

**GLOBAL VOLUME REGISTRATION FOR
MULTIPLE MOTION TYPES IN RESTING-STATE
FUNCTIONAL MAGNETIC RESONANCE IMAGES**

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INSERT ABSTRACT HERE

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1.0 INTRODUCTION

Resting-state functional magnetic resonance imaging (rs-fMRI) measures the blood oxygen level dependent signal in an organ or organ system. This property makes rs-fMRI an invaluable tool for evaluating a patient’s neurodevelopmental status or examining functional networks in his brain. To gather enough data to fully evaluate these networks, a series of image volumes must be acquired over a period of several minutes. In a standard rs-fMRI (?), one new image volume is obtained approximately once every two to three seconds. To gather high quality data on such a short timescale, the rs-fMRI suffers from two major limitations: rs-fMR images have low physical resolution and are highly susceptible to motion. The first limitation can be addressed by obtaining an MR image with high physical resolution and registering the rs-fMRI to this structural image, but the second limitation requires the patient to remain as still as possible for the entire duration of the scan. This task is particularly difficult for populations of certain ages or populations who suffer from conditions that affect neurodevelopment. As a result, it is common for an image from a member of one of these populations to contain too much motion to be used in clinical or research applications.

Various clinical and behavioral protocols have been developed in an attempt to prevent patients from moving during MRI scans, though many of these protocols are not applicable to younger populations. In particular, a neonate or fetus cannot understand instructions to stay still, and young children who can understand the command have difficulty following it. Sedation is not advisable for these young populations. After a rs-fMR image is acquired, however, it is possible to reduce the positional effects of motion in the image sequence.

Various methods have been developed to mitigate the effects of motion after the rs-fMRI is acquired. While different post-acquisition motion correction pipelines utilize different processing techniques, they generally begin with global volume registration. Global volume

registration is the process used to align all volumes in a rs-fMRI sequence into the same physical space. Traditionally, all volumes in the sequence are registered directly to one volume. This approach can be effective in images where the subject remains still throughout the duration of the scan, but is not as successful in images containing high quantities of patient movement.

We proposed an alternative volume registration framework which takes into account the spatio-temporal relationships between sequential volumes in the rs-fMRI sequence. We previously demonstrated the feasibility of this technique on a high-motion neonatal data set. Herein, we apply it to preadolescent and fetal images and evaluate its motion correction potential with respect to the traditional volume registration framework within a larger post-acquisition motion correction pipeline.

While correcting motion within an rs-fMRI is important both for clinical use and research applications, we are also interested in the motion itself. In addition to evaluating a global volume registration framework in the context of a fully motion correction pipeline, we also investigate the relationships between a patient’s motion and their clinical outcomes. This analysis is valuable for each of our subject populations for different reasons. For the preadolescent patients, we are investigating the relationship between in-scan motion, neurocognitive development, and congenital heart disease status. In the fetal images, we investigate the relationship between FETAL BRAIN DEVELOPMENT AND PLACENTAL GROWTH. These investigations use both supervised and unsupervised machine learning techniques to determine what relationships a computer can detect between these pieces of information.

2.0 BACKGROUND

The topics treated in this chapter can be somewhat obscure. For humanitarian considerations, the chapter will be subdivided.

2.1 RESTING-STATE NETWORKS

The idea of a neuronal network which operated when a person is at rest was proposed in 2001, and then confirmed in 2003 [Raichle et al., 2001] [Greicius et al., 2003]. Resting-state networks are recorded using resting-state functional magnetic resonance images (rs-fMRIs). rs-fMRIs are sequences of image volumes acquired over a period of a few minutes while the patient is in a task-free state. The image volumes themselves have relatively low spatial resolution when compared to structural MRIs, but their temporal resolution is significantly higher as a new volume is acquired every two to three seconds. Each volume records the blood oxygen level dependent (BOLD) signals within the brain at that point in time.

The BOLD signals in rs-fMRI image sequences are analyzed using a process called functional connectivity analysis. Functional connectivity analysis identifies patterns and networks of brain activity. Because the patient is not performing a specific task during a rs-fMRI acquisition, these resting-state networks have the potential to reveal valuable information about a patient's neurodevelopmental status. Some functional connectivity analysis studies have lead to the discoveries of links between specific disruptions in these naturally occurring networks and neurodevelopmental diseases such as autism and attention deficit hyperactivity disorder [Assaf et al., 2010] [Zang et al., 2007]. With further refinements of both acquisition techniques and characterization of these functional networks, clinicians may be

able to use rs-fMRI in early detection protocols to evaluate the neurodevelopmental status of infants and neonates, and in personalized care by identifying patients who may benefit from certain therapies or neuroprotective interventions.

2.2 MEASURING THE EFFECTS OF MOTION

Due to their low spatial and high temporal resolutions, rs-fMRIs are highly susceptible to motion. Even the smallest movement can alter the position of the patient enough to cause the voxels to record signals from different brain regions and tissue types. Even if the movement does not significantly change the recorded position of the subject, it impacts the established spin gradients, which introduces artifacts into the image sequence. Movements cause the orientation of existing spin gradients to change, and the gradients require time to realign to the magnetic field. This recovery time often results in a decrease in the global signal in frames obtained over the following 8-10 seconds, which can affect the functional connectivity analysis [Power et al., 2014].

The effects of motion on rs-fMRIs can be clearly divided into two categories: the effect on patient position and the effect on the recorded BOLD signal.

The effect of motion on patient position is measured in terms of the difference in position between temporally neighboring image volumes. The difference in position is determined using metrics calculated by performing rigid volume registration on the two volumes. In rigid volume registration, one volume is chosen as the reference volume and the other is considered the moving volume. The reference volume remains stationary while the moving volume is translated and rotated in three-dimensional space on top of it. The registration is considered successfully complete when the position of the patient in the moving volume matches the position in the reference volume. The three translation and three rotation parameters used to achieve this alignment are used to calculate the positional change between the image volumes, which is often called the framewise displacement (FD).

Several researchers have proposed different methods for calculating the FD. Power et al., Jenkinson et al., and Dosenbach et al. each propose a slightly different method for

calculating the FD [Power et al., 2012] [Jenkinson et al., 2002] [Dosenbach et al., 2017]. All three FD calculations produce correlated metrics: the FD metric proposed by Power et al. produces measurements approximately twice as large as the metric proposed by Jenkinson et al., and Dosenbach et al. reported a high correlation between their FD and Powers FD [Yan et al., 2013] [Dosenbach et al., 2017].

The effects of motion on the BOLD signal are a little more difficult to measure. They occur because motion disrupts the magnetic spin gradients present in the patient during the scan. The spin gradients need time to recover to the correct magnetic field orientation, and up to eight to ten seconds may pass before the recovery is complete [Power et al., 2014]. While the spin gradients are reorienting, the recorded BOLD signal may vary between temporally neighboring volumes. These changes can be measured using the temporal derivative of the variance in the BOLD signal intensity (DVARs) between the frames [Power et al., 2012].

Even though the effects of motion on the patient position and the recorded signal can be measured, we still need gold standard criteria to determine whether an image containing motion can be used. Patients move slightly due to breathing and cardiac function, and the BOLD signal naturally fluctuates over time. Some motion is expected; however, we need to know how much motion can be present in the image before it is considered to be corrupted by it. Power et al. established thresholds for FD and DVARs to determine the usability of a pair of images:

- FD less than or equal to 0.2 mm from previous volume, and
- DVARs less than or equal to 25 units on a normalized scale of [0, 1000] signal units [Power et al., 2014]

Image volumes that meet these criteria are considered to be low-motion. van Dijk et al. established that approximately five minutes of low-motion data is sufficient for use in functional connectivity analysis [van Dijk et al., 2012]. Unfortunately, it is often difficult to obtain enough low-motion data from patients to use in these analyses.

2.3 MOTION PREVENTION

Various techniques and protocols have been developed to prevent patients from moving during the image acquisition process. Not all of these techniques are suitable for all patient populations, and some techniques have been designed specifically for certain populations.

2.3.1 Sedation

Sedation can be used to help a patient tolerate an MRI scan. Murphy and Brunberg retrospectively analyzed seven weeks of data from the MR department and found that 14.2% of their adult patients some form of sedation [Murphy and Brunberg, 1997]. In a study about claustrophobia and MR acquisitions, ELEPHANTS report that out of 55,734 patients who underwent MRI scans, a total of 1,004 patients experienced claustrophobia and 610 of these patients required intravenous sedation before their scans [Dewey et al., 2007]. Even though sedation allowed the patients mentioned in this paragraph to undergo an MRI scan, the authors of both studies note that sedation can result in adverse events and advise the reader to avoid patient sedation if possible.

Sedation can be used with pediatric patients, though the risks are more significant than with adult patients. Studies have shown that sedation for pediatric imaging can lead to hypoxemia and inappropriate sedation levels during image acquisition [Malviya et al., 2000]. Some pediatric patients can also expect “motor imbalance and gastrointestinal effects,” as well as agitation and restless for a period of hours after waking from sedation.

A report from the American Academy of Pediatrics and the American Academy of Pediatric Dentistry outlines the minimum set of criteria needed for a pediatric patient to be sedated for a procedure [Coté and Wilson, 2016]:

- The patient must be a suitable candidate for sedation based on their medical history and medical needs.
- At least one responsible person must be with the patient at the medical facility, though the report recommends that two adults are present for patients who use car seats to

travel to and from the facility. This practice ensures that one adult can monitor the patient after the procedure while the other adult drives.

- The clinician administering the sedation must have immediate access to emergency facilities, personnel, and equipment and should monitor the patient for adverse events including respiratory events, seizures, vomiting, and allergic reactions.
- There must be a clear protocol outlined for immediate access to these emergency services.
- Emergency equipment and drugs appropriate for the patient's size and age must be immediately available in case the patient needs to be resuscitated.
- Informed consent must be obtained prior to the procedure.
- Instructions for what to expect and how to transport the patient home safely must be provided to the patient's responsible adult.
- The patient may be held at the facility for prolonged monitoring after the procedure.
- The patient's food and drink intake prior to the procedure should be taken into account to minimize the risk of pulmonary aspiration.
- The patient's health status must be evaluated and verified by the sedation team prior to the procedure.
- The information about the procedure must be correctly documented.
- The facility should have a dedicated recovery area, and the status of the patient should be recorded when he is discharged. The patient should not be discharged if his level of consciousness and oxygen saturation do not meet recognized guidelines.

This report clearly states that the levels of monitoring suggested within should serve as minimum levels of involvement: clinicians should increase patient monitoring as needed for complex cases. Rutman has a similar and detailed perspective on patient monitoring during and after sedation, suggesting that two independent medical personnel should be present during the scan and one should be present until the patient is discharged [Rutman, 2009]. Rutman also notes that all sedation and monitoring equipment must be MR compatible, which is a simple but important safety constraint. This constraint may make sedation less advisable if the appropriate equipment is not available.

Sedation in neonatal and infant populations is not recommended. The U. S. Food and Drug Administration (FDA) issued a warning in late 2016 about repeated use of sedation or

general anesthesia in patients under three years of age or in pregnant women in their third trimester [FDA, 2016]. The warning states that while a single, relatively short exposure to sedative and anesthetic drugs is unlikely to impact the patient, the effects of prolonged exposure to these drugs are still being studied. Studies of sedative and anesthetic drugs in multiple animal models have shown that these drugs can lead to loss of nerve cells in the brain when the animals undergo prolonged, repeated exposure to them during period of brain development. More data is needed to determine if this effect translates to humans.

2.3.2 Education, Distraction, and Behavioral Techniques

Educational material can be used to help the patient understand what to expect during an MRI scan as well as to teach the patient different behavioral coping strategies. The education materials can be used either before arrival at the imaging facility or upon arriving at the imaging facility.

Most of the formal literature focuses on educational, distraction, and behavioral techniques to use during pediatric MRI scans. Many of the following approaches could be adapted for use with adults.

In a review of the available literature, Alexander found several commonly used techniques to educate, comfort, and distract pediatric patients during radiology procedures. Tools such as educational coloring books and short videos can expose patients to the types of equipment they can expect to see using a familiar, engaging medium. Pediatric patients can learn coping strategies to employ during the scan such as breathing techniques, imagery, and positive statements. Alexander notes that allowing a pediatric patient to choose a behavioral coping strategy gives the patient a sense of control and may encourage the patient to cooperate during the MRI acquisition [Alexander, 2012].

Mock scanners and MRI simulators can also help the patient feel more comfortable during the scan. Barnea-Goraly et al. showed that both a commercial MRI simulator and a low-tech mock scanner desensitized pediatric patients between four and ten years of age to the MRI scanner with the results that 92.3% of the acquired images could be used in high-resolution anatomical studies [Barnea-Goraly et al., 2014].

During the MRI acquisition, headphones with music or stories and MR compatible video goggles can distract patients [Alexander, 2012] [Barnea-Goraly et al., 2014] [Harned and Strain, 2001]. Khan et al. found that a relatively simple moving light show can be helpful in distracting younger patients [Khan et al., 2007]. Garcia-Palacios et al. performed a case study comparing the efficacy of music and immersive virtual reality tools as distractions during a mock scan [Garcia-Palacios et al., 2007]. They suggest that immersive virtual reality may help decrease patient anxiety during a scan more effectively than music alone.

Another source of distraction for pediatric patients could be the patient’s parent or parents. Having a parent involved with the scanning process may calm the patient and encourage him to cooperate; however, parental distress can further upset an anxious patient and complicate the scanning process [Alexander, 2012].

These techniques for educating the patient and helping the patient cope with the anxiety that can come with an MRI scan all depend on the ability of the patient to understand instructions and communicate with the scan team. Due to the gap in communication abilities, these techniques are not useful for young patients such as neonates, infants, and toddlers. Other patient populations, such as those with developmental delays and neurobehavioral disorders, may also have difficulty adhering to these protocols. Even in patients with developed and intact communication skills, the techniques outlined here do not actively prevent the patient from moving during the scan: they only help the patient feel more comfortable with the MRI environment.

2.3.3 Feed and Sleep Protocols

Neither sedation nor educational and behavioral techniques are appropriate to use with neonatal patients, but rs-fMRIs in neonates and infants are invaluable in studying early brain development and neurological diseases [Smyser and Neil, 2015]. A set of protocols have been developed specifically for scanning neonates without sedation. These protocols are referred to as “feed and sleep” or “feed and bundle” protocols.

Windram et al. describe a protocol in which the infant is deprived of food for four hours prior to the scan [Windram et al., 2011]. At the scanning facility, the patient is fed by his

mother, swaddled, and placed in a vacuum-bag immobilizer for the duration of the scan.

Rather than deprive the patient of food prior to the scan, Gale et al.’s protocol recommends timing the scan so that the patient is fed after arrival on site and less than 45 minutes before the scan [Gale et al., 2013]. The patient’s ears are protected from the noise of the MR scanner by a layer of dental putty, followed by headphones, and held in place by a hat. The patient is the swaddled and placed in the scanner once he is asleep. Additional foam padding is used to cushion the patient’s head and provides extra noise protection.

Mathur et al. describe a protocol similar to the previous two: the patient’s feeding schedule is adjusted so that he feeds 30-45 minutes before the scan time, and he is swaddled, given ear protection, and placed in a vacuum-bag immobilizer [Mathur et al., 2008].

These protocols are generally successful: when performed correctly, the neonatal patient usually sleeps for the duration of the MRI scan. However, the patient may shift slightly while asleep or may wake up and move mid-scan.

2.4 PROSPECTIVE MOTION CORRECTION

Since motion cannot be completely eliminated from rs-fMRI scans, different approaches have developed for correcting for the effects of motion after the scan. These approaches can be divided into two groups: those that monitor the patient’s motion during the scan and those that work solely on the acquired sequences.

2.4.1 Optical Motion Correction

Several groups have developed methods for actively accounting for changes in the patient’s position during an MRI scan. Optical-based methods record the patient’s position using a combination of markers placed on the patient and one or more MR compatible optical cameras placed the scanner bore. The changes in the patient position from one time point to the next are used to update the MR parameters in real-time. Real-time updates of the MR parameters result in less spatial and spin-history effects of motion in the acquired sequences.

The first report of successful prospective motion correction using optical cameras and markers was by Zaitsev et al. in 2006 [Zaitsev et al., 2006]. Their dual camera system was located outside of the MRI scanner and focused on the patient inside the system. Four reflective markers were attached to a modified mouthpiece originally designed for patient immobilization. Changes in the translation and rotation of the patient were recorded and processed during the exam. The processed changes were sent in real-time to the MRI scanner which used them to update the gradient orientations and RF frequencies and phases at every time point during the acquisition process.

Aksoy et al. simplify this approach by using a single in-bore optical camera and replacing the 3D markers with a small 2D chessboard grid [Aksoy et al., 2008]. Properties intrinsic to the camera as well as information about the camera’s placement within the MRI scanner were recorded prior as part of a calibration process. During the scan, patient movements recorded using the optical camera were used to calculate the relationship between the patient’s position at the current time point in the physical space and the patient’s position at the initial time point in the MR space. The transformation needed to translate between these two positions was calculated on a laptop and passed to the MRI scanner to correct for motion in real-time.

The camera used to record the position of the chessboard is mounted on the head coil. If the patient moves his head significantly, the camera will only be able to record the position of part of the chessboard marker. This limitation makes it difficult for the computer vision processing to identify the independent features on the standard chessboard. Forman et al. modified the chessboard marker to improve its flexibility [Forman et al., 2011]. To differentiate between the different blocks in the chessboard, they added a unique, machine readable symbol to each black block in the chessboard. The symbols were chosen to be unique even in the event of rotation so that the identification of each block would be robust to rotation movements. The chessboard marker was embedded with MR-detectable agar so that the position of the marker could be detected in the MRI scan as well as by the in-bore camera. At each point during the scan, the image recorded by the in-bore camera was sent to a computer independent from the MRI controller. The independent computer detected the blocks of the chessboard and identified their spatial locations using the symbols contained within them. Their positions were checked by confirming the locations of the symbols with

respect to each other. The confirmed locations of the corners of the black boxes were used to estimate the position of the patient, which was then sent to the MRI controller so that the magnetic gradients and RF hardware could be updated for the time point. The authors note that the latency of the system is a significant limitation to their system, but overall they experienced an increase in the accuracy of the estimates of the patient’s position.

The methods discussed above have a few limitations due to the optical camera setups. For precise real-time motion correction, the camera or cameras must be carefully placed so that the position of the marker on the patient can be recorded. They must have a clear line of sight, which means they will be in the same room as the MRI scanner, if not within the scanner bore. The cameras and markers must be MR compatible, and the positions of the cameras and markers in physical space relative to the visual markers on the patient must be known. These positions are key for the calculations used to measure the motions. Even if the motion measurements are accurate, the changes in position that are recorded and used to adapt the scan parameters will only be true for rigid body motion of the body part to which the markers are attached: any distortion of soft tissue will not be accurately accounted for during the motion correction.

2.4.2 Within-Image Motion Correction

Dosenbach et al. have developed a tool to evaluate motion in rs-fMRI sequences as they are acquired [[Dosenbach et al., 2017](#)]. It registers each frame to the initial frame of the rs-fMRI sequence immediately after the new frame is recorded. The parameters produced by this registration are used to calculate the framewise displacement between pairs of frames, which is then compared to a set of displacement thresholds associated with the scan quality. The number of frames that meet each threshold is used to determine how many more frames are needed to obtain five minutes of low-motion frames. This method for assessing the quality of a scan in real time is useful for ensuring images are acquired with a sufficient number of low-motion frames. It can also aid the technologists in determining whether to prematurely terminate a scan, which may be desirable if the amount of time needed to obtain enough low-motion frames is greater than the amount of time remaining for the patient in the scanner.

2.4.3 General Limitations of Prospective Motion Correction

Prospective motion correction actively changes the image as it is acquired. In order to view a scan not impacted by prospective motion correction, the patient must undergo a second scan. It may be wise to build the second image acquisition into the same scan period as the prospectively motion corrected scan: unsuccessful prospective motion correction has the potential to drastically corrupt the acquired scan [Zaitsev et al., 2017].

MacClaren et al. note that while prospective motion correction reduces inhomogeneities in the B_0 field, the B_0 field will change when the patient moves [?].

Both types of prospective motion correction introduce a delay into the scanning process. The delay is due to the additional processing of some metrics to determine the patient's position, the transmission of these metrics to the MR scanner, and the adjustments the scanner makes to its next set of measurements.

Though prospective motion correction has great power for managing motion during a scan, it cannot be used to recover motion-corrupted data in existing repositories.

2.5 RETROSPECTIVE MOTION CORRECTION

Many groups have put significant effort into developing techniques for motion correction after the scan is acquired. Here, we discuss several commonly techniques including global volume registration, denoising, and filtering.

2.5.1 Global Volume Registration

2.5.2 Denoising

2.5.3 Filtering

2.6 VARIANTS OF GLOBAL VOLUME REGISTRATION

Liao et al. suggested that a rs-fMRI sequence could be viewed as a hidden Markov model, and reflected this idea in their suggested registration framework [Liao et al., 2016]. Their framework uses the transformation of the previous volume to the reference volume as the initial transformation for the current volume and the reference volume.

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