Intrinsic Connectivity Contrast: A Novel Contrast Mechanism for Investigating a Wide Range of Brain Disorders

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Introduction

Functional connectivity mapping using fMRI, first described over 10 years ago by Biswal, has recently gained in popularity. This approach utilizes BOLD fMRI signals obtained with subjects in the resting-state. Brain regions with high resting state connectivity are thought to be involved in the same network and the more well-formed the network, the stronger the connectivity. All of the connectivity work to date has been centered on evaluating connectivity between a seed region or seed voxel and other regions-of-interest (ROIs) – essentially examining one connection at a time. This approach is problematic however as it does not provide a comprehensive assessment of the connectivity across the whole-brain and it is highly sensitive to the choice of ROIs, the definition of which, based on anatomy, function, or an atlas, is often difficult.

Method

This work introduces a novel contrast mechanism reflecting intrinsic connectivity on a per voxel basis throughout the brain. This connectivity contrast can be viewed in multiple ways and here we will describe at least 3 different ways. The most general approach is to form a full connectivity map. In this measure the intensity of a given voxel in an image reflects the strength of the connections (measured as a correlation between time-courses) between that voxel and all the other voxels in the brain. To obtain this measure, a connectivity correlation analysis is performed between the time-course of the voxel of interest and each and every other voxel in the brain. These correlations are summed (or combined with a weighted sum of squares), and the voxel intensity is replaced by the net correlation sum. A high intensity therefore suggests that the voxel has strong connectivity to other areas of the brain, whereas a low intensity suggests that the voxel is not strongly connected. This calculation is repeated for each voxel relative to all the other voxels in the brain. The final image then shows the subjects brain in a gray scale map where the gray scale intensity for each voxel represents how strongly that voxel is connected to other parts of the brain. Other connectivity measures include: Ipsilateral Connectivity: Same as above but the connectivity for any seed voxel is compared only with all the other voxels in the *same hemisphere*; and Contralateral Connectivity: Same as above but the voxel connectivity is only measured with respect to all the voxels in the *opposite hemisphere.* The connectivity contrast can be display as a gray scale image or with a colormap reflecting the net strength of connectivity.

Results & Discussion

These connectivity maps can be used to examine intrinsic functional connectivity for a wide range of disorders where the underlying neuronal connectivity might be altered including: stroke, Alzheimer's, Parkinson's, epilepsy, schizophrenia, bipolar disorder, post traumatic stress disorder, and traumatic brain injury to name a few. For specific patient groups an additional contrast can be performed. Rather than looking at the intensities calculated as described above, we perform a statistical comparison between the individual patients connectivity contrast map (either full connectivity, ipsilateral, or contralateral as described above) and the connectivity contrast maps of a control group normal subjects (matched according to age, race, gender, or whatever). In these single subject to group comparisons areas of net increase or decrease in connectivity relative to the control group will be observed. Similarly, multiple groups can be contrasted with one another also using these maps. We have applied this method in assessing 15 patients who presented for surgical intervention for intractable epilepsy and 40 healthy control subjects. Results are shown below for a single epilepsy patient ipsilateral connectivity map contrasted with a control group of healthy volunteers. Blue areas represent regions of decreased intrinsic connectivity relative to the control subjects while hot colors indicate regions showing increased connectivity.

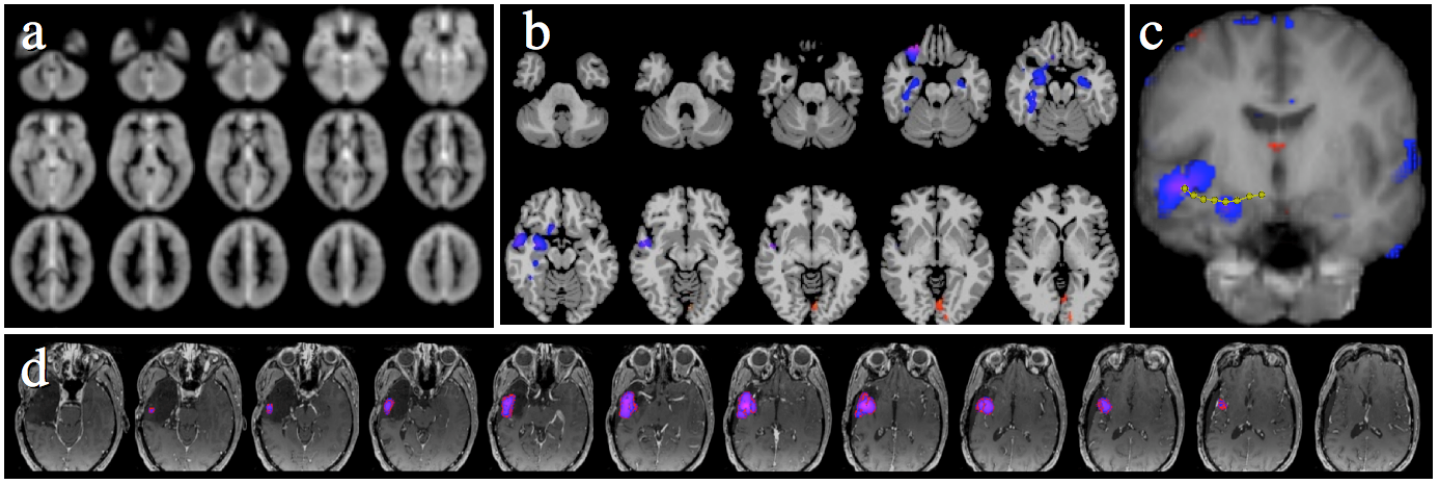

Figure showing a composite connectivity contrast volume from 40 normal volunteers (a), and a contrast of an intrinsic connectivity map for a single epilepsy patient (b) versus the 40 control subjects (blue show regions of decreased ($p<0.05$) connectivity, red increased, in the patient relative to the controls. Depth electrodes shown in (c) also indicated seizure activity coming from this temporal/insular region. The right anterior temporal lobe was resected as shown in (d) with the area identified as having abnormal connectivity highlighted in purple. The patient was seizure free 6 months post-op indicating this was likely the region that was generating seizure activity. Similar results have been found in 15 other patients.

While the ipsilateral connectivity contrast is the simplest measure to interpret in terms of lateralization of altered connectivity, connectivity contrast in the contralateral and full measures were sometime different. More subjects need to be run, and the results validated with either depth electrode data or surgical outcome measures to fully understand the meaning of these contrast maps. However this approach presents for the first time a task-free functionally based contrast mechanism that can be translated to a clinical assessment of neuronal connectivity across a range of disorders.