EXPLORING AND CORRECTING MOTION IN RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGES OF CONGENITAL HEART DISEASE PATIENTS

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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 and 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, behavioral, and technical protocols have been developed in an attempt to prevent patient motion from impacting the acquired rs-fMR image. Sedation can be used to immobilize a patient during a scan, but it requires additional personal to perform safely and it involves a great time commitment from the patient. Sedation is also not recommended for use in young children and fetal patients. Behavioral and educational techniques can be employed to prepare a patient for stressors he may experience during an rs-fMRI scan, but these approaches do not prevent the patient from moving out of boredom, discomfort, or distress. Several groups have developed techniques to compensate for motion as the image is acquired, but these techniques often require additional MR compatible equipment and can

only be utilized during the scan. After a rs-fMR image is acquired, however, it is possible to reduce the positional effects of motion in the image sequence.

Many 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 relatively still throughout the duration of the scan, but is not as successful in images containing high quantities of patient movement.

We have developed an alternative volume registration framework which takes into account the spatiotemporal relationships between sequential volumes in the rs-fMRI sequence and uses these relationships during the registration process. We have demonstrated the feasibility of this technique on a high-motion neonatal brain rs-fMRI data set and compared it to the traditional registration framework. Herein, we evaluate it further in the context of a complete motion correction pipeline across several patient populations.

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, specifically to further the study of congenital heart disease (CHD) across the lifetime of the patient.

Our aims for this project are as follows:

- **Aim 1.** Evaluate the impact of global volume registration within a complete motion correction pipeline in simulated and clinical data.
- **Aim 2.** Study the motion patterns in the different populations to formally describe age-group or clinical status related motion patterns.
- **Aim 3.** Employ machine learning techniques to (a) measure the impact of motion on image harmonization in multi-center studies, and (b) evaluate the relationship between motion and cognitive, clinical, and behavioral outcomes of CHD patients.

We have a large set of neurological rs-fMRIs for both healthy control and CHD neonatal, preadolescent, and adult subjects. We also have a set of neurological and placental rs-fMRIs for fetal patients. We will apply both the tradition and novel registration frameworks to all images in our different cohorts and evaluate the impact of each framework on each image after passing it through a complete motion correction pipeline. The original and registered images will be used to address the aims discussed in this chapter.

The remainder of this document is laid out as follows. In Chapter 2, we discuss congenital heart disease, its relationship with neurological conditions, and methods for evaluating neurological conditions. We elaborate on the use of resting-state functional magnetic resonance images (rs-fMRIs) for investigating functional brain networks in Chapter 3. Chapter 4 transitions into methods for analyzing MRIs, machine learning techniques, and our approach to statistical analysis. We discuss the data we use in Chapter 5, and explain the experiments we plan to do in Chapter 6.

2.0 NEURODEVELOPMENT, CONGENITAL HEART DISEASE, AND FUNCTIONAL CONNECTIVITY

2.1 CONGENITAL HEART DEFECTS

Congenital heart defects and congenital heart disease (CHD) both refer to defects in the heart or the vessels around the heart which formed during fetal development. Heart defects affect how blood moves into, through, and away from the heart. CHD can affect any combination of heart chambers and blood vessels with varying degrees of severity. The lesions prevent the cardiopulmonary system as a whole from functioning correctly, but pinpointing and treating the defects effectively can be a complex process.

There are a number of genetic and environmental factors associated with CHD [Mozaffarian et al., 2016]. Genetic conditions such as Down syndrome, Turner syndrome, 22q11 deletion syndrome, Williams syndrome, and Noonan syndrome are associated with different CHD presentations. Maternal behaviors such as smoking and binge drinking are known to cause heart problems in the fetus. Other maternal risk factors are obesity, folate deficiency, and living at a high altitude. Paternal exposure to phthalates, anesthesia, sympathomimetc medications, pesticides, and solvents may increase the risk of the fetus for developing CHD. While there are quite a few factors in this list, there are many CHD cases whose causes are unknown.

The process of diagnosing CHD can begin before birth. A specialized ultrasound test called fetal echocardiography can detect heart abnormalities as early as the second trimester of the pregnancy. Additional tests, such as amniocentesis and follow-up ultrasounds may be needed to determine treatment options. Generally, severe CHD cases present and are detected at earlier stages, but minor defects may not become apparent until the patient is older. The incidence of CHD in live births vary across countries and continents: the

Table 15-3. Estimated Prevalence of Congenital Cardiovascular Defects and Percent Distribution by Type, United States, 2002* (in Thousands)

	Prevalence, n			Percent of Total		
Type	Total	Children	Adults	Total	Children	Adults
Total	994	463	526	100	100	100
VSD†	199	93	106	20.1	20.1	20.1
ASD	187	78	109	18.8	16.8	20.6
Patent ductus arteriosus	144	58	86	14.2	12.4	16.3
Valvular pulmonic stenosis	134	58	76	13.5	12.6	14.4
Coarctation of aorta	76	31	44	7.6	6.8	8.4
Valvular aortic stenosis	54	25	28	5.4	5.5	5.2
TOF	61	32	28	6.1	7	5.4
AV septal defect	31	18	13	3.1	3.9	2.5
TGA	26	17	9	2.6	3.6	1.8
Hypoplastic right heart syndrome	22	12	10	2.2	2.5	1.9
Double-outlet right ventricle	9	9	0	0.9	1.9	0.1
Single ventricle	8	6	2	0.8	1.4	0.3
Anomalous pulmonary venous connection	9	5	3	0.9	1.2	0.6
Truncus arteriosus	9	6	2	0.7	1.3	0.5
HLHS	3	3	0	0.3	0.7	0
Other	22	12	10	2.1	2.6	1.9

Average of the low and high estimates, two thirds from low estimate.[24]ASD indicates atrial septal defect; AV, atrioventricular; HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

*Excludes an estimated 3 million bicuspid aortic valve prevalence (2 million in adults and 1 million in children).

†Small VSD, 117 000 (65 000 adults and 52 000 children); large VSD, 82 000 (41 000 adults and 41 000 children).

Source: Data derived from Hoffman et al.[24]

Figure 1: Table of prevalences of congenital heart defects borrowed temporarily from [Mozaffarian et al., 2016].

United States reports approximately 4-10 CHD case per 1,000 live births, while Europe and Asia see about 6.9 and 9.3 CHD cases per 1,000 live births [Mozaffarian et al., 2016]. A breakdown of prevalence rates of some of the most common lesion types can be seen in 2.1. As screening tools become more effective, it is expected that these rates will increase as defects are detected earlier.

Once a patient is diagnosed with one of these defects, the specific nature of his case must be clearly documented. The documentation of CHD using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) has 25 high level codes representing various presentations of CHD, but these codes used on their own are often not sufficient for describing a patient's true condition [Mozaffarian et al., 2016]. Additional ICD-9-CM codes may be used to communicate the finer details of a patient's condition.

Financial burden: high for certain defects, medium costs for surgical interventions for other lesions, still processing [Mozaffarian et al., 2016]

Complications and comorbidities: heart failure, infections? Children with CHD at 19-

fold risk for stroke (216) [Mozaffarian et al., 2016]

Mortality: still processing information. Overall, the mortality for CHD patients is declining. [Mozaffarian et al., 2016]

2.1.1 From Long-Term Risk of Hemorrhagic Stroke in Young Patients with CHD

Giang et al performed a study comparing the prevalence of cardiac conditions in patients with and without CHD born between 1970 and 1993 in Sweden. They found that patients who had a CHD diagnosis were at about eight times higher risk for intracerebral hemorrhage and subarachnoid hemorrhage than their non-CHD counterparts. The CHD patients were also more likely to suffer from arrhythmia and heart failure.

2.2 CHD AND NEURODEVELOPMENT

Recent research has found that there is a link between CHD and neurodevelopment.

To address:

- Common combinations
- Joint treatment?
- Additional risks?
- Joint financial and emotional burden on caretakers?
- CHD, neuro, and aging? Dementia/Alzheimer's?

2.3 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.

3.0 MRI ACQUISITION AND IMAGE CLEANING BACKGROUND

This chapter covers the technical aspects of the work to be completed. These topics include current methods for managing motion in medical images, metrics for measuring motion, and machine learning techniques being used to

3.1 SOURCES OF MOTION

During every MRI scan, the patient will undergo small movements due to regular bodily functions. Minuscule movements caused by cardiac activity may disrupt scans with high spatial resolution or with high sensitivity to the movement of blood molecules. Larger movements caused by respiration result in motion artifacts in images of the thoracic and abdominal cavities.

Other motions seem more random. The patient may fidget in the scanner or shift his gaze when he becomes bored during a scan. If the patient falls asleep during a scan, there may be slight movement as the body relaxes. Certain MRI protocols are known to produce loud sounds: during one of these protocols, the patient may become surprised and jump in response to the unexpected sound. Clausterphobic patients may become agitated.

3.2 EFFECTS OF MOTION

Due to their low spatial and high temporal resolutions, rs-fMRIs are highly susceptible to all types of motion outlined in the previous section. 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).

The effects of motion on the BOLD signal are 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.

Metrics used for calculating the FD and the changes in BOLD signal will be discussed more thoroughly later in this chapter.

3.3 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 populations.

3.3.1 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 factility, 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 [Unknown, 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.

3.3.2 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 commerical 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.

3.3.3 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.

3.4 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.

3.4.1 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.

Several companies have developed commercial products for prospective motion correction in neurological images. KintetiCor's system uses a high resolution camera and a physical marker to detect motion. The camera's resolution allows it to detect respiratory and cardiac motion through changes in skin displacement on the patient's forehead. The physical marker consists of pair of rectangles containing several concentric circles which are connected via a bridge across the nose. Any patient movement is reflected in the movement of the markers, which is also tracked through the camera. Both the camera system and the marker are MR compatible. Another company, TracInnovations, uses a stereo camera system to track all patient motion. At the start of the scan, the stereo camera obtains a point cloud of the patient's position at that time. The points in the point cloud are averaged together to create a primary marker. Small facial motions, cardiac motion, and respiratory motion, are monitored using the point cloud. Larger head motions are monitored using both the point cloud and the primary marker. These two systems both allow prospective motion correction to be turned on or off: if the prospective motion correction is off, the system will still acquire the motion parameters so that the motion can be corrected retrospectively.

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.

3.4.2 External Sensors

Signal based tracking: wired NMR field probes, wireless inductivity coupled markers, off-resonance markers; require sequence modification and possibly longer scan time?

Tracking respiration with respiratory bellows -¿ use gating to acquire image during "expected state", bin data according to when it was recorded during the breathing cycle

Cardiac: pulse oximeter (delay relative to central pulse) ECG: less reliable at high field strengths (Frauenrath et al JMRI 2012; 36: 364-72 Acoustic cardiac triggering: Frauenrath et al, Investigative Radiology 2009, Frauenrath et al J Cardiovascular MR 2010

Additional sensors complicate the scan setup

Detection using RF coils? Changes conductivity and RF power (Buikman et al MRI 1988)

3.4.3 Intra-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.

3.4.4 General Limitations of Prospective Motion Correction

Maclaren et al. note that while prospective motion correction reduces imhomogeneities in the B_0 field, the B_0 field will still change when the patient moves [Maclaren et al., 2013]. As a result, 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.

These alterations to the image acquisition during prospective motion correction actively change 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].

Finally, 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.

3.5 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.

3.5.1 Global Volume Registration

The rs-fMR image is stored in computer memory as a set of 3D matrices. The values in corresponding cells of each matrix are considered to be aligned in this digital space (voxel space). The voxel space is defined by the imaging protocol and relates to the physical space through the spatial resolution of the image. Even though the spatial and voxel spaces for the image align, the contents of the image volumes may be misaligned due to patient

movement. Because we cannot assume that an image is completely motion-free, we cannot directly compare the contents of each image volume in the rs-fMRI sequence. However, we can use image registration to align the contents of the image volumes to reduce the impact of motion on patient position.

Image registration is the process of morphing the contents of one image so that they overlap optimally with another image. The morphing operations include translation, rotation, scaling, skewing, and nonlinear adjustments. The linear and affine operations in this list should be used to perform rigid body registrations for organs such as the brain. Nonlinear operations can be used to fine-tune the alignment of more pliable organs such as the liver. All morphing operations are applied to one image (the moving image) repeatedly until it's contents optimally match those of the static reference image as determined by a chosen similarity metric.

One of the earliest examples of image registration was described by Friston et al. in 1995 [Friston et al., 1995]. They performed image registration on positron emission tomography (PET) scans and MRI scans of a human brain. During the registration process, one scan was designated as the "reference" image, which remained stationary, and the other scan was designated as the "object" image, which was transformed to match the reference image. Constraining the alignment process to transforming a single image into the coordinates of the other image rather than transforming both images into an independent coordinate frame simplifies the registration process.

When performing image registration on a sequence of image volumes, one volume must be chosen as the reference image for the entire sequence. In subsequent work, Friston et al. used the first volume in the rs-fMRI sequence as the universal reference image [Friston et al., 1996]. They demonstrate that image registration across the entire image sequence reduces the effects of motion on the image sequence, though they do note that motion also effects the image due to changes in the spin history of the image. These effects are not correctable by global volume registration alone and are addressed later in this chapter.

One drawback to Friston et al.'s volume registration framework is that it only minimizes the differences between all the image volumes in the sequence and the reference volume. The key word here is minimizes: minimizing differences between image volumes does not mean

that there are no differences between the image volumes. There may still be differences between other pairs of image volumes in the sequence that do not include the reference volume.

Variations on Friston et al.'s framework have been developed over the last two decades. 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]. They still use the first volume in the image sequence as the reference volume. Their framework uses the transformation of the previous volume to the reference volume to initialize the transformation for the current volume and the reference volume.

3.5.2 Denoising

Denoising techniques can be applied to a rs-fMRI after global volume registration is completed. They consist of regressions of various confound variables.

Regression of the global signal (global signal regression, GSR) corrects for variance between temporal signals within a voxel and for the mean BOLD signal across all voxels [Power et al., 2014] [Satterthwaite et al., 2013] [Yan et al., 2013a] [Yan et al., 2013b]. GSR has been shown to reduce spuriously increased long-distance correlations in functional connectivity studies, but may inadvertently weaken shorter-distance connections [Jo et al., 2013][Power et al., 2
[Satterthwaite et al., 2012].

Other regression parameters which have been investigated include the six realignment parameters and their first-order derivatives [Power et al., 2012] [Satterthwaite et al., 2012] [van Dijk et al., 2012], realignment parameters from surrounding timpoints [Patriat et al., 2017] [Power et al., 2014] [Satterthwaite et al., 2013] [Yan et al., 2013b], signals from white matter or cerebral spinal fluid [Power et al., 2014] [Satterthwaite et al., 2013] [Yan et al., 2013b] [Jo et al., 2010], and components identified using principal or independent component analysis [Pruim et al., 2015] [Salimi-Khorshidi et al., 2014] [Behzadi et al., 2007]. Regression of each of these sets of parameters has been shown to reduce the effects of motion in the sequence but not remove them entirely [Power et al., 2015] [Parkes et al., 2017].

3.5.3 Filtering

Filtering, which is also referred to as censoring, involves the identification and removal or interpolation of frames containing high quantities of motion. Two popular techniques are scrubbing and spike regression. Power et al.s scrubbing technique removes frames with more than 0.2 mm of FD [Power et al., 2012]. Spike regression identifies frames with large FD and replaces them with interpolated volumes [Satterthwaite et al., 2013]. Unfortunately, these filtering techniques ultimately result in the loss of data as frames are removed from the sequence. A third technique called despiking detects signal spikes at the voxel level and interpolates over the spikes [Jo et al., 2013] [Patel et al., 2014]. Despiking does not remove frames, but could accidentally remove valuable signals.

3.5.4 Spin History Distortion Correction

A number of post-acquisition methods have been developed specifically to correct for distortions due to the impact of motion on the magnetic field. The usability of these dynamic distortion correction methods has been studied in a few specific cases, but their generalizability has yet to be confirmed in a broader range of fMRI studies [Zaitsev et al., 2017].

3.6 MEASURING MOTION

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., 2013b] [Dosenbach et al., 2017].

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.

4.0 METHODS

4.1 VOLUME REGISTRATION AND MOTION CORRECTION

4.2 PATTERN DETECTION

4.3 TOOLS

Cite nipypy, ANTs, FSL, etc. here

4.4 METRICS AND ANALYSES

Power et al. thresholds

Correlation ratio matrix

Statistical tests

Dice coefficients?

5.0 DATA

The data used to test the hypothesis and aims introduced in the previous chapter are drawn from several subject populations. Because motion causes problems in MR images across all stages of life, we used images from cohorts of healthy and CHD fetal, neonatal, preadolescent, and adult subjects gathered in as part of ongoing studies. Data from these studies was obtained through studies approved by the IRB at the Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh. The data is stored and accessed in compliance with all HIPPA policies.

We use data from a simulated phantom as well as healthy adult human phantoms. The healthy adult human phantom data collection was also approved by the IRB at the Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh and is stored and accessed in compliance with all HIPPA policies.

The final data set we use is from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

5.1 NEONATAL SUBJECT POPULATION AND IMAGES

Neonatal subjects are recruited as part of a prospective observational study. The subjects were scanned using a 3T Skyra (Siemans AG, Erlangen, Germany). They were unsedated during the scans and a "feed and bundle" protocol was used to prevent motion during the scans [Windram et al., 2011]. The newborns were positioned in the coil to minimize head tilting. Newborns were fitted with earplugs (Quiet Earplugs; Sperian Hearing Protection, San Diego, CA) and neonatal ear muffs (MiniMuffs; Natus, San Carlos, CA). 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 interplane resolution of 4x4 mm, slice thickness of 4 mm, and 4 mm space between slices. The acquired images contained 150 volumes where each volume consisted of 64x64x32 voxels^3.

5.2 PREADOLESCENT SUBJECT POPULATION AND IMAGES

As part of a multicenter study of CHD in preadolescents, we collected rs-fMRIs from nine sites throughout the United States. These images were of patients in the age range of XX to XX years who either had CHD or were healthy with no neurocognitive impairments. In addition to the MRI scans, subjects who participated in this study were asked to participate in other testing (GET DETAILS FROM NANCY).

- How were the images gathered?
- How were the patients recruited?
- What are the imaging protocol details?
- What other information was collected?

5.3 ADULT SUBJECT POPULATION AND IMAGES

As the prognosis for patients with CHD improves, their life expectancy also increases. The aging CHD population presents new questions about the connection between CHD and neurocognitive challenges associated with aging. As patients age, there is an expectation that their images will contain less motion for a time. If a patient begins to show signs of cognitive impairment due to aging, it can be expected that their images will begin to contain more motion as their neurocognitive state deteriorates.

We include a cohort of adult subjects over a wide range of ages in our study. The purpose of using images from this cohort is to demonstrate the generalizability of the DAG-based framework to adult patients as well as its use in different clinical populations. This cohort is being studied as part of an ongoing, prospective study of CHD and neurodevelopment. The data collected for these subject includes rs-fMRIs, behavioral, and clinical data from XX healthy and XX CHD adult subjects.

- How were the images gathered?
- How were the patients recruited?
- What are the imaging protocol details?
- What other information was collected?

5.4 FETAL SUBJECT POPULATION AND IMAGES

Fetal subjects have different constraints on their physical environment than neonates, preadolescents, and adults. As a result, they exhibit unique patterns of motion. The previous subject cohorts discussed in this chapter have the following commonalities: the subject experiences the full effects of gravity, the subject is lying on his back in an MRI scanner, and the subject's head motion is limited by the head coil within the MRI. Any motion in these images is a direct result of the subject himself moving, whether passively (cardiac motion and breathing) or actively (fidgeting or looking around).

A fetal subject is scanned in vivo. He is suspended in amniotic fluid within his mother. The amniotic fluid has buoyancy that reduces the effects of gravity and allows a fetal subject significant freedom of movement. The fetus can rotate, shift, and flip in ways that can only be accomplished when floating in a body of water. The properties of the uterus constrain the physical space in which a motion could occur, but not as much as the head coil and gravity do to the other patient cohorts. A fetus is not guaranteed to be in any specific position at the start of the scan: the scan begins when the mother is ready, not when the fetus achieves a certain pose.

The fetal subjects underwent fetal echocardiography scans in a cardiac clinic to determine whether they were healthy or had a form of CHD. They were then scanned on an MRI scanner. Images of the fetal brain and the placenta were acquired for each subject.

We are interested in both the fetal brain and placental images for our work because of the relationship between placenta and brain development. However, these organs have very different physical properties. The fetal brain is a rigid structure floating and moving within the amneotic fluid. It undergoes translation and rotation as a single unit due to passive and active maternal and fetal motions. The placenta, on the other hand, is anchored in place on the uterine wall. It may undergo small translations or rotations due to maternal motion, but it will respond differently to fetal motion. Fetal motions cause nonlinear deformations of the pliable placenta that can only be adequately accounted for using nonlinear registration algorithms. Nonlinear registrations have the potential to deform brain images into physically impossible shapes, so the fetal brain and placenta were manually segmented in their respective images so that each organ could undergo independent motion correction.

The segmenters were one of a group of four researchers. While one researcher trained the other three group members, the interrater agreement between them is still being determined.

- Fetal patients scanned between XX and XX weeks gestational age.
- Imaging protocol details?
- What other information is collected about fetus and/or mom?

5.5 SIMULATED PHANTOM IMAGES

Every MRI scanner is different, so a stand-in model for an organ or tissue type is often used to calibrate an MRI scanner. The model is designed to have specific physical properties which mimic the physical properties of the organ or tissue. These properties can be accurately measured during the design process of this model so that the radiologist or researcher looking at images of the model can know the ground truth of the model. Because these models mimic true organs and tissues, they are called phantoms.

We will generate a simulated phantom image using the rs-fMRI of a healthy adult male. A single volume will be selected from the rs-fMRI sequence. This volume will be duplicated to create a generated image with 150 instances of the same volume. This sequence will be our base phantom sequence.

A copy of the base phantom sequence will be made and a subvolume in the same location of every volume will be selected. In the subvolume of each frame, a small amount of noise generated using a normal Gaussian distribution will be added to simulate changes in blood oxygen level-dependent signal over time. The noise will be generated from a normal Gaussian distribution will be added to each frame. This image sequence will be referred to as our BOLD phantom sequence.

5.6 HUMAN PHANTOM IMAGES

One of the major challenges in the medical imaging field is collecting a large enough set of data with a high enough quality to generate statistically significant results. As part of a multisite study, a set of FOUR healthy adult male subjects were scanned at NINE different sites within a period of TEN WEEKS.

These subjects are considered human phantoms because of their health adult status, but they still may contain some motion. Their images are included in this study so that we can determine the consistency and effects of the motion correction pipeline on images of the same subject across time.

- What machines were used?
- What were the scanning protocols?
- Are there any preliminary analyses/results on this data?

6.0 AIMS

6.1 VOLUME REGISTRATION IN A MOTION CORRECTION PIPELINE

All images in each data set and cohort first underwent both types of registration independently. The registered and original images are compared to the Power etl. al. usability thresholds. The results at this stage answer the question of whether or not the DAG-based registration technique is more effective than the traditional registration technique for reducing motion in the initial step of a motion correction pipeline. Next, each pair of registered images will undergo a motion correction via the ICA pipeline outlined by XXXX and implemented as XXX tool. The results of this experiment show how the DAG-based framework fits into an existing, comprehensive motion correction pipeline.

6.1.1 Simulated Phantom

The phantom experiments will be used to probe the volume registration technique. By applying the DAG-based and traditional registration techniques to the base phantom sequence, we will be able to evaluate the degrees of positional and signal change errors each technique may introduce into the registration process. After determining the baseline error, we will apply both registration techniques to the BOLD phantom sequence. The registered versions of the BOLD phantom sequence will be compared to each other and to the original BOLD phantom sequence to determine how well each registration retains the BOLD signal.

JENNA tie in idea about how to know if a signal processing technique is actually preserving or recovering the signal of interest, and about how the signal that is measured might not be the signal of interest. Does not necessarily belong here.

6.1.2 Human Phantom

The human phantom images from all sites will be used both as a set of true healthy control adults and as examples of low motion images of the same subjects taken at multiple sites.

6.1.3 Clinical Images

Neonatal Cohort. Our set of neonatal subjects includes a cohort of 74 healthy neonates. Each subject in this cohort underwent an MRI scan, and the rs-fMRIs obtained during this process were compared to Power et al.'s positional and signal change usability thresholds. Of the 74 subjects, 17 of them had rs-fMRIs which did not meet the usability criteria. These high motion images were used to test the feasibility of the DAG-based volume registration framework.

These images were ideal for the feasibility study for two reasons. First, the neonates were healthy, which eliminates disease status as a confounding variable in the analysis of the registered images. Second, the neonates in this study were scanned using a feed and sleep protocol. Because the neonates were asleep during the scan, they generally did not move very much. The high-motion neonates are an obvious exception to this concept, but many of the high-motion images contained long periods where the subject was stationary. Evaluating the DAG-based framework on data with various patterns of motion and different periods of low and high motion allowed us to explore the effects of the DAG-based algorithm in different combinations of motion features. Third, these images were too corrupted by motion to be used in other analyses. Applying both the DAG-based framework and the traditional registration framework to these images provided the opportunity to compare the performances of both registration frameworks to each other in the context of the usability gold standard thresholds.

Note: paper submitted for puplication.

Preadolescent Cohort. The multicenter imaging study of preadolescent subjects provides a unique opportunity to evaluate the efficacy of the DAG-based framework on a large subject cohort containing variable amounts of motion. The outcome of this experiment will be used in the next experiment to determine if there are any site-specific or vendor-specific

variables influencing patient motion.

Adult Cohorts. The adult cohorts encompass many clinical outcomes...

Fetal Cohort. As the fetal subjects have both neurological and placental images, their data will be used to examine the impact of volume registration on different organ types.

6.2 DETECTING POPULATION-DEPENDENT PATTERNS OF MOTION

Are there any patterns in motion that are similar

- within age groups?
- within clinical groups?
- within groups scanned at the same site?
- associated with a certain outcome?

Machine learning techniques can be used to classify images as belonging to different groups, but many of these techniques use difficult to interpret "black box" logic. In some cases, examining the logic behind a classification reveals patterns in a dataset which a human missed but a computer detected. One example is a system trained to differentiate between pictures of red foxes and pictures of artic foxes. Its classification accuracy was XX%, but further examination revealed that the system used the presence of snow in an image led the system to label that image as containing an artic fox. CITATION NEEDED

WILL ALSO USE REGRESSION AND STATISTICAL TESTS

To ensure that there are no confounding signals such as those in the previous example are present in our datasets, we first use unsupervised machine learning techniques to identify correlations between subject images and their demographic data. The techniques we will use are several types of clustering (agglomerative, k-means, and spectral) as well as principle component analysis (PCA) and regression. Features of the images before and after registration will be used as training data for each model and different demographic features will be used as the true classes. The demographic data for each subject includes the subject's age at the time of scan, gender, race, dominant hand, and scan site. (NOTE: THAT SENTENCE

IS FOR MULTISITE STUDY DATA, NEED TO SPECIFY, ALSO NEED TO GET ALL CLINICAL DATA.)

Any demographic features which influence the division of patients into groups will be reported and accounted for during later analyses.

After identifying and accounting for demographic groups, we will expand the analysis to clinical and behavioral outcomes.

Use pediatric, neonatal, and fetal images

Proposed topic for a paper: different subject populations exhibit different patterns of motion according to age and clinical factors.

6.3 EVALUATE RELATIONSHIPS BETWEEN MOTION AND OUTCOMES

In addition to evaluating the effects of the DAG-based framework within the context of a motion correction pipeline, the registered images are used to explore the relationship between motion and clinical outcomes. Unsupervised machine learning techniques such as agglomerative clustering and k-means clustering are applied to the data. The results of the clustering techniques elucidate whether there are patterns in motion specific to certain patient groups. These groups could include patients with similar clinical outcomes, patients from the same site, or potentially other clinical or demographic groups.

JENNA - EXPAND

6.4 OTHER POTENTIAL AREAS I'M THINKING ABOUT

Machine Learning for Optimal Motion Correction Start with a classification module for identifying severity of motion between template volume, previous volume(s), and current volume. The classifications will be based either on the patterns identified in Aim 2, or on the positional and signal change differences between the volumes of interest.

After the severity of the motion reflected in a volume is determined...

Aim 4: Does Motion Correction Recover True Signal? Hinted at earlier in first section of chapter, should it get its own section?

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