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The impact of image smoothness on intrinsic functional connectivity and head motion confounds

Dustin Scheinost [a,*], Xenophon Papademetris [a,b], R. Todd Constable [a,b,c]

[a] Department of Diagnostic Radiology, Yale University, New Haven, CT, USA
[b] Department of Biomedical Engineering, Yale University, New Haven, CT, USA
[c] Department of Neurosurgery, Yale University, New Haven, CT, USA

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ABSTRACT

We present a novel method for controlling the effects of group differences in motion on functional connectivity studies. Resting-state functional magnetic resonance imaging (rs-fMRI) is a powerful tool that allows for the assessment of whole-brain functional organization across a wide range of clinical populations. However, as highlighted by recent studies, many measures commonly used in rs-fMRI are highly correlated with subject head movement. A source of this problem is that motion itself, and motion correction algorithms, lead to spatial smoothing, which is then variable across the brain and across subjects or groups dependent upon the amount of motion present during scanning. Studies aimed at elucidating differences between populations that have different head-motion characteristics (e.g., patients often move more in the scanner than healthy control subjects) are significantly confounded by these effects. In this work, we propose a solution to this problem, uniform smoothing, which ensures that all subject images in a study have equal effective spatial resolution. We establish that differences in the intrinsic smoothness of images across a group can confound connectivity results and link these differences in smoothness to motion. We demonstrate that eliminating these smoothness differences via our uniform smoothing solution is successful in reducing confounds related to the differences in head motion between subjects.

Introduction

Resting-state functional magnetic resonance imaging (rs-fMRI) is an emerging tool that allows for the analysis of whole-brain functional organization without *a priori* knowledge (Smith, 2012). By measuring the functional connectivity of brain regions via correlation of spontaneous fluctuations in the blood-oxygen-level dependent (BOLD) signal (Biswal et al., 1995, 2010; Lowe et al., 1998), rs-fMRI can easily be applied clinically as it can be task- and performance-free. This technique has great clinical potential in a range of neurological diseases including those populations for whom the burden of complex cognitive tasks is greatest. While rs-fMRI is maturing as a modality, a recent set of papers have shown that most functional connectivity measures are highly correlated with subject movement (Power et al., 2012; Satterthwaite et al., 2012, 2013; Van Dijk et al., 2012; Yan et al., 2013). In many cases, comparisons between control groups and clinical populations, where rs-fMRI may have the most potential, are confounded by systematic differences in head movement between the groups. The interaction between study group, motion, and functional connectivity is currently a major obstacle in the development and clinical application of rs-fMRI.

Current approaches aimed at reducing the impact of motion on functional connectivity have focused generally on controlling for subject head motion. Controlling for motion is achieved by removing high-motion data (Power et al., 2012), by regressing motion at a group level (Satterthwaite et al., 2012), by matching data sets for motion (Tian et al., 2006), or by regressing higher motion terms (Satterthwaite et al., 2013). However, these approaches do not entirely eliminate motion confounds (Yan et al., 2013). One potential issue with removing time points or regressing several motion terms is that potentially real changes in connectivity associated with motion can be removed along with artifacts (Scheinost et al., 2013). Other approaches that do not rely explicitly on controlling for motion, such as removal of global signal and additional normalization, have been suggested as potential solutions to motion confounds (Power et al., 2014; Yan et al., 2013).

The primary contribution of this paper is to introduce the use of iterative smoothing as a method to reduce motion confounds of the form that arise when significant differences in motion are present between experimental groups. This approach works without needing to explicitly control for motion. First, we establish that an image's intrinsic smoothness is correlated with both region-of-interest (ROI)-based and voxel-based measures of connectivity and show that differences

* Corresponding author at: Magnetic Resonance Research Center, 300 Cedar St, PO Box 208043, New Haven, CT 06520-8043, USA. Fax: +1 203 785 6534.
E-mail address: dustin.scheinost@yale.edu (D. Scheinost).

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in smoothness across a sample can confound connectivity. Next, we show that subject head motion is correlated with this intrinsic smoothness suggesting that increased image smoothness is caused by head motion and motion correction. Finally, we demonstrate that eliminating these differences in image smoothness, by smoothing all images to a uniform level across the sample, is an effective way to reduce motion-related confounds in functional connectivity studies. We demonstrate that our method has at least equivalent performance compared to other current strategies focused on minimizing motion confounds, while not relying on excluding high motion frames from the data.

Methods

Subjects

We selected the Oulu data set from the 1000 functional connectivity project (Biswal et al., 2010) (http://www.nitrc.org/plugins/mwiki/index.php/fcon_1000/). This data set was chosen due to the large number of subjects ($n = 103$) and due to the tight age range (range = 20–23 years, mean = 21.5 years, standard deviation = 0.6 years) in order to minimize any age-related effects on motion (Van Dijk et al., 2012) or connectivity (Fair et al., 2008; Hampson et al., 2012). Full demographic information and imaging parameters can be found elsewhere (Biswal et al., 2010). Briefly, for each subject, the data set included a high-resolution anatomical magnetization prepared rapid gradient echo (MPRAGE) and a resting-state functional image. The functional images were acquired with a TR of 1.8 s, an imaging matrix of 64×64, 28 slices, voxel dimensions of $4 \times 4 \times 4.4$ mm, and 245 frames. We also selected the Cambridge data set from the 1000 functional connectivity project to use in a replication study that is presented in the Supplemental Materials section.

Preprocessing

A standard preprocessing pipeline was used. All images were slice time and motion corrected with fourth-order B-spline interpolation using SPM (http://www.fil.ion.ucl.ac.uk/spm/). Unless otherwise specified, all further analysis was performed using BioImage Suite (www.bioimagesuite.org; (Joshi et al., 2011)). The functional images were then smoothed with a Gaussian kernel with full width half max (FWHM) of 6 mm or the uniform smoothing algorithm (see Uniform Smoothing section). Several covariates of no interest were regressed from the data including linear and quadratic drift, six rigid-body motion parameters, mean cerebrospinal fluid (CSF) signal, mean white-matter signal, and mean global signal. The white matter and CSF areas were defined on a template brain (Holmes et al., 1998), eroded to ensure only white matter or CSF signal would be included, and warped to the subjects' space using a series of transformations described below. Finally, the data were low-pass filtered via temporal smoothing with a zero mean unit variance Gaussian filter (approximate cutoff frequency = 0.12 Hz).

Uniform smoothing

In order to create a uniform level of smoothness across the data set (thus minimizing group differences associated with image smoothing), each subject's functional run was smoothed with AFNI's 3dBlurToFWHM (http://afni.nimh.nih.gov/afni). This program iteratively smoothes a functional series using a diffusion-based smoothing scheme until the images are smoothed to approximately the desired level. Specifically, the *-detrend*, *-automask*, and *-temper* options were used. These options mask the data so only voxels within the brain are used in the smoothing, remove high-order polynomials trends from the data so that the estimated smoothness minimizes the impact of spatial structure, and increase the tolerance used for matching the estimated image smoothness to the desired smoothness. Both global and local smoothness are smoothed to approximately the desired level of smoothness. The input was the slice-timed and motion corrected data and was smoothed to an FWHM of 6 mm. Additional information about this program can be found in the Supplemental Materials section.

ROI-based connectivity metrics

To evaluate the effect of image smoothness and motion on connectivity, we performed a standard ROI-based ("seed") analysis using an ROI centered in the posterior cingulate cortex (PCC, MNI coordinates: 0, −55, 26). The PCC ROI was defined on the MNI reference brain as a 9 mm cube and transformed back (via the inverse of the transforms described below) into individual subject space. The time course of the PCC in a given subject was then computed as the average time course across all voxels in the PCC ROI. This time course was correlated with the time course for every other voxel in the gray matter to create a map of r-values, reflecting ROI-to-whole-brain connectivity. These r-values were transformed to z-values using Fisher's transform yielding one map for each subject representing the strength of correlation to the PCC ROI. This PCC connectivity was chosen to be consistent with other studies (Satterthwaite et al., 2013; Van Dijk et al., 2012; Yan et al., 2013).

Voxel-based connectivity metrics

In addition to ROI-based connectivity analysis, we examined the relationship between image smoothness/motion and a voxel-wise connectivity metric based on the network theory metric *degree*. *Degree* is simply the sum of all connection weights to a particular node in a network. For our purposes, each voxel is treated as a separate node and all connections are functions of the correlation between the time courses for any two voxels. We examined *degree* based on a binary network (Buckner et al., 2009; Martuzzi et al., 2011). In this case, a connection (correlation) threshold of $r = 0.25$ was used to determine if two voxels were connected and degree was simply the count of all such connections above this threshold. After preprocessing, *degree* was calculated for each functional run. A gray matter mask was first applied to the data so only voxels in the gray matter were used in the calculation. The gray matter mask was defined on a template brain (Holmes et al., 1998), dilated to ensure full coverage of the gray matter, and warped to each individual subjects' space using a series of transformations described below. The time course for each voxel was correlated with every other time course in the gray matter and the voxel-based metrics described above were calculated. As global signal regression is known to create ambiguity in the sign of the correlation, we only considered positive correlations in calculating the voxel-base connectivity metrics (Buckner et al., 2009; Cole et al., 2012). To account for differences in brain size across participants, individual *degree* maps were normalized by one of two methods. For the first method, the *degree* maps were divided the total number of voxels in the individual subject's gray matter mask. For the second method, the *degree* maps were converted to z-scores by subtracting the mean across all voxels and dividing by the standard deviation across all voxels. In the following sections, we refer to the output of the first normalization method simply as *degree* or *degree* maps, while we refer to the output of the second normalization method as normalized *degree* or normalized *degree* maps. While *degree* can be sensitive to the choice of connection threshold (Scheinost et al., 2012), the presented motion and smoothing confounds were robust over a large range of thresholds ($0.10 < r < 0.75$). We chose this metric instead of ROI-to-ROI connectivity based on a high-resolution parcellation of the brain (Finn et al., 2013; Shen et al., 2013) because *degree* represents a generalization of this approach as each voxel is treated as an ROI and has potential clinical utility (Constable et al., 2013).

Common space registration

To make inferences at the group level, all single-subject results were warped to a common template space through the concatenation of a series of linear and non-linear registrations. The functional series were