A Series Registration Framework to Recover Resting-State Functional Magnetic Resonance Data Degraded By Motion

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Abstract

Data retention is a significant problem in the medical imaging domain. For example, resting-state functional magnetic resonance images (rs-fMRIs) are invaluable for studying neurodevelopment but are highly susceptible to corruption due to patient motion. The effects of patient motion can be reduced through post-acquisition techniques such as volume registration. Traditional volume registration minimizes the global differences between all volumes in the rs-fMRI sequence and a designated reference volume. We suggest using the spatiotemporal relationships between subsequent image volumes to inform the registration: they are used initialize each volume registration to reduce local differences between volumes while minimizing global differences. We apply both the traditional and novel registration methods to a set of healthy human neonatal rs-fMRIs with significant motion artifacts (N=17). Both methods impacted the mean and standard deviation of the image sequences’ correlation ratio matrices similarly; however, the novel framework was more effective in meeting gold standard motion thresholds.

Introduction

In the biomedical informatics domain, it is often difficult to recruit a large sample population to perform a prospective study. Subjects who meet the criteria for any given study are difficult to find, and even more difficult to retain. One of the best ways to lose a study participant is to ask him to return to the study site to repeat his testing.

Unfortunately, this reality is all too common, especially in the neurological imaging field. Imaging research analyzing patterns of brain activity in patients in a quiet, non-stimulated state has led to important discoveries about links between brain function and neurodevelopmental diseases such as autism and attention deficit hyperactivity disorder\textsuperscript{1,2}. These and other studies have led to increased interest in early brain development, often through the use of neonatal resting-state functional magnetic resonance images (rs-fMRIs).

![Image](image.png)

**Figure 1.** A functional magnetic resonance image shows activity in different areas of the brain over a period of time. Images that are taken when (a) the patient is exposed to an auditory stimulus show activated networks different from the networks which are active in (b) task-free resting-state images.

During an rs-fMRI scan, the subject lays in the scanner in a task-free resting state. Every few seconds, a new whole brain 3D image (image volume) is recorded. Each image volume contains information about the subject’s brain activity in the form of blood oxygen level dependent (BOLD) signals. The signal recorded by the MRI scanner is a combination of the BOLD signal and changes in the spin gradients. The BOLD signal indicates brain activity, but the changes in the spin gradients distort the BOLD signal in the recorded image signal. The patterns of signals between sequential volumes are analyzed to reveal various local and global neuronal networks. For example, the fMRI in Figure 1a shows neuronal networks in red and yellow activated by an auditory stimulus. However, not all fMRIs have...
a stimulus associated with them: in Figure 1b, the patient is in a task-free resting-state and the default mode network in green shows activation.

This analysis depends on the assumption that the subject remained perfectly still for the entirety of the scan. Due to the spatial resolution of the rs-fMRI, the smallest movements can cause voxels to record signals from different brain regions and tissue types. Even if a movement does not significantly change the recorded position of the subject, it impacts the established magnetic spin gradients, which require approximately 8-10 seconds to realign to the magnetic field. This recovery time decreases the global signal in frames obtained during this time, causes image artifacts, and affects the functional connectivity analysis. A minimum of 5-10 minutes of data unaffected by motion can be sufficient for an rs-fMRI to be used in functional connectivity studies; however, a recent study found that longer rs-fMRI sequences result in increased precision during analysis. These findings have a significant impact on the use of neonatal rs-fMRI: it is difficult to safely prevent a neonate from moving for even five minutes, so gathering enough low-motion rs-fMRI sequences for functional connectivity analyses is a challenge.

The usability of an rs-fMRI sequence is defined in terms of changes in patient position and image signal between sequential volumes. The change of the patient’s position between subsequent frames is called the framewise displacement (FD). Several researchers have developed FD metrics; herein, we use the FD metric defined by Power et al. However, FD only measures the positional effects of motion, not the effects of motion on the magnetic spin gradients: the changes in the image signal are more complex than the changes in the subject’s position. Changes in the recorded signal between neighboring frames can be measured using the temporal derivative of the variance in the image signal intensity (DVARS). DVARS values are a fair approximation of changes in the BOLD signal.

Efforts have been made to attempt to prevent motion from impacting rs-fMRI. Clinical protocols including education, sedation, and distraction techniques can be used to reduce a patient’s movements during acquisition, but these protocols are either not effective, not safe, or often not compatible with rs-fMRI for all populations. Tools have been developed to measure and correct for motion in rs-fMRIs as they are acquired; but whether the motion is measured optically or via MRI signal processing, these methods do not prevent motion and cannot be used to recover motion-corrupted data in existing repositories. The bulk of motion mitigation research focuses on the development of post-acquisition techniques.

While many different post-acquisition motion correction pipelines exist, they generally begin with a form of volume registration. The goal of volume registration is to optimize the orientation of every volume so that the differences between them and the reference volume are minimized. Unfortunately, minimizing differences between the reference volume and the other volumes in the sequence does not guarantee that the registered image sequence will have minimal differences between sequential volumes. As the usability of an rs-fMRI is defined using differences between sequential volumes, not between all volumes and the reference volume, this traditional registration framework is insufficient for its purpose.

We propose an alternative approach to volume registration which utilizes the spatiotemporal relationships between subsequent volumes to inform the registration process. We apply both the DAG-based framework and the traditional framework to a set of high-motion neonatal rs-fMRIs. We compare the performance of the two registration techniques in terms of positional similarity across the entire sequence and in terms of the FD and DVARS thresholds proposed by Power et al. and Smyser et al.

**Methods**

**Subjects**

Neonates were recruited as part of an ongoing prospective observational study performed at Children’s Hospital of Pittsburgh of UPMC (CHP). The study is HIPAA compliant and was approved by the Institutional Review Boards at both the University of Pittsburgh and CHP. Normal referents were recruited either from healthy pregnant volunteers or postnatally from a normal newborn nursery as part of control subjects for a longitudinal study of brain development in fetuses and neonates with congenital heart disease (CHD).

Subjects unsedated and scanned using a 3T Skyra (Siemens AG, Erlangen, Germany), using a “feed and bundle” protocol to prevent motion during the scans. Newborns were fitted with earplugs (Quiet Earplugs; Sperian Hearing Protection, San Diego, CA) and neonatal ear muffs (MiniMuffs; Natus, San Carlos, CA), then positioned in the coil to minimize head tilting. An MR-compatible vital signs monitoring system (Veris, MEDRAD, Inc. Indianola, PA) was used to monitor neonatal vital signs. All scans were performed using a multi-channel head coil. The parameters for the resting-state BOLD MR scans were FOV=240 mm and TE/TR=32/2020 ms with an interplane resolution of 4x4 mm,
a slice thickness of 4 mm, and a 4 mm center-to-center spacing. The acquired sequences contained 150 volumes where each volume consisted of 64x64x32 voxels.

**Figure 2.** (a) Traditional volume registration may fail if the image contains too much motion, but (b) a rs-fMRI sequence can be viewed as an DAG: each node in the graph is a single frame, and position of the subject in each frame is only dependent on its position in the previous frame.

All images underwent both volume registration techniques demonstrated in Figure 2 and were compared to Power et al.’s thresholds of acceptability for their FD and DVARS metrics\(^1\). According to these thresholds, a volume in a sequence is considered usable if it has an FD change of less than or equal to 0.2 mm from the previous volume and a DVARS change of less than or equal to 25 units from the previous volume on a normalized range of [0, 1000] units. Seventeen subjects’ rs-fMRIs did not meet these criteria and were used in this study.

**Traditional Global Registration**

Traditional volume registration is the process of optimizing the alignment of every volume in a sequence to a single reference volume (Figure 2a). In our implementation, we use the first volume in each sequence as the reference volume, though other options have been used in other studies\(^29,30\). Then, for each volume \(J_i\) in the sequence, the transformation \(\phi_{i,0}\) to align \(J_i\) to the reference volume \(J_0\) is calculated. The transformations are then applied to each volume to obtain the registered volume \(J_i'\):

\[
J_i' = \phi_{i,0}J_i
\]

The registered image sequence consists of the set of registered images \([J_0, J_1', J_2', ..., J_{N-1}'\) for all \(N\) images in the original sequence.

This framework only minimizes the global differences between the reference volume and the other volumes in the sequence. Large local differences between sequential volumes can occur when the registration process’s cost function falls into a local minimum. The local minima might be the best solution the registration process can find to align two volumes with large differences in the subject’s position. If the patient’s positions in many volumes of the sequence are very different from its position in the reference volume, the registration will fail to produce a sequence that minimizes both the global and local differences between volumes.

**Global Registration with Local Prealignment**

In our proposed framework, we treat the rs-fMRI sequence as a directed acyclic graph (DAG). A DAG consists of a set of nodes connected to each other by directed edges such that once a node has been traversed, there is no path back to it. The form of our DAG resembles a Markov chain: each volume in the sequence is represented as a node, and the relationships between sequential volumes are represented as directed edges connecting the node for volume \(i\) to that of volume \(i+1\). The parallel perspectives of the sequence as a set of images and of the sequence as a DAG can be seen in Figure 2b.

The cost of transitioning from one node to the next in our DAG represents the combination of the positional transformation needed to align volume \(i\) to volume \(i+1\) and the signal change between the volumes. This representation can be written as

\[
J_{i+1} = \phi_{i,i+1}J_i + \Delta s_{i,i+1} + \epsilon_i
\]
where $J_i$ and $J_{i+1}$ are volumes $i$ and $i+1$, $\phi_{i,i+1}$ is a matrix of transformation parameters that must be applied to $J_i$ to achieve the patient’s position in $J_{i+1}$, $\Delta t_{i,i+1}$ is the matrix of changes in BOLD signal, and $\epsilon$ is the matrix of changes in the recorded signal due to the effect of motion on the spin gradients. Currently, there is no way to estimate the change in BOLD signal and the change in the recorded signal due to motion without incorporating additional information about the MRI scanner and the patient that is not included in an rs-fMRI. Instead, these parameters are treated as a single entity. We simplify our representation of the relationship between two volumes to

$$J_{i+1} = \phi_{i,i+1} J_i + \epsilon_i^s$$

(3)

Here, we use the notation $\epsilon^s$ to represent the change in recorded signal due to BOLD changes and motion across any pair of volumes. This quantity is ignored during the registration process and can be calculated after the registration is complete.

After aligning $J_i$ and $J_{i+1}$, we will use the calculated value $\phi_{i,i+1}$ to initialize the registration between volumes $J_{i+1}$ and $J_{i+2}$:

$$J_{i+2} = \phi_{i+1,i+2} J_{i+1} + \epsilon_i^{s*}$$

$$= \phi_{i+1,i+2} (\phi_{i,i+1} J_i + \epsilon_i^s) + \epsilon_i^{s*}$$

$$= \phi_{i+1,i+2} \phi_{i,i+1} J_i + \phi_{i+1,i+2} \epsilon_i^s + \epsilon_i^{s*}$$

(4)

As in the previous equation, the quantities $\phi_{i+1,i+2} \epsilon_i^s$ and $\epsilon_i^{s*}$ are ignored during the registration process. The simplified version of Equation 4 is

$$J_{i+2} = \phi_{i+1,i+2} \phi_{i,i+1} J_i$$

(5)

More generally,

$$J_k = \prod_{n=j}^{k-1} \phi_{n,n+1} J_j$$

(6)

It is important to note that the direct transformation $\phi_{j,k}$ cannot be guaranteed to equal the product of the individual transformations due to the limitation of local minima in the cost function disrupting the registration process. Calculating the individual transformations $\phi_{n,n+i}$ and multiplying them together prevents the registered image from containing large local differences between volumes while globally optimizing the alignment within the sequence.

Implementation

Both registration frameworks described in this section were implemented in Python using the nipype (Neuroimaging in Python Pipelines and Interfaces) library31. Affine volume registration was performed using ANTs (Advanced Normalization Tools)32. The metric used to estimate the dissimilarity between the pairs of volumes being registered was cross-correlation with a local window size of 5 voxels.

Experiments and Evaluations

The global volume registration techniques were applied to all 17 resting-state BOLD MR images. After the registrations, each subject had three sequences associated with it: the original sequence, the sequence registered using the traditional framework, and the sequence registered using the DAG-based framework. The registered sequences were compared to each other using their correlation ratios matrices as well as the FD and DVARS between all subsequent volumes.

The correlation ratio is an asymmetrical, spatially informed measure of the overlap between images33. It is calculated as:

$$\eta = \frac{\sum_x (\bar{v}_x - \bar{v})^2}{\sum_{x,y} (v_{xy} - \bar{v})^2}$$

(7)

where $x$ indicates the image, $y$ indicates the voxel in image $x$, $v_{xy}$ is the value of voxel $y$ in image $x$, $U_x$ is the average voxel value for image $x$, and $\bar{v}$ is the average of all voxel values in both images. The correlation ratio matrix was generated by calculating the correlation ratio for every possible pair of volumes in the sequence using FLIRT (FMRIB’s Linear Image Registration Tool)34,35. The correlation ratio matrix was used to compare the recorded signal in each image before and after each registration technique.

The FD and DVARS metrics defined by Power et al. were calculated using the FSLMotionOutliers tool6. These
Metrics were calculated for each image and were used for evaluation of the efficacy of the registration frameworks.

Results

Image Signal in Original and Registered Images

(a) Subject with the highest original correlation ratio average.

(b) Subject with median original correlation ratio average.

Figure 3: Correlation ratio matrices for two subjects. The three graphs for each subject show the correlation ratios between every possible volume pair in the original sequence, the traditionally registered sequence, and the DAG registered sequence. Darker colors indicate a higher correlation ratio and lower similarity between the volumes. Both registration methods produce sequences with better inter-volume coherence than the original sequences.

For both subjects 1 and 8, the original sequence had high correlation ratios between many pairs of volumes, and those pairs of volumes have lower correlation ratios in the corrected images. The correlation ratio matrices show that both versions of both registration methods produced rs-fMRI sequences with less variability than the original images.

Figure 4: The average and standard deviation of the correlation ratios of each sequence for each subject.
The mean and standard deviation of the correlation ratios for all sequences can be seen in Figure 4. The errorbars marked with circles represent the original sequences. The errorbars marked with triangles represent the sequences registered using the traditional global registration method. The errorbars marked with squares represent the sequences registered using the DAG-based registration method. This figure shows that the original unregistered sequences generally have higher average correlation ratios and more variation across the correlation ratio matrix than the registered images for nearly all subjects.

Comparison of Motion Correction Methods

Table 3. The mean, median, standard deviation, skewness, and kurtosis of the histograms of FD and DVARS values for all image types were calculated. The histograms for the DAG-based method have lower means, medians, and standard deviations than those of the first volume correction method.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>FD Values (mm)</th>
<th>DVARS Values (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Registration</td>
<td>Traditional</td>
</tr>
<tr>
<td>Mean</td>
<td>1.07</td>
<td>2.18</td>
</tr>
<tr>
<td>Median</td>
<td>0.3</td>
<td>1.46</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>1.97</td>
<td>2.35</td>
</tr>
<tr>
<td>Skewness (-)</td>
<td>3.86</td>
<td>3.08</td>
</tr>
<tr>
<td>Kurtosis (-)</td>
<td>23.29</td>
<td>17.74</td>
</tr>
</tbody>
</table>

The FD and DVARS values were calculated to determine how many volumes in each registered sequence met the gold standard usability thresholds. The FD and DVARS values were viewed as distribution functions representing the effects of no registration, traditional registration, and DAG-based registration. These distributions were compared using the Kolmogorov-Smirnov test, which compares the empirical distribution functions of two samples. The FD and DVARS values of all sequences were statistically significantly different at $p < 2.2E^{-16}$. The statistics of the FD and DVARS histograms of both motion correction methods can be seen in Table 3.

Table 4. The number of frames recovered by each global volume registration framework for each threshold.

<table>
<thead>
<tr>
<th>Threshold</th>
<th>No Registration</th>
<th>Traditional</th>
<th>DAG-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>FD (0.2 mm)</td>
<td>966</td>
<td>175</td>
<td>569</td>
</tr>
<tr>
<td>DVARS (25 units)</td>
<td>781</td>
<td>78</td>
<td>297</td>
</tr>
<tr>
<td>Both</td>
<td>619</td>
<td>61</td>
<td>258</td>
</tr>
<tr>
<td>Both (%)</td>
<td>24.27</td>
<td>2.39</td>
<td>10.11</td>
</tr>
</tbody>
</table>

Power et al.’s usability thresholds were used to determine how many volumes were recovered by each framework. Table 4 shows the number of volumes meeting each threshold, with the traditional and DAG-based frameworks recovering 2% and 10% of volumes, respectively. These results show that the DAG-based registration technique produces sequences with lower FD and DVARS values than the traditional global registration method does.

Discussion

Resting-state BOLD MR images are used to evaluate the functional architecture of a patient’s brain. Because resting-state BOLD images are highly susceptible to motion, the development of strong post-acquisition motion correction techniques is vital. Current pipelines for mitigating motion after sequence acquisition vary in terms of efficacy and effectiveness, but all begin with global volume registration. In this study, we compared the corrective performance of two global volume registration methods, the traditional framework and a novel DAG-based framework, on a set of 17 neonatal rs-fMRIs.
We structure our DAG model using a constraint similar to the Markov property: each frame is only connected to the immediately subsequent frame in our graph. This constraint allows the registration from the previous volume to the reference volume to be used to initialize the registration of the current volume to the reference volume. The initializations help the registration process globally and locally optimize the alignments of the image volumes to the reference volume.

The correlation ratio matrices, and FD and DVARS values were calculated for each sequence. Examination of the correlation ratio matrix statistics indicates that volume registration reduces some effects of motion in rs-fMRIs. The histograms of the FD and DVARS values of the registered sequences show that the DAG-based method was better able to correct volumes to meet Power et al.’s thresholds than the traditional registration method. Overall, these results indicate that the DAG-based global registration method is better able to reduce the effects of motion in neonatal images than the traditional global registration method. While no whole sequences were recovered, many high-motion volumes within each sequence were recovered by the DAG-based registration method but not by the traditional registration method.

Motion Patterns

Figure 5: The effects of the registration frameworks on the correlation ratios fall into 3 categories: (a) decreased correlation ratio means and standard deviations, (b) increased correlation ratio means and/or standard deviations, and (c) no significant effect.

Upon further examination of the correlation ratio matrices, three different effects of registration were noted. These effects consist of: reduction of correlation ratio mean and standard deviation, increase in correlation ratio mean or decrease only in the correlation ratio matrix’s standard deviation, and no significant effect.

The first effect is characterized by a reduction in correlation ratio mean and standard deviation after registration. Two examples of this effect can be seen in Figure 5a. For both subjects, the initial correlation ratio matrices contain subsequences with low motion frames and subsequences with medium amounts of relatively smooth motion. The medium motion subsequences were short and scattered throughout the sequences. They are still present in the registered images’ correlation ratio matrices, though to a lesser extent.

The second effect is characterized by an increase in the mean of the correlation ratio or a decrease only in the standard deviation of the correlation ratio matrix. The patterns of motion associated with this effect are shown in Figure 5b. For both cases, the correlation ratios after registration show lower maximum correlation ratio values, but more correlation ratios in these matrices have higher values. These changes indicate that the registration frameworks may have reduced the largest motions in those sequences, but then unintentionally increased the motion in the remainder of the sequence. It is possible that removing a contiguous chunk of high motion frames from the beginning of the sequence could prevent the increase in motion from occurring during registration.
The third effect is characterized by a lack of significant change in the correlation ratio matrix mean and standard deviation. The correlation ratio matrices for the sequences that exhibited this effect can be seen in Figure 5c. The standard deviations of the correlation ratios for these matrices are small, which means that the matrices themselves appear to contain large variations. Since these large variations only encompass a relatively small range of correlation ratios, the subject likely made frequent, random, small motions rather than occasional smooth motions. This type of motion would require the application of additional motion mitigation pipelines in order to recover the sequence.

Relation to Existing Work

To the best of our knowledge, there are two other studies that use prealignment during volume registration and support our conclusions. Notably, Jenkinson et al. developed a search-based hybrid global-local optimization method that avoids local minima\textsuperscript{35}. Their method chooses the volume at the middle time frame as the reference volume and performs two sets of registrations in parallel: registration of the subsequent volumes to the reference volume and registration of the prior volumes to the reference volume. In each direction, the results of the most recent registration are used to initialize the next registration. The results of their technical analysis suggest that these prealignments more effectively reduce motion in the registered images than the traditional framework. However, this work only evaluates the impact of their registration framework on adult brain images with little motion or planned and controlled motion.

Recently, Liao et al. reported on a feasibility study of using an HMM-based framework for volume registration in 10 fetal rs-fMRIs\textsuperscript{36}. Liao et al.’s dataset consisted of 10 fetal rs-fMRIs. In each of these sequences, the fetal brain, fetal liver, and placenta were manually segmented in the first volume of the sequence as well as in five other randomly chosen volumes. The overlaps of these manual segmentations before and after registration were measured using the Dice coefficient. The Dice coefficients increased more after registration using Liao et al.’s framework than the traditional framework; however, their measure of positional change only quantifies the changes in position between the six pairs of manually segmented volumes. The 10 sequences used in this study contained approximately 300 volumes each, which suggests that a more comprehensive analysis on a larger dataset is needed to validate this approach to reducing motion in fetal images.

Our work extends both Jenkinson et al.’s and Liao et al.’s by evaluating a registration framework similar to both of theirs on a set of high-motion neonatal images, which were not studied in either of these reports. We perform a comprehensive analysis of the registered images using a pair of gold standard usability thresholds and by examining patterns of motion throughout the entire image sequence using a similarity metric.

Limitations and Future Work

Subject motion during rs-MRI scans affects both the recorded position and orientation of the subject as well as the established magnetic spin gradients within the skull. The DAG-based technique can correct the positional effects of motion, but it cannot correct the effects of the motion that disrupt the magnetic spin gradients. It is possible for this effect to be mitigated during image acquisition: methods exist for prospectively estimating subject motion and changing slice positions in each volume. Unfortunately, retrospective techniques to correct for spin gradient effects require shot-to-shot modeling of macroscopic B0 fields and are beyond the scope of the present research.

In the future, we plan to apply the DAG-based technique to other patient populations such as fetal, preadolescent, and adult populations. Then we will be able to perform an accurate comparison to Jenkinson et al. and Liao et al.’s works. We aim to generalize our registration framework to characterize the motion of different organ types, such as the fetal brain and placenta. We also plan to use our analysis process to characterize different types of motion in several populations.

Conclusions

In this feasibility study, we applied two global registration methods to set of rs-fMRIs of 17 healthy neonates. We showed that both the DAG-based and traditional registration techniques reduce the amount of motion in the images as measured using correlation ratio matrices. We then showed that the DAG-based framework is better at correcting images to a pair of established gold standard thresholds for rs-fMRI usability than the traditional framework. In the future, we plan to apply the DAG-based framework to other patient populations and multi-organ problems.
Acknowledgments

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References


