# Fusion of Structural-Functional Brain Images Reveals Differences in Schizophrenia in a Multi Site Study

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## *Introduction*

It is a common practice to acquire multi-modal information in brain imaging studies. For example structural MRI (sMRI) is collected with functional MRI (fMRI). Each modality provides both unique and common information about different aspects of the brain. The brain is a vastly interconnected organ and it is reasonable to expect local changes to result in modulations of brain activity in distant regions. The disconnection hypothesis of schizophrenia [2] states that the neural mechanisms of schizophrenia are not circumscribed and that schizophrenia may be characterized by a deficit of interconnections between different brain regions. In this study we introduce techniques to measure how gray matter concentration, measured using sMRI, is correlated with functional activity, measured using fMRI, while performing a sensorimotor (SM) task. Our results show that correlation between structure and function is stronger in healthy controls (HC) than in patients with schizophrenia (SZ).

## *Methods*

94 HCs and 85 SZs were imaged as part of a large study (Mind Clinical Imaging Consortium) at four different sites and each participant had given written, informed and IRB approved consent at their respective sites. After removing outliers based on fMRI data and selecting subjects to match demographics we reduced the data set to 70 subjects in each group. The SM task was designed to robustly activate the auditory cortex. It is an on/off block design and during the on-block, 200ms tones were presented. There were eight tones at different pitches along a scale and were presented in ascending and descending cycles. After each tone the subject was required to press a button with the right thumb. Scans were acquired with either a GE or Siemens scanner with field strength of 1.5 or 3.0T. Scanning parameters varied slightly between sites. Structural and functional images were down sampled to voxel size=3.4x3.4x4mm$^3$. Preprocessing steps included motion correction, spatial normalization and smoothing. sMRI images were segmented to obtain gray matter maps and fMRI data were reduced to activation maps.

## *Comprehensive Spatial Correlation Analysis*

The 3 dimensional brain images contained about 60,000 (*N*) voxels. Images of subjects belonging to a certain group were used to compute sMRI and fMRI matrices where voxels were placed along the columns and subjects along the rows. Let $\mathbf{x}_i$ and $\mathbf{y}_j$ be the column vectors across all subjects for the $i^{th}$ voxel from sMRI and the $j^{th}$ voxel from fMRI respectively. Our interest was in finding the correlation between $\mathbf{x}_i$ and $\mathbf{y}_j$ where *i* and *j* varied independently from 1 to *N*. An analysis of this nature requires a large structural-functional cross correlation matrix ($\mathbf{R}_{\mathbf{SF}}$) of size *N* x *N*. Computing $\mathbf{R}_{\mathbf{SF}}$ is not easy due to limitations in computer memory and the interpretation of $\mathbf{R}_{\mathbf{SF}}$ will be based on reduced statistics. We introduce efficient techniques to obtain three statistics of $\mathbf{R}_{\mathbf{SF}}$ without fully computing it. Method1: Find the histogram of its elements. This is a modification of a technique we introduced in [1] to fuse multiple fMRI images. Method2: Find the mean of $\mathbf{R}_{\mathbf{SF}}$ along its rows. Method3: Segment $\mathbf{R}_{\mathbf{SF}}$ into AAL atlas regions and find the inter-regional mean. In Method1 we compute a row of $\mathbf{R}_{\mathbf{SF}}$, find its histogram, repeat the procedure for all rows of $\mathbf{R}_{\mathbf{SF}}$ and finally add the individual histograms. Method1 gives a general sense of the degree of structural-functional correlation. Method2 gives a map of how a structural voxel is correlated to all functional voxels. Method3 reduces the *N*x*N* $\mathbf{R}_{\mathbf{SF}}$ to 116 x 116 structural-functional inter-regional correlations (there are 116 anatomical regions specified in the AAL atlas). All three methods are applied to data from HC and SZ separately and differences between the metrics are detected.

## *Results*

Method1: The difference between HC and SZ histograms (Fig 1) showed that HC had a higher number of correlations near +0.2 and -0.2 than SZ, and SZ had higher number of correlations at zero correlation than HC. Correlation value of 0.2 has a significance of $P<0.05$ for 70 subjects. Method2: From the difference (HC-SZ) map (Fig 2) of how a structural voxel is correlated to all functional voxels, it is seen that HCs shows significant positive correlations in the cerebellum and in the same region SZ showed mostly negative correlations. Method3: While investigating significant ($P<0.01$) inter-regional correlation differences between HC and SZ (Fig 3) we found that HC showed positive correlations between AAL atlas structural regions of cerebellar vermis with functional regions of rolandic_oper, calcarine, fusiform and heschl. In SZ there were negative interregional correlations between structural regions of cingulum and paracentral_lobule and functional regions of putamen, pallidum and temporal_pole.

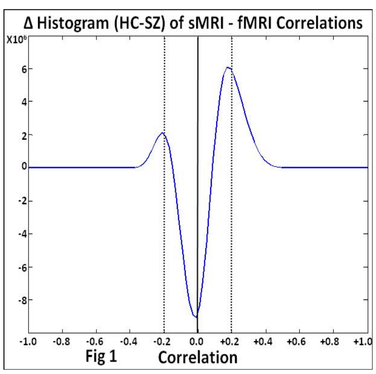


Fig 1

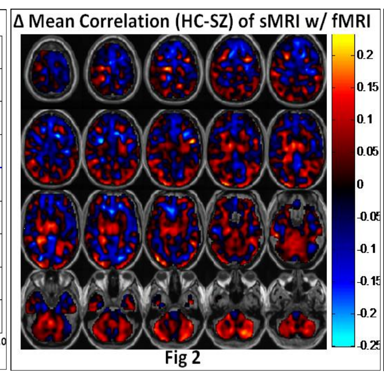


Fig 2

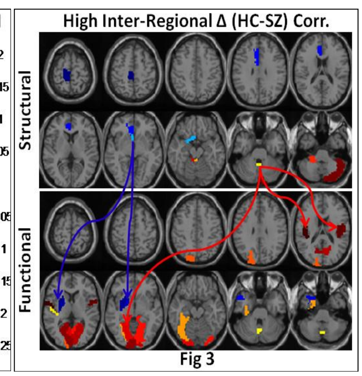


Fig 3

## *Discussion*

Method1: Results indicate that the inter-relationship between structure and function is stronger in HC than in SZ for the SM task. This may arise as a result of a compromised connectivity in SZ. This interpretation supports the disconnection hypothesis of schizophrenia [2]. Results from Methods 2 and 3 again support the disconnection hypothesis as well as the theory of cognitive dysmetria [3] where schizophrenia is modeled as a dysfunction in cortical-subcortical-cerebellar circuitry. Method3 did not show high correlation between structure and function either in HC or SZ from the same region and this should encourage researchers to explore correlations between distant regions. We introduce a data analytic approach to comprehensively investigate structural and functional correlation and show that results from this approach can reveal new differential features between patients with schizophrenia and healthy controls. Using three methods we show how to reduce data from a large matrix to yield information about inter-modality correlations, spatially locate regions with high correlations and find networks with high correlations. Results from all three methods indicate that structural-functional integrity is weaker in patients with schizophrenia than in healthy controls. The method presented can be easily applied to fuse data from different modalities to find further interconnections. We demonstrate how a data fusion technique can be successfully applied to join brain imaging data to reveal unique information that cannot be evaluated using any one modality.

## *References*

[1] Michael et al, *in press*, HBM (2008), [2] Friston, Schizophr Res 30(2):115-25 (1998) [3] Andreasen et al Schizophr Bull 24(2):203-18 (1998)

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