Supplementary Materials and Methods: Brain network analysis methodology

MRI acquisition

MRI was performed on fixed brains using a 7T animal MRI scanner (BrukerBioSpin MRI GmbH). High-resolution three-dimensional T1 weighted images were obtained in the brain samples by a Modified Driven Equilibrium Fourier Transform (MDEFT) sequence in the UN model with the following parameters: Time of Echo (TE) = 3.5 ms, Time of Repetition (TR) = 4000 ms, 0.7-mm slice thickness with no interslice gap, 70 coronal slices, in-plane acquisition matrix of 188 × 188 and Field of View (FoV) of 28 × 28 mm^2, resulting in a voxel dimension of 0.15 × 0.15 ×0.7 mm^3. In the PU model, high-resolution three-dimensional T2-weighted images were obtained in the brain samples by a RARE (Rapid Acquisition with Relaxation Enhancement) sequence with the following parameters: TE=9 ms, TR=4843.7 ms, RARE factor=4, 0.7mm slice thickness with no interslice gap, 70 coronal slices, in-plane acquisition matrix of 256 × 256 and Field of View (FoV) of 32×32 mm^2, resulting in a voxel dimension of 0.125 × 0.125 × 0.7 mm^3. In both models, diffusion-weighted images (DWI) were acquired using a diffusion sequence covering 30 gradient directions with a b-value of 3000 s/mm^2 together with a baseline (b = 0 s/mm^2) image. Other experimental parameters were: TE = 26 ms, TR = 250 ms, 0.7 mm slice thickness with no interslice gap, 70 coronal slices, in-plane acquisition matrix of 40 × 40 , FoV of 28 × 28 mm^2, resulting in a voxel dimension of 0.7 × 0.7 × 0.7 mm^3. The total scan time for DWI was 3h6 min, for MDFET-T1 was 1h45min and 3min52s for RARE-T2 acquisitions.

Pre-processing and tractography

Brain tissue was segmented from the background in the T1 (UN) and T2 (PU) volumes based on the Otsu threshold method [1]. In the case of DWI, brain tissue was segmented from the background by means of an in-house algorithm previously described [2] that takes advantage of the high SNR of the brain tissue on the average diffusion volume. Diffusion Toolkit (http://trackvis.org/dtk/; date last accessed: August 2015) was used to estimate the diffusion tensor image (DTI) and perform tractography, considering a fractional anisotropy (FA) threshold of 0.1.

Brain parcellation

Automatic brain parcellation of the subjects' brain was performed using the New Zealand Rabbit MRI atlas [3]. The atlas was defined considering a T1 template, so in the PU model a previous step was required by modifying image intensity in order to simulate RARE acquisition contrast. Then, elastic registration was performed between the correspondent atlas template (T1 or RARE-adapted) to each subject's brain using a consistent block matching algorithm [4]. The elastic transformation was applied to the ROI labels, obtaining a parcellation of each brain in 60 ROIs. Coherence between the T1- and RARE-based parcellation was evaluated by scanning one subject using both modalities. Parcellation obtained from both images was compared, observing similar results in both cases (global Dice Coefficient = 0.97) [3].

In order to align the labels obtained for each subject in the T1 or T2 volumes to its corresponding DWI, affine registration between T1 or T2 and the

baseline diffusion image was performed with IRTK (www.doc.ic.ac.uk/~dr/software/; date last accessed: August 2015) [5]. Discrete values of the labels were preserved by nearest neighbor interpolation in both transformations. ROIs comprising only white matter (WM) tissue were discarded, leaving a total of 44 regions for each subject (see Table A at the end of this document), each of them considered as a brain network node.

Network extraction

Brain network of each subject was extracted by means of an in-house algorithm as previously described [6], defining a network edge e_{ij} between two nodes if there is at least one streamline starting in one node and ending in the other one. In order to assign weights to each edge $e_{ij,}$ we considered the average fractional anisotropy (FA) along all the fibers connecting each pair of regions *i* and *j* [6]. Hence, FA-weighted (FA-w) were obtained from each subject.

Network analysis

Graph theory network features characterizing the global functioning of each network were computed using the Brain Connectivity Toolbox [7]. Particularly, we assessed infrastructure (average strength), integration (weighted global efficiency) and segregation (weighted local efficiency) of each weighted network.

Table A: Regions of interest used as nodes in the structural brain networks.

ID	Label	Name	ID	Label	Name
1	FCx-L	Frontal cortex L	**23**	Len-L	Lenticular nucleus L
2	FCx-R	Frontal cortex R	**24**	Len-R	Lenticular nucleus R
3	MFCx-L	Medial frontal cortex L	**25**	Th-L	Thalamus L
4	MFCx-R	Medial frontal cortex R	**26**	Th-R	Thalamus R
5	CiCx-L	Cingulate cortex L	**27**	Am-L	Amygdala L
6	CiCx-R	Cingulate cortex R	**28**	Am-R	Amygdala R
7	PiCx-L	Piriform cortex L	**29**	OlB-L	Olfactory bulb L
8	PiCx-R	Piriform cortex R	**30**	OlB-R	Olfactory bulb R
9	ECx-L	Entorhinal cortex L	**31**	Hc-L	Hipopocampus L
10	ECx-R	Entorhinal cortex R	**32**	Hc-R	Hipopocampus R
11	PaCx-L	Parietal cortex L	**33**	FB-L	Forebrain L
12	PaCx-R	Parietal cortex R	**34**	FB-R	Forebrain R
13	OcCx-L	Occipital cortex L	**35**	CeH-L	Cerebellar hemisphere L
14	OcCx-R	Occipital cortex R	**36**	CeH-R	Cerebellar hemisphere R
15	InCx-L	Insular cortex L	**37**	Ht	Hypothalamus
16	InCx-R	Insular cortex R	**38**	Ve	Vermis
17	TeCx-L	Temporal cortex L	**39**	BF	Basal forebrain
18	TeCx-R	Temporal cortex R	**40**	De	Diencephalon
19	Cl-L	Claustrum L	**41**	Me	Mesencephalon
20	Cl-R	Claustrum R	**42**	Po	Pons
21	Cau-L	Caudate nucleus L	**43**	MO	Medulla oblongata

22	Cau-R	Caudate nucleus R	**44**	Spt	Septal nuclei

Abbreviations: R: right, L: Left

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