Some brains are more strongly functionally connected than others: a resting-state fMRI study of inter and intra network coherence

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Introduction: Coherent spontaneous fluctuations in fMRI signal between brain regions that share a common functional specialisation (functional connectivity, FC) define intrinsic connectivity networks (ICNs) [1]. ICN dynamics are of critical importance in supporting human brain function and behaviour [2] and alterations in ICN coherence have been implicated in chronic pain [3] and Alzheimer's disease [4]. The spatial patterns of ICNs are highly consistent across individuals [5]. However, a comprehensive study of the temporal relationships between the spontaneous, resting-state activity of multiple ICNs is lacking despite offering insight into the natural organisation of, and communication between, the brains primary functional units. We used independent component analysis (ICA) to define the major, bilateral ICNs and seed-based FC to investigate: 1) Inter-Inter ICN FC, if ICN FC was related to the strength of FC within a different ICN; 2) Inter-Intra ICN FC, if ICN FC was related to the FC between that ICN and a different ICN; 3) Cortical-Thalamocortical FC, if ICN FC was related to the FC between that ICN and the thalamus.

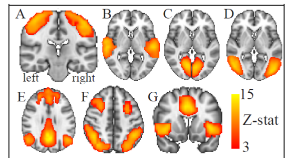

Fig 1. Spatial maps of SM (A), AD (B) PV (C), LV (D), DMN (E), DAN (F) and SAL (G) ICNs identified by group ICA showing all ROIs used for FC

Methods: Fifty-five subjects (28 males, age=25±4yrs) underwent a six-minute resting-state fMRI experiment. Subjects were instructed to keep their eyes open and think of nothing in particular. Whole-brain BOLD-weighted data were acquired using a Philips 3T Achieva (gradient-echo EPI, flip angle 80°, SENSE=2, 3x3x4mm^3 voxels, TE=35ms; TR=2s, 32 slices, 150 volumes). Using FSL 4.1.8 (www.fmrib.ox.ac.uk/fsl) BOLD data were motion corrected and RETROICOR was used to reduce cardiac and respiratory physiological noise. Data were spatially smoothed (5mm), registered to the MNI standard brain and temporally concatenated across subjects. MELODIC was used to decompose this group data into 20 maximally spatially-independent components [6]. From these components seven ICNs were selected for further analysis based on their spatial similarity to previously reports [1,5]: 1) default mode (DMN); 2) dorsal attention (DAN) 3) saliency (SAL); 4) sensorimotor (SM); 5) auditory (AD); 6) primary visual (PV) and 7) lateral visual (LV) networks (Fig 1) and we define specific regions of interest (ROIs) from these component maps. We manually divided the sensory networks (SM, AD, PV, LV) into left and right (L&R) hemisphere regions and the DMN, DAN and SAL into their major nodes (Fig 1). DMN: posterior cingulate (PCC), medial prefrontal cortex (mPFC), L&R inferior parietal lobe (IPL). DAN: L&R intra-parietal sulcus (IPS), L&R medial frontal cortex (mFC). SAL: L&R insula and anterior cingulate (ACC). ROIs were defined by centering a 3x3x3 voxel cube (12x12x16mm) on the maximum z-statistic voxel, located centrally in each region. Anatomical masks (Harvard-Oxford subcortical atlas, FSLatlas tools) were used to define L&R thalamus to investigate thalamocortical FC. All ROIs were then registered to each individual's data. To facilitate FC analysis BOLD data were low-pass filtered (0.008<f<0.08Hz) and the six motion parameters, ventricular, white-matter and global-brain signals were removed with linear regression [7]. For each subject, seed-based FC analysis [7] was performed to measure the strength of BOLD signal correlation (Pearson's R) between ROIs. Inter ICN FC was defined as the mean R-value between the L&R SM, AD, PV, LV, IPL, IPS and insula ROIs. Additionally, anterior-posterior Inter ICN FC was assessed for PCC-mPFC and insula-ACC. Intra ICN FC was defined as the mean R-value between a seed ROI in one ICN and a target ROI in a different ICN. Intra ICN FC target ROIs were: left SM, AD, PV, LV and IPS along with the PCC (DMN) and ACC (SAL). Linear correlation of R-values was used to investigate: 1) Inter-Inter ICN FC, e.g. AD FC vs IPL FC. 2) Inter-Intra ICN FC, e.g. AD FC vs AD-PCC FC. 3) Cortical-Thalamocortical (C-THC) FC, e.g. AD FC vs AD-thalamus FC.

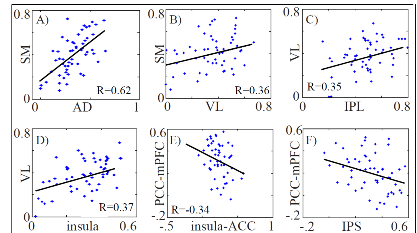

Fig 2. Inter-Inter ICN FC Significant correlations between the FC within one ICN and the FC within a different ICN.

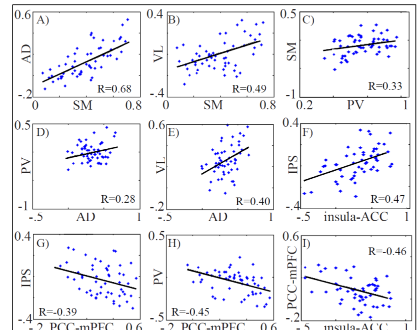

Fig 3. Inter-Intra ICN FC Significant correlations between the FC within one ICN and the FC between that ICN and a different ICN

Results: MELODIC group ICA resolved patterns of coherent fluctuations in fMRI signal due to ongoing brain processes in seven well-known ICNs (Fig 1). Seed based FC analysis revealed significant relationships between the temporal dynamics of these spatially distinct networks. <u>Inter-Inter ICN FC:</u> Fig 2 illustrates several instances where the strength of FC within one ICN was related to the FC within another ICN. Starting with L&R connectivity: FC within the SM ICN was significantly positively correlated with FC within the AD and VL (Fig 2 A,B). VL FC was also positively correlated with both DMN IPL FC and SAL insula FC (Fig2 C,D). Examining anterior-posterior FC showed significant negative correlations between DMN PCC-mPFC FC and the FC between L&R SM and insula-ACC SAL (Fig 2 E,F). <u>Inter-Intra ICN FC:</u> Fig 3 illustrates several instances where the strength of FC within one ICN was related to the FC between that ICN and another. FC within the SM ICN was positively correlated with the FC between the SM ICN and the AD, VL and PV ICNs (Fig 3 A,B,C). FC within the AD ICN was positively correlated with FC between the AD ICN and the PV and VL ICNs (Fig 3 D,E). FC within the DAN was positively correlated with FC between the DAN and the SAL (Fig 3 F). Additionally, negative correlations were observed between the PCC-mPFC FC of the DMN and the strength of connectivity between the PCC and the DAN, PV and SAL ICNs (Fig 3 G,H,I). <u>C-THC FC:</u> The strength of FC within the PV, AD and SM ICNs was significantly negatively correlated with the FC between those ICNs and the contralateral thalamus (Fig 4 A,B,C). A positive correlation was observed between DMN PCC-mPFC FC and the FC between the PCC and the thalamus (Fig 4D).

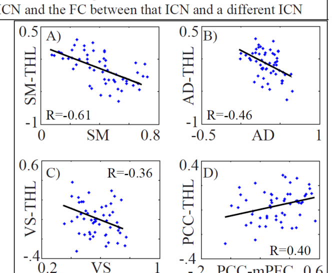

Fig 4. C-THC FC Correlation between a given ICNs FC and its thalamocortical FC

Discussion: This study indicates that some people`s brains are more strongly functionally connected than others in two ways: 1) Individuals with stronger cross-hemisphere connectivity within a given ICN display stronger L&R FC within a different ICN as demonstrated for the SM, AD, VL, insula and the IPL (Fig 2). Additionally, interesting inverse relationships were observed such that individuals with higher SAL FC display significantly lower FC in the DMN than individuals with low SAL FC. 2) The strength of FC within the SM, AD, VL and PV is predictive of how strongly correlated the activity of these sensory ICNs is to each other. Furthermore, a more strongly connected SAL network was associated with stronger FC between the SAL and the DAN and weaker FC between the SAL and the DMN, We do not believe these correlations can be explained by physiological confounds as correction for cardiac and respiratory noise was performed. Furthermore, variability in the rate and depth of subjects breathing was not found to be related to the strength of their ICN FC. The competitive relationship between the spontaneous fluctuations of the DMN, DAN and SAL ICNs extends previous reports of an inverse relationship between DMN and SAL FC [8]. Inter-Intra FC relationships have consequences for information transfer between brain regions, linked to reports that performance of the Erikson-Flanker task was related to the anticorrelation between the individual's DMN and DAN during the resting-state [9]. These results suggest that ICN functional connectivity can represent more than just coherent signalling between the most functionally related brain regions, instead it may provide a deterministic parameter of the functional collaboration and antagonism of multiple functional networks. Therefore Inter-Inter and Inter-Intra ICN relationships may present a powerful methodology for studying malfunctions of network synchrony in disease pathologies. Finally we observe that FC within PV, SM and AD ICNs was related to the coupling between that sensory ICN and the contralateral thalamus. Negative FC measurements can be induced by global-signal removal which causes a decreasing shift in the correlation values. We therefore interpret the negative C-THC FC correlation observed here as indicating that stronger FC with the thalamus disrupts the intrinsic FC within sensory ICNs resulting in reduced signal coherence between cortical hemispheres. In contrast, increased FC between the PCC and the thalamus is associated with stronger FC within the DMN.

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