Chapter 6

Goal-equivalent finger force variation in fMRI brain activity

6.1 Introduction

Our EEG study of a coordinated bimanual finger force task of Chapter 4 demonstrated distinct cortical maps associated with automatic variable force combinations. While EEG signals contain high temporal resolution useful to find oscillatory features in the machine learning technique we used, their spatial resolution is insufficient to make inferences about the exact location(s) of cortical activity associated with goal-equivalent variability. In this chapter, we verify our EEG results of goal-equivalent variability, and use functional Magnetic Resonant Imaging (fMRI) to scan whole brain activity while participants repeatedly perform the same bimanual task. The aim of this study is to determine if Blood Oxygen Level Dependent (BOLD) signals may detect motor cortical activity correlated with goal-equivalent variability, thus supporting our previous results using a different modality.

6.2 Methods

Participant population

We recruited 9 healthy participants (5 males and 4 females, 7 right-handed, 1 left-handed and 1 ambidexterous) with a mean age 27.3 ± 3.4 (range, $25 - 36$). The studies we describe here were performed at the University of Southern California and approved by the University of Southern California Institutional Review Board. All participants provided informed consent.

Overview of experiments

We used a task similar to our EEG experiment (Babikian, Kanso & Kutch 2017) where participants applied simultaneous left and right index finger forces to repeatedly match the sum of their forces to a target feedback force. We used functional Magnetic Resonance Imaging (fMRI) to simultaneously measure brain activation associated with goal-equivalent variability in output forces. Our analysis was based on finding a relationship between the ratio of left index finger M1 activity (right M1) to right index finger M1 activity (left M1), and the ratio of left index finger force to right index finger force. A positive correlation would imply that the automatic variation in motor output is encoded in the primary motor cortex.

Finger force task

Participants performed a bimanual finger force task that involved abducting both index fingers simultaneously against pressure pads (Biopac Systems, Inc., California, USA). We used pressure pads to ensure compatibility with MRI. Participants lied in supine position in the scanner and held to a custom-made handle bar where they could extend their index fingers to abduct against the pressure pads. We chose a single target force level of 2 Newtons (N) that was easy to achieve for all. Participants received continuous visual feedback of their current total finger force as well as the fixed target, without individual force feedback. Each repetition of the task consisted of 5 seconds of rest where a fixation crosshair was shown, and 10 seconds of target hold with active feedback of the sum of forces. Participants performed a total of 26 repetitions each.

An example of one participant's force repetitions is shown on Figure 6.1b. During each repetition of the task, the sum of forces was kept at 2.5N (top trace), while individual forces fluctuated.The participant performed some repetitions with higher right finger force than left ($F_R > F_L$), and other repetitions with higher left finger force than right ($F_L > F_R$). To summarize the combination of forces used by the participant on each repetition of the task, we computed separate averages for F_R and F_L across time starting one second after the target was displayed (to allow for reaction time and force stabilization) and ending half a second before the target disappeared (to exclude the return to baseline force). A total of 26 combinations of F_R versus F_L along with a 95% covariance ellipse for one participant are shown in Figure 6.1c. The major axis of the covariance ellipse represents the goal-equivalent direction along which all combinations do not affect the task of producing 2.5N of total finger force. The orthogonal direction is the non-goal-equivalent direction.

fMRI acquisition

We measured brain activation associated with goal-equivalent variability using fMRI.

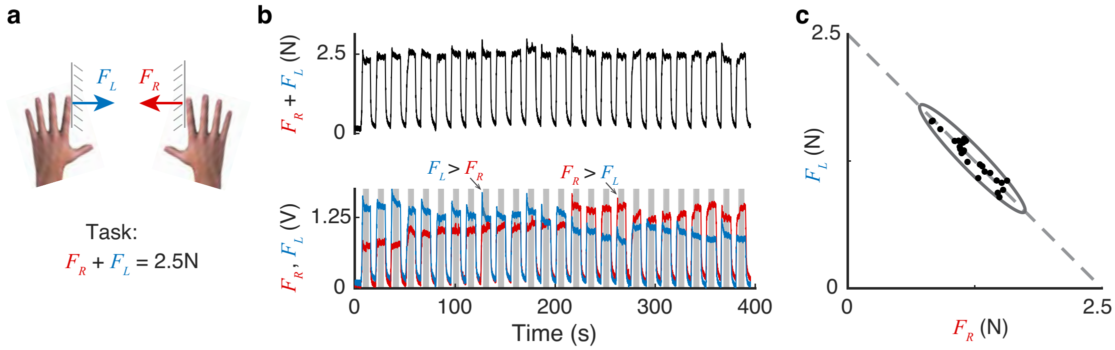

Figure 6.1: Experiment setup and force output. **a**. The participant lies down in the MRI scanner and repeatedly exerts left (F_L) and right (F_R) index finger forces simultaneously, while keeping the sum of the two constant at a target force of 2.5 Newtons (N). Only the sum of forces is shown to the participant as feedback on a screen, along with the target force level; **b**. example of a representative participant's repeated force holds. The top trace shows the participant maintained the sum of the two forces at 2.5N, while the bottom traces show the left (in blue) and right (in red) forces for the same repetitions. The interval shaded in gray (1 second after the start and 0.5 second before the end of the hold period) is used to determine the time average of individual forces in each repetition; **c**. average right versus left forces during all task repetitions for the same participant with a 95% covariance ellipse fit.

We used a 3-Tesla (GE Signa Excite) with an eight-channel head coil. We positioned participants supine while viewing a fixation crosshair, and placed foam pads to limit head motion. We collected T2-weighted echo planar image volumes with blood oxygen level- dependent (BOLD) contrast (echo time, 34.5 ms; flip angle, 90; field of view, 220 mm; pixel size, 3.43 mm) continually every 2.5 s during the imaging run. Each volume consisted of 37 axial slices (3 mm slice thick- ness, 0.5 mm interslice gaps) that covered the brain from vertex to cerebellum. We additionally acquired a T1-weighted high-resolution anatomical image from each participant.

We preprocessed each participants fMRI data using the Functional Magnetic Resonance Imaging of the Brain Expert Analysis Tool (FMRIB FEAT, http://fsl.fmrib.ox.ac.uk/fsl/), which included skull extraction using the brain extraction tool (BET) in FSL (FMRIB Software Library), slice timing correction, motion correction, and spatial smoothing using a Gaussian kernel with full-width half-maximum of 5 mm and nonlinear high-pass temporal filtering (100 s). We extracted appropriate signals given the hemodynamics response time.

Correlation of force output with primary motor cortex activity

After extracting the BOLD signals, we defined regions of interest (ROIs) consisting of the left and right Primary Motor Cortices (M1s) corresponding to the voluntary activation of right and left index fingers (from http://neurosynth.org). The ROI voxel locations were in normalized units (MNI); and we used FSL along with each participant's structural brain image to map the voxel locations contained in each ROI from standard MNI space to participant-specific coordinates.

The analysis of BOLD signals across left and right M1s was carried out at the participant level. For each participant, the BOLD signals from the voxels corresponding to each M1 were extracted. Then, for each M1, the BOLD signals were averaged across its voxels to obtain one time series for M1-left and another time series for M1-right. The BOLD signals during target matching repetitions were extracted from the timing-corrected signals.

To understand the relationship between left and right M1 BOLD signals and right and left forces, for each participant, we computed the following ratios each repetition: $\frac{F_R}{F_L}$ and $\frac{\text{BOLD-M1}_L}{\text{BOLD-M1}_R}$. We then examined the relationship between these values across all repetitions by fitting a line to $\frac{F_R}{F_L}$ versus $\frac{\text{BOLD-M1}_L}{\text{BOLD-M1}_R}$: a positive slope would indicate that as the right finger applied relatively higher force than left, the left M1 had relatively higher neural activity with respect to right M1.

For group analysis, we used a linear mixed-effects (LME) model to quantify the association between $\frac{\text{BOLD-M1}_L}{\text{BOLD-M1}_R}$ and $\frac{F_R}{F_L}$. The LME model of the BOLD ratio $\frac{\text{BOLD-M1}_L}{\text{BOLD-M1}_R}$ contained a fixed-effects term for force ratio $\frac{F_R}{F_L}$:

$$\frac{\text{BOLD-M1}_L}{\text{BOLD-M1}_R} \sim \frac{F_R}{F_L} + \epsilon. \tag{6.1}$$

Prior to fitting the LME model, the distribution of $\frac{\text{BOLD-M1}_L}{\text{BOLD-M1}_R}$ was converted to a standard normal distribution (mean 0, std = 1) for each participant to ensure the data was comparable across all participants. We examined the p-value for the fixed-effect of force ratio on BOLD ratio, and considered $p < 0.05$ as evidence for a statistically significant relationship between cortical activity and goal-equivalent variation in finger forces.

6.3 Results

We found that all 9 participants achieved the task with a significantly higher variance of repeated forces along the goal-equivalent direction than the non-goal-equivalent direction. In Figure 6.2a, we show the 95% covariance ellipses of all 9 participants, along with the goal-equivalent line. The relative variance along the goal-equivalent direction is greater than in the orthogonal direction in all participants, as illustrated in Figure 4.2b. The ratios of goal-equivalent variance to the sum of both non-goal-equivalent and goal-equivalent variances in all participants were significantly greater than 0.5 ($p < 0.0001$).

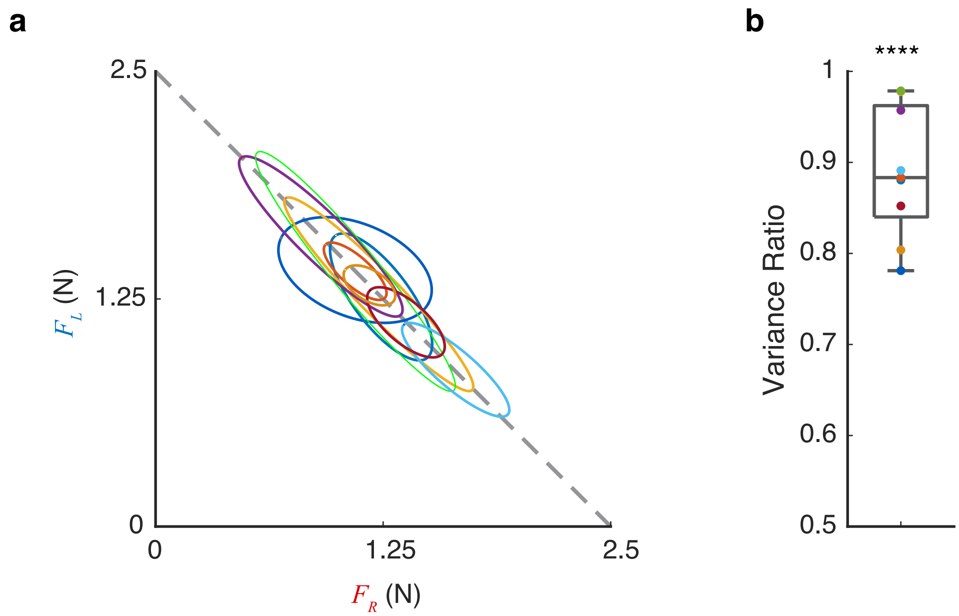

Figure 6.2: Covariance ellipses and force variance ratio of 9 participants. **a**. 95% covariance ellipses of all participants. The covariance ellipse of each participant was constructed using the average left and right forces from all repetitions of the task (see Figure 6.1c). **b**. boxplot of the ratio of goal-equivalent force variance to the sum of goal-equivalent and non-goal-equivalent variance. The ratio was significantly greater than 0.5 ($p < 0.0001$, ****).

The relationship between force ratio and BOLD ratio for the 26 repetitions of one participant is shown in Figure 6.3. The figure indicates that as the ratio $\frac{F_R}{F_L}$ increased, the BOLD ratio $\frac{\text{BOLD-M1}_L}{\text{BOLD-M1}_R}$ also increased, as shown by the positive slope of the fitted line.

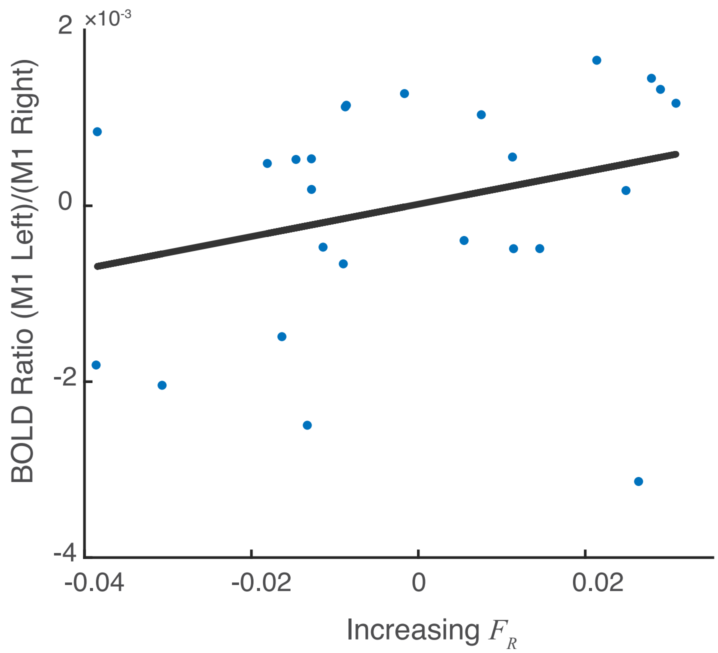

Figure 6.3: Relationship between force ratio and BOLD ratio for the 26 repetitions of one participant. The x-axis represents a relative increase in right force, while the y-axis is a normalized BOLD ratio of left M1 to right M1. The fitted line has a positive slope indicating a relatively higher right force was associated with a relatively higher left M1 activity.

Our LME model for group analysis indicated that force ratio had a significant effect on BOLD ratio ($p < 0.05$). Figure 6.4 illustrates the normalized BOLD ratios $\frac{\text{BOLD-M1}_L}{\text{BOLD-M1}_R}$ of all participants compared with their force ratios $\frac{F_R}{F_L}$ across all repetitions. The fitted line had a positive slope of 0.134 with $p = 0.043$. Our results showed that repetitions for which $F_R > F_L$ were generally associated with BOLD-M1$_L$ > BOLD-M1$_R$ across participants.

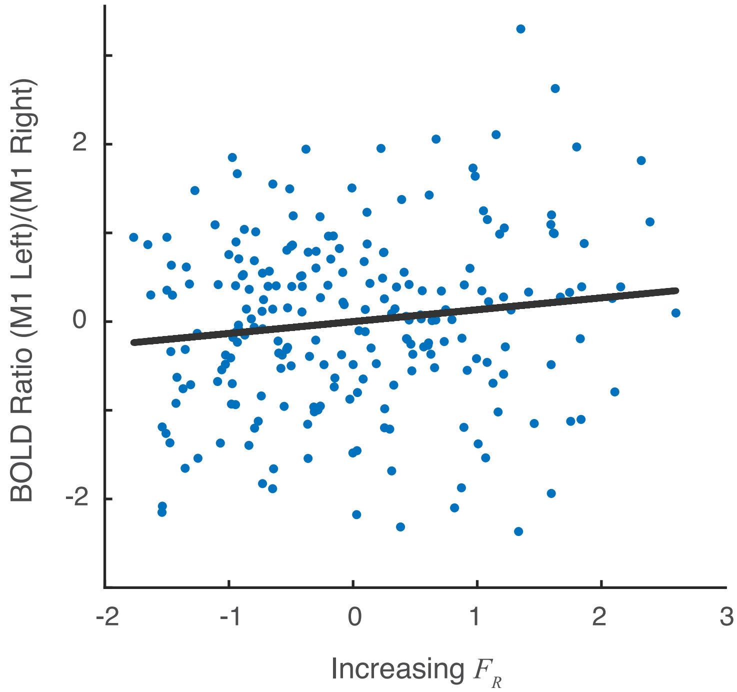

Figure 6.4: Relationship between force ratio and BOLD ratio for the all repetitions of all participants. The x-axis represents a relative increase in right force, while the y-axis is a normalized BOLD ratio of left M1 to right M1. The fitted line has a positive slope of 0.134 ($p < 0.05$) indicating a relatively higher right force was associated with a relatively higher left M1 activity during automatic goal-equivalent force variation.

6.4 Discussion

We observed a goal-equivalent variability in individual forces during repetitions of the finger force task in all of our participants. This result is consistent with previous studies with similar multi-finger tasks (Latash et al. 1998, Latash et al. 2001, Scholz & Schöner

1999, Seay et al. 2006), and also with our goal-equivalent force output results of Chapter 4: when two or more fingers of a hand applied forces that matched to the sum of forces of all employed fingers, a variability in individual forces is seen over repetitions while keeping the sum of forces constant. We additionally found that goal-equivalent finger force variation was associated with cortical activity. In particular, we observed relatively higher neural activity in the left M1 than right when relatively higher right force than left was applied, and vice-versa. While fMRI studies have shown an increase in BOLD signals associated with increasing voluntary contralateral FDI activation, we observed an association between relative right and left BOLD signals and automatic changes in relative left and right forces. This would conclude an agreement with our experimental results that automatic force variability is at least in part produced in the primary motor cortex, shown using two modalities: EEG which measures cortical activity with high temporal resolution, and fMRI which provides high spatial resolution.

Although there was significant association between left and right BOLD signals of M1 and goal-equivalent finger force variation, this association was not as strong as our EEG results suggested (p-value just below 0.05). We believe that our study had some limitations that could not be addressed at the time of data collection because of lack of equipment or resources; but that could be modified in future studies for a better study design.

Some of the limitations that we believe affected our results follow. First, our resources and timing of data collection allowed the recruitment of only 9 subjects, which may be an insufficient number for significant results. Moreover, due to time restrictions during scanner runs, we were only able to collect 26 repetitions per subject. The hold time of the target matching portion of the task (5 seconds) may also have been too short for a very low resolution of image samples (one 3D image every 2.5 seconds), which yielded only one BOLD value per repetition after timing corrections. Second, our pressure pads that measured fingertip forces were not always accurate, as their gains often fluctuated across participants. Future studies could solve this issue by using higher quality force sensors compatible with fMRI. Finally, due to our pressure pads saturating at higher forces, we were obligated to use a low target (sum of forces) of 2.5 N, resulting in very small changes in individual forces across repetitions. These changes may have been too small to be detected in the contralateral BOLD signals. Again, better force sensors would allow for higher force targets resulting in higher relative changes in individual finger forces, hopefully to be better detected in BOLD signals.