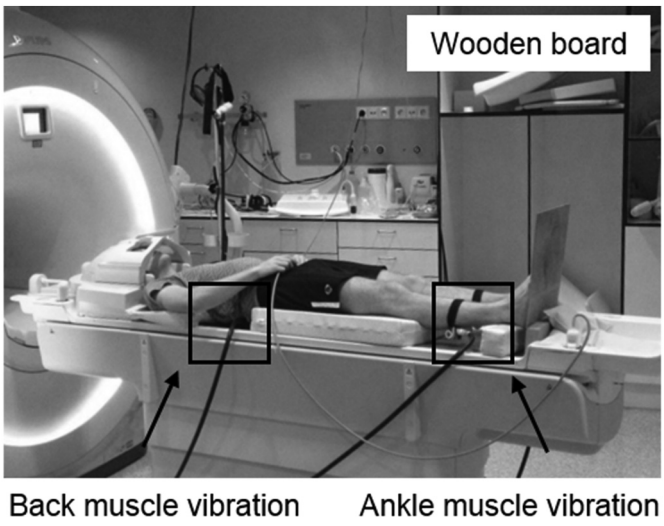

Fig. 1. Experimental set-up of muscle vibration during fMRI scanning.

During each fMRI run, three conditions were administered in a block-design: 60 Hz muscle vibration ('Ankle 60 Hz' or 'Back 60 Hz'), 20 Hz muscle vibration ('Ankle 20 Hz' or 'Back 20 Hz') and rest (no vibration). Participants were familiarized with the vibratory stimuli before scanning commenced. Each vibration condition (60 Hz and 20 Hz) was presented three times per fMRI run, with the order pseudo-randomized across runs, and each vibration block was followed by a 'rest' block (i.e., six rest blocks per run). Each block had a duration of 18 s, and was preceded by a short auditory cue (3 s) that informed participants about the following condition (i.e., either "vibration" or "rest"). Activation and deactivation of the muscle vibrators, and presentation of the auditory cues were synchronized with fMRI scanning through a custom-made, in-house built program using LabVIEW software (National Instruments, TX, USA).

Vibration at 60 Hz was chosen as the 'stimulation condition', as it optimally stimulates muscle spindle Ia afferents and evokes an illusion of movement (Roll and Vedel, 1982; Roll et al., 1989). However, to control for the simultaneous activation of vibrotactile skin receptors, vibration was also applied at 20 Hz, which stimulates muscle spindle Ia afferents only weakly - without eliciting clear muscle-lengthening illusions (Naito et al., 1999; Radovanovic et al., 2002; Roll and Vedel, 1982; Roll et al., 1989). The contrast "60 Hz > 20 Hz" was used to reveal neural activity related to muscle spindle (proprioceptive) stimulation in the absence of vibrotactile responses (Cignetti et al., 2014; Fontan et al., 2017). At the end of the scanning session, a T1-weighted, high-resolution structural MRI scan was acquired for anatomical detail (whole-brain, 3D-TFE gradient echo sequence, voxel size: 1x1x1.2 mm^3, FOV: 218x250x250 mm^3, flip angle: 8°, TR: 9.6 ms, TE: 4.6 ms, TA: 6.43 min).

After scanning, we verified that no subjects had experienced any pain. Moreover, participants were asked to describe the sensations they felt during muscle vibration, for each muscle and frequency. Important to note, we did not disclose why muscle vibration was applied during fMRI. Hence, participants did not expect an illusion of movement to occur. If participants reported a conscious illusion of movement during vibration, they were asked to describe this illusion in detail (i.e., Which body part was involved and what was the direction of the illusory movement?). Experiencing a clear illusion of movement was coded as '1', while the absence of an illusion was coded as '0'. Chi-square tests determined between-group differences in vibration-induced illusions, while McNemar tests determined whether the frequency of experiencing a movement illusion differed between 60 Hz and 20 Hz (significance threshold set at $\alpha < 0.05$). These analyses were performed in SPSS (version 25, IBM, USA).

2.5.2. Pre-processing of fMRI data

Functional volumes were pre-processed and statistically analyzed with SPM12 (revision number 6906, Wellcome Department of Imaging Neuroscience, UK), implemented in Matlab R2017b (Mathworks, MA, USA). The T2*-weighted functional images of each run were realigned to the first image using rigid body transformations, optimized to minimize the residual sum of squares between the first image and each following image within each run. During this step, a mean functional image was created and six realignment parameters describing head motion were estimated (i.e., three rotations, three translations). The T1-weighted structural scan was co-registered to the mean functional image using affine transformations (rigid body, scaling, shearing) optimized to maximize the normalized mutual information between both images. The co-registered structural image was brought into Montreal Neurological Institute (MNI) standard space by using the unified segmentation approach (Ashburner and Friston, 2005) and the ICBM space template - European brains. During this step, the structural image was

segmented into white matter, gray matter, cerebrospinal fluid, non-brain tissue by using the default tissue probability maps (TPM) of SPM12, by estimating a non-linear deformation field that best overlays the TPMs on the individual structural image. These resulting parameters were applied to the co-registered functional images to normalized them to MNI space using 4th degree B-spline interpolation. Finally, the normalized functional images were resampled to a 2x2x2 mm^3 voxel size, and spatially smoothed with an isotropic 3D Gaussian smoothing kernel (5 mm full-width at half maximum).

The six realignment parameters were used to calculate the frame-wise displacement (FD) and DVARS for each run (Power et al., 2012). According to standard criteria, we verified that no fMRI runs contained > 50% volumes with a FD ≥ 0.5 mm and DVARS ≥ 0.5, and that none of the subjects showed excessive head motion during scanning (i.e., mean FD ≥ 0.5) (Power et al., 2012). Finally, a 2x3x2 mixed-design ANOVA with within-subjects factors 'muscle' (ankle, back) and 'run' (3 runs) and between-subjects factor 'group' (NSLBP, healthy) showed that groups did not differ in terms of head motion during scanning (main effect of 'group', interaction effects of 'group x run', 'group x muscle' and 'group x muscle x run' on mean FD, $p > 0.05$). To note, a significant main effect of 'muscle' on mean FD (F(Airaksinen et al., 2006; Fontan et al., 2017) = 8.959, $p = 0.005$) indicated that participants in both groups exhibited larger head motion during scans with back compared to ankle muscle vibration, across runs (Ankle: 0.15 ± 0.06 mm, Back: 0.17 ± 0.06 mm). However, as mentioned above, all mean FD values fell well below the standard cut-off of 0.5 mm (*Run 1 Ankle*: NSLBP 0.16 ± 0.08 mm, healthy 0.15 ± 0.03 mm, $p = 0.714$; *Run 2 Back*: NSLBP 0.16 ± 0.08 mm, healthy 0.16 ± 0.03 mm, $p = 0.643$; *Run 3 Ankle*: NSLBP 0.15 ± 0.07 mm, healthy 0.15 ± 0.05 mm, $p = 0.978$; *Run 4 Back*: NSLBP 0.17 ± 0.07 mm, healthy 0.16 ± 0.04 mm, $p = 0.694$; *Run 5 Ankle*: NSLBP 0.17 ± 0.07 mm, healthy 0.15 ± 0.03 mm, $p = 0.245$; *Run 6 Back*: NSLBP 0.19 ± 0.08 mm, healthy 0.17 ± 0.04 mm, $p = 0.249$).

2.5.3. First-level analysis of fMRI data

At the individual subject level, stimulus-dependent changes in BOLD signal were modeled as boxcar regressors time-locked to the onsets and durations of the vibration blocks (Ankle 60 Hz, Ankle 20 Hz, Back 60 Hz, Back 20 Hz) and auditory cues. Rest was modeled implicitly. The boxcar regressors were convolved with the canonical hemodynamic response function (HRF) of SPM12, and entered into a first-level general linear model (GLM) for each participant. To control for the effect of head motion on the BOLD signal, the six realignment parameters were included as nuisance covariates. Moreover, constant terms were added as covariates of no interest to account for shifting signal levels across runs. Finally, fMRI data were high-pass filtered (1/128 Hz) to remove low-frequency scanner signal drifts, and the autoregressive AR (Airaksinen et al., 2006) model from SPM was fit to the residuals of the fMRI time series to account for temporal autocorrelations. To reveal brain activity related to the processing of ankle and back proprioceptive inputs, in the absence of vibrotactile responses, individual SPM (t)-contrasts 'Ankle 60 Hz > Ankle 20 Hz' and 'Back 60 Hz > Back 20 Hz' were calculated, respectively (Cignetti et al., 2014; Fontan et al., 2017). Moreover, individual SPM (t)-contrasts (Ankle 60 Hz > Ankle 20 Hz) - (Back 60 Hz > Back 20 Hz) and (Back 60 Hz > Back 20 Hz) - (Ankle 60 Hz > Ankle 20 Hz) examined within-group differences between ankle and back proprioceptive processing.

2.5.4. Second-level analysis of fMRI data

The resulting (t)-contrast images were entered into a second-level, random-effects GLM for each group. One-sample *t*-tests conducted in each group tested the effect of ankle ('Ankle 60 Hz > Ankle 20 Hz') and back ('Back 60 Hz > Back 20 Hz') proprioceptive processing on brain activation, as well as the within-group difference between ankle and back proprioceptive processing. The results were thresholded at $p < 0.05$ family-wise error (FWE-) corrected for multiple comparisons across the whole brain.

No differences in proprioceptive use during postural control (the main behavioral outcome of interest) were found between groups (See below). Therefore, comparing brain activity patterns during proprioceptive processing between groups by performing two-sample t-tests would be difficult to interpret. However, we tested whether activation patterns during proprioceptive processing were related to behavioral measures of proprioception. To do so, we regressed the contrast images testing for proprioceptive processing (i.e., 'Ankle 60 Hz > Ankle 20 Hz' and 'Back 60 Hz > Back 20 Hz') against the postural control measures (COP displacement during vibration, RPW ratio and STSTS performance, assessed on the unstable support surface) across both groups. We selected the unstable support surface condition, because it requires an additional reweighing of proprioception, and is thus more challenging compared to the stable support surface condition (Ivanenko et al., 1999; Kiers et al., 2012). The postural control measures were added as covariates of interest at the second level without centering (i.e., four separate random effect analyses per muscle were used). One-sample *t*-tests including the postural control measures of all subjects explored positive and negative correlations between brain activity and behavior across groups. Finally, two-sample t-tests were used to investigate whether the relationship between brain activity and behavioral measures of postural control differed between groups. To do so, two-sample t-tests including the postural control measures (i.e., COP displacement during ankle muscle vibration, COP displacement during back muscle vibration, RPW ratio, duration to perform STSTS movements, all assessed on the unstable support surface) for each of the groups separately compared brain-behavior correlations between groups (i.e., interaction contrasts ('0 0 1 -1' and '0 0 -1 1'). A similar approach was used to assess how brain activity during proprioceptive processing was related to fear of movement (i.e., TSK scores included as covariate of interest). The strength of the related correlation coefficients was calculated by using the following formula:, $r = \sqrt{\frac{t^2}{t^2 + degrees\ of\ freedom}}$ with t = maximum t-value of the respective cluster.

The results were thresholded at $p < 0.05$ after FWE-correction for multiple comparisons applied over small spherical volumes (SVC, 10 mm radius) around a priori selected locations of activations in regions of interest (ROI), based on published fMRI-based research on the neural processing of ankle proprioceptive stimuli (Goble et al., 2011) and back mechanosensory stimuli (Boendermaker et al., 2014), and on fear processing (Etkin and Wager, 2007) (See Table 2). To illustrate significant results, beta parameter estimates of the '60Hz > 20Hz' contrasts were extracted within each significant peak with the MarsBaR ROI toolbox (version 0.44, http://marsbar.sourceforge.net/) (Brett et al., 2002). Significant activation peaks were labeled with the Automated Anatomical Labeling (AAL) toolbox in SPM12 (Tzourio-Mazoyer et al., 2002). Moreover, cytoarchitectonic areas from the SPM Anatomy Toolbox (Eickhoff et al., 2007; Eickhoff et al., 2005) with a probability > 30% were reported.

3. Results

3.1. Behavior

3.1.1. Postural control

The results showed that groups did not differ in proprioceptive dominance (main effect of 'group', 'support surface x group' interaction on RPW ratio, $p > 0.05$). However, a significant main effect of 'support surface' on RPW ratio (F(Airaksinen et al., 2006; Fontan et al., 2017) = 19.86, $p < 0.0001$, $\eta_p^2 = 0.901$) indicated that both groups relied relatively less on ankle proprioception and/or relatively more on back proprioception during standing on the unstable compared to the stable support surface (See Fig. 2). These results were corroborated by the ANOVA of COP displacements during muscle vibration. Groups did

Table 2
Coordinates used for small volume correction.

		MNI coordinates				
Region of interest	Side	x	y	z	Reference	Activation
Inferior frontal gyrus	R	44	22	−14	Goble et al., 2011	Ankle
Inferior frontal gyrus	R	48	42	−4	Goble et al., 2011	Ankle
Inferior parietal cortex	R	60	−44	48	Goble et al., 2011	Ankle
Precentral gyrus	R	50	10	38	Goble et al., 2011	Ankle
Precentral gyrus	R	48	4	46	Goble et al., 2011	Ankle
Precentral gyrus	R	50	6	48	Goble et al., 2011	Ankle
Putamen	R	34	10	−6	Goble et al., 2011	Ankle
Thalamus	R	14	−8	0	Goble et al., 2011	Ankle
Thalamus	L	−20	−6	8	Goble et al., 2011	Ankle
S1	R	18	−36	66	Boendermaker et al., 2014	Back
S1	L	−16	−46	68	Boendermaker et al., 2014	Back
Opercular-insular cortex	R	32	−20	10	Boendermaker et al., 2014	Back
Opercular-insular cortex	L	−44	−34	20	Boendermaker et al., 2014	Back
ACC	R	10	36	20	Boendermaker et al., 2014	Back
ACC	L	−12	38	18	Boendermaker et al., 2014	Back
Mid-cingulate cortex	L	−12	22	32	Boendermaker et al., 2014	Back
Mid-cingulate cortex	R	8	−10	40	Boendermaker et al., 2014	Back
Mid-cingulate cortex		0	12	26	Etkin and Wager, 2007	Ankle, back
Cerebellum lobules IV-V	R	8	−46	−14	Boendermaker et al., 2014	Back
Cerebellum lobules IV-V	L	−8	−44	−16	Boendermaker et al., 2014	Back
Amygdala	R	26	2	−28	Etkin and Wager, 2007	Ankle, back
Amygdala	L	−16	−8	−12	Etkin and Wager, 2007	Ankle, back
Parahippocampal gyrus	R	16	2	−20	Etkin and Wager, 2007	Ankle, back
Parahippocampal gyrus	L	−24	−6	−28	Etkin and Wager, 2007	Ankle, back

Abbreviations: R = right, L = left, MNI = Montreal Neurological Institute, S1 = primary somatosensory cortex, ACC = anterior cingulate cortex.

not differ in terms of COP displacements (main effect of 'group', 'support surface x group' interaction, 'muscle x group' interaction, 'support surface x group x muscle' interaction: all $p > 0.05$). However, a significant 'support surface x muscle' interaction effect (F(Airaksinen et al., 2006; Fontan et al., 2017) = 37.98, $p < 0.0001$, $\eta_p^2 = 0.500$) and significant main effects of 'support surface' (F(Airaksinen et al., 2006; Fontan et al., 2017) = 14.97, $p < 0.0001$, $\eta_p^2 = 0.283$) and 'muscle' (F(Airaksinen et al., 2006; Fontan et al., 2017) = 6.10, $p = 0.018$, $\eta_p^2 = 0.138$) were found. The post-hoc tests revealed that both groups relied less on ankle proprioception when standing on the unstable compared to the stable support surface ($p < 0.0001$). The use of back proprioception did not differ between support surfaces ($p = 0.129$). Moreover, during standing on the stable support surface, both groups relied more on ankle compared to back muscle proprioception ($p < 0.0001$). This difference was not found in the unstable support surface condition ($p = 0.73$) (See Fig. 2).

Finally, the ANOVA of STSTS performance showed that patients with NSLBP needed significantly more time to perform the STSTS task compared to healthy controls across both support surfaces (main effect of 'group' (F(Airaksinen et al., 2006; Fontan et al., 2017) = 5.48, $p = 0.025$, $\eta_p^2 = 0.126$) (See Fig. 2). Moreover, both groups performed the five STSTS movements slightly, though significantly, slower on the unstable compared to the stable support surface (NSLBP: stable = 13.6 ± 3.8 s, unstable = 14.0 ± 3.6 s; healthy: stable = 11.4 ± 3.6 s, unstable = 12.0 ± 1.8 s). No interaction effect of 'support surface x group' was found ($p = 0.748$).

3.1.2. Pain-related fear of movement and correlation with postural control

Patients with NSLBP showed significantly higher levels of fear of movement compared to the healthy group (NSLBP: 33 ± 8, HC: 27 ± 5, $p = 0.005$). Based on the cut-off values proposed by Vlaeyen et al. (1995), six patients with NSLBP showed high fear of movement (TSK > 37), in contrast to none of the healthy individuals. Finally, neither group showed significant correlations between fear of movement and postural control (COP displacement during vibration, RPW ratio, STSTS performance) ($p > 0.05$).

3.2. Functional imaging

3.2.1. Movement illusions during muscle vibration

McNemar tests showed that the frequency of experiencing a movement illusion was significantly higher during 60 Hz compared to 20 Hz ankle muscle vibration in both groups (NSLBP: 13/20 during 60 Hz, 2/20 during 20 Hz, $p = 0.001$, healthy: 15/20 during 60 Hz, 5/20 during 20 Hz, $p = 0.002$). Moreover, patients with NSLBP more often reported an illusion of trunk/pelvic movement during 60 Hz compared to 20 Hz back muscle vibration (9/20 during 60 Hz, 2/20 during 20 Hz, $p = 0.016$). In the healthy group, this difference in the frequency of experiencing a movement illusion was nearly significant (10/20 during 60 Hz, 5/20 during 20 Hz, $p = 0.063$). Chi-square tests showed that groups did not differ in experiencing vibration-induced illusory movements (Ankle: 60 Hz: $p = 0.731$, 20 Hz: $p = 0.407$; Back: 60 Hz: $p = 1.00$, 20 Hz: $p = 0.407$).

3.2.2. Brain activity during proprioceptive processing in the NSLBP group

During ankle proprioceptive processing, patients with NSLBP showed significant bilateral brain activity in the paracentral lobule (corresponding to M1), superior temporal gyrus, rolandic operculum, putamen, insula, and cerebellum. Moreover, significant brain activity during ankle proprioceptive processing was found in the right postcentral gyrus (S1), supplementary motor area (SMA), S2, thalamus and inferior parietal lobule, and in the left precuneus and mid-cingulate cortex. During the processing of back proprioception, the NSLBP group exhibited significant brain activation in the right Heschl's gyrus and right S2 (See Table 3, Fig. 3).

Furthermore, results revealed that patients with NSLBP exhibited increased brain activity in the left paracentral lobule (corresponding to foot region in M1), right SMA, right putamen and bilateral cerebellum during the processing of ankle compared to back proprioception (See Table 4). In contrast, no brain regions showed increased brain activation during the processing of back compared to ankle proprioception.

3.2.3. Brain activity during proprioceptive processing in the healthy group

One-sample t-tests showed that healthy individuals exhibited

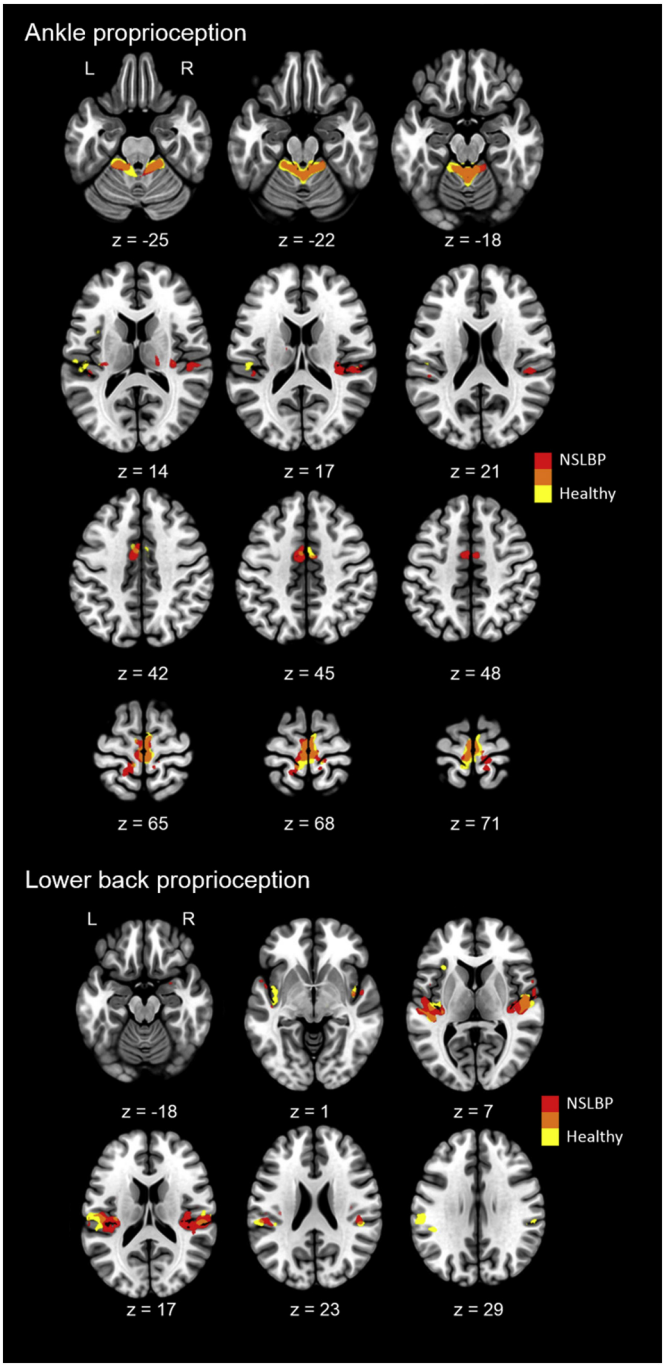

Fig. 2. Mean COP displacements during ankle and back muscle vibration (top), Relative Proprioceptive Weighting ratio (RPW) (bottom left) and duration to perform five sit-to-stand-to-sit (STSTS) movements (bottom right) when standing on a stable and unstable support surface in patients with NSLBP (gray) and healthy individuals (white). Error bars represent standard deviations.

significant brain activity in the bilateral paracentral lobules, insulae, putamina, mid-cingulate cortices and cerebellum, in the left S2 and left superior temporal gyrus, and in the right SMA, right supramarginal gyrus and right thalamus during the processing of ankle proprioception (See Fig. 3 and Table 5). Moreover, during back proprioceptive processing, healthy individuals demonstrated significant brain activity within two very small clusters in the right S2 (MNI = 54–26 16, z-value = 5.172, pFWE < 0.05, cluster size = 2 voxels) and right insula (MNI = 44–10 -2, z-value = 5.077, pFWE < 0.05, cluster size = 2 voxels).

Table 3
Significant brain activity during the processing of ankle and back proprioception in patients with NSLBP.

		MNI coordinates (mm)			
	Side	x	y	z	z-value
A. Ankle proprioception					
Cluster 1 (751 voxels)					
Cerebellar vermis 3	R	6	−44	−20	7.716
Cerebellum lobule IV-V	L	−18	−38	−24	7.342
Cerebellum lobule IV-V	R	18	−38	−24	7.265
Cerebellar vermis 4/5	L	0	−50	−10	6.818
Cerebellum lobule IV-V	L	−10	−42	−20	6.788
Cerebellar vermis 4/5	R	2	−62	−6	6.025
Cerebellar vermis 3	R	2	−42	−4	5.542
Cluster 2 (622 voxels)					
Paracentral lobule (M1, 4a)	L	0	−28	68	7.205
Paracentral lobule	L	0	−20	74	6.999
Precuneus (SPL 5 L)	L	−16	−42	66	6.064
Postcentral gyrus (M1, 4a)	R	14	−32	74	5.729
Postcentral gyrus	R	12	−40	74	5.536
SMA	L	−8	−18	80	5.354
SMA	R	8	−22	64	5.321
Paracentral lobule	L	−10	−38	76	5.315
Paracentral lobule	R	8	−24	80	5.161
Cluster 3 (143 voxels)					
Mid-cingulate cortex	L	−6	−6	44	7.175
Mid-cingulate cortex	L	−4	2	44	5.832
SMA	R	6	−6	48	5.796
Cluster 4 (46 voxels)					
Putamen	L	−30	−8	6	6.647
Putamen	L	−28	0	6	5.159
Cluster 5 (221 voxels)					
Putamen	R	32	−6	6	5.881
Insula (OP2)	R	34	−22	14	5.838
Rolandic operculum (IPL)	R	46	−30	20	5.765
Superior temporal gyrus (IPL)	R	54	−30	16	5.488
Rolandic operculum (OP1 SII)	R	50	−22	12	5.471
Supramarginal gyrus	R	54	−30	26	5.303
Cluster 6 (56 voxels)					
Rolandic operculum	R	50	−2	4	5.879
Heschl's gyrus (primary auditory cortex)	R	52	−10	4	5.567
Cluster 7 (35 voxels)					
Thalamus	R	20	−24	10	5.856
Thalamus	R	18	−16	12	5.420
Cluster 8 (12 voxels)					
Superior temporal gyrus	R	52	8	−4	5.505
Cluster 9 (23 voxels)					
Superior temporal gyrus (primary auditory cortex)	L	−44	−32	14	5.464
Cluster 10 (15 voxels)					
Insula	L	−44	4	2	5.342
Cluster 11 (19 voxels)					
Insula	L	−28	−24	14	5.335
Cluster 12 (11 voxels)					
Rolandic operculum	L	−54	0	4	5.333
B. Back proprioception					
Cluster 1 (35 voxels)					
Heschl's gyrus (primary auditory cortex)	R	52	−10	4	5.453
Rolandic operculum (SII)	R	54	−22	14	5.281
Heschl's gyrus (primary auditory cortex)	R	48	−20	6	5.037

Threshold set at $p < 0.05$ FWE-corrected across the entire brain. Minimum cluster size = 10 voxels. Significant peaks are labeled with the Automated Anatomical Labeling (AAL) toolbox. Cytoarchitectonic areas from the SPM Anatomy Toolbox with a probability > 30% are provided between brackets. Peaks > 8 mm apart are reported. MNI = Montreal Neurological Institute, R = right, L = left, M1 = primary motor cortex, SPL = superior parietal lobule, IPL = inferior parietal lobule, SII = secondary somatosensory cortex, OP = parietal operculum.

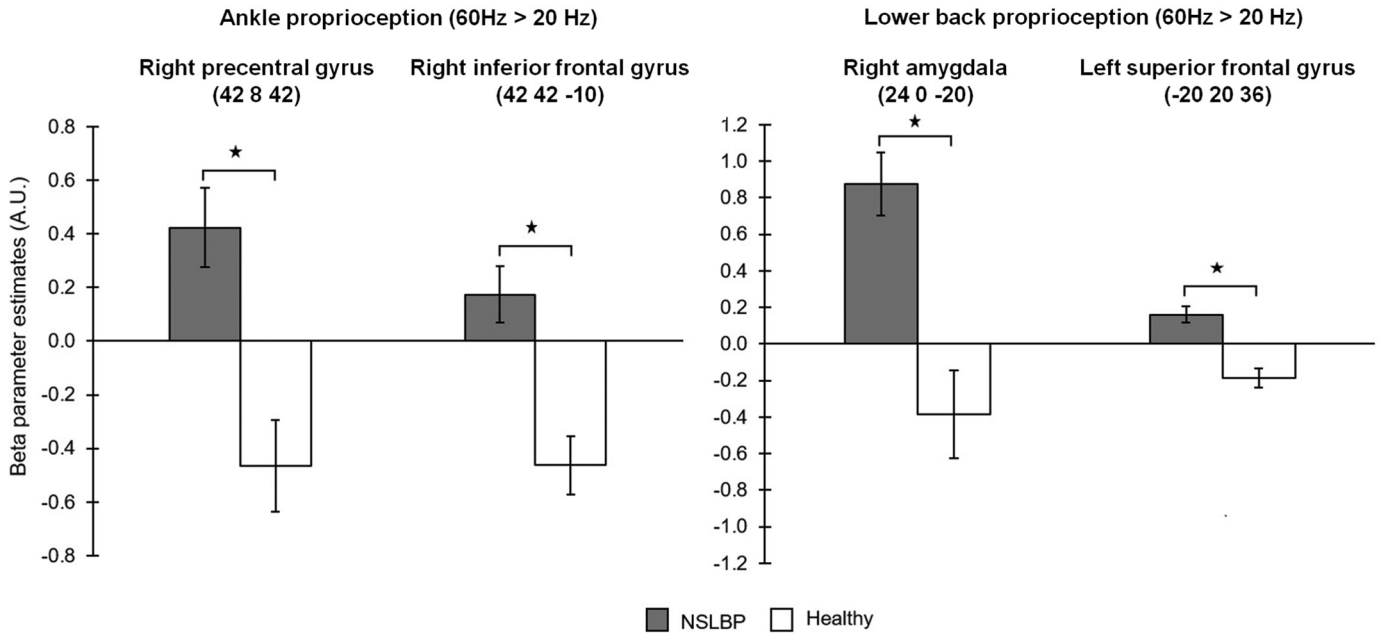

Fig. 3. Significant brain activity during proprioceptive processing. The left panel visualizes brain activity during ankle proprioceptive processing ('60 Hz > 20 Hz') for each group (NSLBP in red, healthy in yellow, overlap in orange). The results were thresholded at $p < 0.05$ voxel-wise FWE-corrected. The right panel displays brain activity during the processing of back proprioception ('60 Hz > 20 Hz') for each group (NSLBP in red, healthy in yellow, overlap in orange). For visualization purposes, a voxel-wise threshold of $p < .00001$ uncorrected was used. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4
Significantly increased brain activity during the processing of ankle compared to back proprioception in patients with NSLBP (paired t-test).

		MNI coordinates (mm)			
	Side	x	y	z	*Z*-value
Cluster 1 (160 voxels)					
Cerebellar vermis 3	R	14	−40	−24	6.258
Cerebellar vermis 4/5	L	−2	−48	−12	5.922
Cerebellar vermis 3	R	6	−44	−20	5.920
Cerebellar vermis 4/5	L	−2	−56	−8	5.127
Cluster 2 (28 voxels)					
Cerebellum lobule IV-V	L	−18	−38	−24	6.081
Cerebellum lobule IV-V	L	−10	−42	−22	5.113
Cluster 3 (14 voxels)					
Putamen	R	32	−8	6	5.698
Cluster 4 (91 voxels)					
SMA	R	2	−18	70	5.652
Paracentral lobule (M1, 4a)	L	−6	−28	66	5.472

Threshold set at $p < 0.05$ FWE-corrected across the entire brain. Minimum cluster size = 10 voxels. Significant peaks are labeled with the Automated Anatomical Labeling (AAL) toolbox. Cytoarchitectonic areas from the SPM Anatomy Toolbox with a probability > 30% are provided between brackets. Peaks > 8 mm apart are reported. MNI = Montreal Neurological Institute, R = right, L = left, SMA = supplementary motor area, M1 = primary motor cortex.

Finally, the results revealed significantly increased brain activity within the right paracentral lobule (corresponding to foot region in M1) and the bilateral cerebellum (left lobule IV-V, right lobule III) during the processing of ankle compared to back proprioception (See Table 6) in the healthy group. The reversed contrast of back vs. ankle proprioception did not yield significant results.

3.2.4. Correlations between brain activity during proprioceptive processing and postural control

3.2.4.1. Proprioceptive use during postural control. **Ankle proprioception:** A marginally significant correlation between brain activity in the left thalamus and smaller backward COP displacements during ankle muscle vibration on the unstable support surface was observed across groups. This correlation indicated that increased activation in the left thalamus was related to smaller postural responses on ankle muscle vibration, suggesting a more optimal use of ankle proprioception during postural control (See Table 7). Moreover, a marginally significant group difference in the relationship between brain activity in the right amygdala (MNI 18–6 -16, p(FWE)SVC = 0.057, $t = 3.84$) and COP displacements during ankle muscle vibration on the unstable support surface was observed. Post-hoc analyses showed that greater activation in the right amygdala correlated with larger backward COP displacements during ankle muscle vibration (indicating a less optimal use of ankle proprioception during standing) in the NSLBP group, but with smaller backward COP displacements during ankle muscle vibration (representing a better use of ankle proprioception) in the healthy group (though none of these correlations survived SVC-correction, See Fig. 4).

Back proprioception: Across groups, brain activity in the right amygdala was correlated with smaller COP displacements during back muscle vibration on the unstable support surface, indicating a less optimal use of back proprioception during standing (See Table 7). Furthermore, significant group differences in correlation between brain activity and COP displacements during back muscle vibration during standing on the unstable support surface were found in the right anterior cingulate cortex (MNI 10 38 16, p(FWE)SVC < 0.001, $t = 4.40$), right mid-cingulate cortex (MNI 10–8 34, p(FWE)SVC = 0.049, $t = 4.65$), left superior parietal lobule (5 M) (MNI -8 -46 62, p(FWE)SVC = 0.044, $t = 3.42$), and bilateral cerebellar lobules V (Right: MNI 12–54 -16, p(FWE)SVC = 0.039, $t = 4.24$; Left: MNI -16 -48 -20, p(FWE)SVC = 0.032, $t = 3.80$). Follow-up analyses with each group revealed that these interaction effects were mainly driven by a negative relationship between brain activity and the behavioral index in healthy controls (though the correlations in the right cerebellar lobule and left superior parietal lobule in healthy subjects did not survive SVC-correction, See Fig. 5).

Moreover, a significant group difference in correlation between

Table 5
Significant brain activity during the processing of ankle proprioception in healthy individuals.

		MNI coordinates (mm)			
	Side	x	y	z	*Z*-value
Cluster 1 (961 voxels)					
Cerebellum lobule IV-V	L	−14	−40	−20	Inf
Cerebellum lobule III	R	12	−40	−22	7.204
Cerebellar vermis 4/5		0	−56	−8	7.121
Cerebellar vermis 3	R	4	−46	−20	7.065
Cerebellum lobule IV-V	L	−22	−38	−26	7.036
Cerebellum lobule IV-V	R	28	−38	−34	6.115
Cluster 2 (606 voxels)					
Paracentral lobule (M1, 4a)		0	−32	70	6.380
Paracentral lobule	R	4	−22	72	6.333
SMA	R	4	−12	68	5.870
Paracentral lobule	L	−8	−38	72	5.788
Paracentral lobule	L	−8	−14	66	5.338
Paracentral lobule	L	−12	−36	64	5.326
Paracentral lobule	L	−8	−20	82	5.104
Cluster 3 (11 voxels)					
Supramarginal gyrus	R	46	−32	24	5.795
Cluster 4 (10 voxels)					
Putamen	R	30	−6	10	5.744
Cluster 5 (38 voxels)					
Putamen	L	−32	−10	6	5.730
Putamen	L	−28	0	8	5.697
Cluster 6 (31 voxels)					
Insula	L	−34	−20	8	5.721
Superior temporal gyrus	L	−40	−16	−2	5.081
Cluster 7 (95 voxels)					
Rolandic operculum (OP1 SII)	L	−48	−24	16	5.680
Superior temporal gyrus	L	−46	−30	8	5.558
Postcentral gyrus (OP1 SII)	L	−56	−20	14	5.298
Cluster 8 (65 voxels)					
Mid-cingulate cortex	L	−6	−2	44	5.638
Mid-cingulate cortex	R	6	−6	44	5.589
Mid-cingulate cortex	R	8	4	36	5.430
Cluster 9 (26 voxels)					
Insula	R	50	6	−4	5.591
Insula	R	46	−8	0	5.236
Cluster 10 (47 voxels)					
Insula	L	−34	8	10	5.553
Insula	L	−42	0	8	5.389
Cluster 11 (15 voxels)					
Thalamus	R	18	−16	6	5.328

Threshold set at $p < 0.05$ FWE-corrected across the entire brain. Minimum cluster size = 10 voxels. Significant peaks are labeled with the Automated Anatomical Labeling (AAL) toolbox. Cytoarchitectonic areas from the SPM Anatomy Toolbox with a probability > 30% are provided between brackets. Peaks > 8 mm apart are reported. MNI = Montreal Neurological Institute, R = right, L = left, M1 = primary motor cortex, SII = secondary somatosensory cortex, OP = parietal operculum.

brain activity and proprioceptive dominance (RPW ratio) on the unstable support surface was found only in the right cerebellar lobule V (MNI 12-50-18, p(FWE)SVC = 0.011, $t = 4.02$). The post-hoc analyses showed that lower RPW ratios, indicating a more optimal use of proprioception, were associated with larger brain activity in the NSLBP group, but with less brain activity in the healthy group (See Fig. 5). To note, the correlation between brain activity and RPW ratio in the NSLBP group did not survive SVC-correction.

3.2.4.2. STSTS performance. **Ankle proprioception:** Across groups, brain activity in the right IFG (orbital part), left amygdala and left hippocampus was significantly related with a slower STSTS performance on the unstable support surface (See Table 7). Moreover, a significant group difference in correlation between brain activity and STSTS performance on the unstable support surface was observed in the right IFG (pars triangularis, MNI 50 34 0, p(FWE)SVC = 0.044, $t = 3.72$). Follow-up within-group analyses revealed that higher brain activity in the right IFG correlated with a faster STSTS performance in the healthy group, but with a slower performance in the patients with NSLBP (See Fig. 4), though correlations in both groups did not survive SVC-correction.

Correlations between brain activity during proprioceptive processing and fear of movement.

Back proprioception: Individuals across groups showing more fear of movement (i.e., higher TSK scores) exhibited larger brain activity during back proprioceptive processing in the left cerebellar lobule V (MNI -8 -46 -8, p(FWE)SVC = 0.018, $t = -4.77$, $r = -0.61$), and right postcentral gyrus corresponding to the back region in S1 (MNI 20–36 62, p(FWE)SVC = 0.044, $t = -3.81$, r: −0.53). However, no correlation between fear of movement and brain activity during ankle proprioceptive processing across groups, nor significant group differences in correlation strength between brain activity and fear of movement were found.

4. Discussion

This study was the first to examine brain activity during proprioceptive processing in individuals with and without NSLBP. The results revealed that patients with NSLBP were more fearful of movement and needed more time to perform the STSTS task compared to the controls. Unexpectedly, we did not reveal significant group differences in proprioceptive use during standing. However, the relationship between brain activity during proprioceptive processing and proprioceptive postural control differed between patients with NSLBP and healthy controls in the superior parietal lobule and cerebellum.

4.1. Brain activity during proprioceptive processing: group activations

During ankle proprioceptive processing, individuals with and without NSLBP activated a widely distributed, largely overlapping brain network that aligned well with previous research (Cignetti et al., 2014; Fontan et al., 2017; Goble et al., 2011; Goble et al., 2012; Iandolo et al., 2018; Naito et al., 2007). This network comprised (Airaksinen et al., 2006) sensorimotor regions (including S1, M1, SMA, mid-cingulate cortex, putamen and anterior cerebellum) suggested to contribute to the formation of dynamic postural limb representations in order to allow fast corrections of movement, and (Altmann et al., 2007) parietal areas, such as the supramarginal gyrus and the inferior parietal lobule, which integrate multi-modal somatic signals from different body parts with environmental information, and support higher-order perceptual-proprioceptive processes, such as body- and self-awareness (Cignetti et al., 2014; Goble et al., 2011; Goble et al., 2012; Morita et al., 2017; Naito et al., 2016a; Naito et al., 2007; Naito et al., 2016b). Moreover, significant activity was found in the superior temporal gyrus, a multi-sensory processing area (Dieterich and Brandt, 2008) that has shown involvement in proprioceptive processing and postural control (Findlater et al., 2016; Karim et al., 2012; Karim et al., 2014; Kavounoudias et al., 2008; Kenzie et al., 2016; Naito et al., 2005).

During back proprioceptive processing, patients with NSLBP activated the right S2, which aligned well with previous studies on lumbar proprioceptive processing (Boendermaker et al., 2014; Meier et al., 2014), and the right primary auditory cortex (i.e., Heschl's gyrus). Activation within the latter was relatively unexpected, as it is typically associated with auditory information processing (Wasserthal et al., 2014). However, previous research demonstrated that the Heschl's gyrus is also important in proprioceptive processing and spatial localization, regardless of the sensory modality (Altmann et al., 2007; Findlater et al., 2016; Radovanovic et al., 2002). To note, the healthy group also showed brain activity in the right S2, as well as in the right insula during back proprioceptive processing, though these clusters were only very small when FWE-correction was applied.

The extent of brain activity during back proprioceptive processing was smaller compared to previous work (Boendermaker et al., 2014;

Table 6
Significantly increased brain activity during the processing of ankle compared to back proprioception in healthy individuals (paired t-test).

		MNI coordinates (mm)			
	Side	x	Y	z	*Z*-value
Cluster 1 (131 voxels)					
Paracentral lobule (M1, 4a)	R	2	−26	70	5.911
Paracentral lobule (M1, 4a)	L	−6	−30	74	5.607
Cluster 2 (28 voxels)					
Cerebellum lobule IV-V	L	−16	−38	−22	5.889
Cerebellum lobule IV-V	L	−22	−38	−28	5.229
Cluster 3 (11 voxels)					
Cerebellum lobule III	R	12	−40	−24	5.510

Threshold set at $p < 0.05$ FWE-corrected across the entire brain. Minimum cluster size = 10 voxels. Significant peaks are labeled with the Automated Anatomical Labeling (AAL) toolbox. Cytoarchitectonic areas from the SPM Anatomy Toolbox with a probability > 30% are provided between brackets. Peaks > 8 mm apart are reported. MNI = Montreal Neurological Institute, R = right, L = left, M1 = primary motor cortex.

Meier et al., 2014). This could be explained by differences in the stimulus used (i.e., muscle vibration vs. imposed intervertebral movement), and by the fact that we corrected for the simultaneous activation of vibrotactile receptors, in contrast to previous studies (Boendermaker et al., 2014; Meier et al., 2014). In the current study, correction for concurrent vibrotactile stimulation was performed by contrasting brain responses during 60 Hz and 20 Hz vibration. However, we cannot rule out that brain responses to 60 Hz and 20 Hz back muscle vibration overlapped in magnitude and location, resulting in contrast (t)-maps that only survived more lenient significance thresholds. This hypothesis was supported by an exploratory group-level analysis of brain activity using a cluster-based threshold of $p < 0.05$ (FWE-corrected) following a primary uncorrected threshold of $p < 0.0001$ (Woo et al., 2014). The results demonstrated significant brain activity in the bilateral S2, Heschl's gyrus, insula, inferior parietal lobule, rolandic operculum and parietal operculum during back proprioceptive processing in both groups (See Supplemental Table I).

4.2. Brain activity during proprioceptive processing: within-group differences

Both groups showed increased brain activity during the processing of ankle compared to back proprioception. However, the spatial extent of this increased activation was larger in the NSLBP group compared to the healthy group (See Tables 4 and 6). Indeed, only the NSLBP group demonstrated increased brain activity in the anterior cerebellar vermis and the right putamen. The anterior vermis is part of the 'sensorimotor' cerebellum (Stoodley and Schmahmann, 2009; Stoodley et al., 2012), and has been shown to play a crucial role in regulating the upright standing posture (Caeyenberghs et al., 2015; Coffman et al., 2011; Colnaghi et al., 2017), whereas the right putamen is suggested to play an important role in analyzing proprioceptive signals, in-between lower-level somatosensory and higher-order associative processing (Goble et al., 2012).

4.3. Correlations between brain activity during proprioceptive processing and postural control

In contrast to earlier research (Brumagne et al., 2004; Brumagne et al., 2008; Claeys et al., 2011), patients with NSLBP did not exhibit an impaired use of proprioception during postural control. Indeed, both groups adequately decreased the use of ankle proprioception when switching from the stable to the unstable support surface. This inconsistency with previous studies could be explained by the presence of a continuum of proprioceptive postural control changes in the NSLBP population, as recently proposed by van Dieën et al. (2018). In this review, an elegant explanation for the inconsistent findings characterizing the current literature on motor control changes in patients with NSLBP is provided. The authors argue that motor control changes (incl. postural control changes) in NSLBP might present themselves along a continuum, with two so-called "phenotypes" at either end. The first phenotype exhibits "tight" control through co-contraction and increased reflex gains of trunk muscles and enhanced attention (van Dieën et al., 2018), which could induce smaller COP displacements during vibration and a loss of variability in proprioceptive postural control in some patients with NSLBP. In contrast, the second phenotype shows "loose" control with reduced co-contraction (van Dieën et al., 2018), and potentially increased COP displacements during vibration. Between these phenotypes, a group of individuals exhibiting optimal proprioceptive postural control might exist. Such a continuum of proprioceptive postural control strategies might have been present in the current NSLBP sample, as substantial variability in the postural responses on muscle vibration was found (see Fig. 2). However, the presence of such a continuum, and the phenotypes at either end, remains to be demonstrated in larger samples with NSLBP. Second, disparities between our results and those of previous research could relate to differences in disability; the current NSLBP group showed higher disability indices (mean ODI-2 = 19.5%) compared to patients with NSLBP in previous studies (mean ODI-2 = 8.8% in (Claeys et al., 2011)). Third, differences in the level of psychosocial contribution might explain disparities between our and previous results. However, this hypothesis cannot be verified at this time, as previous studies using the TSK did not investigate a potential relationship with proprioceptive use during postural control (Claeys et al., 2011). Also, it is possible that other psychosocial determinants than fear of movement, e.g., anticipation of pain, perceived threat, and perceived harmfulness of the

Table 7
Voxel-wise regression analysis, correlation between brain activity during proprioceptive processing and postural control across groups.

			MNI coordinates (mm)			t-value	Correlation coefficient
	Side	$p(FWE)_{SVC}$	x	y	z		
Ankle proprioception							
COP displacement during ankle muscle vibration on the unstable support surface							
Thalamus (prefrontal)	L	0.057	−18	−6	8	3.98	0.54
STSTS performance on the unstable support surface							
Inferior frontal gyrus (*p. orbitalis*)	R	0.024	46	42	−8	3.97	0.54
Amygdala (p. laterobasalis)	L	0.029	−26	−4	−26	4.15	0.56
Hippocampus (CA1)	L	0.049	−20	−12	−24	3.71	0.52
Back proprioception							
COP displacement during back muscle vibration on the unstable support surface							
Amygdala (p. laterobasalis)	R	0.049	26	0	−26	- 3.49	- 0.49

Significant peaks are labeled with the Automated Anatomical Labeling (AAL) toolbox. Cytoarchitectonic areas from the SPM Anatomy Toolbox with a probability > 30% are provided between brackets. MNI = Montreal Neurological Institute, R = right, L = left.

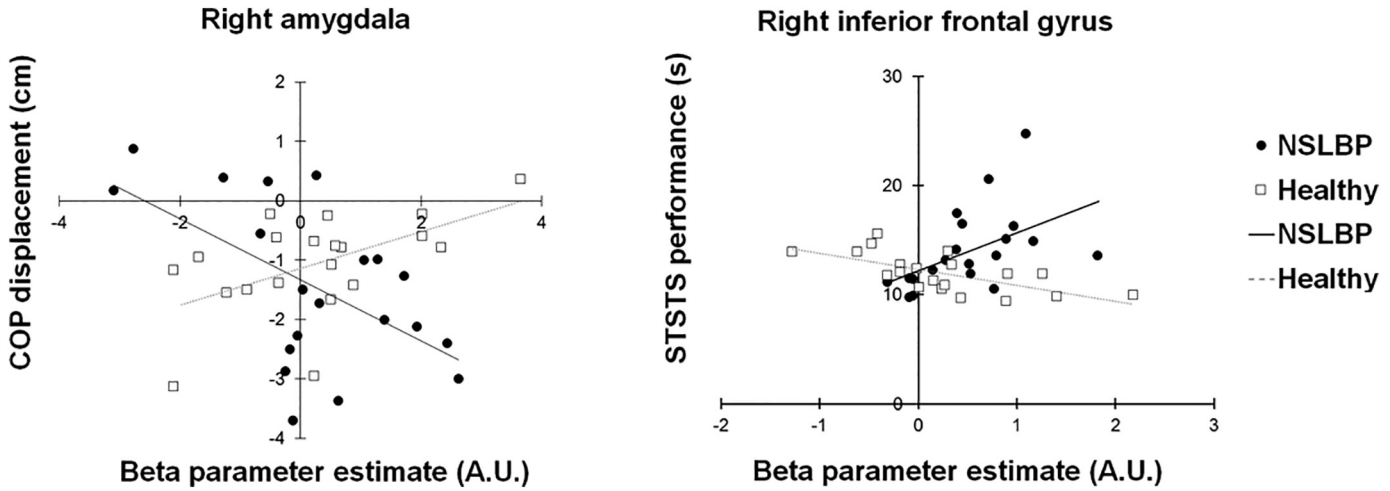

Fig. 4. Group differences in the relationship between brain activity during ankle proprioceptive processing and postural control in patients with NSLBP and healthy controls. COP: center-of-pressure, STST: sit-to-stand-to-sit, NS: non-significant after SVC-correction.

postural task, correlate to postural control. However, this needs to be investigated in future studies.

Because group differences in proprioceptive use during postural control could not be found, we did not compare brain activity between groups. Instead, we examined covariance between brain activity and behavioral measures of proprioceptive postural control across groups, and then further explored group differences in brain-behavior relationship. The results revealed that, across groups, increased activation during ankle proprioceptive processing in the left thalamus, well-known for its role in gating and modulating sensory input flow to the cortex (Sherman and Guillery, 2006), tended to correlate with a reduced use of ankle proprioception during standing on the unstable support surface. This strategy is considered to be more optimal, as ankle proprioception loses reliability due to a mismatch between perceived and actual ankle angles in this particular condition (Ivanenko et al., 1999; Karim et al., 2012). These results are in line with previous research in healthy subjects (Jahn et al., 2004), patients with ischemic thalamic infarction (Karnath et al., 2000), and individuals with progressive neuronal degeneration of subcortical nuclei (Zwergal et al., 2011) demonstrating the importance of the thalamus for static postural control. Furthermore, we found across groups that individuals exhibiting higher activation of the right amygdala during back proprioceptive stimulation were less able to up-weight back proprioception when needed. Interestingly, patients with NSLBP also demonstrated a stronger association between activation of the right amygdala during ankle proprioceptive processing and an impaired use of ankle proprioception compared to healthy individuals (near significant interaction effect). The amygdala plays a crucial role in the emotional

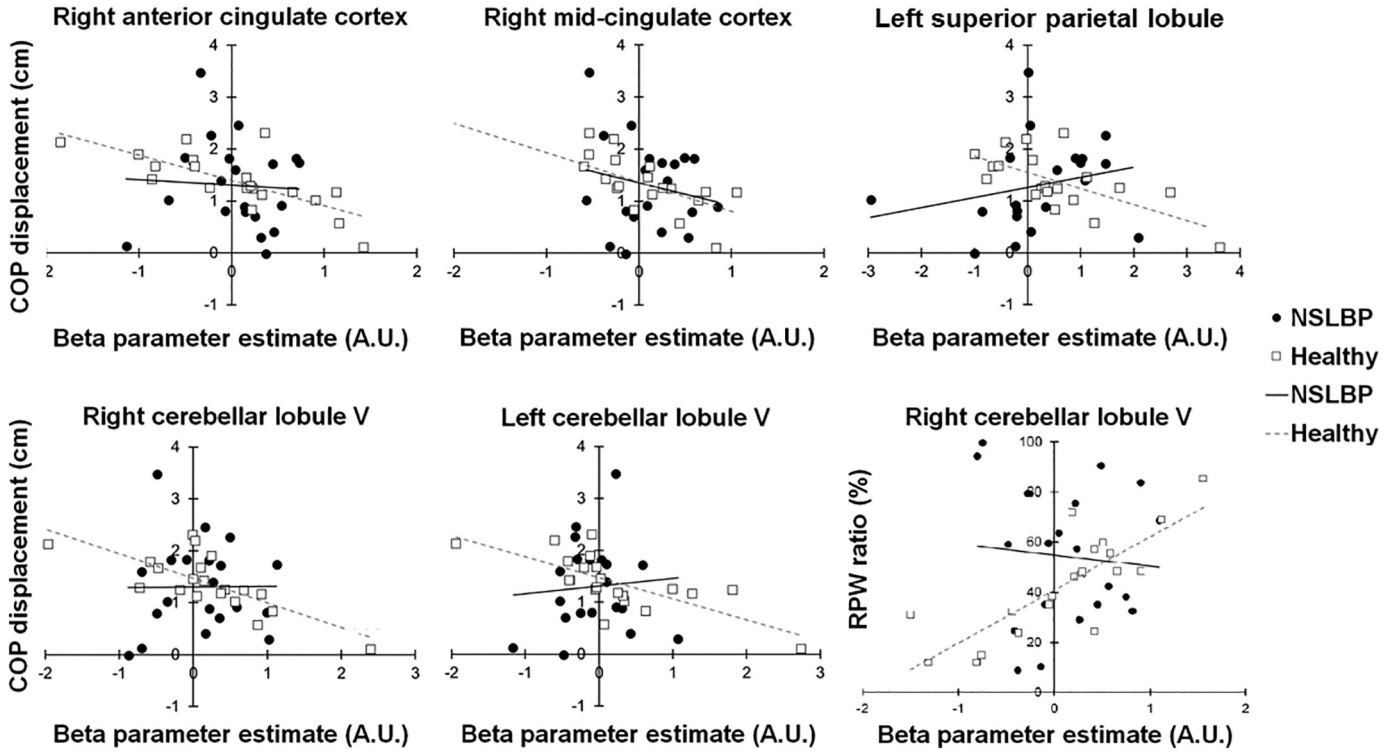

Fig. 5. Group differences in the relationship between brain activity during back proprioceptive processing and postural control in patients with NSLBP and healthy controls. COP: center-of-pressure, RPW: relative proprioceptive weighting, Sign: significant after SVC-correction, NS: non-significant after SVC-correction.

processing of sensory inputs linked to e.g., fear and disgust (Phan et al., 2002; Costafreda et al., 2008) and is important in fear conditioning, threat detection and vigilance regulation (Davis and Whalen, 2001; Phelps and LeDoux, 2005). Together, these results could indicate that proprioceptive stimulation induced a shift of neural resources towards threat detection, or a heightened fear-response, in some individuals, which in turn negatively influenced postural control.

Furthermore, the results revealed a significant difference between groups in the association between activity in the bilateral cerebellar lobules V and left superior parietal lobule during back proprioceptive processing and the use of proprioception during standing on the unstable support surface. For the cerebellar lobules, this result was driven by a significant negative relationship between brain activity and behavioral scores in the healthy control group, indicating that more brain activity correlated with a less optimal use of proprioception (left cerebellar lobule: increased brain activity correlated with smaller COP displacements during back muscle vibration; right cerebellar lobule: increased brain activity correlated with higher RPW scores). For the left superior parietal lobule, the follow-up analysis showed that while increased activity was associated with a better use of back proprioception in the NSLBP group (i.e., larger response on back muscle vibration), it correlated with a less optimal use of back proprioception (i.e., smaller response on back muscle vibration) in the healthy controls). The superior parietal lobule receives multimodal somatosensory signals from primary areas and processes it at a higher level (Scheperjans et al., 2005), while the cerebellar lobule V is crucial for sensorimotor and postural control (Stoodley and Schmahmann, 2009; Stoodley et al., 2012; Manto et al., 2012; Zwergal et al., 2012). Hence, these results could suggest that some patients with NSLBP were adequately able to increase the use of back proprioception when needed, though this required an over-activation of the superior parietal lobule compared to healthy controls.

Though group differences in proprioceptive use during static standing could not be found, patients with NSLBP did perform worse on the dynamic STSTS task, which was consistent with earlier research (Claeys et al., 2012). Previous studies from our research group demonstrated a neural basis for this postural control impairment in patients with NSLBP, i.e., a slower STSTS performance correlated with a cortical thinning of the anterior cingulate cortex and a topological reorganization of the structural brain network (Caeyenberghs et al., 2017; Pijnenburg et al., 2016). In the current study, it was demonstrated that activity in the left amygdala, left hippocampus and orbital part of the right IFG (or orbitofrontal cortex) during ankle proprioceptive processing correlated with a slower STSTS performance across groups. The hippocampus plays a crucial role in learning, episodic memory and spatial navigation (O'Keefe and Nadel, 1978; Eichenbaum, 2000; Squire and Wixted, 2011), while the right orbitofrontal cortex has been shown to be important for maintaining an upright standing posture during complex postural conditions (Goble et al., 2012; Helmich et al., 2016). Moreover, patients with NSLBP exhibited a stronger correlation between a worse STSTS performance and increased activity of triangular part of the right IFG, involved in the integration of multi-sensory inputs (Amemiya and Naito, 2016; Naito et al., 2016a; Naito et al., 2016b), during ankle proprioceptive processing compared to the healthy group (interaction effect). These results possibly suggest that over-activation of the IFG in the NSLBP group was insufficient (or perhaps detrimental) for optimal dynamic postural control. However, as no proprioceptive stimulation was provided during the STSTS task, as highlighed in the limitations, above-mentioned results need to be interpreted with caution.

4.4. Pain-related fear of movement

Finally, the results showed that patients with NSLBP reported significantly more fear of movement than the healthy group, corroborating previous studies (Vlaeyen and Crombez, 1999). However, no significant correlations with postural control were found. This could be explained by the notion that fear of movement is only associated with altered task performance if patients overestimate the painfulness of the movements they are asked to perform (Huijnen et al., 2010). It is possible that none of the patients with NSLBP in the current study expected the postural control tasks to provoke pain. This highlights that “generalized” fear of movement (as assessed with TSK) might not be as relevant as “situational” fear of movement that depends on each individual's history of pain during movement (Ellingsen et al., 2018). Moreover, contemporary evidence indicates that fear avoidance is context-dependent and becomes most prominent when threats are imminent and inevitable (Glombiewski et al., 2015; Meulders et al., 2011; Vlaeyen et al., 2016). This was not the case in the current study, as we never intended to create a context of ‘danger’ or ‘unsafety’ when evaluating postural control.

4.5. Limitations

A number of limitations must be acknowledged. First, by using a ROI approach and small volume correction to examine group differences in proprioceptive processing, legitimate results in other brain areas may have been missed. However, our a priori selection of ROIs was based on previously published studies that used highly similar experimental protocols to investigate neural correlates of proprioception with fMRI. Second, the cross-sectional design of this study does not allow conclusions on causality between brain changes, postural control impairments and NSLBP to be made. Third, the use of a slightly lower cut-off of 18% on the ODI-2, compared to the proposed cut-off of 20%, to include moderately disabled patients with NSLBP can be considered as a limitation (Fairbank and Pynsent, 2000). However, this value was chosen to ensure that patients complied with the remaining eligibility criteria, mainly in view of fMRI-compatibility. Fourth, though differences between the vibration protocols used during fMRI-scanning and the evaluation of proprioceptive postural control were minimized (i.e., identical stimulation areas and frequency, demonstrated concurrent validity of pneumatic compared to electromagnetic vibrating devices, similar tension on straps as vibrators were applied by the same experienced researcher, equal levels of anticipation/attention as the purpose of applying muscle vibration was not disclosed in either test session, occluded vision in both sessions), we cannot exclude that the 3 s difference in stimulus duration and differences in body position (lying during fMRI vs. standing during postural control assessment) influenced the activation of muscle spindles and/or processing of proprioceptive inputs. In terms of the difference in body position, withdrawal reflexes, for example, have been shown to be modulated by functional context; while during weight-bearing, a painful stimulation at the foot sole induced an unloading of the stimulated leg and loading of the contralateral leg, the same stimulus elicited a flexion of the leg during sitting (Andersen et al., 1999; Andersen et al., 2003). Hence, future research should investigate brain activity during proprioceptive processing online, during upright standing when the proprioceptive system is challenged. Moreover, as EMG activity was not recorded due to incompatibility with the fMRI and vibration environments, we cannot rule out that re-afferences from involuntary muscle contractions evoked by muscle vibration influenced brain activity patterns. However, previous fMRI-studies either reported very limited (Radovanovic et al., 2002) or no EMG activity during muscle vibration (Amemiya and Naito, 2016; Naito et al., 1999). Furthermore, STSTS performance was evaluated indirectly by recording the total duration to execute five successive STSTS movements. Although time is a rather indirect measure of functional behavior, this outcome measure was chosen as it demonstrates good test-retest reliability in patients with NSLBP (Denteneer et al., 2018), because it can discriminate between patients with NSLBP and pain-free subjects (Caeyenberghs et al., 2017; Claeys et al., 2012; Pijnenburg et al., 2015; Pijnenburg et al., 2016), and because it is a highly functional activity of daily life. Moreover, Claeys

et al. (2012) demonstrated that the slower performance of STSTS movements observed in patients with NSLBP was determined by slower preparatory/transitional phases (but not slower movement phases), during which optimal pelvic and proprioceptive postural control is crucial (Claeys et al., 2012). However, we cannot rule out that between-group differences in lower limb strength, pain, psychological factors, motor planning and short-term memory, in addition to proprioceptive impairments, influenced STSTS performance. Additionally, the results on proprioceptive reweighting during postural control were not in line with our expectations. Future studies should investigate the existence of a continuum of proprioceptive postural control changes within the NSLBP population, and the potential influence of psychosocial aspects other than fear of movement, such as the expected harmfulness of movements, on postural control. Moreover, the use of non-linear measures of COP displacement in response to muscle vibration, as well as during the recovery after muscle vibration could be considered to investigate static postural control impairments in NSLBP (van den Hoorn et al., 2018). Finally, the cortical mapping of lower back proprioception could benefit from future studies investigating more optimal stimulation paradigms.

5. Conclusions

This study was the first to examine brain activity during proprioceptive processing in individuals with and without NSLBP. The results revealed that patients with NSLBP showed more fear of movement and needed more time to perform a STSTS task compared to pain-free controls. Though no significant group differences in proprioceptive use could be found, substantial between-subject variability in the NSLBP group suggested the presence of subgroups exhibiting intact versus impaired proprioceptive postural control. The brain-behavior correlations demonstrated that, in order to maintain an optimal ability to adapt proprioceptive use to the immediate postural demands, patients with NSLBP might require increased activation of a sensory processing region. Moreover, applying proprioceptive stimuli elicited increased activation of brain areas involved in threat detection and fear processing in some individuals, which was associated with a worse proprioceptive postural control. These findings may help to elucidate the neural correlates of postural control impairments in individuals with NSLBP. However, future studies are needed to clarify the cause-effect relationship between functional brain changes and NSLBP, and to examine which interventions could aid in normalizing brain changes and postural control in this population.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101881.

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