Distinctive alterations in the functional anatomy of the cerebral cortex in pain-sensitized osteoarthritis and fibromyalgia patients

Supplementary Material

Supplementary Methods

Supplementary Figures

Supplementary Tables
Supplementary Methods

Iso-Distant Average Correlation (IDAC) maps

A novel mapping was used to characterize the functional structure of the cerebral cortex based on Iso-Distant Average Correlation (IDAC) measures. Essentially, IDAC mapping expands well-established MRI measures of local functional connectivity [6-8] by combining the connectivity maps of varying distances. Composite IDAC maps may uniquely inform the connectivity-related specialization of the cerebral cortex as local connectivity is distance-specific to a large extent and proved to discriminate well between major classical anatomo-functional cortical areas [2,5].

Image processing

Imaging data were processed using MATLAB version 2016a (The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping software (SPM12; The Wellcome Department of Imaging Neuroscience, London).

Anatomical and functional images were visually inspected to detect possible acquisition artifacts. Functional MRI images were slice-time corrected, realigned and then smoothed by convolving the image with a 4x4x4mm3 full width at half maximum (FWHM) Gaussian kernel.

The resulting realignment parameters were used for scrubbing, namely, discarding motion-affected volumes [3]. For each subject, mean inter-frame motion measurements [4] served as an index of data quality to flag volumes of suspect quality across the run. At time points with mean inter-frame motion > 0.3 mm, the corresponding volume, the immediately preceding and the succeeding two volumes were all discarded. Using this procedure, a mean (± SD) of 3.4 (± 10.2) volumes from the total of 180 volumes included in the fMRI sequence were removed in the Osteoarthritis Sample 1; mean 2.7 (± 6.2) in the corresponding control group; mean 3.6 (± 5.9) in the Fibromyalgia Sample 1; mean 6.2 (± 12.8) in the corresponding control; mean 5.3 (± 10.6) in the Osteoarthritis Sample 2; and mean 0.9 (± 2.5) in the Fibromyalgia Sample 2.

Image volumes were then co-registered to their anatomical images with an affine transformation. A warping matrix was also estimated for every subject to match a group template created from the 3D anatomical individual acquisitions and then to the Montreal Neurological Institute (MNI) space using DARTEL normalization [1]. Image volumes were re-
sliced to 3x3x3 mm. Estimated DARTEL normalizations to the MNI space were applied to the IDAC results to enable group inferences.

IDAC computations (see below) were conducted in a gray matter mask split into left and right hemispheres, so that no adjacent voxels from the medial regions of one hemisphere would be locally associated with those from the other hemisphere. The two hemispheres were brought back together once the IDAC values had been calculated. The left and right hemisphere gray matter masks were obtained by setting a threshold of $p > 0.4$ on the gray matter probability maps obtained from the DARTEL group template. As IDAC value estimations were carried out in every subject’s native space, the template masks were back-transformed with the inverse estimated normalization.

In IDAC computation analyses, all time series were regressed on the 6 rigid body realignment parameters and their first-order derivatives, and on the average white matter, CSF and global brain signals extracted from the native tissue masks. Finally, all functional MRI time series were band-passed with a Discrete Cosine Transform (DCT) filter letting through frequencies in the 0.01-0.1 Hz interval.

Cases were excluded from initial larger samples on the grounds of imaging quality and the strict mean inter-frame motion [4] criterion of $> 0.2$ mm: Osteoarthritis Sample 1; 2 cases were excluded from an initial sample of 33. The corresponding control group; 1 from a sample of 24. Fibromyalgia Sample 1; 2 from a sample of 40. Its corresponding control group; 1 from a sample of 36. Osteoarthritis Sample 2; 1 from a sample of 35. Fibromyalgia Sample 2; 2 from a sample of 65.

Whole-cortex IDAC maps were generated by estimating the average temporal correlation of each voxel with all its neighboring voxels placed at increasingly separated Euclidean iso-distant intervals. IDAC was computed in native space separately for each hemisphere after realignment and smoothing. Three IDAC maps were obtained at distance intervals 5-10mm, 15-20mm and 25-30mm.

Multi-distance IDAC color maps were obtained from the overlay of the three IDAC maps using an RGB color codification (see Figures). RGB color channels enabled the display of three values simultaneously. RED corresponding to the results from 5-10mm IDAC map analyses, GREEN from 15-20mm and BLUE from 25-30mm. The overlapping of these primary colors produces a full range of secondary colors.
**Definition of Iso-Distant Average Correlation (IDAC)**

We defined the concept of “Iso-Distant Average Correlation” (IDAC) to describe the pattern of correlation decay in the close vicinity of a voxel [2]. IDAC$_i(h)$ was consequently defined as the average temporal correlation of voxel $i$ with all the voxels located at a given Euclidean distance interval $h$. Functional MRI data sets being a discrete sample, any distance interval $h$ must be necessarily transformed into a discrete iso-distant interval $H_k=(h_k, h_{k+1})$, with $h_k$ being a set of successively increasing distances covering the whole vicinity of a given voxel (see Figure).

The set of iso-distant intervals $H_k$ were selected so that temporal correlations were mainly positive, decreased monotonically and in which horizontal axon collaterals were considered likely to form local networks. For the present study, we defined 3 iso-distant intervals: 5-10mm, 15-20mm and 25-30mm, with constant thicknesses but increasing number of voxels.

We first computed a correlation matrix $C$ of Pearson coefficients comparing the functional MRI signal time course of all the voxels in our study mask with each other’s.

$$C_{i,j} = \frac{\sum_{k=1}^{M} (Y_{i,k} - \bar{Y}_i) \cdot (Y_{j,k} - \bar{Y}_j)}{\sqrt{\sum_{k=1}^{M} (Y_{i,k} - \bar{Y}_i)^2} \cdot \sqrt{\sum_{k=1}^{M} (Y_{j,k} - \bar{Y}_j)^2}}$$

where $M$ is the length of the functional MRI signal time series and $i$ and $j$ index all the voxels entering our study mask. We then transformed the Pearson correlation matrix $C$ into a Gaussian distributed $z$-score correlation matrix $Z$ by applying a Fisher transform.

$$Z_{i,j} = \frac{\sqrt{M-3}}{2} \cdot \ln \left( \frac{1 + C_{i,j}}{1 - C_{i,j}} \right)$$

We obtained then IDAC$_i(h_k)$ by averaging the correlation coefficients of voxel $i$ with all the voxels $j$ belonging to the interval $H_k$.

$$IDAC_i(h_k) = \frac{\sum_{j \in H_k} Z_{i,j}}{N_{k,i}}$$

In short, IDAC values are defined as the mean correlation $z$-score between one voxel’s functional MRI signal and the functional MRI signal of all the voxels within the iso-distant interval $H_k$. Note that, for a given distance interval $k$, the number of voxels within the concentric iso-distant interval $N_{k,i}$ is not necessarily the same for every voxel $i$ due to the edge effects of the study mask.
**Figure.** fMRI Temporal correlations between one voxel ("seed") and its neighboring peripheries present a characteristic decreasing spatial gradient. LEFT: Fisher-transformed z-scores of a correlation map with a “seed” voxel in the visual area from a single subject. Voxel resolution is 3x3x3mm and results are constrained to distance intervals $h_k<$30mm and within the subject’s native gray-matter mask (blue shade). RIGHT: Six different Iso-distant intervals as they are used to calculate different IDAC values in our study.

**Supplementary References**

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Supplementary Figures

**Supplementary Figure 1.** Group-by-distance interaction (i.e., group [patients, controls] by distance [5-10 mm, 15-20 mm and 25-30 mm]) significant results in knee osteoarthritis and fibromyalgia patients compared with their respective control groups.

**Supplementary Figure 2.** Negative correlation between age and IDAC values (short distance, 5-10 mm) in knee osteoarthritis patients at a lower threshold (clusters at p < 0.01 surviving whole-brain family-wise error [FWE] correction (p< 0.05)). This analysis indicates that, although the effect was marginal in osteoarthritis, it was also in the direction of age-related local connectivity weakening in auditory cortex in osteoarthritis.
**Supplementary Tables**

**Supplementary Table 1.** Functional MRI statistical results. Clinical conditions *versus* the corresponding reference control subject groups

|                        | Cluster-level | Peak-level |             |             |          |
|------------------------|---------------|------------|-------------|-------------|----------|
|                        | Voxels        | $P_{FWE-corr}$ | $x$  | $y$  | $z$  | $F$   | $p$    |

### MAIN EFFECT OF GROUP

**Osteoarthritis vs Controls**

- Left Insular Cortex: 709 voxels, $P_{FWE-corr} = 9e-19$, $x = -32$, $y = -24$, $z = 15$, $F = 24.6$, $p = 2e-6$
- Left Visual Cortex: 333 voxels, $P_{FWE-corr} = 4e-11$, $x = -41$, $y = -90$, $z = 6$, $F = 24.2$, $p = 2e-6$
- Right Insula/Operculum: 382 voxels, $P_{FWE-corr} = 1e-11$, $x = 49$, $y = 0$, $z = 3$, $F = 27.0$, $p = 6e-7$
- Right Visual Cortex: 77 voxels, $P_{FWE-corr} = 0.002$, $x = 37$, $y = -69$, $z = 6$, $F = 21.6$, $p = 7e-6$

**Fibromyalgia vs Controls**

- Left Somatosensory Cortex: 307 voxels, $P_{FWE-corr} = 6e-10$, $x = -65$, $y = -12$, $z = 39$, $F = 19.1$, $p = 0.00002$
- Left Auditory Cortex: 47 voxels, $P_{FWE-corr} = 0.04$, $x = -68$, $y = -15$, $z = 9$, $F = 18.6$, $p = 0.00002$
- Left Somatosensory Cortex, medial: 84 voxels, $P_{FWE-corr} = 0.002$, $x = 46$, $y = -9$, $z = 30$, $F = 22.9$, $p = 3e-6$
- Right Somatosensory Cortex, superior: 64 voxels, $P_{FWE-corr} = 0.009$, $x = 31$, $y = -24$, $z = 42$, $F = 27.6$, $p = 4e-7$
- Right Somatosensory Cortex, medial: 66 voxels, $P_{FWE-corr} = 0.008$, $x = 7$, $y = 15$, $z = 81$, $F = 14.7$, $p = 0.0002$
- Right Visual Cortex: 142 voxels, $P_{FWE-corr} = 0.00002$, $x = 49$, $y = -84$, $z = 12$, $F = 28.8$, $p = 2e-7$
- Right Visual Cortex: 64 voxels, $P_{FWE-corr} = 0.009$, $x = -78$, $y = 21$, $z = 14$, $F = 21.4$, $p = 6e-6$

### GROUP BY DISTANCE INTERACTION

**Osteoarthritis vs Controls**

- Left Insular Cortex: 299 voxels, $P_{FWE-corr} = 2e-11$, $x = -38$, $y = 12$, $z = -15$, $F = 17.6$, $p = 1e-7$
- Anterior Cingulate Cortex: 51 voxels, $P_{FWE-corr} = 0.01$, $x = 4$, $y = 36$, $z = 15$, $F = 14.1$, $p = 2e-6$
- Frontal Pole: 53 voxels, $P_{FWE-corr} = 0.008$, $x = -20$, $y = 63$, $z = -3$, $F = 8.8$, $p = 0.0002$
- Right Insular Cortex: 282 voxels, $P_{FWE-corr} = 3e-10$, $x = 46$, $y = 0$, $z = 3$, $F = 25.1$, $p = 4e-10$

**Fibromyalgia vs Controls**

- Left Somatosensory Cortex: 196 voxels, $P_{FWE-corr} = 6e-8$, $x = -59$, $y = -12$, $z = 12$, $F = 11.3$, $p = 0.00002$
- Medial Visual Cortex: 96 voxels, $P_{FWE-corr} = 0.0002$, $x = 1$, $y = 84$, $z = 12$, $F = 10.5$, $p = 0.00004$
- Right Somatosensory Cortex: 216 voxels, $P_{FWE-corr} = 3e-8$, $x = 52$, $y = -15$, $z = 12$, $F = 11.7$, $p = 0.00002$
- Right Visual Cortex: 55 voxels, $P_{FWE-corr} = 0.01$, $x = 43$, $y = -75$, $z = 6$, $F = 13.3$, $p = 4e-6$
- Angular Gyrus: 88 voxels, $P_{FWE-corr} = 0.0004$, $x = 52$, $y = -51$, $z = 45$, $F = 10.3$, $p = 0.00006$

$P_{FWE-corr}$, $P$ (Family-Wise Error-corrected), whole brain. $x$ $y$ $z$, coordinates in Montreal Neurological Institute space.
### Supplementary Table 2. Functional MRI statistical results. Osteoarthritis versus fibromyalgia

| Cluster-level | Peak-level |
|---------------|------------|
| **Voxels**    | **$P_{\text{FWE-corr}}$** | **x** | **y** | **z** | **t** | **p** |
| **MAIN EFFECT OF GROUP** | | | | | | |
| Fibromyalgia < Osteoarthritis | | | | | | |
| Left Somatosensory Cortex, medial | 54 | 0.05 | 1 | -15 | 66 | 3.7 | 0.0001 |
| Left Somatosensory Cortex, inferior | 66 | 0.02 | -68 | -12 | 21 | 4.3 | 0.00001 |
| Left Somatosensory Cortex, superior | 63 | 0.02 | -26 | -18 | 48 | 5.2 | 2e-7 |
| Right Somatosensory Cortex, superior | 116 | 0.001 | 31 | -21 | 54 | 4.6 | 3e-6 |
| Right Somatosensory Cortex, medial | 58 | 0.04 | -2 | -9 | 63 | 4.2 | 0.00002 |
| **PATIENT GROUP BY DISTANCE INTERACTION** | | | | | | |
| Left Frontal Operculum | 300 | 4e-11 | -35 | 63 | -6 | 12.8 | 5e-6 |
| Left Sensorimotor Cortex | 45 | 0.02 | -38 | -15 | 30 | 10.7 | 0.00003 |
| Left Anterior Medial Frontal Cortex | 115 | 0.00002 | -14 | 69 | 0 | 11.7 | 0.00001 |
| Left Temporo-Occipital Cortex | 67 | 0.002 | -62 | -63 | -12 | 13.0 | 4e-6 |
| Left Parieto-Occipital Cortex | 119 | 0.00002 | -47 | -75 | 33 | 10.4 | 0.00005 |
| Left Dorsolateral Frontal Cortex | 60 | 0.004 | -26 | 39 | 42 | 9.3 | 0.0001 |
| Left Parietal Operculum | 61 | 0.004 | -56 | -30 | 15 | 8.9 | 0.0002 |
| Left Precuneus | 45 | 0.02 | -8 | -57 | 57 | 8.0 | 0.0004 |
| Right Somatosensory Cortex, inferior | 118 | 0.00003 | 52 | 0 | 24 | 16.0 | 3e-7 |
| Right Inferior Parietal Lobe | 277 | 4e-10 | 61 | -63 | 27 | 16.5 | 2e-7 |
| Right Medial Visual Cortex | 169 | 6e-7 | -2 | -63 | 18 | 14.7 | 9e-7 |
| Right Sensorimotor Cortex | 82 | 0.001 | 31 | -18 | 45 | 13.2 | 3e-6 |
| Right Medial Frontal Cortex | 77 | 0.001 | 4 | 57 | 0 | 9.0 | 0.0002 |

$P_{\text{FWE-corr}}$, $P$ (Family-Wise Error-corrected), whole brain. x y z, coordinates in Montreal Neurological Institute space.
**Supplementary Table 3.** Functional MRI statistical results. Age Correlation analysis

|                           | Cluster-level | Peak-level |
|---------------------------|---------------|------------|
|                           | Voxels | P<sub>FWE-corr</sub> | x y z | t   | p     |
| **Osteoarthritis plus Fibromyalgia** |         |            |       |     |       |
| Left Auditory Cortex      | 344    | 3e-9       | -59 -18 0 | 4.5  | 4e-6  |
| Left Visual Cortex        | 129    | 0.0002     | 1 -102 -9 | 4.4  | 0.00001 |
| Left Somatosensory Cortex, medial | 58    | 0.04       | 4 -18 48  | 4.1  | 0.00003 |
| Left Orbitofrontal Cortex| 94     | 0.003      | -11 15 -18 | 3.6  | 0.0002 |
| Right Auditory Cortex     | 123    | 0.001      | 55 -9 -12  | 3.6  | 0.0002 |

| **Osteoarthritis (short distance, 5-10mm)** |          |            |       |     |       |
| Left Frontal Pole          | 187    | 3e-6       | -41 51 3 | 4.7  | 0.00002 |
| Right Frontal Pole         | 74     | 0.009      | 43 60 -3 | 4.0  | 0.0002 |

| **Fibromyalgia (short distance, 5-10mm)** |            |       |     |       |
| Left Auditory Cortex       | 72     | 0.005    | -59 -18 0 | 3.8  | 0.0002 |
| Left Medial Visual Cortex  | 127    | 0.00007  | 1 -102 -9 | 5.5  | 4e-7  |
| Left Somatosensory Cortex  | 75     | 0.004    | -47 -21 51 | 3.8  | 0.0001 |
| Left Somatosensory Cortex, opercular | 51    | 0.03     | -56 -15 21 | 3.3  | 0.001 |
| Left Insula                | 118    | 0.0001   | -35 21 -3  | 4.5  | 0.00002 |
| Left Orbitofrontal Cortex  | 157    | 9e-6     | -35 54 -15 | 4.7  | 0.00001 |
| Right Somatosensory Cortex | 131   | 0.0001   | 43 -21 51  | 4.4  | 0.00002 |
| Right Visual Cortex        | 290    | 1e-8     | 22 -105 -6 | 5.4  | 5e-7  |
| Right Insula               | 102    | 0.0007   | 46 18 -9  | 4.5  | 0.00002 |
| Right Prefrontal Cortex    | 56     | 0.03     | 55 18 24  | 3.9  | 0.0001 |

P<sub>FWE-corr</sub>, P (Family-Wise Error-corrected), whole brain. x y z, coordinates in Montreal Neurological Institute space.