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Experience-dependent neuroplasticity in trained musicians modulates the effects of chronic pain on insula-based networks – a resting-state fMRI study

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Abstract

Recent resting-state fMRI studies associated extensive musical training with increased insula-based connectivity in large-scale networks involved in salience, emotion, and higher-order cognitive processes. Similar changes have also been found in chronic pain patients, suggesting that both types of experiences can have comparable effects on insula circuitries. Based on these observations, the current study asked the question whether, and if so in what way, different forms of experience-dependent neuroplasticity may interact. Here we assessed insula-based connectivity during fMRI resting-state between musicians and non-musicians both with and without chronic pain, and correlated the results with clinical pain duration and intensity. As expected, insula connectivity was increased in chronic pain non-musicians relative to healthy non-musicians (with cingulate cortex and supplementary motor area), yet no differences were found between chronic pain non-musicians and healthy musicians. In contrast, musicians with chronic pain showed decreased insula connectivity relative to both healthy musicians (with sensorimotor and memory regions) and chronic pain non-musicians (with the hippocampus, inferior temporal gyrus, and orbitofrontal cortex), as well as lower pain-related inferences with daily activities. Pain duration correlated positively with insula connectivity only in non-musicians, whereas pain intensity exhibited distinct relationships across groups. We conclude that although music-related sensorimotor training and chronic pain, taken in isolation, can lead to increased insula-based connectivity, their combination may lead to higher-order plasticity (metaplasticity) in chronic pain musicians, engaging brain mechanisms that can modulate the consequences of maladaptive experience-dependent neural reorganization (i.e., pain chronification).

Keywords: experience-dependent neuroplasticity, insula, musicians, chronic pain, resting-state fMRI, sensorimotor training.

1. Introduction

Musical training has been widely used as a framework for understanding the mechanisms by which experience can modify various aspects of brain function and structure (Barrett et al., 2013; Herholz and Zatorre, 2012; Jancke, 2009; Klein et al., 2016; Lappe et al., 2011; Pantev et al., 2015; Rosenkranz et al., 2007; Schlaug, 2015). A common finding is that accumulated musical training leads to several adaptive (i.e., beneficial) effects on the brain, meaning that plastic changes in neural systems correlate with enhanced performance at behavioral levels (Foster and Zatorre, 2010; Hyde et al., 2009; Schneider et al., 2002). This principle has also been supported by training paradigms with adult non-musicians (Chen et al., 2012; Lahav et al., 2007). In trained musicians, however, earlier commencement with skill acquisition coincides with a greater extent of neuroplastic changes (Baer et al., 2015; Elbert et al., 1995; Kleber et al., 2016; Penhune, 2011; Schlaug, 2015; Steele et al., 2013). On the other hand, extensive repetitive sensorimotor training required for mastering a musical instrument also has a dark side. Particularly, as extensive practice routines can also lead to the development of focal dystonia (Altenmüller, 2003) and chronic pain (Steinmetz et al., 2015). While compromised motor function in focal dystonia has been attributed to maladaptive changes in the brain (Altenmüller et al., 2015; Altenmüller and Muller, 2013), however, the pathophysiology underlying chronic pain in skilled musicians remains unknown.

Epidemiological studies indicate that about 80% of musicians experience musculoskeletal pain syndromes throughout their careers (Cruder et al., 2018; Kok et al., 2016; Steinmetz et al., 2015), an incidence rate that is about 60% higher than in the general population (Breivik et al., 2006) and that it is even higher in music students (Brandfonbrener, 2009; Steinmetz et al., 2012). Etiological factors that have been linked

to this above-average occurrence of pain syndromes include age, gender, accumulative playing time in combination with repetitive movements and instrument specific ergonomics, high-stress performance situations, and psychological traits (Ioannou et al., 2018; Jabusch et al., 2004; Kenny and Ackermann, 2013; Steinmetz et al., 2015). However, a neural explanation is lacking. We propose that the heightened and continuous integration of sensory and motor information may facilitate the development of pain syndromes, in line with primate genesis models of repetitive strain injuries (Byl et al., 1996).

Neurobiological investigations of pain syndromes have associated the transition from acute to chronic pain with maladaptive processes in neural circuits (Kuner and Flor 2016). This includes altered brain dynamics associated with impaired descending inhibition (Gebhart, 2004; Porreca et al., 2002), abnormal brain connectivity patterns during resting state (Balenzuela et al., 2010; Baliki et al., 2011; Baliki et al., 2014; Ichesco et al., 2014), and maladaptive cortical reorganization (Flor et al., 1997; Flor et al., 1995). Within these brain dynamics, the insular cortex is consistently reported as a critical network-hub in the processing of both acute and chronic pain (Cottam et al., 2018; Tan et al., 2017). Specifically, the posterior insula (PI) is associated with pain discrimination and the anterior insula (AI) with pain awareness (Craig, 2002; Craig, 2009b; Segerdahl et al., 2015; Wiech et al., 2014). Increased functional connectivity between the insula and other modulatory brain areas (i.e., anterior cingulate cortex, ACC, and medial prefrontal cortex, mPFC) has therefore been suggested as a form of maladaptive neuroplasticity that contributes to pain chronification (Baliki et al., 2011; Cifre et al., 2012; Ichesco et al., 2012; Ichesco et al., 2014).

On the other hand, recent resting-state fMRI studies with healthy musicians also reported increased insula-based connectivity compared to healthy non-musicians,

particularly with brain regions involved in body awareness, salience processing, executive control, and emotional experience (Luo et al., 2014; Zamorano et al., 2017). The insula is also known to support interoceptive awareness (Critchley et al., 2004), which seems to be enhanced in musicians and dancers (Christensen et al., 2017; Schirmer-Mokwa et al., 2015). An enhancement of sensory awareness following sensorimotor training may thus be associated with insula-based plasticity, representing a neural correlate for comparable acute pain sensitivity in healthy musicians and chronic pain patients relative to healthy non-musicians at the behavioral level (Zamorano et al., 2014). This suggests that experience-dependent adaptation of the insula at the network level could pose a risk for the development of pain-related maladaptive neuroplastic processes, for example by provoking the loss of central endogenous pain control mechanisms (Bushnell et al., 2013; Ossipov et al., 2014). However, recent studies have found that musicians are able to segregate and integrate task-related multisensory signals in the presence of sensory perturbations by adaptively regulating insula connectivity in order to maintain performance accuracy (Kleber et al., 2017; Kleber et al., 2013). A similar strategy could be employed to help regulating sensory inputs and pain perception in order to continue musical performance and practice in the presence of repetitive strain injuries.

To address and dissociate these questions, we examined patterns of fMRI resting-state brain connectivity in musicians and non-musicians both with and without chronic pain. Acknowledging the importance of the insula as a sensory integration hub, we used a seed-based approach following the functionally defined tri-partite model of insula sub-regions provided by Deen and colleagues (2011). We hypothesized that insula-based connectivity with posterior (PI), ventral anterior (vAI), and dorsal anterior (dAI) insula reflects changes in central processing due to intensive sensorimotor training and chronic pain. Following our previous behavioral observations (Zamorano et al., 2014), we

proposed that healthy musicians and chronic pain non-musicians would demonstrate similar patterns of insula co-activation. Given that, both chronic pain and sensorimotor music training have been associated with greater insula connectivity (Baliki et al., 2011; Cifre et al., 2012; Ichesco et al., 2014; Luo et al., 2014; Zamorano et al., 2017), we furthermore expected accumulative effects in neural circuits in chronic pain musicians. Alternatively, we also considered the possibility that enhanced regulation of multisensory inputs might lead to different insula connectivity patterns in chronic pain musicians (Kleber et al., 2017; Kleber et al., 2013).

2. Materials and methods

2.1. Participants

Participants with chronic pain consisted of 12 professional classical musicians (chronic pain musicians, CPM; mean age 26.4 ± 8.7 yrs) and 14 non-musicians (chronic pain non-musicians, CPNM, 31.9 ± 7.8 yrs). All of them suffered from persistent upper back pain (neck and/or dorsal back pain) for more than 6 months, of which three participants suffered additionally from lower back pain. Healthy participants consisted of 11 classical musicians (healthy musicians, HM; mean age 32.3 ± 11.4 yrs) and 12 non-musicians (healthy non-musicians, HNM; 28.1 ± 7.3 yrs), who also participated in our previous study (Zamorano et al., 2017). No participant used opiates, gabapentin, or pregabalin for pain treatment. One CPM and three CPNM occasionally used nonsteroidal anti-inflammatory drugs (NSAIDs) and/or paracetamol. Medication for non-pain related disorders involved birth control and female hormonal drugs (n = 3 CPM). Three CPNM took benzodiazepine (1-5mg per day), of which one also took serotonin reuptake inhibitors. One HM was removed due to fMRI artifacts. Due to reported sex differences in the processing of pain (Fillingim et al., 2009), all participants were female. Exclusion criteria included the presence of neurological

diseases or pregnancy. All participants were verbally informed about the details of the study and provided written consent. The study was performed in accordance with the Declaration of Helsinki (1991) and approved by the Ethics Committee of the Balearic Islands.

2.2. Musical Expertise

All musicians were conservatory-trained instrumentalists. CPM consisted of 8 string, 3 keyboard, and 1 wood-wind players. Seven CPM were musical students and five were professional orchestral musicians and soloist. HM consisted of 5 string, 2 piano, and 4 wood-wind players. Five HM were musical students and the other six were professional orchestral and soloist musicians. The average amount of accumulated musical training was 19.2 (± 9.4) years for CPM and 20.5 (± 5.9) years for HM. The average hours of daily practice was 4.1 (± 1.7) and 3.6 (± 2.2) hours, respectively. The average age at commencement with formal musical training was 7.2 (± 2.6) years in CPM and 8.6 (± 2.9) years in HM. Non-musicians did not receive any kind of formal or informal musical training.

2.3. Psychometric and clinical assessment

All participants completed the Spanish versions of Beck's Depression Inventory II – BDI (Sanz et al., 2003) and the State-Trait Anxiety Inventory - STAI (Spielberger et al., 1971). The Edinburgh Handedness Inventory determined handedness (Oldfield, 1971). Chi-square tests were adopted for testing the distribution of right and left hand dominance in all groups. Participants with chronic pain underwent a semi-structured clinical interview, including questions about pain duration, intensity, and location, as well as psychosocial factors involved in the maintenance of pain by completing the West-Haven Yale Multidimensional Pain Inventory of Pain - WHYMPI (Kerns et al., 1985). Moreover, subjective ratings of current pain intensity were assessed immediately

after the rs-fMRI scan in all participants to control for the possible effects of the scanner noise and the restrained posture on discomfort and pain.

2.4. fMRI image acquisition and preprocessing

fMRI image acquisition and preprocessing parameters were equal to our previous study (Zamorano et al., 2017). Magnetic resonance imaging was performed with a 3 Tesla Signa HDx scanner (General Electric, GE Healthcare, Milwaukee, WI). Whole brain echo-planar images (n=240) were acquired over a period of 10 minutes with eyes closed (32 transversal slices per volume; 3 mm slice thickness; 90 degrees flip angle; repetition time [TR]: 2500 ms; echo time [TE]: 35 ms; 64 x 64 matrix dimensions; 200 mm field of view). Structural imaging consisted of T1-weighted images (176 slices per volume; repetition time [TR]: 7796 ms; echo time [TE]: 2.98 ms; matrix dimensions, 512 x 512; 240 mm field of view; 1 mm slice thickness; 12 degrees flip angle). Scanner noise was decreased by -36db using in-ear hearing protection. In addition, MRI foam-cushions were placed over the ears to restrict head motion and to further reduce scanner noise.

Functional image preprocessing was performed with the Data Processing Assistant for Resting-State fMRI (DPARSF; Chao-Gan and Yu-Feng, 2010) based on the Statistical Parametric Mapping software package (SPM8; http://www.fil.ion.ucl.ac.uk/spm) and the Data Processing & Analysis of Brain Imaging toolbox (DPABI; http://rfmri.org/DPABI DPARSF_V3.1_141101). The first 10 volumes from each data set were discarded prior to preprocessing. Following slice-time correction and co-registration, gray and white matter were segmented from co-registered T1 images using the unified segmentation model (Ashburner and Friston, 2005). The resulting parameter file was used to normalize the functional images ($3mm^3$ voxel size) to standard Montreal Neurological Institute (MNI) stereotactic space, subsequently smoothed with an isotropic Gaussian kernel (FWHM: $6mm^3$). Nuisance regression parameters included

white matter (WM), cerebrospinal fluid (CSF), and the six head motion parameters. WM and CSF masks were generated using SPM's a priori tissue probability maps (empirical thresholds: 90 % for WM mask and 70 % for CSF mask). No global signal regression was performed to avoid introducing distortions of BOLD signal (Murphy et al., 2009). Head motion was below 2.0 mm maximum displacement or 2.0º of any angular motion for all participants. A temporal filter (0.006–0.1 Hz) was applied to reduce low frequency drifts and high frequency physiological noise.

2.5. Voxel-wise functional connectivity analyses

Six functionally segregated insular subdivisions were provided as template images in MNI stereotactic space by Deen and colleagues (2011). They consisted of (left and right) posterior (PI), dorsal anterior (dAI), and ventral anterior (vAI) insula (mean coordinates are given in Supplementary Table S1). These six regions of interest (ROIs) were used as seeds to determine their individual connectivity patterns (averaged time course) and were entered into a voxel-wise correlation analysis to generate functional connectivity maps. Correlation coefficients were converted into z values using Fisher's r-to-z transformation in order to improve data normality before submitting them to statistical analyses (Rosner, 2011).

2.6. Statistical analyses

2.6.1. fMRI

Statistical analyses were performed in SPM8 and data entered into a 2 x 2 full-factorial ANOVA with the factors MUSICIANSHIP (musicians *vs* non-musicians) and PAIN (chronic pain *vs* healthy) for each of the six insula sub-divisions, analogous to our previous approach (Zamorano et al., 2017). First, we performed post-hoc one-sample t-tests to validate connectivity patterns per insula subdivision in each group against

previously published data (Deen et al., 2011; Uddin et al., 2014; Zamorano et al., 2017). For this reason, voxel-based familywise error corrected (FWER) significance threshold of $p < 0.05$ was employed for this test to be maximally comparable with these previous studies.

An F-test assessed main and interaction effects between the factors MUSICIANSHIP and PAIN, followed by post-hoc Student's t tests comparing (i) CPNM with HNM, (ii) HM with CPNM, (iii) CPM with CPNM, and (iv) CPM with HM.

For the aforementioned tests, we used a cluster-extent based thresholding method to correct for multiple comparisons. Cluster-extent based thresholding reflects the spatially correlated nature of fMRI signal, accounting for the fact that individual voxel activations are not independent of the activations of their neighboring voxels in spatially smoothed data (Friston et al. 2000; Heller et al. 2006; Wager et al. 2007). This widely used method in fMRI research is more sensitive (i.e., more powerful) to detect true activations in studies with moderate sample sizes (reducing Type II errors), while effectively controlling for Type I errors (Friston et al. 1994; Smith and Nichols 2009; Woo et al. 2014)(Nichols and Hayasaka, 2003). We employed cluster-extent based thresholding using Monte Carlo simulation as implemented in DPABI's instantiation of AlphaSim (Cox, 1996; Song et al., 2011; Yan et al., 2016). We used a stringent primary voxel-threshold of $p< 0.001$ and smoothness estimation based on the spatial correlation across voxels to reduce the possibility of obtaining false positive clusters (i.e., inaccurate FWER correction at $p<.05$) and/or large activation clusters, which also improves the degree of confidence in inferences about specific locations/voxels (Woo et al., 2014). Only clusters surviving the FWER probability threshold were used for statistical inference.

2.6.2. Behavioral

The effects of age, anxiety, and depression on musicians and non-musicians were assessed using analyses of variance (ANOVAs) with the between-subject factors MUSICIANSHIP (musicians *vs* non-musicians) and PAIN (chronic pain *vs* healthy individuals). Age and psychometric test results (STAI and BDI questionnaires) were used as dependent variables. Significant interactions were examined using Bonferroni corrected post-hoc pairwise comparisons.

In CPM and CPNM, two-sample t-tests were performed on the variables "pain duration", "pain intensity", and the "WHYMPI" subscales. In musicians, two-sample t-tests were also run on music experience data. Statistical significance was set to $p < 0.05$. Analyses were carried out with SPSS (v.19, SPSS Inc., Chicago, IL, USA).

2.6.3. Regression

Multiple regression analyses were performed in SPM8 for each insular ROI to assess connectivity maps in relation to the amount of years suffering pain and pain intensity in CPM and CPNM. In CPM, multiple regressions were also performed with accumulated musical training. Cluster-extent FWER correction was applied as detailed above.

In order to estimate the magnitude of both significant behavioral and functional connectivity results, we computed effect sizes for F-tests, multiple regression, and post-hoc t-tests using the formulas of *Cohen's f^ (f^ = sqrt((df$_{effect}$/N)(Feffect - 1)), Cohen's f2 (f2= R2/1-R2),* and *Cohen's d (d = 2t / sqrt(df))*, respectively (Cohen, 2013). In a second step, to control for an overestimation of effect sizes due to the moderate sample size of our groups, we posteriorly adjusted *Cohen's d* by computing the *unbiased Cohen's d:* $d_{unbiased} = d\,[1 - (3 / 4df - 1)]$ (Fritz et al., 2012).

Significantly activated peak-voxels refer to MNI coordinates. Anatomical areas were assigned using the Anatomy Toolbox whenever possible (Eickhoff et al., 2005).

Otherwise, the Automated Anatomical Labeling atlas of Tzourio-Mazoyer was used (AAL; 2002).

2.7. Data availability

The data that support the findings of this study are available upon reasonable request from the corresponding author, [AZ]. The data are not publicly available due to legal restrictions, as the containing information could compromise the privacy of research participants.

3. Results

3.1. Demographic and psychometric data

Chi-square tests revealed that handedness did not differ in any of the groups formed by the factors MUSICIANSHIP and PAIN (X^2 (4, N = 48) = 2.244, p =0.523). Likewise, ANOVAs (Table 1) revealed no significant differences in age (F(1,44) = 3.07, p = 0.61; $\tilde{f}$ = 1.37), anxiety (STAI-state: (F(1,43) = 3.32, p = 0.075; $\tilde{f}$ = 1.45), or depression (BDI, (F(1,43) = 1.051, p = 0.311; $\tilde{f}$ = 0.21). Post-hoc t-tests revealed no significant differences between CPM and CPNM regarding pain intensity ratings (t(1,23) = 0.424, p = 0.521; d_{unb} = 0.17) and pain duration (t(1,23) = 0.987, p = 0.331; d_{unb} = 0.40). In contrast, pain interference with other activities (WHYMPI) was significantly different between CPM and CPNM for household chores activities (t(1,23) = 3.201, p < 0.005; d_{unb} = 1.31), outdoor work (t(1,23) = 2.451, p < 0.05; d_{unb} = 1.00), social activities (t(1,23) = 2.237, p < 0.005; d_{unb} = 0.91), and general activity (t(1,23) = 3.396, p < 0.005; d_{unb} = 1.39), indicating greater interferences in non-musicians (Table 1). CPM and HM did not differ with respect to their total years of training (t(1,20) = 0.447, p = 0.660; d_{unb} = 0.19), daily amount of practice (hours) (t(1,20) = 0.132, p = 0.896; d_{unb} = 0.05), and age of onset with music training (t(1,20) = 1.196, p = 0.246; d_{unb} = 0.52).

Table 1. Psychometric and clinical characteristics of all participants

	Musicians		Non-musicians	
	Chronic pain (n=12)	Healthy (n=10)	Chronic pain (n=14)	Healthy (n=12)
Age (y)	26.4 (8.7)	32.3 (11.4)	31.9 (7.8)	28.1(7.3)
Dominant Hand (L/R)	2/10	1/9	1/13	0/12
Age of onset musical training	7.2 (2.6)	8.6 (2.9)	N/A	N/A
Accumulated musical training (years)	19.2 (9.4)	20.5 (5.9)	N/A	N/A
Daily music practice (hours)	4.1 (1.7)	3.6 (2.2)	N/A	N/A
Average pain intensity (0-10 NRS)	4.1 (2.0)	N/A	3.6 (2.0)	N/A
Pain intensity after scan	3.25 (2.4)	0.27 (0.45)	3.76 (2.4)	0 (0)
Duration of pain (years)	7.2 (3.5)	N/A	8.6 (5.8)	NA
Depression	6.7 (5.8)	6.2 (6.7)	9.4 (9.7)	4.6 (3.8)
State Anxiety	18.4 (10.5)	12.1 (5.4)	10.8 (6.8)	14.2 (11.6)
Trait Anxiety	17.4 (8.8)	12.4 (3.8)	17.1 (12.2)	13.8 (8.4)
WHYMPI				
Interference	1.8 (1.1)	N/A	2.2 (1.6)	N/A
Support	3.7 (1.1)	N/A	3.1 (1.6)	N/A
Pain Severity	2.6 (1.2)	N/A	2.7 (1.3)	N/A
Life-Control	3.7 (1.3)	N/A	3.8 (1.2)	N/A
Affective Distress	2.2 (1.4)	N/A	2.5 (1.5)	N/A
Negative Responses	1.0 (1.5)	N/A	0.7 (0.9)	N/A
Solicitous Responses	3.5 (0.8)	N/A	3.5 (1.5)	N/A
Distracting Responses	3.4 (1.3)	N/A	2.9 (1.4)	N/A
Household Chores	1.3 (0.9)	N/A	2.5 (0.9)**	N/A
Outdoor work	2.9 (0.9)	N/A	3.8 (0.9)*	N/A
Activity away from home	2.6 (1.4)	N/A	3.6 (1.1)	N/A
Social activities	3.1 (1.7)	N/A	4.3 (1.1)*	N/A
General activity	2.5 (0.7)	N/A	3.5 (0.7)**	N/A

Abbreviations: L, left; R, right; N/A, not applicable. Pain intensity: 0 = no pain at all and 10 = the strongest imaginable pain. WHYMPI: The West Haven-Yale Multidimensional Pain Inventory. All values represent mean and standard deviation (SD) in brackets. * = $p<0.05$, ** = $p<0.005$.

3.2. Voxel-wise functional connectivity of insular subdivisions

3.2.1. Main connectivity patterns across groups

Whole-brain connectivity maps for left and right PI, dAI, and vAI in each group are shown in Supplementary Figures S1, S2 and S3. Overall connectivity patterns replicate those reported previously (Deen et al., 2011; Uddin et al., 2014; Zamorano et al., 2017). For the sake of clarity, we only summarize the main patterns for each insula subdivision in this section.

The *posterior insular* (PI; Figure S1) showed consistent sensorimotor connectivity patterns, including bilateral primary motor (M1), primary and secondary somatosensory cortices (S1 and S2), as well as the putamen and the globus pallidus. Connectivity also involved the supramarginal gyrus (SMG), superior and middle temporal gyrus (STG, MTG), the insula (dAI, vAI), the operculae (frontal, temporal, and rolandic), and the middle cingulate cortex (MCC).

The *dorsal anterior insula* (dAI; Figure S2) showed consistent connectivity patterns with bilateral supplementary motor area (SMA proper and pre-SMA), the putamen and the globus pallidus. Connectivity also involved the SMG, Heschl's gyrus, STG, MTG, the insula (PI, vAI), the operculae (frontal, temporal, and parietal), the inferior frontal cortex (IFC), and the anterior cingulate cortex (ACC).

The *ventral anterior insula* (vAI; Figure S3) showed consistent connectivity with bilateral frontal and the orbitrofrontal cortices, the insula (PI, dAI), the operculae (orbital, frontal, and temporal), the ACC and MCC, premotor cortex (BA6), SMA, auditory regions in the STG, and parietal regions. Connectivity also involved the basal ganglia (putamen, pallidum, and caudate) and the thalamus.

3.2.2. Main and interactions effects for musicianship and chronic pain

A main effect of MUSICIANSHIP was found in left dAI and bilateral vAI (Figure 1A, Table 2). In the **left dAI,** this involved *right* middle frontal gyrus (MFG) and *right* pregenual ACC (pgACC). In the **left vAI**, this involved *left* pgACC and in the **right vAI**, the *right* superior frontal gyrus (SFG) and pgACC.

A main effect of PAIN was found in bilateral PI and right vAI (Figure 1B, Table 2).
In the **PI,** this involved the cerebellum (*bilateral* Lobule VII and left vermis). In the **right vAI**, this involved the *right* cuneus.

An interaction effect was found between PAIN and MUSICIANSHIP in all insula subdivisions except the left dAI (Figure 1C, Table 2).
In the **left PI**, this involved *left* orbitofrontal cortex (OFC) and in the **right PI**, the *left* OFC, temporal pole, and SMA.
In the **right dAI**, this involved *bilateral* OFC and *right* temporal pole.
In the **left vAI**, this involved *right* superior frontal gyrus (SFG), *right* SII, SMG, *left* thalamus, right putamen, and hippocampus and in the **right vAI**, the *left* SFG, *right* SII, SMG, anterior MCC, SMA, and SPL (BA5).

Post-hoc comparisons revealed a consistent pattern, indicating increased connectivity in CPNM and HM, and decreased connectivity in CPM and HNM (Fig. 2, Tables 3 & 4).

Table 2. Main effects and interaction of musicianship and chronic pain

Seed			Left Insula						Right Insula					
Connectivity region	(*area*)		*Cluster size*	Coordinates MNI *x*	*y*	*z*	*F*	*f*	*Cluster size*	Coordinates MNI *x*	*y*	*z*	*F*	*f*
Main Effect of Musicianship														
dAI														
SFG	(*BA6*)	R	51	30	6	54	18.90	4.01	-	-	-	-	-	-
pgACC	-	R	45	12	36	18	22.20	4.32	-	-	-	-	-	-
vAI														
SFG	-	R	-	-	-	-	-	-	36	24	27	51	19.03	4.02
pgACC	-	R	46	3	42	18	19.69	4.10	79	6	39	15	23.91	4.54
Main Effect of Chronic Pain														
PI														
Cerebellum														
	Lobule VIIa	R	-	-	-	-	-	-	75	21	-78	-48	24.51	4.42
	Lobule VIIb	R	52	12	-72	-	19.38	3.91	-	-	-	-	-	-
	Vermis	R	39	6	-90	-	21.49	4.13	-	-	-	-	-	-
vAI														
Cuneus		R	-	-	-	-	-	-	37	12	-87	39	17.92	3.75
Interaction between Musicianship and Chronic Pain														
PI														
OFC	*(Fo3)*	L	86	-42	24	-9	25.92	4.77	132[a]	-42	24	-12	16.96	3.82
Temporal pole	*(BA38)*	L	-	-	-	-	-	-	132[a]	-45	18	-21	21.60	4.34
SMA	-	L	-	-	-	-	-	-	38	-6	24	45	19.25	4.09
dAI														
OFC	*(Fo3)*	L	-	-	-	-	-	-	64	-39	21	-15	32.96	5.40
OFC	*(Fo3/BA47)*	R	-	-	-	-	-	-	56[a]	36	27	-18	27.50	4.92
Temporal	pole	R	-	-	-	-	-	-	56[a]	45	18	-18	22.16	4.40
vAI														
SFG	-	R	51	21	12	45	22.23	4.41	-	-	-	-	-	-
SFG	-	L	-	-	-	-	-	-	53	-21	12	45	18.11	3.96
aMCC	-	R	-	-	-	-	-	-	57[a]	6	15	33	19.15	4.07
SMA	(BA6)	R	-	-	-	-	-	-	57[a]	3	12	45	20.73	4.25
SPL	(5c) / BA5)	R	-	-	-	-	-	-	46	3	-30	45	18.78	4.03
SII	(PF & OP1)	R	53	54	-36	15	17.47	3.88	76[a]	51	-27	12	16.31	3.74
SMG	(hIP1)	R	64	51	-42	30	26.61	4.84	76[a]	63	-36	15	20.56	4.23
Hippocampus	(CA2)	R	67[a]	33	-12	-15	18.33	3.98	-	-	-	-	-	-
Putamen	-	R	67[a]	33	-12	0	12.83	3.29	-	-	-	-	-	-
Thalamus	(P&S)	L	55	-23	-21	3	20.44	4.22	-	-	-	-	-	-

MNI coordinates and local maxima of whole-brain differences (t-contrasts) in insula-based network connectivity during resting state between chronic pain non-musicians (CPNM), chronic pain musicians (CPM), and healthy non-musicians (HNM). The comparison between healthy musicians (HM) and CPNM yielded no significant differences. Only results that survived a cluster-extent based threshold of $p<0.05$ (FWER correction) are shown. T-values of significantly activated peak-voxels refer to MNI coordinates ([a] = same cluster). Brodmann Areas (BA) labeling was performed using the Automatic Anatomic Labeling toolbox (AAL; 2002). Probabilistic cytoarchitectonic maps for structure–function relationships in standard reference space were assigned using the Anatomy Toolbox (Eickhoff et al., 2005). Abbreviations: PI, posterior insula; dAI, dorsal anterior insula; vAI, ventral anterior insula; aMCC, anterior middle cingulate cortex, pgACC, pregenual anterior cingulate cortex; ITG, inferior temporal gyrus; SFG, superior frontal gyrus; SMA,

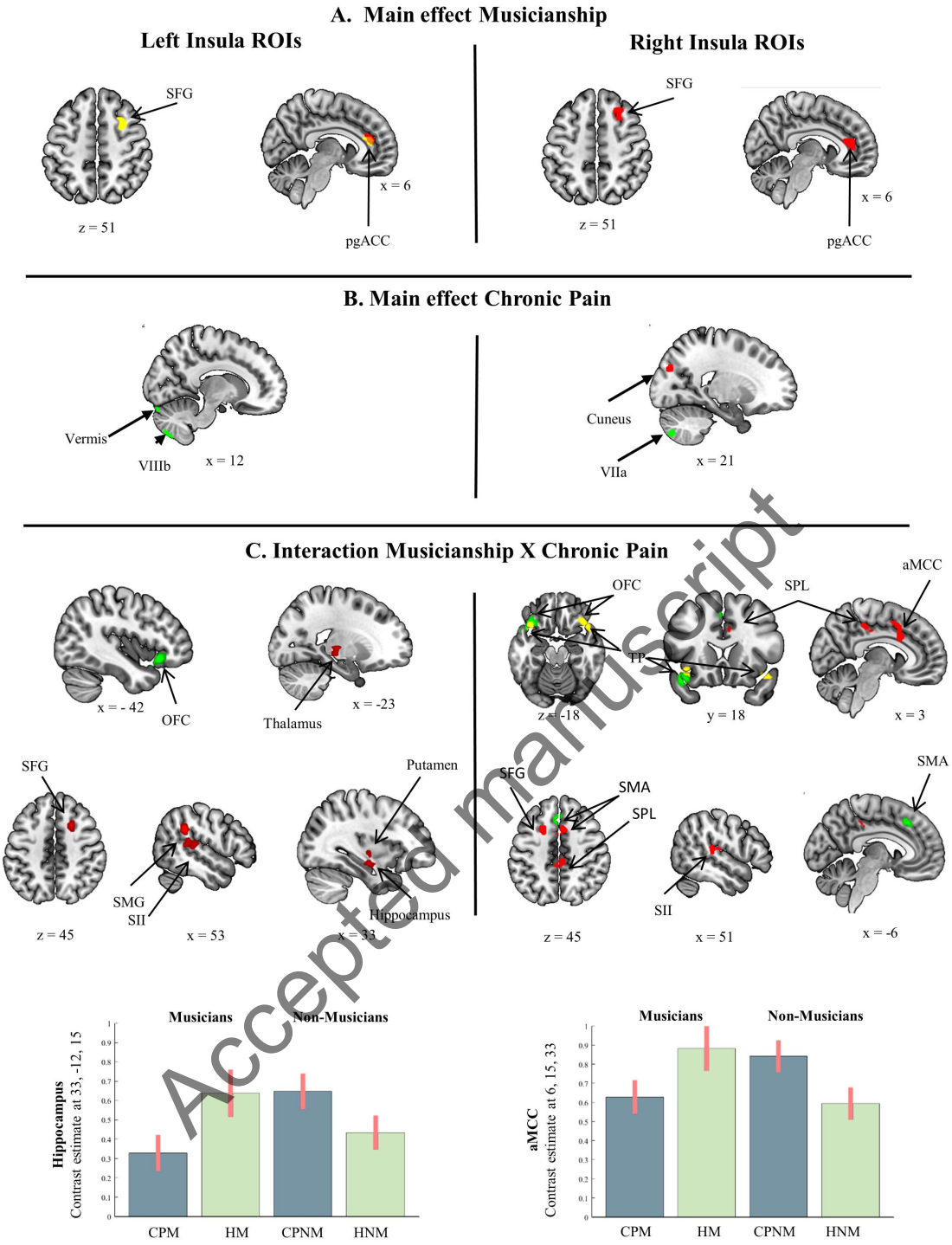

Figure 1. Results from a linear contrast (F-test), showing significant main and interaction effects of insula connectivity during resting-state. Significance thresholds for between-group differences were set at p>0.05 (FWER), using a cluster-extent based thresholding method. (A) Main effect of musicianship. (B) Main effect of chronic pain. (C) Interaction effect between musicianship and chronic pain. Bar graphs show contrast estimates and 90% confidence intervals. The direction of this interaction was identical across regions. Colors indicate connectivity with insula subdivisions: green = posterior insula (PI); yellow = dorsal anterior insula (dAI); red = ventral anterior insula (vAI). Right side represents right insula connectivity and left side represents left insula connectivity. Abbreviations: SMG, supramarginal gyrus; SMA, supplementary motor area, SFG, superior frontal gyrus; aMCC, anterior middle cingulate cortex; pgACC, pregenual anterior cingulate cortex; SFG, superior frontal gyrus; OFC, orbitofrontal cortex; SII, secondary somatosensory cortex; TP, temporal pole; VII-VIII, cerebellar lobules.

3.2.3. Difference connectivity maps between CPNM and HNM

Increased insular connectivity was found in CPNM compared to HNM (Figure 2A, Table 3) between the following regions:

The **left vAI** with the *right* pgACC and the **right vAI** with the *right* SMA, anterior MCC, pgACC, and insula.

The reversed contrast yielded no significant differences.

Table 3. Post-hoc comparisons of connectivity patterns: CPNM *vs* HNM and CPM *vs* CPNM

Seed			Left Insula						Right Insula					
Connectivity region	(*area*)		*Cluster size*	Coordinates MNI *x*	*y*	*z*	*t*	d_{unb}	*Cluster size*	Coordinates MNI *x*	*y*	*z*	*t*	d_{unb}
Contrast CPNM vs HNM														
vAI														
pgACC	(*Area 33/BA24)*	R	39	6	30	15	3.93	1.16	68	6	30	15	4.83	1.43
aMCC	*(BA32)*	R	-	-	-	-	-	-	56[a]	6	12	38	3.43	1.01
SMA	*(BA32)*	R	-	-	-	-	-	-	56[a]	12	9	51	4.96	1.47
vAI	*(BA13)*	R	-	-	-	-	-	-	36	36	12	-15	5.15	1.52
Contrast CPM vs CPNM														
PI														
Cerebellum	*(Vermis)*	R	-	-	-	-	-	-	109	0	-51	-3	-5.07	1.50
dAI														
ITG	(*BA8)*	L	-	-	-	-	-	-	91	-57	-18	-27	-4.32	1.27
Hippocampus	*(CA2)*	R	46	30	-12	-15	-4.13	1.22	96	30	-12	-15	-4.86	1.43
Cerebellum	*(Vermis)*	R	39	6	-45	-9	-4.55	1.35	-	-	-	-	-	-
vAI														
Hippocampus	*(CA2)*	R	47	30	-12	-15	-4.61	1.36	35	30	-12	-15	-4.14	1.22

MNI coordinates and local maxima of whole-brain differences (t-contrasts) in insula-based network connectivity during resting state between chronic pain non-musicians (CPNM), chronic pain musicians (CPM), and healthy non-musicians (HNM). The comparison between healthy musicians (HM) and CPNM yielded no significant differences. Only results that survived a cluster-extent based threshold of $p<0.05$ (FWER correction) are shown. T-values of significantly activated peak-voxels refer to MNI coordinates ([a] = same cluster). Brodmann Areas (BA) labeling was performed using the Automatic Anatomic Labeling toolbox (AAL; 2002). Probabilistic cytoarchitectonic maps for structure–function relationships in standard reference space were assigned using the Anatomy Toolbox (Eickhoff et al., 2005). Abbreviations: PI, posterior insula; dAI, dorsal anterior insula; vAI, ventral anterior insula; aMCC, anterior middle cingulate cortex, pgACC, pregenual anterior cingulate cortex; ITG, inferior temporal gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area.

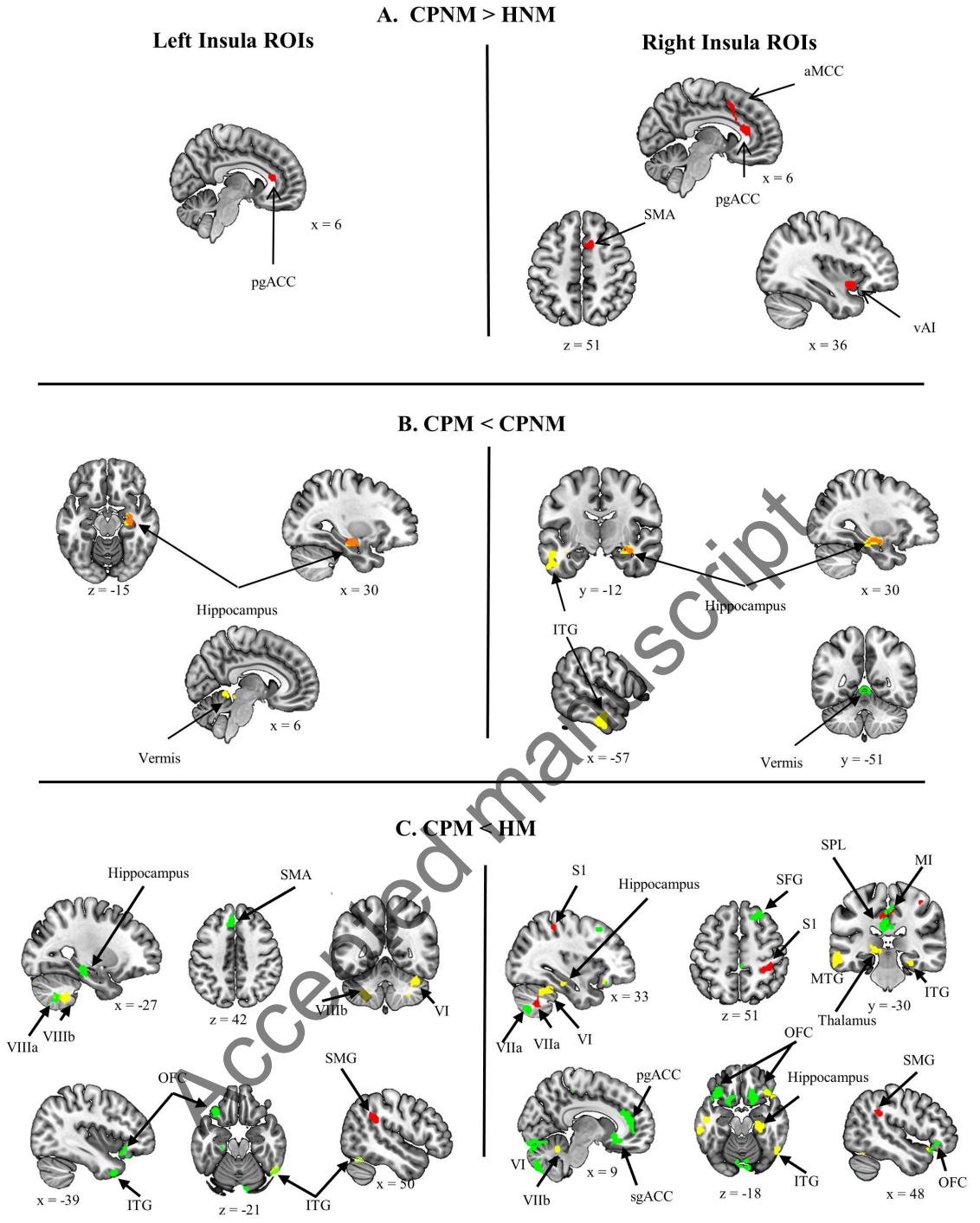

Figure 2. T-maps showing significant group differences in functional insula connectivity during resting-state. Significance thresholds for between-group differences were set at p>0.05 (FWER), using a cluster-extent based thresholding method. (A) Chronic pain non-musicians (CPNM) showed increased connectivity compared to healthy non-musicians (HNM). (B) Chronic pain musicians (CPM) showed decreased connectivity compared to CPNM. (C) CPM showed decreased connectivity compared to healthy musicians (HM). Colors indicate connectivity with respective insula subdivisions: green = posterior insula (PI); red = ventral anterior insula (vAI); yellow = dorsal anterior insula (dAI). Right side represents right insula connectivity and left side represents left insula connectivity. Abbreviations: SMG, supramarginal gyrus; SPL, superior parietal lobe; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; aMCC, anterior middle cingulate cortex; pgACC, pregenual anterior cingulate cortex; SFG, superior frontal gyrus; OFC, orbitofrontal cortex; M1, primary motor cortex; S1, primary somatosensory cortex; VII-VIII, cerebellar lobules.

3.2.4. Difference connectivity maps between HM and CPNM

Significant differences between HM and CPNM were limited to the tertiary visual cortex with the **left dAI** (coordinates: -6, -90, 33, t = 3.88), the **right dAI** (coordinates: -6,-90, 33, t = 4.77), and the **right vAI** (coordinates: -6, -90, 33, t = 3.49).

3.2.5. Difference connectivity maps between CPM and CPNM

Decreased functional connectivity was found in CPM compared to CPNM (Figure 2B, Table 3) between the following regions:

The **right PI** with the vermis in the cerebellum. The **left dAI** with the *right* hippocampus and the vermis, and the **right dAI** with the *right* hippocampus and the *left* inferior temporal gyrus (ITG). The **bilateral vAI** with the *right* hippocampus.

The reversed contrast yielded no significant differences.

3.2.6. Difference connectivity maps between CPM and HM

Decreased connectivity was found in CPM compared to HM (Figure 2C, Table 4) between the following regions:

The **left PI** with *bilateral* ITG, *left* OFC, *left* hippocampus, and *right* cerebellum (Lobule VI, VII, and VIII), and the **right PI** with *bilateral* OFC, *right* SFG and *left* MFG, *right* ACC, *left* SPL, *left* rectus gyrus, and *right* cerebellum (Lobule VI and VII).

The **left dAI** with *right* ITG and the cerebellum (lobule VI, VII and VIII), and the **right dAI** with *bilateral* inferior temporal gyrus (ITG), *left* MTG, *right* hippocampus, *left* thalamus, *right* OFC, and the cerebellum (Lobule VI).

The **left vAI** with *right* SMA and the **right vAI** with *right* S1, *bilateral* MCC, *right* SMG, and the cerebellum (Crus 1 and Lobule VII).

No differences were found for the reversed contrast.

Table 4. Post-hoc comparisons of connectivity patterns: CPM *vs* HM

Seed			Left Insula						Right Insula					
Connectivity region	(*area*)		*Cluster size*	Coordinates MNI *x*	*y*	*z*	*t*	d_{unb}	*Cluster size*	Coordinates MNI *x*	*y*	*z*	*t*	d_{unb}
PI														
SFG	*(BA8)*	L	62	-42	21	-12	-4.31	1.27	67	24	27	51	-5.03	1.49
OFC	*(Fo3/BA47)*	R	-	-	-	-	-	-	108	-36	30	-21	-4.86	1.43
OFC	*(BA47)*	L	-	-	-	-	-	-	50	38	27	-18	-4.23	1.25
OFC	*(Fo2/BA11)*	R	-	-	-	-	-	-	81	15	21	-15	-4.09	1.21
sgACC	*(s24)*	R	-	-	-	-	-	-	100	5	21	-9	-3.79	1.22
pACC	*(BA32)*	L	-	-	-	-	-	-	199[a]	9	43	12	-4.35	1.28
SMA	*(BA6)*	L	70	-5	33	42	-4.83	1.43	199[a]	6	27	42	-4.21	1.24
M1	*(4a)*	L	-	-	-	-	-	-	193[a]	-1	-33	51	-4.11	1.21
PCC	-	L	-	-	-	-	-	-	193[a]	-3	-42	21	-3.99	1.18
Hippocampus	*(DG)*	L	37	-27	-27	-12	-4.58	1.35	-	-	-	-	-	-
ITG	-	L	41	-39	12	-42	-4.17	1.23	-	-	-	-	-	-
ITG	*(FG2)*	R	49	57	-63	-27	-3.91	1.15	-	-	-	-	-	-
Cerebellum														
	Lobule VI	R	44	3	-78	-15	-3.56	1.05	119	6	-84	-24	-4.59	1.35
	Lobule VIIb	R	36	12	-75	-57	-4.83	1.43	-	-	-	-	-	-
	Lobule VIIa	R	-	-	-	-	-	-	181	18	-78	-48	-5.18	1.53
	Lobule VIIIa	L	46	-24	-60	-45	-3.97	1.17	-	-	-	-	-	-
dAI														
OFC	*(BA47)*	R	-	-	-	-	-	-	36	38	27	-18	-4.42	1.30
MTG	*(BA21)*	L	-	-	-	-	-	-	54	-	-30	-15	-5.10	1.51
ITG	-	L	-	-	-	-	-	-	55	-	-15	-30	-4.60	1.36
ITG	*(FG2/BA37)*	R	41	54	-57	-21	-4.02	1.19	51	51	-63	-21	-4.34	1.28
Thalamus	*(Parietal)*	L	-	-	-	-	-	-	39	-	-33	-6	-4.69	1.39
Hippocampus	*(Subiculum)*	R	-	-	-	-	-	-	153	24	-21	-18	-4.61	1.36
Cerebellum														
	Lobule VI	R	111[a]	36	-51	-30	-4.48	1.32	153	33	-42	-27	-5.33	1.57
	Lobule VIIa	R	111[a]	33	-57	-36	-4.16	1.23	-	-	-	-	-	-
	Lobule VIIIb	L	57[a]	-	-48	-48	-4.34	1.28	-	-	-	-	-	-
vAI														
S1	*(BA2 & 3)*	R	-	-	-	-	-	-	38	30	-39	51	-4.37	1.29
SPL	*(BA5/5m)*	L	-	-	-	-	-	-	75[a]	-6	-36	45	-4.58	1.35
SPL	*(BA5/5ci)*	R	-	-	-	-	-	-	75[a]	3	-30	45	-4.27	1.26
SMG	-	R	98	48	-42	27	-4.55	1.34	40	48	-42	30	-3.90	1.15
Cerebellum														
	Lobule VIIa	R	-	-	-	-	-	-	78	33	-60	-45	-4.07	1.20

MNI coordinates and local maxima of whole-brain differences (t-contrasts) in insula-based network connectivity during resting state. Only clusters that survived the FWER probability threshold are shown. Only results that survived a cluster-extent based threshold of $p<0.05$ (FWER correction) are shown. T-values of significantly activated peak-voxels refer to MNI coordinates ([a] = same cluster). Brodmann Areas (BA) labeling was performed using the Automatic Anatomic Labeling toolbox (AAL; 2002). Probabilistic cytoarchitectonic maps for structure–function relationships in standard reference space were assigned using the Anatomy Toolbox (Eickhoff et al., 2005). Abbreviations: PI, posterior insula; dAI, dorsal anterior insula; vAI, ventral anterior insula; aMCC, anterior middle cingulate cortex; pgACC, pregenual anterior cingulate cortex; ITG, inferior temporal gyrus; M1, primary motor cortex; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; S1, primary somatosensory cortex; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SPL, superior parietal lobe; VII-VIII, cerebellar lobules.

3.3. Regression Results

Among individuals with chronic pain (CPNM and CPM), multiple regression allowed us to determine which regions involved in the insula-based networks (Table 5) corresponded to chronic pain intensity ratings, the duration of chronic pain symptoms, and years of accumulated music training.

In CPM, the duration of chronic pain symptoms did not correspond to insula connectivity patterns. Chronic pain intensity ratings corresponded with both *increased* and *decreased* connectivity patterns in insula-based networks (Figure 3A, Table 5):

In the **right dAI**, higher pain intensity was linked to increased connectivity with *bilateral* pgACC and right dorsolateral prefrontal cortex (DLPFC).

In the **right vAI**, higher pain intensity was linked to decreased connectivity with *right* subgenual ACC.

Accumulated musical training corresponded with patterns of *increased* insula connectivity (Figure 3B, Table 5):

In the **left** and **right PI** greater musical experience was linked to increased connectivity with *bilateral* ventrolateral prefrontal cortex (VLPFC).

In the **left vAI**, more experienced CPM participants showed increased connectivity with *left* primary auditory cortex.

Table 5. Correlations between insula connectivity maps with pain duration, pain intensity, and accumulated music training

Seed			Left Insula							Right Insula						
Connectivity region	*(area)*		*Cluster size*	Coordinates MNI *x*	*y*	*z*	*t*	*R*	f^2	*Cluster size*	Coordinates MNI *x*	*y*	*z*	*t*	*R*	f^2
Pain Intensity (CPM)																
dAI																
DLPFC	-	R	-	-	-	-	-	-	-	39	48	21	27	14.13	0.617	0.61
pgACC	-	R	-	-	-	-	-	-	-	43[a]	3	30	12	18.09	0.620	0.62
pgACC	-	R	-	-	-	-	-	-	-	43[a]	-6	45	9	10.13	0.610	0.59
vAI																
sgACC		R	-	-	-	-	-	-	-	34	0	33	-9	-12,11	-0.612	0.60
Accumulated Musical Training (CPM)																
PI																
VLPFC		L	56	-51	33	6	10.33	0.667	0.80	32	-48	39	-9	11.66	0.668	0.80
VLPFC		R	90[a]	54	36	-6	16.36	0.667	0.80	76	51	39	-3	16.55	0.675	0.83
vAI																
A1		L	62	-51	-15	0	13.48	0.664	0.78	-	-	-	-	-	-	-
Pain Duration (CPNM)																
dAI																
Precuneus		L	-	-	-	-	-	-	-	40	-3	-66	45	9.04	-0.771	1.46
M1	*(Area 4a)*	R	-	-	-	-	-	-	-	39	0	-39	69	5.05	-0.744	1.23
vAI																
Precuneus		L	-	-	-	-	-	-	-	43	-6	-66	42	-9.34	-0.766	1.42
M1	*(Area 4a)*	L	-	-	-	-	-	-	-	39	0	-39	69	-5.05	-0.738	1.19
Calcarine-RSC		L	-	-	-	-	-	-	-	123	-16	-58	10	-6.86	-0.740	1.21
Pain Intensity (CPNM)																
dAI																
RVM		R	-	-	-	-	-	-	-	38	6	-33	-42	- 8.97	-0.559	0.45

MNI coordinates and local maxima of from regression analyses testing for correlations between each insular subdivision connectivity map with the amount of years suffering clinical pain, the clinical pain intensity, and accumulated musical training (musicians only). Correlations with pain duration yielded no significant effect in CPM. Only results that survived a cluster-extent based threshold of $p<0.05$ (FWER correction) are shown. T-values of significantly activated peak-voxels refer to MNI coordinates (a = same cluster). Abbreviations: A1, Primary auditory cortex; CPNM, chronic pain non-musicians; CPM, chronic pain musicians; PI, posterior insula; dAI, dorsal anterior insula; vAI, ventral anterior insula; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; pgACC, pregenual anterior cingulate cortex; RSC, Retrosplenial

In CPNM, multivariate regression revealed a correspondence between both the duration of chronic pain symptoms and pain intensity with patterns of *decreased* insula connectivity:

Pain duration (Figure 3C, Table 5):

In the **right dAI**, longer duration of chronic pain was related to decreased connectivity with regions involved in the Default Mode Network (DMN; *left* precuneus) and Sensorimotor Network (SMN; right M1, Area 4a).

In the **right vAI**, longer duration of chronic pain symptoms was related to decreased connectivity within regions of the DMN (*left* precuneus and retrosplenial cortex) and the SMN (M1, Area 4a).

Pain intensity (Figure 3D, Table 5):

In the **right dAI**, higher pain intensity was related to decreased connectivity with the rostral ventromedial medulla (RVM).

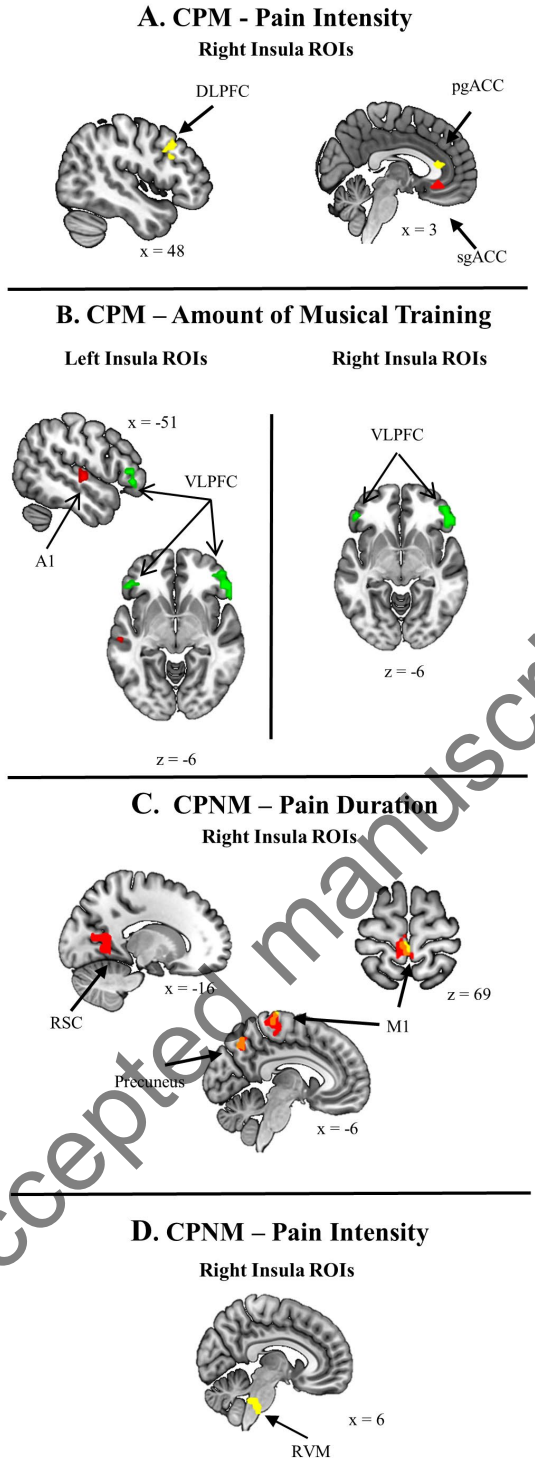

Figure 3. Results from multiple regression analyses for each insular ROI to assess connectivity maps in relation to the amount of years suffering pain and pain intensity in CPM and CPNM. In CPM, multiple regressions were also performed with accumulated musical training. A.) Pain intensity in chronic pain musicians (CPM). Insula connectivity maps did not correlate significantly with chronic pain duration in this group. B) Amount of accumulated music training in CPM. C) Pain intensity chronic pain non-musicians (CPNM). D. Pain intensity in CPNM. Significance thresholds were set at $p>0.05$ (FWER), using a cluster-extent based thresholding method. Detailed information is provided in Table 5. Colors indicate connectivity with respective insula subdivisions: green = posterior insula (PI); red = ventral anterior insula (vAI); yellow = dorsal anterior insula (dAI). Right side represents right insula connectivity and left side represents left insula connectivity. Abbreviations: RSC, retrosplenial cortex; M1, primary motor cortex; RVM, rostroventral medulla; DLPFC, dorsolateral prefrontal cortex; pgACC, pregenual ACC; sgACC, subgenual ACC.

4. Discussion

In the present study, we used resting-state fMRI to investigate insula-based connectivity patterns in musicians and non-musicians both with and without chronic back pain. The principal findings that emerged from this study where (i) that both extensive sensorimotor training in healthy musicians and chronic pain in non-musicians can trigger similar changes within neural networks involved in multisensory processing, whereas (ii) insula connectivity was significantly decreased in CPM compared to both HM and CPNM. This novel finding suggests that although both intensive musical training and chronic pain, taken in isolation, have been associated with increased insula-based connectivity, the presence of chronic pain in professional musicians appears to produce the reversed pattern.

4.1. Insula connectivity in chronic pain non-musicians

The insula is implicated in a large number of widely different functions, ranging from pain, interoception, language, and sensorimotor processes to salience detection, homeostasis, emotions, empathy and higher-order cognitions (Craig, 2011; Nieuwenhuys, 2012). Specifically, the insula participates as a centrally located brain region in the switching between networks states involved in the detection of salient events, including sensory and pain processes (Brooks and Tracey, 2007; Cauda et al., 2011; Cottam et al., 2018; Menon and Uddin, 2010; Seeley et al., 2007; Segerdahl et al., 2015; Uddin, 2015; Uddin et al., 2014; Wiech et al., 2010). Hierarchically organized along a posterior-to-mid-to-anterior integration scheme (Craig, 2002; Craig, 2009b), pain discrimination has been associated with the posterior insula (PI) (Segerdahl et al., 2015; Wiech et al., 2014), and pain evaluation with the mid/dorsal anterior insula (dAI; cognitive), as well as the ventral anterior insula (vAI; affective) (Ploghaus et al., 1999; Ploner et al., 2011; Wiech et al., 2010).

Resting-state fMRI studies have demonstrated distorted neural communication in different types of chronic pain, characterized as distinct patterns of neural reorganization (Baliki et al., 2014; Cottam et al., 2018) that involve increased insula connectivity with the ACC, mPFC, and bilateral insula (Baliki et al. 2011; Cifre et al. 2012; Ichesco et al. 2014). In accordance with these data, the comparison of CPNM and HNM in the current study confirmed increased connectivity between bilateral vAI and pgACC (affective evaluation), and between right vAI with aMCC, SMA (motor guidance), and the ipsilateral insula (Figure 2A, Table 3).

This pattern coincides with higher pain-related inferences in CPNM with daily activities, indicating that alterations in brain circuits are related to behavioral and motivational consequences of chronic pain (Wiech and Tracey 2013). Both animal and human studies highlight a role of the pgACC in the affective evaluation of pain states (Bliss et al., 2016; Johansen et al., 2001) and the corresponding regulation of autonomic outputs (Vogt, 2005). Together with the insula, the pgACC is involved in the encoding of emotional and motivational aspects of pain, thus contributing to the development of chronic pain (Baliki and Apkarian, 2015; Bliss et al., 2016). The aMCC is moreover associated with pain avoidance behavior (Vogt, 2005) and related adaptive control (Shackman et al., 2011), encompassing a network that involves the anterior insula and SMA (Cauda et al., 2011; Hoffstaedter et al., 2014). In the same line of evidence, longer duration of chronic pain was associated with decreased connectivity with the motor cortex and regions of the DMN, whereas higher ratings of pain intensity were linked to decreased connectivity with the RVM, suggesting altered descending pain modulation (Lee et al. 2008).

4.2. Insula connectivity in healthy musicians

In a previous resting-state fMRI study, we found enhanced insula-based connectivity in HM compared to HNM with key constituents of large-scale networks involved in salience, executive, and affective processing (Zamorano et al., 2017). Although a specific role of the insula in music perception and production has not yet been established, insula functions support music by contributing to our sense of time (Craig, 2009a; Wittmann et al., 2010), the integration of sound (Bamiou et al., 2003; Remedios et al., 2009; Wong et al., 2004), as well as the emotional and cognitive evaluation of music (Altenmüller et al., 2014; Koelsch, 2014). Structure and function of the anterior insula have been linked to the perception of internal bodily states (i.e., interoception; Critchley et al., 2004), which is enhanced in classically trained musicians and dancers (Christensen et al., 2017; Schirmer-Mokwa et al., 2015). Such skills likely support music production, which depends on a highly developed capacity to segregate and integrate sensory information with the planning and execution of motor actions (Brown et al., 2015; Chen et al., 2012). Particularly, the right anterior insula has been identified as a key region that supports motor accuracy by gating multisensory signals of salience as a function of musical expertise (Kleber et al., 2017; Kleber et al., 2013).

Considering that both musical training and chronic pain drive behaviorally relevant changes in perceptual systems (Herholz and Zatorre, 2012; Kuner and Flor, 2016), we hypothesized that enhanced integration of multisensory information is a common characteristic underlying corresponding reorganization within insula-based networks. Consistent with this notion, we found no evidence for differences in insula connectivity patterns between HM and CPNM (Figure S1, S2, and S3), except for the tertiary visual cortex (V3). We speculate that both extensive sensorimotor training in musicians and chronic pain in non-musicians may trigger comparable adaptations within neural networks involved with multisensory processing, thus confirming analogous behavioral

results in which similar pain sensitivity was found in HM and CPNM relative to HNM (Linari-Melfi et al., 2011; Zamorano et al., 2014).

Indeed, a comparison of connectivity patterns of CPNM versus HNM in the current study and HM versus HNM in a previous study (Zamorano et al., 2017) indicates partly overlapping (between right vAI with right ACC and MCC) but also distinct patterns of increased connectivity, the latter being mainly related to sensorimotor regions involved in music performance. This could reflect evidence for shared neural correlates between HM and CPNM related to the relative salience of sensory inputs (Uddin, 2015; Zamorano et al., 2014). In fact, non-nociceptive and nociceptive stimulation engage not only overlapping brain areas (Iannetti et al., 2008; Mouraux and Iannetti, 2009) but non-nociceptive signals also activate nociceptive pathways (Legrain et al., 2011; Valentini et al., 2012). Specifically, the posterior and anterior insula respond equally to pain perception and non-nociceptive stimulation (Liberati et al., 2016), thus lending support to our hypothesis.

4.3. Insula connectivity in chronic pain musicians: Evidence for Metaplasticity

Metaplasticity refers to the "plasticity of synaptic plasticity" (Abraham and Bear, 1996), which can broadly be defined as synaptic correlates of an individual's learning history (Muller-Dahlhaus and Ziemann, 2015). This concept has recently been applied to a musical framework, in which early experience-dependent optimization of neural functions can modulate subsequent neuroplasticity of the nervous system in ways that may either facilitate or prevent maladaptive changes (Altenmüller and Furuya, 2016). Based on above's hypothesis that HM and CPNM may share common mechanisms of sensory perception and related insula-based connectivity (Zamorano et al., 2017; Zamorano et al., 2014), we initially expected that chronic pain would further aggravate

these form of neuroplasticity in musicians (Baliki et al., 2014; Kuner and Flor, 2016). However, the opposite was the case.

Decreased insula connectivity was found in CPM relative to both HM and CPNM. Compared to CPNM, this involved regions implicated in memory and learning (hippocampus and ITG), and sensorimotor characteristics of pain (cerebellum) (Figure 2B, Table 3), whereas decreased insular connectivity compared to HM (Figure 2C, Table 4) was focused on brain regions associated with sensorimotor processing (S1, M1, SMG, ACC, MCC, and cerebellum), reward (OFC), and memory (hippocampus, ITG and MTG). These regions were also identified in an interaction effect between PAIN and MUSICIANSHIP, perhaps indicating a form of metaplasticity.

Sensory perturbation studies with healthy musicians suggest a close relationship between insula activation patterns and task-related modulation of sensory inputs during motor performance (Kleber et al., 2017; Kleber et al., 2013). Specifically, when somatosensory input was perturbed during singing via anesthesia of vocal fold mucosa, right anterior insula activity was down-regulated and its connectivity with bilateral primary auditory cortex (A1), S1, and M1 decreased in trained singers. Conversely, when auditory feedback was masked with noise, right anterior insula activity was up-regulated and its functional connectivity with inferior parietal, frontal, and voice-relevant somatosensory-motor areas was increased. Importantly, this pattern was mirror-reversed in non-musicians and did not support vocal performance. We speculate that musicians may employ similar strategies to dissociate movements from pain perception, perhaps as an intrinsically developed pain coping mechanism (Fields, 2004; Wiech and Tracey, 2013; Zeidan et al., 2015).

In the current study, regression results in CPM showed that higher pain intensity correlated with increased connectivity between the right dAI and the pgACC (i.e.,

similar to CPNM *vs* HNM) but also with decreased connectivity between the right vAI with the subgenual ACC. Interestingly, activity in this region is inversely related to pain relief in chronic pain patients (Schweinhardt et al., 2006; Zeidan et al., 2015) and may be linked to lower pain-related interference with other activities, which we observed in CPM compared to CPNM in the current study. The latter findings are remarkable, considering the comparable levels pain intensity between CPM and CPNM on one hand yet the same amount of musical practice between CPM and HM on the other hand. Based on these data, we propose that professional musicians cope more efficiently with pain to continue playing their instrument (Gasenzer et al., 2017; Steinmetz et al., 2015) and may experience less fear of pain-related movements (Picavet et al., 2002).

4.4. The role of appraisal and motivation in CPM

Among the common regions that showed decreased connectivity with the anterior insular in CPM relative to both HM and CPNM were the hippocampus and the ITG. Both are associated with pain reappraisal, emotional coping, as well as the learning and consolidation of emotional memories (Ji et al., 2003; Tracey and Mantyh, 2007; Vachon-Presseau et al., 2016). When pain becomes chronic, increased connectivity between the hippocampus and the posterior insula can be observed (Mutso et al., 2014), whereas hippocampal dysfunctions have been linked to diminished pain perception (Gol and Faibish, 1967), despite a preserved capacity to detect light touch (Liu and Chen, 2009). Decreased connectivity of the insula with the hippocampus and ITG could therefore reflect emotional coping mechanisms (Pecen et al., 2017; Zeidan and Vago, 2016)

Brain areas central to reward and motivated behavior are critical for the modulation of acute pain and the mediation of chronic pain (Navratilova and Porreca, 2014), suggesting that the brain's (mesocorticolimbic) emotion circuitry is not only affected by

but also crucially involved in the control and coping of persistent pain (Vachon-Presseau et al., 2016). In this context, it should be mentioned that musicians often describe pain as an inherent and inevitable characteristic of high-level musical performance practice (Dommerholt, 2009; Gasenzer et al., 2017), following a "no pain, no gain" model that is associated with positive expectations, appetitive motivational states, and the conscious or subconscious choice to ignore pain (Fields, 2004, 2014; Quarrier, 1993). As emotional satisfaction can profoundly reduce or even reverse brain activation patterns during painful stimulation (Colloca and Benedetti, 2006; Kamping et al., 2016), motivational aspects of playing an instrument may engage protective factors that can help musicians to cope with pain (Fields, 2004; Tracey and Mantyh, 2007).

4.5. Limitations

Several limitations must be considered in this study. First, only female participants were tested due to reported sex-differences in the processing of pain (Fillingim et al., 2009). Therefore, we cannot make inferences regarding the effects of pain and sensorimotor training on insula-based functional connectivity in male musicians. Second, the small sample size of this study presents an additional limiting factor for generalizing our results. Third, we did not perform acute pain sensitivity tests, which prevents us from making more behaviorally relevant conclusions. However, we found similar behavioral patterns in a previous study with HM and CPNM (i.e., comparable tactile and pain sensitivity; Zamorano et al., 2014), which supports the current results. Likewise, although three CPNM reported using centrally acting medication, the overall results in this group are in line with previously published effects of pain on brain networks. Moreover, no CPM used centrally acting drugs, therefore excluding the possibility that reduced insula connectivity in this group could be explained on this basis. Another limitation of resting state fMRI that should be taken into account is the exposure to

scanner noise, which can reduce the robustness and the replicability of functional connectivity findings within the somatosensory, auditory, and motor networks (Andoh et al., 2017). However, prior rs-fMRI studies have not revealed significant differences in auditory network activation between musicians and non-musicians due to scanner noise (Palomar-Garcia et al., 2017). Moreover, we found no evidence for altered pain ratings due to discomfort related to body position or scanner. Future studies may also consider alternative strategies for estimating resting state networks as a function of chronic pain and musicianship, such as high-density EEG (Klein et al., 2016).

4.6. Conclusions

To the best of our knowledge, this is the first study investigating interactions between chronic pain and extensive sensorimotor training (i.e. musical training) in the brain. The observed patterns of decreased and increased insula connectivity between professional musicians and non-musicians with and without chronic pain indicates that the effects of chronic pain on professional musicians and non-musicians are inversed. In conclusion, our data suggest that unnatural postures may be a necessary but not a sufficient explanation for the above-average prevalence of pain syndromes among professional musicians (Steinmetz et al., 2015). Instead, we propose that heightened sensory awareness facilitates the transition to chronic pain in combination with peripheral overuse injuries, which may occur as a consequence of individual practice routines (Dommerholt, 2009; Williamon and Valentine, 2000). Furthermore, insula connectivity patterns in professional musicians with chronic pain suggest novel mechanisms of pain modulation, which may be related to multisensory integration and motivational factors that can have important implications for the assessment and treatment of pain.

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Competing interests

The authors report no competing interests

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Figure Captions

Figure 1

Results from a linear contrast (F-test), showing significant main and interaction effects of insula connectivity during resting-state. Significance thresholds for between-group differences were set at p>0.05 (FWER), using a cluster-extent based thresholding method. (A) Main effect of musicianship. (B) Main effect of chronic pain. (C) Interaction effect between musicianship and chronic pain. Bar graphs show contrast estimates and 90% confidence intervals. The direction of this interaction was identical across regions. Colors indicate connectivity with insula subdivisions: green = posterior insula (PI); red = ventral anterior insula (vAI); yellow = dorsal anterior insula (dAI). Right side represents right insula connectivity and left side represents left insula connectivity. Abbreviations: SMG, supramarginal gyrus; SMA, supplementary motor area, SFG, superior frontal gyrus; aMCC, anterior middle cingulate cortex; pgACC, pregenual anterior cingulate cortex; SFG, superior frontal gyrus; OFC, orbitofrontal cortex; SII, secondary somatosensory cortex; TP, temporal pole; VII-VIII, cerebellar lobules.

Figure 2

T-maps showing significant group differences in functional insula connectivity during resting-state. Significance thresholds for between-group differences were set at p>0.05 (FWER), using a cluster-extent based thresholding method. (A) Chronic pain non-musicians (CPNM) showed increased connectivity compared to healthy non-musicians (HNM). (B) Chronic pain musicians (CPM) showed decreased connectivity compared to CPNM. (C) CPM showed decreased connectivity compared to healthy musicians (HM). Colors indicate connectivity with respective insula subdivisions: green =

posterior insula (PI); red = ventral anterior insula (vAI); yellow = dorsal anterior insula (dAI). Right side represents right insula connectivity and left side represents left insula connectivity. Abbreviations: SMG, supramarginal gyrus; SPL, superior parietal lobe; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; aMCC, anterior middle cingulate cortex; pgACC, pregenual anterior cingulate cortex; SFG, superior frontal gyrus; OFC, orbitofrontal cortex; M1, primary motor cortex; S1, primary somatosensory cortex; VII-VIII, cerebellar lobules.

Figure 3

Results from multiple regression analyses for each insular ROI to assess connectivity maps in relation to the amount of years suffering pain and pain intensity in CPM and CPNM. In CPM, multiple regressions were also performed with accumulated musical training. A.) Pain intensity in chronic pain musicians (CPM). Insula connectivity maps did not correlate significantly with chronic pain duration in this group. B) Amount of accumulated music training in CPM. C) Pain intensity chronic pain non-musicians (CPNM). D. Pain intensity in CPNM. Significance thresholds were set at $p>0.05$ (FWER), using a cluster-extent based thresholding method. Detailed information is provided in Table 5. Colors indicate connectivity with respective insula subdivisions: green = posterior insula (PI); red = ventral anterior insula (vAI); yellow = dorsal anterior insula (dAI). Right side represents right insula connectivity and left side represents left insula connectivity. Abbreviations: RSC, retrosplenial cortex; M1, primary motor cortex; RVM, rostroventral medulla; DLPFC, dorsolateral prefrontal cortex; pgACC, pregenual ACC; sgACC, subgenual ACC.