

Supporting Information

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SI Text

Additional fMRI–ECG Measurements. Two patients and two control subjects participated in an additional functional MRI (fMRI) measurement, in which the subject's heart rate was simultaneously recorded.

Two channels of ECG (sampling frequency, 250 Hz) were measured with magnet-compatible electrodes along with photoplethysmography and respiration signals with an integrated amplifier in the fMRI scanner. The ECG was adjusted with the fMRI signal off-line; data were low-pass filtered (12 Hz) and R-peaks were enhanced by multiplying the ECG signal with the time-shifted photoplethysmography signal. Optionally, time-domain independent component analysis was used to improve the R-peak detection. The resulting RR time-series was finally visually approved.

The mean fMRI signal of the specific regions of interest (ROIs) (*Analysis of functional connectivity in Materials and Methods*) and the corresponding RR time-series were interpolated into 2-Hz sampling frequency. The mutual dependencies of the signals were studied by computing their cross-correlations.

Correspondingly, respiration signal, adjusted with the fMRI in time-domain, was downsampled to 2 Hz and cross-correlated with ROI signals.

The heart rates varied from 54 to 65 beats per min, and no systematic dependence between signal variability and heart or respiration rate could be determined. Furthermore, time-lagged correlations between ROI signals and RR time-series showed similar correlation profiles across different ROIs of each individual.

Table S1. Statistically significant differences between patients and controls

Seed	L Insula	R Insula	ACC
RAI	+	–	–
RMI	–	+	–
LPI	–	–	+
LAI	–	–	+
aMCC	–	–	–
pACC	+	+	+
VisCx	–	–	–

Statistically significant differences ($P < 0.001$) between patients and control control subjects in connectivities between different seed regions and left (L) insula, right (R) insula, and ACC. Anterior cingulate cortex, ACC; anterior middle cingulate cortex, aMCC; left anterior insula, LAI; left posterior insula, LPI; right anterior insula, RAI; posterior anterior cingulate cortex, pACC; right middle insula, RMI; visual cortex, VisCx.

Table S2. Clinical details of the patients

Patient no.	Age (yr)	Sex	Site of pain	Etiology	Duration (yr)	Intensity	
						Week	Day
1	54	M	R upper limb	Cervical spine degeneration	16	7	5
2	46	M	R lower limb	CRPS II	16	5.5	5.5
3	46	M	R lower limb	Posttraumatic osteoarthritis	2	7	3
4	48	M	R upper limb	Unclear	3	7	5
5	54	F	Lumbar spine	Lumbar spine degeneration	18	2.5	2.5
6	38	M	Lumbar spine	Lumbar spine degeneration	1	8	6.5
7	63	M	L upper limb	Phantom limb pain	30	8	8
8	41	F	Lumbar spine	Lumbar spine degeneration	4	5	5
9	50	M	Lumbar spine	Lumbar spine degeneration	2	8	8
10	67	M	Both knees	Postsurgical	3	5.5	4

F, female; L, left; M, male; R, right. Mean intensity of pain during the last week and on the day of the measurement is given on a 0 to 10 scale, where 0 is no pain at all and 10 is the worst pain imaginable.

Table S3. Medication of all 10 patients

Patient no.	Daily doses of drugs used for pain relief	Other drugs
1	Acetaminophen 500 mg + codeine 30 mg × 4	Candesartan 16 mg × 1 for hypertension
2	Pregabalin 25 mg × 2, amitriptyline 20 mg × 1	
3	Gabapentin 800 mg × 4, amitriptyline 100 mg × 1, tramadol 150 mg × 1	
4	Amitriptyline 12.5 + 75 mg	Nifedipine 20 mg × 1 for hypertension
5	Pregabalin 100 mg × 1	
6	Pregabalin 150 mg × 2, nortriptyline 50 mg × 1	
7	Pregabalin 150 mg × 2, acetaminophen 500 mg + codeine 30 mg 2 × 3–4	
8	Ibuprofen 800 mg × 2, acetaminophen 500 mg + codeine 30 mg 1–2 × 1–4, pregabalin 25 + 75–100 mg	Bisoprolol 2.5 mg × 1 for cardiac insufficiency
9	Mirtazapine 15 mg × 1, buprenorphine 0.4 mg × 2–3, pregabalin 150 mg × 2, nortriptyline 50 mg × 1	Ramipril 2.5 mg × 1 + hydrochlorothiazide 12.5 mg × 1 + amlodipine 5 mg × 1 for hypertension
10	Gabapentin 300 mg × 2, tramadol 150 mg × 1, acetaminophen 500 mg + codeine 30 mg × 1	