Using fMRI BOLD Imaging to Motion-Correct Associated, Simultaneously Imaged PET Data

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Using fMRI BOLD Imaging to Motion-Correct Associated, Simultaneously Imaged PET Data

A Thesis Submitted in Partial Fulfilment of the
Requirements for the Degree of
Master of Science

By:

Joseph M. Williamitis
B.S.B.E., Wright State University, 2018

2021
Wright State University
WRIGHT STATE UNIVERSITY

GRADUATE SCHOOL

MARCH 17, 2021

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY JOSEPH M. WILLIAMITIS ENTITLED USING fMRI BOLD IMAGING TO MOTION-CORRECT ASSOCIATED, SIMULTANEOUSLY IMAGED PET DATA BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

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ABSTRACT

Williamitis, Joseph, M. M.S., Department of Neuroscience, Cell Biology, and Physiology, Wright State University, 2021. Using fMRI BOLD Imaging to Motion-Correct Associated, Simultaneously Imaged PET Data.

Because magnetic resonance (MR) and positron emission tomography (PET) scanning sessions last long durations, motion blur during scanning constitutes a problem for clinical interpretation. To counteract this, motion-correction algorithms have been developed to reduce smearing between scan slices of MRI, but these algorithms are not commonplace for PET. This feasibility study determined if applying MRI motion-correction algorithms to simultaneously acquired PET data improved PET signal clarity in specific brain regions. Seven subjects received increasing levels of PET tracers while undergoing two separate simultaneous PET/MRI scans. We modified existing fMRI algorithms to apply them to the accompanying PET data. We hypothesized gray matter activity was low due to motion-blurring, and correction would result in increased signal intensity. We evaluated this and other internal brain regions using a Wilcoxon Signed-Rank statistical test. We failed to reject the null hypothesis as no regions showed significant differences between the motion-corrected and raw data.
# TABLE OF CONTENTS

## I. INTRODUCTION

A. Pet Scanning
   a. PET Physics
   b. Data Acquisition
   c. Difficulties with Reconstruction
   d. Potential Impact of Motion on Data Collection

B. Magnetic Resonance Imaging
   a. MRI Physics
   b. T2*-weighted Imaging
   c. BOLD and Echo-Planar Imaging
      i. BOLD Imaging
      ii. Echo-Planar Imaging
   d. Motion Correction
      i. Suppression while Scanning
      ii. Removal of Motion Artifacts

C. Simultaneous PET/MR

D. Hypothesis

## II. METHODS

A. Study Overview

B. Institutional Review Board and Ethical Oversight

C. Participants

D. Experimental Design
   a. Simultaneous PET/MR Protocol
   b. PET Imaging Protocol
   c. MRI Protocol

E. Data Analysis
1. MRI  
   a. Motion Estimates from BOLD Data  
   b. Region of Interest Masks  

2. PET  
   a. Pre-Processing  
   b. Application of fMRI Motion Estimates  
      i. Produce Motion-Correction Matrix Files for PET Data  
      ii. Apply Transformation Matrices to PET Data  
   c. Extracted Intensity Values from Region of Interest  
   d. Data Screening  
   e. Statistical Analysis  

III. RESULTS  
   A. Mask Overlays and Data Analysis  
   B. Gray Matter  
   C. White Matter  
   D. Caudate  
   E. Thalamus  
   F. Putamen  
   G. Hippocampus  
   H. Power Analysis and Summary Table  

IV. DISCUSSION  
   A. Data  
   B. Limitations of Study  
   C. Other Possible Contributing Factors  
   D. Conclusions  

V. REFERENCES  

VI. APPENDIX A


LIST OF FIGURES

FIGURE 1: Visual Representation of PET Scanning Annihilation Event 2
FIGURE 2: Example of Filtered Back Projection Algorithm Processing 3
FIGURE 3: Examples of Photon Detection Defects 4
FIGURE 4: Examples of T1-weighted, T2-weighted, and FLAIR MRI Scanning 7
FIGURE 5: Example of fMRI BOLD Scanning 9
FIGURE 6: Example Motion Artifacts in MR Scanning 10
FIGURE 7: Typical PET Scan Example 12
FIGURE 8: Typical MRI Scan Example 13
FIGURE 9: Three-second slice of our PET data. 14
FIGURE 10: Corresponding three-second slice of the MRI data. 14
FIGURE 11: Experimental Setup 18
FIGURE 12: Freesurfer Segmentation of Data 20
FIGURE 13: Field of View Offset Differences 22
FIGURE 14: Ventricle Masks Used for PET Tracer Normalization 26
FIGURE 15: Gray Matter Mask Example 27
FIGURE 16: Gray Matter Data Boxplot 28
FIGURE 17: White Matter Mask Example 28
FIGURE 18: White Matter Data Boxplot 29
FIGURE 19: Caudate Mask Example 29
FIGURE 20: Caudate Data Boxplot 30
FIGURE 21: Thalamus Mask Example 30
FIGURE 22: Thalamus Data Boxplot 31
FIGURE 23: Putamen Mask Example 31
FIGURE 24: Putamen Data Boxplot 32
<table>
<thead>
<tr>
<th>FIGURE</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Hippocampus Mask Example</td>
<td>32</td>
</tr>
<tr>
<td>26</td>
<td>Hippocampus Data Boxplot</td>
<td>33</td>
</tr>
<tr>
<td>27</td>
<td>Passive Listening Block Representation</td>
<td>43</td>
</tr>
<tr>
<td>28</td>
<td>Example Auditory-Stroop responses</td>
<td>44</td>
</tr>
<tr>
<td>TABLE</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1</td>
<td>Inclusion and Exclusion Criteria for Experimentation</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>Gray Matter Wilcoxon Signed-Rank Test Results</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>White Matter Wilcoxon Signed-Rank test results</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>Caudate Wilcoxon Signed-Rank test results</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>Thalamus Wilcoxon Signed-Rank test results</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>Putamen Wilcoxon Signed-Rank test results</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>Hippocampus Wilcoxon Signed-Rank test results</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>Summary Table of p-Values</td>
<td>33</td>
</tr>
</tbody>
</table>
LIST OF EQUATIONS:

EQUATION 1: Example Transformation Matrix 22
EQUATION 2: Rotation Matrix Calculation 23
EQUATION 3: Offset Matrix Calculation 23
EQUATION 4: Final Transformation Matrix Calculation 23
DEDICATION

This thesis is dedicated to my parents Tony and Ann, who have sacrificed more than I could ever imagine to get me to where I am today. This is also dedicated to my brother Tommy, I miss you every day.
A. **INTRODUCTION**

A. **PET Scanning**

a. **PET Physics**

Positron Emission Tomography (PET) scanning utilizes radioactive elements to visualize functional processes occurring in the body. The positron-emitting tracer is designed to congregate in a specific region within the body after a brief time (Konik, *et al.*, 2011). For example, glucose labeled with $^{18}$F accumulates in the brain and tumors, as glucose accumulates in areas of the body with greater metabolism.

When injected, the positrons emitted by the radioactive molecule are released and combine with nearby electrons resulting in the emission of two incident 511kEv gamma rays, which are recognized by the detectors surrounding the patient (Figure 1). PET scanning is very sensitive to slight changes in metabolic activity and can show movement of oxygen, glucose, and other small-scale molecules inside the active body (Miranda, *et al.*, 2019). Because radiolabeled isotopes can label many different types of molecules, they can be used to examine many different types of physiological functions, and can be applied to a wide variety of PET scans. This sensitivity for direct measurement of metabolic processes, as well as being effective for the diagnosis and evaluation of cancer and other tumors are two of the largest advantages of PET scanning (Gilman, *et al.*, 2017). Because of this, PET scanning is commonplace even though its resolution is poorer than many other common types of medical imaging protocols.

b. **Data Acquisition**

PET scanning detects “coincidence events” in which two photons collide and deflect in opposite 180-degree directions. Detectors are placed in a ring around the
patient, and detect these 180-degree coincident gamma rays typically within a six to twelve nanosecond window (Gilman, *et al.*, 2017). Following the detection of coincident events, a line of response (LOR) is drawn between the two detectors, as shown in Figure 1 below.

![Diagram](image)

*FIGURE 1: Visual representation of photon annihilation event and detection (Abdulla, 2020).*

The ring around the patient during PET scanning is composed of gamma camera detectors. These gamma cameras typically contain sodium iodide crystals that measure the various intensities of the gamma rays emitted while scanning. When gamma rays strike the crystals, a light photon is produced, which is then translated to an electrical signal (Tong, Alessio, and Kinahan, 2010). Only a fraction of the radiation produced during scanning impacts the gamma cameras, and even fewer travel the correct angle in order to collide with the crystal. Because of this, the electrical signals received from the photons must be amplified, before being digitized and relayed to the computer (Tong, Alessio, and Kinahan, 2010).

The most common way of producing an image from the PET scan projection detectors is referred to as filtered back projection (FBP). This sorting process uses basic sorting algorithms in order to piece the collection of LORs back into a usable image (Figure 2). This procedure was originally developed for computed tomography (CT), and was then adapted for PET scanning, as they share similar detection procedures. FBP algorithms
are also frequently used for PET because they contain very simple transforms which have a low burden on computation resources and can typically be run on common machines (Deák, et al., 2013).

FIGURE 2: Example of FBP algorithm reconstruction of data (Noll, 2004).

FBP makes use of the detectors by blocking the light (backprojecting) between multiple detectors around the particle of interest in order to ascertain qualities about the particle, i.e. shape, opacity, density, etc. (Deák, et al., 2013).

c. Difficulties with Reconstruction

Reconstruction techniques of PET tend to be poor, and the reconstructed images may appear noisy due to scatter and random events recorded during scanning, unable to be removed via reconstruction (Tong, Alessio, and Kinahan, 2010). Photon scatter occurs when at least one of the annihilation photons is diverted from its original path, and is recorded by a detector outside of the original LOR. Random events involve two separate annihilation events occurring in close time proximity but are recorded as a coincident pair of photons, as they occur within the coincident nanosecond time window. Both scatter and
random coincidence detection are shown in Figure 3. Receptor “dead time,” or the time needed to recalibrate the sensor after a coincident event is recorded, also affects the quality of image reconstruction, as does detector sensitivity correction for non-orthogonal photon detection angles (Tong, Alessio, and Kinahan, 2010).

![FIGURE 3: Examples of possible photon detections and defects during PET scanning](Konik, et al., 2011).

Quantitative PET scanning also requires attenuation correction due to differing rates of photon absorption by human tissue between the annihilation event and the detection by the sensors along the LOR. As gamma rays pass through matter, the probability of absorption to take place is proportional to the thickness and density of the material or tissue within the body. The further a gamma ray travels, the lower intensity it will have before contacting the incident surface of the detectors. Different anatomical tissues attenuate photons differently, and various densities and dimensions of said tissues
lead to different attenuation values. Not only do tissue proportions and properties adjust attenuation correction, but LORs travel different lengths to the scanners and are attenuated differently (Konik, et al., 2011). Higher energy gamma rays have a lower probability of being subjected to attenuation than lower energy photons, and as such, the gamma rays originating from deeper within the body are attenuated accordingly.

Although attenuation-corrected PET images are more accurate depictions than non-attenuated images, the correction process can still be prone to significant problems. Annihilation events occurring deeper into the body send gamma rays through greater quantities of tissue, leading to weaker signals being collected by the scanners. Due to this change of attenuation, structures deeper in the body are shown to contain erroneously lower rates of tracer uptake (Tong, Alessio, and Kinahan, 2010).

Early types of PET scanners only had one ring of detectors, and thus could only acquire 2D images across a single transverse plane. Modern PET scanners now contain multiple rings of detectors in a cylinder, with two different methods of reconstructing data from the updated scanner design. These types of scanners can treat each ring of detectors separately and can perform transverse 2D reconstruction of PET images, as well as the incorporation of some or all the rings together to form 3D images. By allowing different coincident events and LORs to be detected along the same ring, as well as between rings, the scanner reconstructs the image as a 3D volume instead of a singular transverse plane image. 3D PET imaging techniques have higher sensitivity due to more coincident events being detected, but they are much more sensitive to scatter and random coincidences (Figure 3) due to more detectors being active at any given time (Tong, Alessio, and Kinahan, 2010). Special consideration must also be given to computational resources, as reconstructing a 3D image takes considerably more effort and capabilities than 2D (Konik, et al., 2011).

d. Potential Impact of Motion on Data Collection
Due to the length of time some PET scans require in order to monitor metabolic processes and the signal being summed across this entire duration to produce a single 3D image, limitation of movement during data collection is of concern to clinicians and researchers to prevent data spoilage (Catana, 2015). Because PET scanning is a delicate procedure that detects very small changes in metabolic activity, motion can significantly affect data quality (Montgomery, et al., 2006). As previously mentioned, motion can cause either detection from same source placed in two different areas or detection in different sources placed in same area, leading to limited anatomical resolution, and image clarity (Catana, 2015).

B. Magnetic Resonance Imaging

a. MR Physics

A magnetic resonance imaging (MRI) machine uses a strong cryogenic magnet in order to adjust the electrical fields or “spin” of the protons of hydrogen atoms. Because of the prevalence of water in the human body, there are large quantities of hydrogen atoms affected by the directionality of the magnetic field (Gillman, et al., 2017). These atoms also absorb energy, then expend this energy at specific frequencies proportional to the magnetic field. The MRI will then emit a radio frequency (RF) pulse in order to alter the alignment of the hydrogen atoms within the static magnetic field. This causes a shift in the hydrogen atoms and, as the RF pulse energy dissipates, the altered protons relax, while expending energy, and realign with the static magnetic field (Berger, et al., 2018). This is referred to as the relaxation time, and different MRI sequences measure various relaxation times, depending on the tissue being scanned (Hendee, Ritenour, and Hoffmann, 2003).

The most prevalent sequences used in MRI scanning are the T1-weighted and T2-weighted scans. T1, or longitudinal relaxation time, measures the rate at which the disrupted protons revert to equilibrium, or to reorient to the static magnetic field (Hendee,
Ritenour, and Hoffmann, 2003). T2 measurements correspond to the transverse relaxation time of the scan, or the rate in which the disrupted protons attain equilibrium, or become out of phase with others. Using each of these scans, different images can be obtained by changing the “weights” of images based on the type of scan performed (Liu, et al, 2020). In T1 scans, the time between each RF pulse (repetition time, or TR) is much shorter than T2, where the TR is much longer. In a T1-weighted scan, cerebrospinal fluid (CSF) is darkly colored, while in a T2-weighted image it is brightly colored, as shown in Figure 3 below (Liu, et al, 2020). A fluid-attenuated inversion recovery (FLAIR) image, nullifies and suppresses fluids in the brain, namely the CSF, in order to examine periventricular structures (Hoinkiss, et al, 2019), also shown in Figure 3 below.

FIGURE 4: Examples of T1-weighted, T2-weighted and FLAIR scanning outputs (Preston, 2016).

The electromagnetic waves from the affected protons are then measured and translated into an image based on the alignments of the electromagnetic spin of the hydrogen atoms. As the misaligned atoms return to their natural state, they release energy that is detected by the coil above the patient (Liu, et al, 2020). Once detected by the coil, they are then transformed into an electrical current, then Fourier-transformed in order to reveal a full image depending on the amounts of energy given from the various tissues (Liu, et al, 2020).
b. **T2*-Weighted Imaging**

T2*-weighted ("T2 star") imaging is a specific sequence used in MRI in order to determine the effective T2 time rather than the theorized T2 time. When a longitudinal magnetization is applied to the body in the transverse plane using an RF pulse, there are unintended effects caused by the MR magnet (Chavan, *et al.*, 2009). The transverse magnetization decays rapidly because of the strong magnetic field, and the T2* measurements also incorporate the effects of the magnetic field inhomogeneity. Essentially, the observed T2 weighted time constant (T2*) is the combination of the natural T2 reorientation of the hydrogen spin knocked out of alignment added to the natural effects of the strong magnetic field of the MR machine (T2) (Chavan, *et al.*, 2009).

c. **BOLD and Echo-Planar Imaging**

i. **Blood-Oxygen Level Dependent Imaging**

Blood-Oxygen Level Dependent (BOLD) Imaging is a method used to generate functional MRI (fMRI) images. This method of scanning relies on cerebral blood flow (CBF) to indirectly measure brain activity and respond to differences in oxygen needs across the brain tissue (Hendee, Ritenour, and Hoffmann, 2003). When a certain part of the brain is activated, there is a slight, two- to six-second delay from activation to the re-routing of oxygenated blood, and thus, there is an initial deficiency of oxygenated hemoglobin (O$_2$Hb) and an abundance of carbon dioxide (CO$_2$) and deoxygenated hemoglobin (dO$_2$Hb) (Hendee, Ritenour, and Hoffmann, 2003). As CBF increases in the activated region, the excess CO$_2$ and dO$_2$Hb are removed and this considerable change in oxygenation is detected by the fMRI (Hendee, Ritenour, and Hoffmann, 2003). Figure 4 below shows collected fMRI scans, which show the increased CBF oxygen delivery to the regions of the brain responsible for the actions listed below each cerebral image.
FIGURE 5: fMRI visualization of increased oxygen delivery to different parts of the brain as oxygen need increases based on the task being performed (Tung, M., (n.d.)).

ii. **Echo-Planar Imaging**

Echo-planar imaging (EPI) is a newly-developed method of MR imaging that considerably decreases the duration of scanning times (Poustchi-Amin, *et al.*, 2001). While some forms of traditional MRI techniques can take upwards of twenty to thirty minutes, EPI allows image collection in twenty to one hundred milliseconds, and if increased contrast and resolution are needed, the time window becomes just a few seconds total (Chavan, *et al.*, 2009). Because this time window is so short, artifacts due to motion are nearly always removed, and monitoring of quickly occurring physiological processes becomes possible with MRI (Chavan, *et al.*, 2009). Typically, EPI is used for imaging the brain, but has been shown to be versatile, and is often used for MR imaging of the heart and abdomen as well. EPI is generally becoming more commonplace for MR machines, and has become much more common in recent times (Gillman, *et al.* 2009).

d. **Motion Correction**

Motion artifacts that appear during MRI scanning can have drastic effects on the data being collected (Catana, 2015). The effects of motion can be clearly seen in Figure 5 below, and motion must be minimized on all levels to prevent smearing and artifacts of the MRI image.
There are several methods of suppressing and correcting motion both during MRI scanning and afterwards, with the data itself being altered. These have varying degrees of success and widely depend on the types of scans being performed (Catana, 2015).

i. **Motion Suppression while Scanning**

Suppression of motion while scanning involves decreasing movement of patients during the actual scanning procedure. Physically restraining patients and sedating patients have shown some success for the removal of motion during long-duration scanning (Hendee, Ritenour, and Hoffmann, 2003). These methods are especially effective for children and younger patients who may have difficulty following instructions, as well as claustrophobic and anxious patients of all ages. For short-duration scanning, patients can be instructed to hold their breath for a short period of time to limit the amount of motion propagated by the breathing process. These methods of motion suppression have shown to be effective techniques in some versions of scanning, but with the possibility of unpredictable and erratic behaviors of various patients, they are typically not
as effective as post-scanning removal of artifacts (Hendee, Ritenour, and Hoffmann, 2003).

ii. **Removal of Motion Artifacts**

Aside from changing the patient environment, there are many methods that can be performed and adjusted from outside the scanning room. Phase-encoding algorithms have been developed to track and correct patient breathing automatically without the need for breath-holding, and can be applied to longer scans during which cessation of breathing would not be comfortable or possible (Hendee, Ritenour, and Hoffmann, 2003). These are referred to as respiratory-ordered phase encoding techniques (ROPEs), and do not require other intermittent scans to correct for breathing movement (Catana, 2015). Likewise, various other cyclical or constant motion effects can be removed with algorithms specifically developed for other physiological occurrences during scanning. In addition to motion-correction algorithms, fast-scanning techniques have also been developed as a way to decrease the time needed for various MRI scanning procedures (Catana, 2015).

B. **Simultaneous PET/fMRI**

While many different algorithms and adjustments have been developed for MRI motion suppression, PET scanning motion correction procedures are still in their infancy (Guo, et al., 2018). The combination of both PET and MRI scanning has been studied extensively over the years in order to find a medium between both scanning methods (Chen, et al., 2018). While PET scanning has a very high molecular sensitivity and can follow a large number of biological processes, it has limited spatial resolution and may have inadequate anatomical details required for clinical analysis. Figure 7 demonstrates the limited resolution available on a typical PET scan.
FIGURE 7: Typical PET scan image (McMains and Tantibanchachai, 2016).

On the other hand, MRI scanning has high anatomical detail and contrast, but the sensitivity of MRI scanning is several orders of magnitude lower than PET (Chen, et al., 2018). Figure 8 shows a typical MRI scan, demonstrating this increased anatomical and spatial resolution. Thus, an effective union of the two techniques has been of interest to researchers for many years (Grant, et al., 2017).
FIGURE 8: Typical MRI scan (Preston, 2006).

Due to the fact that BOLD imaging is not a direct measurement of brain activity but rather an indirect measure of oxygen consumption across the tissue, PET has been combined with BOLD scanning in order to examine biological processes in vivo with high anatomical resolution. With software, co-registration could potentially be used to “fuse” the separately acquired fMRI and PET data, which could transform many research and clinical applications, especially for patients that require both forms of scanning (Catana, 2017). Speed, patient comfort, and increased spatial resolution would be extremely beneficial for clinicians and researchers, and could greatly accelerate the current state of medical imaging as a whole (Catana, 2017). As shown in Figures 9 and 10, the collection differences of PET data and fMRI data, disallows for direct correction between data and image sets, and must be adjusted.
FIGURE 9: Three-second slice of our PET data.

FIGURE 10: Corresponding two-second slice of the MRI data.
C. **Hypothesis**

In this study we attempted to apply previously developed MRI motion-correction algorithms to simultaneously acquired PET data, leading to a clearer, more refined motion-corrected PET image. After motion-correction is applied to the PET image, less blurring of the image should be shown. Motion would cause the lower-intensitied nearby white matter to blur into the gray matter, lowering the intensity of gray matter without motion correction. With gray matter having a higher concentration of metabolically active neuronal cell bodies, we expected to see increased gray matter intensity and metabolism due to motion correction removing spatial blurring. Because the white matter is not as metabolically active, and less susceptible to motion blur as it is located away from the gray matter margins of the brain, we hypothesized that changes to the white matter would be minimal, while gray matter intensity changes would be pronounced.
II. METHODS

A. Study Overview

Our objective was to determine the feasibility of applying MR motion correction algorithms to simultaneously acquired PET data in order to improve the clarity of the PET image. This was a retrospective and non-interventional post-hoc secondary analysis of anonymized MR/PET data collected during a separate study described in Appendix A.

B. Institutional Review Board and Ethical Oversight

All subjects involved in the original study provided informed consent in compliance with the Wright State University Institutional Review Board, Indiana University Institutional Review Board, and the Air Force Medical Support Agency Surgeon General’s Research Oversight Committee. The anonymized data from the original study contained no sensitive or protected health information, or identifying features. Subjects were enrolled in this original study via physical and digital flyers provided through the Indiana Clinical and Translational Sciences Institute (CTSI) in accordance with the Indiana University Institutional Review Board protocol.

C. Participants

After a web-based screen, potential participants were contacted via email in order to set up a phone eligibility interview. Participants then met in person for an official informed consent appointment with MRI screening, detailed in Table 1. A total of 40 subjects were screened for the original study, and 24 subjects provided consent for experimentation. Five subjects did not complete the study, and 12 subjects withdrew because of scheduling conflicts due to COVID-19.
Seven completed imaging for simultaneous PET/MR motion-correction. We used the anonymized data from these subjects in the current study, and were blinded to subject demographics outside of data provided.

**TABLE 1: Inclusion and exclusion criteria required to take part in the original study.**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>● Between 18 and 50 years of age</td>
<td>● Conditions that would preclude the completion of an MRI scan, such as claustrophobia, pacemaker, pregnancy, etc.</td>
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<tr>
<td>● Able to read and write in English</td>
<td>● Serious medical illness</td>
</tr>
<tr>
<td>● Right-handed</td>
<td>● History of brain cancer or other brain disease</td>
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<tr>
<td>● Normal or corrected to normal vision</td>
<td>● Hearing loss</td>
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<tr>
<td>● Able to lay supine for an hour</td>
<td>● Able to hold still during MRI scanning</td>
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D. **Experimental Design**

In order to apply the fMRI motion correction algorithms to the PET data, both scans were completed simultaneously. As shown in Figure 11, subjects underwent MRI scanning while being injected with a PET tracer to generate concurrent images. Subjects underwent two separate scans, five days apart. Simultaneous image collection allowed motion correction details from the MR image to be applied to the PET image.

1. **Simultaneous PET/MR Protocol**
2. **PET Imaging Protocol**

An intravenous solution of fluorodeoxyglucose (FDG) and saline was continuously administered via power injector (MEDRAD MRXperion, Bayer Healthcare LLC, Berlin, Germany) to each subject at a rate of 0.01 ml/sec for up to 90 minutes during scanning. The maximum initial activity was 17 mCi, for a maximum injected activity of 10 mCi per session. This protocol was reviewed and approved by the Indiana University Radiation Safety Committee. Participants were required to fast for six hours before their scheduled dual MR/PET scanning appointments in order to prevent the FDG from competing with normal glucose uptake. A blood sample was taken to measure the fasting glucose and compared to the acceptable range of 70 to 120 mg/dL to validate fasting compliance.

PET data were collected continuously in large list-mode (LLM) format. Data were collected in one bed position with 127 transverse slices of 344 x 344 pixels (2.0863 x 2.0863 mm$^2$), and smoothed with a 5-mm isotropic Gaussian kernel.

3. **MRI Protocol**
Imaging was performed on a 3T Siemens Biograph mMR scanner (Siemens Healthineers AG, Erlangen, Germany). Magnetic resonance imaging was collected via 64-channel head and neck coils designed for the mMR, with consideration to photon attenuation properties (Siemens Healthineers AG, Erlangen, Germany).

Auditory function was the predominant focus for the original study. Three separate tasks were performed by the subjects in order to induce the hemodynamic and metabolic response (Appendix A), then the subject would relax while arterial spin labeling was acquired.

Auditory protocol and instruction framework were delivered by in-ear headphones with consideration for photon attenuation (Siemens Healthineers AG, Erlangen, Germany). Visual fMRI tasks were presented on a projection screen (Hyperion, Psychology Software Tools, Sharpsburg, PA) and the subject used a handheld signaling device to give response input with their index fingers (Lumina, Cedrus Corporation, San Pedro, CA). The repetition time (TR) pulse was digitized, delivered to the mMR scanner, and then recorded within the LLM data as an external signal.

E. Data Analysis

1. MRI

a. Motion Estimates from BOLD Data

The fMRI BOLD data informed the motion estimates to apply to the concurrent PET data. Spatial filtering was applied to the data before processing with the FMRIB Software Library (FSL), which motion-corrected the BOLD data by loading the entire time series and defaulting to the middle volume as the template image.

Once the middle volume was located, algorithms began a triangulated determination of changes between the middle volume and the two adjacent volumes of data. These changes became the motion-correction parameters, and the adjacent volumes were corrected accordingly. Once motion parameters between the middle and
adjacent volumes were found, a transformation was performed to estimate new parameters between the adjacent volumes, and the volumes beside them. This pattern continued outward until the entire sequence was motion-corrected (Jenkinson, et al., 2002). The center of mass was then calculated for the BOLD data in order to align the two data sets for future comparison.

b. Region of Interest Masks

In order to localize regions of interest (ROIs) for comparison, the program Freesurfer (Fischl et al., 2002, 2004a; Dale et al., 1999; Fischl et al., 1999a) was used to segment the T1 MRI data, acquired before the functional imaging, into individual domains representing different cortical structures (e.g. left and right hemispheres, cerebellum, brainstem) and subcortical structures (e.g. basal ganglia, diencephalon, or other limbic structures), as shown in Figure 12.

![Freesurfer segmentation of experimental subject MRI data; different colors correspond to distinct cortical structures.](image)

FIGURE 12: Freesurfer segmentation of experimental subject MRI data; different colors correspond to distinct cortical structures.

Masks were generated in T1 space for the segmented regions using FSL command line utilities, and signal intensities were extracted in the raw and motion-corrected scan data for each mask were investigated.

Due to greater glucose consumption of neuronal somas present in the gray matter (Hendee, Ritenour, and Hoffmann, 2003), we expected to see increased gray matter intensity as the gray and white matter regions became more distinct. Because we expected motion to be most pronounced near the edges of the brain due to blurring, the
gray matter and white matter of the brain were selected for testing. Internal structures were also selected to determine if motion-correction of the PET data had significant improvements on the brain as a whole, and not just the edge. The putamen, thalamus, caudate, and hippocampus were selected due to their small size and susceptibility to motion. In order to normalize for the amount of PET tracer within the brain at a given time, a mask of the ventricles was also created.

2. PET
   a. Pre-Processing

   To produce the PET images, the LLM PET data were reconstructed via filtered back projection using proprietary software (JSRecon, Siemens Healthineers, Erlangen, Germany) off-scanner. A two-point Dixon fat and water MRI sequence was used for anatomic localization of the PET data due to the absence of a CT data set. Attenuation maps were then created from this sequence in order to model four different compartments: tissue, fat, bone, and air. Segmented bitmaps were converted into linear attenuation coefficient maps (μ-maps) with an assumed photon energy of 511 keV. Relative scatter correction was related to a single scatter simulation (SSS) in order to estimate the collective scatter contribution across the field of view (FOV) with regard to initial activity and attenuation maps. After scatter correction, the PET data were binned into three-second time increments to create volumes matching the fMRI data. These volumes were then combined and assembled into a 4D PET image.

   b. Application of fMRI Motion Estimates

   The PET image was then overlaid onto the fMRI image with the program FSLeyes (McCarthy, 2020), part of the FSL package, to begin the motion-correction process. To start the procedure, the fields of view (FOV) needed to be equalized. While the PET FOV is fixed, the fMRI FOV is digitally controlled by the operator, and the offset between the two was manually determined for each subject and session, and adjusted accordingly. As
shown in Figure 13, the PET FOV (gray) was larger, and the parameters were used to transform the fMRI center of mass to PET space.

![Figure 13: Visual representation of 3D field of view offsets between fMRI (orange) and PET data (gray).]

i. Produce Motion-Correction Matrix Files for PET Data

Once the FOVs were equalized, the fMRI center of mass was converted to PET space, and transformation matrices were created using the offset between the fMRI and PET images. Equation 1 shows an example transformation matrix.

[Equation 1]:

\[
M = \begin{bmatrix}
    a_{11} & a_{12} & a_{13} & b_1 \\
    a_{21} & a_{22} & a_{23} & b_2 \\
    a_{31} & a_{32} & a_{33} & b_3 \\
    0 & 0 & 0 & 1
\end{bmatrix}
\]

In the above 4x4 matrix M, the upper-left 3x3 submatrix (a) represents a rotation transform, and the upper-right submatrix (b) represents a translation transform. The volume-specific rotation and translation estimates with respect to the middle volume were resampled and converted to volume-specific transformation matrices for PET application.
To produce these volume-specific matrices, rotation matrices for the original x, y, and z dimensions received from the program MCFLIRT (Jenkinson, et al., 2002), a part of the FSL data package. The angles of rotation were calculated (Equations 1 and 2) and combined via matrix multiplication (Equation 2). The center of mass offset and transformation values were added to this matrix to create a final 4 x 4 FSL-specific matrix (Equation 3).

[Equation 2]:

\[
[R_x] = \begin{bmatrix}
1 & 0 & 0 \\
0 & \cos \theta & -\sin \theta \\
0 & \sin \theta & \cos \theta
\end{bmatrix}
\]

Where \( \theta = x \)-components of fMRI rotation estimates from MCFLIRT

\[
[R_y] = \begin{bmatrix}
\cos \theta & 0 & \sin \theta \\
0 & 1 & 0 \\
-\sin \theta & 0 & \cos \theta
\end{bmatrix}
\]

Where \( \theta = y \)-components of fMRI rotation estimates from MCFLIRT

\[
[R_z] = \begin{bmatrix}
\cos \theta & -\sin \theta & 0 \\
\sin \theta & \cos \theta & 0 \\
0 & 0 & 1
\end{bmatrix}
\]

Where \( \theta = z \)-components of fMRI rotation estimates from MCFLIRT

[Equation 3]:

\[ [R] = [R_x] \cdot [R_y] \cdot [R_z] \]

[Equation 4]:

\[
[R_{offset}] = (\text{Center of Mass} \cdot \text{Voxel Dimension}) + \begin{bmatrix}
x_{offset} \\
y_{offset} \\
z_{offset}
\end{bmatrix}
\]

Where x, y, and z are changes in PET and MRI FOV (mm)

[Equation 4]:

\[
[R_{final}] = \left[ [R] [R_{offset}] ; 0 \ 0 \ 0 \ 1 \right]
\]

ii. Apply Transformation Matrices to PET Data
Once the final transformation matrices were calculated, the program `applyxfm4D` (Jenkinson, 2002), another part of the FSL data package was used to apply these volume-specific matrices on a volume-by-volume basis to the 4D PET data. The results were motion-corrected PET datasets based on fMRI estimates of motion.

c. **Extracted Intensity Values from Region of Interest**

We next measured the efficacy of motion-correction algorithms on specific ROIs from the PET data. The T1 MRI image was registered with both the mean raw and newly created motion-corrected PET data transformations. This registration was performed to begin to align the mask images with the T1 data along the same coordinate system in space, allowing the intensity of the T1 image to be collected within the mask boundaries. These new PET transforms were then applied to the ROI masks created with the fMRI data, and the average voxel intensity was collected from the masks for both the raw and motion-corrected PET data. Once the intensities were obtained, a ratio was created of the ROIs to the metabolically inactive brain ventricles to normalize the amount of PET tracer at a given time within the brain.

d. **Data Screening**

For the initial data screening, only PET sequences three, four, and five were used for analysis due to the insufficient tracer present in runs one and two. We manually removed erroneous data points and anomalies detected by visualization of the data, or falling outside of three standard deviations from the sample mean.

e. **Statistical Analysis**

All statistical analyses were performed in Microsoft Excel 2019 and SPSS Statistics (IBM). We applied a 95% confidence interval ($\alpha = 0.05$) and tested the data for a normal distribution and homoscedasticity. After finding the data were not normally distributed with a Shapiro-Wilk test, we employed a Wilcoxon Signed-Rank test to
compare ROI data. We also performed a post-hoc power analysis in SPSS to determine the risk for Type II error, given the small sample size of seven subjects.
III. RESULTS

A. Mask Overlays and Data Analysis

The masks for each region were overlaid over the fMRI data in order to isolate each region of interest for analysis. Because CSF spaces should contain only artifactual PET signal, they were considered for use to normalize the amount of PET tracer at a given time. Data from the ventricles were compared across each run of increasing PET tracer, and changes in metabolic activity were found to be negligible. PET data were then normalized to the average intensity of the ventricles for each scan. A mask of the ventricles is shown in Figure 14.

![Example ventricle mask overlaid on the T1 image. This mask was used to normalize the amount of tracer for each scanning sequence.](image)

Because the data were not normally distributed as determined by a Shapiro-Wilk test, we used the Wilcoxon Signed-Rank test to compare raw and motion-corrected
intensities within the ROIs. In order to determine whether the results were significant, both p and H values were evaluated on a 95 percent confidence interval (p < 0.05).

B. Gray Matter

![Gray Matter Image](image_url)

FIGURE 15: Example mask of cerebral gray matter used for analysis.

The gray matter mask was applied to both the day one and two scans for each subject. The raw and motion-corrected intensity values were not different (p = 0.8361) [Table 2, Figure 16].

TABLE 2: Gray Matter Wilcoxon-Signed Rank test results – values normalized to CSF.

<table>
<thead>
<tr>
<th></th>
<th>Gray Matter Raw</th>
<th>Gray Matter MC</th>
<th>p-Value</th>
<th>H-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.5048</td>
<td>1.5339</td>
<td>0.8361</td>
<td>0.04281</td>
</tr>
<tr>
<td>Sample Size (n)</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank Sum (R)</td>
<td>1598.5</td>
<td>1641.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R^2/n</td>
<td>63880.0563</td>
<td>67363.0562</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
C. White Matter

The white matter mask was applied to both the day one and two scans for each subject. The raw and motion-corrected intensity values were not different (p = 0.6932) [Table 3, Figure 18].

**TABLE 3: White matter Wilcoxon Signed-Rank test results - values normalized to CSF.**

<table>
<thead>
<tr>
<th></th>
<th>White Matter Raw</th>
<th>White Matter MC</th>
<th>p-Value</th>
<th>H-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.2232</td>
<td>1.2435</td>
<td>0.6932</td>
<td>0.1556</td>
</tr>
<tr>
<td>Sample Size (n)</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank Sum (R)</td>
<td>1579</td>
<td>1661</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R²/n</td>
<td>62331.025</td>
<td>68973.025</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 18: White matter data boxplot.

D. Caudate

FIGURE 19: Example mask of caudate used for analysis.

The caudate mask was applied to both the day one and two scans for each subject. The raw and motion-corrected intensity values were not different (p = 0.8399) [Table 4, Figure 20].

**TABLE 4: Caudate Wilcoxon Signed-Rank test results - values normalized to CSF.**

<table>
<thead>
<tr>
<th></th>
<th>Caudate Raw</th>
<th>Caudate MC</th>
<th>p-Value</th>
<th>H-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.5007</td>
<td>1.5027</td>
<td>0.8399</td>
<td>0.04083</td>
</tr>
<tr>
<td>Sample Size (n)</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank Sum</td>
<td>1599</td>
<td>1641</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
E. Thalamus

The thalamus mask was applied to both the day one and two scans for each subject. The raw and motion-corrected intensity values were not different ($p = 0.6442$) [Table 5, Figure 22].

**TABLE 5: Thalamus Wilcoxon Signed-Rank test results - values normalized to CSF.**

<table>
<thead>
<tr>
<th></th>
<th>Thalamus Raw</th>
<th>Thalamus MC</th>
<th>p-Value</th>
<th>H-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.3786</td>
<td>1.3803</td>
<td>0.6442</td>
<td>0.2133</td>
</tr>
<tr>
<td>Sample Size (n)</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank Sum (R)</td>
<td>1668</td>
<td>1572</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 22: Thalamus data boxplot.

F. Putamen

FIGURE 23: Example mask of putamen used for analysis.

The putamen mask was applied to both the day one and two scans for each subject. The raw and motion-corrected intensity values were not different ($p = 0.7876$) [Table 6, Figure 24].

TABLE 6: Putamen Wilcoxon Signed-Rank test results - values normalized to CSF.

<table>
<thead>
<tr>
<th></th>
<th>Putamen Raw</th>
<th>Putamen MC</th>
<th>p-Value</th>
<th>H-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.5007</td>
<td>1.5027</td>
<td>0.7876</td>
<td>0.07259</td>
</tr>
<tr>
<td>Sample Size (n)</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank Sum</td>
<td>1592</td>
<td>1648</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 24: Putamen data boxplot.

G. Hippocampus

FIGURE 25: Example mask of hippocampus used for analysis.

The hippocampus mask was applied to both the day one and two scans for each subject. The raw and motion-corrected intensity values were not different (p = 0.1874) [Table 7, Figure 26].

**TABLE 7: Hippocampus Wilcoxon Signed-Rank test results - values normalized to CSF.**

<table>
<thead>
<tr>
<th></th>
<th>Hippocampus Raw</th>
<th>Hippocampus MC</th>
<th>p-Value</th>
<th>H-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.1811</td>
<td>1.1883</td>
<td>0.1874</td>
<td>1.7379</td>
</tr>
<tr>
<td>Sample Size (n)</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
H. Power Analysis and Summary Table

To determine the risk for Type II error, a post-hoc power analysis was performed. A power value of 0.80 was used, and the calculated study power value was 0.253, showing that the sample size for this study was underpowered. A summary of the determined p-values is shown in Table 8.

**TABLE 8: Summary of p-values for regions investigated.**

<table>
<thead>
<tr>
<th>Region</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray Matter</td>
<td>0.8361</td>
</tr>
<tr>
<td>White Matter</td>
<td>0.6932</td>
</tr>
<tr>
<td>Caudate</td>
<td>0.8399</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.6442</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.7876</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.1874</td>
</tr>
</tbody>
</table>
IV. DISCUSSION

A. Data

We assessed the feasibility of applying MR motion-correction algorithms to simultaneously acquired PET data to improve the clarity of the PET image. We expected to see an increase in intensity for the gray matter, while the white matter would have minimal changes; but we failed to reject the null hypothesis, as the differences between the raw and motion-corrected data were not significant for any of the isolated regions.

Due to the intensive computational load needed in order to motion-correct both the MR and PET data, the minimal effects found at the end of data analysis were not substantive enough in order to warrant this to be an effective method of motion-correction. During the study, we used a supercomputer cluster to process and apply these transformation matrices and algorithms to the data. While using a supercomputer, the data processing took from several hours to several days to complete, much too long for standard computing hardware to accomplish for the minimal effects seen in the study.

B. Limitations of Study

Due to the 2020 COVID-19 pandemic, only seven subjects were scanned for the two subsequent dual PET and MR studies. Because of this, the sample size used in this study was not extremely large, and could have contributed to the minimal effects seen during the duration of the study. With our power analysis finding, we found the study sample size to be underpowered with a power value of 0.253. With more data available, more conclusive results could have been drawn, as well as investigation into what could
be adjusted to cause a more significant difference in the results between raw and motion-corrected data.

C. Other Possible Contributing Factors

Because the PET data was attenuated before motion-correction, this could have led to significant effects on the average intensity values collected during experimentation. With attenuation correction normalizing the intensity of the PET ROIs before the motion-correction process, the differences between the raw and motion-corrected datasets was shown to be minimal. If the experimental procedure was to be completed again, attenuation should not be applied to the PET data until after the motion-correction process was completed.

Another potential factor that could alter the collected data could be the variability of PET tracer uptake from subject to subject. With more scans and more participants for experimentation, uptake of PET tracer could possibly be studied more extensively and modeled more correctly as a function of time for each subject involved in the study. However, because this study was only designed as a feasibility study, these considerations were not investigated at the time.

D. Conclusions

Because typical hospitals do not contain supercomputers readily available for data processing, nor the long time frame in order to process the dual PET/MRI data effectively, the current, extensive motion-correction procedure investigated is not recommended for continued investigation. Also with the considerable volume of scanning that occurs daily in hospitals, the data processing we investigated for this study is just not a feasible option in its current form. Simpler algorithms that enact a considerably smaller computational load could be developed and implemented in order to decrease the computational stress of motion correction of the acquired data. Likewise, algorithms with notable and clear differences between motion-corrected and raw scan data could be developed in order to
necessitate motion-correcting the received imaging data. These processes could be effective means to motion correct in the future with considerable development, but in their current state, these algorithms are not realistic solutions for motion correction as they stand today.
V. REFERENCES


Catana, C. (2015). Motion Correction Options in PET/MRI. *Seminars in Nuclear Medicine, 45*(3), 212–223. https://doi.org/10.1053/j.semnuclmed.2015.01.001


Motion Artifact Correction with MotionScout. (2019). [image], from https://www.robinmedical.com/motion_artifact.html


40


APPENDIX A:

Full Task Details from Original Study

A. Scanning Protocol

The original study consisted of an in-person informed consent session, and five successive data collection sessions. On Day One and Day Five, each subject underwent a simultaneous PET/MRI scan and was required to fast for six hours beforehand. Each participant performed a blood glucose test on Days One and Five, and a normal value (70 to 120mg/dL) was required to progress in the study. On Days Two, Three, and Four each subject performed some training exercises for a subsequent study. Female participants were required to take a urine-based pregnancy test on Days One and Five, and a negative result was necessary to continue participation in the study.

All MRI sequences used in this study were obtained from the Siemens library and adjusted for study design. The human auditory system was predominantly used for the combination PET and fMRI study.

B. Tasks Performed

Three separate tasks were performed by the subjects in order to induce the hemodynamic and metabolic response, then the subject would relax while arterial spin labeling was acquired. These three tasks consisted of passive listening, an auditory Stroop test, and a brain control test, and were administered in a 60-second control, 60-second task block pattern for a total of ten minutes and 14 seconds, with the first 14 seconds discarded.

a. Passive Listening
During the passive listening task, the subject was notified that a dot would be projected on the screen and they would hear sounds in their headphones. The subject was told to relax, focus on the dot stimulus, and keep their body still. The audio presented was white noise at a constant volume and duration presented in an on-off block pattern as shown in Figure 25.

![Diagram of on-off block pattern](image)

**FIGURE 27:** Passive listening block representation. During the “on” position, white noise was administered into the participants’ headphones. During the “off” position, no sound was delivered (Sherwood, 2019).

b. **Auditory Stroop Task**

For the auditory Stroop task, the subject would be shown words on the screen and would also hear words in the headphones. The subject was instructed to press buttons on their clickers with either their left or right index finger in order to give a response, while keeping their body still. The volume and pitch of the words were changed to be congruent (control) or incongruent (task) with the words projected on the screen. Participants were then told to select the word on the screen that matched the pitch and loudness of the spoken word (i.e. high, low). An example of this test is shown in Figure 26.
FIGURE 28: Examples of the auditory Stroop correct responses. The red dot signified that the subject used their index finger on the clicker for a response. The spoken work may be congruent or incongruent, but subjects are instructed to overlook the actual spoken word (Sherwood, 2019).

c. **Brain-Control Task**

Finally, for the brain control task, the subject was shown a stimulus on the screen saying “focus on breathing” (task), or “focus on sound” (control), during which they could hear sounds in their headphones. The auditory stimulus sent was white noise at constant volume for the entire duration of the task.